John C. Hall
Brian J. Hall *Editors*

Cutaneous Drug Eruptions

Diagnosis, Histopathology and Therapy

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ISBN 978-1-4471-6728-0 ISBN 978-1-4471-6729-7 (eBook)
DOI 10.1007/978-1-4471-6729-7

Library of Congress Control Number: 2015949115

Springer London Heidelberg New York Dordrecht

Printed on acid-free paper

Springer-Verlag London Ltd. is part of Springer Science+Business Media (www.springer.com)

For the wonderful authors who made this book a reality
and the patients to whose care they are so selflessly dedicated.
Thank you also to the patients who graciously allowed their
photographs to be used so this book could come to fruition.

Introduction

Use of medications in the population as a whole is increasing, and as the baby boomer cohort ages, more people will survive with chronic illnesses, and with new medical advances, there is an ever-increasing transplant population. One of the most difficult aspects of polypharmacy is allergic and toxic reactions to drugs. The skin is often the only or the earliest harbinger of multi-organ system damage in these patients. The skin is also the most easily observed and biopsied.

Therefore, a textbook covering all aspects of this challenging dilemma seems apropos. That is what this treatise attempts to do. And in so doing, we hope to create an accessible resource for early detection and resolution of cutaneous drug reactions.

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Abbreviations

5-MOP	5 methoxypsoralen
6-MP	6-mercaptopurine
6-TG	6-thioguanine
AA	Arachidonic acid
ABCD	Acquired brachial cutaneous dyspigmentation
ACE	Angiotensin converting enzyme [inhibitor]
ACE-I	Angiotensin-converting enzyme inhibitors
ADR(s)	Adverse drug reaction(s)
AE	Anagen effluvium
AED(s)	Antiepileptic drug(s)
AEs	Adverse effects
AGA	Androgenetic alopecia
AGEP	Acute generalized exanthematous pustulosis
AHEI	Acute hemorrhagic edema of infancy
AIN	Acute interstitial nephritis
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANA	Antinuclear antibody
ANCA	Anti-neutrophil cytoplasmic autoantibodies/antibodies/ antibody
ARBs	Angiotensin receptor blockers
ARDS	Acute respiratory distress syndrome
ARS	Acute retroviral syndrome
AST	Aspartate aminotransferase
AZA	Azathioprine
BCC	Basal cell carcinoma
BP	Bullous pemphigoid
BPAg2	Bullous pemphigoid antigen 2
BPL	As B-cell lymphoma-like pseudolymphoma
BRAF	Rapidly accelerated fibrosarcoma kinase B
BSA	Body surface area
BUN	Blood urea nitrogen
CAD	Chronic actinic dermatitis
cADRs/CDARs	Cutaneous adverse drug reactions
c-AMP	Cyclic-AMP
CAPS	Cryopyrin-associated periodic syndrome
CCB(s)	Calcium channel blocker(s)

CD	Crohn's disease
CIA	Chemotherapy-induced alopecia
CLA	Cutaneous lymphocyte-associated antigen
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
COX	Cyclooxygenase
CPK	Creatine phosphokinase
CPL	Cutaneous T-cell lymphoma-like pseudolymphoma/ cutaneous pseudolymphoma
CREST	Calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, teleangiectasias
CRP	C-reactive protein
CSF(s)	Colony-stimulating factor(s)
CSS	Churg-Strauss syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
cuSCCs	Keratoacanthomas-type squamous cell carcinomas
CVD	Collagen vascular diseases
DFSP	Dermatofibrosarcoma protuberans
DH	Dermatitis herpetiformis
DHS	Drug hypersensitivity syndrome
DIBP	Drug-induced bullous pemphigoid
DIDMOHS	Drug-induced delayed multi-organ hypersensitivity
DIEM	Drug-induced erythema multiforme
DIF	Direct immunofluorescence
DIHS	Drug-induced hypersensitivity syndrome
DIV	Drug-induced vasculitis
DLE	Discoid lupus erythematosus
DM	Dermatomyositis
DMARD	Disease-modifying antirheumatic drug
DMT1	Type 1 diabetes mellitus
DNA	Deoxyribonucleic acid
DRESS	Drug rash/reaction with eosinophilia and systemic symptoms
Dsg-1	Desmoglein 1
Dsg-3	Desmoglein 3
DTH	Delayed-type hypersensitivity
DVT	Deep-vein thrombosis
EBA	Epidermolysis bullosa acquisita
EBV	Epstein-Barr virus
ECMO	Extracorporeal membrane oxygenation
EED	Erythema elevatum diutinum
EGFR(s)	Epidermal growth factor receptor(s)
EGFRi	Epidermal growth factor receptor inhibitors
EM	Erythema multiforme
EMG	Electromyography
EMPACT	Erythema multiforme associated with phenytoin/ phenobarbital and cranial radiation therapy
EN	Erythema nodosum

EPDS	Erosive pustular dermatosis
EPF	Eosinophilic pustular folliculitis
ESR	Elevated erythrocyte sedimentation rate
FcεRI	High-affinity IgE Fc receptor
FDC	Fixed-dose combination
FDE(s)	Fixed drug eruption(s)
GBFDE	Generalized bullous FDE
G-CSF	Granulocyte colony stimulating factors
GIST	Gastrointestinal stromal tumor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GnRH	Gonadotropin-releasing hormone
GPA	Granulomatosis with polyangiitis
GPP	Generalized pustular psoriasis
GVHD	Graft-versus-host disease
H & E	Hematoxylin and eosin [stain]
HAART	Highly active antiretroviral therapy
HAEM	HSV-associated EM/herpes-associated EM
HCTZ	Hydrochlorothiazide
HCV	Hepatitis C virus
HER	Human epidermal receptor
HFS	Hand–foot syndrome
HHV	Human herpes virus
HISN	Heparin-induced skin necrosis
HIT	Heparin-induced thrombocytopenia
HITT	Heparin-induced thrombocytopenia and thrombosis
HL	Hodgkin's lymphoma
HLA	Human leukocyte antigen
HPLC	High-pressure liquid chromatography
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease
IFN(s)	Interferon(s)
IGDR	Interstitial granulomatous drug reaction
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRIS	Immune response inflammatory syndrome
IRS	Immune reconstitution syndrome
ISH	In situ hybridization
IVIG	Intravenous immunoglobulin
J-SCAR	Japanese Research Committee on Severe Cutaneous Adverse Reaction
KS	Kaposi sarcoma
LABD	Linear IgA bullous dermatosis
LCV	Leukocytoclastic vasculitis
LDH	Lactate dehydrogenase
LINA	Linear IgA
LMWHs	Low-molecular-weight heparins
LTT	Lymphocyte transformation test

MAPK	Mitogen-activated protein kinase
MAR	Medical administration record
MBI	Mucosal barrier injury
MCD	Mast cell degranulation [test]
MED	Minimal erythema dose
MF	Mycosis fungoides
MIAN	Methotrexate-induced accelerated nodulosis
MKi	Multikinase inhibitors
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MRSA	Methicillin-resistant staphylococcus aureus
MSH	Melanocyte-stimulating hormones
MTX	Methotrexate
NAC	N-acetylcysteine
nbUVB	Narrow-band ultraviolet-B
NEH	Neutrophilic eccrine hidradenitis
NMSC	Non-melanoma skin cancer
NPFDE(s)	Non-pigmenting fixed drug eruption(s)
NSAIDs	Nonsteroidal anti-inflammatory drugs/anti-inflammatories
OCPs	Oral contraceptive pills
OI(s)	Opportunistic infection(s)
P	Perinuclear
PAN	Polyarteritis nodosa
pANCA	Perinuclear antineutrophilic cytoplasmic antibodies
PCR	Polymerase chain reaction
PCT	Porphyria cutanea tarda
PDGFR	Platelet-derived growth factor receptor
PEP	Post-exposure prophylaxis
PF	Pemphigus foliaceus
PF4	Platelet factor 4
PG	Pyoderma gangrenosum
PMLE	Polymorphous light eruption
PNGD	Palisaded neutrophilic granulomatous dermatitis
PNP	Paraneoplastic pemphigus
PR3	Proteinase 3
PSAI	Psoriasis area severity index
PTU	Propylthiouracil
PUVA	Psoralen plus ultraviolet A/plus UVA
PV	Pemphigus vulgaris
RA	Rheumatoid arthritis
RAAST	Radioallergosorbent test
RAF	Rapidly accelerated fibrosarcoma kinase
RANTES	Regulated on activation, normal T expressed and secreted
Rapa	Rapamycin
RegiSCAR	[European] Registry of Severe Cutaneous Adverse Reaction
RND	Rheumatoid neutrophilic dermatitis
ROS	Reactive oxygen species
SCAR(s)	Severe cutaneous adverse reaction(s)

SCC	Squamous cell carcinoma
SCF	Stem cell factor
SCLE	Subacute cutaneous lupus erythematosus
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SIRS	Systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SSLR	Serum sickness-like reaction
SSRI	Selective serotonin reuptake inhibitor
TE	Telogen effluvium
TEN	Toxic epidermal necrolysis
TEN/SJS	Toxic epidermal necrolysis/Stevens-Johnson Syndome
TNF	Tumor necrosis factor
TPL	T-cell lymphoma-like pseudolymphoma
TPMT	Thiopurine-S-methyltransferase
Treg	Regulatory T [cells]
TTP	Thrombotic thrombocytopenic purpura
UFH	Unfractionated heparin
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WISN	Warfarin-induced skin necrosis
ZVD	Zidovudine

Part I

The Skin and Drug Interactions

Immunology of Cutaneous Drug Eruptions

1

Jon A. Dyer

Abstract

Adverse drug reactions (ADRs) are divided into type A (pharmacotoxicologic) and type B (hypersensitivity) reactions. Type B ADRs represent ~10–15 % of all ADRs, and immune-mediated hypersensitivity drug reactions account for ~10 % of type B ADRs. These hypersensitivity reactions are reproducible with repeat drug exposure and occur at drug dosages tolerated by normal patients. The immune mechanisms leading to type B severe cutaneous adverse reactions to drugs (SCARs) are diverse and incompletely understood. Ongoing research is shedding some light on these diverse reaction patterns, but also generating new questions. While the human immune system functions as a seamless syncytium, the intellectual compartmentalization of the immune system into various "arms" makes it easier to comprehend. Certain of these arms appear to predominate in the various types of SCARs noted clinically.

Keywords

Pharmacotoxilogic • Pharmacogenetic • Pharmacoepegenitic • Human leukocyte antigen (HLA) • Haplotypes • Hapten • Hapten independent model • Altered peptide repetoire model • Prohapten • T-cells • T-cell receptor (TCR) • Severe cutaneous adverse reactions (SCARs) • Adverse drug reactions (ADR)

Adverse drug reactions (ADRs) are divided into type A (pharmacotoxicologic) and type B (hypersensitivity) reactions. Type B ADRs represent ~10–15 % of all ADRs, and immune-mediated hypersensitivity drug reactions account for ~10 % of type B ADRs. These hypersensitivity reactions are reproducible with repeat drug exposure and occur at drug dosages tolerated by normal patients. The immune mechanisms leading to type B severe cutaneous adverse reactions to drugs (SCARs) are diverse and incompletely understood. Ongoing research is shedding some light on these diverse reaction patterns, but also generating new

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_1

Table 1.1 Gel and Coombs Hypersensitivity reactions

		Mediator	Mechanism(s)	Clinical phenotypes
Type I	Immediate	IgE	Ag binding to mast cell/ basophil surface receptors	Urticarial, anaphylaxis, angioedema
Type II	Antibody-mediated (cytotoxic)	IgM, IgG	Ab binds to Ag leading to complement driven cell lysis or cell-mediated cytotoxicity or recruitment of neutrophils/ monocytes	Goodpasture's; ANCA vasculitis; drug-induced thrombocytopenia; hemolytic anemia
Type III	Immune complex	IgM, IgG, IgA	Ag-Ab complexes deposit in tissue – trigger recruitment of leukocytes and activation	Serum sickness reaction; Henoch-Schönlein purpura
Type IV	Delayed-type	T-lymphocytes	Activated T cells produce cytokines causing inflammation leading to tissue effects or directly attack cells	
	Type IVa Monocytic	Th1 CD4+: IFN-γ, TNF	IFN-γ stimulated KC and MC cytokine production	Allergic contact dermatitis
	Type IVb Eosinophilic	Th2 CD4+: IL-4, IL-5, IL-13	Th2 cytokines and eotaxin recruit eosinophils	DIHS
	Type IVc Cytotoxic T cells	Cytotoxic CD8+ or CD4+ T cells: IFN-γ; TNF	Activated cytotoxic T cells induce KC lysis	SJS/TEN
	Type IVd Neutrophilic	Th17 CD4+: IL-17, IL-22, IL-8	Th17 cell derived IL-17/IL-22 stimulate KC secretion of IL-8 leading to neutrophil recruitment	AGEP

questions. While the human immune system functions as a seamless syncytium, the intellectual compartmentalization of the immune system into various "arms" makes it easier to comprehend. Certain of these arms appear to predominate in the various types of SCARs noted clinically.

Both adaptive and innate aspects of the immune system may contribute to the development of SCARs. The classic Gel and Coombs delineation of delayed type hypersensitivity reactions highlights recognized mechanisms that lead to the development of different SCARs (Table 1.1).

Genetic factors have long been recognized to have a strong contributory role, and with improvements in genetic analysis, the mechanisms by which specific inherited polymorphisms contribute to specific SCARs are being clarified. This has led to the development of the fields of pharmacogenetics and pharmacogenomics. Further elucidation of these mechanisms may lead to the development of pharmacoepigenomics/pharmacoepigenetics as better understanding of the effect of environmental factors on the genome leading to predisposition or resistance to SCARs is understood. Genetic factors influence the development of SCARs in a variety of ways. Inherited variations in drug-metabolizing enzymes may increase the production of immunogenic drug metabolites (variable metabolism by variants of cytochrome p450 enzymes or altered drug processing by variations in epoxide hydrolase). Additionally, specific haplotypes of human leukocyte antigen (HLA), which play a primary role in T cell stimulation, have long been recognized to contribute to increased risk of SCARs.

Genetic factors, drug pharmacology, and immune responses interact in complex fashions to create the potential for SCARs. Better understanding of these interactions and how they lead to SCARs will lead not only to improved therapeutic interventions, but also allow pharmacogenomic testing to preemptively assess patients for risk of reactions to specific drugs.

Models of Drug Allergy Development

Several models exist to explain how MHC-dependent T-cell stimulation by drugs develops, triggering the immune responses that leads to SCARs.

The classic *hapten/prohapten model* proposes that a small neutral molecule becomes immunogenic upon binding to a protein. There are various mechanisms by which this could develop; a small molecule binding to a high molecular weight protein then becomes immunogenic. Prohapten molecules can become immunogenic after metabolism to intermediates that are reactive and can then bind to proteins. This allows presentation via HLA molecules to T cells and development of an immune response. After re-exposure, memory T cells proliferate, triggering an inflammatory response over 24–72 h.

A second mechanism is the *hapten independent* (*p-i model*) where direct interaction of the drug with immune receptors occurs without a prior sensitization phase. The interaction is directly with T cell receptors or MHC molecules and can explain how some drugs trigger T cell activation without prior exposure. A final concept, *the altered peptide repertoire model*, suggests that an altered milieu of self-peptides is presented to or recognized by T cells due to drug binding in the antigen-binding cleft of certain HLA molecules thus triggering the immune response. This is exemplified by abacavir, which appears to non-covalently bind in the F-pocket of HLA-B*5701 altering the shape of the cleft and the peptides that bind it.

Pharmacogenetics

An increased risk of SCARs in association with specific HLA types has long been recognized. Table 1.2 summarizes better-known associations and their representative populations.

The recognition of these associations has led to pharmacogenetic screening for high-risk alleles. Examples include screening for HLA-B*5701 in patients to be treated with abacavir, and the drug should not be used in patients who carry HLA-B*5701. For allopurinol, screening for HLA-B*5801 is recommended in high-risk populations, such as those with Han Chinese or Thai descent. Genetic screening for the HLA-B*1502 allele in patients with Asian ancestry is recommended prior to starting carbamazepine and it should not be used if the allele is present. A variety of studies have demonstrated the cost effectiveness of screening for these known alleles in high-risk populations (Asia) and HLA-B screening is performed prior to initiation of abacavir, allopurinol, and carbamazepine in Thailand.

Inherited variations in other systems important to the immune response (8- TCR subtypes) or metabolism of drugs in the skin (skin specific metabolic enzymes) may also play predisposing roles in the development of SCARs. While most drug metabolism occurs in the liver with few metabolites reaching the skin, drug-metabolizing enzymes do exist in the skin including some that are skin specific. While genetic variations in these enzymes and associated variation in risk of drug reactions has not been extensively studied it is an area of ongoing research.

A comprehensive review of basic immunology is beyond the scope of this chapter, and specific types of SCARs will be reviewed later in this volume. However, several SCARs will be briefly mentioned to highlight basic concepts in immunology leading to adverse reactions. The reader is referred to specific chapters for more detail on the clinical aspects and treatments of these conditions.

Stevens-Johnsons Syndrome/Toxic Epidermal Necrolysis (SJS-TEN)

Stevens-Johnsons syndrome/Toxic epidermal necrolysis (SJS-TEN) is one of the most feared SCARs. SJS/TEN is a type IVc hypersensitivity reaction where aberrant T cell activation triggers keratinocyte (KC) death and variable amounts of epidermal detachment. While specifics of this aberrant immune response in SJS/TEN are the subject of ongoing investigation, CD8+ cytotoxic T cells play a primary role. This is in contrast to the more common maculopapular drug exanthems, which account for ~90 % of drug eruptions, where cytotoxic CD4+ T cells are implicated. For T cell degranulation to occur there must be direct contact between T cells and antigen presenting cells (APCs) and the T cell receptor (TCR) must recognize specific antigen (Ag) bound to MHC. Granulysin released from degranulating cytotoxic T cells is likely a key player in the clinical findings of SJS/TEN.

Table 1.2 HLA haplotypes associated with cutaneous drug reactions

Drug	Allele	Population	Clinical syndrome	OR (95 % CI)	*P*-value	FDA Recommended Genetic Testing	Reference
Abacavir	HLA-B*5701	Australian	DIHS	117 (29–481)	<0.0001		22
		US European	DIHS	1945 (110–34,352)		Yes	23
		US African	DIHS	900 (38–21,045)		Yes	23
Allopurinol	HLA-B*5801	Han, Korean, Thai, European	SJS-TEN	96.6 (24–381)	<0.001	No	24
		Han		580 (34–9781)	4.7×10^{-24}		25
		Thai	SJS-TEN	348 (19–6337)	1.6×10^{-13}	No	26
		Korean	SJS-TEN	179 (10.2–3152)		No	27
		Korean	DIHS	161 (18–1430)	1.45×10^{-10}	No	28
Carbamazepine	HLA-B*1502	Canadian	SJS-TEN	38.6 (2.7–2240)	0.002		29
		Han, Thai, Malaysian	SJS-TEN	113 (51–251)	$<1\times10^{-5}$	Yes	30
		Han, Thai, Malaysia, Korean	SJS-TEN	80 (28–224)	0.07	Yes	31
	HLA-A*3101	Han	DIHS	12 (3.6–41)	0.002	Warning	32
		Korean	DIHS; SJS-TEN	12 (4.5–34); 6.5 (1.4–30)	2.9×10^{-6}; 0.03	Warning	33
		Japanese	SJS-TEN	16 (4.8–56)	0.0004	Warning	34
		European	DIHS; SJS-TEN	12.4 (1.3–121); 26 (5–116)	0.03; 8×10^{-5}	Warning	35
		Han, Korean, Japanese, European	DIHS; SJS-TEN	9.5 (6.4–14)	<0.000001	Warning	30
	HLA-B*1511	Korean	SJS	18.4 (4–88)	0.002	No	33
		Han	SJS-TEN	31 (2.8–350)	0.01	No	36
		Japanese	SJS-TEN	16.3 (4.8–56)	0.0004	No	34

Dapsone	HLA-B*1301	Chinese	DIHS	20.5 (11.6–36.5)	6.8×10^{-25}	No	37
Lamotrigine	HLA-B*38	European	SJS-TEN	6.8 (2–21)	<0.02		38
	HLA-B*1502	Han	SJS-TEN	3.6 (1–11.6)	0.03		39
Methazolamide	HLA-B*5901	Korean	SJS-TEN	250 (13–4814)	<0.001	No	40
Nevirapine	HLA-B*3505	Thai	All	18.9 (4.9–80)	$<1.2 \times 10^{-4}$		41
	HLA-DRB1*0101	Australian	DIHS	4.8 (1.6–14.7)	<0.01		42
	HLA-Cw8	Sardinian	DIHS	14.6 (2.4–88)	<0.05		43
	HLA-C*0401	Malawian	SJS-TEN	5.2 (2.4–11)	0.0002		44
	HLA-Cw*04	Han	DIHS	3.6 (1–11)	0.03		45
Phenytoin	HLA-B*1502	Thai	SJS-TEN	18.5 (1.8–188)	0.005		46
		Han	SJS-TEN	4.3 (2–9.4)	<0.0003	Warning	39
Sulfamethoxazole	HLA-B*38	European	SJS-TEN	8.6 (3.5–21)	<0.003		38

Injection of granulysin into mice leads to clinical findings identical to SJS/TEN.

Additionally, cell surface receptor Fas and Fas ligand (FasL) interaction can trigger KC apoptosis. Activated T cells and NK cells express FasL, however its expression can be induced in KCs. Soluble FasL may be produced by KC in response to T cell derived TNFα and IFN-γ. Blockage of Fas-FasL signaling with intravenous immunoglobulin (IVIg) derived Fas-FasL blocking antibodies has been proposed as a mechanism by which intravenous immunoglobulin (IVIg) works in SJS/TEN, however the role of IVIg in SJS/TEN remains controversial.

As noted above and in Table 1.2, genetic factors, such as HLA-B*1502 in Han Chinese, play an important role in predisposition toward SJS/TEN. Recognition of these pharmacogenetic predispositions has led to the recommendation for pretreatment HLA testing in high-risk populations for abacavir, phenytoin, and carbamazepine. The American College of Rheumatology now recommends HLA testing prior to allopurinol therapy in high-risk populations.

More recent reports suggest that specific T-cell receptor subtypes may also play a role. In an attempt to explain why a small percentage of HLA-B*1502 carriers tolerate carbamazepine, investigators discovered an absence of a specific TCR subtype. Variations in other elements of the immune synapse, such as TCR, could explain lack of/or weaker associations of high-risk subtypes such as HLA-B*1502 and carbamazepine-induced SJS/TEN (Fig. 1.1) in non-Han Chinese.

Variations in individual drug metabolism likely play a role as well. In patients who develop SJS/TEN from sulfa drugs (Fig. 1.2), there is an increased percentage of "slow acetylators" as compared to control populations. While the mechanism is not understood, slow acetylation appears to increase with poorly controlled HIV infection and could contribute to the increased incidence of drug reactions in that population.

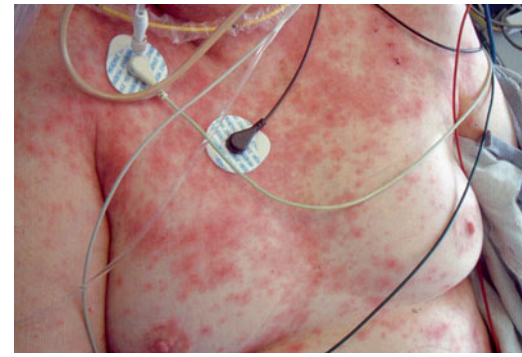

Fig. 1.1 Inflammatory, erythematous, and papular dermatitis over the anterior trunk caused by carbamazepine

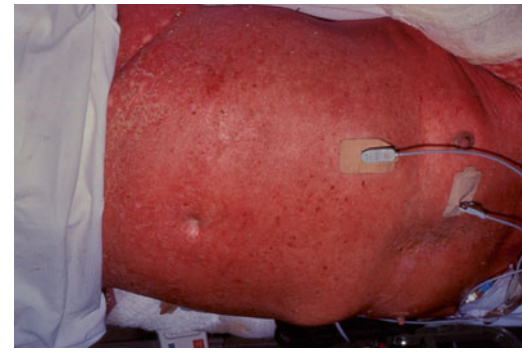

Fig. 1.2 Generalized dermatitis over the trunk with erythema and early erosions caused by sulfamethoxazole

Pustular Drug Reactions

Pustular drug reactions (such as acute generalized exanthematous pustulosis – AGEP) develop due to stimulation of specific immunologic pathways, which lead to neutrophil recruitment and activation (Type IVd). Neutrophil recruitment is regulated by Th17 immune responses via the production of IL-17. IL-17 and IL-22 stimulate KC to express IL-8, which is a strong recruiter for neutrophils. CD4+ T helper and CD8+ cytotoxic T cells are found in cutaneous infiltrates of AGEP. Reports of rapid resolution of AGEP after treatment with TNFα blockers may validate the role of these pathways in development of neutrophilic eruptions. AGEP exhibits clinical similarity to pustular psoriasis. Recently monogenic familial pustular psoriasis was associated with mutations in IL-36 antagonist (IL-36Ra), which lead to increased signaling of the IL-36 pathway once activated. The role of IL-36 in AGEP is under investigation.

Drug-Induced Hypersensitivity Syndrome (DIHS)

DIHS is considered a type IVb hypersensitivity reaction where production of typical Th2 cytokines such as IL-4, IL-13, and IL-5 (increased in early stages of DIHS) and increased expression of IL-5 and eotaxin in lesional skin leads to eosinophil recruitment.

However, the role of the eosinophil in the direct pathogenesis of DIHS is unclear. There are several features which set DIHS apart from other drug reaction syndromes. While most drug eruptions start 1–2 weeks after initiation of therapy, DIHS exhibits a delayed onset (3 weeks to 3 months after initiation of the causative drug). Paradoxical worsening is often noted 3–4 days after withdrawal of the offending drug. Additionally, there is a limited repertoire of drugs associated with the development of DIHS.

Genetic factors also play a role in risk of DIHS. The association of DIHS from the anti-HIV drug abacavir and HLA-B*5701 is well recognized, likely due to changes in the antigen binding groove of HLA-B*5701 resulting from binding of abacavir, leading to altered recognition of self antigens (see above). Similar findings were noted with HLA-B*1502 in cases of DIHS with carbamazepine.

With more detailed study it is becoming clear that there is drug-specific heterogeneity in DIHS. Elevated eosinophils are commonly noted in cases triggered by carbamazepine, but are much less common when abacavir, dapsone, and lamotrigine are the culprits. Allopurinol is often associated with more prolonged disease courses, as well as renal involvement, but other common features of DIHS are rare when it is the causative agent. Thus DIHS is likely a spectrum of individual Type IV (often b) hypersensitivity reactions triggered by specific drugs with some exhibiting overlapping features. The role of viral reactivation in DIHS is discussed below.

Viral Reactivation and Drug Eruptions

The initial detection of human herpes virus 6 (HHV-6) via PCR from blood samples of patients with DIHS in the 2–3 weeks after onset triggered further investigation into the role of viral reactivation in adverse drug reactions.

Mechanisms of Viral/Immune Interaction Leading to Drug Allergy

After clearance of an initial viral infection (for example, HSV) from the skin, there is a small fraction of resident memory T cells that remain to protect peripheral tissue from reexposure to virus. These T_{RM} cells persist for at least 6 months after infection and express CD8, VLA-1, and CD103, which are important for epithelial localization. They are distinct from central memory T cells as they exhibit low expression of CD62L and CD122 but high expression of CD69. They also exhibit a steady state crawling behavior between KC. This migratory dendritic behavior allows detection of antigen expressing target cells in minutes to hours. Skin resident CD8 + T_{RM} cells are long-lived, non-circulating, and better than circulating T_{CM} cells at giving quick long-term protection against skin viral infection. They function to produce a "pathogen alert" for protection against further viral infection or proliferation. The TCR of T_{RM} cells functions almost like a toll-like receptor (TLR) on innate immune cells and T_{RM} cells may act as a bridge between adaptive and innate immune responses.

Recent studies examining the role of T_{RM} cells in fixed drug eruption (FDE) has revealed increased numbers of T_{RM} cells in lesional skin. Recent mouse studies suggest heterologous viral infection of mice leads to a narrow oligoclonal T cell repertoire specific to highly cross-reactive epitopes of different viruses. One current hypothesis suggests that drug antigens recognized by these broadly cross-reactive cells, originally evolved to protect the skin from herpes viruses, triggers their activation, leading to killing of surrounding KC and the formation of the typical FDE. FDE shows similar histologic features to more severe eruptions such as SJS/TEN, which leads to the question of why FDE is limited in scope relative to the more widespread eruptions. Recruitment of FoxP3+ regulatory T

(Treg) cells into FDE lesions, possibly facilitated by mast cell produced IL-16, appears critical for preventing CD8+ T_{RM} and T_{CM} from excessively activating at the inflammatory site. These Tregs may play critical role in limiting the spread of the drug reaction such that FDE stay localized. Dysfunction or impairment of Treg cells would then be hypothesized to contribute to the spread of the reaction, allowing progression to SJS/TEN.

Whether the associated viral reactivation is causal, a modifying or exacerbating factor, or a byproduct of the immune dysregulation of ADRs is not yet clear, but the arguments are compelling. There are some similarities in phenotype between viral reactivation of herpes virus family members after acute onset of immunosuppression and the clinical syndrome of DIHS. Actively replicating herpes viruses (HHV-6, HHV-7, EBV, and CMV) are noted in 30–80 % of DIHS cases. Clear examples (ampicillin rash in mononucleosis) of viral infection occurring before onset of drug allergy exist, and viral infection may be an additional event needed for drug sensitization to progress to allergy. Certain drugs may potentiate or trigger viral replication, and drugs known to cause DIHS often reactivate herpes viruses in vitro. For example, B cells with EBV exposed to causative drugs such as sulfamethoxazole, carbamazepine, or allopurinol began producing viral particles. Additionally, amoxicillin potentiates HHV-6 replication.

HHV-6 appears to be of central importance. Recent work suggests the skin is a primary and crucial point for HHV-6 transmission and reactivation in the setting of DIHS. Monomyeloid precursor cells harboring HHV-6 appear to facilitate HHV-6 transmission to skin CD4+ T cells, which is necessary for HHV-6 replication.

While HHV-6 reactivation is common in DIHS, other viruses such as EBV, HHV-7, and CMV are also commonly reactivated in sequence during DIHS in a progression similar to that seen in GVHD. Reactivation often begins with HHV-6 or EBV and then progresses to HHV-7 and eventually to CMV. The magnitude of HHV-6 reactivation seems to correlate with the severity of the inflammatory reaction in DIHS.

CD8+ T effector cells, also directed against herpes viruses, drives the clinical symptoms of DIHS. Similar to what has been seen in FDE, in the acute stage of DIHS there is rapid expansion of functional CD4+ FoxP3+ T reg cells, while in SJS/TEN these cells are impaired. This expansion of regulatory T cells (Treg) in DIHS, while appearing to play a protective role from progression to SJS/TEN, could also block antiviral T cell responses. Hypogammaglobulinemia is seen early in course of DIHS, which could also contribute to impaired antiviral responses. Flaring of DIHS after withdrawal of the offending drug has been hypothesized to have similarity with immune reconstitution syndrome (IRS) as seen in patients with HIV upon restoration of CD4+ T cells.

Conclusions

Many intersecting factors contribute to the development of ADRs and SCARs. While the causative drug itself or its metabolites are important, a complex web of factors contribute to the eventual phenotype. Inherited variations in immune system components, such as HLA types or T cell receptors, as well as enzymes involved in drug metabolism, whether systemic, or specifically localized to the skin, are critical and better understanding of them has enabled pharmacogenetic testing to identify at-risk patients before they are exposed to potentially causative drugs. Further research on skin-specific metabolic enzymes is an attractive target for future investigation. The role of viral reactivation in specific ADRs/SCARs is a subject of much investigation. Viral reactivation represents yet another attractive therapeutic target for these conditions. It is not hard to imagine a future where, prior to initiation of a drug, especially one known to cause ADRs/SCARs, testing for a variety of HLA types, alleles of metabolic enzymes, previous viral infection, and variations in other inherited immune molecules will be done with a single blood test to relatively accurately predict the risks associated with that drug for that specific patient, thus realizing the full promise of pharmacogenomics.

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Principles of Diagnosis of Cutaneous Drug Eruptions

2

John C. Hall

Abstract

Drug reactions are one of the most common cutaneous diseases in a generalist's or a dermatologist's office. The five drugs to be most considered are nonsteroidal anti-inflammatories, sulfa derivatives, antibiotics, anti-seizure medications, and allopurinol. Finding the culprit drug and stopping it can avoid risk of a more systemic reaction such as other organ system damage, anaphylaxis, vasculitis, more severe skin disease, and the known painful or pruritic, unsightly consequences of a milder reaction. This chapter will attempt to making finding the etiology of drug rash less confusing and hopefully more fruitful.

Keywords

Urticarial • Dose related • Allergic • Toxic • Generalized • Symmetric • Morbilliform • Life-threatening

Determining the Reaction: Allergic or Toxic?

The diagnosis of cutaneous drug eruptions can be made more easily if the determination is first made as to whether an allergic or a toxic reaction is occurring in the skin (Table 2.1). If the reaction is allergic, such as urticaria, then any drug can theoretically be the cause, but if it is toxic, such as in ecchymosis, then you are looking for a drug that causes bleeding.

Treatment

My treatment for urticarial drug reactions is a nonsedating antihistamine, adding histamines at several-day intervals, working up to sedating antihistamines and a 10-day course of oral Prednisone, or intarmuscular Celestone (6 mgms/cc) or 1 cc,

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_2

Table 2.1 Skin drug eruptions: immunologic vs. toxic

	Allergic	Toxic
Clinical	Urticaria, morbilliform, etc.	Mimics action of drug
Histopath	Nonspecific	Mimics action of drug
Dose of drug	Not dose-related, idiosyncratic	Less dose may cure; Universal at high enough dose
Complications	Can develop anaphylaxis	Excessive bleeding
Treatment	Antihistamines, corticosteroids	Stop the medication
Cross reaction with other meds	Common	Does not occur

Kenalog (40 mgm/cc.) The Celestone lasts 1–2 weeks. The Kenalog lasts 3–4 weeks. The Prednisone dose that I use is (10 mgm/tab) 5 tabs each am with food, and lower by 1 tab every 2 days for a total dose of 30 tabs over 10 days. I have this prescription pretyped since I use it so often. (For nonurticarial drug eruptions, I use the antihistamines only to treat symptoms and the steroid regiments above to treat the rash.)

If the urticarial eruption is associated with shortness of breath, wheezing, trouble swallowing, lightheadedness, and diaphoresis, I use subcutaneous epinephrine with a dose based on weight, and admission to the hospital with intravenous corticosteroids and antihistamines, and, most importantly, elimination of all drugs. Remember that mouthwash, breath fresheners, birth control pills, toothpaste, candies, inhalants, eyedrops, medication patches, and topicals (especially on mucous membranes) can all be culprits for minor or major drug reactions and need to be considered as the cause.

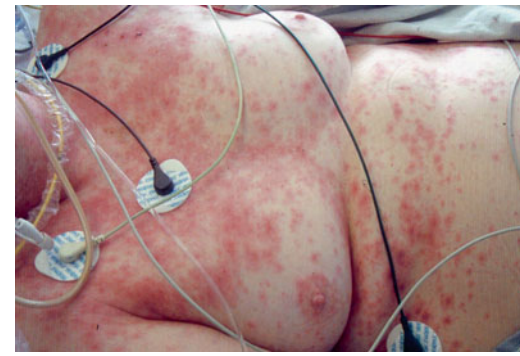

Fig. 2.1 A morbilliform drug eruption (which is the most common) over the anterior trunk due to Tegretol use. Notice the monotony of individual papules that maintain the same color and coalesce into a symmetrical distribution. Sparing in the intertriginous areas, as it does here, or at sites of pressure, is common

Making the Diagnosis

In general, a drug eruption should be suspected if the skin condition is symmetric, generalized, and sudden in onset (Fig. 2.1). Once suspected, there are three basic ways to discover the underlying cause in patients on multiple drugs:

1. Discontinue the suspected drug and see if the skin condition resolves. Remember that untreated drug eruptions can last 2–3 weeks. Rechallenge, if the reaction was not severe and if the drug is felt to be essential, it can be tried again.
2. A more scientific approach, but often not possible, is to discontinue all medications and add them back at 1-week intervals to see which medication causes the reaction.
3. Finally, all nonessential drugs can be stopped and, if the eruption resolves, then the offending medications can be discontinued permanently or added back at 1-week intervals.

The timing of drugs can be helpful. If a medication was started days before the skin became a target, then that medication is always to be suspected. Remember that a drug can be taken for weeks, months, or even years before an allergic skin reaction appears.

There is another approach to drug reactions in the skin if a drug is a common cause of such a reaction and the skin condition occurred days after the drug was started and, most importantly,

the drug is considered essential. If the skin condition is not severe, then the offending drug can be continued, with the skin treated symptomatically. This may not be an ideal solution, but it might be the only one that can be done safely (see Table 2.2).

Unfortunately, the laboratory test that will allow the diagnosis of a drug reaction with some sense of certainty and identify which drug is the culprit is not here or on the horizon of medial science.

The generalist may need consulting to find the most essential medications for a given patient. The dermatologist can help in deciding which medications are the most likely culprits. The rule of five has been helpful in my practice in eliminating the drug culprit. The five most common drugs or drug categories, which account for 95 % of all drug reactions, in the author's opinion, are: (1) antibiotics; (2) antisiezure medications; (3) non-antibiotic sulfa derivatives; (4) nonsteroidal anti-inflammatory drugs, or NSAIDS; and (5) allopurinol. This group of drugs need to be emphasized since uncommon manifestations of drug reactions in the skin to common drug offenders can be said to be more common than skin reactions to drugs that seem to leave the skin on its own.

Table 2.2 Algorithm for finding etiology of drug eruption

1. Recent (within 2 weeks of rash) drug most likely the cause.
2. Not recent, but single drug probably the cause, but consider toothpaste, breath fresheners, chewing gum, menthol cigarettes, mouthwash, candies, and foods.
3. Not recent, multiple drugs
A. Not life-threatening reaction – 2 options
Option 1.) Eliminate commonest drugs to cause a reaction:
(a) Antibiotics
(b) NSAIDS
(c) Anti Seizure drugs
(d) Sulfa derived drugs
(e) Allopurinol
Option 2.) Eliminate all non-essential drugs – can add back at 2-week intervals
B. Severe Reaction (TEN, SJS, Anaphylaxis, DRESS, exfoliative dermatitis)
Stop all medications and do not restart most common drugs or non-essential drugs. Add essential drugs cautiously at 2-week intervals if absolutely necessary

The skin pathologist is often left with drug reactions as a diagnosis of exclusion, with increased eosinophils as the debatable holy grail of the drug eruption. To exclude other, more ominous, skin diseases vis-à-vis cutaneous T-cell lymphoma is not a small contribution of the dermatopathologist.

A final note is the warning to not overdiagnose drug eruptions. Since we are depending on the inexact science of clinical observation, the tendency to incriminate a medication is probably overstated. The culprit diagnoses that can mimic a drug reaction include infections (viral exanthems, military tuberculosis, secondary syphilis, and rheumatic fever are examples); urticaria caused by something other that a drug (underlying diseases, food allergies, and stress are examples); contact dermatitis (due to chemicals on clothing or chemicals carried in the air); generalized id reactions from localized inflammatory tinea (kerion); stasis dermatitis and others; skin diseases (such as lichen planus, pityriasis rosea, diffuse granuloma annularae, sclermomyxedema, and generalized psoriasis); cutnaneous T-cell lymphoma and eczema, especially when presenting as a generalized exfoliative erythroderma. Maybe most important, underlying diseases that may present with a diffuse symmetrical clinical reaction pattern, such as collagen vascular diseases (lupus erythematosus, juvenile rheumatoid arthritis, dermatomysositis); paraneoplatic syndromes; systemic mastocytosis; vasculitides; and amyloidosis.

Conclusions

The most important point to be made about drug etiology in a patient in which a drug reaction is suspected is to stop all medication immediately in a life-threatening reaction such as TEN/SJS, urticaria with shortness of breath, trouble swallowing, wheezing, drop in blood pressure, or other signs of anaphylaxis, exfolitive dermatitis, and DRESS. In less severe reactions for medications felt necessary, rechallenge at 2-week intervals can be

done. If a drug is necessary, then tolerance can cautiously be tried. Dapsone for pneumocystis prophylaxis is an example of this. There is no reliable blood or skin tests that can prove the cause of a drug reaction. Cross-reaction between medications is always an important issue to be kept in mind.

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Histopathology of Drug Reactions

3

Brian J. Hall and Beth Ruben

Abstract

Cutaneous drug reactions can produce a variety of histopathologic inflammatory and even neoplastic patterns. Therefore, it is crucial to communicate to the dermatopathologist if a drug-related condition is suspected. When complicated histologic patterns are in view, the dermatopathologist should have a higher index of suspicion for a drug reaction as well. In this chapter, we will review common drug reactions patterns, and attempt to elucidate helpful histopathologic clues that point to the cutaneous condition being related to drug administration.

Keywords

Cutaneous drug reactions • Histology • Dermatopathology • Pathology • Eosinophils • Drug-induced pathology

Introduction

Cutaneous drug reactions can produce a variety of histopathologic inflammatory and even neoplastic patterns. Hence it is vitally important to know the clinical history and knowing if the clinician is suspecting a drug reaction. However, since the clinical morphologic appearance of many drug-induced diseases can so closely mimic the "true" non-drug-induced form, the pathologist should maintain a low threshold for suggesting the possibility of a drug-induced condition, as treatments may be significantly different. It is often stated that the skin may display only limited reaction patterns to different noxious stimuli, and with drug reactions this is also the case. However, certain clues can help point the observant pathologist or dermatopathologist to the correct diagnosis. We hope to summarize these most important clues in this chapter.

This chapter was also constructed with the idea that the reader has a basic understanding of the classic histologic findings of dermatologic conditions that can be mimicked when the skin reacts to a medication. If the reader desires a more detailed

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_3

summary of the histologic features of these entities, it is recommended that the reader peruse a more in-depth dermatopathologic tome.

Pathologic Characteristics of Common Drug Reactions

Morbilliform (Maculopapular) Drug Eruptions (Exanthems)

This is the most common type of drug reaction. Morbilliform drug reactions have been associated with a number of inflammatory patterns. In one large study, a superficial perivascular and interstitial infiltrate containing eosinophils and sometimes neutrophils was described as the most common pattern. Vacuolar interface changes and/or spongiosis can also be present with or without Civatte bodies (individually dead or dying keratinocytes). Sometimes a nondescript sparse lymphocytic infiltrate is evident. Therefore, a definitive diagnosis may be difficult, and hence the importance of clinical information. A descriptive diagnosis, consistent with or compatible with a morbilliform drug eruption may be the only diagnosis a pathologist can render, even with accurate clinical history.

The histologic differential diagnosis depends on the predominant histologic pattern at hand and may include erythema multiforme, viral exanthem, connective tissue disorders such as lupus erythematosus, and dermatomyositis, early graft vs. host disease, urticaria, and early leukocytoclastic vasculitis, among others.

Urticarial Drug Reactions

This is the second most common pattern of drug reaction. Urticarial drug reactions are histologically indistinguishable from other urticarial reactions, such as idiopathic urticaria, and an arthropod bite reaction displaying a perivascular to interstitial infiltrate of lymphocytes, eosinophils, and occasionally neutrophils and sometimes dilated lymphatics in later lesions.

As noted above, the differential diagnosis histologically includes idiopathic urticaria, arthropod bite reaction, urticarial vasculitis, and on occasion tinea (dermatophytosis).

Fixed Drug Eruptions

Initially, there is an acute vacuolar interface reaction, with necrotic keratinocyte along the junctional zone (i.e. the stratum corneum is still "basket-weave") and there is no evidence of an altered cornified layer. This can progress to subepidermal vesiculation, and necrotic keratinocytes can also be found throughout the epidermis. In addition, there is a variable superficial and deep perivascular infiltrate composed in addition to lymphocytes, often of granulocytes, including neutrophils and eosinophils. There may be papillary dermal edema. This pattern is in contrast to erythema multiforme (EM), which can appear very similar except that in lesions of EM, the dermal inflammatory infiltrate is typically composed predominantly of lymphocytes (Fig. 3.1).

Established lesions that recur show similar features as in acute cases, but melanophages are also present in the superficial dermis.

The histologic differential diagnosis includes mainly erythema multiforme, urticarial bullous pemphigoid, and on occasion erythema dyschromicum perstans and variants.

Photosensitive (Photoallergic and Phototoxic) Drug Reactions

The photoallergic pattern may be difficult to distinguish from a prototypical spongiotic eczematous dermatitis. The perivascular infiltrate may on occasion extend to involve the deep vascular plexus. In severe acute cases, spongiotic vesiculation may occur. Long-standing lesions may show signs of chronicity, including stellate or multinucleate mesenchymal cells, telangiectasia, and lichenification. The histologic differential diagnosis includes other spongiotic dermatitides such as allergic contact dermatitis. The phototoxic reaction can be likened to a sunburn reaction, and the hallmark is epidermal necrosis of varying degree. On occasion, erythema multiforme and TEN/SJS might be considered.

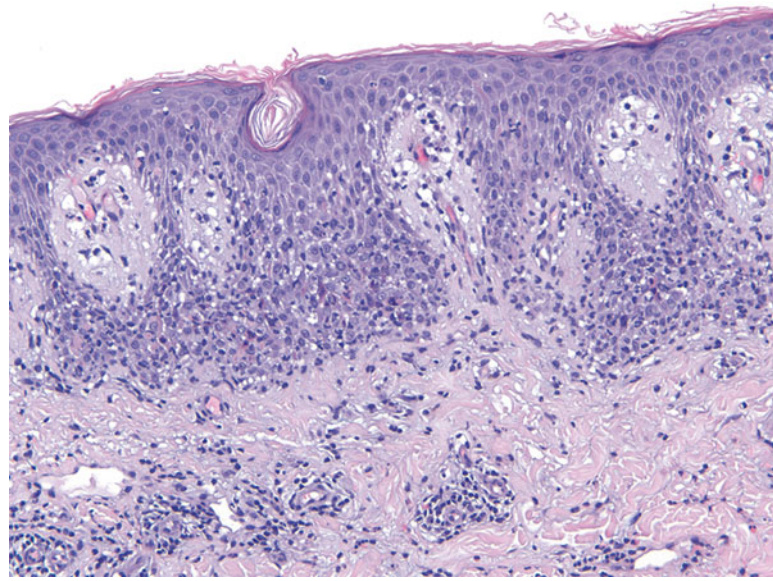


Fig. 3.1 Fixed drug eruption. There is an acute interface reaction, with an infiltrate containing granulocytes and melanophages (200×)

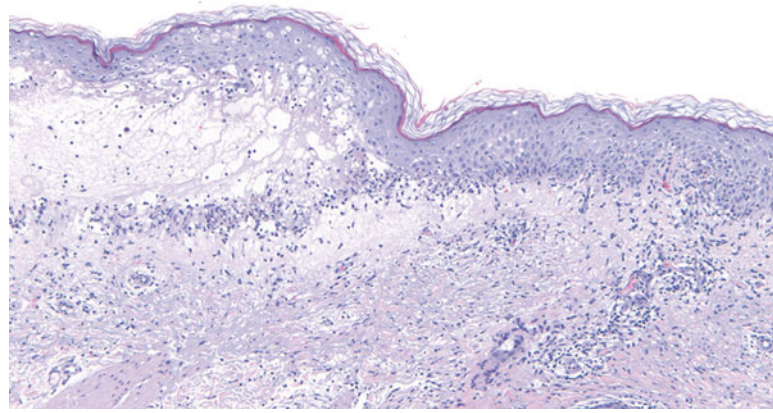


Fig. 3.2 Erythema multiforme. An acute interface reaction lies adjacent to a zone of subepidermal vesiculation (100×)

Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

EM, SJS, and TEN are clinically different diseases, and classification depends in part upon the total body surface area involved by the disease. Lesions range from targetoid to vesicular, and in the case of TEN, larger expanses of epidermal necrosis. Although EM can be caused by drugs, infections are much more common, whereas, in contrast, drugs such as sulfonamides, antibiotics, anticonvulsants, and some NSAIDs are the major causes of SJS and TEN.

Histologically, EM, SJS, and TEN may have significantly overlapping features, and on occasion can be indistinguishable. All demonstrate a vacuolar interface reaction of varying intensity, also depending on the age of the lesion. The infiltrate is largely lymphocytic, and usually superficial, and eosinophils may also be present. Necrotic keratinocytes are also present in varying degree. In all forms of the disease, the process is acute, and thus the stratum corneum will retain its normal basket-weave pattern. Minor patterns also occasionally present include spongiosis and ballooning of keratinocytes . As vacuolar alteration progresses, a subepidermal vesicle or bulla may form (Fig. 3.2). In TEN, there is often full-thickness epidermal necrosis early in the course, and a sparse infiltrate (Fig. 3.3)

The differential diagnosis includes fixed drug eruption, acute graft vs. host disease, pityriasis

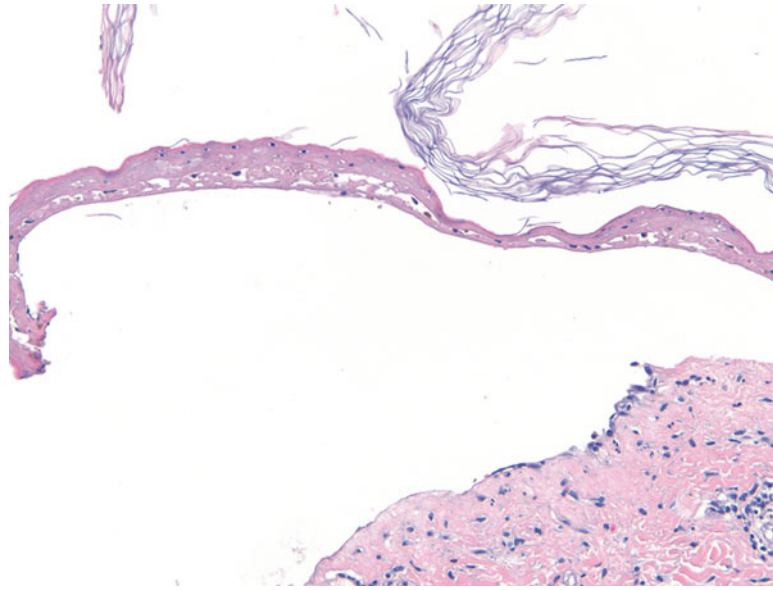


Fig. 3.3 Toxic epidermal necrolysis. There is full thickness epidermal necrosis, detachment of the epidermis, and a sparse dermal infiltrate (200×)

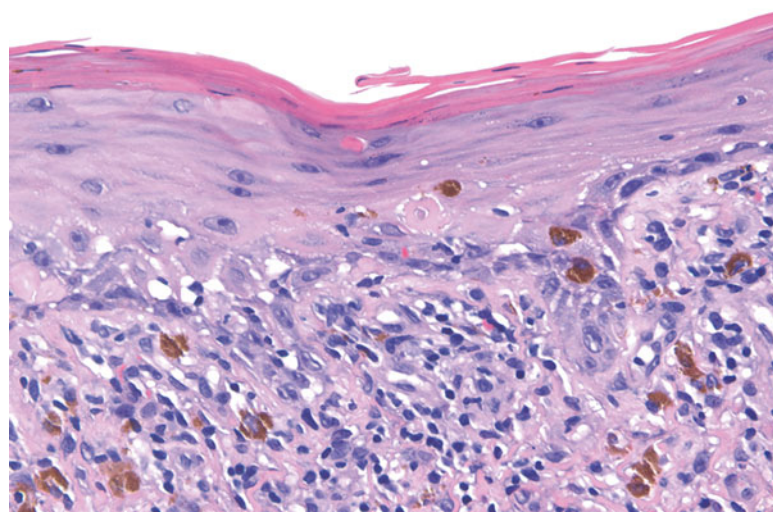


Fig. 3.4 Lichenoid drug eruption. In addition to a lichenoid infiltrate containing eosinophils, there are necrotic keratinocytes positioned superficially within the epidermis (400×)

lichenoides et varioliformis acuta (PLEVA), connective tissue disease and phototoxic dermatitis.

Lichenoid Drug Reactions

Histologically, the pattern can be indistinguishable from lichen planus, with irregular epidermal hyperplasia, hypergranulosis, and hyperkeratosis, and both may contain eosinophils. However, focal parakeratosis is more often observed in lichenoid drug eruption. Another clue is the presence of dyskeratotic keratinocytes (cytoid bodies) in the granular and cornified layer. The inflammatory infiltrate may be deeper and may also contain plasma cells (Fig. 3.4).

The differential diagnosis also includes lichen planus-like keratosis (benign lichenoid keratosis), lichenoid photodermatitis, and on occasion, lupus erythematosus.

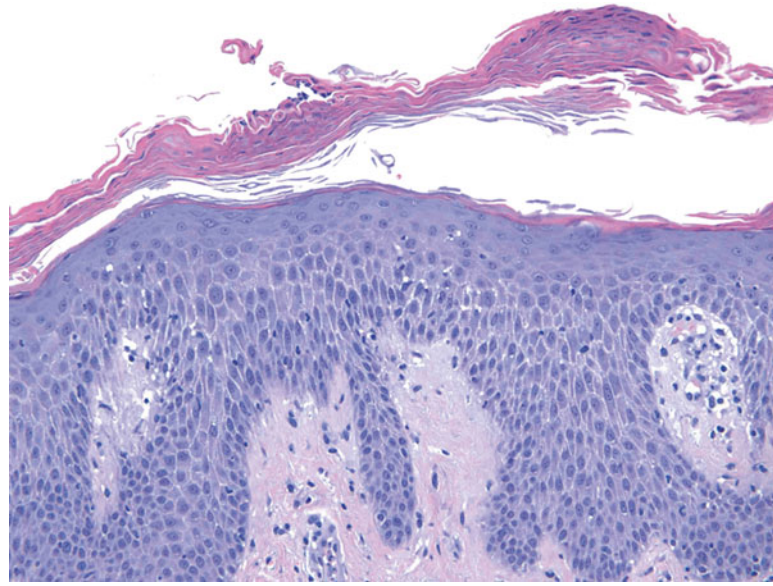


Fig. 3.5 Psoriasiform dermatitis due to TNF-alpha inhibitor. There is psoriasiform epidermal hyperplasia, parakeratosis, and occasional neutrophils as well as slight spongiosis, a pattern closely mimicking psoriasis, in a patient being treated for inflammatory bowel disease (200×)

Spongiotic Drug Reactions

Drug eruptions are usually included in the differential diagnosis of spongiotic (eczematous) dermatitis. There are no particularly distinguishing features, although eosinophils are usually present in drug eruptions. If other patterns are also present, forming a more complex pattern,—for example, cytotoxic/interface changes—this may point to a drug eruption.

The histologic differential diagnosis includes other spongiotic dermatoses such as atopic dermatitis, allergic contact dermatitis, id reaction, nummular dermatitis, seborrheic dermatitis, and dermatophytosis.

Pityriasis Rosea (PR)-Like Drug Eruptions

Often the histology is indistinguishable from typical PR reactions unrelated to drugs. Clinically, a herald patch is not evident. Histologic clues include eosinophils, subepidermal edema, and sometimes apoptotic keratinocytes, but clinical suspicion must be high.

The histologic differential diagnosis includes conventional pityriasis rosea, erythema annulare centrifugum, pigmented purpuric dermatosis, dermatophytosis, guttate psoriasis, and pityriasis lichenoides chronica.

Psoriasiform Drug Eruption

This, too, may appear similar histologically to classic psoriasis, but diagnostic features such as suprapapillary plate thinning and tortuous papillary dermal capillaries may be absent. Reactions to tumor necrosis factor (TNF) inhibitors, used in treatment of psoriasis and other autoimmune diseases, including inflammatory bowel disease, may present with a variety of reaction patterns, but most commonly a spongiotic to psoriasiform dermatitis. Separating this from psoriasis when used in treatment of that disorder can prove challenging (Fig. 3.5).

The histologic differential diagnosis includes conventional psoriasis, dermatophytosis, lichen simplex chronicus, pityriasis rubra pilaris, and chronic (eczematous) dermatitis, among others.

Drug-Induced Bullous Pemphigoid

This is also indistinguishable histologically from non-drug-induced bullous pemphigoid. Clinically it

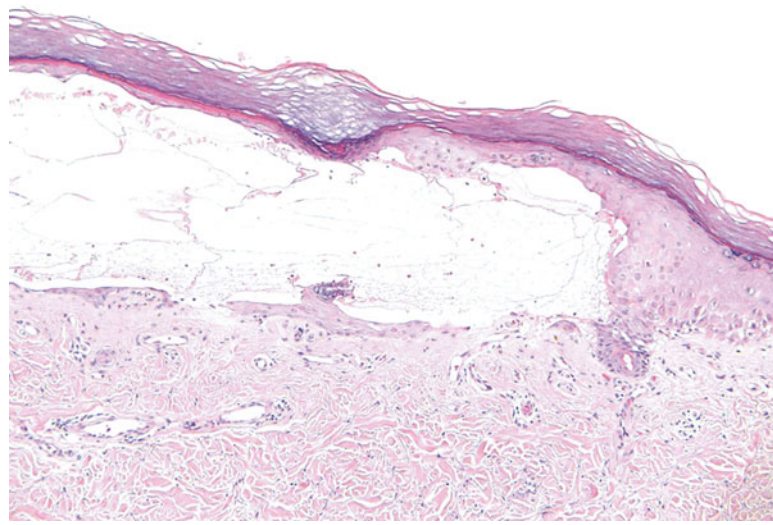


Fig. 3.6 Pseudoporphyria due to voriconazole. A pauci-inflammatory subepidermal bulla is evident, with some re-epithelialization (100×)

tends to occur in younger patients, and in salt-split skin immunoreactants may be found on the floor of the blister rather than the roof (as in idiopathic bullous pemphigoid). Direct immunofluorescence (DIF) findings are similar to non-drug-induced cases.

Differential diagnosis also includes epidermolysis bullosa acquisita (EBA), cicatricial pemphigoid, and, rarely, porphyria cutanea tarda and pseudoporphyria.

Drug-Induced Pseudoporphyria

NSAIDs are the most common culprit. Voriconazole toxicity has more recently been associated with this pattern. This is often indistinguishable from non-drug-induced cases, but papillary dermal eosinophils may be a clue. The absence of solar elastosis may be a clue to distinguish from PCT (Fig. 3.6).

The histologic differential diagnosis also includes pauci-inflammatory bullous pemphigoid, bullous amyloidosis, and EBA.

Acute Generalized Exanthematous Pustulosis (AGEP)

This subcorneal pustular dermatitis is a close mimic of pustular psoriasis. Clinical features, including the time course of the eruption and its resolution upon withdrawal of a putative drug culprit, may be essential. Histologically, subcorneal pustules are often present in a background of spongiosis. Scattered apoptotic keratinocytes, if present, can be a helpful clue. Papillary dermal edema is also more common than in pustular psoriasis. The dermis shows a mixed infiltrate, often with eosinophils and neutrophils, but a similar infiltrate can be present in pustular psoriasis. Eosinophils are less common in conventional plaque psoriasis. As with most skin specimens that contain neutrophilic pustules, a PAS-D stain could be considered to rule out a fungal infection (Fig. 3.7).

The histologic differential diagnosis (in addition to pustular psoriasis and bullous dermatophytosis) includes subcorneal pustular dermatosis (also known as Sneddon-Wilkinson disease), candidiasis, pemphigus foliaceus, IgA pemphigus, and bullous impetigo.

Interstitial Granulomatous Drug Reactions

These have been described for several drugs, including TNF inhibitors such as adalimumab (Humira), calcium channel blockers, ACE Inhibitors, beta-blockers, lipid-lowering agents, and others. There is often an interstitial infiltrate of histiocytes and lymphocytes, typically with

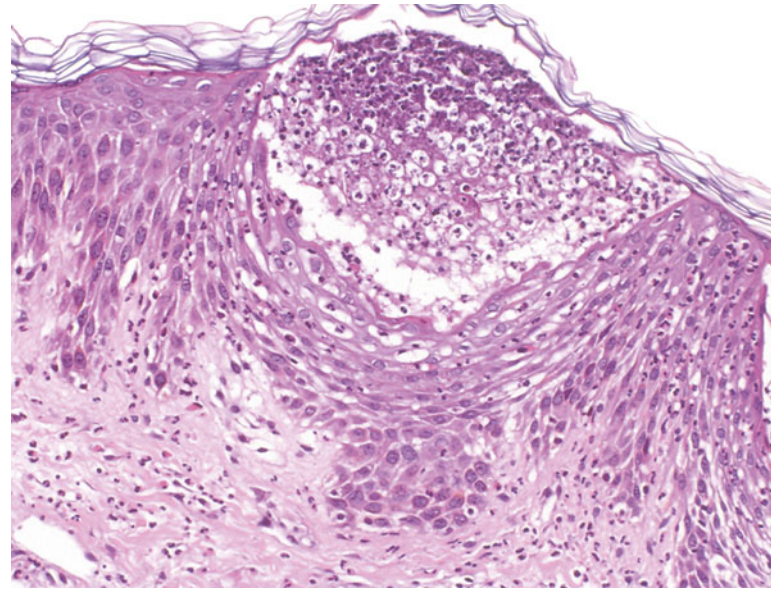


Fig. 3.7 Acute generalized exanthematous pustulosis. There is a subcorneal neutrophilic pustule with slight spongiosis, with a subjacent infiltrate containing eosinophils (200×)

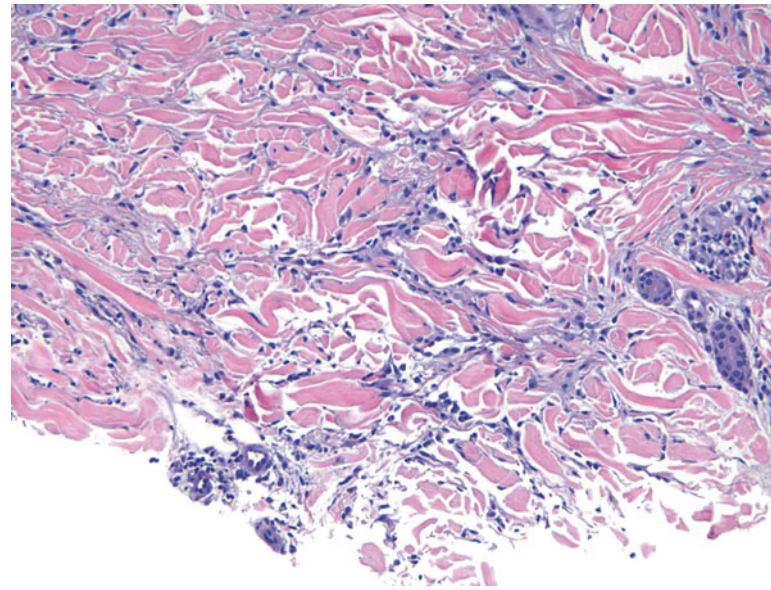


Fig. 3.8 Interstitial granulomatous dermatitis due to a TNF-alpha inhibitor. The interstitial and slightly palisaded infiltrate of histiocytes is a close mimic of granuloma annulare (200×)

variable alteration of collagen and elastic fibers, and occasionally interspersed neutrophils and eosinophils. A vacuolar interface reaction may be observed concurrently (Fig. 3.8).

The main histologic differential diagnosis is interstitial granuloma annulare, but interstitial granulomatous dermatitis with arthritis, interstitial mycosis fungoides, and early eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) can be considered as well.

Pseudolymphomatous Drug Reactions

These have historically been divided into two different categories of drug reactions that histologically mimic lymphoma. The first is a hypersensitivity syndrome with an acute onset, severe skin disease, hematologic abnormalities (including hyperpeosinophilia and atypical lymphocytes), other organ involvement, especially

hepatic, and lymphadenopathy (now known by the name of drug rash with eosinophilia and systemic symptoms or DRESS) . The pseudolymphomatous variant is but one of many patterns associated with DRESS, to be discussed in more detail below. A second type has a more insidious onset without other associated symptoms and can be difficult to distinguish from lymphoma. This section will discuss the latter type.

Pseudolymphomatous drug eruptions can mimic either B-cell or T-cell lymphoma and also lymphoid hyperplasia. The B-cell patterns are more common. There is typically a dense, nodular, top-heavy (meaning lymphocyte nodularity is most dense towards the superficial dermis or dense throughout) lymphocytic infiltrate. Much rarer are pseudolymphomatous drug reactions that mimic a T-cell lymphoma, often mycosis fungoides, with a band-like infiltrate containing occasional atypical lymphocytes. A mix of plasma cells, histiocytes, and eosinophils in addition to small lymphocytes can be a clue to the diagnosis of a pseudolymphoma. Epidermotropism and adnexotropism are rare and more common in lymphoma. Immunohistochemical stains and genotypic analysis may be necessary to exclude lymphoma, and a full discussion of such studies is beyond the scope of this chapter.

The differential diagnosis also includes a pseudolymphomatous reaction to an arthropod bite, as well as pseudolymphomatous folliculitis and pseudolymphomatous lupus erythematosus.

Erythroderma

On occasion, a drug eruption can be manifest as erythroderma. A biopsy in this setting can be disappointing with respect to elucidating the cause, as many conditions which can eventuate in erythroderma, including psoriasis, may have similar histologic features in this setting, and may include eosinophils within the infiltrate, unlike typical plaque-type psoriasis, for example. The Sézary variant of cutaneous T-cell lymphoma may also lack diagnostic features in this setting, but atypical lymphocytes can be helpful. The gold standard for this diagnosis rests on peripheral blood studies, however, including flow cytometry.

The histologic differential diagnosis also includes pityriasis rubra pilaris, subacute spongiotic (eczematous) dermatitis, scabetic dermatitis, and DRESS.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) or Drug-Induced Delayed Multiorgan Hypersensitivity (DIDMOHS)

DRESS may display a variety of histologic patterns from urticarial to interface, to spongiotic to psoriasiform, and pseudolymphomatous (Fig. 3.9). The clinical criteria, including evidence of organ damage, are essential to arriving at the diagnosis. This is a severe form of adverse drug reaction with a mortality rate of 10 %, and a prolonged resolution phase upon long-term treatment with corticosteroids. Despite the name, eosinophils may be present or absent histologically. Dyskeratotic keratinocytes can be a helpful clue, as in other drug eruptions, and some may be present high with the epidermis. The papillary dermis may be edematous, and vascular dilatation can also be seen. DRESS can sometimes mimic a cutaneous lymphoma histologically, with slightly atypical lymphocytes present, and sometimes a band-like infiltrate as in mycosis fungoides.

Linear IgA (LIGA) Bullous Dermatosis-Like Drug Eruption

This is indistinguishable from non-drug induced LIGA, except that there is loss of linear IgA along the dermal-epidermal junction on direct immunofluorescence (DIF) upon removal of the responsible drug. The typical histology of LIGA includes a subepidermal vesicle with numerous neutrophils, and often eosinophils, and a superficial perivascular lymphocytic infiltrate. Positive DIF with linear IgA along the dermal-epidermal junction is necessary for the diagnosis.

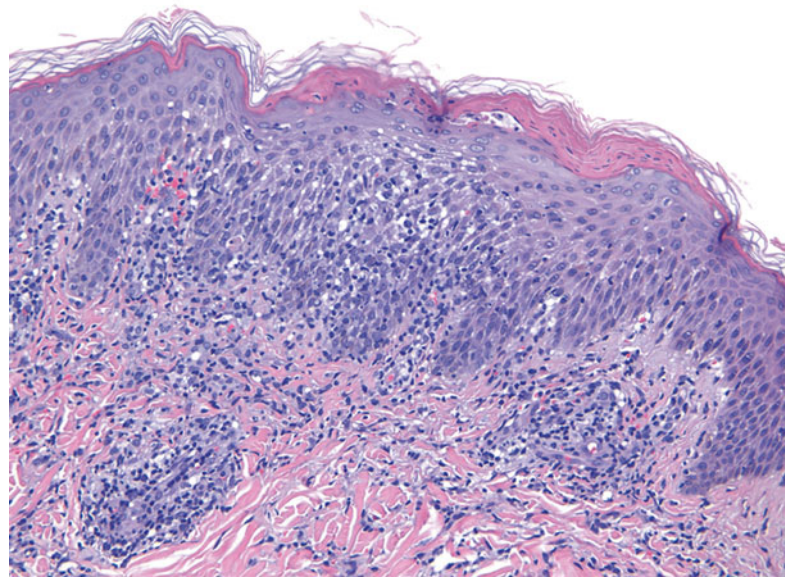


Fig. 3.9 Drug reaction with eosinophilia and systemic symptoms (DRESS). A psoriasiform spongiotic reaction with dyskeratosis is evident. The infiltrate also contained eosinophils (200×)

The differential diagnosis includes dermatitis herpetiformis, bullous pemphigoid and variants, and bullous lupus erythematosus.

Warfarin-Induced Skin Necrosis

Warfarin-induced skin necrosis is a very rare complication of warfarin (Coumadin) therapy (affecting approximately 1 in 10,000 patients on warfarin), and usually occurring early in the therapeutic period. Microscopically, the lesions appear as a thrombotic vasculopathy, with fibrin thrombi within small vessels throughout the dermis, without a significant surrounding inflammatory infiltrate. Extravasated red blood cells are common and, eventually, the thrombotic vessels lead to cutaneous necrosis of varying degree. The findings in heparin- and enoxaparin-induced coagulopathy are similar (Fig. 3.10).

The main differential diagnosis includes other thrombotic vasculopathies such as purpura fulminans, antiphospholipid antibody syndrome, cryoglobulinemia, clotting factor abnormalities, cryofibrinogenemia, cocaine-induced retiform purpura (recently described), homocystinemia, and thrombotic vasculopathies due to infection. Other ancillary laboratory studies may be needed such as culture, and hypercoagulability testing (inherited and acquired).

Chemotherapy-Related Drug Reactions

In a skin biopsy from a patient who is being treated with systemic chemotherapy and/or radiation, with radiation recall, striking keratinocyte atypia, including mitotic figures in some cases, and dysmaturation can often be seen, and should not be mistaken for malignant or premalignant change. This can be observed as part of an eruption, but also in normal-appearing skin. There may be a loss of normal polarity of kertatinocytes in the basilar and spinous layers, and scattered atypical keratinocytes with large nuclei but also abundant cytoplasm. Some specific agents such as etoposide, are associated with starburst mitotic figures (Fig. 3.11). As always, clinicopathologic correlation is also very important to make sure the patient has received a medication that could explain the keratinocyte atypia and point to a chemotherapeutic culprit and/or recent radiation therapy.

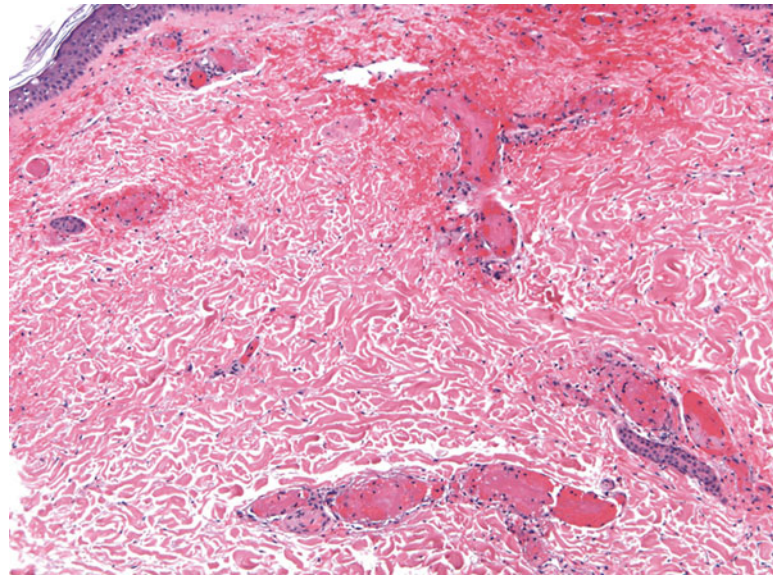


Fig. 3.10 Coumadin necrosis. Multiple fibrin thrombi are evident, without a significant associated inflammatory infiltrate (100×)

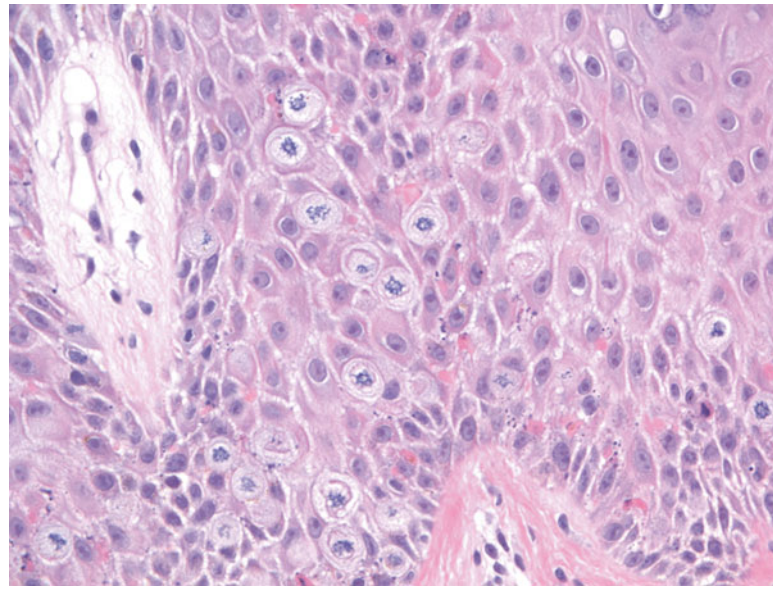


Fig. 3.11 Chemotherapy reaction due to etoposide. There is keratinocyte dysmaturation, consisting of enlarged keratinocytes within the lower epidermis (loss of normal polarity), and many mitotic figures with a starburst pattern of chromatin are evident (200×)

There are also a few specific diseases related to chemotherapy that need to be mentioned, and are discussed below.

Hand–Foot Skin Reaction (a.k.a Palmar-Plantar Eerythrodysesthesia)

The multi-targeted tyrosine kinase inhibitors sorafenib and sunitinib are the two most common culprits, but other chemotherapeutic agents have been implicated, especially cytosine and arabinoside. Histologically, it presents with intraepidermal, subcorneal, or even subepidermal vesicle formation with extensive and linear keratinocyte necrosis with intracytoplasmic eosinophilic bodies. This is followed by acanthosis and hyperkeratosis/parakeratosis. Dermal telangiectasias and a sparse lymphocytic infiltrate without eosinophils may be noted. The diagnosis is usually made clinically, and thus histologic descriptions are scant.

Bleomycin, Cisplatin, Busulfan and Other Chemotherapeutic Agents

These agents can cause skin hyperpigmentation following prolonged use (see also section below on other drugs that can cause hyperpigmentation). Bleomycin classically causes "flagellate streaks" or reticulate pigmentation that histologically shows a marked increase of melanin pigment within basal keratinocytes and melanophages in the papillary dermis, with a normal number of melanocytes. A lymphocytic vasculitis has been described in one case.

The histologic differential diagnosis includes postinflammatory hyperpigmentation, erythema dyschromica perstans, and resolving lichen planus.

Neutrophilic Eccrine Hidradenitis

This classically shows a dense neutrophilic infiltrate surrounding and typically localized to eccrine glands. This progresses to prominent vacuolar change of the basement membrane and finally to necrosis of the eccrine glands. Numerous chemotherapeutic agents have been implicated, but infectious etiologies and malignancies unrelated to chemotherapy have also been associated with this pattern.

The histologic differential diagnosis includes Sweet syndrome, cryopyrin-associated periodic syndrome (CAPS), cellulitis, and palmoplantar eccrine hidradenitis.

Drugs that Can Cause Hyperpigmentation

Minocycline-Induced Hyperpigmentation

This is characterized by brown/black pigmented granules freely within the dermis and often deposited along elastic fibers, within macrophages, along vessels, and surrounding eccrine units within myoepithelial cells. Hemosiderin and/or melanin can be detected. Three distinct types of pigmentation occur and stain differently histologically depending on the type. Type I (Fig. 3.12a) minocycline typically affects the face and is Perls' stain positive. Type II (Fig. 3.12b) typically occurs on normal skin of pretibial areas and forearms and is Perls' and Fontana Masson stain positive. Type III (Fig. 3.12c) gives a muddy-brown pigmentation to all sun exposed skin and is only positive for Fontana Masson stain. Type III minocycline is slightly different histologically in that it shows increased melanin staining in the basal layer of keratinocytes and dermal melanophages. The pigment deposition is not as widespread as in types I and II.

The main histologic differential diagnosis is with other drug deposition such as argyria, ochronosis, and amiodarone, and sometimes blue nevus/dermal melanocytosis variants.

Amiodarone

In rare patients being treated with amiodarone for cardiac dysrythmias, blue-gray skin pigmentation can occur on sun-exposed areas in patients on long-term high-dose therapy. Histologically it shows yellow-brown granules that are deposited within macrophages that are often found around blood vessels and along the junction of the papillary and reticular dermis. The granules stain positively with Fontana-Masson, PAS, Ziehl-Nielson, and Sudan black. Although the pigment was originally thought to be due to lipofuscin deposition, more recent research suggests that amiodarone skin hyperpigmentation appears to be due to direct drug deposition.

The histologic differential diagnosis includes argyria, minocycline hyperpigmentation, melasma, and post inflammatory hyperpigmentation.

Argyria (Silver Deposition)

At one point, argyria was much more common due to use of medications containing silver salts. Currently, occupational exposure, and especially colloidal silver preparations used in the alternative health industry and available on the Internet, have resulted in a resurgence. The histology consists of numerous small brown-black granules that are typically deposited around sweat glands, pilosebaceous units, and within elastic fibers in the superficial dermis (Fig. 3.13).

Chrysiasis (Gold Deposition)

In some patients receiving gold injections for rheumatoid arthritis and pemphigus treatment, blue-gray pigmentation can occur. Histologically round to oval black granules deposited within macrophages that often surround blood vessels are seen. The deposition is typically found in the papillary and mid dermis.

Hydroquinone

Hydroquinone is typically used to lighten the skin, but it can at times cause hyperpigmentation if formulations are used for too long. It is also used in some antimalarial drug formulations. These cases are typically seen in patients in malaria-endemic areas. Prolonged use has also been associated with exogenous ochronosis.

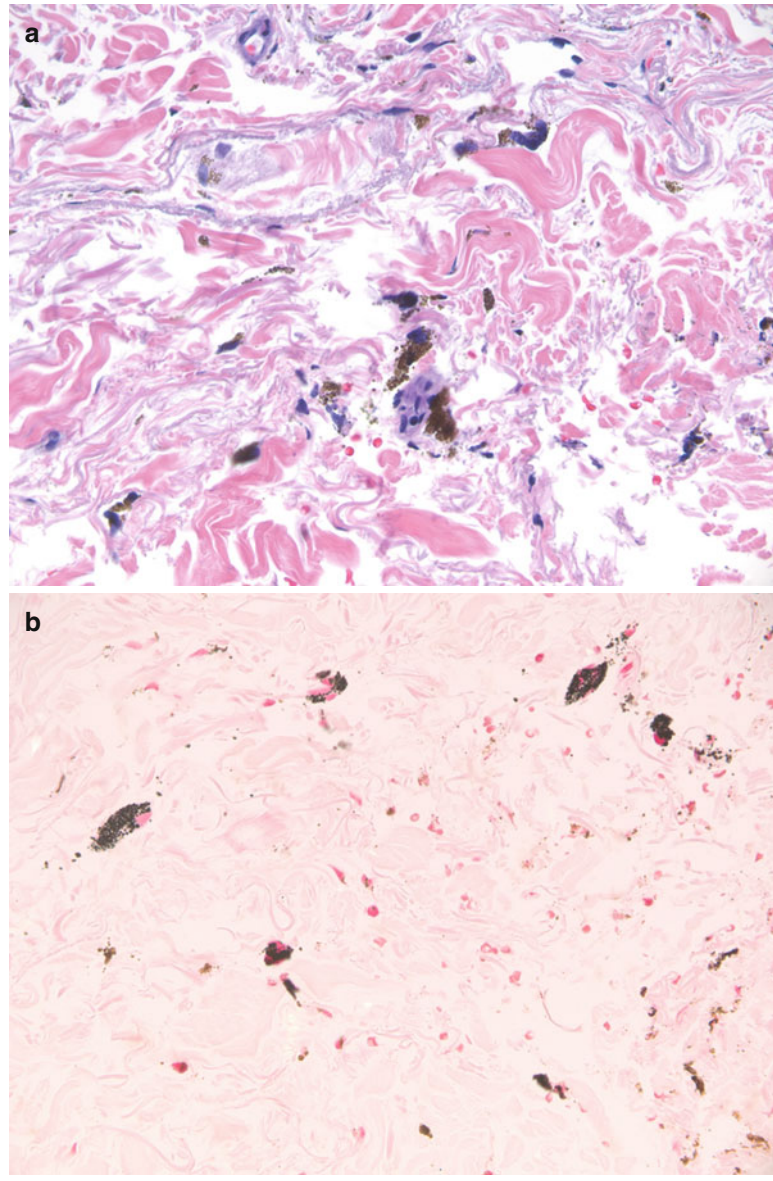


Fig. 3.12 (**a**) Minocycline pigmentation type II. Pigmented macrophages are present within the reticular dermis. They stain with both (**b**) Fontana-Masson and (**c**) Perls' stains (400×)

Fig. 3.12 (continued)

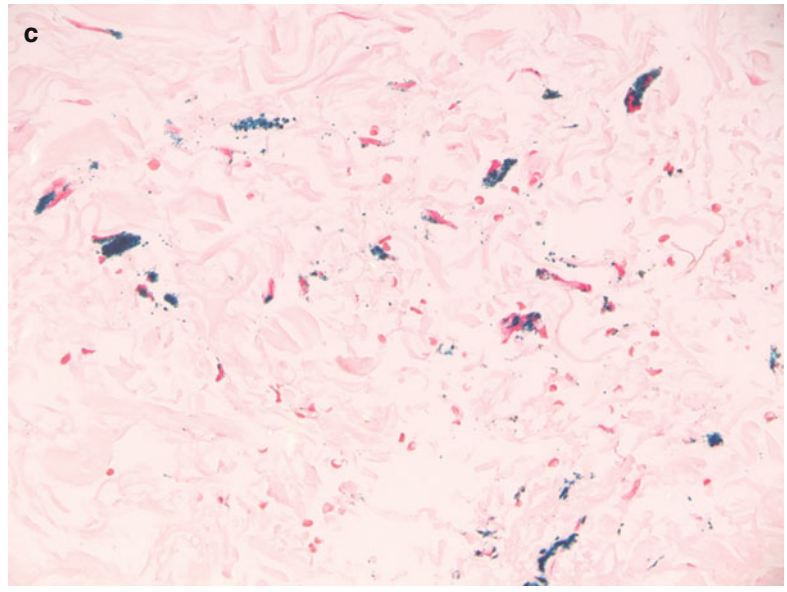
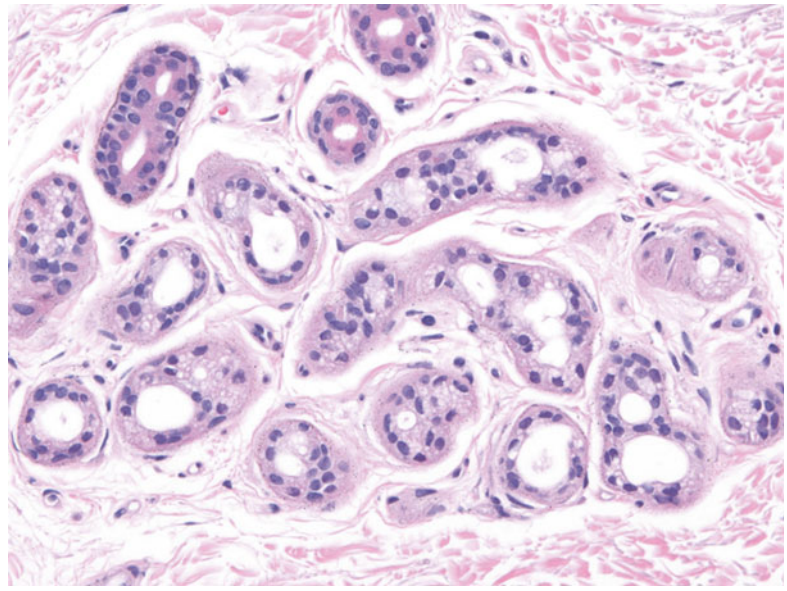


Fig. 3.13 Arygyria. Fine silver granules are evident in the basement membrane surrounding eccrine coils (400×)



Skin biopsy is typically not needed for diagnosis (because detailed clinical history is usually sufficient) but will typically show features of ochronosis, which is indistinguishable from alkaptonuric ochronosis. Banana-shaped brown to yellow ("ochre") pigmented fibers are evident within the superficial dermis (Fig. 3.14). These pigment deposits can displace the collagen and elastic fibers. At times histiocytes will also take up pigment, and pigment may also be found as extracellular granular deposits.

There are also a variety of other conditions that are beyond the scope of this chapter, and can also be extremely difficult to distinguish from non-drug-induced forms without proper clinical history or clinical suspicion. They are listed here:

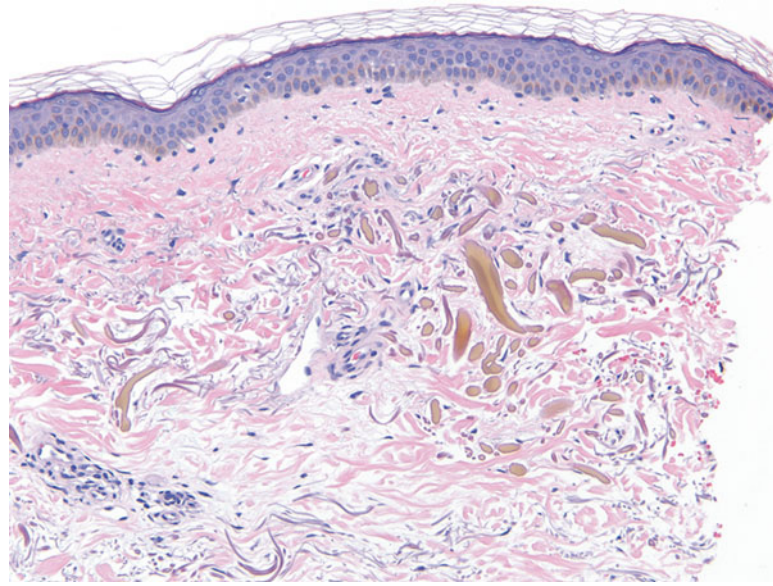


Fig. 3.14 Ochronosis. Golden banana-shaped fibers are evident in the superficial dermis (200×)

- Lupus-like drug reactions
- Leukocytoclastic vasculitis
- Drug-induced Sweet syndrome
- Sclerodermoid drug reactions
- Acneiform drug reactions
- Drug-induced eosinophilic pustular folliculitis
- Drug-induced pemphigus
- Pigmented purpuric dermatoses
- Exogenous ochronosis

For histologic features of these conditions, as well as histologic differential diagnoses, a general dermatopathology textbook is recommended.

Conclusions

As the number and class of medications increases, and the longer these are used in clinical practice, it should be expected that these iatrogenic dermatologic reactions are also observed in higher frequency. It will be important for both the dermatologist and pathologist to keep up with the literature of newly reported reactions to help decipher if a certain drug can be implicated in the histopathologic findings. However, as such reactions share or may duplicate features seen in other inflammatory and even neoplastic conditions, this can be a difficult undertaking. Communication between clinician and pathologist regarding the onset of the cutaneous eruption in relation to any possible new drugs will remain paramount. It is also important to keep in mind the possibility of a drug reaction whenever the histopathologic picture is complex and/or does not seem to fit a known entity.

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Principles of Treatment of Cutaneous Drug Eruptions

4

Cindy E. Owen and Jeffrey P. Callen

Abstract

Cutaneous drug eruptions are a major health concern and may affect up to 1 % of patients taking systemic medications, and are seen in 2–3 % of hospitalized patients. Most reactions are mild and self-limited upon discontinuation of the medication, but severe and life-threatening reactions are also possible. Appropriate management of patients requires a thorough knowledge of the spectrum of drug reactions, the culpability of suspected medications based on reaction type and timing, patient-specific risk factors for drug reactions, and treatment options to limit mortality and sequelae of drug reactions. Drug reactions can be either acute (e.g., urticaria, exanthematous eruptions, and Stevens Johnson syndrome) or chronic (e.g., acneiform, pigmentary, and psoriasiform eruptions). This chapter will focus on the treatment principles of the acute cutaneous drug eruptions.

Keywords

Systemic medications • Acute drug reactions • Urticaria • Exanthematous eruptions • Stevens Johnson syndrome

Introduction

The cornerstone of management of cutaneous drug reactions is the identification and prompt withdrawal of the offending medication. The possibility that the reaction is a severe cutaneous adverse reaction (SCAR) should be considered in all patients presenting with a suspected drug rash. If the patient is suspected of having a SCAR, then inpatient management may be required and would include appropriate workup for systemic complications. After removing the

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_4

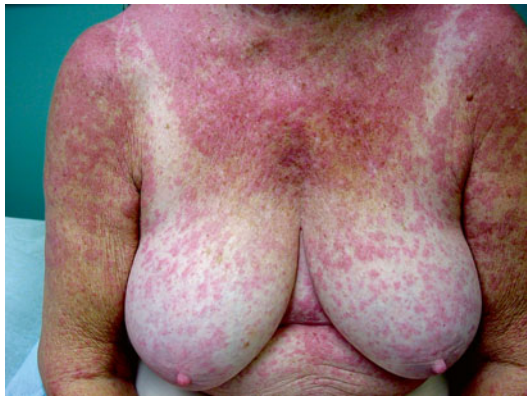

Fig. 4.1 Exanthematous (morbilliform) drug eruption. Erythematous macules and papules, some coalescing

suspected medication and assessing for possible SCAR, further treatment will depend on the nature and extent of the reaction. This chapter will address treatment approaches based on the reaction type, with a focus on acute drug eruptions.

Exanthematous Drug Eruptions

Also referred to as morbilliform or maculopapular drug reactions, exanthematous eruptions are the most common type of cutaneous drug reaction. The rash presents 1–2 weeks after the onset of medication exposure as a symmetric eruption of macules and possibly papules that become confluent (Fig. 4.1). The eruption may appear shortly after cessation of medications used for short courses (e.g. antibiotic therapy). The rash begins on the trunk and upper extremities typically, but may become widespread. Exanthematous drug eruptions are typically pruritic but patients are otherwise well. Clinicians should assess the patient for the presence of facial edema, fever, lymphadenopathy, eosinophilia, dusky or painful skin lesions, and/or mucous membrane involvement, as these are clues to possible SCARs. The main differential diagnosis to consider is a viral exanthem, especially in children.

After withdrawal of the offending medication, the rash resolves in 1–2 weeks without sequelae. Treatment is not required, but can provide relief from pruritus. Topical steroids and sedating antihistamines are often used to this end. Systemic corticosteroids are not required in most cases. When the inciting medication is a short-term but essential treatment for the patient (e.g., an antibiotic indicated for a life-threatening infection), it is reasonable to continue the medication while treating the symptoms of the exanthematous eruption. Monitoring for development of systemic symptoms and/or severe adverse reaction while treating through the eruption is advisable, but it does not appear that this type of reaction can progress to a SCAR.

Urticaria and Angioedema

Lesions of urticaria consist of transient, erythetmatous or pale, edematous plaques, sometimes with an annular appearance (Fig. 4.2a). Angioedema may accompany urticarial drug eruptions and represents rapidly progressive edema of the dermis and subcutaneous tissues (Fig. 4.2b). Treatment of drug-induced acute urticaria without angioedema may only require the application of cooling and antipruritic lotions (menthol- or phenol-containing) after removing the suspected medication. For patients requiring systemic medications, it is reasonable to start with a non-sedating antihistamine given daily until the rash clears. If this is not sufficient, then a classic (sedating) antihistamine can be added or substituted. Corticosteroids are generally not indicated.

Angioedema accompanies urticarial in 50 % of cases and may be associated with anaphylaxis. In the setting of anaphylaxis or angioedema that compromises the airway, subcutaneous epinephrine is indicated in addition to antihistamines. Systemic corticosteroids may also be administered. Strict avoidance of the offending medication in the future is essential, making patient education a major goal in the management of angioedema with or without anaphylaxis.

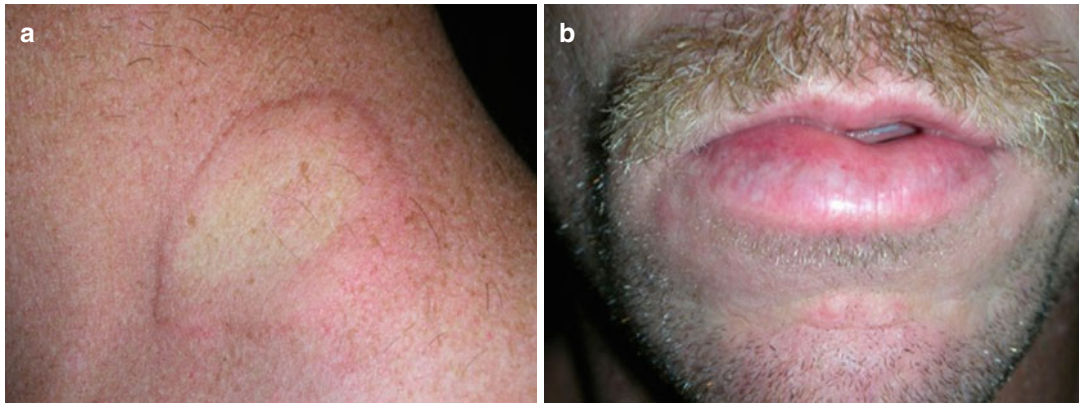

Fig. 4.2 (**a**) Wheal of acute urticarial. Erythematous, edematous, annular appearing plaque. (**b**) Angioedema of the lower lip

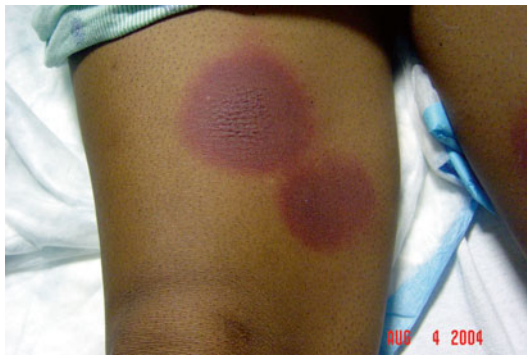

Fig. 4.3 Fixed drug eruption. Round, well-demarcated, erythematous plaques, one with a dusky center

Fixed Drug Eruption

Fixed drug eruptions appear as round to oval sharply demarcated erythematous and edematous plaques, sometimes with a dusky center that may become bullous (Fig. 4.3). The lesions appear 1–2 weeks after an initial exposure and within 24 h upon re-exposure. Lesions typically recur at the same sites with subsequent eruptions, but new sites may appear with recurrences. Generalized fixed drug eruptions can occur rarely and may mimic Stevens Johnson Syndrome. Lesions favor the lips, hands, feet and genitalia, but may occur anywhere. Treatment is not required, but if lesions are symptomatic, then antihistamines and topical corticosteroids can be used. For patients with generalized bullous FDE, a short course of systemic steroids can be used.

Phototosensitive Drug Eruptions

There are two types of photosensitive drug eruptions: phototoxic and photoallergic. Both are initiated by the combination of the causative medication and ultraviolet A light (UVA) exposure. Phototoxic eruptions present as an exaggerated sunburn, possibly with blisters. Prevention is the best treatment since these reactions are often predictable based on the medication prescribed. Photosensitive eruptions should be treated like sunburns, with cool compresses, emollients, and analgesics. If blisters are present, then wound care to prevent infection should be emphasized.

Photoallergic drug reactions are eczematous, pruritic eruptions in sun-exposed areas. This reaction can be treated with topical corticosteroids. For severe cases, a tapering 2- to 3- week course of prednisone may be required. For both types of reactions, discontinuation of the medication should be considered during the eruption. If the medication must be restarted or continued,

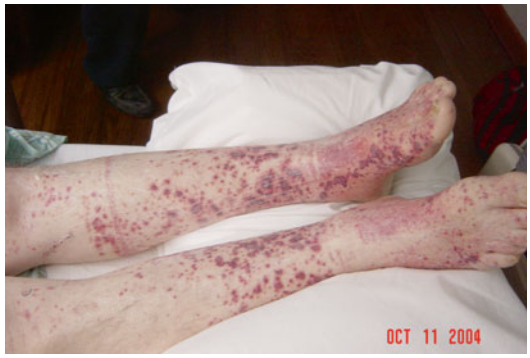

Fig. 4.4 Leukocytoclastic vasculitis. Petechiae and palpable purpura

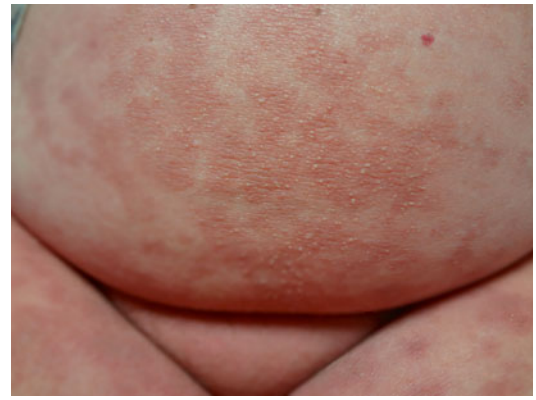

Fig. 4.5 Acute generalized exanthematous pustulosis (AGEP). Non-follicular-based minute pustules on an erythematous base

then the patient should be educated on photoprotection, including the use of broad-spectrum sunscreens.

Drug-Induced Hypersensitivity Vasculitis

Drug-induced hypersensitivity vasculitis presents with palpable purpura and possibly a maculopapular rash with a temporal relationship to an offending drug (Fig. 4.4). Noncutaneous organ involvement is possible and should be assessed for in the examination and workup. Other findings may include urticaria, arthralgia, fever, lymphadenopathy, low serum complement levels, and elevated erythrocyte sedimentation rate or C-reactive protein. Biopsy of the skin reveals leukocytoclastic vasculitis. Immunofluorescence microscopy can reveal IgM, IgG, or IgA in cases that are induced by a drug, and therefore we do not routinely recommend performance of such testing when there is an obvious drug that was a presumed cause. Infections can cause a similar clinical scenario and should be excluded as a cause where possible. If the leukocytoclastic vasculitis is due to a medication, then discontinuation of the suspect medication should lead to resolution of signs and symptoms within a few weeks. If the vasculitis is severe or does not improve after stopping the inciting medication, the patient may be treated with non-steroidal anti-inflammatory drugs, colchicine, dapsone, or systemic steroids. For cases with progressive or severe systemic disease, immunosuppressive, steroid-sparing agents can be considered.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is caused by drugs in the majority of cases, and occurs hours to days after the offending medication is started. It presents as tiny, numerous, non-follicular-based pustules occurring on a background of erythema (Fig. 4.5). The reaction typically begins in the flexural areas but can become diffuse. Fever may accompany an AGEP reaction, along with leukocytosis and neutrophilia. Prognosis is excellent and the course is typically self-limiting, resolving within 1–2 weeks after stopping the medication. Management beyond withdrawal of the causative medication is supportive care. Pustules typically resolve with superficial desquamation forming a collarette of scale. Coalescence of pustules, however, can result in a clinical picture similar to toxic epidermal necrolysis. In cases with extensive desquamation, wound care should be emphasized to avoid infection, and patients should be monitored for electrolyte imbalances. This may include non-adhesive and/or antiseptic dressings. In mild cases, symptoms and pruritus can be controlled

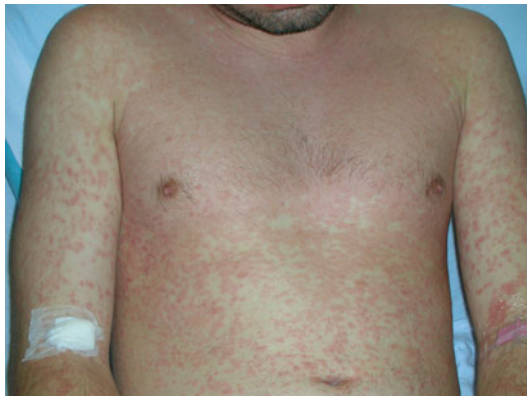

Fig. 4.6 Morbilliform eruption in a patient with DRESS syndrome. Erythematous macules and papules coalescing into plaques

with topical steroids, followed by emollients during the post-pustular phase. Drugs that induce AGEP can produce a positive patch test result with pustules at the site of application. A positive patch test can be confirmatory, but a negative patch test does not rule out a medication as a potential cause.

Drug Reaction with Eosinophilia and Systemic Symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening eruption with a long (2- to 8-week) latency following drug exposure. Skin findings begin with a morbilliform eruption that progresses to involve over 50 % body surface area with confluent, infiltrative plaques (Fig. 4.6). Exfoliative dermatitis, scale, purpura, bullae secondary to edema, and pustules may also be present. Additional signs and symptoms may include facial edema, fever, lymphadenopathy, and malaise. After excluding other causes of the clinical presentation (infection, lymphoma, autoimmune disease), workup for internal organ involvement should include a complete blood count, comprehensive metabolic panel (including liver function tests), urinalysis, pulse oximetry, creatine kinase, troponins, and electrocardiogram. Further testing may be warranted based on signs, symptoms, and results of these screening tests, as shown in Table 4.1.

Table 4.1 Recommended investigations for patients suspected of having DRESS

Recommended tests for suspected DRESS	Tests to exclude alternative diagnoses	Further investigations (based on patient presentation)
CBC	Blood cultures	CT scan
CMP (esp creatinine)	Hepatitis profile	Abdominal ultrasound
Liver function tests	Antinuclear antibodies	Endoscopy
Urinalysis	Lymph node biopsy if concern for malignancy	Biopsy of affected organs/ sites
Creatine kinase, troponin	–	PT/INR
Pulse oximetry	–	–
EKG	–	–
Inflammation markers (CRP, ESR)	–	–
PCR for HHV 6, HHV 7, CMV, EBV	–	–

After identifying and discontinuing the suspect medication, the treatment for DRESS depends on the severity and organ systems involved. For patients with skin disease and minor liver transaminase elevations, treatment can be supportive and aimed at alleviation of symptoms. Topical steroids and emollients with or without wet wraps can be used for skin discomfort and pruritus. If the patient has extensive exfoliative dermatitis, fluid and electrolyte monitoring and correction may be needed. Systemic corticosteroids should be reserved for patients with pulmonary or kidney involvement (liver disease has not been shown to respond to systemic steroids). Doses of 0.5–2 mg/kg/day of prednisone (or equivalent dose of another systemic glucocorticoid) are recommended until disease stabilizes or improves. Systemic steroids should be tapered slowly over an 8- to 12-week period to avoid relapse. Monitoring for resolution of systemic involvement should be performed at regular intervals during the taper, and shortly afterwards, since relapse is possible. Treatment with steroid-sparing immunosuppressive agents

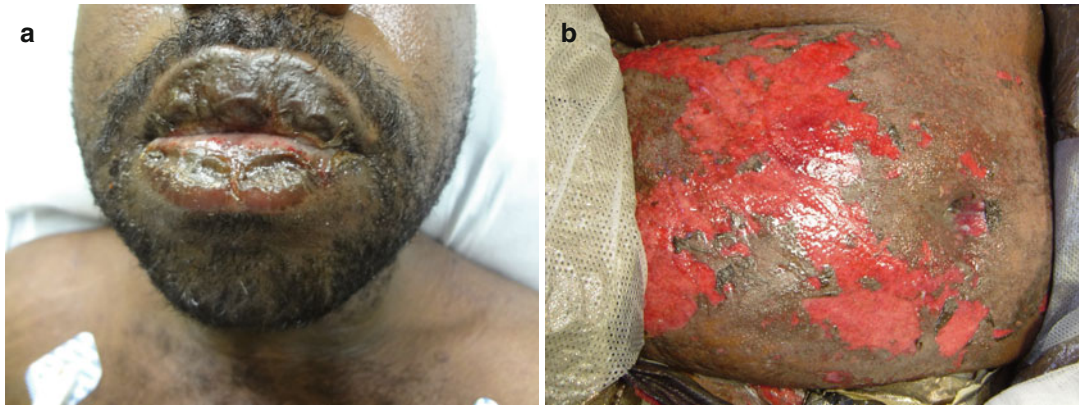

Fig. 4.7 (**a**) Hemorrhagic crust of the lips in a patient with Stevens-Johnson Syndrome. (**b**) Full thickness necrosis and sloughing of the epidermis in a patient with TEN

and intravenous immunoglobulin (IVIG) has been reported, however, their use is not routinely recommended. Patients with progressive, severe liver involvement may require transplantation.

Autoimmune sequelae can follow DRESS syndrome by months or years. The most common are autoimmune thyroid disease that can result in hypothyroidism and the development of insulin-dependent diabetes mellitus. Patients should be monitored for development of these and other autoimmune sequelae at regular intervals after recovery from DRESS syndrome.

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous eruptions characterized by epidermal detachment and mucosal involvement at two or more sites (Fig. 4.7a, b). The distinction between SJS and TEN depends on severity, with SJS defined as <10 % detachment and TEN as >30 % detachment. SJS/TEN overlap is diagnosed when epidermal detachment is between 10 and 30 %. As with all drug eruptions, identification and withdrawal of the offending drug is imperative upon diagnosis. Because SJS/TEN carry a risk for death, the physician should quickly determine the value of a prognostic indicator, the SCORTEN. The SCORTEN uses clinical and laboratory parameters to predict the mortality for patients with SJS/TEN (see Table 4.2). The SCORTEN should be determined on the first and third days of hospitalization, with the highest value giving the best prognostic indication. Any patient with a SCORTEN of 2 or higher, or with extensive epidermal detachment, should be managed in a specialized unit, preferably a burn unit.

Supportive care for SJS/TEN includes fluid and electrolyte management, temperature and pain control, nutritional support, and intensive

Table 4.2 SCORTEN prognostic scoring system for SJS/TEN

SCORTEN[a]	
Prognostic factors (one point each)	
Age >40 years	
Malignancy	
Body surface area detached >10 %	
Heart rate >120 beats per minute	
Serum urea >10 mmol/l	
Serum glucose >40 mmol/l	
Serum bicarbonate <20 mmol/l	
SCORTEN score	Predicted mortality (%)
0–1	3.2
2	12.1
3	35.3
4	58.3
5 or more	>90

[a]The SCORTEN score should be evaluated on Days 1 and 3 of hospitalization, using the higher of the two scores to predict mortality

wound care. Sepsis is the leading cause of death in SJS/TEN, so sterile handling and aggressive wound care is essential. Prophylactic antibiotics are not recommended, but frequent wound cultures, blood cultures, and cultures of indwelling lines and catheters should be obtained, with initiation of antibiotics as indicated by culture findings and signs of infection. Choice of dressing varies, but many centers now use nanocrystalline gauze materials for wrapping as these are nonadherent and can be left in place for up to 7 days (depending on the product selected). Silver sulfadiazine is not recommended in SJS/TEN patients in whom sulfonamides allergy is a concern. Silver nitrate or silver-imbued nanocrystalline gauze can be used for disinfection. Leaving detachable skin in place ("anti-shear" wound care) is recommended by many experts, but some centers use debridement or whirlpool therapy to remove the detachable skin. Studies comparing the two methods are limited, but observational studies do not demonstrate a difference in re-epithelialization or survival rates.

Patients with SJS/TEN require fluid replacement due to increased water loss from detached skin, but not to the same degree as burn patients. Burn estimates for fluid replacement can be reduced by 1/3 for SJS/TEN based on body surface area. Nutritional support should begin immediately. Oral feeding via a nasogastric tube in patients unable to eat is favored over parenteral nutrition to reduce microbial translocation from the gut.

Ophthalmology should be consulted upon admission. Daily lubrication and cleaning may be sufficient, but for severe ocular involvement, topical corticosteroids, amniotic membrane placement (to cover conjunctival surfaces), and scleral spacers may be indicated to prevent long-term sequelae.

Females with SJS/TEN should be evaluated by gynecology to assess for vulvovaginal involvement. Long-term complications of vulvovaginal involvement include adhesions and vaginal adenosis. These can be prevented with use of topical (or intravaginal) corticosteroids, soft vaginal molds, and suppression of menstruation during the acute phase of SJS/TEN.

No adjunctive therapies for SJS/TEN have been proven effective. Systemic corticosteroids, intravenous immunoglobulins (IVIG), cyclosporine, and TNF-alpha inhibitors are the most common adjunctive therapies used in practice. Data to support the use of any of these medications is limited. Only one randomized, placebo-controlled trial has been performed for adjunctive treatment in TEN. This study compared thalidomide to placebo and had to be stopped early due to increased mortality rate in those treated with thalidomide. While insufficient evidence exists to support the use of any particular adjunctive therapy, there are suggestions to guide use of the most common adjuncts based on expert opinion. If the decision is made to use IVIG, the treatment regimen recommended is 1 g/kd/day for three consecutive days, preferably started within 24–48 h of symptom onset. Side effects of IVIG can include renal impairment, thrombotic events, pulmonary edema, and hemolysis, among others. Use in patients with preexisting renal disorders or cardiovascular disease is associated with higher risk for complications. In patients with low IgA levels, there is an increased risk for anaphylaxis. If this preexisting condition is known at the time of admission, then IgA-depleted formulations of IVIG should be selected. Systemic steroid use in TEN is controversial, especially given a theoretical increased risk for sepsis, increased catabolism, and slower re-epithelialization. If selected, systemic corticosteroids should be administered early in the course of the disease (within 24–48 h of symptom onset), given for less than 5 days, and used only in patients with SJS or SJS/TEN overlap rather than those with extensive body surface area involved. Cyclosporine use is supported by a few case series and case reports, dosed at 3–5 mg/kg/day. Side effects of hypertension, renal impairment, and infection may limit use or affect patient selection. Case reports of tumor necrosis factor inhibitors suggest benefit. A single infusion or 5 mg/kg of infliximab or a single 50 mg injection of etanercept have been used successfully in a very small number of patients.

Patients should be counseled about future avoidance of the inciting medication and any medications

that may cross react with the culprit medication, as re-exposure may be fatal. Long-term follow-up may be necessary given the likelihood of cutaneous, oral, dental, vulvovaginal, and pulmonary sequelae, as well as the increased risk of death that persists for up to 1 year following SJS/TEN.

Conclusions

Cutaneous adverse reactions to medications are common, occurring in 2–3 % of hospitalized patients. Rash is listed as a possible side effect for most medications. Certain medications are more likely to result in cutaneous adverse reactions, however, and these include NSAIDs, antibiotics, and antiepileptics. Key elements in the evaluation of a patient with a suspected drug reaction include a review of the patient's medication list (including over-the-counter and herbal medications, and recent vaccinations, or infusions/shots including contrast media); accurate details regarding the timing of medication initiation; the nature of the eruption; history of previous drug reactions; history of atopy; coexisting medical conditions (including recent viral infections); and family history of severe cutaneous adverse reactions. Identifying and stopping the culprit medication rapidly is of primary concern, as early discontinuation may limit the severity of the eruption and will allow the patient to restart/continue other important medication not likely related to the eruption. Tests to confirm drug imputability exist (lymphocyte transformation testing, patch testing, or prick testing) but sensitivity varies by drug reaction type and by medication. Drug rechallenge can be considered in closely monitored settings. This is contraindicated for severe cutaneous adverse reactions, however.

Preventing cutaneous drug reactions, especially SCARs, is now possible with the burgeoning field of pharmacogenetics. Screening tests for vulnerable populations are increasingly available and healthcare providers should maintain awareness of the recommendations for pharmacogenetic screening. Providers should also be aware that some drug eruptions can mimic naturally occurring diseases, and that some common skin conditions can be induced by medications. For example, acneiform eruptions due to epidermal growth factor inhibitors, subacute lupus erythematosus induced by hydrochlorothiazide (Fig. 4.8), psoriasis and psoriasiform eruptions induced by interferon therapy, lichenoid eruptions due to antihypertensives, and autoimmune bullous diseases such as linear IgA bullous dermatosis due to vancomycin. Providers ought to consider the possibility of drug-induced skin disease in all patients presenting with a new or worsening skin condition.

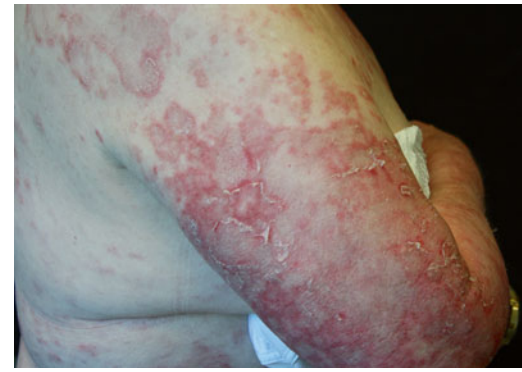

Fig. 4.8 Drug-induced subacute cutaneous lupus (SCLE). Annular erythematous plaques with peripheral scale in a photodistribution

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Part II

Drug Skin Reactions and Clinical Subgroups

Morbilliform Drug Eruptions

5

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Abstract

Morbilliform drug eruptions, also called exanthematous drug eruptions, are a form of delayed cutaneous hypersensitivity characterized by erythematous macules or papules that coalesce to form large plaques. The eruption usually occurs 5 days to 2 weeks after administration of the causative agent. The most common causes are antibiotics, anti-epileptics, allopurinol, non-steroidal anti-inflammatories (NSAIDS), anxiolytics, anti-hypertensives, and diuretics. They can also be associated with viral infections, illicit drug use, blood products, IV contrast media, and may have a genetic predisposition. With the cessation of the causative drug, morbilliform eruptions usually resolve within 1–2 weeks. The main histological features of morbilliform drug eruptions are a superficial and deep perivascular infiltrate and interstitial spongiotic and psoriasisiform dermatitis in conjunction with vacuolar interface changes. Although not completely understood, the immunological mechanisms for morbilliform drug eruptions involve a type IVb and IVc hypersensitivity reaction, as described by Gell and Coombs. Treatment for exanthematous drug reactions includes cessation of the causative agent and treatment of symptoms associated with the reaction, particularly pruritus.

Keywords

Morbilliform drug eruptions • Exanthematous drug eruptions • Cutaneous drug reactions • Drug eruptions • Adverse drug reactions

Introduction

Morbilliform drug eruptions, also known as maculopapular or exanthematous drug eruptions, are the most common drug reactions affecting the skin, accounting for up to 95 % of all drug eruptions. Reactions to drugs are quite common and can be classified into type A reactions if they

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_5

relate to the pharmacological activity of the drug, and type B reactions if the reaction is immune mediated. Because morbilliform drug eruptions are due to immune hypersensitivity, they are categorized as a type B reaction. Gell and Coombs proposed a system for categorizing allergic reactions into four categories based on pathogenesis. Type I reactions are immediate-type reactions that occur within an hour of drug administration and are caused by drug-specific immunoglobulin (Ig) E antibodies. Type II and type III reactions, also known respectively as cytotoxic and immune complex reactions, are caused by drug-specific IgG or IgM antibodies and are much less common than Type I reactions. Type IV reactions, also known as delayed hypersensitivity reactions, are mediated by T cells and occur between an hour and several days after drug exposure. Morbilliform drug eruptions are in the type IV category and are classified as non-immediate drug reactions.

Causal Agents

Common drugs that cause morbilliform eruptions include antibiotics (i.e. cephalosporins, aminopenicillins, sulfanomides), anti-epileptics, allopurinol, NSAIDs, anxiolytics, anti-hypertensives and diuretics. Higher risk drugs, defined as drugs causing a morbilliform eruption in more than 3 % of users, include allopurinol, aminopenicillins, cephalosporins, anti-epileptic agents, and antibacterial sulfonamides. Morbilliform drug eruptions may occur more frequently in illicit drug users who use opiates, barbituates, amphetamines, and marijuana. A major side effect of some systemic azole antifungal agents, such as itraconazole and fluconazole, is a morbilliform eruption.

Certain inflammatory disorders, such as viral infections, greatly increase the chance of developing a morbilliform eruption after ingestion of a drug. The frequency of aminopenicillin-induced exanthematous eruptions is almost 100 % in patients with infectious mononucleosis, an acute disease caused by the Epstein-Barr virus (EBV).

Morbilliform reactions often occur together with drug-induced acute interstitial nephritis (AIN) in patients treated with β-Lactam antibiotics (i.e. methicillin) and cephalosporins. In the non-dermatologic literature, the classic triad of low-grade fever, skin rash, and arthralgia has been described as occurring in about one-third of patients with methicillin, nafcillin, or oxacillin-induced AIN. Clinically, many of these patients may meet criteria for drug reaction with eosinophilia and systemic symptoms (DRESS), however AIN may also be seen in patients presenting with benign morbilliform eruptions that do not meet criteria for DRESS.

Other, less common, causes of drug-associated morbilliform eruptions include blood, blood products, and intravascular (IV) iodinated contrast. According to the Boston Collaborative Drug Surveillance carried out in 37,000 patients, only about 29 of 1,000 patients who developed an adverse cutaneous reaction had a reaction from a blood product. Late reactions to IV contrast media are reactions that occur between 1 h and 1 week after contrast media injection. The most common type of reaction to IV contrast media is a skin reaction, specifically a maculopapular rash. Other skin reactions include angioedema, urticaria, and erythema. The risks for a skin reaction to IV contrast media are higher in patients who have had previous late adverse skin reaction to IV contrast or who are on interleukin-2 treatment. Pathophysiology and management of an IV contrast reaction are the same as a drug-induced morbilliform eruption.

Genetic predisposition is an important factor for certain adverse drug eruptions. Severe drug hypersensitivity reactions have been associated with particular HLA alleles. These include abacavir and HLA-B*5701, carbamazepine and HLA-B*1502/A*3101, and allopurinol and HLA-B*5801. After comparison to African-American populations, Caucasians were shown to exhibit not only more abacavir-induced hypersensitivity reactions but also a higher frequency of HLA-B*5701. HLA-B*1502 is primarily seen in Han Chinese populations and increases the risk for Stevens-Johnson Syndrome (SJS) caused by carbamazepine. The risk of carbamazepine-induced drug eruptions in

non-Asian populations is increased with HLA-A*3101. Also, allopurinol-induced SJS is more common in Asian populations with the HLA-B*5801 allele than in Caucasian populations with the same allele.

Clinical Presentation

Morbilliform drug eruptions present as erythematous macules and/or papules that coalesce into larger plaques (Fig. 5.1). The eruption is described as "morbilliform" because of its similarity to measles and usually occurs 5 days to 2 weeks after the causative medication is started. Lesions usually begin on the trunk and successively spread symmetrically to the extremities (Figs. 5.2 and 5.3). In addition, the eruption can appear in areas of trauma or pressure, subsequently spreading symmetrically to the extremities. Morbilliform drug eruptions can be polymorphous, manifesting as morbilliform or urticarial lesions on the limbs, confluent erythema on the thorax, and purpura on the ankles and feet. In patients that are thrombocytopenic, the rash may appear purpuric but is not usually palpable (Fig. 5.4). Atypical two-zone targetoid papules may also be seen and should not be confused with the early lesions of SJS/TEN (Fig. 5.5) or erythema multiforme (EM).

Associated symptoms in patients with morbilliform drug eruptions include pruritus and low-grade fever. Furthermore, mucous membranes are usually spared, which helps to differentiate morbilliform drug eruptions from more severe reactions, such as SJS/TEN or DRESS. Early phases of SJS/TEN, DRESS, and acute graft-versus-host disease (GVHD) may present as a morbilliform eruption. Certain signs or "red flags" suggest a more severe cutaneous hypersensitivity reaction. For example, the timing of the eruption is important, as a later onset of 2–3 weeks is more common in DRESS and SJS/TEN. DRESS is usually caused by allopurinol, sulfa drugs, anti-epileptics, and dapsone. Constitutional symptoms of fever, myalgias and arthralgias, as well as edema of the face, diffuse eruption covering >50 % BSA, infil-

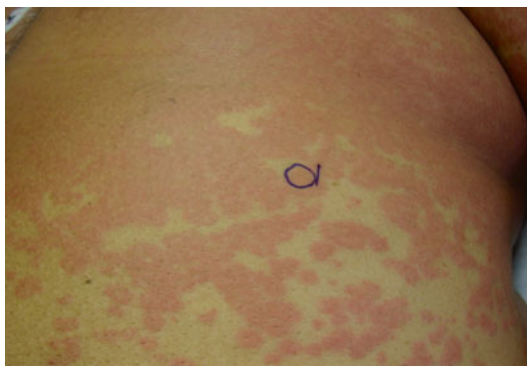

Fig. 5.1 A typical morbilliform drug eruption, with pink erythematous papules coalescing into larger plaques

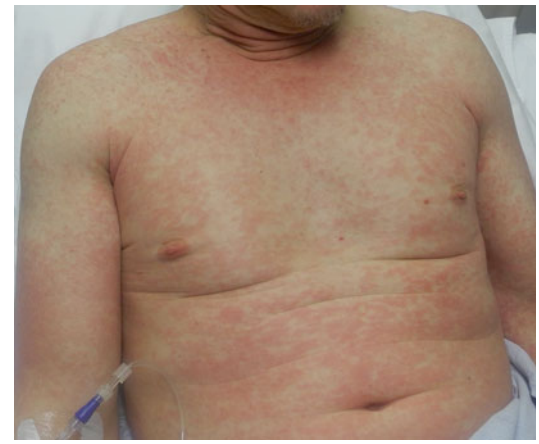

Fig. 5.2 Morbilliform drug eruption in an adult patient with pink erythematous papules coalescing into larger plaques, predominantly affecting the trunk

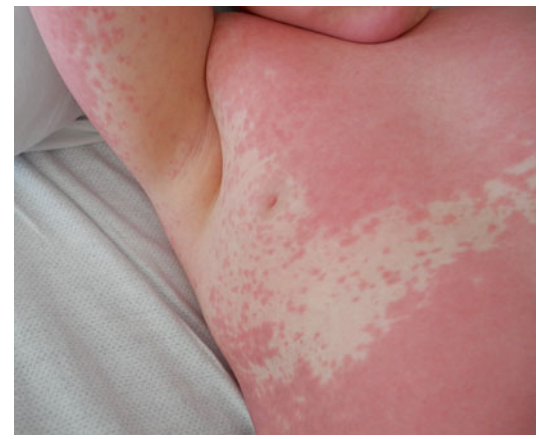

Fig. 5.3 Morbilliform eruption in a male pediatric patient

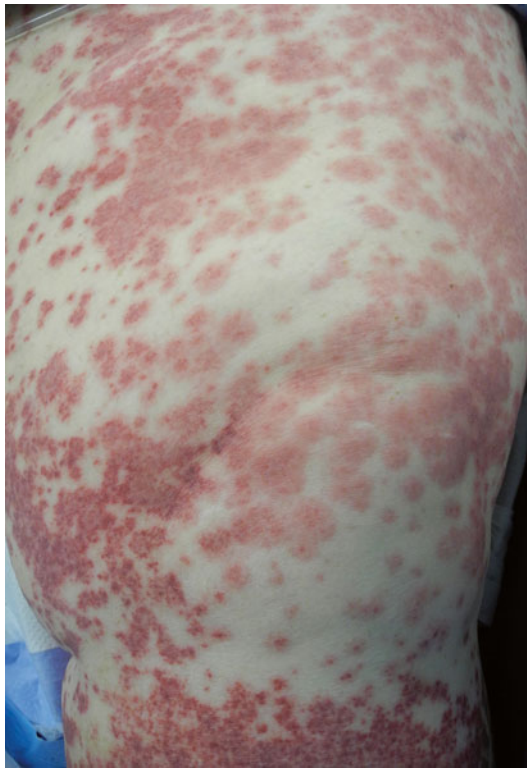

Fig. 5.4 Purpuric appearance of a morbilliform drug eruption in a patient with thrombocytopenia

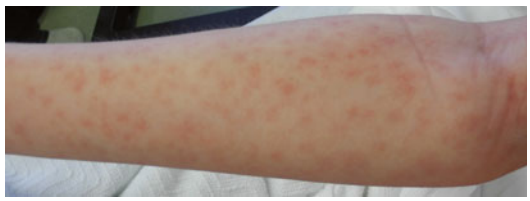

Fig. 5.5 Flat atypical targetoid lesions in a patient with a morbilliform drug eruption

trative edematous lesions, purpura, blisters, edema of hands and feet, and lymphadenopathy are all signs of DRESS more often than morbilliform eruptions. Mucosal involvement occurs in 20 % of cases of DRESS and peripheral blood eosinophilia is seen in most patients, unlike morbilliform eruptions. Finally, lesions on the mucous membranes along with painful or dusky skin are seen more commonly with TEN or SJS than with morbilliform eruptions.

Morbilliform eruptions usually disappear spontaneously after 1 or 2 weeks, but if the causative agent is introduced again, the eruption can reappear in a shorter time frame. During resolution of the eruption, desquamation often occurs, and in people with darker skin tones, postinflammatory hyperpigmentation is common.

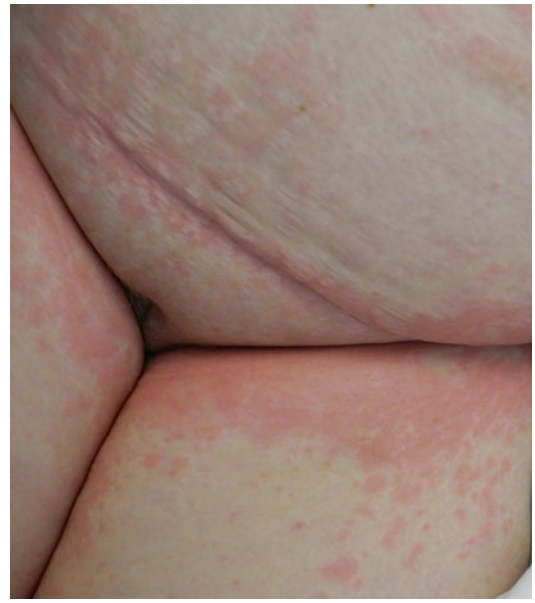

Fig. 5.6 Axillary involvement in a patient with the SDRIFE-variant of a morbilliform drug eruption

Rare variants of morbilliform drug eruption include the symmetrical drug-related intertriginous and flexural exanthem (SDRIFE), which has an inverse, or flexural, distribution and is usually induced by aminopenicillins. SDRIFE presents as a maculopapular eruption of the flexural areas (inguinal and perianal skin) with a V-shaped pattern on the medial thighs and diffuse erythema of the buttocks within a few days of exposure to the offending drug (Figs. 5.6 and 5.7). Infrequently, allergic contact dermatitis to nickel or mercury can cause lesions resembling SDRIFE.

Diagnosis

The differential diagnosis for morbilliform reactions is different for pediatric patients compared to adult patients. Children usually develop a morbilliform rash due to a virus or other infections.

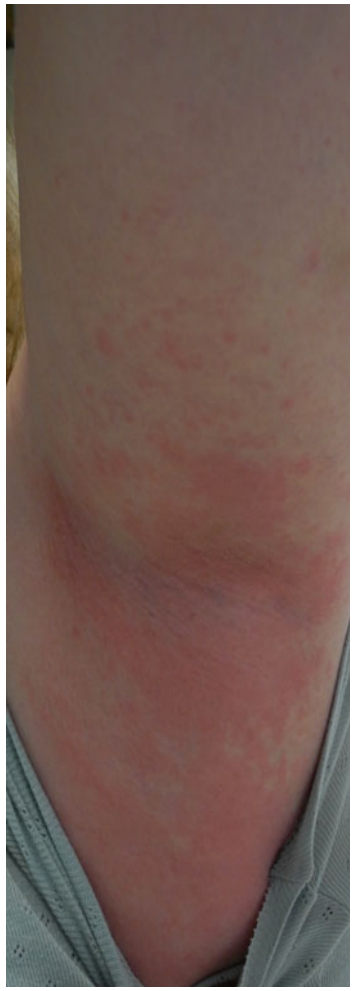

Fig. 5.7 Bilateral inguinal involvement in a patient with the SDRIFE-variant of a morbilliform drug eruption

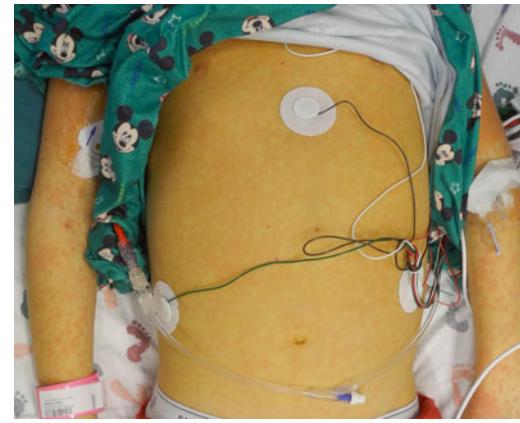

Fig. 5.8 Jaundice and a morbilliform eruption in pediatric patient secondary to primary HLH with liver involvement

Infectious etiologies include viruses (e.g. EBV, enteroviruses, adenovirus, early HIV, cytomegalovirus, human herpes virus type 6, human parvovirus B19, measles); bacteria (scarlet fever, mycoplasma infection); and streptococcal or staphylococcal toxins. The clinical presentations of the viruses are often indistinguishable from a morbilliform drug reaction and although the causative agent is often never found, certain labs including Rapid Strep Test (RST) or rapid antigen detection test (RADT), throat culture, ASO titer, anti-DNase antibody, and heterophile antibody test may be helpful to identify the cause. In the era of declining vaccination rates and increase in measles in the United States, measles IgM and IgG serologies may be useful to obtain in affected patients, particularly those whose vaccination histories cannot be verified. Rare causes of a morbilliform eruption in pediatric patients include Kawasaki Disease, hemophagocytic lymphohistiocytosis (HLH) and Juvenile idiopathic arthritis (Fig. 5.8).

In contrast, a drug etiology is more common for adults. The differential diagnosis includes DRESS, TEN, SJS, connective tissue disease (i.e. acute cutaneous lupus erythematous), acute GVHD, pityriasis rosea, allergic contact dermatitis, secondary syphilis, atopic dermatitis, and adult-onset Still disease. Viral and infectious exanthems are less likely for adults.

The diagnosis of a morbilliform drug reaction requires both the cessation of the offending drug and observation of a resolution of the eruption. The Naranjo algorithm or Naranjo Scale is a commonly used questionnaire that allows physicians to assess the likelihood of a drug-induced eruption. The probability of a drug causing the reaction is scored as definite, probable, possible, or doubtful. A lower score corresponds with a lower probability of a drug cause for the eruption.

In complex cases, such as patients with multiple comorbidities taking multiple different drugs, or cases where the culprit drug has not been identified, a detailed patient history should be taken. The patient should be asked about past and current medications, both over-the-counter

Table 5.1 Drug table

Morbiliform eruption appears at Day 0 ↓

Day	−7	−6	−5	−4	−3	−2	−1	0	1	2
Drug A			X	X	X	X	X	X		
Drug B	X	X	X	X	X	X	X	X		
Drug C							X	X	X	X
Drug D								X	X	X

To make a drug table, the potential causative medications are entered in the left most column. Next, the days in which the patient received each medication are marked with an "X." In this example, both drugs A and B are potential causative agents because they are within the window typical for morbiliform drug eruptions. Drugs C and D are unlikely to be the causative medications as they were started the day before and the day the rash appeared, respectively

and prescription, in order to establish a chronologic relationship between drug exposure and onset of the rash. For hospitalized patients, a review of the medical administration record (MAR) is essential. For patients transferred from outside institutions, including nursing homes or outside hospitals, a careful review of outside records should be performed. It is also recommended that records from the patient's pharmacy be obtained, as often patients may not be familiar with the specific names of their medications. When multiple medications are potential culprits, creating a drug table may be helpful (Table 5.1).

Although laboratory tests are not necessary for morbilliform drug eruptions, they may be useful when the clinical diagnosis is uncertain, in the presence of symptoms suggesting a severe drug reaction or in hospitalized patients. General laboratory tests include a complete blood cell count with differential as well as liver and kidney function tests, including urinalysis. A finding of eosinophilia or atypical lymphocytes is suggestive of DRESS. Similarly, abnormal liver function tests or evidence of renal dysfunction, including proteinuria or hematuria, may be seen in more severe drug reactions. Specific immunologic tests including patch testing, intradermal testing with delayed cutaneous readings, or in vitro tests for delayed reaction (i.e. lymphocyte transformation/activation tests, upregulation of activation markers on T cells, cytokine assays, and drug-induced cytotoxicity assays) can be performed 1–6 months after clinical symptoms have resolved, although this is not usually done in day-to-day practice.

Skin biopsies are often not helpful when evaluating patients with morbilliform eruptions as the histological pattern is often non-specific and does not identify the causative agent or etiology. Nonetheless, biopsy may be indicated when the diagnosis is uncertain. Possible indications for a skin biopsy include, but are not limited to, underlying immunosuppression, severe systemic symptoms, fever >38 °C (100.4 °F), symptoms involving internal organs, presence of erythroderma, blistering, purpura, or pustules, involvement of mucous membranes, and multiple drugs involved without a definite chronological relationship with the morbilliform drug reaction.

Pathogenesis

Although the exact pathophysiology is not completely understood, morbilliform drug eruptions are most likely the result of an immunological response. As discussed above, morbilliform drug eruptions are type IV or delayed-type hypersensitivity reactions. Gell and Coombs described four subtypes for type IV T-cell responses: type IVa, IVb, IVc, IVd. In type IVa responses, T cells produce interferon (IFN)-γ-activated macrophages which typically manifests as eczema. Type IVb responses are mediated by T cells producing type 2 helper (T_H2) cytokines (interleukin (IL) 4 and 5), which in turn induce B cells to produce antibodies and mast cell and eosinophil responses. Type IVc responses are induced by CD4+ and CD8+ T cells. Type IVd responses occur through recruitment and activation of neutrophils by T cells via production of a chemokine (CXCL8) and typically manifest as acute generalized exanthematous pustulosis.

Morbilliform drug eruptions appear to be driven by both Type IVb and Type IVc responses. It is believed that T lymphocytes, specifically CD4+ and CD8+ T cells, that express the cyto-

toxic granule proteins perforin and granzyme B, are generated and proliferate in response to drug hapten presentation by Langerhans cells. These proteins bind both covalently and non-covalently to MHC-II-peptide complexes on keratinocytes. The cytotoxic granule proteins trigger cell death by forming pores in the cell membrane of keratinocytes and inducing degradation of their DNA. Some drugs exhibit alternative mechanisms to activate the immune system. For example, sulfamethoxazole may bind directly to the MHC-peptide complex and T-cell receptor in a non-covalent way.

Upregulation of cytokines and chemokines has also been reported as a result of drug-induced morbilliform reactions. Both type 1 (i.e. IFN-γ, TNF-α) and type 2 (i.e. IL-5) cytokines can be seen in morbilliform drug reactions. The increase in IFN-γ accounts for the upregulation of MHC class II on keratinocytes, which allows drug presentation to CD4+ T cells. IL-5 and eotaxin (CCL-11) are upregulated in morbilliform drug reactions and are key factors in regulating the growth, differentiation, and activation of eosinophils, which explains the increased number of eosinophils typically seen on histology in morbilliform drug eruptions. Additionally, recruitment of CD4+ and CD8+ T cells in morbilliform drug eruptions can be partly attributed to CCL27 (CTACK)-CCR10.

Histopathology

Although biopsy tends to be non-specific, the most common histological pattern observed in morbilliform drug eruptions is a superficial and deep perivascular mixed infiltrate and interstitial spongiotic and psoriasisiform dermatitis in conjunction with interface dermatitis of the vacuolar type. The most characteristic histological feature of the epidermis is mild spongiosis (97 %) with a greater involvement of the lower layers. This spongiosis is often accompanied by mild hyperplasia (72 %), which helps distinguish drug eruptions from psoriasiform dermatitides such as psoriasis vulgaris, chronic atopic dermatitis, and nummular dermatitis. Occasionally, necrotic keratinocytes in suprabasal layers can be seen. Lymphocytes are also present in the epidermis, but not in high numbers. At the dermoepidermal junction, vacuolization is present either focally or continuously, and is associated with scattered lymphocytes and occasional necrotic keratinocytes. Vacuolar interface dermatitis can also be seen in fixed drug eruptions and EM-like drug eruptions, but these are characterized by prominent vacuolization, a high number of lymphocytes, and necrotic keratinocytes.

The dermis contains a perivascular accumulation composed of lymphocytes (100 %) and eosinophils (60 %) accompanied by neutrophils (50 %). An interstitial infiltrate in the papillary dermis can also be found, most often with a patchy distribution, and composed mainly of lymphocytes and neutrophils, as opposed to the reticular dermis, which may have an infiltrate composed of more eosinophils than neutrophils. Histological findings in patients with long-standing morbilliform drug eruptions show minor increases in thickness of epidermis, mild spongiosis, presence of hyperkeratosis and parakeratosis, as well as signs of scratching, such as lichenification.

The histologic differential diagnosis of morbilliform drug eruption includes viral exanthemata, fixed drug eruption, EM, acute GVHD, and acute lupus erythematosus. Viral exanthems are difficult to differentiate histologically from morbilliform drug eruptions.

In acute GVHD, neutrophils and eosinophils are rare, which helps to distinguish it from morbilliform drug eruptions. Additionally, GVHD also has satellite cell necrosis and may track down the follicle. Nevertheless, histopathology should not be used to differentiate between a drug reaction and GVHD because the diagnosis is primarily clinical. The presence of GVHD in other organs, including the liver and bowel, are more indicative of GVHD.

Management

Treatment for benign morbilliform drug eruptions is primarily symptomatic and supportive. The initial step in treating morbilliform drug

eruptions is to stop the administration of the causative drug. Subsequently, topical corticosteroids and oral antihistamines can be given to help alleviate pruritus. If no improvement is observed and symptoms worsen, an alternative diagnosis should be considered. In severe cases, systemic glucocorticoids (i.e. prednisone 0.5–1 mg/kg per day) should be considered after ruling out infection. In some cases, the offending drug may be continued when it is vital to the patient's well-being and there are no valid substitutes for the drug. Ultimately, the morbilliform drug eruption should resolve usually 1 or 2 weeks after cessation of the drug regardless of treatment method. Patients with benign morbilliform eruptions may be rechallenged without fear of the rash progressing to an urticarial or anaphylactoid type reaction.

Conclusions

Morbilliform drug eruptions are the most common type of drug-induced skin reaction and are mainly caused by allopurinol, aminopenicillins, cephalosporins, anti-epileptic agents, and antibacterial sulfonamides. Although the pathogenesis for these drug eruptions is not fully understood, morbilliform drug eruptions are most likely the result of a delayed immune response. Exanthematous drug eruptions are best diagnosed using a patient's drug history and by excluding a viral infection. Although skin biopsies may be performed, these are usually not necessary in the right clinical setting in order to make a diagnosis and may not be helpful as a means of diagnosis, since histological findings are not very specific. Fortunately, once the causative drug is identified and suspended, the reaction should clear within 1–2 weeks.

Suggested Reading

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Drug-Induced Urticaria

6

Tarek S. Shaath, Vikas K. Patel, Anand N. Rajpara, Garth R. Fraga, and Daniel J. Aires

Abstract

Urticaria, often referred to as hives, is one of the most commonly diagnosed dermatologic disorders in emergency departments and urgent care facilities. Due to the wide variety of manifestations and etiologies, it is of great importance to rapidly recognize the condition, work up potential causes, and institute appropriate clinical treatment. In this chapter we aim to educate clinicians about the etiology, presentation, and management of the three subtypes of urticaria commonly induced by drugs: acute, chronic, and contact urticaria.

Keywords

Urticaria • Drug reactions • Eruption • Acute urticaria • Chronic urticaria • Contact urticaria • Drug-induced urticaria • Angioedema

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Introduction

Urticaria is a common cutaneous reaction characterized by recurrent skin and mucosal edema in the superficial papillary dermis layer of the skin. The phenomenon is generally self-limiting, and half of all cases are caused by viral upper respiratory tract infections, drugs, food, and insect bites. The remaining 50 % of causes are idiopathic. This chapter will focus on drug etiologies of urticaria, most of which are due to penicillins and non-steroidal anti-inflammatory (NSAID) drugs. Drugs may elicit acute urticaria, exacerbate chronic urticaria, or evoke contact urticaria, either as allergens or pseudoallergens.

J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_6

Epidemiology and Pathophysiology

Of all drug-induced eruptions in the skin, urticaria is one of the most common, second only to maculopapular exanthems. The incidence of urticaria from any cause is difficult to define, but likely occurs at least once within the lifetime of 12–25 % of people. The incidence of drug-induced urticaria in the inpatient setting is 0.16 %, and extends to 9 % in outpatient dermatology clinics. Drugs may induce three subtypes of urticaria, each with its own etiology and pathomechanism. This section discusses the causes and mechanisms of acute urticaria, chronic urticaria, and contact urticaria.

Acute Drug-Induced Urticaria

Acute urticaria is the most prevalent of the three subtypes of urticaria due to drugs, and is common in both adults and children. By definition, acute urticaria (Fig. 6.1) persists for fewer than 6 weeks in duration. It is mediated by both immunologic and non-immunologic mechanisms. The immunologic mechanisms are allergic reactions, which may involve either a type I or type III hypersensitivity reaction. Non-immunologic urticarias are pseudoallergic reactions driven by direct modification of mast cell sensitivity. The mechanism responsible for drug-induced acute urticaria can be specific to the type of drug ingested prior to the eruption. Drugs known to cause urticaria are listed below (adapted from Mathelier-Fusade P. Drug-induced urticarias PMID 16461991):

- Antibiotics: penicillins, cephalosporins, macrolides, aminoglycosides, tetracyclines, sulfonamides, vancomycin
- Nonsteroidal anti-inflammatory agents: ibuprofen, naproxen sodium
- Salicylates
- Angiotensin-converting enzyme inhibitors
- Antifungal agents: fluconazole, ketoconazole
- Opioids: morphine, codeine, meperidine, fentanyl
- Dextromethorphan
- Betadine (povidone-iodine)

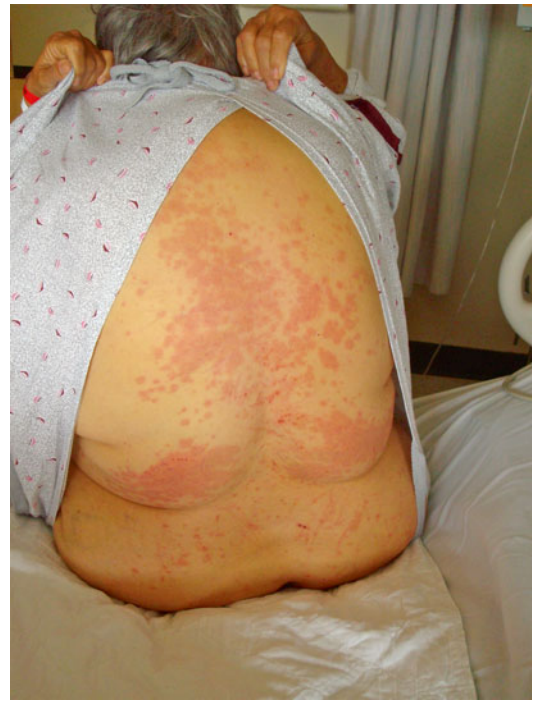

Fig. 6.1 Symmetric urticarial drug eruption due to cephalexin over the back. This was acute and discontinuation of the drug resulted in rapid resolution

- Muscle relaxants: atracurium, vecuronium, succinylcholine, curare
- Thrombolytics: alteplase, urokinase
- Protamine sulfate
- Antineoplastics
- Steroids
- Progesterone
- Polypeptide hormones: insulin, corticotrophin, vasopressin
- Enzymes: trypsin, streptokinase, chymopapain
- Hydantoins
- Sorbitol complexes
- Hydralazine
- Quinidine
- Dextrans
- Mannitol
- Vaccines
- Vitamins
- Radiographic contrast agents

Type I hypersensitivity is the pathomechanism proposed for penicillin-induced acute

urticaria. It is an immune-dependent mechanism that requires an initial sensitization period, during which no allergic reaction usually occurs. The sensitization results in synthesis of drug-specific immunoglobulin E (IgE) antibodies, the Fc portion of which is then bound by high-affinity IgE Fc receptors (FcεRIs) present on the surface of mast cells. This leaves the antigen-binding site exposed to the extracellular space, ready to bind its antigen. When a parent drug or one of its metabolites binds to drug-specific IgE antibodies anchored within the plasma membrane of mast cells, crosslinking of two adjacent Fc receptors may occur. This sequence activates mast cells, the effector cells in urticaria. Activation incites the degranulation of mast cell contents, releasing histamine and other vasodilators into the extracellular environment. The resulting vasodilation leads to increased vascular permeability and extravasation of intravascular fluid. This sequence forms clinically evident wheals. β-lactam antibiotics are the most common culprits of drug-induced acute urticaria by this immediate hypersensitivity allergy. This mechanism may also play a role in chronic urticaria, discussed later.

Acute urticaria may also be mediated immunologically by a type III hypersensitivity reaction that involves immune-complex activation of the complement cascade. This process begins when immunoglobulins G or M (IgG, IgM) combine with an excess of drug antigen, forming multiple antibody-antigen immune complexes. These immune complexes activate the classical complement pathway, through which anaphylatoxins are produced that act on mast cells and basophils to trigger the release of vasodilators. This phenomenon is referred to as serum sickness and is associated with systemic symptoms, including fever, arthritis, neuritis, and papular rash. The onset is subacute, beginning between 6 days and 3 weeks after ingestion of a culprit drug. A set of drugs known to cause serum sickness is listed here (adapted from PMID 16461991). The urticarial rash resolves several weeks after drug cessation.

- Penicillins and cephalosporins
- Aspirin
- Captopril
- Sulfonamides
- Phenytoin
- Globulin preparations
- Para-aminosalicylic acid
- Allopurinol
- Arsenic and Mercury derivatives
- Barbiturates
- Furazolidone
- Gold salts
- Griseofulvin
- Halothane
- Hydralazine
- Methyldopa
- Iodides
- Penicillamine
- Piperazine
- Procainamide
- Quinidine
- Streptokinase
- Thiouracils

Non-immunologic pathomechanisms may also elicit an acute-type urticaria. Some drugs act directly on mast cells to increase degranulation of histamine and vasodilatory mediators, without prior sensitization. Drugs that induce urticaria by this mechanism include opiates, codeine, amphetamine, polymyxin B, atropine, muscle relaxants, hydralazine, pentamidine, quinine, and radiocontrast media.

The etiology of drug-induced acute urticaria may be multifactorial in some cases. For example, benign viral illnesses are known to sensitize mast cells and cause acute urticaria. If treated with NSAIDs, infection-related urticaria may be exacerbated by a mechanism discussed hereafter in the context of chronic urticaria.

Chronic Drug-Induced Urticaria

Chronic urticaria differs from acute urticaria by its time course. It is defined as a relapsing, remitting urticaria with lesions reappearing at least twice per week for longer than 6 weeks, usually in the absence of any identifiable cause (Fig. 6.2). The prevalence of chronic urticaria is between

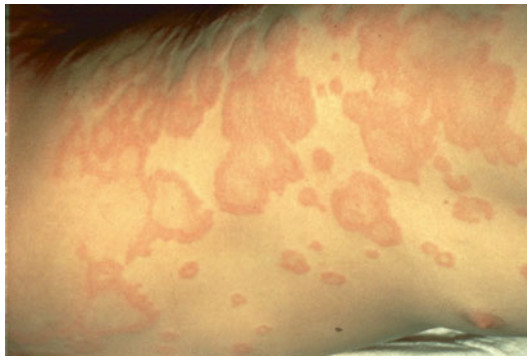

Fig. 6.2 Annular pink plaques with clear centers on the left flank in a patient on multiple medications. The exact etiology was not determined and was chronic in nature

0.5 and 3 %, and is rare in children. Chronic urticaria is usually an idiopathic preexisting condition which may be exacerbated by drugs through similar mechanisms responsible for acute urticaria. Mainly, the non-immunologic pathomechanism is involved, in which drugs worsen chronic urticaria by directly increasing mast cell mediator release. Drugs which may exacerbate chronic urticaria include NSAIDs, codeine, and morphinic agents. About 30–75 % of patients suffering from chronic urticaria may experience angioedema after taking aspirin or NSAIDs.

Another pathomechanism implemented in chronic urticaria is a specific pharmacological hypersensitivity related to NSAID intake. This pseudoallergic reaction aggravates chronic urticaria after aspirin or NSAID intake. The prevalence of NSAID-induced urticaria and angioedema in all patients ranges between 0.1 and 0.3 %. Aspirin and NSAIDs are cyclooxygenase (COX) inhibitors that cause pseudoallergic reactions by altering metabolite levels in the arachidonic acid metabolism pathways. Inhibition of COX 1 and COX 2 increases the levels of cysteinyl leukotrienes, leading to vasodilation and edema, causing wheal-and-flare eruptions in patients hypersensitive to these medications. This mechanism is considered a pharmacological side effect rather than a true allergy since no immunogenic phenomenon transpires.

Contact Urticaria

The third type of urticaria related to drug use is contact urticaria. This side effect arises after the application of topical medications. Ordinarily, the more likely adverse reaction caused by topical medications is an eczematous contact dermatitis. However, urticaria can also result as a transient wheal-and-flare eruption. The process may occur within a few minutes to an hour of application, and resolves in fewer than 2 h after removal of the offending topical agent. Contact urticaria develops as a result of both type I hypersensitivity and non-immunologic mechanisms.

The immunologic mechanism may result in generalized urticaria whereas the non-immunologic mechanism usually remains localized to the area of application. Topical antibiotics are common culprits, including penicillin, cephalosporins, gentamycin, neomycin, bacitracin, streptomycin, and chloramphenicol, when administered in topical formulations like ointments, creams, or eye drops. Neomycin causes localized contact dermatitis in addition to contact urticaria. Bacitracin has been reported to cause severe anaphylaxis. Topical anesthetics such as benzocaine and lidocaine within EMLA cream have also been reported to cause contact urticaria. Chlorhexidine, known to cause contact dermatitis and photosensitive reactions, may also cause contact urticaria. Other non-immunologic contact reactions may occur following the handling of substances like ammonium, persulphate (hair perming solution), cinnamic aldehyde, benzoic acid (found in cosmetics and food), and other topical cosmaceuticals (Fig. 6.3). There have been increasing reports of contact urticaria immediate-type hypersensitivities, and severe anaphylactic shock in handlers of these compounds.

Angioedema

Urticaria is associated with angioedema in 40 % of patients, defined by deep edema within the reticular dermis or subcutaneous tissue. Angioedema should not be viewed as a separate entity, but rather a clinical variant of urticaria at a deeper skin depth (Fig. 6.4). Angioedema differs

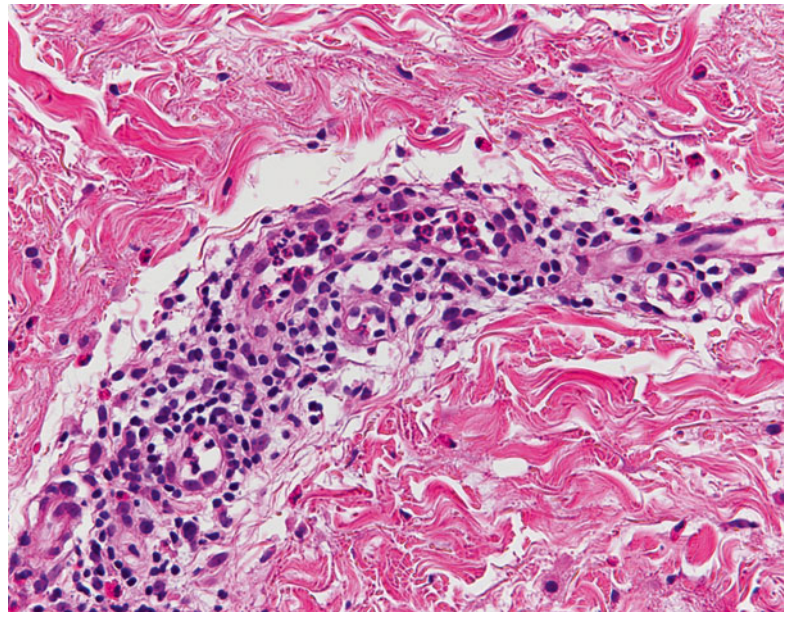

Fig. 6.3 Contact urticaria due to a shampoo. Note that, unlike most cases of contact dermatitis, there is no eczematous or epidermal component, but erythema and edema indicative of an urticarial reaction with dermal edema and vasodilatation

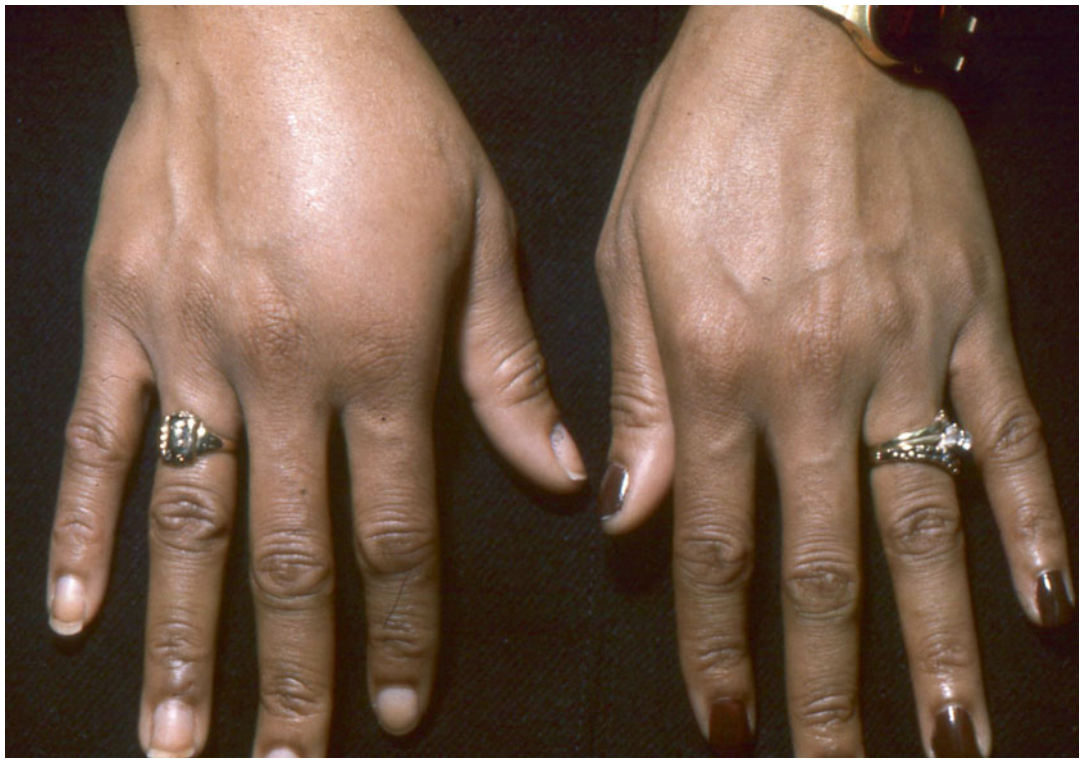

Fig. 6.4 Angioedema of the hand on the left, with an area of large, deep swelling

from urticaria by its ill-defined borders, pale- to skin-color, association with pain and tenderness, and duration of up to 72 h. The phenomenon typically localizes to the lips, eyelids, genitalia, and extremities. Angioedema is a known side effect of angiotensin-converting enzyme (ACE) inhibitors, and occurs between 0.1 and 0.2 % of patients receiving ACE inhibitors. The mechanism involved is due to the potent inhibition of kinase II by the ACE inhibitor. This leads to an increase in bradykinin levels, which results in continued prostaglandin E2 synthesis, leading to vasodilation, increased vascular permeability, and increased fluid leakage into the interstitial space.

Presentation

Regardless of the time course and subtype, urticarial wheals present similarly as rapidly emerging, pink to pale plaques with central clearing and surrounding erythematous flare. These transient lesions may be round, oval, or serpiginous in shape, range from a few millimeters to several centimeters in size, and appear anywhere on the body, including the palms, soles, and scalp. They are intensely pruritic and may evoke a burning sensation, but are not usually painful. The distribution is usually random and asymmetric, although chronic urticarial lesions can recur in repeat locations. By definition, lesions appear within minutes to hours, and persist for fewer than 24 h after onset. Upon resolution, there are no residual ecchymoses or discolorations, unless trauma due to scratching was involved. If lesions are painful, or leave residual ecchymoses, then urticarial vasculitis should be considered as a diagnosis.

In acute urticaria, lesions appear within a few hours to days after the drug is taken, and disappear within several days after withdrawal of the drug. If the urticaria is due to an allergy caused by an IgE-dependent immune mechanism, the disease is generalized and potentially fatal, whereas pseudoallergic events are rarely fatal. In chronic urticaria, lesions may resolve from time to time, but repeatedly relapse, preventing the patient's complete recovery. In contact urticaria, lesions are usually localized to the site of application, but in some cases the urticaria may generalize.

Histopathology

Histological sections of urticaria commonly display dermal edema with mild dilation of dermal blood vessels. Absent are signs of vessel damage and leukocytoclasia. Cellular infiltrations are evident perivascularly with sparse densities of neutrophils, macrophages, eosinophils, and lymphocytes.

Differential Diagnosis

- Exanthematous drug eruption: history of drug intake, possible low-grade fever, lesions appearing as fixed maculopapular confluent wheals bilaterally and symmetrically on the trunk
- Contact dermatitis (allergic or irritant): carefully-elicited history of offending agent exposure, lesions apparent only at site of contact
- Urticarial dermatitis: elderly patients with urticarial- and eczematous-appearing lesions in bilateral symmetric distribution on trunk and extremities
- Urticaria pigmentosa (mastocytosis): brownish maculopapular lesions, induced in children by rubbing, heat, sunlight exposure, or spontaneous cause, positive Darier sign upon skin rubbing
- Autoimmune bullous diseases (bullous pemphigoid, pemphigus): may present with urticarial lesions early in the course, later progressing to subepidermal blisters; often symmetrical, with predilection for the trunk and flexor surfaces
- Arthropod bite: fixed pruritic papules, usually appearing on exposed areas, usually during summer months
- Pruritic urticarial papules and plaques of pregnancy (PUPPP): during third trimester or immediately post-partum; small, fixed papular urticarial lesions with coalescence; may feature eczematous changes, vesicles, or target-oid lesions; predominantly involves trunk and proximal extremities
- Urticarial vasculitis (small vessel vasculitis): predominantly affects the skin and is the main disorder in the differential of chronic urticaria;

lesions last more than 24 h, burn rather than itch, and resolve with hyperpigmentation and bruising; purpura and necrosis may be evident; systemic symptoms may be present, especially in connective tissue diseases

Diagnosis and Management

The diagnosis of urticaria is usually clinical and begins with a comprehensive history. Information of significance includes time of onset; frequency and duration; diurnal variation, size, shape and distribution; subjective symptoms of pruritus and pain; presence of angioedema; past history of allergies, infections, and diseases; family history of atopy; occupational history; response to attempted therapies; and most importantly, the use of drugs including antibiotics, NSAIDs, injections, hormones, and alternative remedies. When properly obtained, a comprehensive history is sufficient to make an accurate diagnosis and precludes the need for an extended diagnostic workup. Since urticaria is self-limiting, the primary concern is to rule out life-threatening anaphylaxis and provide medication to relieve severe pruritus.

Confirmation of a suspected clinical diagnosis may be established by skin-prick tests and immunologic assays like the radioallergosorbent test (RAST), which detects disease-specific IgE antibodies. Efficacy of these diagnostic tests is limited to the selection of drugs for which testing is available. Drugs commonly tested include penicillin, aminopenicillin, cephalosporin, and insulin. Of note, skin-prick tests can occasionally cause an anaphylactic shock and therefore must be performed under close supervision in a clinical setting.

The most important step in patient management upon discovery of a drug-induced urticarial eruption is immediate withdrawal of the offending agent. Many clinicians wisely withdraw a drug based on self-reported patient allergies. However, allergies to β-lactams are frequently overdiagnosed. In patients who report a history of penicillin allergy, only 10–20 % are truly allergic when assessed by skin-prick testing. Additionally, upon subsequent oral challenge with penicillin in patients who self-report an allergy, skin rash is rarely reproducible. Therefore, patients who report an anecdotal drug allergy may be good candidates for skin-prick or oral challenge testing to determine actual presence of allergy. Nonetheless, removal of a suspected agent is imperative when a patient presents with new onset urticaria soon after taking a drug known to commonly elicit urticaria.

Withholding the offending agent is typically sufficient in treating drug-induced urticaria. However, should pharmacologic treatment be necessary after drug cessation, it primarily consists of H1 antihistamines, of both the classic first-generation (sedating) and newer second-generation classes. If antihistamines fail to mitigate urticarial symptoms, second-line therapies may be considered in addition to antihistamine therapy. The use of these second-line agents should be guided by current specific indications and guidelines. A current prescribing manual should be consulted for details, and appropriate weight-based dosing calculated. Second-line agents for the treatment of urticaria include prednisone, epinephrine, doxepin, montelukast, thyroxine, colchicine, sulfasalazine, and if severe and unremitting, omalizumab. Systemic corticosteroids are also used such as 1 cc of IM Celstone Soluspan (6 mgms per cc) or 50 mgms of prednisone each A.M. with food for 2 days and then decrease by 10 mgms every 2 days for a 10-day course.

In patients allergic to aspirin and NSAIDs, treatment involves avoidance. However, new evidence suggests the use of COX-2 selective inhibitors, such as celecoxib, can be safely administered in patients with chronic urticaria who are sensitive to NSAIDs. Patient sensitivity to NSAIDs is associated with overproduction of cysteinyl leukotrienes and mast cell activation, mediated by inhibition of COX-1. Therefore, theoretically, COX-2 inhibitors should not produce pseudoallergic reactions in patients with chronic urticaria who are sensitive to NSAIDs. In fact, there are numerous reports of patients with a clinical history of NSAID-induced skin eruptions

demonstrating good tolerability of COX-2 inhibitors. As always, clinical judgment is essential when prescribing NSAIDs. Reports of urticaria elicited by COX-2 inhibitors do exist. There is no absolute guarantee of safety with use of these drugs in patients who are sensitive to NSAIDs.

Perhaps more importantly, NSAID dose should be reevaluated in patients who develop adverse reactions upon intake. Interestingly, treatment with NSAIDs at normal doses appears to be well-tolerated, even in patients who have previously experienced urticaria due to NSAID use. Normalization of NSAID dose is imperative to prevent future urticarial eruptions. However, it is best to find a substitutive medication of a different drug class. Acetaminophen is a valid option in doses less than 1000 mg, since it is a weak inhibitor of the COX-1 enzyme. In patients for whom a substitute is not possible, as in those requiring aspirin for daily thromboembolic prophylaxis, desensitization may be an effective method to allow safe drug intake. Once desensitized to aspirin, patients can maintain desensitization with a daily aspirin dose.

Conclusions

Urticaria is a treatable condition which can severely impact patient quality of life. Management includes avoidance of triggers, desensitization, and/or treatment of the causal underlying illness. New-generation antihistamines are the mainstay of pharmacologic treatment, effectively mitigating symptoms in most patients. The side effect profiles are low, and dosage may be increased for non-responding patients. Acute urticaria can often be managed by a general practitioner. However, chronic urticaria can benefit from referral to a specialist, often a dermatologist or allergist, to search for drug etiologies or other causes.

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Erythema Multiforme and Drug Reactions

7

Eric Dean Merrill and Carol W. Stanford

Abstract

Erythema multiforme (EM) is an acute, immune-mediated mucocutaneous condition that characteristically presents with acrally distributed targetoid lesions. The disease is often self-limited, and treatment is frequently unnecessary. Although many factors have been associated with EM, the study of EM remains difficult due to various inconsistencies in terminology. Herpes simplex virus (HSV) causes the vast majority of EM cases, but drugs and *Mycoplasma pneumoniae* are also described in the literature. EM-like drug reactions are likely of different pathogenesis than herpes-associated EM. Drug reactions are frequently implicated in more serious disease, such as Stevens-Johnson syndrome, which can show papules and plaques that are targetoid lesions of EM. Thus, making the clinical distinction between EM and its more severe counterparts is crucial.

Keywords

Erythema multiforme • Target lesions • Stevens-Johnson syndrome • Herpes simplex virus • Immune-mediated • Drug exposure

Introduction

Erythema multiforme (EM) is an acute, immune-mediated mucocutaneous condition that characteristically presents with acrally distributed targetoid lesions. Definitions of EM have varied over the years, making the study and classification of EM extremely difficult. Most reported cases are due to herpes simplex virus (HSV) infections (Fig. 7.1), but other causes such as *Mycoplasma pneumoniae* and drug reactions have been implicated. However, whether HSV-associated EM

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_7

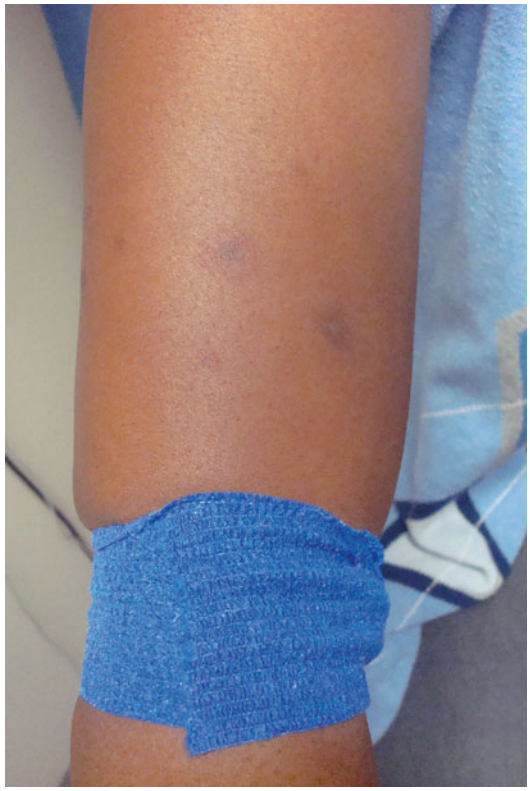

Fig. 7.1 Atypical target lesions with dusky center (typical of people of color) and surrounding erythema in a patient who flares with episodes of genital HSV

(HAEM) and EM of other causes, such as drug-induced EM (DIEM) and *M. pneumoniae-associated* EM, are part of the same disease process remains under debate.

Historical Perspective

In 1866, Ferdinand von Hebra described an acute, self-limited, mild skin disease characterized by symmetrically distributed, evolving skin lesions. The lesions presented with an acral distribution and had a tendency for recurrences. For much of the nineteenth century, morphologists had identified many different types of "erythema" and used terms such as "erythema papulatum", "erythema tuberculatum", "erythema annulare", "erythema iris", "erythema gyratum", and "herpes iris." von Hebra concluded that each of these terms

Fig. 7.2 Purulent conjunctivitis in patient with typical target lesions of erythema multiform on areas of the skin not seen in the figure

represented different stages of the same disease, which he called "erythema exudativum multiforme." The term multiforme exemplifies not the multiple presentations of EM, but instead multiple morphologic stages of the same lesions.

Following the original description of the disease, the term erythema multiforme has been used to describe various diseases, many only minimally resembling von Hebra's original description. In 1922, Stevens and Johnson described a disease in two boys with acute febrile illnesses and skin lesions somewhat resembling those of EM, along with associated stomatitis and severe purulent conjunctivitis (Fig. 7.2). Stevens and Johnson recognized that this was distinct from von Hebra's disease and coined "a new eruptive fever with stomatitis and ophthalmia," which by the 1940s became known as Stevens-Johnson syndrome (SJS). In 1950, Thomas et al. recognized a distinction between the two diseases, and used EM minor to characterize von Hebra's classic mild disease, and EM major to refer to a more severe disease, consistent with SJS. In 1956, Lyell described toxic epidermal necrolysis (TEN), a more severe disease with extensive skin sloughing. EM minor, EM major, SJS, and TEN were considered to be part of the same disease spectrum, with each term describing a different level of severity.

Until the 1980s and 1990s, the terminology surrounding EM became even more muddled. As mentioned previously, EM major and SJS were

often used synonymously. Other literature defined EM as only involving one mucosal surface, whereas SJS involved at least two. Others classified the diseases based on etiology. Such inconsistencies have made gathering meaningful epidemiologic and etiologic data extremely difficult.

Current Classification of Erythema Multiforme

By the 1980s, researchers began to further characterize EM, SJS, and TEN. Howland et al. noted that EM minor, using a definition close to that described by von Hebra, was frequently associated with HSV. This disease tended to be less severe than sulfonamide-associated disease, which had more widespread lesions and increased mucosal involvement. Of note, the authors defined the two presentations as EM minor and EM major.

In 1993, recognizing the confusing terminology, Bastuji-Garin et al. proposed a classification scheme to differentiate EM, SJS, and TEN. Hospitalized patients with suspected erythema multiforme, SJS, or TEN were examined. Four clinical patterns emerged: typical targets, raised atypical targets, flat atypical targets, and macules with or without blisters. Additionally, the percentage of body surface area (BSA) of detached or detachable epidermis was calculated. Five diagnostic categories were proposed:

- *Bullous EM:* detachment below 10 % of the BSA plus localized typical targets or raised atypical targets
- *SJS:* detachment below 10 % of the BSA plus widespread macules or flat atypical targets
- *Overlap SJS/TEN:* detachment between 10 and 30 % of the BSA plus widespread macules or flat atypical targets
- *TEN with spots with or without blisters*: detachment above 30 % of the BSA plus widespread macules or flat atypical targets
- *TEN without spots:* detachment above 10 % of the BSA with large epidermal sheets and without any macule or target

Both dermatologists and non-dermatologists used this classification scheme, and were able to successful classify lesions with 68–100 % concordance. Furthermore, the authors concluded that EM can be clinically distinguished from SJS and TEN based on morphology, distribution, and etiology.

Using similar classification, Assier et al. confirmed the finding that EM and SJS could be distinguished based on clinical pattern. They also provided evidence that etiologic agents for EM and SJS are distinct, with EM being related to herpes and SJS being more related to drugs. Subsequently, a case-control prospective study with 552 patients confirmed the distinction between EM and SJS, and stated that SJS and TEN are the same disease, with TEN being more severe. This study classified EM as having typical targets, raised atypical targets in a localized, acral pattern with less than 10 % blister involvement. Notably, no distinction was made between EM minor and EM major in these studies. Today, the terminology EM minor and EM major are still in use, but now refer to EM without mucosal involvement and with mucosal involvement, respectively.

Epidemiology

Reported prevalence rates of EM are typically <1 %. However, a paucity of research exists on EM prevalence. In addition to difficulties in classification, the acute nature of the condition and a lack of a reporting registry also contribute to scant epidemiologic data. EM typically affects young adults who are 20–40 years old, but children and the elderly can be affected. Over one-third of cases may be recurrent, and recurrence is even more common in HAEM. Mortality rates for EM are not well reported, but are thought to be low. Conversely, SJS and TEN have mortality rates of approximately 5 and 30 % respectively.

Presentation and Characteristics

The classic presentation as described by von Hebra remains the most important clue for diagnosis of EM. The classical form of EM arises

1–14 days following an episode of herpes labialis or herpes genitalis. Following a period of either absent or mild prodrome, symmetrically distributed lesions develop on the extensor surfaces of the extremities, commonly the dorsal aspects of the hands. The lesions evolve to become characteristic targetoid lesions, which last from 1–4 weeks and resolve in a self-limited fashion. The following discussion will focus on the mild disease most consistent with the disease originally described by von Hebra.

Prodromal Symptoms

EM cutaneous findings are rarely preceded by prodromal symptoms, and when present, these symptoms tend to be mild. When prodromal symptoms occur, fever, malaise, headache, cough, rhinitis, sore throat, myalgia, arthralgia and nausea occur 7–14 days before cutaneous lesion development. Whether the prodromal symptoms are a result of the EM disease process itself, or associated with underlying cause (e.g., HSV infection) can be difficult to distinguish.

Morphology

The earliest cutaneous manifestations are round, erythematous macules, which quickly evolve to papules, which may be surrounded by an area of blanching. At this point, the lesions can resemble insect bites or urticarial hives. Lesions then enlarge and develop concentric alterations in morphology in color. Lesions generally range from 2 to 20 mm in size. The central area of the lesion gradually darkens, and either a central blister with a necrotic blister roof, an area of epidermal necrosis without a blister, or an area of crusting develops. This central area may be beefy red, white, yellow, or gray with a darker gray-to-blue rim of color at the edge. Immediately surrounding the area of epidermal necrosis is a dark red, inflammatory zone, which is surrounded by a lighter color, edematous ring. At this point, the lesions are described as targets, or iris lesions, due to their three concentric zones: the central dusky zone, the pink edematous zone, and the peripheral red ring. In individuals with more pigmented skin, the entire area of central necrosis may be dark gray. The lesions may become more complex, and may coalesce, develop central erosions or crusting, or develop central clearing. The inflammatory process in an individual area may remit, and relapse at a later time, further diversifying the appearance. Patients may also have multiple stages of lesions at any one time. The lesions typically heal without scarring, but post-inflammatory hypo- (Fig. 7.3) or hyper-pigmentation may occur, especially in more pigmented skin.

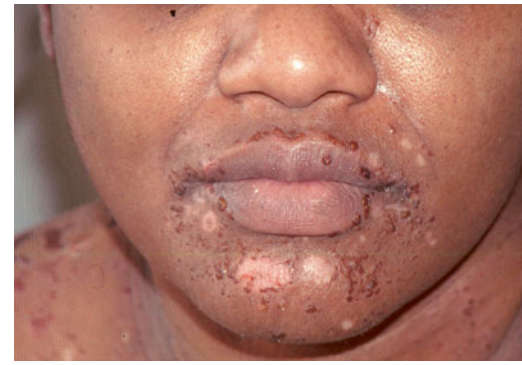

Fig. 7.3 Residual areas of oval hypo-pigmentation around the mouth in a patient with erythema multiforme due to lisinopril. The white areas should resolve, but it may take 4–6 months

Cutaneous Distribution

Lesions typically present symmetrically, with a predilection for the dorsal aspects of the hands and extensor surfaces of the extremities. Hundreds of lesions may be present. Other areas of involvement, although less frequent, are skin of the palms, soles, flexural aspects of the extremities, neck, perineum, ears, and face. The lesions can spread first from extensor surfaces to flexor surfaces, and then centripetally, but involvement of the trunk is less common and less pronounced. The isomorphic phenomenon, also known as koebnerization, and photoaccentuation are thought to play a role in the cutaneous distribution of lesions. Of note, koebnerization is only thought to occur prior to cutaneous eruption, and once skin lesions are present, the phenomenon no longer occurs.

Mucous Membrane Lesions

Although von Hebra's original description of EM did not involve the mucous membrane, significant literature describes such an association.

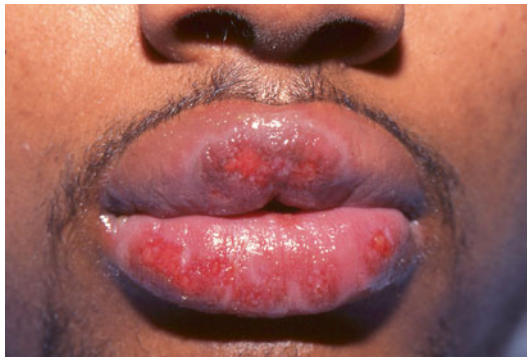

Fig. 7.4 Erosions over the lip of erythema multiforme secondary to ibuprofen

Estimates on mucous membrane involvement range from 25 to 70 %. When mucosa is involved, it usually occurs simultaneously with, but may occur before or after, cutaneous manifestations. Mucous membrane involvement may rarely occur in the absence of cutaneous involvement. The oral mucosa is most commonly involved, with the labial mucosa, buccal mucosa, non-attached gingivae, and vermillion lip being common locations (Fig. 7.4). The lesions range from diffuse oral erythema and edema to multifocal superficial ulcerations. Other reported mucous membranes include ocular, genital, upper respiratory, and pharyngeal mucosa.

Associated Symptoms

EM tends to be localized to the skin and mucous membranes with few systemic symptoms. When symptoms occur, patients complain of mild malaise, itching and burning over the skin, and pain associated with mucosal erosions. Fever, myalgia, arthralgia, and intense headache are rarely present.

Course of Illness

New lesions usually occur over 3- to 5-day periods, but may also erupt over 1–2 weeks. In this "eruptive" phase, lesions may occur in groups. Lesions tend to heal in less than 4 weeks. Lesions do not scar, but may lead to hypo- or hyper-pigmentation.

Complications

Complications in EM are typically minor. Oral involvement may lead to decreased oral intake, which can lead to dehydration. More serious complications such as keratitis, conjunctival scarring, uveitis, or even permanent vision loss, have been reported. Also reported are esophagitis, esophageal strictures, and upper airway lesions leading to pneumonia. Whether or not these more serious complications are truly a result of EM is debatable. Instead, these cases could have been misclassified as the more severe SJS and TEN.

Atypical Presentations

EM lesions are not always classical, and clinical manifestations of EM vary from patient to patient. Atypical lesions are not "targetoid," but instead only have two concentric zones and have areas of palpable, round, edematous lesions with poorly defined borders.

Drug-Induced Erythema Multiforme (DIEM)

Much of the early literature regarding DIEM included sulfonamide-induced disease, which was characterized by large bullae, widespread disease, severe mucosal involvement, fever, and prostration. These reactions were often termed EM major, and are likely better characterized as SJS. A challenge exists when lesions are associated with a drug exposure, and present with targetoid lesions in an atypical pattern, but do not have mucosal involvement or skin sloughing, and thus do not fit the description of SJS. These lesions may be best classified as an EM-like reaction, distinct from classical EM. When these reactions occur, the lesions are often flat atypical two-zoned targets. In addition to atypical skin lesions, DIEM is more likely to have a flu-like prodrome, is more likely to involve mucous membranes, and is less likely to be recurrent.

Mycoplasma pneumoniae-Associated Erythema Multiforme

While *M. pneumoniae* continues to be considered an etiologic agent of EM, the clinical presentation is distinct from that of HAEM (Table 7.1),

Table 7.1 Comparison between HAEM and EM-like drug reactions

	HAEM	DIEM or EM-like drug reactions
Cutaneous findings	Typical presentation with symmetric and acral distribution of raised targetoid lesions	More frequently atypical presentation with macular and atypical targets, trunk more likely to be involved
Prodrome	Absent, or minor	More frequently present, and more severe
Severity	Self-limited and mild	Can become more severe
Mucous membrane involvement	Mostly limited to oral mucosa	More mucous membrane involvement with increased severity
Pathogenesis	Delayed type hypersensitivity with Th1 cells and IFN-γ production	Toxic injury to keratinocytes mediated by TNF-α
Histology	Dermal and epidermal changes as described in text	Similar, but increased keratinocyte necrosis, decreased T cells, and decreased dermal edema
Recurrence	Likely to recur with reactivation of HSV	Less likely to recur

and some authors believe that *M. pneumoniae* causes SJS, but not EM. *M. pneumoniae-associated* disease usually affects children and young adults. *M. pneumoniae*-associated EM is similar to HAEM in that it presents with targetoid lesions roughly half of the time, and that the lesions tend to erupt on the extremities and spread centripetally. In contrast to HAEM, prodromal symptoms are common, and patients have symptoms of fever, chills, sore throat, cough, runny nose, malaise, and myalgia 2 days to 2 weeks prior to rash development. Skin lesions tend to be maculopapular or vesiculobullous, and oral lesions tend to be more pronounced. Other mucosa surfaces are also affected commonly, with reported involvement of the genitalia, urethra, ocular mucosa, and anus. Overall, the disease tends to be more severe than HAEM and more frequently requires hospitalization.

Etiology

Determining the etiology of EM is difficult due to inconsistencies in classification, low prevalence, and underreporting of less serious cases. EM has been linked to many factors including infections, medications, malignancy, autoimmune disease, radiation, immunizations, and menstruation. The majority of EM is caused by infectious agents (90 %), with the herpes simplex virus being most common. *M. pneumoniae* has also been associated with EM, which is particularly important in children. Drug-induced EM has been reported in less than 10 % of cases. The three best-described causes will be further discussed.

Erythema Multiforme Due to Herpes Simplex Virus (HAEM)

The link between herpes simplex virus, whether type 1 or type 2, and EM is well known, with documentation of a relationship dating back over a century. Today, HSV accounts for the vast majority of cases. HAEM, especially reactivation of HSV, tends to follow a mild progression, with characteristic targetoid lesions as described above. Of note, subclinical HSV infection has been associated with EM, and many cases of EM with unknown etiology may be due to such infections. Some rare etiologies of EM such as sunlight, X-ray, tuberculosis, menses, and even certain drugs may cause EM via indirect mechanisms such as reactivating a latent HSV infection. HAEM rarely has systemic symptoms, and mucosal involvement is generally mild and limited to the oral cavity.

Erythema Multiforme Due to Drugs

The literature is full of case reports detailing different drugs with EM-like reactions. To

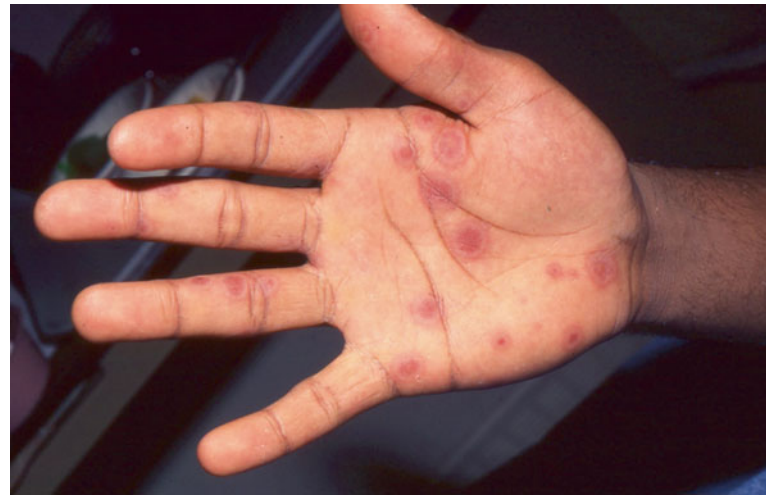

Fig. 7.5 Typical targetoid, or iris, lesions of erythema multiforme on the palm of the same patient as Fig. 7.4 due to ibuprofen

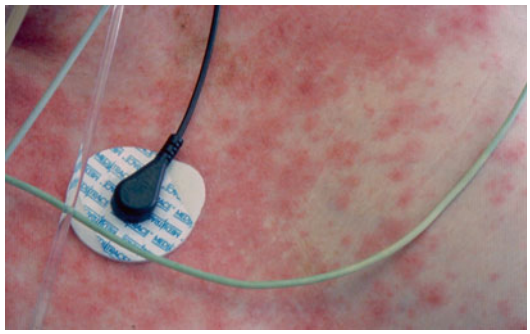

Fig. 7.6 Somewhat atypical targetoid papules and plaques with central darker red papules. This patient was having a erythema-type reaction to carbamazepine

name a few, sulfonamides (trimethoprim, sulfamethoxazole); non-steroidal anti-inflammatories (Fig. 7.5); penicillins; anticonvulsants (barbiturates, carbamazepine, Fig. 7.6); hydantoins; valproic acid; allopurinol; antifungals; oxicam (piroxicam, tenoxicam); imidazole; chlormezanone; systemic corticosteroids; cephalosporins; quinolones; and tetracycline have all been implicated. Newer drugs such as candesartan cilexetil, rofecoxib, metformin, adalimumab, bupropion, and ciprofloxacin have also been associated with EM. Whether these are cases of true EM, or instead are EM-like reactions that belong to different pathologies, is debatable. Attempts over the last few decades have been made to distinguish EM from its imitators, and to elucidate risk factors and etiologic agents. In each of these studies, drugs account for only a small portion of EM cases, and are more frequently associated with more severe disease such as SJS and TEN. Rarely does DIEM present according to von Hebra's original description.

Erythema Multiforme Due to Mycoplasma Pneumonia

An association between *M. pneumoniae* and EM date back to the 1940s and 1950s. During this time, a severe mucocutaneous disease followed many cases of "atypical pneumonia," with some skin lesions resembling EM. Given the significant heterogeneity in defining EM, many cases were classified as either EM major or SJS, which at the time were often considered synonymous. Many documented cases of *M. pneumoniae-associated* EM describe a severe disease that starts with prodromal symptoms and is followed by eruption of lesions on multiple mucosal surfaces, and bullous skin lesions accompanied by malaise and fever. This description is distinct from von Hebra's original description and is more consistent with SJS. The association between SJS and *M. pneumoniae* is well documented, and authors such as Tay et al. concluded that *M. pneumoniae* is associated with SJS, but not EM. Despite these conclusions, many case reports and some clinical trials

continue to implicate *M. pneumoniae* as a cause of EM. The association remains unclear at best, but cases of EM attributed to *M. pneumoniae* may simply represent milder and/or atypical forms of SJS that classification schemes are unable to distinguish.

Other Causes of Erythema Multiforme

Other etiologies of EM are rare, and literature regarding such associations is sparse. The following have been implicated in EM: malignancy (specifically leukemia, lymphoma, gastric adenocarcinoma, renal cell carcinoma, and extrahepatic cholangiocarcinoma); other viral causes such as EBV, CMV, and VZV; bacteria such as *Corynebacterium diphtheria*, hemolytic streptococci, *Legionella pneumophila*, Salmonella, *Mycobacterium leprae* and pneumococcus; autoimmune diseases such as graft-versus-host disease, inflammatory bowel disease, polyarteritis nodosa, sarcoidosis, and systemic lupus erythematosus (Rowell's syndrome); and other factors such as radiation exposure, food additives, chemicals, and immunizations.

Recurrent Erythema Multiforme

In some patients, EM is not an isolated event, and recurrences occur. When recurrent disease is present, patients have an average of six events per year, and an average disease duration of 6–10 years. Recurrent EM is most commonly associated with recurrent HSV infection, with associations ranging from 23 to 100 %, with some authors thinking that true recurrent EM is only caused by HSV. However, most cases of recurrent HSV infection do not lead to EM, and even in patients with recurrent HAEM, lesions do not follow every reactivation of HSV. In addition to HAEM, documented cases of recurrent EM include *M. pneumoniae*, hepatitis C, menses, polymorphic light eruption, complex aphthosis, and foodstuff such as benzoic acid. In certain studies, up to 60 % of cases had no identifiable cause. Other studies have implicated subclinical HSV as the culprit in these "idiopathic" cases.

Persistent Erythema Multiforme

Persistent EM is a rare variant described as the continuous appearance of typical and atypical cutaneous and/or mucosal lesions. Very few cases of persistent EM have been described in the literature. Lesions of persistent EM tend to be papulonecrotic or bullous and to have widespread involvement. Reported etiologies include HSV, Epstein-Bar virus, hepatitis C, influenza virus, cytomegalovirus, inflammatory bowel disease, and various neoplasms.

Pathogenesis

Most literature regarding the pathogenesis of EM is based on research of HAEM. More recently, differing mechanisms have been described for DIEM and HAEM.

Herpes-Induced EM

HAEM is at least in part mediated by delayed-type hypersensitivity, likely via a cell-mediated immune reaction against cells expressing viral antigen, *pol*. The pathogenesis of EM is best studied following cases of recurrent herpes simplex. Several key findings have led to the current theory on the pathogenesis of HAEM. These include the following discoveries: fragmented virus, but not intact virus, is present in HAEM skin lesions; sequences of HSV DNA are expressed in skin lesions, which leads to lesion development; T-helper type 1 (Th1) cells that produce interferon-γ (IFN-γ) are present in lesions; and CD34+ cells, precursors of Langerhans cells in the skin, are thought to carry viral fragments to the skin. The key points in the pathogenesis will now be detailed.

The HSV virus, whether from oral or genital lesions, is transiently present in the blood following a recurrent infection. The virus is then phagocytosed, digested, and fragmented by macrophages and CD34+ cells and then localized to the epidermis, likely due to skin homing receptor cutaneous lymphocyte antigens. The fragmented viral DNA is transferred to keratinocytes, and is localized to the basal and lower spinous cells layers.

E-cadherin and other adhesion molecules are upregulated leading to the binding of HSV-containing Langerhans cells to endothelial cells and accounts for the dermal inflammatory process. The *pol* viral DNA is expressed in the keratinocyte cell layer, which leads to activation of HSV-specific CD4+ T1 helper cells. Cytokines such as interferon-γ (IFN-γ) are produced, which leads to nonspecific inflammatory amplification, characterized by sequestration of lymphocytes, monocytes, and natural killer cells. The outcome of this inflammatory process includes lysis of surrounding keratinocytes, release of cytotoxic factors, keratinocyte growth arrest, and apoptosis.

Genetics

Genetic variation may account for the observation that most patients with recurrent HSV infections do not develop EM. Certain human leukocyte antigen (HLA) subtypes have been associated with increased risk of developing EM. HLA-DQB*0301 is associated with development of HAEM. Recurrent EM has been associated with HLA-A33, HLA-B15, HLA-B35, HLA-B62, and HLA-DR53. Extensive mucosal involvement has been associated with HLA-DQB1*0402.

Drug-Induced EM

Drug-induced EM appears to have a distinct pathogenesis compared to HAEM. Tumor necrosis factor-α (TNF-α), perforin, and granzyme B appear to cause the epidermal destruction seem in DIEM. TNF-α is produced by monocytes/macrophages, as opposed to the Th1 cells of HAEM. IFN-ϒ is notably absent in DIEM. While HAEM is thought to be a form of delayed-type hypersensitivity with CD4 cells, DIEM is thought to be a result of toxic injury and without antigen dependence. Histologically, DIEM is relatively devoid of T-cells, with less inflammation and increased keratinocyte necrosis.

Histology

While the histopathologic findings may not be diagnostic of EM, a compatible histology is helpful for narrowing diagnosis and for ruling out other similar diseases. The histology can change during the course of the lesion and is also dependent on the location of the biopsy. There are three subtypes of lesion: dermal, mixed and epidermal.

The dermal lesions are the earliest changes in EM and are more prominent in biopsy from the periphery of the lesions. Dermal changes consist of endothelial cell swelling, vascular dilation, papillary dermal edema, and perivascular mononuclear cell infiltration.

Epidermal changes develop throughout the course of EM and are most prominent as the disease evolves and in the central, dusky portion of the lesion. Epidermal changes consist of hydropic or liquefactive degeneration of the basal epidermal cells as well as necrosis of individual keratinocytes.

If damage to the dermal-epidermal interface is extensive, a subepidermal blister with a roof of damaged epidermis can form. A mild to moderate lymphohistiocytic infiltrate in a lichenoid pattern can occur at the dermal-epidermal junction. Of note, two features incompatible with EM include a large number of neutrophils in early lesions and a leukocytoclastic vasculitis. Neutrophils can be involved in EM, but they tend to occur in later lesions.

Direct immunofluorescence (DIF) may reveal granular C3 or IgM in the upper dermal blood vessels, granular C3 along the basement membrane, and focal epidermal cells with granular C3 staining. However, these findings are not pathognomonic or diagnostic. The value of DIF is to exclude other diagnoses such as dermatitis herpetiformis and bullous pemphigoid.

The histology of DIEM mostly resembles that of HAEM, but has fewer T-cells, less dermal inflammation, and increased keratinocyte necrosis.

Differential Diagnosis

Urticaria

Urticarial lesions, also known as hives or wheals, are intensely pruritic plaques. While size and shape of the lesions can resemble EM, urticaria can be distinguished on the basis that EM lesions appear within the first 72 h of disease and the

lesions are fixed and can last several days to weeks as opposed to urticarial lesions, which are transient and disappear within 24 h. Urticarial lesions also may continue to appear and disappear over the course of the disease. The central necrosis and duskiness of EM is also helpful in differentiation, as urticaria lesions have a central zone of erythema or normal skin. Histologically, while both may have dermal edema, characteristic epidermal changes of EM are notably absent in urticaria. Angioedema, or coexisting mucosal edema, is common in urticaria.

Stevens-Johnson Syndrome (SJS)

As discussed previously, SJS and EM are now believed to be distinct disorders. SJS is characterized by widespread erythematous or purpuric macules or flat atypical targetoid lesions. SJS more commonly affects the trunk first, and spreads distally. Constitutional symptoms are common and more severe in SJS than EM, and lesions are frequently painful. Mucosal involvement is prevalent and can be severe, and often more than one mucosal surface is involved. Drug exposure causes the majority of SJS. Histology does not adequately distinguish SJS from EM, but SJS may show more extensive epidermal necrosis and fewer inflammatory cells. The distinction between the two diseases is crucial, as SJS has higher morbidity and mortality and can transition to TEN.

Fixed Drug Eruption

Fixed drug eruptions occur 1–2 weeks following the first exposure to a drug, and within 24 h on re-exposure. Similar to EM, fixed drug eruptions present with dusky erythematous plaques with or without central bullae or necrosis. Lesions are typically much fewer in quantity than EM. Histologically, a fixed drug eruption has deeper extension of infiltrate along with prominent pigment incontinence. A thorough drug history is paramount, and treatment involves discontinuation of the drug.

Autoimmune Blistering Diseases

Morphological variants of blistering diseases, such as bullous pemphigoid (BP), paraneoplastic pemphigus (PNP), linear IgA bullous dermatosis (LABD), pemphigus vulgaris (PV), and dermatitis herpetiformis (DH) may resemble the target lesions of EM. Classic presentations of these diseases can be differentiated based on the prominent blistering, however, atypical presentations can be difficult to distinguish from EM. In such cases, histology as well as immunofluorescence can help make the diagnosis. BP is a chronic autoimmune blistering disorder that is associated with basement membrane deposition of IgG and C3 on DIF. Histologically, PNP and EM both show interface dermatitis changes, but PNP also shows acantholysis, which is not present in EM. DIF shows cell surface IgG deposition in PNP and serologically, desmoglein 1, desmoglein 3, and antiplakin antibodies can be seen in PNP but not EM. Pemphigus vulgaris is a chronic, relapsing and remitting disease that presents with multiple shallow, irregular, painful ulcers proceeded by vesicles or bullae. It can be distinguished from EM by the presence of antibodies against desmoglein, DIF with a fish-net appearance, and a positive Nikolsky's sign. DH is associated with gluten enteropathy and demonstrates granular deposition of IgA in the papillary dermis on DIF while LABD (congruent with its name) shows a linear deposition of IgA along the dermal-epidermal junction on DIF.

Sweet's Syndrome

Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, can be paraneoplastic or related to infection. Clinically, erythematous plaques of Sweet's syndrome can resemble EM, although patients with Sweet's syndrome usually appear very ill. The histologic appearance of a dense neutrophilic infiltrate readily distinguishes the two, as neutrophils are a minor and late finding in EM.

Rowell's Syndrome

Rowell's syndrome refers to the presence of both EM-like lesions and lupus erythematosus cutaneous lesions (discoid, subacute cutaneous, or acute cutaneous). Diagnostic criteria include lupus, EM-like lesions, chilblains, positive ANA in a speckled pattern, rheumatoid factor, and SS-A

and SS-B antibodies. Whether Rowell's syndrome-associated EM is truly EM remains under debate.

Acute Hemorrhagic Edema of Infancy (AHEI) (Finkelstein's Disease)

In infants younger than 2 years old, AHEI can resemble EM with circular or targetoid, purpuric, edematous plaques. Targets are typically both three-zoned targets and raised edematous two-zone targets. Histology reveals a lueukocytoclastic vasculitis. AHEI is a benign, self-limited disease, and is pathologically distinct from EM.

Polymorphous Light Eruption

Polymorphous light eruption (PMLE), which occurs following ultraviolet radiation exposure, may mimic lesions of EM. PMLE is characterized by recurrent papulovesicles and plaques. The histology of EM and PMLE can be similar, but PMLE is characterized by dermal edema with a superficial and deep perivascular lymphocytic infiltrate, distinct from the dermal-epidermal interface pattern seen in EM.

Cutaneous Small Vessel Vasculitis (e.g., Urticarial Vasculitis and Henoch-Schönlein Purpura)

Cutaneous vasculitis classically present with palpable purpura, but the lesions may also be targetoid with a raised, dusky, violaceous center and erythematous border. Skin biopsy shows a leukocytoclastic vasculitis and DIF testing can readily distinguish EM from vasculitis.

Workup and Diagnosis

The diagnosis of EM is mostly based on clinical features. The first important clue is the finding of an acute, self-limited or episodic skin disease with the presence of targetoid lesions, raised typical papules, and mucosal involvement that present in an acral distribution. Other clues that point toward the diagnosis of EM include a history of signs and symptoms of an HSV infection. *M. pneumoniae* and recent drug exposure should be considered in EM-like eruptions.

Although biopsy is not specific for EM, the presence of characteristic histology can aid in making the diagnosis, and help rule out other pathologies. There is no distinct pattern of direct immunofluorescence and indirect immunofluorescence in EM, but both can help distinguish autoimmune bullous diseases.

Laboratory values are of limited value as they are non-specific for EM, although erythrocyte sedimentation rate, white blood cell count, and liver function tests may be elevated.

When EM is suspected, patients should be evaluated for common inciting factors. Since EM is most commonly caused by HSV, relevant clinical history such as recent oral or genital lesions should be obtained. Additionally, if oral or genital lesions are present, they should be sampled to assess for the presence of the virus through a Tzanck smear, PCR studies, or viral culture. When subclinical HSV is suspected, serologic testing may be of use. Negative tests for IgM and IgG antibodies exclude HSV as the inciting factor. However, antibody titers are not useful in detecting recurrence of HSV.

In patients with EM with a history of respiratory symptoms, *M. pneumoniae* should be suspected. A chest radiograph, PCR testing of throat swabs, and serologic tests for *M. pneumoniae* should be ordered.

Though most cases of EM do not lead to severe complications, some cases with severe mucosal involvement may lead to inadequate oral intake and dehydration, in which case hospitalization and supportive management may be necessary.

Treatment

Herpes-Associated Erythema Multiforme

Most cases of HAEM are mild and self-limited, and thus, treatment is not necessary. Treatment is usually reserved for severe cases with extensive mucosal involvement as well as recurrent disease, which can also be associated with increased morbidity. The average time between herpes genitalis or labialis episode and onset of EM is 8

days. Once EM eruptions have begun, treatment with antivirals are no longer effective. Treatment should be aimed at symptomatic relief of burning and pruritus, and involves topical corticosteroids and oral antihistamines.

Drug-Induced Erythema Multiforme

The most important step in treating DIEM is to discontinue the inciting agent.

Recurrent Erythema Multiforme

Since most recurrent EM is caused by HSV, first-line therapy generally involves antiviral prophylaxis. Treatment choices include acyclovir, valacyclovir, and famciclovir. Continuous oral therapy, intermittent oral therapy, and topical therapy have been attempted. Topical antiviral therapy was not shown to be effective in treating recurrent EM. While oral antivirals given at the first sign of recurrent HSV infection (intermittent oral therapy), have shown to be somewhat effective, continuous oral therapy, generally for >6 months, achieves disease suppression and can lead to disease remission and is the most effective therapy. Unfortunately, after discontinuation of prophylaxis, many patients who were in remission relapse and require continuation of therapy. Some recurrent EM is resistant to antiviral therapy, and other approaches have been implemented. Other drugs that have been used with some success in treating resistant recurrent EM include azathioprine, dapsone, and mycophenolate mofetil. Other treatments that have been used include immunoglobulin, hydroxycholoroquine, thalidomide, and cyclosporine.

Mucosal Disease

Since mucosal disease is responsible with the majority of morbidity associated with EM, treatment of severe mucosal lesions can be necessary. For mild oral involvement, a combination of viscous lidocaine, diphenhydramine, and aluminum and magnesium hydroxide has been suggested. If oral involvement becomes debilitating, systemic glucocorticoids with doses of prednisone of 40–60 mg per day tapered over 2–4 weeks have been successfully used. This approach has been questioned in all but the most serious cases, as it may increase the risk of recurrence. Ocular involvement requires an immediate referral to an ophthalmologist to prevent complications.

Conclusions

Erythema multiforme is a mild, self-limited disease that characteristically follows HSV infections. Distinguishing EM from its more severe counterparts is crucial, and is based mostly on the clinical presentation of EM. While drugs and many other etiologies have been associated with EM, they likely represent a small fraction of cases.

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Drug-Induced Vasculitis

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Abstract

Drug-induced vasculitis is defined as inflammation of blood vessels due to an adverse effect of a drug. Histologically, vasculitis is defined as an inflammatory cell-mediated infiltration and destruction of blood vessels. Vasculitis can be either primary, as seen in granulomatous polyangiits, or secondary, when associated with drugs, infection, malignancy, or connective tissue disease.

While the exact pathogenesis of drug-induced vasculitis remains unclear, it is strongly believed to be an immune-complex mediated process. Many drugs are associated with vasculitis and nearly every class of drug has been implicated. The most common drugs associated with vasculitis are propylthioruacil, hydralazine, minocycline, allopurinol, D-penicillamine, sulfasalazine, penicillins, cephalosporins and several immunomodulating agents, discussed below. Diagnosis of drug-induced vasculitis is often challenging, as there are no pathognomonic clinical or histological features to distinguish it from other causes of vasculitis. It is also very difficult to prove that an exposure to a drug led to cutaneous vasculitis. Severity of drug-induced vasculitis can range from mild, and self-limiting to severely progressive and even fatal. A high index of suspicion should be maintained for vasculitic lesions that arise in the setting of recent introduction of a new drug. Suspicious agents should be promptly withdrawn, as resolution often occurs soon after discontinuation of the offending drug.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_8

Keywords
Vasculitis • Drug-induced vasculitis cutaneous drug reaction • Leukocytoclastic vasculitis • Anti-neutrophil cytoplasmic autoantibodies (ANCA)

Introduction

Vasculitis is an inflammatory cell-mediated process resulting in the dysfunction and destruction of blood vessels. Vasculitis can be idiopathic, autoimmune-mediated, or precipitated by drugs. Drug-induced vasculitis (DIV) is defined as a vasculitis due to a drug or toxin when other causes have been excluded.

Vasculitis caused by drugs can be limited to the skin (referred to as hypersensitivity vasculitis, cutaneous small vessel vasculitis, or leukocytoclastic vasculitis) or affect multiple organs of the body due to involvement of small and medium-sized muscular arteries. The former is usually a mild and self-limiting illness affecting the skin, while the latter may be a severe and life-threatening disease causing multiple organ failure. The distribution of the antigen responsible for the vasculitis determines the pattern of vessel involvement.

Causal Agents

Many drugs in nearly every drug class have been associated with drug-induced vasculitis. The most commonly cited drugs are hydralazine, propylthiouracil, methimazole, sulfasalazine, minocycline, D-penicillamine, sulfonamides, allopurinol, penicillins, and immunomodulating agents such as tumor necrosis factor alpha, interferon, and granulocyte-macrophage colony stimulating factor (GM-CSF), as noted in the list below. Medications used for the treatment of acne vulgaris, such minocycline and isotretinoin, have also been associated with vasculitis. Anti-thymocyte globulin-induced serum sickness may present with cutaneous leukocytoclastic vasculitis as well (Fig. 8.1).

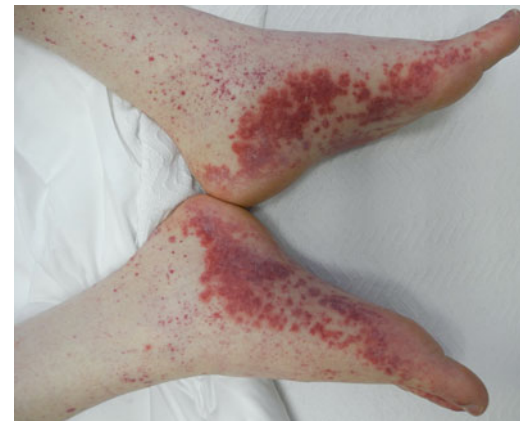

Fig. 8.1 Leukocytoclastic vasculitis secondary to anti-thymocyte globulin in the setting of serum sickness

Drugs Associated with Vasculitis

- Hydralazine
- Minocycline
- Isotretinoin
- Methimazole
- D-penicillamine
- Hydralazine
- Levamisole
- Penicillin
- Cephaolosporins
- Methotrexate
- Cocaine
- Propylthiouracil
- Interferon
- Adalimumab
- Etanercept
- Infliximab
- Sulfasalazine
- Phenytoin
- Allopurinol
- Quinolones
- Granulocyte colony stimulating factor
- Methamphetamine
- Anti-thymocyte globulin

The most frequently cited drugs associated with DIV are those belonging to a subset of drugs associated with anti-neutrophil cytoplasmic autoantibodies (ANCA). ANCA are antibodies to antigens in cytoplasmic granules of neutrophil and monocyte lysosomes with distinct staining patterns. ANCA is usually found in idiopathic vasculitic disorders such as granulomatosis with polyangiitis (GPA), Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MPA). Patients with development of ANCA from drug exposure may present with similar clinical features as patients with idiopathic ANCA-associated disease with associated skin, kidney, and lung involvement. Medications associated with ANCA include propylthioruracil, methimazole, hydralazine, minocycline, sulfasalazine, and monteleukast, as noted in the list below. Minocycline can also cause a severe, ANCA-negative vasculitis that mimics PAN. Propylthiouracil has been associated with ANCA-positive vasculitis more so than methimazole. One study comparing the serological and clinical profiles of patients with ANCA-associated autoimmune disease demonstrated milder disease and lower relapse rates in patients who had ANCA-positive antithyroid medication-induced vasculitis compared to patients with ANCA-positive idiopathic systemic vasculitis.

Drugs Associated with Vasculitis and ANCA

- Hydralazine
- Propylthiouracil
- Methimazole
- Minocycline
- Monteleukast
- Interferon
- Tumor necrosis factor-alpha
- Sulfasalazine
- Cocaine
- Levamisole-tainted cocaine

Illegal drugs have also been associated with drug-induced ANCA vasculitis. The illicit or recreational drugs that have most commonly been associated with vasculitis include the sympathomimetic drugs cocaine, methamphetamine, and 3,4-methylenedioxymethamphetamine ("Ecstasy"). More recently, there have been numerous reports of levamisole-tainted cocaine causing vasculitis and vasculopathy. This combination seems to be especially potent in inducing blood vessel disease, which is contributing to the increased incidence of cocaine-related vasculopathy/vasculitis. It is therefore important for clinicians to screen for substance abuse in patients whose presentation is consistent with DIV.

Clinical Presentation

Patients with drug-induced vasculitis may have similar clinical presentations to patients with idiopathic vasculitis. The skin is the most commonly affected organ in drug-induced vasculitis, and can range from involvement of small vessels (arterioles, capillaries, and venules) to more severe disease affecting small- to medium-sized arteries. Typical skin findings suggestive of small-vessel involvement include palpable purpura, petechiae, erythematous morbilliform eruption, urticaria that leaves behind ecchymosis, and small hemorrhagic vesicles (seen in Fig. 8.1). Small- to medium-sized artery involvement presents as livedo reticularis, inflammatory retiform or stellate purpura, subcutaneous nodules, hemorrhagic bullae, ulcers and, in severe cases, digital gangrene (Figs. 8.2, 8.3, and 8.4). While extremely rare, oral mucous membranes including the hard palate and oropharynx can be affected. Such cases have been reported in propylthiouracil (PTU)-induced ANCA-positive

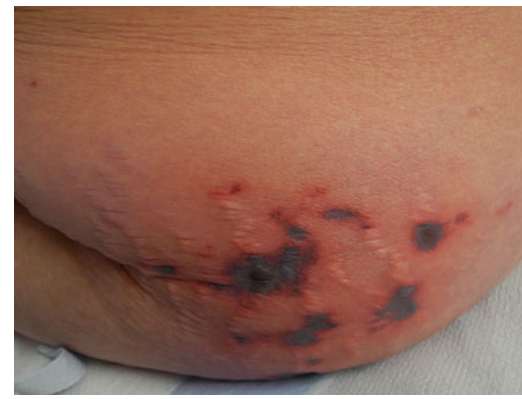

Fig. 8.2 PTU-induced vasculitis necrotic presenting as retiform and stellate purpura, nodules and skin necrosis on the trunk

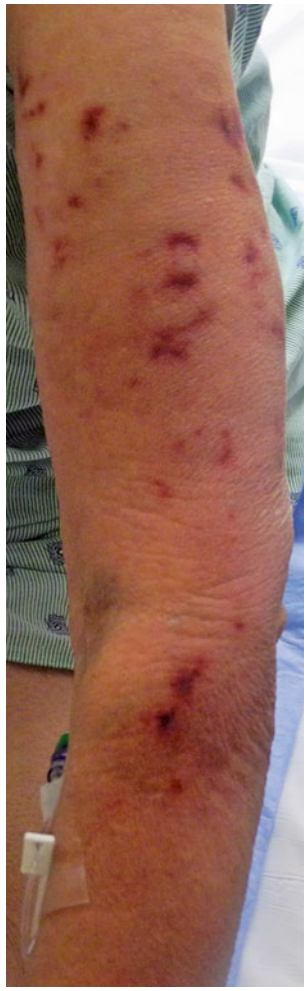

Fig. 8.3 PTU-induced vasculitis presenting as retiform and stellate purpura, nodules and skin necrosis on the upper extremity

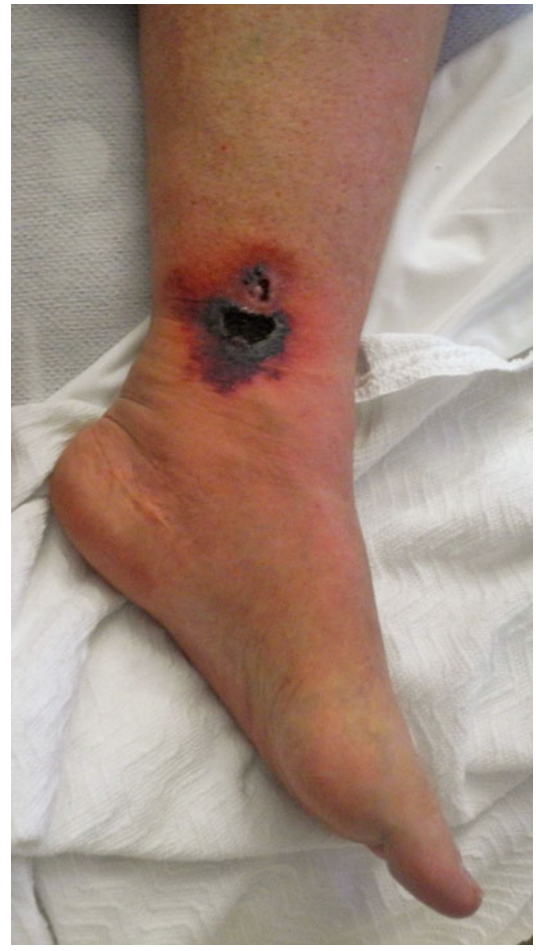

Fig. 8.4 PTU-induced vasculitis presenting as a stellate, purpuric ulcerated plaque

disease (Fig. 8.5). Severity of drug-induced vasculitis can range from mild disease, limited to the skin alone, to a more severe and widespread, systemic disease causing multiple organ failure. While the majority of cases of drug-induced vasculitis tend to involve only the skin, they can be accompanied by systemic symptoms such as fever, malaise, weight loss, and arthralgia. Other organs may also be involved, such as the brain, kidneys, lungs, heart, and liver. After cutaneous involvement, the kidney is the most commonly affected internal organ, with affected patients presenting with hematuria and proteinuria and evidence of glomerulonephritis or interstitial nephritis. Involvement of the lung tends to occur in more severe cases and has been associated with intra-alveolar hemorrhage and acute respiratory distress syndrome (ARDS).

The development of vasculitis typically occurs about 7–10 days after drug exposure, which is believed to correlate with formation of immune complexes and their deposition into blood vessels. Cutaneous lesions in the majority of patients with drug-induced vasculitis usually present on the lower extremities (as shown in Fig. 8.1). Lesions appearing on the trunk, upper extremities, face—including

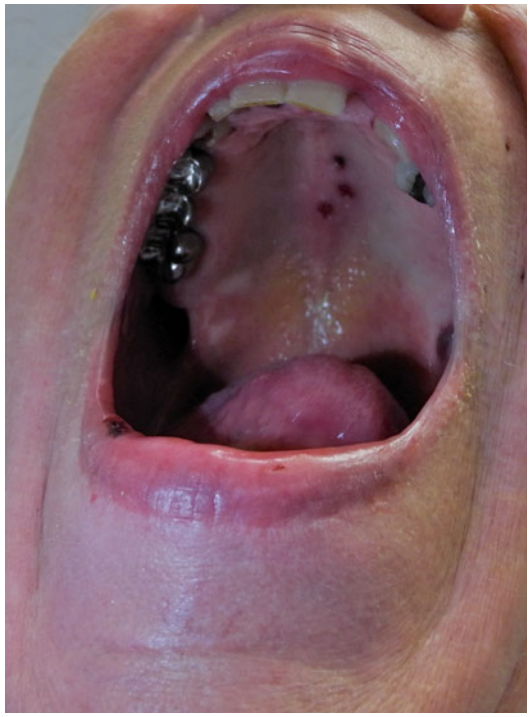

Fig. 8.5 Stellate-shaped oral ulcerations secondary to PTU-induced vasculitis

nose and ears—and neck are reported more often with ANCA-positive DIV or idiopathic vasculitides. Furthermore, patients with systemic disease are more likely to complain of painless lesions and paresthesias, or have cutaneous necrosis.

Minocycline-induced ANCA-positive vasculitis has been associated with several cases of biopsy-proven polyarteritis nodosa (PAN). The majority of cases have occurred in teenagers and young adults treated with minocycline for acne vulgaris. Patients may present with fever, weight loss, arthralgia, and myalgia, with livedo reticularis and tender subcutaneous nodules as the most common skin manifestations. Cases of ANCA-negative PAN have also been reported after minocycline ingestion.

Vasculitis has also been associated with the use of the anti-TNF-alpha agents infliximab, etanercept, and adalimumab. In these cases, the skin is the most affected organ (63 % of cases), presenting as palpable purpura, ulcerations, and

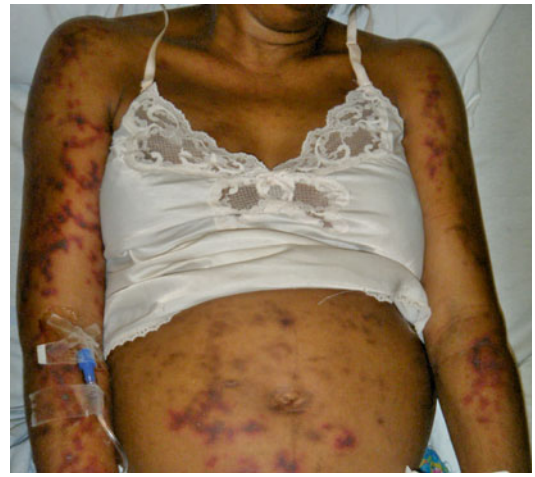

Fig. 8.6 Levamisole-tainted cocaine vasculitis/vasculopathy presenting as diffuse retiform purpura involving the trunk and upper extremities

erythematous macules. The majority of patients found to have leukocytoclastic vasculitis after treatment with anti-TNF-alpha agents have had resolution of their lesions after discontinuation of the drug. However, in patients who were subsequently treated with a different TNF-alpha blocker, there was a higher rate of recurrence of LCV. Golimumab, a TNF-alpha antagonist recently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, has also been associated with luekocytoclastic vasculitis in a recent case report.

As mentioned earlier, levamisole, an antihelminthic drug used in animals, has been linked to cocaine-induced vasculitis. Nearly 70 % of cocaine in the United States is contaminated with levamisole, which serves as a filling agent and is believed to potentiate the effect of cocaine. Levamisole is associated with agranulocytosis and venous thromboembolism, with multiple cutaneous manifestations, including ecchymoses, purpura, hemorrhagic bullae, and in severe cases, necrosis of lips, ears, nose, and cheeks. Patients with levamisole-tainted cocaine vasculopathy often have lesions affecting the lower extremities and the ear, in particular the external pinna (Figs. 8.6, 8.7, and 8.8). Patients are

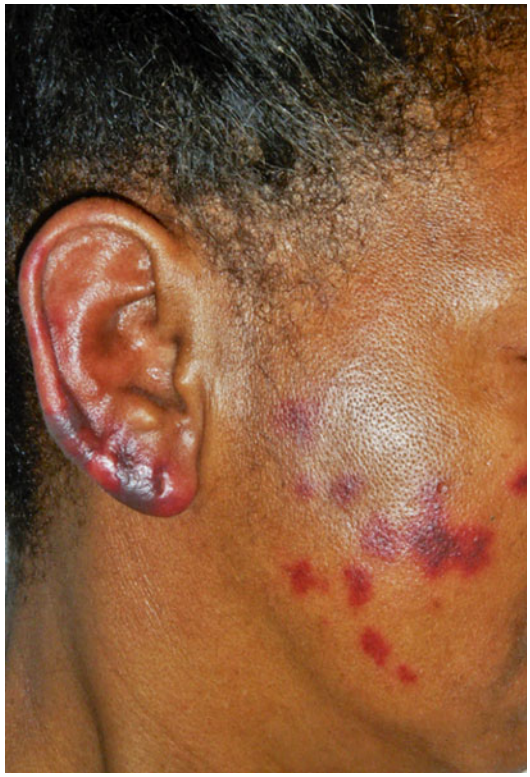

Fig. 8.7 Levamisole-tainted cocaine vasculitis/vasculopathy presenting as diffuse retiform purpura, skin necrosis involving the face and pinna of ears

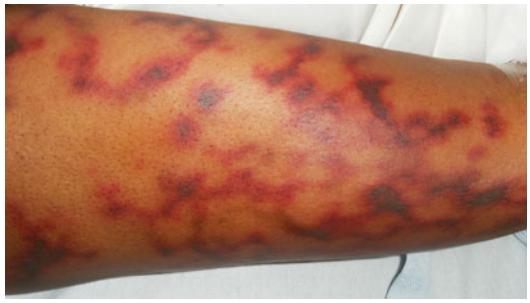

Fig. 8.8 Levamisole-tainted cocaine vasculitis/vasculopathy presenting as diffuse retiform purpura on the upper extremities (close-up view)

usually ANCA positive and may present with renal and pulmonary involvement, with or without vasculitis. Other positive auto-immune serologies have been reported as well including ANA, antiphospholipid antibodies, and rheumatoid factor. In fact, the presence of multiple positive autoimmune antibodies occurring simultaneously in the same patient is strongly suggestive of levamisole-tainted cocaine vasculitis. Patients may have atypical immunofluorescence (IIF) ANCA patterns as well as discordant IF and enzyme-linked immunosorbent assays (ELISA) combinations, such as P-ANCA with anti-PR-3 IgG, and C-ANCA with anti-MPO IgG. The titers of each study may also be inappropriately out of proportion to each other. Histologically, levamisole-adulterated cocaine may present as a leukocytoclastic vasculitis involving small and medium-sized vessels, a thrombotic vasculopathy, or both.

Diagnosis

Distinguishing drug-induced vasculitis from idiopathic vasculitis is particularly challenging. It may also be very difficult to prove that a medication caused a drug reaction. A thorough evaluation to rule out other systemic causes of vasculitis, such as chronic infection, rheumatologic disorders, or malignancy, as well as primary or idiopathic vasculitic syndromes such as GPA and PAN is warranted, as the diagnosis of drug-induced vasculitis is one of exclusion. Excluding other mimickers of drug-induced vasculitis such as antiphospholipid antibody syndrome, warfarin necrosis, calciphylaxis, cholesterol embolization, amyloidosis, purpura fulminans, thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia and thrombosis (HITT) and drug-induced lupus-like disease are essential. A skin biopsy of the affected skin is important in making a definitive diagnosis.

A thorough drug history, with particular attention to those medications ingested in the last 6 months, should be obtained. It is important to perform a comprehensive review of prescribed medications, over-the-counter medications, herbal and nutrition supplements, as well as any illicit drugs taken in the last 6 months. Interestingly, vasculitis has also been reported in patients taking a medication for a long period of

time (months to years), particularly when stopping a chronic medication and then restarting it shortly thereafter. The likelihood of a drug serving as the cause of vasculitis increases if there is a temporal relation of the skin lesions with the initiation of a drug, or if removal of the agent leads to clinical improvement. It is also likely if re-exposure leads to redevelopment of vasculitic lesions and if there is published data showing a strong association between the drug in question and DIV. Additionally, an extensive drug history and physical examination, including detailed descriptions of lesions and photographs of the eruption, should be obtained. Useful laboratory tests include a complete blood count with differential, liver function studies, urinalysis, blood urea nitrogen, creatinine, serum cryoglobulins, serum and urine protein electrophoresis, Hepatitis B and C serologies, ANCA studies for IF and ELISA, ANA with extractable nuclear antigens, rheumatoid factor, and complement levels.

While there are no concrete clinical or histologic findings to confidently diagnose drug-induced vasculitis, there are features of drug-induced vasculitis that can aid in the diagnosis, including rapid or sudden onset and solitary skin involvement, as cutaneous vasculitis is the most common, and at times the only, manifestation of DIV. In one study, it was noted that cutaneous vasculitis is seen in 63 % of drug-induced vasculitis whereas it is present in only 25 % of idiopathic vasculitides. The lesions of DIV are generally localized to the lower extremities and tend to be of the same age, whereas primary vasculitides tend to have lesions of different durations and morphologies occur. Inflammatory retiform purpura, skin necrosis, livedo racemosa, nodules, and ulceration affecting the acral surfaces as well as the face, ears, nose, breasts, and extremities are usually signs of small or medium artery involvement, which can occur in both systemic idiopathic disease and ANCA-positive DIV.

Peripheral blood eosinophilia is more common in vasculitis related to an underlying systemic illness (79 %) compared to vasculitis limited to the skin alone (22 %). Patients with levamisole and thyroid medication-induced disease can also have transient neutropenia or leukopenia than can predispose them to life-threatening infections.

Renal vasculitis is more likely to be found in idiopathic vasculitis (75 % of cases) compared to drug-induced vasculitis (19 % of cases), while arthralgias and skin lesions are more common with drug-induced vasculitis than idiopathic vasculitis.

DIV patients are also more likely to have other positive autoimmune antibodies, including myeloperoxidase-ANCA, antinuclear antibody (ANA), IgM anticardiolipin antibodies, anti-histone antibodies, and low C4 complement levels when compared to those with idiopathic vasculitis. Lastly, patients with idiopathic vasculitis typically produce ANCAs to only one neutrophil antigen, whereas in drug-induced vasculitis, ANCAs are directed to one or more neutrophil cytoplasm antigens, most commonly myeloperoxidase, cathepsin G, lactoferrin, and elastase.

Management

In the majority of cases, vasculitis caused by a drug is self-limiting once the offending agent has been removed. Prompt discontinuation of the suspected drug usually leads to resolution of symptoms within days to weeks. Early detection and removal of the offending agent is critical in decreasing the risk of irreversible organ damage and the morbidity and mortality associated with vasculitis caused by the suspected drug. Sequelae are rare, but when present are usually associated with renal dysfunction in patients who developed glomerulonephritis or acute interstitial nephritis during the course of the illness. Patients found to be ANCA-positive are more likely to have a severe illness, at times necessitating the use of immunosuppressive therapy.

The course of the disease is typically much shorter for drug-induced vasculitis compared to idiopathic forms of vasculitis. Supportive treatment with antihistamines, aspirin, and anti-inflammatory agents can be used for symptoms such as pruritus, myalgias, and arthralgias that

often accompany any form of vasculitis. In patients with extensive involvement and multiple organ involvement, recovery time may be longer. The use of corticosteroids or immunosuppressive agents may be necessary to prevent irreversible organ damage. In patients who develop DIV associated with ANCA, ANCA titers may be used to assess disease severity and monitor response after the drug has been withdrawn. In a study describing a patient who developed ANCA antibodies after exposure to a proton-pump inhibitor, the p-ANCA and MPO-ANCA levels, which were initially positive, became negative after withdrawal of the drug and tapering of prednisone.

For eruptions that do not resolve after removal of the suspected agent, an idiopathic or underlying systemic disorder should be considered. Systemic medications that have been used and shown to help resolution of vasculitis include dapsone, colchicine, methotrexate, azathioprine, cyclophosphamide, and cyclosporine. Plasmapheresis has also been used in severe cases of ANCA-associated DIV when immunosuppression is not possible due to underlying infection. Special care should be taken when using potent therapeutic agents due to their associated toxicities and well-known side effect profiles, and all forms of therapy should be tailored to the severity of organ involvement.

Histopathology

The skin lesions of vasculitis exhibit a pattern of perivascular neutrophils on histology, which is termed fibrinoid necrosis. Microscopically, lesions of DIV show a pattern of **i**nflammation of small vessels, particularly post-capillary venules. However, involvement of small- and medium-sized arteries can occur, especially in ANCA-associated disease. These findings are often grouped under the histological term leukocytoclastic vasculitis. In such specimens, fibrin deposits, neutrophilic infiltrate, and hemorrhage are observed within the vessel wall. Two patterns have been described, including mononuclear cell dominant versus polymorphonuclear cell dominant. The latter type can be necrotizing or non-necrotizing. The histologic findings in vasculitic lesions caused by drugs cannot be differentiated from other causes of vasculitis. Occasionally, ANCA-associated DIV may demonstrate both leukocytoclastic vasculitis and thrombotic vasculopathy.

Pathogenesis

The exact mechanism by which drugs cause vasculitis remains unknown. However, an immunopathogenic process appears to be playing a major role. It is believed that drugs serve as haptens and trigger an immune response mediated by the formation and deposition of immune complexes (typically IgG, IgA, or IgM) complement and fibrin on blood vessel walls, which can be detected under direct immunofluorescence. The process appears to involve the release of activated anaphylatoxins C3a and C5a, which leads to the recruitment of inflammatory mediators such as neutrophils, mast cells, lymphocytes, and macrophages, as well as adhesion molecules, such as intracellular adhesion molecule-1, P-selectin, and E-selectin. Complement activation following immune complex deposition triggers the production of tumor necrosis factor (TNF)-alpha, interferon gamma, and multiple cytokines (IL-1b, Il-2, IL-6, and IL-8), which further propagate the infiltration of inflammatory cells, leading to vascular tissue damage.

In patients who develop drug-induced vasculitis in the setting of ANCA, the underlying pathogenesis is believed to occur through an ANCA-related activation of inflammatory cells and the apoptosis of neutrophils, which lead to the release of pro-inflammatory cytokines, propagating further inflammation and endothelial cell damage. The burst in cytokines and the ensuing reactive oxygen species that are produced in turn lead to the classic destruction of vessel walls and the histologic pattern of fibrinoid necrosis seen on histology.

There have been no prospective or longitudinal studies to determine the prevalence of drug-induced vasculitis. Based on the existing

literature, drug-induced vasculitis appears to occur more often in females than in males, and in young adult women, possibly reflecting the increased incidence of thyroid disease in this population. Another risk factor for drug-induced vasculitis is the ingestion of a medication that has been associated with ANCA positive or negative vasculitis, as noted in the lists earlier in this chapter.

Conclusions

Drug-induced vasculitis is a common cause of vasculitis and is likely mediated by immune complex and complement deposition, with subsequent inflammation and destruction of small- to medium-sized blood vessels. Showing causality between a drug and vasculitis is extremely difficult, and diagnosis remains one of exclusion. Patients with a suspected drug-induced vasculitis should undergo a comprehensive evaluation for systemic causes of vasculitis, including infection, connective tissue disorders, malignancy, and idiopathic vasculitis. A thorough history, physical examination, screening laboratory tests, and skin biopsies should be obtained. The most common agents implicated include propylthioruacil, hydralazine, minocycline, allopurinol, sulfasalazine, D-penicillamine, penicillins, cephalosporins, and several immunomodulating agents. Illegal drugs such as cocaine, levamisole-tainted cocaine, and methamphetamines have been associated with the development of drug-induced vasculitis, and therefore a thorough history of illicit drug use should be obtained. ANCA-associated DIV is associated with the use of anti-thyroid medications, hydralazine, minocycline, and immunomodulating agents, and may present with a more severe illness. The severity of DIV ranges from mild to life-threatening, with management tailored to the severity of the presentation. Withdrawal of the suspected agent should lead to resolution in days to weeks.

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Pigment Changes and Drug Reactions

9

Shinjita Das and A. Shadi Kourosh

Abstract

Medications have long been known to cause pigmentary changes of the skin. While this frequently occurs as post-inflammatory changes of a resolving drug-induced rash, medications can also directly promote dyspigmentation through stimulation of melanin production and/or deposition of drug (or drug metabolite) within the skin. Medications can also cause hypo- or depigmentation. Drug-induced pigmentary changes depend on factors such as the particular drug (or heavy metal) and level of deposition or melanocyte stimulation (or inhibition of melanogenesis). Drug-induced dyschromias have historically been categorized in a medication-class based manner. Because the clinician is generally faced with a patient whose chief complaint is dyspigmentation (which comes in varying shades), we propose a color-based approach for understanding drug-induced dyschromias.

Keywords

Drug or medication-induced hyperpigmentation • Hypopigmentation • Depigmentation • Discoloration • Dyspigmentation • Leukoderma • Poliosis

Introduction

Skin dyspigmentation has a wide range of etiologies. While intrinsic conditions (such as melasma, metabolic or nutritional derangements, and inflammatory disorders) often cause hyperpigmentation, extrinsic sources must be entertained as potential culprits when a patient presents with chief complaint of skin discoloration. The mechanisms by which exogenous agents can induce hyperpigmen-

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_9

tation include increase in melanin production (by existing melanocytes or through melanocyte proliferation) and/or deposition of drug or metabolite within the epidermis or dermis. Epidermal melanin deposition will be perceived as brown, while dermal pigment or drug deposition will appear blue-gray to blue-black pigmentation due to the light-scattering phenomenon known as the Tyndall effect. For comparison, the blue-gray pigmentation appreciated with dermal melanocytosis and superficial placement of dermal fillers are also the result of the Tyndall effect. While hyperpigmentation is the most common form of drug-induced dyschromia, clinicians should be aware of the possibility for certain medications to induce hypo- or depigmentation (leukoderma or poliosis).

During the evaluation of a patient with cutaneous dyschromia, the possibility of a drug-induced etiology may be more apparent if the patient is currently using the offending agent. However, if the patient is no longer on the culprit medication, a thorough history and physical examination is essential for correct diagnosis, treatment, and counseling. We suggest the following approach to a patient with dyspigmentation:

1. Physical examination–emphasis on colors seen, distribution (e.g. photo-exposed vs. non-photo-exposed), extent of involvement (localized vs generalized), and involvement of hair, nails, or mucous membranes.
2. Past medical history–emphasis on determining history of cancer, rheumatologic disorders, endocrinologic disorders, cardiac diseases, HIV, Hansen's disease, and psychiatric disorders. This information not only offers the clinician clues about medications that are potentially culprits in pigmentary change, but also informs about potential effects on drug metabolism.
3. Medication history–both past and present. Note dosing, duration of treatment, and concomitant sun exposure while on the suspected medications.

Since patients generally present with complaints of skin discoloration (without necessarily realizing that a medication could be the culprit), the clinician must be able to discern the various shades of hyperpigmentation and maintain drug-induced etiologies on his or her differential. In order to facilitate an appreciation for the subtleties in drug-induced pigmentary changes, we thus organize the following sections by color.

Drug-Induced Pigment Changes Based on Color

White Dyspigmentation (Leukoderma)

Drug-induced skin hypo- or depigmentation has been associated with a number of different medications, both topical (most commonly) and systemic, and is generally caused by direct melanocyte destruction. The clinical changes are generally noted months after initiation of treatment and, in the case of depigmentation, histology is identical to idiopathic vitiligo with absence of melanocytes. In the case of hypopigmentation, there may be no histologic changes, as the defect is at the level of melanogenesis. Skin will typically repigment after discontinuation of the culprit, though this can take years and be incomplete. Among patients with underlying vitiligo or genetic predisposition (based on family history), superimposed drug-induced leukoderma tends to have a lower rate of repigmentation.

Topical Agents That Can Cause Leukoderma

Occupational and cosmetic exposures are the most frequent sources of this form of dyspigmentation. Most patients who develop contact leukoderma do not have a personal history of vitiligo, but a recent epidemiologic study demonstrated that these patients may actually have a family history of vitiligo, thus suggesting a genetic predisposition. The patient with suspected chemical leukoderma will present with acquired well-demarcated depigmented macules or patches (sometimes preceded by erythema) within sites of repeated exposure to a particular chemical. The most commonly involved sites are the face, hands, and feet, though patients may develop

Table 9.1 Agents that cause contact leukoderma

Most potent phenol and catechol derivatives	Non-phenolic/catecholic agents
Hydroquinone	Mercury
Monobenzyl ether of hydroquinone	Arsenic
p-tert-Butylchatechol	Cinnamic aldehyde
p-tert-Butylphenol	*p*-phenylenediamine (PPD)
p-tert-Amylphenol	Benzyl alcohol
–	Azelaic acid
–	Corticosteroids
–	Physostigmine
–	Chloroquine
–	Fluphenazine

leukoderma at sites distant from the primary exposure. These patches can be distinguished from idiopathic vitiligo by the appearance of areas of satellite depigmentation. However, the hypopigmented macules of contact leukoderma can be difficult to distinguish from those of idiopathic guttate hypomelanosis and tuberous sclerosis, thus emphasizing the importance of obtaining a thorough history.

The underlying agents of chemical leukoderma are aromatic or aliphatic derivatives of phenols and catechols, which are structurally similar to tyrosine. They are converted by tyrosinase-related protein 1 to reactive oxygen species that are destructive to melanocytes. The most potent include monobenzylether of hydroquinone, hydroquinone, *p-tert*-Butylcatechol, *p-tert*-Butylphenol, *p-tert*-Amylphenol. Some non-phenolic/catecholic agents associated with chemical leukoderma include mercury, arsenic, cinnamic aldehyde, *p*-phenylenediamine (PPD), benzyl alcohol, azelaic acid, corticosteroids, physostigmine, chloroquine, and fluphenazine (Table 9.1).

While contact leukoderma is classically associated with industrial materials, there are a number of commonly encountered products that can cause leukoderma. Phenols and catechols have been identified in commonly encountered products, such as deodorants, detergents, latex gloves, adhesives, insecticides, disinfectants, perfumes, varnish resins, photographic chemicals, rubber sandals, and paints. PPD, found commonly in hair dyes, is the most common cause of contact leukoderma from cosmetics. While it classically affects the scalp/face of patients exposed to hair dyes, it can also be an occupational exposure in hairstylists. More recently, synthetic black-henna tattoos (which are formulated with PPD) have been associated with contact leukoderma. PPD found in black socks and shoes can cause leukoderma of the feet. Azo dyes in eyeliners, lipliners, and lipsticks have also been implicated in contact leukoderma.

Unintentional Leukoderma from Topical Prescription Medications

Imiquimod is commonly prescribed for dermatologic conditions such as warts and non-melanoma skin cancers. There are reports in the dermatology literature of imiquimod inducing vitiligo-like skin hypopigmentation in patients treated for superficial basal cell carcinoma as well as from treatment of genital warts. It is unclear if the pigmentary changes are due to benzyl alcohol within the vehicle (previously reported cause of leukoderma) or T-cell mediated cytotoxicity toward melanocytes. The effect seems to be persistent in follow-up as long as 18 months after discontinuation of imiquimod.

Topical corticosteroids are a mainstay in the treatment of dermatologic conditions. The clinician should remain vigilant of the multiple cutaneous side effects of topical corticosteroids, including epidermal atrophy and skin hypopigmentation. There have been reports of streaks of linear hypopigmentation after unintentional administration of intralesional corticosteroids into veins during cutaneous injections.

Intentional Leukoderma from Prescription Medications

Cultural fascination with skin lightening dates back to ancient times. Arsenic and mercury were used in creams for bleaching skin, and arsenic was used in face powders by European aristocrats in 1400 AD. While the toxicity of these heavy metals has prompted elimination from skin bleaching creams, other agents have been formulated for their depigmenting properties.

Hydroquinone (1,4-dihydroxybenzene) is found in both over-the-counter and prescription

skin-lightening agents. It causes oxidation of melanin, tyrosinase, and phenol oxidases into reactive species (semiquinones and quinones) that prevent melanogenesis by inhibition of tyrosinase. Over-the-counter skin bleaching creams usually contain 2 % hydroquinone, while prescription strength can range from 3 to 4 %. A number of over-the-counter topicals that are not necessarily marketed as skin-bleaching creams may contain hydroquinone, and can thus cause unwanted leukoderma. Chronic use of hydroquinone (usually 6–8 % formulations) can cause paradoxical hyperpigmentation in the form of exogenous ochronosis (discussed in a later section). Monobenzylether of hydroquinone (monobenzone, 4-(benzyloxy) phenol) is used for permanent depigmentation in patients with extensive vitiligo of greater than 50 % body surface area.

Systemic Medications That Can Cause Leukoderma

Several medications have been implicated in drug-induced leukoderma. Photo-exposed sites tend to be preferentially affected.

Tyrosine kinase inhibitors have been developed for the treatment of many malignancies, including chronic myelogenous leukemia and gastrointestinal stromal tumors (imatinib); metastatic renal cell carcinoma (sunitinib); and non-small cell lung cancers (gefitinib, a single tyrosine kinase inhibitor). Depigmentation results from inhibition of c-kit, a tyrosine protein kinase involved in melanocyte development. Imatinib can cause localized or widespread hypo- or depigmentation in darker-skinned patients. Much less commonly, it can cause hyperpigmentation of the skin, hair, nails, and oral mucosa. Sunitinib has been reported to cause early facial depigmentation in a patient with no personal or family history of vitiligo and has also been associated with intermittent leukotrichia. Gefitinib has recently been reported to induce leukoderma in a patient undergoing treatment for metastatic squamous cell carcinoma of the parotid gland.

Methylphenidate applied as a topical patch for the treatment of attention-deficit-hyperactivity disorder has been associated with application-related contact dermatitis, urticaria, and hair loss. It has recently been implicated in contact leukoderma (confirmed by Wood's lamp examination and biopsy) at sites of application of the methylphenidate patch. It is unclear whether the true culprit was the laminate film (which contains polyester/ethylene vinyl acetate), adhesive (acrylic or silicone), or the active agent methylphenidate itself. It was not clear in this study whether there was any spontaneous repigmentation after discontinuation of the methylphenidate patch.

Other medications associated with cutaneous hypopigmentation include clonidine, chloroquine, minoxidil, botulinum toxin, and thiotepa.

Poliosis or Leukotrichia Caused By Medications

Poliosis circumscripta (patch of white hair among a group of otherwise normal follicles) is generally associated with genetic syndromes, such as piebaldism, Waardenburg syndrome, and tuberous sclerosis. Though very rare, it bears mention that several topical and systemic medications have been reported to cause poliosis.

Topical Agents Associated with Poliosis

Chloramphenicol (topical antibiotic) has been associated with whitening of eyelashes and periorbital cutaneous hypopigmentation following allergic contact dermatitis to the agent in a patient who had undergone surgery for eyelid ptosis. The proposed mechanism of the pigmentary changes was attributed to T-cell mediated hypersensitivity that caused selective loss of either melanin or melanocytes. In this case, the poliosis and hypopigmentation persisted at 9-month follow-up.

Imiquimod can induce leukoderma (see above) as well as poliosis. While unclear, purported mechanisms include the possibility of benzyl alcohol (fragrance preservative), induced chemical leukoderma, or activation of cytotoxic T-cells that destroy melanocytes.

Prostaglandin $f_{2\alpha}$ analogs, such as latanoprost, travaprost, and bimatoprost, are used topically in the treatment of glaucoma. They have been

reported to cause whitening of a few eyelashes scattered among normal-colored lashes. They are thought to limit melanogenesis via tyrosinase inhibition. It is unclear how long the effect persists, as one report demonstrated near complete repigmentation within 10 months after the medication was discontinued, and another report saw persistent poliosis at 2 months follow-up of 7 patients. This paradoxical poliosis is of particular interest to the dermatologist, since bimatoprost is prescribed to promote hypertrichosis and darkening of lashes and has been noted to cause darkening of the iris.

Systemic Medications Associated with Poliosis

Acitretin is FDA-approved for the treatment of psoriasis, but off-label uses include treatment of various disorders of keratinization, such as Darier's disease, pityriasis rubra pilaris, keratodermas, and diseases on the ichthyosis spectrum. It is well known to induce alopecia but was recently reported to cause diffuse poliosis concurrently with alopecia of the scalp and body. The patient's hair regained normal pigmentation after cessation of the medication.

Cetuximab, an epidermal growth factor receptor inhibitor used in the treatment of metastatic colorectal cancer and head/neck squamous cell carcinomas, has been implicated in numerous cutaneous adverse effects. Recently, it was associated with poliosis of the eyelashes in conjunction with trichomegaly in a patient with metastatic colorectal cancer. When the medication was discontinued due to disease progression, the patient's poliosis resolved within a month. The mechanism of poliosis is not understood.

Chloroquine is classically associated with blue-gray hyperpigmentation of the skin. However, there are reports associating this medication with hypopigmentation of hair in blondes and red-heads and even hypopigmentation of freckles. Sunitinib has been associated with intermittent leukotrichia following rounds of treatment (with repigmentation in between treatments). It also causes leukoderma (see above).

Yellow, Orange, and Red Dyspigmentation

Systemic Medications That Cause Yellow, Orange, or Red Dyspigmentation

Quinacrine (mepacrine) is an antimalarial agent for the treatment of lupus erythematosus and is generally added onto either hydroxychloroquine or chloroquine to avoid the theoretical additive rentinal toxicity of the latter two medications and to improve efficacy. Chronic ingestion can cause yellow to yellow-brown discoloration of the skin, sclera, and nails that mimics jaundice. Histologically, yellow-brown pigment within histiocytes can be seen throughout the dermis. The dyspigmentation is short-lived, often resolving within a few months after discontinuation of the medication. This dyspigmentation will not be apparent in darker-skinned individuals.

Multikinase inhibitors sorafenib and sunitinib have been reported to cause deep yellow dyspigmentation diffusely in patients as early as the first few weeks of treatment. Notably, sclerae and mucous membranes are spared, and the discoloration resolves upon discontinuation of the medications. Sorafenib is approved for the treatment of metastatic renal cell carcinoma, unresectable hepatocellular carcinoma, and radioactive iodine-resistant thyroid cancer. Sunitinib is approved for GI stromal tumors, metastatic renal cell carcinoma, and pancreatic neuroendocrine tumors.

Clofazimine is FDA-approved for the treatment of leprosy, though its anti-inflammatory properties are harnessed in off-label treatment of several inflammatory and granulomatous skin diseases. When this deep red-to-orange colored lipophilic riminophenazine dye localizes to the fat, it can cause orange-red dyspigmentation of the skin, conjunctivae, and body fluids. This early discoloration can start within a couple of weeks of medication initiation and resolves within months after discontinuation of treatment. With longer duration of treatment, patients can develop violet-brown to blue-gray discoloration of lesional skin.

Sunless-Tanning Agents That Can Cause Orange Discoloration

Canthaxanthin is a synthetic carotenoid that, when combined with beta-carotene, produces a color that resembles a natural tan (golden-orange color) upon deposition within the subcutaneous fat. In addition, this pill causes stool to become a deep red, imparts an orange hue to plasma, and causes deposits within the retina. It has been associated with both liver and retinal damage.

Dihydroxyacetone is the active ingredient in sunless tanning products. It reacts with free amino acids in sweat and keratin to produce a brown color called melanoidin, which resembles a suntan in people of fair skin types. Dermatologists should remind their patients to apply sunscreens after using self-tanning creams and lotions, as they do not confer any degree of photoprotection.

Melanocyte-stimulating hormones (MSH) are a class of peptide hormones that stimulate skin and hair melanogenesis via stimulation of melanocortin receptors. Synthetic analogs of α-MSH have been developed for the purpose of photoprotection. These include afamelanotide (melanotan) and melanotan II. The former seems to decrease photosensitivity in patients with solar urticaria and erythropoietic porphyria, and afamelanotide is already prescribed in Italy and Switzerland for patients with erythropoietic protoporphyria. It has not yet gained FDA approval in the United States. Afamelanotide with narrowband UVB phototherapy seems to be a promising new treatment approach for vitiligo.

Dietary Intake That Can Cause Orange Discoloration

Carotenemia presents with a yellow-orange dyspigmentation of the skin due to excessive consumption of carotene-containing foods (carrots, squash, pumpkin, yellow turnips, sweet potatoes, peaches, apricots, papayas, mangoes, and egg yolk). Carotene is excreted through the liver and epidermis. During times of heavy excretion, the stratum corneum can reabsorb carotene, thus explaining the prominent pigmentation on the palms and soles, which bear thicker stratum corneum. Other sites include areas of pressure overlying joints (elbows, knees, knuckles, and ankles), and face (nasolabial grooves, upper eyelids). Patients with hypothyroidism and eating disorders can also present with carotenemia. Patients of darker skin types may only present with pigmentation of the palms and soles. Importantly, patients are not pruritic, have no involvement of the sclerae and mucous membranes, and have normal-colored urine and stool, thus differentiating carotenemia from jaundice. Carotenemia can also lead to xanthochromia of cerebrospinal fluid. Lycopenemia presents as orange-yellow discoloration that occurs from over-consumption of lycopene, a red carotenoid found in fruits and vegetables, such as tomatoes, beats, chili beans, and berries. Once patients reduce their dietary intake of lycopene-containing foods, their discoloration gradually resolves over the ensuing weeks.

Green Dyspigmentation

Copper is well-known to cause blue-green dyspigmentation of skin, hair, and nails. There has been a report of a green dyschromia of multiple seborrheic keratoses in a patient who swam regularly in a pool that had copper concentration double the levels approved by the U.S. Environmental Protection Agency. This dyspigmentation quickly resolved after the patient stopped swimming in the pool. Extended exposure to chlorine can cause green discoloration of light-colored hair.

Bronze Dyspigmentation

Arsenic is a ubiquitous heavy metal used in the production of numerous commercial products, such as pesticides, herbicides, insecticides, feed additives, and wood preservatives. Globally, the most common source of arsenic exposure is through contaminated well- and groundwater. Cutaneous manifestations of arsenic exposure occur after long-term exposure, when skin levels are greater than 200 mcg/L. The lipid-soluble trivalent form absorbs through the skin and can deposit within the epidermis and dermis as well

as stimulate epidermal melanin synthesis. Patients present with non-photo-distributed bronze hyperpigmentation, particularly on the trunk, with accentuation of the folds. Some patients can develop diffuse hyperpigmentation or melanotic macules. Arsenic can also deposit within the nail bed and appear as transverse white bands (Mee's lines, which can also be seen with thallium deposition).

Iron salts can cause permanent hyperpigmentation at sites of intravenous, intramuscular, or topical administration (the latter with Monsel's solution, ferric subsulfate, which is used to attain superficial wound hemostasis). The genetic iron-overload condition hemochromatosis can cause generalized bronze hyperpigmentation. Histology will reveal pigment bound to collagen fibers and deposition within dermal macrophages. This results in a reddish-brown, bronze, or blue-gray hyperpigmentation (Fig. 9.1). While the hyperpigmentation is generally thought to be permanent, there is a recent report of Monsel solution-induced facial hyperpigmentation that improved over 20 months with adapalene 0.1 % cream.

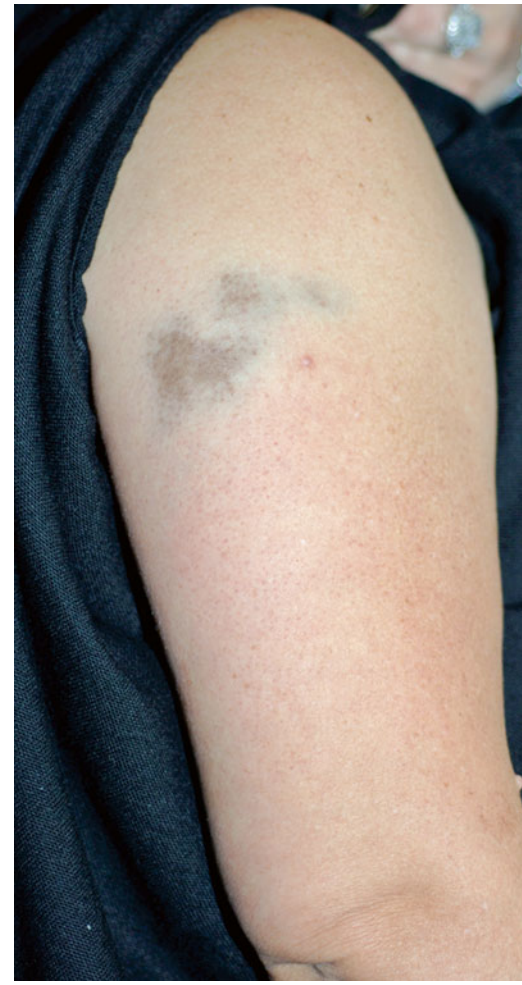


Fig. 9.1 Gray-blue/tan dyspigmentation on the right upper arm following administration of intramuscular iron replacement in an anemic 47-year-old woman. Histology revealed iron deposition throughout the dermis (Courtesy of Dr. Richard A. Johnson, MD (Boston, MA))

Brown Dyspigmentation

Table 9.2 summarizes drug-induced brown dyspigmentation. Oral contraceptives can cause hyperpigmentation of the nipples, stimulate generation of new melanocytic nevi, and cause melasma. Histologically there are greater numbers of melanocytes and increase in melanin synthesis. They are also associated with fixed drug eruptions (see below).

Zidovudine (AZT), a nucleoside reverse transcriptase inhibitor for HIV treatment, is classically associated with longitudinal melanonychia. However, it can also cause diffuse mucocutaneous hyperpigmentation, particularly in patients of darker skin types. There can be accentuation in photo-exposed areas. Histologically, there is increased melanin in macrophages within the epidermis and dermis. This temporary discoloration will fade gradually after discontinuation of AZT.

Hydroquinone, which is used as a topical bleaching agent, can cause an irritant dermatitis that leads to post-inflammatory hyperpigmentation. Prolonged use of a 6–8 % formulation can cause paradoxical hyperpigmentation in the form of exogenous ochronosis. This is characterized by blue-black hyperpigmentation, and histologically shows yellow-brown irregularly shaped fragments within the dermis.

Imatinib can rarely cause hyperpigmentation, though hypo- or depigmentation are far more common pigmentary changes. Repigmentation of gray hair can also be seen, as can melanonychia and oral mucosal dyspigmentation.

Table 9.2 Drug-induced brown dyspigmentation

Medication	Indication	Sites	Comments
Hydroquinone	Skin bleaching	Sites of application	Can cause irritant dermatitis, exogenous ochronosis (blue-black hyperpigmentation)
Imatinib	Chronic myelogenous leukemia	Oral mucosa, nails, hair	Usually leukoderma; can see repigmentation of gray hairs, melanonychia
Oral contraceptives		Face, nipples	Melasma, stimulate production of new melanocytic nevi
Psoralens	PUVA (psoriasis, vitiligo, mycosis fungoides, etc.) Furocoumarin exposure through fruit/vegetables/ plants	Photo-exposed	Also phytophotodermatitis
Zidovudine	HIV	Skin, nails, mucosa; possible accentuation in photo-exposed sites	Longitudinal melanonychia; hyperpigmentation more prominent in darker skin types
Chemotherapy			
Bleomycin	Hodgkin's disease, testicular carcinoma, pancreatic cancer, head/neck squamous cell carcinoma	Sites of scratching, joints, pressure	Flagellate hyperpigmentation
Busulfan	Chronic myelogenous leukemia; conditioning regimen for SCT	Face, chest, forearms, abdomen	Negative iron stains
Carmustine	Brain tumors, multiple myeloma, lymphoma, off-label mycosis fungoides	–	Applied topically for MF
Cyclophosphamide	Off-label JIA, lupus neprhritis	Skin and mucosa (nails, palmoplantar, teeth)	–
Dactinomycin	Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma, gestational trophoblastic neoplasia, malignant hydatidiform mole	Face	–
Daunorubicin	Leukemia, lymphoma, breast, uterine, ovarian, lung cancers	Photo-exposed	–
Doxorubicin	Leukemia, lymphoma, breast, uterine, ovarian, lung cancers	Palmoplantar, small joints hands	–
Fluorouracil	Solid tumors	Photo-exposed Overlying veins	Photosensitive eruption; supravenous serpentine hyperpigmentation
Hydroxyurea	Hematologic malignancies, sickle cell anemia, off-label for derm	Back, sites of pressure	Also lichenoid drug eruption
Methotrexate	Oncology Rheumatology Dermatology	Photo-exposed	UV recall dermatitis
Nitrogen mustard (meclorethamine)	Mycosis fungoides (topical)	Lesional skin	–

Psoralens can cause generalized brown dyschromia after UVA exposure (oral psoralens, PUVA) or linear/circumscribed hyperpigmentation after topical psoralen application (or in the form of phytophotodermatitis). On skin biopsy, there is increased number of follicular melanocytes and increased melanin. Similar reactions may be seen with other plants and herbal supplements that contain furocoumarins, such as limes, celery, fennel, and parsnip.

Unintentional skin hyperpigmentation can result from the use of cosmetics. A classic example is Riehl melanosis, a photoallergic contact dermatitis to cosmetic agents that contain fragrances and essential oils.

Chemotherapeutic Agents That Cause Brown Hyperpigmentation

Nitrogen mustard (mechlorethamine) applied topically for the treatment of mycosis fungoide can cause a diffuse hyperpigmentation, with accentuation of lesional skin. Pathology will show keratinocytes with disaggregated melanosomes and increased melanocytes.

Methotrexate is used for treatment applications in oncology, rheumatology, and dermatology. It can cause not only hyperpigmentation in photo-exposed areas, but also a photosensitive eruption that resolves with temporary post-inflammatory hyperpigmentation from a photosensitivity eruption. Methotrexate is also implicated in photo-recall type reactions. This can be a delayed response if high-dose methotrexate is given after exposure.

Bleomycin is a glycopeptide antibiotic that inhibits DNA, RNA, and protein synthesis. It is used in the treatment of a number of cancers, including Hodgkin's disease, testicular carcinoma, pancreatic cancer, and squamous cell carcinoma of the head and neck. Bleomycin causes a brown hyperpigmentation with unique flagellate appearance (thought to be the result of minor trauma, such as scratching). There can also be hyperpigmentation at sites of pressure and over joints. Histologically, a normal number of melanocytes but increased epidermal melanin is seen. While docetaxel, shiitake mushrooms, dermatomyositis, and adult-onset Still's disease are also associated with flagellate erythema, hyperpigmentation was considered unique to bleomycin until a recent report of bendamustine-induced flagellate hyperpigmentation in a patient undergoing treatment for chronic lymphocytic leukemia.

Busulfan is an alkylating agent used for the treatment of chronic myelogenous leukemia and as part of conditioning regimens for stem cell transplantation. It can cause widespread hyperpigmentation (particularly on the face, chest, forearms, and abdomen) that mimics Addison's disease but with notable sparing of palmar creases. The dyschromia resolves within months after stopping the medication and will recur with re-exposure. Histology reveals increased melanin within basal keratinocytes and melanin within dermal macrophages. Of note, there are normal numbers of melanocytes, and iron stains are negative, thus indicating melanin rather than hemosiderin deposition. While the exact mechanism of hyperpigmentation is unknown, it is thought that this alkylating agent inactivates sulfhydryl groups within the skin, thereby releasing inhibition of tyrosinase, thereby allowing for melanin production and subsequent hyperpigmentation.

Carmustine (BCNU) is an alkylating agent for the treatment of brain tumors (glioblastoma multiforme, and other malignant gliomas), multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphoma. It is prescribed in dermatology for the off-label treatment of mycosis fungoides. When applied topically, carmustine causes brown hyperpigmentation of the skin. Skin biopsy shows basal melanocyte hyperplasia and pigment deposition within keratinocytes.

Cyclophosphamide is another alkylating agent used for treatment of internal malignancies and various rheumatologic conditions. It can cause generalized hyperpigmentation of both skin and mucosal surfaces. The pigment has a tendency to deposit in nails, palmoplantar surfaces, and teeth. After the medication is discontinued, the pigmentation will slowly fade, usually over 6–12 months.

Several antibiotics used as chemotherapies have also been associated with skin and nail hyperpigmentation. Dactinomycin is used for treatment of a number of solid tumors and also causes generalized hyperpigmentation, particularly of the

face. The dyschromia tends to fade after discontinuation of the medication. The anthracycline antibiotics intercalate into DNA and are used in the treatment of leukemias, lymphomas, breast, uterine, ovarian, and lung cancers. Daunorubicin produces hyperpigmentation that tends to occur in photo-exposed regions but can also involve the nails. Doxorubicin hyperpigmentation localizes to the palmoplantar surfaces and over the small joints of the hands. Histologically, there is both increased melanocyte proliferation and epidermal melanin content.

5-Fluorouracil is a pyrimidine analog used in the treatment of solid tumors. It can cause a photosensitive eruption that results in post-inflammatory hyperpigmentation. It can also cause cutaneous hyperpigmentation overlying veins into which the chemotherapy was infused (supravenous serpentine hyperpigmentation) as well as target other sites, such as the dorsal hands, palmoplantar surfaces, and radiation ports.

Hydroxyurea is used in the treatment of hematologic malignancies and sickle cell anemia, and has off-label dermatologic applications. It can cause prominent hyperpigmentation on the back and over sites of pressure. This hyperpigmentation is reversible, as is the post-inflammatory hyperpigmentation that can occur after a hydroxyurea-induced lichenoid eruption.

Fixed Drug Eruptions

Fixed drug eruptions are characterized by the appearance of well-demarcated round or oval patches or plaques of erythema (or even bullous variants), preferentially on acral (hands and feet) and mucosal (oral and genital) sites. Initial exposure can produce the eruption 1–2 weeks after starting an offending medication; subsequently, the eruption recurs at the same site(s) within a day after re-exposure. It is possible that with repeated exposures, the number of sites involved can increase. Symptoms associated with fixed drug eruptions are minimal, and patients are otherwise well. Fixed drug eruptions heal with crust and eventually develop a dusky brown color that is more prominent in darker skinned individuals.

Though fixed drug eruptions are thought to be allergic reactions, the pathophysiology is not well understood. Skin biopsy is characterized by interface changes and mixed dermal infiltrate consisting of lymphocytes, neutrophils, histiocytes, and eosinophils. Histology of older plaques will show prominent pigment incontinence. Sites of recurrent fixed drug eruptions will reveal deeper melanophages within the dermis.

While many medications have been associated with fixed drug eruptions, the most common culprits include sulfonamides (with trimethoprim-sulfamethoxazole or co-trimoxazole as the most common cause of fixed drug eruption), tetracyclines, acetaminophen, barbiturates, and NSAIDs. The frequency of phenolphthalein-induced fixed drug eruptions has decreased since it is no longer used in the formulation of laxatives. Piroxicam, pseudoephedrine, and sorafenib have been reported to cause non-pigmenting variants that do not leave residual hyperpigmentation. Table 9.3 provides a list of medications associated with fixed drug eruptions (not exhaustive).

Phytophotodermatitis

Phytophotodermatitis is a non-immunologic phototoxic dermatitis that occurs in patients exposed to UV light after ingestion or skin contact with plants containing photosensitizing agents known as furocoumarins (e.g. psoralens, angelicin, bergaptol, and xanthotal). The most commonly implicated plant family is *Umbelliferae* (e.g. parsnip, celery, parsley, fennel, wild rhubarb); others include *Rutacae* (e.g. lime, lemon, grapefruit, rue, orange), *Moraceae* (e.g. fig), and *Leguninosa* (e.g. beans).

The eruption is generally appreciated 24 h after exposure (peaking at 48–72 h) and can range from mild erythema to severe blistering. The clinician should consider phytophotodermatitis when evaluating a patient demonstrating hyperpigmented streaks (Fig. 9.2) or blistering that follows the path of the photosensitizing agent on the skin. Classic cases follow outdoor picnics or trips to the beach, where patients have been squeezing limes or lemons. Characteristic sites of involvement include the face, chest, hands, and lower legs. The clinician should be cognizant that hyperpigmentation may be mistaken for child abuse, for example when thumbprint-shaped

Table 9.3 Medications associated with fixed drug eruptions

Antimicrobials	**Anticonvulsants**	**Cardiac**	**Miscellaneous**
TMP-SMX[a]	Phenytoin	Beta-blockers	Allopurinol
Acyclovir	Barbiturates	Clopidogrel	Amide local anesthetics
Amoxicillin[b]	Carbamazepine	Flecainide	Bismuth
Ceftriaxone	Chlordiazepoxide	Heparin	Colchicine
Clarithromycin	Lamotrigine	Hydrochlorothiazide	Cyclophosphamide
Erythromycin	**Anthistamines**	Nifedipine	Dapsone
Fluconazole	Cetirizine	Ticlopidine	Dextromethorphan
Fluoroquinolones	Diphenhydramine	**Chemotherapeutics**	Estrogen, OCPs[a]
Griseofulvin	Hydroxyzine	Docetaxel,	Gabapentin
Metronidazole[b]	Loratadine	Paclitaxel	Hydroxyurea
Penicillins	**Analgesics**	Procarbazine	Omeprazole
Rifampin	NSAIDs[a]	–	Phenolphthalein (laxative)
Terbinafine	Acetominophen[b]	–	Phenylephrine
Tetracyclines[b]	Codeine	–	Pseudoephedrine[b]
	Metamizole	–	Quinine (tonic water)
	–	–	Theophylline

[a]*TMP-SMX* Trimethoprim-sulfamethoxazole (most common cause of fixed drug eruption, also known as co-trimoxazole), *OCPs* oral contraceptive pills, *NSAIDs* non-steroidal anti-inflammatory drugs
[b]Common cause

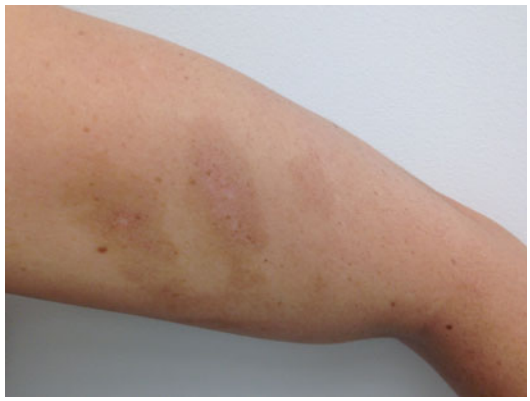


Fig. 9.2 Brown hyperpigmentation of phyotophotodermatitis in a 27-year-old patient

patches are seen on the trunk of children after parents have handled furocoumarins.

"Berloque" dermatitis refers to phytophotodermatitis on the face and neck from perfumes containing natural oils of bergamot; the decreased use of artificial oil of bergamot has made this a rare clinical finding. The clinician should be aware of the possibility of exaggerated phototoxic eruptions in patients taking furocoumarins topically or systemically for light treatments (PUVA and photodynamic therapy). Such patients should be advised to avoid both excess UV exposure post-therapy and furocoumarin-containing foods. No treatment is necessary for phytophotodermatitis, though topical steroids may be used for inflammation or pruritus. The hyperpigmentation generally fades over the course of weeks to months.

Gray Dyspigmentation

Blue-Gray Dyspigmentation

Antimalarials, such as chloroquine and hydroxychloroquine, can cause gray to blue-black dyschromia. This classically occurs on the pretibia with hydroxychloroquine, though other sites, such as face (Fig. 9.3a) and mucosal surfaces, can also be involved (including hard palate Fig. 9.3b and sclerae). The dyspigmentation results from melanin-drug complex deposition within the dermis as well as hemosiderin deposition around capillaries. While the dyschromia can fade somewhat after discontinuation of the medication, it generally does not resolve completely.

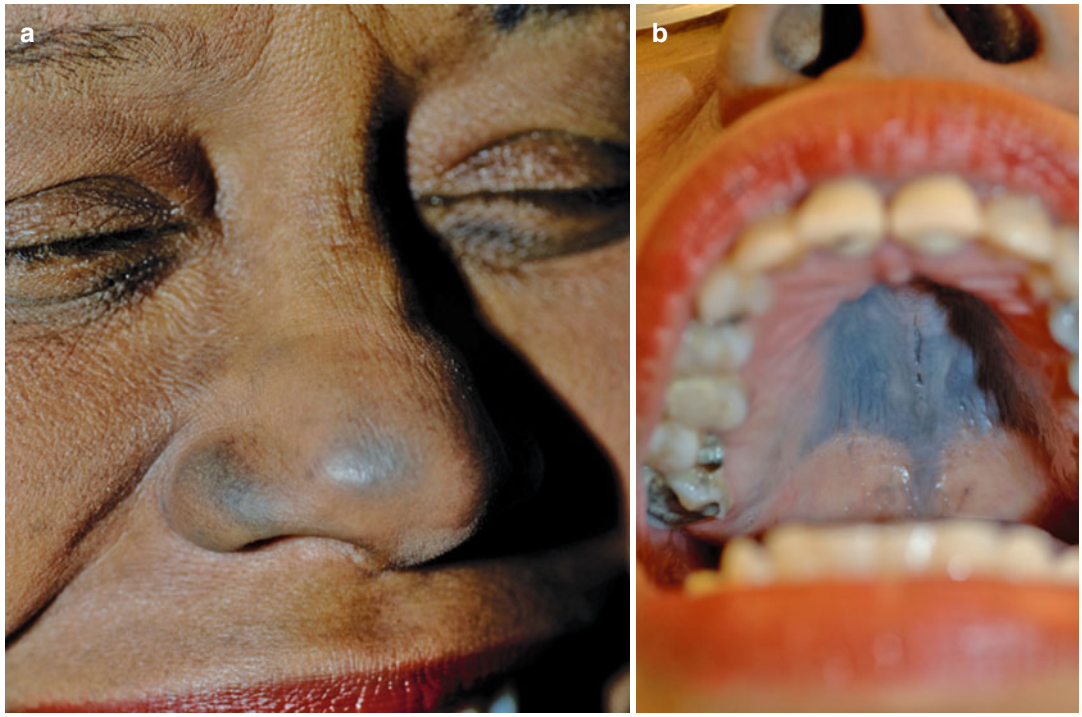
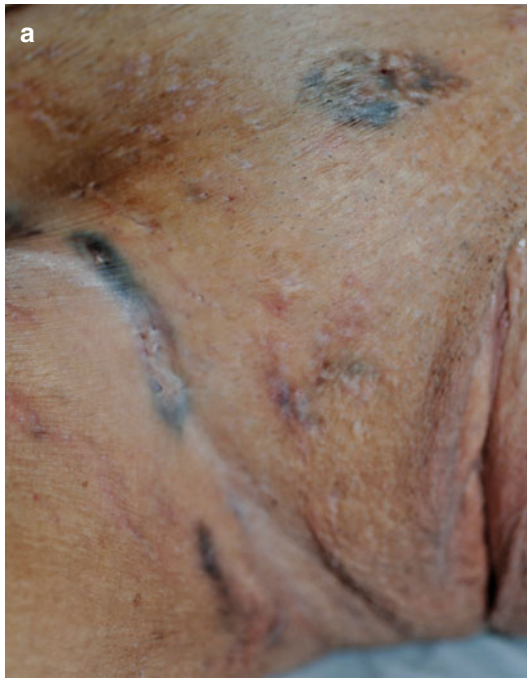


Fig. 9.3 (**a**, **b**) Blue-black hyperpigmentation of (**a**) the nose and (**b**) hard palate in a 57-year-old woman with cutaneous lupus erythematosus who was on both quinacrine and hydroxychloroquine (Courtesy of Dr. Richard A. Johnson, MD (Boston, MA))

Minocycline, frequently prescribed by dermatologists for acne and rosacea (and less commonly for immunobullous and granulomatous dermatoses), causes blue-gray to blue-black dyspigmentation of the skin. Upon oxidation, minocycline turns from its native yellow, lipid-soluble form to black and is associated with four categories of hyperpigmentation. Type I dyspigmentation is characterized by blue-gray hyperpigmentation at sites of prior inflammation and scars (Fig. 9.4a). Type II hyperpigmentation presents with blue-gray macules on normal skin, usually on the arms or legs (particularly the shins, Fig. 9.4b–left, right). Type III hyperpigmentation is characterized by a more diffuse "muddy-brown" appearance in sun-exposed areas. Finally, Type IV dyschromia presents within scar tissue specifically on the trunk. Patients may also develop dyspigmentation of non-cutaneous sites, including sclerae (Fig. 9.4c), oral mucosa (Fig. 9.4d), teeth (Fig. 9.4e), thyroid, bones, and nails.

The etiology of Types I and II minocycline dyspigmentation is dermal deposition of iron-containing pigment granules, whereas melanin-containing pigment granule deposition can also occur in Type II dyspigmentation. Type III

Fig. 9.4 (**a**) Blue-gray hyperpigmentation within scars (Type I) of a 55-year-old woman who had been on minocycline for years as treatment for hidradenitis suppurativa (Courtesy of Dr. Richard A. Johnson, MD (Boston, MA)). (**b**) Blue-gray minocycline hyperpigmentation on the shins (Type II) of a 35-year-old woman (*left*) and 93-year-old woman (*right*) (Courtesy of Dr. Richard A. Johnson, MD (Boston, MA)). (**c**) Blue dyspigmentation of the sclerae in a patient who had been on minocycline for years as part of his treatment regimen for pemphigus vulgaris. (**d**) Blue-gray gingival hyperpigmentation in a 58-year-old woman who had been on minocycline for 1 year (Courtesy of Dr. Richard A. Johnson, MD (Boston, MA)). (**e**) Gray discoloration of the middle-third of the teeth in a woman on minocycline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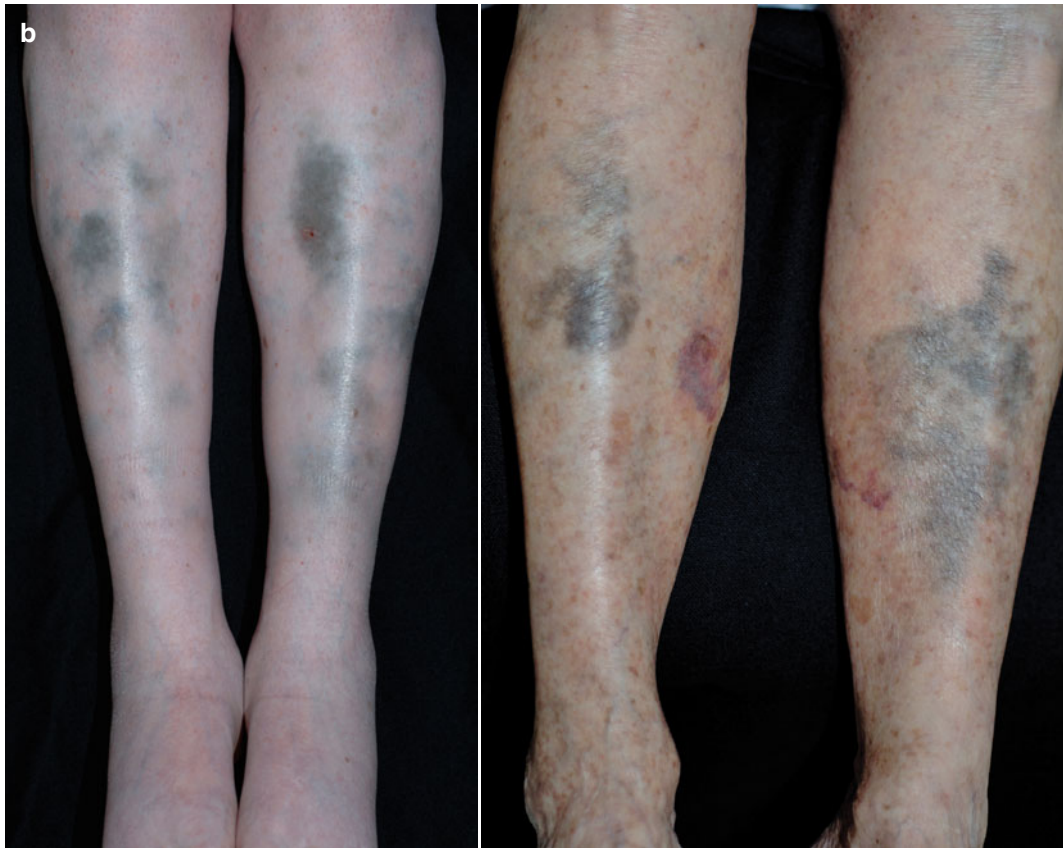
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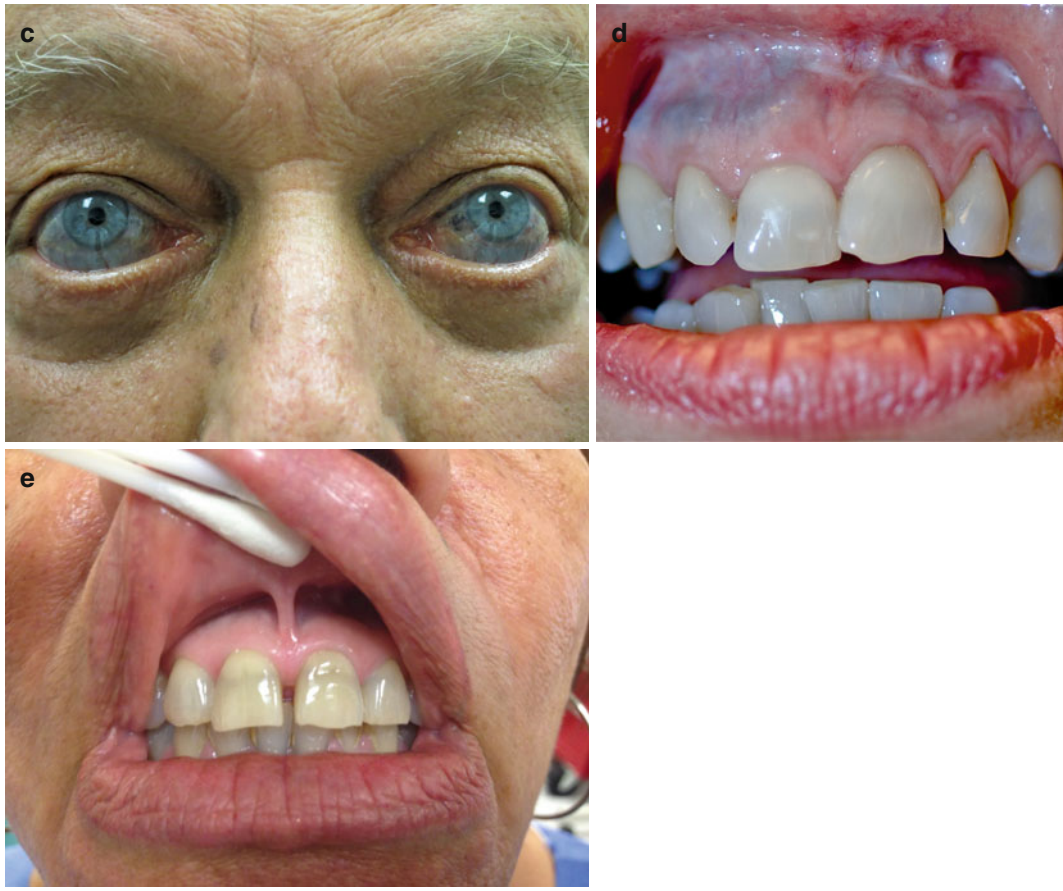

Fig. 9.4 (continued)

dyspigmentation results from increased melanin deposition in the epidermal basal layer and/or dermal melanophages. For Type IV hyperpigmentation, histology will reveal pigment throughout the dermis as well as within dendritic cells, and notably the pigment is chelated with calcium rather than iron. Minocycline discoloration generally fades after the medication is discontinued, but this can take years. Q-switched lasers can be beneficial for pigment removal in types I and II minocycline dyspigmentation.

Heavy metals, which enter a patient's system either percutaneously or hematogenously, can produce blue-gray dyspigmentation after absorption and deposition within the skin. The effects are generally seen following years of treatment.

Bismuth was used in the past for the treatment of the venereal diseases and is the primary ingredient in Pepto-Bismol, which is an over-the-counter drug used in the treatment of minor gastrointestinal upset (e.g. nausea, gastric reflux, and diarrhea). Bismuth granules deposit into both the papillary and reticular dermis and cause a blue-gray dyschromia of the face, neck, and dorsal hands. Oral mucosa and gingiva can also be involved.

Gold is FDA-approved for the treatment of rheumatoid arthritis (chrysotherapy), and it has been used off-label as an adjunctive treatment for pemphigus vulgaris. Gold particles (which are larger and more irregular than silver granules) deposit within dermal macrophages around vessels and eccrine glands. Exposure to UV light causes permanent blue-gray dyspigmentation in photo-exposed sites, especially periorbitally, and is referred to as chrysiasis. This occurs years after exposure to parenteral gold treatment. There have been reports of

Table 9.4 Heavy-metal-induced dyspigmentation

Metal	Indication	Color	Sites	Comments
Arsenic	Contamination (well water, pesticides, herbicides, wood preservatives)	Bronze	Trunk (folds accentuated)	Also diffuse hyperpigmentation, melanotic macules; Mee's line (transverse white bands)
Bismuth	Venereal diseases; indigestion/diarrhea	Blue-gray	Face, neck, dorsal hands; oral mucosa, gingiva	In Pepto-Bismol
Gold (Chrysiasis)	Rheumatoid arthritis	Blue-gray	Photo-exposed	Iatrogenic from Q-switched lasers (treatment = PDL)
Silver (Argyria)	Topicals used in wound healing	Blue-gray, slate-gray	Face, forearms, hands >sclerae, oral mucosa, lunula	Most common heavy-metal dyschromia seen by dermatologists
Titanium	Orthopedic screws	Blue-black	Skin overlying the screws	–
Mercury	Bleaching creams	Slate-gray	Skin folds	–

iatrogenic chrysiasis in patients treated with Q-switched lasers; thus, it is very important to obtain history of treatment with gold salts prior to initiating laser therapy in any patient. Though chrysiasis is permanent, there have been reports of improvement with pulsed-dye laser treatment.

Silver ingestion or chronic topical application can lead to argyria, bluish-gray or slate-colored dyschromia that occurs most commonly on the face, forearms, and hands. Silver-induced hyperpigmentation is the most common form of heavy-metal induced pigmentation seen by dermatologists. Argyria can also involve the sclerae, oral mucosa, and lunulae of the nails. Localized argyria has become more common due to silver-containing topical agents that promote wound healing through the antimicrobial and anti-inflammatory properties of silver. While argyria is diagnosed clinically, skin biopsy will show small refractive silver granules throughout the dermis, with preponderance around the eccrine glands. There is also increased melanin within the epidermal basal layer and in dermal macrophages. Even after discontinuation of silver-containing agents, hyperpigmentation is usually not reversible.

Titanium screws from orthopedic surgery have been shown to cause blue-black dyschromia of the overlying skin. Table 9.4 lists heavy-metal-induced causes of hyperpigmentation.

Slate-Gray Dyspigmentation

Mercury-containing topical agents can cause slate-gray dyspigmentation that is more prominent in the skin folds and is a permanent side effect. The dark brown granules deposit in the upper dermis (within macrophages, freely among collagen fibers, or in association with elastic fibers). The pigmentation is thought to arise from both metal granule deposition and increased epidermal melanin.

Amiodarone, an antiarrhythmic, can cause slate-gray to violaceous dyschromia in photo-exposed sites, especially the face. This is generally more evident in lighter-skinned patients who have been on amiodarone continuously for long periods of time. The dyspigmentation generally resolves gradually months to years after discontinuation, but there are reports of permanent dyschromia. Histologically, there is a perivascular distribution of yellow-brown granules within dermal macrophages.

Diltiazem, a calcium-channel blocker used for treatment of hypertension, angina, and arrhythmias, causes slate-gray to gray-brown dyschromia with perifollicular accentuation in photo-exposed sites of darker-skinned individuals (skin type IV–VI). Skin biopsy will show a mild lichenoid infiltrate with many dermal melanophages.

Psychotropic medications (such as chlorpromazine, thioridazine, imipramine, desipramine, and amitriptyline) cause slate-gray dyschromia in photo-exposed areas, from golden-brown pigment granule deposition in the papillary dermis.

Blue-Black Dyspigmentation

Hydroquinone is commonly prescribed as a bleaching cream for the treatment of hyperpigmentation. It commonly causes an irritant dermatitis resulting in temporary post-inflammatory hyperpigmentation, though a greater concern is the development of paradoxical exogenous ochronosis in the form of blue-black dyschromia. While this occurs most frequently with higher concentrations (6–8 %) of hydroquinone, there are reports of exogenous ochronosis from concentrations as low as 2 % applied topically for years. It is important to be aware that patients may present after years of using over-the-counter bleaching creams that contain hydroquinone of undisclosed concentrations. Hydroquinone is thought to inhibit dermal homogentisic acid oxidase, thereby allowing homogentisic acid to polymerize and accumulate to form ochronotic pigment. Pathology will show golden-brown "banana-shaped" strands within the dermis. There may be some improvement after discontinuation of hydroquinone. But the dyspigmentation is generally considered permanent and responds minimally to Q-switched lasers. This further complicates the cosmetic concerns of patients who apply hydroquinone-containing agents specifically to lighten areas of dyschromia on the face.

Exogenous ochronosis can also occur from the ingestion of antimalarials and use of products containing phenol, mercury, resorcinol, and picric acid.

Drug-Induced Oral Dyspigmentation

A range of medications can cause oral pigmentation through varying mechanisms. While any part of the mouth may be involved, the hard palate and gingiva are common sites of drug-induced oral hyperpigmentation. Fixed drug eruptions can occur within the oral mucosa as well-demarcated gray-brown macules and often occur concomitantly with genital involvement. The most common causes of oral fixed drug eruptions are clotrimazole and tetracycline. See above for discussion of fixed drug eruptions. Table 9.5 provides an overview of medications implicated in oral dyspigmentation.

Conclusions

The manifold presentations of drug-induced skin, hair, and oral dyspigmentation have been reviewed in this chapter. The mechanism by which medications can induce hyperpigmentation include increase in melanin production (by existing melanocytes or through melanocyte proliferation) and/or deposition of drug or metabolite within the epidermis or dermis. Medications can also cause leukoderma. Detailed history (including underlying diseases and medication timeline) combined with complete physical examination should enable the astute clinician to determine whether a medication is the culprit in pigmentary changes. Particularly when the offending agent has been discontinued, the color and distribution of dyspigmentation can provide clues to identification of etiology and allow the clinician to counsel and manage the patient who presents with complaints of skin dyschromia.

Acknowledgments The authors would like to thank Dr. Richard A. Johnson (Massachusetts General Hospital, Boston, MA) for graciously providing clinical images and for his mentorship.

Table 9.5 Drug-induced oral dyspigmentation

Medication	Color	Location	Mechanism/Histology	Comments
Amiodarone	Blue-gray	Oral mucosa	Increased lipofuscin production	–
Antimalarials Chloroquine HCQ Quinacrine	Blue-gray	Hard palate	Melanocyte stimulation and increased melanin production	–
Chlorpromazine	Brown	Oral mucosa	–	–
Clofazimine	Blue-gray	Buccal mucosa	–	Brown pigmentation in HIV+
Ketoconazole	Brown	Oral mucosa	–	Can caused fixed drug eruption
Anti-tumor Agents	Brown		Increased melanin deposition	–
Bleomycin	Brown	Oral mucosa	–	–
Busulfan	Brown	Oral mucosa	–	–
Cyclophosphamide	Brown	Oral mucosa	–	–
Doxorubicin	Brown	Buccal mucosa, Teeth	–	–
5-FU	Brown	–	–	–
Imatinib	Blue-brown	Hard palate, gingiva, teeth	–	–
Nitrogen mustard			–	–
Heavy metals				
Arsenic	Blue-black	Oral mucosa	Combine with epidermal cell sulfhydryl groups to stimulate tyrosinase	–
Bismuth	Blue-black	Oral mucosa, gingiva	Metal sulfide deposition in superficial vessels (bacteria make hydrogen sulfide)	–
Gold	Light purple	Gingiva	–	–
Lead	Gray or blue-black	Gingival margin ("lead line")	–	–
Mercury	Slate-gray	Gingiva	–	–
Silver	Slate-gray	Oral mucosa, gingiva	–	Amalgam tattoos
OCP	Brown	Gingiva	Melanocyte stimulation and increased melanin production	–
Phenothiazines	Brown	Oral mucosa	Drug-pigment deposits	–
Minocycline	Gray to gray-green	Mid-portion of teeth (adults), tongue	Drug-pigment deposits within alveolar bones	May be only manifestation
Zidovudine	Brown macules	Oral mucosa (darker-skinned individuals)	–	–

HCQ hydroxychloroquine, *OCP* oral contraceptive pill, *5-FU* 5-fluorouracil

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Drug-Induced Photosensitivity

10

Liza Gill and Henry W. Lim

Abstract

Photosensitivity due to topical or systemic drugs can be divided into phototoxicity and photoallergy. Phototoxicity usually presents as an exaggerated sunburn and can occur in anyone exposed to sufficient amounts of the offending drug and adequate wavelengths of radiation. Photoallergy is a type IV delayed hypersensitivity reaction that presents as an eczematous eruption in someone who has previously been sensitized to the drug. A focused history is important in the evaluation of a patient suspected to have drug-induced photosensitivity. Minimal erythema dose (MED) testing and photopatch testing can be helpful. Management includes discontinuation and avoidance of the implicated drug, photoprotection, and symptomatic relief.

Keywords

Photosensitivity • Phototoxicity • Photoallergy • Drug reaction • Drug eruption • Minimal erythema dose testing • Photopatch testing

Introduction

Photosensitivity reactions can be caused by endogenous or exogenous agents. Photosensitivity to endogenous agents includes cutaneous porphyrias. Photosensitivity reactions to exogenous agents occur due to exposure to a drug or chemical and ultraviolet radiation. Discussion in this chapter will be limited to photosensitivity due to exogenous agents, specifically systemic or topical medications.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_10

Most photosensitizers are activated by UVA, with occasional extension into UVB. Photosensitivity reactions due to exogenous agents can be classified as phototoxic or photoallergic drug eruptions. Phototoxicity results from direct tissue injury secondary to a phototoxic agent and radiation. It can occur in anyone on first exposure to sufficient doses of the drug and activating wavelengths of radiation.

Photoallergy is a type IV delayed hypersensitivity response to a compound modified by light (photoallergen). After the initial sensitizing phase, a minimal concentration of the photoallergen and a second exposure to the drug are required before onset of clinical manifestation of photoallergy.

Although there are subtle differences, phototoxic and photoallergic reactions can often have similar clinical appearances. Furthermore, several drugs can cause both types of reactions. However, differences in incidence, amount of drug required to produce the reaction, time of onset after the drug and light exposure, all combined with the clinical and histologic appearances can help distinguish between the two reactions (Table 10.1).

Phototoxicity

Epidemiology

The exact prevalence of phototoxicity in the general population is unknown; however, frequency in photodermatology referral centers ranges from 5 to 15 %.

Pathogenesis

There are substantial differences in the pathogenesis of phototoxicity compared to photoallergy. All patients exposed to sufficient amounts of a phototoxic drug should, theoretically, develop signs and symptoms of a phototoxic reaction upon light exposure. In contrast, as described later in the chapter, photoallergy occurs only in individuals who have been immunologically sensitized to the photoallergen. Various factors prevent the reaction from occurring in everyone exposed to a particular phototoxic agent. For example, the quantity of drug present within the skin will depend on the route of administration and on individual rates of gastrointestinal absorption along with drug

Table 10.1 Features of phototoxicity and photoallergy

	Phototoxicity	Photoallergy
Incidence	High	Low
Amount of agent required for photosensitivity	Large	Small
Onset after exposure to photosensitizer and light	Minutes to hours	24 h or more
Occurs after first exposure	Yes	No
Clinical presentation	Exaggerated sunburn: erythema, edema, vesicles, and bullae; burning, stinging Distribution: exposed skin only	Acute, subacute, or chronic dermatitis; usually pruritic Distribution: exposed skin; may spread to unexposed skin
Pigmentary changes	Frequently resolves with hyperpigmentation	Infrequent
Histopathologic features	Epidermal necrosis, dermal edema, sparse inflammatory infiltrate	Epidermal spongiosis; dermal mononuclear cell infiltrate
Cross-reactions to related agents	No	Yes

Modified from Gould et al. (1995)

distribution and metabolism. On the other hand, the amount of radiation reaching the skin will depend on a person's pigmentation, coverage by hair, and thickness of the stratum corneum.

In phototoxic reactions, light interacts with the photosensitizing chemicals in the skin. The interaction excites electrons in the photosensitizer, leading to unstable singlet or triplet states. Energy is transferred from these unstable compounds as they return to ground state. The transferred energy damages cellular components and organelles, and generates reactive oxygen species. Superoxide anion is considered to be the major oxygen species to cause a phototoxic response. Membrane lipids are most readily oxidized, resulting in disruption of the cellular membrane.

Phototoxic reactions can be classified as being photodynamic (oxygen dependent) or non-photodynamic (oxygen independent). Photodynamic chemicals cause damage by reacting with oxygen in their triplet states to form radicals (type I reaction) or by producing singlet oxygen and oxidizing cell components (type II reactions). Quinolones, NSAIDs, tetracyclines, amitriptyline, imipramine, sulfonylureas, hydrochlorothiazide, furosemide, porphyrins, and chlorpromazine are examples of agents that cause photodynamic phototoxic reactions. Nonphotodynamic chemicals cause damage without oxygen requirements. Photoaddition of 8-methoxypsoralen to pyrimidine bases in DNA is an example of a non-photodynamic reaction.

With either mechanism, a photosensitizing agent interacts with UV to produce a biological change at the cellular or subcellular level. Cellular targets of phototoxic responses depend on the distribution of the drug. Topical agents are more likely to cause damage to keratinocytes. Oral or parenteral agents are more likely to damage mast cells or dermal endothelial cells. Lipid solubility affects subcellular targets of phototoxic agents. Hydrophilic substances are more likely to damage the cell membrane, whereas hydrophobic agents are more likely to diffuse into the cell and damage cytoplasmic or nuclear components.

Clinical Features

Exposure to a systemic or topical phototoxic drug in conjunction with exposure to appropriate UVR can produce phototoxicity. One form of phototoxic response is characterized by delayed erythema and edema 8–24 h after radiation exposure and lasts 2–4 days. Psoralens cause this type of phototoxic response. Alternatively, a more rapid, transient erythema, starting within 30 min of light exposure and lasting 1–2 days can occur, as seen with demeclocycline. For the majority of these drugs, phototoxicity occurs with exposure in the UVA spectrum. The most common clinical presentation of phototoxicity is an exaggerated sunburn, with erythema and edema in sun-exposed areas. Vesicle and bullae formation followed by desquamation may occur in more severe cases. The exaggerated sunburn can be followed by localized areas of hyperpigmentation, which can persist for several months after discontinuation of the drug. While some drugs cause hyperpigmentation by causing melanocyte proliferation and migration, such as psoralens, other drugs produce a slate-gray or golden-brown pigmentation from deposition of the drug or its photoproducts in the skin, such as amiodarone.

Agents That Cause Phototoxicity

Many drugs, both topical and systemic, can cause phototoxic response. This section discusses the most common (see Tables 10.2 and 10.3).

Table 10.2 Common topical phototoxic agents

Topical phototoxic agents	Use
Fluorouracil	Treatment of actinic keratoses
Furocoumarins (i.e. psoralens)	Topical photochemotherapy
Retinoids	Treatment of acne and photoaging

Modified from Lim (2012)

Table 10.3 Common systemic phototoxic agents

Class	Generic names
Antiarrhythmics	Amiodarone Quinidine[a]
Antibiotics	Sulfonamides Tetracyclines Demeclocycline Doxycycline Minocycline Trimethoprim Quinolones Ciprofloxacin Enoxacin[a] Gemifloxacin Lomefloxacin[a] Moxifloxacin Nalidixic acid[a] Norfloxacin Ofloxacin Sparfloxacin
Antifungals	Griseofulvin Itraconazole Ketoconazole Voriconazole
Antimalarials	Chloroquine Quinine[a]
Antineoplastics	Dacarbazine Docetaxel[b] Fluorouracil[b] Methotrexate[b] Paclitaxel Vandetanib Vinblastine
Calcium Channel Blockers	Amlodipine Nifedipine Diltiazem
Diuretics	Furosemide Thiazides Bendroflumethiazide Chlorothiazide Hydrochlorothiazide
Furocoumarins	Psoralens 5-Methoxypsoralen 8-Methoxypsoralen
Hypoglycemics	Sulfonylureas Acetohexamide Chlorpropamide Glipizide Glyburide Tolazamide Tolbutamide
NSAIDs	Alkanone derivative Nabumetone Anthranilic acid derivative Mefenamic acid Cyclooxygenase-2 inhibitor Celecoxib Rofecoxib Enolic acid derivative Piroxicam[a] Proprionic acid derivatives Ibuprofen Ketoprofen Naproxen Oxaprozin Tiaprofenic acid Salicylic acid derivative Diflunisal
Photodynamic therapy	Porfimer Verteporfin
Psychiatric medications	Clozapine Phenothiazines Chlorpromazine Thioridazine Tricyclics Amitriptyline Desipramine Imipramine
Other	Dapsone Hypericin (St. John's Wort)

Modified from Lim (2012)
[a]Also a common photoallergen
[b]Produces a "recall" of previous UVR-induced erythema

Psoralens

Psoralens are well-known drugs with inherent photosensitizing properties that have been utilized for the treatments of diseases such as psoriasis, vitiligo, mycosis fungoides, and atopic dermatitis. Psoralens are used therapeutically with UVA (PUVA) as either systemic preparations or topical agents. Acute adverse side effects of PUVA include erythema, vesicles, pruritus, and nausea; whereas, long-term PUVA therapy is associated with an increased risk of nonmelanoma skin cancer and cataract

formation. Other adverse effects include xerosis, pigment changes, actinic damage, premature skin aging, and exacerbation of underlying skin disease. The psoralen-induced phototoxic reaction targets DNA, which is different from most other phototoxic agents, and peaks from 48 to 72 h after exposure to UVA. This timeline is the rationale for administering PUVA photochemotherapy doses 48–72 h apart. The phototoxic response resolves with varying degrees of hyperpigmentation.

Berloque dermatitis is a type of psoralen phototoxicity that occurred more often in the past with the use of perfumes with high concentration of psoralens, usually 5-methoxypsoralen (5-MOP). It was often seen on the lateral neck and preauricular areas.

Tar Products

Tar and tar-based products cause a unique phototoxic response with burning and stinging almost immediately on exposure to sunlight, called "tar smarts." Although no longer commonly administered, tar-based products such as creams, soaks, and shampoos have been used in some dermatology treatment regimens. Patients treated with these agents should be reminded that sun exposure can cause skin irritation.

Antimicrobials

Antibiotics are a common source of phototoxic reactions. The tetracyclines, a family of anti-inflammatory antibiotics, are one of the most frequent culprits because of the prevalence of their use. Dimethylchlortetracycline (DMCT) was the first tetracycline to be recognized for phototoxicity, which follows a sunburn pattern. Of the two commonly used tetracyclines, doxycycline is a more potent photosensitizer, whereas minocycline has less of a phototoxic effect. The phototoxic response of doxycycline is dose-dependent, with phototoxicity more common at the higher dose of 200 mg/day or above.

The fluoroquinolones, a group of broad-spectrum antibiotics, are also capable of producing a phototoxic reaction. In the late 1980s, the first generation of fluoroquinolones were marketed and labeled as weak photosensitizers. Development of more potent fluoroquinolones has also increased the photosensitivity potential of the antibiotics. Degree of phototoxicity ranges widely among fluoroquinolones due to chemical differences in a side chain in position 8. Levofloxacin and moxifloxacin, two commonly used respiratory fluoroquinolones, have low phototoxic potential, whereas lomefloxacin and sparfloxacin, which have halogens (i.e. fluorine or chlorine) in their side chains, have the greatest phototoxic potential.

The action spectrum of fluoroquinolones-induced phototoxicity is primarily in the UVA range, with some extension into the visible light range. Many fluoroquinolones are rapidly eliminated and do not undergo significant metabolism. For this reason, photosensitivity may be reduced by evening dosing, thus limiting exposure during peak sunlight times. Cystic fibrosis patients have been reported to have a higher incidence of phototoxicity due to ciprofloxacin, perhaps due to their often prolonged courses of therapy.

Voriconazole, a systemic triazole antifungal, can be prescribed for months to years in immunocompromised patients with allogeneic hematopoietic stem cell transplants and chronic graft-versus-host disease. In addition to causing a classic phototoxic reaction, it is noted to increase the risk of hypertrophic actinic keratoses, aggressive cutaneous squamous cell carcinomas and possibly melanoma. Itraconazole has also been reported to cause phototoxic response.

Other phototoxic antimicrobials include ceftazidime, griseofulvin, ketoconazole, and trimethoprim.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs, although designed to reduce inflammation, are a frequent cause of phototoxicity. Benoxaprofen (no longer on the market due to its cholestatic hepatitis side effect) and piroxicam are commonly reported phototoxic agents in the literature. Benoxaprofen and piroxicam undergo photodecarboxylation to produce a photoproduct. This photoproduct then combines with the parent compound, which results in damage to cell membranes, particularly in mast cells and leukocytes. Ibuprofen, ketoprofen, meclofenamide sodium, naproxen, nabumetone, oxaprozen, sulindac, and tiaprofenic acid are implicated agents. A recent report of naproxen-induced phototoxicity describes a lichenoid reaction in a patient with sunbed exposure. Phototoxicity to naproxen is possibly due to irradiation of extracellular naproxen resulting in oxidative and replicative stress to cells. Singlet oxygen, superoxide radical anion, and peroxyl radical species are thought to be formed through photodegradation pathways of naproxen and nabumetone, leading to cellular effects such as lipid peroxidation.

Psychiatric Medications

Chlorpromazine, a phenothiazine antipsychotic less commonly used than in the past, is known as both a phototoxic and photoallergic drug. Chlorpromazine-induced phototoxicity is dependent on UVA in a dose-dependent manner and quickly resolves following drug cessation. Thioridazine, also a phenothiazine antipsychotic, causes photosensitivity less commonly than chlorpromazine. Long-term, high-dose therapy with either drug can result in slate-gray to violaceous hyperpigmentation in photo-distributed areas.

St. John's wort (*Hypericum perforatum*), an over-the-counter agent sometimes used to treat depression, contains the phototoxic agent hypericin.

Antimalarials

Quinine, like chlorpromazine, has also been reported to cause both phototoxic and photoallergic reactions. Quinine, although no longer a first-line agent for malaria, is sometimes used for the treatment of night cramps. The agent occasionally produces an idiosyncratic photodistributed leukomelanoderma. Phototesting demonstrates sensitivity to UVB and UVA in these patients. Uncommonly, hydroxychloroquine also appears to cause phototoxic and photoallergic reactions. A report of phototoxic eruption that progressed to Stevens-Johnson syndrome has been described after ingestion of a combination of antimalarials chloroquine and sulfadoxine pyrimethamine.

Amiodarone

Amiodarone is an antiarrhythmic drug often used when more conventional drug therapy has failed. It has been reported to cause phototoxic reactions in over 50 % of patients taking amiodarone; however, a more recent study found photosensitivity to occur in only 7 of 98 patients. Amiodarone phototoxicity is dose-related and presents as an immediate burning or prickling sensation combined with erythema that rapidly resolves, and then reemerges in 24 h. The phototoxic response is thought to be dependent on UVA and visible light. Elimination half-life is over 200 days, so even if the drug is discontinued, the patient may continue to have problems for months. Its typical phototoxic reaction can often be managed with dose reduction rather than cessation of treatment. Amiodarone phototoxicity frequently is associated with slate-gray pigmentation on sun-exposed areas, which has been shown to be secondary to deposition of a drug metabolite.

Dronedarone is a newer antiarrhythmic drug approved by the U.S. Food and Drug Administration in 2009 for treatment of patients with atrial fibrillation or atrial flutter. It is chemically related to amiodarone but is less lipophilic and has a shorter serum half-life (24 h versus several weeks for amiodarone). These properties limit its potential for adverse effects typically seen with amiodarone. Dronedarone has a substantially lower incidence of phototoxicity (1 %) compared to amiodarone (50 %).

Antihypertensives

Phototoxic antihypertensive agents include diuretics such as hydrochlorothiazide, bendroflumethiazide, and furosemide. The phototoxic dermatitis

in thiazides sometimes presents years after starting to take the drug. There are reports of photoleukomelanoderma following thiazide-induced phototoxicity in the Asian population. Bullous photo-eruptions have rarely been reported in association with furosemide. Dihydropyridines calcium channel blockers, (i.e. nifedipine and amlodipine) in addition to an erythematous phototoxicity, can cause an unusual form of phototoxicity with telangiectasias on photo-exposed sites. Phototoxic reactions to quinapril, an angiotensin converting enzyme (ACE) inhibitor, have been reported in the literature. Although ACE inhibitors are considered to be relatively more tolerable anti-hypertensives, the incidence of adverse effects to ACE inhibitors is estimated at 28 %, half of which occurs in the skin.

Retinoids

Isotretinoin and etretinate have been noted to cause phototoxicity, although photo-testing in patients taking these retinoids or applying topical tretinoin have typically been normal. Retinoid-induced thinning of the stratum corneum, allowing for penetration of a larger quantity of UV into the skin, is the likely cause for the development of phototoxicity in these patients. There may be residual photosensitivity after cessation of systemic retinoids due to their longer half-life.

Anti-neoplastic Agents

5-Fluorouracil is an antineoplastic agent used topically to treat actinic keratoses and systemically for a variety of cancers. It causes phototoxicity in the form of erythema and hyperpigmentation. Methotrexate occasionally produces a "recall" of previous UVR-induced erythema; specifically, the patient develops erythema upon taking methotrexate on sites of previous erythema (such as phototest sites) but no longer exposed to UV. However, photo-testing of patients taking methotrexate has been normal. The mechanism of the "recall" phenomenon remains unclear. Rare reports of a "recall" phenomenon have also been reported with 5-fluorouracil.

Dacarbazine and vinblastine are other antineoplastic agents implicated in photoxic reactions. Recently, UVA-dependent phototoxicity secondary to vemurafenib, a B-RAF inhibitor used for treatment of metastatic melanoma, has been reported. Paclitaxel and docetaxel belong to the taxane class of chemotherapeutics. By stabilizing and preventing breakdown of microtubules, taxanes interfere with cell division. Both agents have been reported to cause phototoxic reactions in conjunction with trastuzumab (a humanized monoclonal antibody against human epidermal growth factor receptor-2) in patients being treated for metastatic breast cancer. Elevation of urinary porphyrin levels suggests an association with porphyrin biosynthesis. A photo-recall phenomenon has been observed with docetaxel.

Phototoxicity followed by hyperpigmentation has been observed with vandetanib. Vandetanib is a multikinase inhibitor of epidermal growth factor receptor, vascular endothelial growth factor receptor, and the RET (rearranged during transfection) kinases currently being tested in cancer treatments. It has been shown to have a number of photosensitive effects in patients treated for metastatic thyroid cancer. Photosensitization was observed in 37 % of patients after a median treatment duration of 8 weeks. Phototoxic reactions ranged from an exaggerated sunburn after moderate sun exposure to severe photodistributed erythematous eruption. Lichenoid eruption, subacute cutaneous lupus erythematosus, erythema multiforme, and positive photopatch test results were also reported.

Porfimer sodium is an intravenous photosensitizer used therapeutically to induce phototoxic damage of systemic tumors. It is associated with a visible wavelength-dependent and persistent photosensitivity that can be severe. Following intravenous injection, patients who have been administered porfimer sodium are advised to avoid bright sunlight and incandescent light for 4–6 weeks. Some patients may develop severe phototoxicity within the infusion arm beyond this period of time, which suggests that the drug persists at a higher concentration, for a longer period of time at the site of injection than elsewhere on the body.

Intravenous medications used in conjunction with laser to treat macular degeneration causes photosensitivity for the first few days after therapy,

Various Manifestations of Phototoxicity

Aside from exaggerated sunburn reactions, there are other unique clinical manifestations of phototoxicity, described below.

Pseudoporphyria

Pseudoporphyria resembles porphyria cutanea tarda, both clinically and histologically. It is characterized by bullae, increased skin fragility, and easy bruising on light exposure, followed by milia and scarring (Fig. 10.1).

Drug-induced pseudoporphyria, unlike porphyria, is not associated with elevated porphyrin levels or abnormalities in porphyrin metabolism. Histologic examination of pseudoporphyria shows dermal-epidermal separation at the lamina lucida and deposits of immunoglobulins at the dermal-epidermal junction and surrounding blood vessel walls. While pseudoporphyria generally resolves with discontinuation of the drug, full resolution can take weeks to months. Pseudoporphyria has been observed with NSAIDs, particularly naproxen. Pseudoporphyria is also caused by amiodarone, β−lactam antibiotics, bumetanide, ciprofloxacin, furosemide, ketoprofen, mefenamic acid, nabumetone, nalidixic acid, oral contraceptives, oxaprozin, sulfonylureas, tetracyclines, tiaprofenic acid, torsemide, and voriconazole. Rare reports of pseudoporphyria with use of celecoxib and rofecoxib, COX-2 inhibitors, have been published.

Photo-Onycholysis

Photo-onycholysis tends to involve the distal third of the nail and is characterized by tenderness to gentle pressure (Fig. 10.2).

Photo-onycholysis usually occurs after more than 2 weeks of exposure to the offending drug. A few hypotheses have been generated to explain why photo-onycholysis may develop. First, the nail is convex in shape, allowing it to focus light like a convex lens. Second, there is little protection from light in the nail bed due to low levels of melanin. Third, there are no sebaceous glands, and thus no lipids, to reduce UV transmission. It is also possible that UVA penetrates normal nails more readily than skin.

Benoxaprofen, chlorazepate dipotassium, fluoroquinolones, oral contraceptives, psoralens, quinine, and tetracyclines have been associated with photo-onycholysis. The atypical antipsychotics olanzapine and aripiprazole have been reported to cause photo-onycholysis, as well. The condition resolves with discontinuation of the offending medication.

Slate-Gray Pigmentation

Slate-gray pigmentation on sun-exposed skin has been associated with several drugs. High-dose amiodarone therapy produces a slate-gray pigmentation. This pigmentation is thought to be due to deposition of amiodarone or one of its metabolites, desethylamiodarone, within the dermis, and improves after cessation of therapy. Pigmentation and susceptibility to phototoxicity

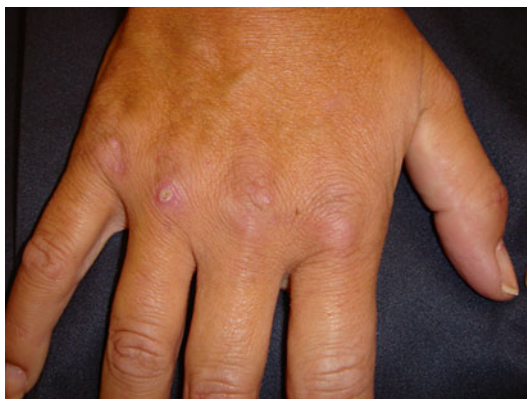

Fig. 10.1 Pseudoporphyria. Note the crusted vesicle on the knuckle

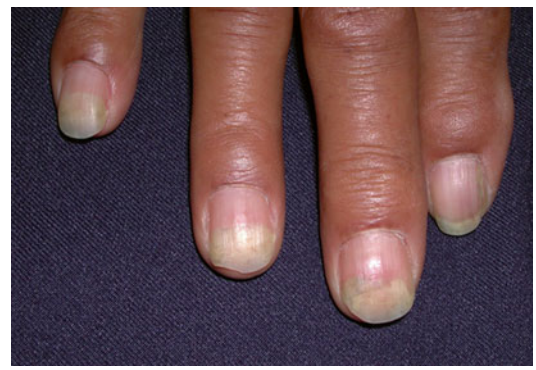

Fig. 10.2 Photo-onycholysis involving distal fingernails in a patient receiving psoralen plus UVA therapy

may continue for months or even years after discontinuation, although most generally clear over a 2-year period. Q-switched laser treatments may be an option for those with persistent pigmentation. Alternatively, desensitization through epidermal thickening and pigmentation effect (artificial hardening) with narrowband UVB phototherapy could be considered in such cases.

In addition to the slate-gray pigmentation, amiodarone can also cause a golden-brown pigmentation in sun-exposed skin. Chlorpromazine can also produce a golden-brown pigmentation in sun-exposed areas that is often followed by slate-gray hyperpigmentation. The slate-gray pigmentation is thought to be induced by formation of a complex of the agent with melanin. Both types of pigmentation are reversible upon cessation of the drug, but can take months to fully resolve. Clozapine can produce a similar slate-gray pigmentation (Fig. 10.3).

Minocycline can induce blue-gray pigmentation on the face, particularly on sites of previous acne lesions. Similar pigmentation can also be noted on forearms or shins (Fig. 10.4). While minocycline-induced pigmentation is most frequently associated with sun exposure, it is not always the case. Q-switched lasers have been used with success in treating minocycline-induced pigmentation.

Diltiazem, a benzothiazepine calcium channel blocker, causes a photo-distributed hyperpigmentation noted in patients on long-term treatment or extended-release formulations. The morphological appearance of the hyperpigmentation is reticulated and slate-gray or blue-gray in color.

Imipramine and desipramine, tricyclic antidepressants, are associated with a slate-gray pigmentation in sun-exposed areas, thought to be due to increased melanin production with pigmentary incontinence and possible drug deposition.

ABCD (acquired brachial cutaneous dyspigmentation) is mottled brown drug-induced photodistributed hyperpigmentation bilaterally over the extensor forearms. Angiotensin converting enzymes are the usual offenders.

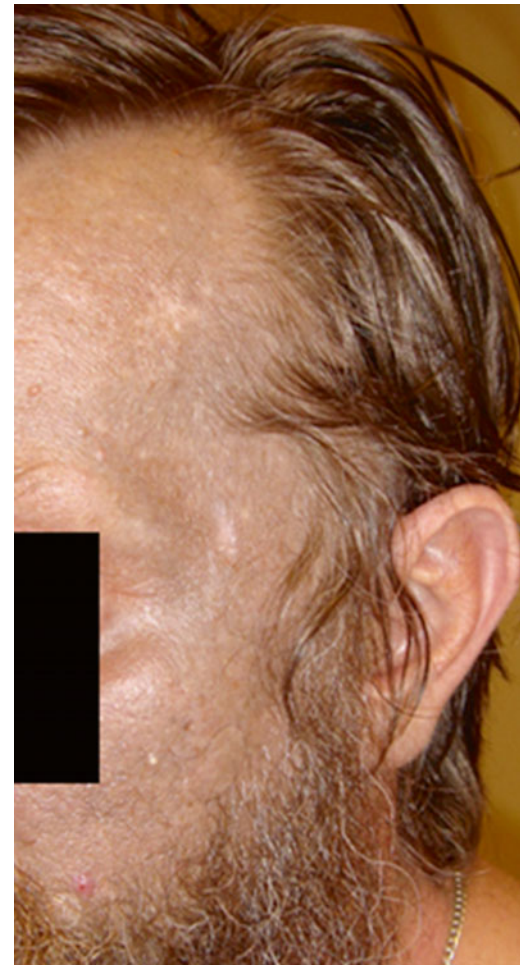

Fig. 10.3 Clozapine-induced slate-gray pigmentation on sun-exposed areas of the face

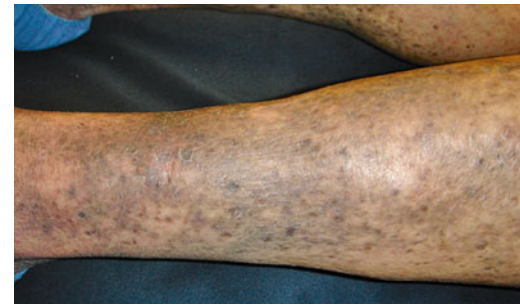

Fig. 10.4 Minocycline-induced blue-gray pigmentation on the shin

Lichenoid Eruptions

Lichenoid eruptions have been reported as a form of phototoxicity, but remains controversial. Lichenoid reactions on sun-exposed areas have been reported after exposure to chloroquine, dapsone, desethylchloroquine, hydrochlorothiazide, hydroxychloroquine, enalapril, fenofibrate,

furosemide, naproxen, quinidine, quinine, tetracyclines, and thioridazine. Histologic examination may show a greater degree of spongiosis and dermal eosinophilic and plasma cell infiltrates when compared to idiopathic lichen planus.

Evolution of Phototoxicity into Chronic Actinic Dermatitis

There are reports of phototoxicity evolving into chronic actinic dermatitis years after cessation of the causative agent. Chronic actinic dermatitis (CAD) presents with pruritus, excoriation, and lichenification on sun-exposed areas. It has been reported with simvastatin, thiazides, quinidine, and quinine. CAD improves or resolves over time in most patients, although this may take several years. Published data show that 79–90 % of patients may have improvement or resolution, and up to 35 % may have resolution of CAD at 15 years post-diagnosis.

Differential Diagnoses

Inflammatory phototoxic reactions should be distinguished from ordinary sunburn, which would require more intense UVR exposure, and systemic lupus erythematosus, which can be distinguished with routine histology (antinuclear antibodies, Anti-Ro/SSA and Anti-La/SSB antibodies).

Pathology

Histologic examination of acute phototoxicity demonstrates necrotic keratinocytes, epidermal spongiosis, edema, and vasodilation with sparse dermal inflammatory infiltrate. Histologic descriptions of the various forms of phototoxicity are discussed above.

Photoallergy

Epidemiology

The exact prevalence of photoallergy in the general population is unknown. However, its frequency at photodermatology referral centers has ranged anywhere from 4 to 8 %. Yet in a recent study from a single center in Shanghai, China, involving 4,957 patients photopatch-tested over a 7-year period, 50 % of patients had a positive photopatch test result.

Pathogenesis

Photoallergic reactions to drugs are thought to be a Type IV (cell-mediated) delayed hypersensitivity response. Pathogenesis of photoallergy requires the presence of UVR to form a photoallergen. There are two mechanisms thought to convert a drug into an immunologically active compound. In one mechanism, stable photoproducts are formed from the interaction between the drug and UVA. One of these photo-products acts as a hapten that conjugates with a carrier molecule to become an antigen. The antigen then stimulates an immune response. Sulfanilamide is thought to cause photoallergy by this mechanism. The photoallergic reaction requires an initial sensitization period before the onset of signs of symptoms. The wavelengths of light that cause activation of photoallergens are mainly in the UVA range, but extend into the UVB range for some photoallergens. Diphenhydramine, for example, has been reported to cause photoallergy with wavelengths in the UVB range but not the UVA range.

In the second mechanism, absorption of photons by the drug results in the formation of an unstable, excited state molecule. As the molecule returns to ground state, energy is released. The energy released is used for conjugation of the product to a protein carrier, resulting in formation of an antigen. Drugs that cause photoallergy through this mechanism include chlorpromazine and halogenated salicylanilides.

After the antigen is formed, by either mechanism, it is taken up by epidermal Langerhans cells and expressed on the cell surface. The Langerhans cells then migrate to regional lymph nodes and activate T lymphocytes. The T lymphocytes then recirculate back to skin sites where the photosensitizing metabolite was exposed to

light. Upon re-exposure, a cascade of events mediated by cytokines results in an inflammatory, photoallergic response.

Drugs thought to cause photoallergy are typically lipid-soluble, low-molecular-weight compounds. As with phototoxic drugs, they tend to have resonating structures capable of absorbing photons from UV.

Clinical Features

Photoallergic reactions occur in individuals previously sensitized to a photoallergen. Onset of symptoms for photoallergic reactions can be delayed 24–72 h after administration of the drug and exposure to light. In an acute reaction, a pruritic, eczematous eruption develops upon exposure to photoallergens and UVR, resembling allergic contact dermatitis. Vesicles and bullae might develop in more severe cases, but this is less commonly seen than in phototoxic reactions. Continued exposure can result in a subacute or chronic phase with erythema, scaling, and/or lichenification. The photoallergic reaction is typically localized to exposed sites, however, repeated exposures can cause progression to more generalized skin involvement.

Agents That Cause Photoallergy

A number of agents, both topical and systemic, have been identified as causing photoallergic reactions (Tables 10.4 and 10.5). This section discusses the most common.

Sunscreens

Since the 1970s, use of sunscreen worldwide has increased significantly. Sunscreen ingredients are one of the most common photoallergens, likely due to their widespread use. However, since the prevalence of photoallergic reactions to sunscreens is low, patients should not be deterred from using sunscreen. The most common sunscreen active ingredients causing photoallergy include benzophenones (especially benzophenone-3 and benzophenone-4), octyl-dimethyl *p*-aminobenzoic acid,

Table 10.4 Topical photoallergens

Group	Chemical name
Sunscreens	Benzophenones Benzophenone-3 Benzophenone-4 PABA derivatives Ethylhexyl dimethyl PABA Cinnamates Cinoxate Ethylhexyl methoxycinnamate Isoamyl-p methoxycinnamate Others Butyl methoxydibenzoylmethane Octocrylene Octyl triazone Phenylbenzimidazole sulfonic acid
Anti-infective agents	Surface disinfectants: halogenated salicylanilides Tetrachlorosalicylanilide Tribromosalicylanilide Skin cleansers Chlorhexidine Hexachlorophene Pesticides Biothionol Dichlorophene Fenticlor Personal care products Triclosan
NSAIDs (topical)	Benzydamine hydrochloride Etofenamate Fepradinol Flufenamic acid Ketoprofen
Phenothiazines	Chlorpromazine Promethazine
Miscellaneous	Olaquindox (antibiotic in pig feed)

Modified from Lim (2012)

Table 10.5 Systemic photoallergens

Class	Generic name
Antiarrhythmics	Quinidine
Antimicrobials	Fluoroquinolones Enoxacin Lomefloxacin Sulfonamides
Antimalarials	Quinine
NSAIDs	Ketoprofen Piroxicam

Modified from Lim (2012)

dibenzoylmethanes, octocrylene, cinnamates, and camphor derivatives. Many patients with a history of photoallergy to ketoprofen have been noted to have positive photopatch test results to octocrylene and benzophenone-3. Although cross-reactivity among the allergens has been proposed, a clear explanation of these clinical findings remains elusive. Inorganic (also known as physical) UV filters, i.e. zinc oxide and titanium dioxide, have not been reported to cause photoallergy. Newer sunscreen agents appear to cause fewer photoallergic responses. Due to their relatively shorter duration on the market, more experience is needed to determine their photoallergenic potential. These agents include methylene *bis*-benzotriazolyl tetramethylbutylphenol, *bis*-ethylhexyloxyphenol methoxyphenyl triazine, dicamphor sulfonic acid, diethylamino hydroxybenzoyl hexyl benzoate, diethylhexyl butamido triazone, drometrizole trisiloxane, ethylhexyl triazone, and terephthalylidene.

Topical Antimicrobials

Along with sunscreen agents, topical antimicrobials make up the most common cause of topical photoallergy in the U.S. Tetrachlorosalicylanilide and tribromosalicylanilide are potent photosensitizers. Although no longer used in bar soaps and shampoos, they may still be found in industrial cleaners in the U.S.

Triclosan, a widely used antibacterial agent in bar soaps and deodorants, is a low-level photosensitizer, with only a few reported cases, despite its high frequency of use.

Dichlorophene (G-4), a rare photosensitizer, is widely used in shampoos, dentifrices, antiperspirants, and "athlete's foot" powder. It is also used in the treatment of fabrics.

Biothionol, a chlorinated phenol used in bar soaps in the 1960s, caused an epidemic of photoallergy in Japan. It is no longer used in bar soaps in the U.S., but may still be found in industrial cleaners and agricultural and veterinary products.

Fenticlor is a chlorinated phenol previously used in antibacterial and antifungal creams and ointments, hair creams, cosmetics, and hand soaps. It is no longer found as an ingredient in commercial products, but is still available for purchase in bulk from manufacturers, suggesting it could be a covert ingredient in unknown products. It is now most commonly used in research, high throughput screening, and unnamed antibacterial and antifungal creams. It is historically a moderate potency photoallergen and may produce false-positive results in photopatch testing.

Hexachlorophene was once a widely used antibacterial agent in over-the-counter skin cleansers in the U.S. The Food and Drug Administration changed its status to a prescription-only product after reports of neurotoxicity. A commercial preparation of the drug, Phisohex, is less frequently used in the U.S. and is a rarely reported photoallergen. Chlorhexidine, an antibacterial agent in skin cleansers and used as a dental rinse, is a rare topical photoallergen.

Olaquindox, an antibiotic added to pig feed, has been implicated in photoallergic reactions in agricultural workers.

Oral Antimicrobials

Oral antimicrobials including hydroxychloroquine, enoxacin, lomefloxacin, and quinine occasionally cause photoallergic reactions.

NSAIDs

While NSAIDs are more frequently associated with phototoxicity, photoallergy has been noted in some compounds. Topical NSAIDs are commonly used in Italy and other Mediterranean countries for inflammation and musculotendinous injuries. Ketoprofen is the most frequent photoallergen reported in photopatch testing studies in Europe. Etofenamate is also a frequent culprit in photoallergic responses. Other reported topical photoallergens include benzydamine hydrochloride, diclofenac, flufenamic acid, ibuprofen, indomethacin, piroxicam, suprofen, and tiaprofenic acid.

Psychiatric Medications

Chlorpromazine, in addition to causing phototoxicity, has been associated with photoallergic contact dermatitis in healthcare personnel administrating the drug in its parenteral form. This problem is less commonly seen with the advent of chlorpromazine syrup. It is the most common photoallergen reported in the Chinese

population. A case of photoallergy to cyamemazine, also a phenothiazine antipsychotic, has also been described.

Miscellaneous

Other miscellaneous drugs thought to be photoallergens include dapsone, diphenhydramine, flutamide, enalapril, promethazine, and sulfonylureas. Tenofovir disoproxil fumarate, an antiretroviral drug widely used as part of highly active antiretroviral therapy (HAART) in HIV-infected individuals, has been reported as a possible photoallergen. HIV patients have increased photosensitivity reactions even without drug exposure.

Differential Diagnoses

Differential diagnosis of photoallergic reactions includes other forms of dermatitis that involve sun-exposed areas, such as airborne contact dermatitis, seborrheic dermatitis, and atopic dermatitis. Of note, in airborne contact dermatitis, sites typically spared by photoallergic contact dermatitis can be involved, such as upper eyelids, submental region, and post-auricular areas. Chronic actinic dermatitis, characterized by lichenification on sun-exposed sites, can be associated with photoallergy, most frequently to airborne allergens.

Pathology

Histologic examination of a photoallergic reaction is identical to that of allergic contact dermatitis, with epidermal spongiosis and an infiltrate of mononuclear cells in the dermis.

Diagnosis of Drug-Induced Photosensitivity

Diagnosis of photo-induced drug eruptions is based mostly on the history given by the patient. The history should be focused on medication history and temporal relationship between the start of the new medication/agent and the onset of the drug eruption. Review of systems should be performed to screen for diseases that can cause photosensitivity, such as systemic lupus erythematosus or porphyria cutanea tarda. On physical examination, one would expect to observe areas of involvement of sun-exposed areas and sparing of non-sun-exposed areas. The classic areas of photo-eruptions include the face, the V of the chest, nuchal region, forearms and hands. Areas of sparing would include non-sun-exposed areas such as the breasts, genitalia, palms, soles, and flexures of the extremities; whereas more subtle areas of sparing would include upper eyelids, submental area, under the nose, nasolabial fold, and post-auricular areas. Widespread eruption suggests systemic photosensitizers, whereas topical photosensitizers produce lesions in areas that have been exposed to both the sensitizing agent and radiation. Vesicular or bullous eruptions are more likely to be associated with phototoxicity, and eczematous eruptions are more suggestive of photoallergy.

Phototesting, photopatch testing, and biopsy are helpful for definitive diagnosis. Phototesting for minimal erythema dose (MED) is most valuable for systemic phototoxicity, while photopatch testing would be helpful for evaluating photoallergy to topical agents. MED testing involves irradiating sun protected skin with gradually increasing doses of UVB (5–100 mJ/cm^2) and UVA (1–18 J/cm^2) to determine minimal erythema dose for each. Erythema at a lower than expected dose for a particular skin type is suggestive of phototoxicity. For most medications, the MED should normalize about 2 weeks after the discontinuation of the offending medication. Theoretically, testing should be repeated 2 weeks or more after discontinuation of the suspected agent to document normalization of MED. However, in most instances, clinical evaluation to ensure the resolution of phototoxicity is sufficient.

Photopatch testing involves applying duplicate sets of photoallergens under occlusion on the skin, typically on the back. One set is kept covered, serving as a control, while the other set is irradiated 24 h later with UVA (5–10 J/cm^2; and for patients with decreased MED to UVA, 50 % MED-A). The irradiated and non-irradiated sites

are examined 24 h after exposure to light. A reaction only on the irradiated site is indicative of photoallergy. A reaction that occurs on both the non-irradiated and irradiated sites, if greater on the irradiated site, suggests that the drug is capable of causing a contact and photocontact allergy. Responses of equal intensity on both sides suggest simple contact allergy.

Histopathology is useful in excluding other photosensitivity diseases. Biopsy specimens from photopatch test sites can be helpful in distinguishing between phototoxicity and photoallergy.

Management of Photosensitivity Disorders

Management is centered on identification and cessation of the implicated drug. When this is not possible, strict adherence to photo protection against UVA and UVB is required. Patients should be counseled on choice of a broad-spectrum sunscreen with SPF ≥30 as well as necessity for reapplication. In the U.S., all sunscreens marketed after December 2012 are mandated by the FDA to have passed an in vitro critical wavelength test of ≥370 nm to be labeled as broad spectrum. Patients should also be warned that window glass offers little protection from UVA, especially UVA >380 nm. A phototoxic drug can also be prescribed for evening dosing so that peak systemic levels occur overnight.

Because phototoxicity and photoallergy can result in erythema, edema, pruritus, and burning, therapy for relief of symptoms may be necessary. Possible interventions include cool wet dressings, soothing lotions, topical corticosteroids, and systemic antipruritic agents. Systemic corticosteroids are reserved for severe cases.

Conclusions

Photosensitivity can be a sign of serious underlying illness, most notably lupus erythematosus. Drugs can also produce this phenomena and should always be considered in this group of patients. We have tried to make this task more reasonable in the chapter we have written.

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Erythema Nodosum as a Drug Eruption

11

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Abstract

Erythema nodosum (EN) is the most common form of panniculitis and is a form of septal panniculitis, or inflammation of the fat. It is associated with many conditions including infections (viral, bacterial, fungal, protozoal), pregnancy, medications, autoimmune conditions, and malignancies. Half of all cases are idiopathic. Associated medications that are known to cause EN include oral contraceptive pills (OCPs), sulfonamides, penicillin, bromides, iodides, TNF inhibitors and granulocyte colony stimulating factors (G-CSF). Clinically, patients present with symmetrically distributed red, tender nodules on the anterior lower legs. Lesions last from days to weeks and then resolve without scarring. Treatment is directed at treating the underlying disorder. Supportive measures include rest, leg elevation, and non-steroidal anti-inflammatory drugs (NSAIDs).

Keywords

Erythema nodosum • Drug eruption • Panniculitis • Infections

Introduction

EN, also called erythema contusiformis and erythema nodosum migrans, is a type of septal panniculitis and is the most common overall cause of panniculitis. Panniculitis is a general term that refers to any type of inflammation in the subcutaneous adipose tissue. EN affects all ages, races, and genders but is seen more commonly in women in their second to fourth decades. It occurs in 1–5 individuals per 100,000 persons. It can be associated with systemic disorders and is considered to be a delayed type of hypersensitivity reaction to various antigenic triggers. These stimuli include infections and chemical agents. Infectious causes (bacterial, viral, fungal, protozoal) are common and account for up to one-third of all cases of EN. Upper-respiratory infections

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_11

(streptococcal and non-streptococcal) and bacterial gastroenteritis have been known to cause EN. Streptococcal upper-respiratory infections are the most common infectious etiology of EN. Other associations include pregnancy, medications, autoimmune conditions, malignancies (most commonly lymphoproliferative), and inflammatory conditions including inflammatory bowel disease (IBD) and sarcoidosis (see section "Conditions associated with erythema nodosum" below). Typically Crohn's disease (CD) is more closely associated with EN than ulcerative colitis. Underlying autoimmune conditions include autoimmune hepatitis, ankylosing spondylitis, antiphospholipid antibody syndrome, Behçet's syndrome, Reiter's syndrome, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Takayasu's arteritis, and Wegener's granulomatosis. One-third of patients with EN have no underlying systemic disease. Half of all EN cases are idiopathic.

Conditions Associated with Erythema Nodosum

- **Infection**:
  Bacterial
  Viral
  Fungal
  Protozoal
- **Pregnancy**
- **Medications**
- **Autoimmune disease**:
  Sarcoidosis
  Inflammatory Bowel Disease (Crohn's disease >Ulcerative colitis)
  Autoimmune hepatitis
  Ankylosing sponylitis
  Antiphospholipid antibody syndrome
  Behçet's syndrome
  Reiter's syndrome
  Rheumatoid arthritis
  Sjögren's syndrome
  Systemic lupus erythematosus
  Takayasu's arteritis
  Wegener's granulomatosis

Clinical Presentation

The clinical manifestations of EN include an acute eruption of tender, red subcutaneous nodules distributed symmetrically over the lower legs, most commonly the shins, that can become confluent (Figs. 11.1 and 11.2). Lesions appear in crops and can occasionally present on the thighs and forearms. They are less likely seen on the face, neck, and trunk in adults, but occur more commonly in children. As the lesions progress, they appear more bruise-like and are referred to as erythema contusiforme. These lesions can last anywhere from days to weeks; new lesions can appear for up to 6 weeks. Lesions do not ulcerate and eventually subside without scarring or atrophy. One-third of cases can recur; recurrences are more common in idiopathic EN. Constitutional symptoms can be present and may not be related to a coexisting systemic disorder; these include fever, arthralgias, and malaise. The pathogenesis of EN is complex; many neutrophils are seen in

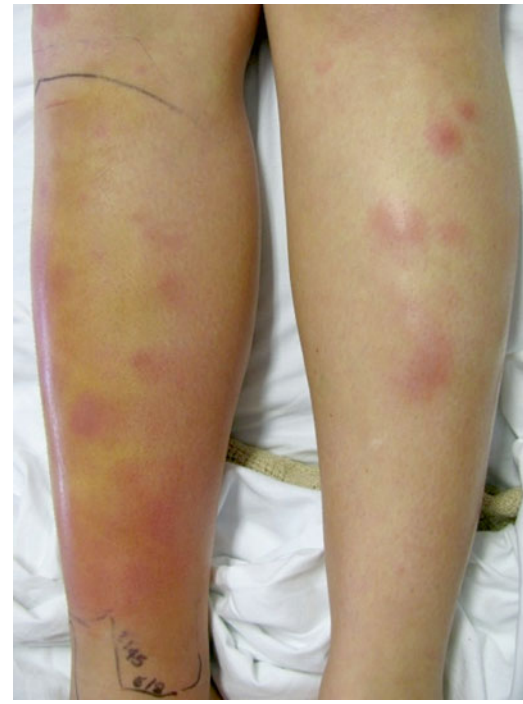

Fig. 11.1 Symmetrically distributed on the anterior shins there are erythematous, warm, indurated plaques that were confirmed to be EN on histopathology

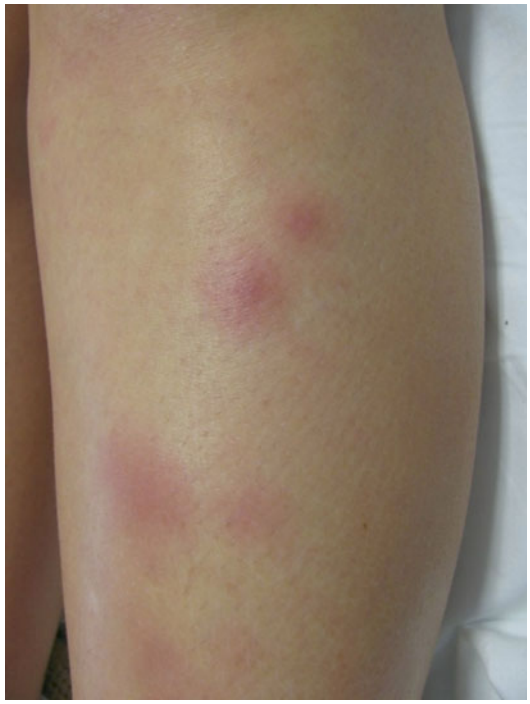

Fig. 11.2 A close-up of the lesions of EN on the left shin

early lesions on histopathology, which lead to the production of reactive oxygen species which lead to further inflammation and tissue damage. This theory is supported by the improvement seen with colchicine, which inhibits neutrophil chemotaxis.

EN as a Drug Eruption

Many medications are associated with EN; common agents include estrogen-containing oral contraceptive pills (OCPs), sulfonamides, penicillin, bromides, iodides, tumor necrosis factor (TNF) inhibitors, and granulocyte colony stimulating factors (G-CSF). There are other, less common, causes of drug-induced EN, as listed here:

- Antibiotics (sulfonamides, penicillin)
- Bromides
- Iodides
- TNF inhibitors
- Granulocyte colony stimulating factors
- Oral contraceptive pills (estrogen containing)
- Progesterone (intramuscular)*
- Azathioprine*
- Vemurafenib*
- Propylthiouracil*
- Interferon*
- *denotes less common cause

Azathioprine (AZA) hypersensitivity reaction can present with EN. A patient had several red-purple nodules on both lower legs 1 week after starting AZA 50 mg daily for bullous pemphigoid (BP), despite having normal thiopurine methyltransferase (TPMT) enzyme activity. Punch biopsy confirmed the diagnosis of EN and there was complete resolution of the lesions within 2 weeks of discontinuing AZA. This is considered an idiosyncratic hypersensitivity reaction to AZA and does not occur commonly.

EN can also be an adverse effect of anti-TNF agents, specifically certolizumab. A patient was being treated for CD with certolizumab (400 mg every 4 weeks); 1 day after her second injection, she noticed a tender, red nodule on her left lateral ankle. Imaging ruled out thrombophlebitis and deep-vein thrombosis (DVT). With each subsequent injection, the patient noticed expanding erythematous plaques on the anterior lower legs that were confirmed histologically to be EN. Once the certolizumab was stopped, the skin lesions started to resolve while the CD flared, supporting the theory that the EN was from the certolizumab rather than the underlying CD.

Vemurafenib is an oral agent used to treat metastatic melanoma; it is an inhibitor of mutated BRAF gene. Similar to other targeted therapies, vemurafenib has been associated with cutaneous adverse events. Two patients who were receiving 960 mg of vemurafenib both developed painful lesions on their arms and legs within 40 days after starting the medication. Biopsy was consistent with EN. A thorough infectious and autoimmune workup was done and was unrevealing, thereby attributing the EN to vemurafenib.

Propylthiouracil (PTU) is a drug used to treat hyperthyroidism. It has various adverse effects, many of which are cutaneous. These cutaneous manifestations include urticaria, pruritus, hair

loss, and erythema multiforme. Some of the rare cutaneous findings associated with PTU include antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis, which has a predilection for the distal extremities and the face but can also involve the ears, trunk, and breasts. Pathology of these lesions would show a small vessel leukocytoclastic vasculitis (LCV). There have been few reports of an ANCA-positive erythema nodosum. The incidence of PTU-induced ANCA positivity is 4–6 %. The time between starting PTU and ANCA positivity ranges from 1 week to 13 years. Approximately 20 % patients with positive ANCA develop vasculitis. A patient with hyperthyroidism had been started on PTU 100 mg daily and after 11 months developed warm, tender, red nodules ranging in size from 1 to 5 cm on bilateral, anterior lower extremities. She also had smaller, similar lesions on her fingers, palms, and wrists. Laboratory analysis revealed a normal complete blood count and a positive perinuclear (p)-ANCA at 1:160 dilution, while her proteinase 3 (PR3)-ANCA level was 0. Pathology confirmed the diagnosis of EN and there was no evidence of vasculitis. PTU was stopped and the EN was treated with thalidomide 75 mg daily. Over the next 3 weeks the lesions resolved, and 3 months later the p-ANCA titer decreased to 1:80. At 5 months, thalidomide was stopped. One year later the patient's skin was clear, with no recurrence of EN.

It has also been well established that EN can be associated with female sex hormones, both estrogen and progesterone. There are various instances that support this theory. First, EN most commonly occurs during the first trimester of gestation, but not the third trimester. Additionally, after puberty EN has a female predominance, but prior to puberty it affects males and females equally. It is believed that the concentration of progesterone or the ratio of estrogen to progesterone plays more of a role than the sole level of estrogen. Another supporting theory is that since the 1980s, the levels of hormones in OCPs have decreased and EN caused by OCPs is very rare these days. A case of reproductive therapy-induced EN was found to be from intramuscular injection of progesterone 50 mg daily for 4 weeks for endometrial preparation. Once the injections were stopped, the patient was changed to topical vaginal progesterone and the lesions subsided and improvement was noted within 2 days.

Interferons (IFNs) have also been known to cause EN and are being used more frequently to treat hepatitis C virus (HCV), specifically pegylated IFNs. Interferons are a group of cytokines that are able to interfere with viral replication, cell proliferation, immunoregulation, and tumor cell growth. There have been many reported dermatologic and rheumatologic side effects associated with IFNs. A 40-year-old female with HCV was treated with IFN alpha-2b (5 MU × 3/week) and ribavirin (1000 mg daily) × 48 weeks. In the 45th week of therapy the patient developed an inflammatory arthritis, a newly positive rheumatoid factor, and tender nodules on bilateral lower extremities that were proven histologically to be EN. The patient was given non-steroidal anti-inflammatory drugs (NSAIDs) until antiviral therapy was completed. After the IFN was stopped, the arthritis and EN both rapidly disappeared. It is believed that those who are HLA DR3 and DR4 have an increased chance of developing IFN-alpha induced autoimmunity, including both rheumatoid arthritis and EN.

Treatment

The treatment options for EN vary. Treatment is mainly supportive and includes NSAIDs and bed rest. Other treatment options include colchicine and potassium iodide. There have been rare cases of potassium iodide triggering EN. Systemic corticosteroids are rarely indicated in EN however, before they are used, it is important to rule out infectious etiologies. Nevertheless, it is important to identify and treat the underlying disorder if one exists.

Conclusions

Erythma nodosum is a panniculitis, usually of the pretibial areas, that can be idiopathic or associated with underlying diseases, especially sarcoidosis. A third possibility that should always be kept in mind is a drug reaction.

These nodules can be painful and debilitating, so finding and eliminating the underlying drug when it is the cause is important. This chapter has attempted to help with the search for the culprit drug.

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Lichen Planus Drug Reactions

12

Carol W. Stanford and Kaitlin Vogt Schiavo

Abstract

Lichen planus is a common chronic, inflammatory, autoimmune mucocutaneous disease. The lesions of lichen planus are most notably described using the six Ps: planar (flat-topped), purple, polygonal, pruritic, papules, and plaques. These characteristic lesions are often covered by the lacy, reticular, white lines known as Wickham striae. The exact etiology of this disease is unknown, however an immune- mediated pathology is well documented in the literature. A mucocutaneous eruption very similar to the idiopathic lichen planus presentation has been reported to be caused by several drug categories and whose recovery depends on the discontinuation of the drug. These drug categories include NSAIDS, ACE inhibitors, antimicrobials, and antiarthritics. The idiopathic disease can be distinguished from the drug eruption by characteristics of presentation and duration.

Keywords

Lichen planus • Polygonal • Wickham striae • Mucocutaneous • Drug eruption

Introduction

Lichen planus is a common chronic, inflammatory, autoimmune mucocutaneous disease. The lesions of lichen planus are most notably described using the six Ps: planar (flat-topped), purple, polygonal, pruritic, papules, and plaques. These characteristic lesions are often covered by the lacy, reticular, white lines known as Wickham striae. The exact etiology of this disease is unknown, however an immune- mediated pathology is well documented in the literature. A mucocutaneous

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_12

eruption very similar to the idiopathic lichen planus presentation has been reported to be caused by several drug categories and whose recovery depends on the discontinuation of the drug.

Presentation and Characteristics

Primary Lesions

Clinically, the lichen planus-like drug-induced eruptions are indistinguishable from the idiopathic lichen planus lesions. The papulosquamous rash is composed of pruritic, flat–topped, violaceous papules and plaques. An extensive and symmetric distribution involving the trunk and limbs is typical of the drug-induced eruption.

Just as idiopathic lichen planus can present with erosive and bullous variants, lichen planus-like drug eruptions may as well. However, the above-described classic presentation is the most common eruption. The drug-induced disease affecting mucosal surfaces has been reported in previous dermatology textbooks as being a rare phenomenon, but oral mucosal lesions are more common than previously thought.

Secondary Lesions

Excoriations are not commonly noted, but due to the pruritic nature of the lesions, patients will often rub the lesions. This could be because scratching the papules may be painful. Hyperpigmentation (Fig. 12.1) is a common sequela following resolution, especially in darker skinned individuals.

Distribution

The lesions most commonly produce an extensive and symmetric outbreak on the trunk and limbs, such as the palmar surfaces and gluteal folds, but they can appear anywhere on the body including the oral mucosa. Whenever one area of the body is affected, a full skin exam should be done to properly assess the extent of disease. The idiopathic disease has a more prominent presentation on the flexor surfaces of the wrists, ankles, lumbar region, and mucosal surfaces than the drug-induced form.

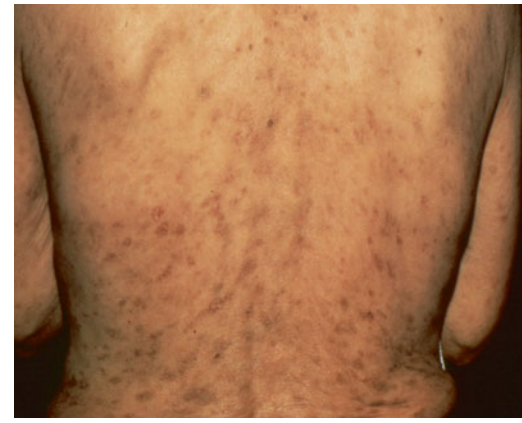

Fig. 12.1 Dramatic hyperpigmentation over the back in a patient on gold therapy. The biopsy was compatible with a lichenoid drug eruption. The newer lesion on the upper back show less pigmentation and more erythema

Course

An extended latent period is noted from the time of drug initiation to the presence of a lichen planus-like skin eruption. The eruptions can occur from 1 month to 2 years after drug initiation, in contrast to most other skin drug eruptions whose latent period is usually confined to between one and two weeks. Certain lichen planus-like skin eruptions may disappear or reoccur intermittently if the offending drug is not discontinued. At the discontinuation of the inciting drug, resolution most commonly occurs within months to years. However, not all lichen planus-like skin eruptions will resolve.

Age Group

Most cases of lichen planus-like drug eruptions occur between 30 and 60 years of age, similar to the idiopathic disease. Pediatric cases of a lichen planus-like drug eruption have been reported, though, and therefore age should not rule out the cause of the skin eruption.

Skin Biopsy

A 4-mm punch biopsy should represent an adequate biopsy of the skin or oral mucosa. Histopathological examination will show a characteristic "saw tooth" pattern of epidermal hyperplasia and hyperparakeratosis with a thickened granular cell layer. The basal cell layer of the epidermis will show vacuolar alteration and the dermal-epidermal junction will demonstrate an intense T-cell infiltration. The presence of eosinophils and lymphocytes extending into the deep dermis involving the follicles and perivascular regions favor a lichen planus-like drug eruption as opposed to an idiopathic outbreak.

Differential Diagnosis

- **Idiopathic lichen planus**: more prominent presentation on the flexor surfaces of the wrists, ankles, lumbar region and mucosal surfaces
- **Secondary syphilis**: Non-pruritic lesions with positive blood serology
- **Psoriasis**: Lesions are scalier with an increased presence on knees and elbows
- **Pityriasis rosea**: Lesions are found in the lines of cleavage of the skin
- **Lichen simplex chronicus**: Plaques found in areas that are easily scratched
- **Prurigo nodularis**: Lesions often confined to extremities

Cause of Idiopathic Lichen Planus

Idiopathic lichen planus has most closely been linked to a T-cell mediated autoimmune process. The triggering agent remains unknown. The basal keratinocyte degeneration is attributed to cytotoxic CD8+ T lymphocytes, while CD4+ helper T lymphocytes lead to destruction in the lamina propria. As the disease progresses, CD8+ lymphocytes are found to increase in number at the sites of the lesions. It is postulated that the underlying mechanism may be due to an imbalance between the CD4+ helper T lymphocytes and T suppressor lymphocyte activity. Kertatinocytes are the main target of the dysregulated T lymphocytes because of their expression of foreign or altered self-antigens on their surfaces.

A significant association between lichen planus and hepatitis C and hepatitis B has been reported. Patients with lichen planus have higher rates of hepatitis C and B infection than the general population, and conversely patients with hepatitis C and B are more likely to develop lichen planus than the general population. The relation between lichen planus and hepatitis seropositivity is even stronger in patients co-infected with HIV. Due to this correlation, many providers will screen all patients presenting with lichen planus for hepatitis C and hepatitis B.

Although the exact mechanism for the disease has not been established, the relatively benign and many times self-resolving nature of lichen planus should be reassuring to the patient. However, protracted courses of the disease have been reported and can be linked to drug-induced eruptions. Lichen planus-like drug eruptions are postulated to be induced by medications altering the balance of cytokines in the immune system or by antigen mimicry. These drug categories include NSAIDS, antihypertensives, antimicrobials, antiparasitics, and antiarthritics. It is important to differentiate the drug-induced disease from the idiopathic disease because recovery of the drug-induced eruption can depend on the identification and withdrawal of the inciting drug.

Differentiating Factors

Skin involvement in adverse drug reactions is common, and the prevalence increases with the addition of new drugs and new drug classes. The diagnosis of drug-induced skin eruptions can often be intuitive, however, lichen planus-like drug eruptions can be especially difficult to diagnose. Lichen planus-like drug eruptions have a protracted latent period. The latent period has been documented as 4–6 weeks in certain drug categories and as long as 3 years in others. The

drug-induced lesions can have a prolonged course, with no improvement after application of topical steroid solutions. Idiopathic lichen planus improves after topical steroid use, so resistance to this treatment should lead to the suspicion of a drug-induced pathogenesis as opposed to the idiopathic disease. While a protracted course not improved by topical steroids is a differentiating factor, it is not reliable in all cases. Lichen planus-like drug eruptions can regress even with continuation of the inciting drug, and can even develop an intermittent course characterized by resolution and reoccurrence of the lesions. Idiopathic lichen planus also commonly develops an intermittent course with periods of resolution and reoccurrence. Due to the similarity in presentations, a mistaken diagnosis of idiopathic lichen planus may be made.

Idiopathic lichen planus and lichen planus-like drug eruptions can be clinically indistinguishable. Histological examination can be a distinguishing factor that is important to help guide treatment selection. The presence of an increased number of necrotic keratinocytes, plasma cells, and eosinophils on histological examination has shown to have a statistical significance in favor of identifying lichen planus-like drug eruptions.

Helpful hints for clinicians to differentiate lichen planus-like drug eruptions from idiopathic lichen planus are in Table 12.1

Table 12.1 Differentiating drug-induced vs. idiopathic lichen planus

Lichen planus-like drug eruption	Idiopathic lichen planus
Protracted course lasting months to years not improved by topical corticosteroids	Shorter course that can be improved by super-potent topical corticosteroids
Histologic examination shows an increased number of necrotic keratinocytes, plasma cells, and eosinophils	Histologic examination will not show eosinophils
Onset after drug initiation, improvement after drug withdrawal, or reoccurrence after drug reintroduction	No causative relationship to drug therapy

Work-Up

The diagnosis is clinical based on the characteristic appearance of purple, pruritic polygonal papules and plaques. When suspecting a lichen planus eruption based on the appearance of the lesions, it is important to first take a thorough prescription and nonprescription drug history, as new drugs or non-prescription drugs can cause lichen planus-like eruptions. It is important to distinguish the idiopathic disease from the drug-induced eruptions because idiopathic lichen planus often requires super-potent topical glucocorticoids as first-line treatment, which can lead to side effects such as skin atrophy and may not resolve the lichen planus-like drug eruption. Clinicians must also remember to rule out pityriasis rosea, prurigo nodularis, lichen simplex chronicus, and other skin conditions that present similarly.

The identification of the offending drug can be complicated by several factors such as simultaneous exposure to several new drugs, interactions between drugs, or the variability in the latent period and appearance of lesions. The drug history should include all drugs started in the last three years, as there can be a protracted latent period. A trial of drug termination should be tried in a lichen planus-like drug eruption (Fig. 12.2) that occurs in the first three months after starting a new drug. Termination drug trials are not always feasible, though, due to necessity of cer-

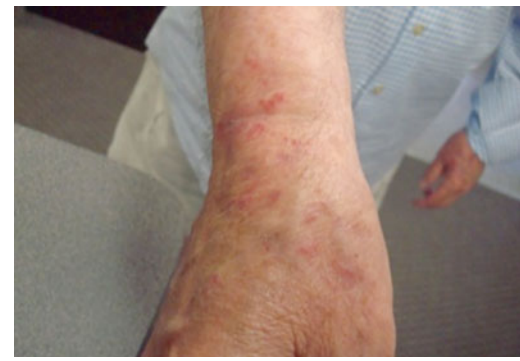

Fig. 12.2 Flat-topped, polygynal papules that were photo-induced in a patient on hydrochorthiazide. The biopsy was compatible with lichen planus, and the skin lesions cleared after the medication was discontinued

tain medications or if there are a large number of possible culprit medications.

If unable to determine if the lichen planus-like lesions are idiopathic or secondary to a drug, and termination drug trials are not feasible, a 4 mm punch biopsy can be performed. Characteristic necrotic keratinocytes, plasma cells, and eosinophils located around vessels increases the suspicion of a drug-induced etiology. This histological finding will then favor termination of drugs that have been reported to cause the reaction if the benefit of resolving the lichen planus skin eruption outweighs the risk of cessation of the drug and an alternative medication can be used in its place. The drug may also be terminated and then restarted after the skin lesions have disappeared, in association with careful monitoring. It is important to note that even if the lichen planus initially resolves with discontinuation of a drug, and the drug is then restarted, the lichen planus-like drug eruption has a chance of not resolving with cessation of the drug the second time.

Screening Tests

Hepatitis B and C screening can be offered to patients due to the increased risk of disease in idiopathic lichen planus and the difficulty in separating idiopathic and drug-induced causes.

Drugs Implicated

Drugs that are implicated in drug-induced lichen planus eruptions include antiarthritics, antihypertensives, antiparasitics, anxiolytics, NSAIDS, immunosuppressants as well as other drugs, as listed here:

- **Antiarthritics**: aurothioglucose, gold salts
- **Antihypertensives**: **angiotensiongen-converting** enzyme (ACE) inhibitor, thiazide diuretics, atenolol, propranolol, labetalol, practolol and methyldopa, spironolactone
- **Antimicrobials**: dapsone, ketoconazole, streptomycin, sulfamethoxazole, tetracycline, penicillamine
- **Antiparasitics**: chloroquine, quinacrine, pyrimethamine
- **Anxiolytics**: lorazepam
- **Nonsteroidal anti-inflammatory agents**: ibuprofen, fenclofenac, naproxen, phenylbutazone
- **Oral hypoglycemic agents**: chlorpropamide, tolazamide, tolbutamide
- **Uricosuric agents**: allopurinol
- **Other**: atabrine, arsenic, ticlopidine

The pathogenesis of the above-mentioned drugs in the development of lichen planus-like drug eruptions is unclear, but some postulations have been documented in the literature:

Nonsteroidal anti-inflammatory agents: Prostaglandins and other arachidonic acid metabolites are known to have effects on epidermal proliferation. Nonsteroidal anti-inflammatory drugs may induce lichen planus-like eruptions due to the potent inhibiting of prostaglandin synthesis causing epidermal alterations.

Beta-receptor antagonist agents: The Beta-adrenergic system is suggested to play a role in cutaneous homeostasis by influencing extracellular signal kinases which affect keratinocyte migration. Alternation in this pathway caused by beta-blockers may lead to lichen planus eruptions.

Tissue necrosis factor (TNF) – alpha antagonist agents: Inhibition of TNF-alpha may allow up-regulation of precursor cytokines such as interferon alpha. Interferon alpha favors the activation of T-cells and may elicit a subsequent inflammatory response responsible for producing a lichen planus-like eruption.

Through case reports, generalizations have been made as to how long the lichen planus-like eruptions remain after discontinuation of the drug. Short-duration drugs include labetalol, tolazamide, and cyanamide. Lichen planus-like eruptions resolve between 2 weeks and 1 month after discontinuation of these drugs. Long-duration drugs include penicillamine, hydrochlorothiazide, spironolactone, propranolol, captopril,

flunarizine, quinidine, and gold. These drugs need to be discontinued for 1 month to 3 years for complete resolution to occur.

Treatment

The treatment includes identification of the inciting drug and cessation or reduction of the dose. Other treatment options are usually restricted to topical corticosteroids. The resolution of the lesions after cessation of the offending drug may be prompt or may commonly take months to years. A mild topical corticosteroid cream may be beneficial after cessation of the drug. Hyperpigmentation is a common sequela during resolution of the lesions, especially in darker pigmented individuals. Hyperpigmentation can be expected to lessen and even resolve with daily lotion and sunscreen application over a long period of time.

There is much discussion on the premalignant character of idiopathic lichen planus. Lesions that demonstrate erosive or ulcerative characteristics should be monitored closely by a physician and undergo biopsy if there is suspicion for squamous cell carcinoma if present on mucous membranes. The reason for malignant potential is uncertain but is postulated it may be due to concurrent use of immunosuppressant therapies.

Main Points

- Lichen planus is a common chronic, inflammatory, autoimmune mucocutaneous disease. The lesions of lichen planus are most notably described using the six P's: planar (flat-topped), purple, polygonal, pruritic, papules and plaques. A mucocutaneous eruption very similar to the idiopathic lichen planus presentation has been reported to be caused by several drug categories.
- Lichen planus-like drug eruptions have a protracted latent period of weeks to months after initiating the inciting drug.
- Idiopathic lichen planus and lichen planus-like drug eruptions can be clinically indistinguishable. Histological examination can be a distinguishing factor in some cases.
- Lichen planus-like drug eruptions will most often not be improved by chronic corticosteroid use.
- Some clinicians encourage hepatitis screenings in patients with lichen planus-like eruptions given their high rate of association

Conclusions

Lichen planus is a disease with characteristic clinical and histopathological characteristics whose etiology is still poorly understood. It is felt by many authors to be an autoimmune disease. Its association with underlying illnesses, especially hepatitis C, is still a topic under investigation but there is no debate that a drug eruption is a difficult part of the differential diagnosis. Being alert to this possibility and discontinuing the offending medication certainly contributes to the care of our patients.

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Pityriasis Rosea-Like Drug Eruptions

13

Kaitlin Vogt Schiavo and Carol W. Stanford

Abstract

Pityriasis rosea is an acute, mild, self-limited papulosquamous skin disease of uncertain etiology. The disease is characterized by the initial presence of a salmon-pink oval patch or plaque deemed the "herald patch." This is followed by the widespread eruption of oval macules, papules, and plaques whose long axis follows the lines of cleavage, resulting in the characteristic "Christmas tree" or "fir tree" distribution. A skin eruption very similar to this presentation has been reported to be caused by several drug categories and whose recovery depends on the discontinuation of the drug. These drug categories include NSAIDS, ACE inhibitors, vaccinations, mood stabilizers, barbiturates, and antihistamines. The idiopathic disease may sometimes be distinguished from the drug eruption by characteristics of presentation and duration.

Keywords

Pityriasis rosea • Herald patch • Papulosquamous • Drug eruption • Scaling collarette

Introduction

Pityriasis rosea is an acute, mild, self-limited papulosquamous skin disease of uncertain etiology. The disease is characterized by the initial presence of a salmon-pink oval patch or plaque deemed the "herald patch." This is followed by the widespread eruption of oval macules, papules, and plaques whose long axis follows the lines of cleavage, resulting in the characteristic

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_13

"Christmas tree" or "fir tree" distribution. A skin eruption very similar to this presentation has been reported to be caused by several drug categories and whose recovery depends on the discontinuation of the drug.

Gilbert's Pityriasis Rosea

Pityriasis rosea is an acute, self-healing papulosquamous exanthem characterized by oval erythematous lesions of the trunk and limbs. Sparing of the face, scalp, palms, and soles is a common characteristic. A larger solitary, oval patch called "herald patch" may precede the generalized eruption by 2–10 days. The generalized rash is characterized by patches that are similar to the initial one, but are smaller and symmetrically oriented, with their long axes along the cleavage lines or "Christmas tree" distribution. Mild malaise may be seen at onset. A collarette of fine scale is seen around the edge of the lesions. The entire rash most commonly disappears within 6–8 weeks. The cause is unknown but human herpes virus (HHV) infection has been implicated. The disease is self-limiting, therefore no treatment is required, but prednisone and erythromycin have been tried by some authors.

Causes

Gilbert's Pityriasis rosea has most closely been linked with a viral etiology, specifically HHV-6 and HHV-7. Factors that support a viral etiology include increased prevalence during the fall, winter, and spring months, as well as clustering of disease occurrence within close contacts such as families, school-aged children, and military personnel. This disease is also commonly associated with prodromal symptoms. However, it remains uncertain whether this disease is due to primary infection or reactivation of the virus. It has been postulated that the reported pityriasis rosea-like drug eruptions are due to reactivation of a virus by drugs, however, major differences have been documented in the literature that seem to differentiate drug-induced pityriasis rosea from the idiopathic disease. Because of these major differences, some literature argues that the pityriasis rosea-like drug eruption is unrelated to the idiopathic disease.

Many articles have implicated the latency and reactivation of HHV-6 and HHV-7. Evidence supporting this hypothesis include: (1) The initial herald patch can occur at sites of trauma that may be representative of the portal of entry, which favors a primary infection; and (2) correlations associated with a reactivation reaction include increased prevalence in those with decreased immunity and high rates of reoccurrence.

The newest evidence seems to disprove such a hypothesis. After studying 12 cases, many differences from Gilbert's pityriasis rosea were observed such as a lack of a herald patch, more confluent lesions, extensive involvement of the extremities, and extreme pruritus, as well as the presence of eosinophils in the dermis in the majority of patients. Virologic evidence of HHV-6 and HHV-7 was searched for in ten of the patients and was detected in the plasma of only one patient. The major clinical differences and lack of HHV positivity calls into question the role of the herpes virus in drug-induced pityriasis rosea-like rashes. Further studies including a larger number of patients are needed in order to help further define HHV-6 and drug-induced pityriasis rosea.

Although no etiology has been proven, the benign self-resolving course of this skin eruption remains reassuring. However, protracted courses of the disease have been reported and it is important to differentiate the drug-induced disease from the idiopathic disease because recovery of the drug-induced eruption depends on the identification and withdrawal of the inciting drug.

Differentiating Factors

Skin involvement in adverse drug reactions is common and the diagnosis is often intuitive, however, certain presentations may imitate and be misdiagnosed as a more common skin

condition such as the idiopathic Gilbert's Pityriasis rosea. The protracted course remains the key identifying factor to differentiate the idiopathic disease from the drug eruption. The morphology can also be used as a differentiating factor in most cases. The Gilbert's idiopathic disease will have the presence of a single herald patch followed by an eruption of multiple salmon-pink lesions with a fine collarette of scaling. Pityriasis rosea-like drug eruption typically will not present with an initial herald patch. Instead, it more closely resembles the secondary eruption of the idiopathic disease, but it consists of fewer, larger, bright violet-to-red macules, patches, and plaques with scaling across the entire lesion. On histological examination these lesions will have an increased presence of increased eosinophils as well as eosinophilia of the blood. The drug eruption lesions tend to be more pruritic than the idiopathic disease, and refractory to antihistamine treatment. The lesions are also more prone to have post-inflammatory hyperpigmentation as a sequela. The drug eruption pityriasis rosea-like lesions have a more common association with oral lesions than the idiopathic disease. The pityriasis rosea-like drug eruptions occur more commonly in older adults as opposed to younger children, as with the idiopathic disease.

Helpful hints for clinicians to differentiate pityriasis rosea-like drug eruptions from idiopathic pityriasis rosea are included in Table 13.1.

Presentation and Characteristics

Primary Lesions Pityriasis rosea-like drug eruption is a papulosquamous rash composed of bright violet-to-red macules, patches, and plaques with scaling across the entire lesion.

Secondary Lesions Excoriations are commonly seen due to severe pruritus unrelieved by antihistamines. Effects of overtreatment with topical steroids can be seen due to the protracted course requiring a longer duration of treatment. These effects include skin atrophy and striae development, most commonly. Contact dermatitis may also develop.

Distribution The macules, patches, and plaques appear mainly on the chest and trunk along the lines of cleavage in the skin. In many cases this creates a "Christmas tree" branching pattern.

Course The bright violet-to-red macules, patches, and plaques will continue to appear for 3–5 months or until the inciting drug has been terminated.

Season There is no seasonal preference as opposed to the idiopathic disease.

Age Group The disease is more common in adults over 35.

Table 13.1 Differentiating drug eruptions from idiopathic pityriasis rosea

Drug eruption-like pityriasis rosea	Gilbert's pityriasis rosea
Absence of initial single herald patch	Presence of initial single herald patch
Bright violet-red lesions	Salmon-pink lesions
Pruritus unrelieved by antihistamines	Pruritus relieved by antihistamines
Presence of increased eosinophils found in blood and skin infiltrate	Few eosinophils found in blood and skin infiltrate
Chronic course lasting 3–5 months	Acute course lasting 6–8 weeks
Fewer larger lesions with scaling involving the entire lesion	Many lesions diffusely on body with collarette of scaling
Oral lesions are more common	Oral lesions are rare
Post-inflammatory hyperpigmentation is a common sequela	Post-inflammatory hyperpigmentation is less commonly seen
More common in patients over age 35	More common in patients aged 10–35

Skin Biopsy Histopathological examination will show acanthosis, focal parakeratosis, mild spongiosis with extravasation of red blood cells, and exocytosis of lymphocytes. A sparse to moderate superficial perivascular lymphohistiocytic infiltrate with many esosinophils can also be seen.

Differential Diagnosis

- **Idiopathic pityriasis rosea**: Herald patch will be present; lesions occur mainly in young adults.
- **Psoriasis**: Lesions have a silvery scale; commonly located on extremities, mainly the elbows and knees.
- **Lichen planus**: Lesions are raised and occur commonly on mucous membranes.
- **Secondary Syphilis**: The patient may report a history of genital lesions and may deny a history of pruritus. Syphilitic papules are infiltrative and have frequent involvement of the palms and soles with lymphadenopathy. A rapid plasma regain test would resolve doubts.
- **Tinea Veriscolor**: Lesions are tan in color and irregularly bordered; lesions will form a dry adherent scale when scratched and fungi are seen on scraping.
- **Seborrheic dermatitis**: The herald patch may be confused with a patch of seborrheic dermatitis, however seborrheic dermatitis lesions will appear as greasy, scaly lesions with a preference of distribution for the face, scalp, and genitalia.
- **Contact dermatitis**: Eczematous features; commonly located on distal extremities in atopic individuals and those with occupational exposure to many chemicals.
- **Nummular Eczema**: Can appear very pruritic, resembling Giblert's pityriasis rosea, however, nummular eczema preferentially localizes to the shins, dorsal hands where pityriasis rosea is unlikely to be found.
- **Pityriasis lichenoides chronica**: May lack a herald patch and have a chronic course like drug-induced pityriasis rosea, but can be differentiated by papules in different stages of evolution.

Work-Up

When suspecting a pityriasis rosea-like drug eruption it is important to take a thorough history, as new drugs or non-prescription drugs can cause pityriasis rosea-like eruptions. The prevalence of these eruptions is believed to be underreported and likely occurs more commonly than previously thought. Since the eruption mimics a common and self-limiting disease, physicians are not prompted to check for a drug association cause until persistence, severity of the lesions, or pruritus require reconsideration of the original diagnosis.

A trial of drug termination should be tried in a pityriasis rosea-like eruption that lasts beyond 6–8 weeks. It is recommended to start termination of drugs that have been reported to cause the reaction or any drugs that were started in the 1–2 weeks previous to the initial eruption. Clinicians must also remember to rule out contact dermatitis in atypical cases of pityriasis rosea eruptions. Contact dermatitis can be differentiated from pityriasis rosea-like drug eruption by its eczematous features, and location of distal extremities.

If drug termination cannot be done do to necessity of the drug, titers of human herpes virus 6 and 7 should be checked to rule out the idiopathic disease. The drug may also be terminated and then restarted after the skin lesions are cleared in association with careful monitoring.

Clinical diagnosis is used to diagnose Gilbert's idiopathic pityriasis rosea and pityriasis rosea-like drug eruptions. Skin biopsy can be used to diagnose Pityriasis rosea eruptions that are in the earlier stages of the disease and do not yet have the characteristic morphology, or in atypical cases. Skin biopsy is not recommended due to increase risk of infection and scarring.

Drugs Implicated

Many drugs have been implicated in causing a drug-induced pityriasis-like rash, as listed below. Such drugs include older, rarely used

drugs like bismuth, arsenicals, gold, barbiturates, and methopromazine.

- Clozapine
- Lithium
- Adalimumab
- Imatinib
- Mustard oil
- Clonidine
- Barbiturates
- Captopril
- Gold
- Ketofen
- Arsenicals
- Bismuth compounds
- Tripelennamine hydrochloride
- Methoxypromazine
- Omeprazole
- Isotretinoin
- Terbinafine
- Benflurafine
- Penicillamine
- Hepatitis B Vaccine
- H1N1 Vaccine

More well-documented pityriasis rosea-like drug eruptions include eruptions caused by ACE inhibitors, NSAIDS, clozapine, anti-TNF alpha inhibitors, and BCR- ABL tyrosine kinase selective inhibitors. Proposed mechanisms of causation are included below:

- **ACE Inhibitors**: Thought to induce increased kinin levels evoking cutaneous inflammation (Fig. 13.1)
- **NSAIDS**: Work by inhibiting cyclooxygenases which may collaterally increase arachidonic acid leading to leukotriene release causing cutaneous inflammation.
- **Clozapine**: Metabolites produced during liver metabolism are thought to induce an inflammatory response leading to a pityriasis rosea-like skin eruption.
- **Anti-TNF alpha agents**: These agents are commonly used as disease modifying agents in rheumatic diseases that have dermatological manifestations, however, these agents have been associated with causing dermatological side effects including a pityriasis-rosea like eruption. It is postulated that the eruption is caused by reactivation of viral infections due to their immunity lowering function or by an immunological reaction to the TNF-alpha antibodies.
- **BCR- ABL tyrosine kinase selective inhibitors**: pityriasis rosea may need early detection and special care in these patients undergoing antineoplastic therapy, as the eruption may demonstrate a herpes virus infection in the severely immunosuppressed.

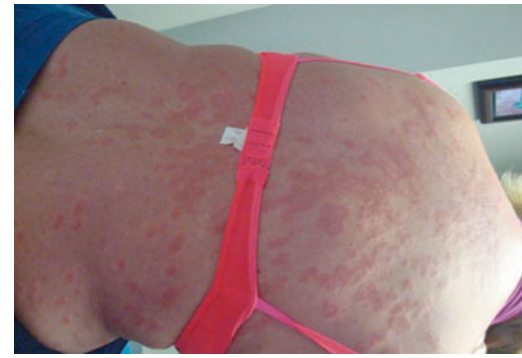

Fig. 13.1 Pityriasis-like drug eruption after stopping lisinopril for a year after years of use and then restarting. The patient had restarted for less than a month. No true herald patch and severe pruritis. The patient does have oval papules and plaques along Langer's lines of cleavage and severe pruritis. The skin cleared within 3 weeks of drug cessation and intramuscular betamethasone 6 mgms

Other commonly used medications reported in case reports to cause a pityriasis rosea-like eruption include metronidazole, D-penicillamine, isotretinoin, levamisole, pyribenzamine, omeprazole, terbinafine, and ergotamine tartrate.

Piyriasis rosea-like rashes have also been described after vaccinations of diphteria, smallpox, pneumococcal, hepatitis B virus, and BCG vaccinations. These vaccinations are thought to either result in a general inflammatory response leading to reactivation of HHV-6 or HHV-7, or the vaccine may mimic HHV, inducing a similar immune response and then skin eruption.

Treatment

Drug-induced pityriasis is mild, tolerable, and mimics the more common and self-limiting idiopathic disease. Because of this, physicians are not compelled to check for a drug association cause until the persistence and severity of the lesions require reconsideration of the original diagnosis. The treatment includes identification and withdrawal of the drug. After cessation of the inciting drug, symptoms should abate within 5–10 days. Symptomatic treatment of pruritus with medications such as antihistamines and corticosteroids can be used in severe cases.

Main points

- Take a thorough history, as new drugs or nonprescription drugs can cause PR-like eruptions. The prevalence of these eruptions is believed to be underreported and it likely occurs more commonly than previously thought.
- Since the eruption mimics a common and self-limiting disease, physicians are not prompted to check for a drug association cause until persistence, severity of the lesions, or pruritus require reconsideration of the original diagnosis.
- Physicians should consider that atypical cases of PR may actually represent a contact reaction.
- Discontinuation of the drug is the only needed treatment, but topical steroids and antihistamines can also be given as needed.

Conclusions

Pityriasis rosea is a common benign condition seen mainly in children and young adults. Its course is usually limited to 6–8 weeks and is characteristic enough that it is usually diagnosed on a clinical basis only. If persistent or recurrent, it is a rare variant, or it may be a reaction to a medication. Knowing this can save the patient frustration and possibly a more extensive workup including a skin biopsy, particularly if the offending drug is identified early in the course of disease.

Suggested Reading

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Psoriasiform Drug Eruptions and Drugs That Flare Psoriasis

14

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Abstract

Drugs may exacerbate pre-existing psoriasis, induce new psoriatic lesions on previously uninvolved skin in patients with existing psoriasis, and precipitate de novo psoriasis in patients irrespective of a family history of psoriasis. The clinical spectrum includes limited or generalized erythematous plaques with thick, large, silvery scales, pustular lesions, or erythroderma. Histopathological examination demonstrates psoriasiform epidermal hyperplasia, parakeratosis with entrapped neutrophils, decreased granular cell layer, focal interface dermatitis, minimal and focal dyskeratosis, and a superficial perivascular lymphocytic inflammatory response with admixed histiocytes and eosinophils. A helpful distinguishing feature of drug-induced psoriasis is the absence of Munro microabscesses, langerhan cells, and vascular changes (tortuous papillary dermal capillaries and related suprapapillary epidermal thinning), with a tendency to exhibit more spongiosis and have less neutrophils and lymphocytes in the epidermis.

An understanding and awareness of elements that may induce, trigger, or exacerbate the disease is of utmost importance in clinical practice today. As new drugs are constantly being developed, prescribed, and ultimately influencing disease progression, the knowledge and systematization of drugs and their potential reactions should be understood and acknowledged. Awareness of the clinicopathologic findings in specific drug

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_14

reactions is essential in making a timely and correct diagnosis. In this chapter, we will discuss the drugs that have a strong association with psoriasis, a considerable association but with insufficient data, and those that are occasionally reported to be associated with aggravation or induction of psoriasis.

Keywords
Psoriasis • Drug-induced psoriasis • Psoriasiform drug reaction • Psoriasiform drug eruption

Introduction

Psoriasis is an exceedingly prevalent skin disease worldwide and psoriasiform drug reactions are recognized as side effects of many medications that are prescribed today. Drug ingestion may result in exacerbation of pre-existing psoriasis, in induction of psoriatic lesions on clinically uninvolved skin in patients with psoriasis, or origination of psoriasis in individuals with or without a family history of psoriasis. The clinical spectrum of drug-induced psoriasis includes limited or generalized erythematous plaques with thick, large, silvery scales, erythroderma, and/or pustular lesions. Additionally, psoriatic arthropathy, scalp changes, and nail alterations may be seen. The latency period between the time of drug administration and drug reactions varies with the type of drug, but can be short (less than 4 weeks), intermediate (4–12 weeks), or long (greater than 12 weeks). Some examples of such medications are NSAIDs (short latency period), anti-malarials (intermediate), ACE-inhibitors (intermediate), lithium (long), and beta-blockers (long). The assessment of a cause-and-effect relationship between medications and psoriasis is challenging, as the clinical course of psoriasis is variable. However, drug-induced eruptions typically regress within a few months of cessation of the triggering medication. Therefore, an understanding and awareness of elements that may induce, trigger, or exacerbate the disease is of utmost importance in clinical practice today. As new drugs are constantly being developed, prescribed, and ultimately influencing disease progression, the knowledge and systematization of drugs and their potential reactions should be understood and acknowledged.

Presentation and Characteristics

Patient Population

Drug eruptions are common. Women, males under age 3, and those with a viral illness (HIV, Epstein bar virus, human herpes virus) are more likely to develop cutaneous drug eruptions of all types. The likelihood of developing a psoriasiform drug eruption increases with the number of medications taken by a patient. Consequently, elderly patients and those with multiple chronic medical conditions are more likely to develop a reaction.

Primary Lesions

Psoriasiform lesions are similar to classic psoriasis, but vary in the distribution, amount of scale, size, and shape. In general, they are less red, less thick, and less scaly than classic plaque-type psoriasis. The knees and elbows are commonly spared (specifically seen with β-blockers). Additional presentations include pustules, erythroderma, and nail abnormalities such as oil spots and pitting.

Secondary Lesions

Mild pruritis can accompany psoriasiform drug eruptions and thus excoriation may be present.

Hemorrhagic crust may be seen as an extension of Auspitz's sign. Koebnerization is often seen.

Distribution

The distribution of psoriasiform lesions varies, but is not limited to the "classic" psoriasis locations of elbows, knees, scalp, buttock, palms, and soles. Often, a psoriasiform drug eruption is generalized. Palmoplantar, scalp, and nail involvement are commonly reported.

Course

The time between initiation of a drug and cutaneous eruption varies from weeks to years. Generally, a flare of existing psoriasis occurs more quickly than the onset of a new psoriasiform dermatitis. Cessation of the offending drug will generally lead to clearing of the psoriasiform dermatitis within 90 days. However, cases of drug-induced psoriasis becoming "de novo" psoriasis persisting after the medication is stopped have been described.

Pathogenesis

The pathogenesis of psoriasiform drug eruptions remains obscure. We have described the pathogenesis with the description of each drug/class of drugs below.

Differential Diagnosis

The distinction between drug-induced, drug-triggered, and de novo psoriasis is of critical significance and importance for appropriate management. The most important disease to distinguish drug-induced psoriasis from is de novo psoriasis vulgaris.

Work-Up

Onset and Duration

If a clinical association between start of the drug and onset of the cutaneous reaction is present, it should be thoroughly documented. If the reaction is drug-associated, the eruption will typically clear within 1–3 weeks of cessation of therapy. Absence of other triggers, including stress, trauma, and infection should be sought.

Drugs

Clinicians should inquire about any prescription and non-prescription medications the patient is taking, including vitamins, and their doses.

Family History

Inquiry about a personal or family history of psoriasis or other cutaneous diseases is imperative.

Other Diseases

Evidence of other systemic diseases is crucial to evaluate.

Laboratory Evaluation

CBC, metabolic panel, and thyroid evaluation are recommended.

Biopsy/Histopathology

A punch biopsy is preferred for evaluation by an experienced dermatopathologist. Histopathologic analysis demonstrates psoriasiform epidermal hyperplasia, parakeratosis with entrapped neutrophils, decreased granular cell layer, inconsistent interface dermatitis, minimal and focal dyskeratosis, and a superficial perivascular lymphocytic inflammatory response with admixed histiocytes and eosinophils. A helpful feature that distinguishes drug-induced from idiopathic psoriasis is the absence of Munro microabscesses, langerhan cells, and vascular changes (tortuous papillary dermal capillaries and related suprapapillary epidermal thinning). Drug-related psoriasis also tends to exhibit more spongiosis, with fewer neutrophils or lymphocytes in the epidermis.

Differentiating Factors

There are no specific criteria established to diagnose drug-induced psoriasiform drug eruptions from psoriasis. However, there are several differentiating characteristics that can aid in this distinction (Table 14.1).

Table 14.1 Differentiating characteristics of drug-induced psoriasiform drug eruptions vs. psoriasis

Drug-induced psoriasisiform eruption	Idiopathic psoriasis
Temporal association of drug initiation and onset of eruption	No association with initiation of drug(s)
Cessation of drug prevents disease progression	No recovery after cessation of drug(s)
Older age of onset	Young age
Possibly resistant to phototherapy	–
Recurrence of skin lesions on re-challenge with offending drug	–

Table 14.2 Drugs and their relationship to psoriasis

Category of drugs/drug classes	Relationship to psoriasis
Absolute causal relationship to psoriasis	β-Blockers, lithium, synthetic antimalarials, nonsteroidal anti-inflammatory drugs, tetracyclines
Substantial but insufficient data supporting relationship with psoriasis	ACE inhibitors, interferons, terbinafine
Drugs occasionally reported to be associated with induction or aggravation of psoriasis	Clonidine, digoxin, amiodarone, quinidine, dihydropyridine calcium antagonists, carbamazepine, valproic acid (sodium valproate), fluoxetine, acetazolamide, sulfonamides, penicillin, amoxicillin, ampicillin, morphine, procaine, cimetidine, ranitidine, gold, mercury, oxandrolone, progesterone, gemfibrozil, potassium iodide, granulocyte-macrophage colony-stimulating factors

Drugs Implicated and Pathogenesis

There are three categories of drugs implicated in psoriasiform drug eruptions: *Strong* association with psoriasis; *Considerable* but insufficient data to support association with psoriasis; and *Occasionally* reported to be associated with aggravation or induction of psoriasis (Table 14.2). They are discussed here in alphabetical order.

Abatacept

A fully human CTLA4-IgG, abatacept is used in the treatment of refractory rheumatoid arthritis. On multiple accounts, it has been reported to cause psoriasiform dermatitis, confirmed on withdrawal and rechallenge. Latent periods ranging from 2 months to 14 months have been reported. Reported morphologies include a widespread psoriasiform eruption, scalp involvement, palmoplantar involvement, and nail dystrophy with onycholysis and yellowing of the nail plate.

Angiotensin-Converting Enzyme Inhibitors (ACEI)

Angiotensin-converting enzyme (ACE) is a zinc-metallopeptidase that converts angiotensin I to the potent vasoconstrictor angiotensin II. It is expressed in a variety of tissues including vascular endothelium, skin, and cells of the immune system. ACE inhibitors (ACEI) are prescribed for the treatment of hypertension and function by blocking the conversion of angiotensin I to angiotensin II by competing with kininase II. Frequently prescribed ACEI include captopril, enalapril, lisinopril, perindopril and ramipril.

ACEI can trigger both induction and exacerbation of psoriasis with an intermediate latency period between 4 and 12 weeks. Case reports in the literature describe various clinical manifestations including guttate, plaque-type, palmoplantar, pustular, and erythrodermic forms of psoriasis associated with the use of ACEI. Biopsies show typical histopathology of psoriasiform dermatitis with hyperkeratosis, parakeratosis, epidermal acanthosis, and variable neutrophilic exocytosis. Resistance to standard treatment modalities is typical for ACEI-induced psoriasis. However, discontinuation of the drug leads to improvement in the psoriatic lesions usually within a few days.

Pathogenesis

Three mechanisms have been postulated in the development of ACEI-induced psoriasis: (1) an allergic, immune-mediated reaction, supported by captopril-induced psoriasis with a positive mast cell degranulation (MCD) test;

(2) a pharmacologic dose-dependent response resulting from augmentation of kinin levels in the skin; and (3) increased levels of substance P. Studies suggest that patients with a family history of psoriasis and a specific ACE genotype exhibiting low ACE activity may be more susceptible to developing psoriasis with ACEI therapy.

Angiotensin Receptor Blockers (ARBs)

Also known as angiotensin II receptor antagonists and AT_1-receptor antagonists or sartans, angiotensin receptor blockers (ARBs) are a group of pharmaceuticals that modulate the renin-angiotensin-aldosterone system. Their main uses are in the treatment of hypertension, diabetic nephropathy, and congestive heart failure. Examples of ARBs include candesartan, cilexetil, losartan, irbesartan, and valsartan. A relationship between ARB treatment and psoriasis has been suggested in several reports. This includes development of psoriasis de novo as well as exacerbation of disease in patients with a history of psoriasis. In the largest report of nine patients, psoriasis developed within six weeks and nine months of initiation of ARB therapy. Interruption of treatment led to regression of the cutaneous lesions over weeks to months. One patient experienced induction of psoriasis by two different ARB agents. The clinical attributes of the ARB-induced psoriasis differed from classic psoriasis, with lesions predominating in sun-exposed areas of hands and forearms, and with severe ungual involvement noted in some patients.

Pathogenesis

ARBs increase angiotensin II levels by inhibiting retroactive control of angiotensin II on renin secretion. Angiotensin II stimulates keratinocyte proliferation and this has been postulated as a mechanism for induction or exacerbation of psoriasis.

Antiepileptics

The aromatic anticonvulsants, phenytoin, carbamazepine, phenobarbital, and lamotrigine are the most common causes of cutaneous drug reactions in this class. These medications have been associated with Stevens-Johnson syndrome and toxic epidermal necrolysis. Other anticonvulsants such as valproate, levetiracetam, and topiramate have been less commonly associated with cutaneous drug eruptions. Both carbamazepine and sodium valproate have been associated with psoriasiform eruptions. Carbamazepine has been reported to cause a generalized psoriasiform eruption, as well as palmoplantar psoriasis with a non-scarring alopecia.

Pathogenesis

The mechanism of action for these eruptions possibly includes formation of a superantigen, delayed hypersensitivity, altered lymphocyte activation, and alterations in epidermal cAMP levels.

Antimalarials

Synthetic antimalarials have long been reported to flare existing psoriasis. Reports of antimalarial-induced psoriasiform dermatitis in patients with no prior history do not exist to date. It has been reported that as many as 18 % of psoriatics flare when treated with synthetic antimalarials. These medications are commonly encountered in treatment of arthritis, connective tissue diseases, and malaria prophylaxis. Reports of progression from plaque-type psoriasis to pustular flares and erythroderma exist. Chloroquine is a more frequent offender than hydroxychloroquine. The pharmacologically related anti-arrhythmic quinidine has also been reported to cause a psoriasiform eruption. The time between initiation of an antimalarial therapy and onset of psoriasis flare ranges from four to twelve weeks.

Pathogenesis

The chemical structure of the antimalarial drugs is very similar to that of dansyl-putrescine, a strong transglutaminase inhibitor. The mechanism of anti-malarial-induced psoriatic flares is thought to be via inhibition of cutaneous transglutaminase enzymes by the antimalarials. This leads to cellular proliferation, thus flaring psoriasis.

β-Blockers

β-adrenergic receptors are present in many cells of the human body, including the immune system and the epithelial skin cells. Two classes are recognized, non-selective and selective, referring to their selectivity of β1- and β2-adrenergic receptors. β-blockers have been reported to cause, aggravate, or induce psoriasiform skin eruptions and/or pre-existing psoriasis (Fig. 14.1), typically 1 month to 2 years after drug initiation. This variation in onset is likely contributed to racial and genetic traits. Many of these agents demonstrate significant cross-reactivity (notably propranolol, oxprenolol, and atenolol).

Researchers are unable to determine if β–blocker-induced cutaneous reactions are true psoriasis, as the psoriasiform eruption occurs more commonly in those with a negative family history of psoriasis. Drug-aggravated psoriasis improves with cessation of the drug, but may not clear completely, suggesting there are other factors at play.

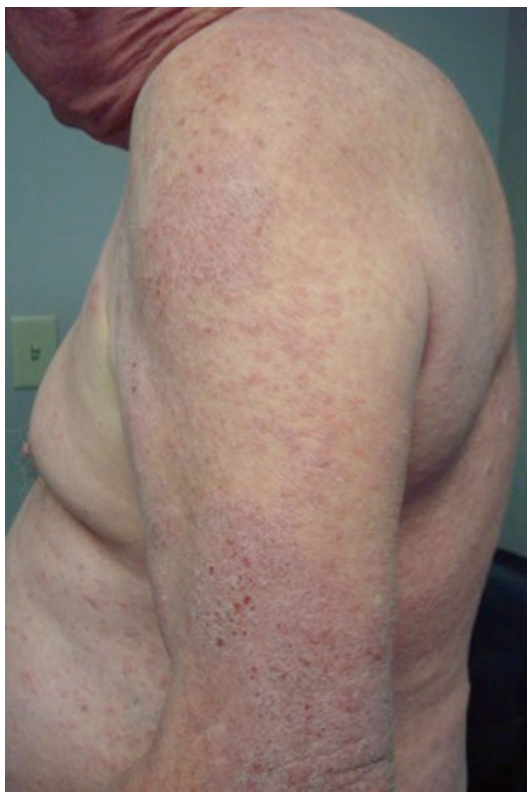

Fig. 14.1 Psoriasiform dermatitis due to propanolol that slowly improved after discontinuation of the drug. Notice thick adherent scale with suggestion of silvery-white scale near the elbow

Propranolol (Inderal), the first non-selective β-blocker, has been reported to cause hyperkeratosis and parakeratosis, consistent with epidermal psoriasiform alteration in guinea pigs after topical application. This suggested that propranolol works immediately on cutaneous β2 receptors. Several cases of oxyprenolol (Trasicor)-induced and exacerbated psoriasiform eruptions have been reported in the literature. Cumberbatch reported that 2–3 weeks after oxyprenolol initiation, an "intense, firey, annular erythema and underlying oedema" developed, consistent with exacerbation of underlying psoriasis, present for 10 years prior. A similar case was reported shortly after, both switching from oxypranolol to propranolol with subsequent disappearance of symptoms. Skin reactions to practolol, a selective β-blocker, are a known side effect, specifically psoriasiform eruptions and exacerbation of pre-existing psoriasis. Three patients have been reported who developed psoriasiform skin eruptions following oral practolol therapy. Many other reports worldwide of psoriasiform drug eruptions following β-blocker administration have been noted: atenolol (Tenormin), cetamolol (Betacor), metoprolol (Lopressor, Seloken), and nadolol (Corgard). Topical application of timolol (Timoptol), in the treatment of chronic open angle glaucoma, was reported to induce psoriasis and to transform psoriasis vulgaris into psoriatic erythroderma, probably through the passage of the β-blocker into the systemic circulation via the conjunctiva, nasal mucosa, or uveal circulation. Tsankov et al. reported the conversion of plaque-type psoriasis in a 50-year-old woman to pustular psoriasis after initiation of pindolol (Visken).

Pathogenesis

The exact mechanism of action of β-blockers on psoriasis still remains unknown. Epidermal cell division is slowed by β-adrenergic stimulation via an increase in cyclic-AMP (cAMP). Therefore, the use of β-blockers presumably interferes with cAMP production via epidermal

β-receptors. This, in turn, decreases cAMP concentration in the epidermis, increases epidermal proliferation, and increases epidermal glycogen levels. This is the picture of a psoriatic dermatitis. Like lithium, β-blockers have been shown to increase phosphorylation in psoriatic T-cells, which may affect intracellular calcium levels as well. Other hypotheses include immunologic mechanisms and delayed-type hypersensitivity.

Botulinum Toxin A (Botox A)

Botox A is a neurotoxin produced by the bacterium *Clostridium botulinum*. It is used therapeutically for the treatment of upper motor neuron syndrome, hyperhidrosis, cervical dystonia, chronic migraine, blepharospasm, strabismus, and glabellar furrows. A case of a psoriasiform eruption temporally related to the injection of botulinum toxin A into the medial rectus muscle to treat an ocular motility disorder was reported. Conversely, other studies have shown efficacy of botulinum toxin A injection for the treatment of inverse psoriasis.

Calcium Channel Blockers (CCBs)

Also referred to as calcium channel antagonists or calcium antagonists, calcium channel blockers (CCBs) are medications that disrupt the movement of calcium through calcium channels. CCBs are used to treat hypertension, angina, and arrhythmia. Examples of CCBs include diltiazem, nifedipine, nicardipine, and verapamil. In an early report from Japan, there were a notable number of psoriasiform eruptions associated in patients treated with CCBs, which resolved or were easily controlled after discontinuation of the drug. The possible role of CCBs as precipitating or exacerbating factors in patients with psoriasis was also supported in a case control study of 150 patients. The median latent period between the beginning of intake of CCBs and psoriasiform eruption is 28 months.

Pathogenesis

It is postulated that CCBs can trigger psoriasis by interfering with calcium influx, which is necessary for normal keratinocyte proliferation and differentiation.

Chlorthalidone

As a diuretic, chlorthalidone is used to treat hypertension and edema. It acts similarly to the thiazide diuretics but does not contain the benzothiadiazine molecular structure. There is a report of two patients who experienced a psoriasiform eruption while taking chlorthalidone.

Cimetidine

Cimetidine is a histamine H_2-receptor antagonist that is largely used to treat heartburn and peptic ulcers. There is a rare report of exacerbation of psoriasis during treatment with cimetidine. Other literature supports use of cimetidine in the treatment of psoriasis, especially in HIV-positive individuals.

Digoxin

As a purified cardiac glycoside, digoxin is used for the treatment of many cardiac conditions, including atrial fibrillation and flutter as well as heart failure. A psoriasiform eruption induced by digoxin was reported and confirmed upon re-exposure. Given a positive migration inhibition factor in this case, it is theorized that the patient had a hypersensitivity reaction to digoxin that caused Koebner phenomenon.

Erlotinib

Erlotinib is a reversible tyrosine kinase inhibitor that acts on the epidermal growth factor receptor (EGFR). It is used to treat non-small cell lung cancer, pancreatic cancer, and several other forms of cancer. Although there are reports of improvement of psoriasis in patients treated with erlotinib for cancer, there is a report of a psoriasiform eruption triggered by erlotinib. It occurred simultaneously with the more common acneiform form erlotinib-induced rash that is thought to portend a good prognosis.

Fluoxetine

Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Fluoxetine-induced psoriasis has been reported in several patients, with or without a personal history of psoriasis.

Pathogenesis

SSRI drugs modulate serotonergic function, a factor that may contribute to the pathophysiology of psoriasis. A serotonergic influence in the pathogenesis of psoriasis may be possible together with a pharmacogenetic difference in the drug metabolism of these patients.

Gemfibrozil

Gemfibrozil is an oral medication used to lower lipids levels. It reduces triglycerides and increases cholesterol carried in high density lipoprotein (HDL) in the blood. It may cause exacerbation of psoriasis, but the mechanism is unknown.

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

Colony-stimulating factors (CSFs) are commonly used for the treatment of pancytopenia following chemotherapy. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has effects on neutrophil function and chemotaxis. There are several reports implicating CSF in the induction or exacerbation of psoriasis.

Pathogenesis

Due to its role in enhancing the function of neutrophils and macrophages, it is suggested that therapeutically administered GM-CSF may amplify and modulate the inflammatory reactions and activated T-cells in psoriasis.

Imiquimod

Imiquimod is an immune response modifier that is approved for treatment of superficial basal cell carcinomas, actinic keratoses, and genital warts. There are several published reports describing cases of psoriasis triggered by imiquimod cream. Most reports are of exacerbation of pre-existing psoriasis with a rare case of induction of psoriasis de novo.

Pathogenesis

Imiquimod activates immune cells through the toll-like receptor 7 (TLR7), commonly involved in pathogen recognition. Cells activated by imiquimod via TLR-7 secrete cytokines (primarily interferon-α (INF-α), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)). These cytokines, particularly INF-α, are capable of inducing psoriasis.

Interferon (IFN)

The immune effects of interferons have been exploited to treat various diseases. Recombinant IFN-α is used for systemic therapy of hematologic malignancies, malignant melanoma, hepatitis B and C, and carcinoid syndrome. There are a number of reports of induction or exacerbation of psoriasis during treatment with IFN-α. The lesions generally resolved within 2 weeks to 6 months after cessation of IFN-α. Psoriatic lesions have also been induced at injection sites of INF-γ.

Pathogenesis

Interferons have various actions that could be related to the pathogenesis of psoriasis, including activation of macrophages, intensification of phagocytosis, and induction of interleukin-1 production and release by keratinocytes.

Lithium

Lithium, used as lithium carbonate, lithium citrate, or lithium benzoate, has a variety of known cutaneous adverse effects, with a documented prevalence of 3.4–45 %. A relationship between psoriasis and lithium was first suspected and then described in 1972 and 1976, respectively. Lithium salts are found in mineral water, and although the mechanism of action remains unclear, is extensively used in the treatment of many psychiatric disorders and as a uricolytic. The therapeutic range for lithium is 0.6–0.12 mEq/L, and plasma levels exceeding 1.5 mEq/L can lead to severe systemic reactions involving the skin, central nervous system, kidneys, thyroid, and gastrointestinal system.

Lithium-associated psoriasis is the most common cutaneous reaction that may or may not be dosage-related. Lithium-associated psoriasis includes the following: exacerbation of established psoriasis, new onset psoriasis, pustular psoriasis, psoriatic arthropathy, psoriatic erythro-

derma, and nail alterations. Of these, exacerbation of pre-existing psoriasis is the most common. In some, treatment-resistant scalp psoriasis is the first manifestation. A rare case of fingernail psoriasis has been reported as the sole manifestation. Many patients report feelings of stress during the recovery and treatment period, which alone can exacerbate psoriasis. Interestingly, patients with psoriasis who had not been treated with lithium or lithium-containing compounds have been reported to have increased lithium plasma concentrations in their blood. Of note, when lithium is used to treat urological issues, cutaneous side effects are not reported, probably owing to the short duration of therapy.

Lithium-triggered psoriasis: The latency period between starting lithium and the exacerbation of pre-existing psoriasis is relatively long, averaging 20 weeks, and may occur after mental status has improved. Generalized pustular psoriasis has been reported after lithium therapy in a patient with pre-existing psoriasis vulgaris.

Lithium-induced psoriasis: The latency period is often longer, averaging 48 weeks, and may also occur after mental status has improved. The true relationship between lithium and de novo psoriasis is questionable, although there has been a reported association with de novo palmoplantar pustular psoriasis. Some have reported that onset of new disease is no higher than in a control group not taking lithium. Lithium-induced psoriasis is often resistant to standard treatments, and some may require dose modification or discontinuation of lithium.

Pathogenesis

The precise mechanism(s) by which lithium compounds exert their effects are still being elucidated. It is clear, however, that lithium directly inhibits cell differentiation and potentiates an increase in the concentration of polymorphonuclear leukocytes in psoriatic lesions, presumably via a deficiency of cyclic-AMP (cAMP). Initial hypotheses regarding lithium's mechanism of action suggested that the induction/aggravation of psoriasis was secondary to a reduction in intraepidermal cAMP levels via a decrease in adenyl cyclase. Chronic lithium therapy, however, has been shown to increase cAMP concentration in the epidermis, presumably via a compensatory mechanism, and it is in chronic lithium therapy that the psoriasis-associated reactions most often occur. More recent studies have not revealed reduced levels of cAMP in psoriatic T-cells. A more recent and promising hypothesis involves recycling of inositol in the epidermis, which is essential for intracellular calcium release. Lithium inhibits the monophosphatase enzyme, which is required for inositol recycling. Thus, calcium release is inhibited, calcium levels drop, and increased proliferation and lack of keratinocyte differentiation result, ultimately triggering psoriasis. Oral inositol supplementation reverses these side effects.

There is contradicting literature on cytokine production in lithium-associated psoriasis. Some researchers report IL-2, IL-6, IL-8, tumor necrosis factor-α, and interferon-γ are elevated in lithium-associated psoriasis, and others say they are closer to normal. These cytokines presumably interfere with the communication of psoriatic keratinocytes. Lithium has been shown to increase the release of inflammatory mediators, via lithium-stimulated neutrophils. Another finding is increased tyrosine phosphorylation in psoriatic T-cells compared to normal cells. This might be relevant to the development of psoriasis.

Interestingly, the antigens most commonly associated with psoriasis have been documented to be sparsely represented in lithium-induced psoriasis, specifically HLA B13, B17, and/or Bw37. Further epidemiologic studies are necessary to determine details regarding the causal relationship between lithium and psoriasis.

Metformin

Metformin is an oral antihyperglycemic agent in the biguanide class that is used in the management of non-insulin-dependent diabetes mellitus (type 2). Metformin works by suppressing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. It lowers both basal and postprandial plasma glucose, and reduces insulin resistance, in type 2 diabetes mellitus. A psoriasiform eruption was described in patient 1 week after initiating

therapy with metformin hydrochloride at 850 mg daily. The eruption resolved with cessation of the medication and recurred with rechallenge.

Mitomycin-C

Mitomycin-C is a chemotherapeutic agent rarely associated with psoriasiform dermatitis. A report of new plaque-type psoriasis in a patient undergoing chemotherapy for breast carcinoma exists. Intravesicular mitomycin-C in urothelial carcinoma has been reported to cause widespread psoriasiform dermatitis.

NSAIDs

Exacerbation of psoriasis and induction of generalized pustular psoriasis have been associated with nonsteroidal anti-inflammatory drugs (NSAIDs). A case of indomethacin-induced psoriasis has been reported in a 51-year-old woman. Psoriatic flares have been seen with local and perioral indomethacin treatment. A clinical exacerbation of psoriasis occurred following systemic and local therapy in 14 of 20 patients with pre-existing psoriasis subsequently treated with indomethacin. Generalized pustular psoriasis has been reported in a patient treated with phenylbutazone.

Although there is the risk of worsening preexisting psoriasis or rarely inducing de novo psoriasis, NSAIDs are still implicated in treatment of psoriasis for several reasons. Corticosteroids successfully treat/manage psoriasis, as they decrease levels of arachidonic acid (AA), which is the building block for prostaglandin synthesis. Additionally, in patients with psoriatic arthritis, NSAIDs have been shown to restrict leukocyte chemotaxis into the epidermis. The lipoxygenase inhibiting-NSAIDs are also promising treatments for psoriasis. When the COX pathway is inhibited, the bioavailability of AA is increased, which subsequently activates the lipoxygenase pathway. These metabolites are integral in psoriatic inflammation.

Pathogenesis

NSAIDs influence the metabolism of arachidonic acid by inhibiting either the cyclo-oxygenase or the lipoxygenase pathway, thus preventing the formation of inflammatory mediators such as prostaglandins, prostacyclins, and leukotrienes. Elevated levels of these inflammatory mediators in psoriatic skin have been found or indirectly confirmed in a several studies.

Potassium Iodide

Potassium iodide has therapeutic applications, either in tablet form or saturated solution, for treatment of hyperthyroidism, radiation poisoning, sporotrichosis, and erythema nodosum Potassium iodide, 500 mg administered orally, was reported to induce generalized pustular psoriasis in two patients.

Pathogenesis

Activation of the enzyme dihydrofolic acid reductase by potassium iodide is postulated as a possible mechanism.

Statins

Statins, or HMG-CoA reductase inhibitors, are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a critical role in the production of cholesterol in the liver. Statins are prescribed in the prevention and treatment of cardiovascular disease. There are a number of statins, including atorvastin, lovastatin, pravastatin, rosuvastatin, and simvastatin. There are reports of statins associated with worsening of disease in psoriatic patients. Conversely, some of the statins, namely simvastatin and atorvastatin, have been found to improve the clinical outcome in patients with psoriatic skin lesions.

Pathogenesis

The observed beneficial effects are contributed to the effects on lipid metabolism, including that in skin, as well as anti-inflammatory and immunomodulatory properties of statins.

Terbinafine

Terbinafine is a member of the allylamine class of antifungal agents that is used to treat dermatophyte

infections of the skin and nails. Although it is generally well tolerated, there are cases in the literature of psoriasis developing after treatment with terbinafine. This includes patients with plaque psoriasis that flared, those with pustular flares, and development of pustular psoriasis de novo. In most cases, the psoriasis developed within a month of starting treatment and resolved upon discontinuation of terbinafine and start of antipsoriatic therapy.

Tetracyclines/Antibiotics

Antibiotics are the most common cause of all cutaneous drug reactions, most commonly the morbilliform types. However, reports of antibiotics causing psoriasiform dermatitis date back in the literature to 1947 with sulfonamides. Psoriasis is also known to flare with infection, begging the question of exacerbation due to infection versus true medication effect. Tetracyclines, including doxycycline, have most commonly been reported to cause psoriasiform dermatitis and flare existing psoriasis. Penicillins, cephalosporins, macrolides, and fluoroquinolones have also been reported to do so. Anti-tuberculosis regimens of isoniazid, ethambutol, rifampicin, and pyridoxine have been associated with a widespread psoriatic dermatitis. It is widely accepted that tetracyclines are photosensitizing agents. Predisposed and psoriatic patients may undergo a Köebner reaction as a result of the photosensitizing characteristics of tetracyclines. Also of note, tetracyclines have been shown to accumulate in higher concentrations in psoriatic lesions than in normal skin.

Pathogenesis

Tetracyclines provoke psoriasis probably through reduction of intracellular c-AMP, or by the interaction of the drug with arachidonic acid and its metabolites.

TNF-α Inhibitors

Hundreds of reports of psoriasiform dermatitis in the setting of TNF-α inhibitor use fill the dermatology, rheumatology, gastroenterology, and pharmacology literature. The majority of these patients have underlying rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, or inflammatory bowel disease.

All three medications in this class, etanercept (Fig. 14.2), infliximab, and adalimumab, have been reported to flare existing psoriasis, lead to new psoriasiform eruptions in patients with no history of psoriasis, and trigger "de novo" psoriasis that remains after the medication is withdrawn. Periods of latency range from 4 to 36 months. Morphologies of induced psoriasis include pustular psoriasis (most common) of both palmoplantar and generalized types, plaque-type, scalp involvement with reports of pityriasis amiantacea and psoriatic alopecia, guttate, inverse, and nail changes. Clearance of the eruptions with medication withdrawal and reappearance on rechallenge has been reported. These eruptions are most commonly reported with infliximab, followed by adalimumab, and least reported with etanercept. This order of frequency is likely related to the rates of use of these specific medications in different inflammatory disorders as well.

Most reported cases of TNF-α inhibitor-induced psoriasis respond to topical treatment only. However, those requiring methotrexate, cyclosporine, PUVA, and UVB phototherapy for clearance have been reported. There is one recent report of successful treatment of adalimumab-induced palmoplantar pustulosis with ustekinumab.

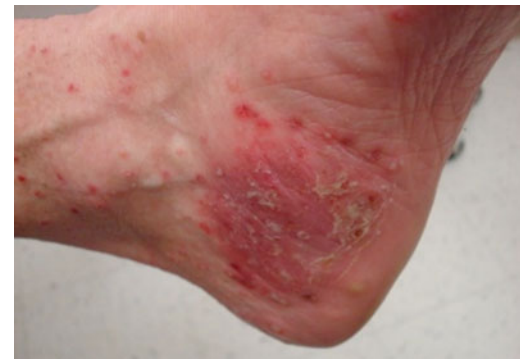

Fig. 14.2 Pustular papulosquamous dermatitis with thick adherent dry scale in a patient who was started on etanercept for rheumatoid arthritis. Slow improvement occurred with discontinuance of the medication

Pathogenesis

The pathogenesis of the eruption is thought to be related to increased autoreactive T-cells, increased type I interferons, and an increase in T_h17 cells. Although more than 2 million patients have been treated with these medications, only hundreds of reports of this specific type of reaction exist, suggesting genetic polymorphisms play a role.

Management and Treatment

The distinction between drug-induced and drug-triggered psoriasis is of crucial importance for appropriate management, which typically utilizes both topical and systemic contemporary therapies. The diagnosis of a psoriasiform drug reaction is made on the morphology of the eruption, a temporal association of the drug to an eruption, and sometimes a biopsy. Stopping the offending agent will generally lead to clearance of the psoriasiform dermatitis within 90 days. However, cases of drug-induced psoriasis becoming de novo psoriasis have been described. If stopping the medication is not a reasonable option or a patient's symptoms warrant faster control, treatments include topical steroids and vitamin D analogs, cyclosporine, oral retinioids, methotrexate, narrow band UVB, and PUVA.

For flares of existing psoriasis, initiation of a TNF-α inhibitor can lead to more optimal control of the disease. Infliximab is the fastest acting of this class. Psoriasiform eruptions seen with certain medications, such as lithium and carbamazepine, often respond to a dose reduction only. Although lithium-treated patients should be closely monitored for the occurrence of all kinds of cutaneous adverse effects, pre-existing psoriasis is not a contraindication for lithium administration. Many patients taking lithium do not have worsening of their skin disease. Psoriasiform eruptions due to β-blockers regress promptly after drug discontinuation. Exacerbation of pre-existing psoriasis by β- blockers is resistant to treatment unless the drug(s) are discontinued. This relationship seen between β-blockers and psoriasis is of great clinical importance, as hypertonia and arrhythmia have been reported in 37 % of patients with psoriasis. Cardiologists may overlook or underestimate the fact that β-blockers worsen psoriasis, and dermatologic consultation is wise in such cases. Regarding tetracyclines, recommendations exist to avoid their use when possible in patients with psoriasis as well as in healthy individuals with a genetic tendency toward psoriasis (positive family history, HLA-B13, B17, B27).

Main Points

- Drugs administered for nondermatological disease may be associated with the induction or exacerbation of psoriasis that can manifest as (1) precipitation of psoriasis de novo in predisposed and nonpredisposed individuals; (2) exacerbation of pre-existing psoriatic lesions; (3) induction of lesions in clinically normal skin in patients with psoriasis; and (4) development of treatment-resistant psoriasis.
- Drugs that appear to have a strong causal relationship to psoriasis are beta-blockers, lithium, synthetic antimalarials, NSAIDS, and tetracyclines.
- The latency period depends upon the offending drug and is categorized as short (<4 weeks), intermediate (4–12 weeks), or long (>12 weeks).
- The clinical spectrum of drug-induced psoriasis is broad and includes limited and generalized plaques, pustular forms, and erythroderma.
- The histopathologic features in drug-provoked psoriasis are also variable. Some drugs produce histopathologic changes characteristic of psoriasis, including hyperkeratosis and parakeratosis, acanthosis, hypogranulosis, and spongiform pustule formation. Others may have considerable spongiosis or lichenoid interface inflammation.

- Diverse pathogenetic mechanisms, both immunologic and nonimmunologic, have been proposed for different drug classes.
- Lesions of drug-induced psoriasis usually regress within a few weeks to several months of discontinuation of the inciting medication.
- The diagnosis of a psoriasiform drug reaction is made on the morphology of the eruption, a temporal association of the drug to an eruption, and sometimes a biopsy.
- Awareness of drugs that induce or exacerbate psoriasis could be of great significance with respect to prophylaxis in predisposed individuals.
- Care providers should remember that these cutaneous side effects are not contraindications to therapy and it is not a universal side effect, as patients with known psoriasis are not guaranteed to have worsening of their condition.

Conclusions

Up to 3.2 % of the population is estimated to have psoriasis. In 2013, it was estimated that up to $135 billion was spent on direct costs of care and indirect costs, such as work loss, due to this condition. The importance of finding an underlying drug exacerbating or causing this condition can easily been appreciated as a major asset in caring for this common and costly disease. Missing a drug-exacerbating psoriasis can lead to increase morbidity and, rarely, mortality in psoriasis victims.

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Acne and Drug Reactions

15

Christopher P. Schiavo and Carol W. Stanford

Abstract

Acne vulgaris is a chronic disease of the pilosebaceous follicle and it is characterized by any combination of open comedones, closed comedones, pustules, cysts, and scarring of varying severity. Factors which promote the development of acne are: increased sebum production, which is influenced by endogenous androgens; ductal hypercornification; abnormal follicular keratinization; colonization of the pilosebaceous ducts by *Propionibacteria acnes*; inflammation; and genetic predisposition. While the majority of acne cases are hormone-dependent juvenile acne, a subset of cases are drug induced, which is defined as the development of an acneiform eruption occurring after medication intake. Several classes of drugs are associated with acneiform eruptions and include: corticosteroids, neuropsychotherapeutic drugs, antituberculosis drugs, immunomodulating drugs, and targeted therapy in the field of oncology. Discontinuation of the drug will lead to recovery from the acneiform eruption, but is rarely mandatory, given the benign nature of acne. The idiopathic disease can be distinguished from the drug eruption by characteristics of presentation, unusual age on onset, unusual location of the lesions, and resistance to conventional acne therapy.

Keywords

Acne vulgaris • Drug-induced acneiform eruption • Papule • Pustule

Introduction

Acne vulgaris is a common skin condition that affects nearly 85 % of all people at some point in their lives. Acne is a chronic disease of the pilosebaceous follicle and it is characterized by any combination of open comedones (blackheads), closed

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_15

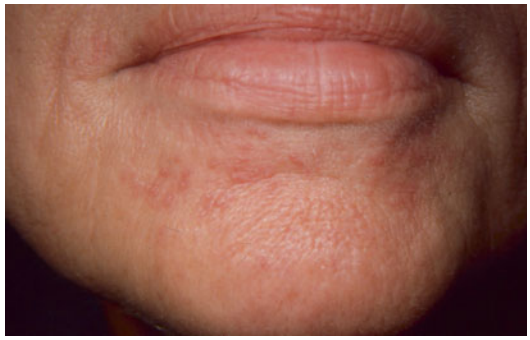

Fig. 15.1 Primary lesions

comedones (whiteheads), pustules, cysts, and scarring of varying severity. The pathogenesis of acne is not yet fully understood, but factors which promote the development of acne are: increased sebum production, which is influenced by endogenous androgens; ductal hypercornification; abnormal follicular keratinization; colonization of the pilosebaceous ducts by *Propionibacteria acnes*; inflammation; and genetic predisposition. While the majority of acne cases are hormone-dependent juvenile acne, a subset of cases are drug induced. Drug-induced acne is defined as the development of an acneiform eruption occurring after medication intake. Several classes of drugs are associated with acneiform eruptions and include: corticosteroids, neuropsychotherapeutic drugs, antituberculosis drugs, immunomodulating drugs, and targeted therapy in the field of oncology. Discontinuation of the drug will lead to recovery from the acneiform eruption, but is rarely mandatory, given the benign nature of acne.

Presentation and Characteristics

Primary Lesions

Monomorphic, inflammatory papules and pustules. Generally there is a lack of comedones and cysts, although they may have a late appearance secondary to the inflammatory lesions (Fig. 15.1).

Secondary Lesions

Comedones and cysts can arise secondary to inflammatory papules and pustules but are often not present. Pits and scars are evident in severe cases.

Distribution

The papules and pustules occur on the face, neck, chest, upper back, and also commonly extend beyond the seborrheic areas to affect the arms, trunk, lower back, and genitalia.

Course

The course can vary. Some may have an abrupt onset of an acneiform eruption in the absence of a history of acne vulgaris or an unusually severe acne flare in a patient with a past history of mild acne vulgaris or an aggravation of pre-existing acne. Depending on the medication inducing the acneiform eruption, papules and pustules may begin appearing within the first weeks of therapy or after several months or years. The acne often continues to appear until the inciting drug has been terminated or temporarily discontinued.

There is no seasonal preference as opposed to the idiopathic disease, and acne is not contagious.

Age Group

Acneiform eruptions can occur in teenage and early adulthood years, which coincide with the time period when hormone-dependent juvenile acne most frequently occurs. Also, they can affect children before teenage years as well as adults >30.

Differential Diagnosis

Idiopathic Acne Vulgaris

Any combination of comedones, pustules, cysts, and scarring of varying severity. Commonly affects adolescents and young adults beginning between 9 and 12 years. Onset can occur in later teenage years and into early adulthood and it lasts, with new outbreaks, for months or years. It subsides in most cases by the early 20s, but occasional flare-ups may occur for years. Occurs on the face and neck and, less commonly, on the back, chest, and arms. More rare locations are the scalp, buttocks, and upper legs.

Contact Dermatitis from Industrial Oils

Eczematous features; commonly located on distal extremities in atopic individuals and those

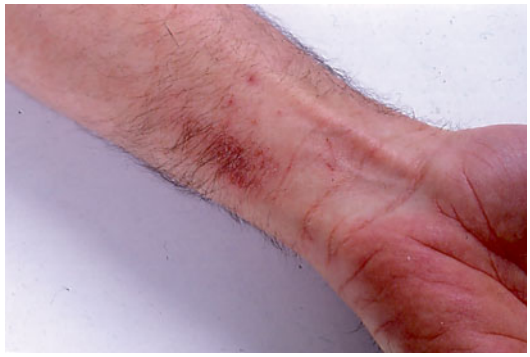

Fig. 15.2 Contact dermatitis from industrial oils

with occupational exposure to many chemicals (Fig. 15.2).

Perioral Dermatitis

Characterized by red papules, small pustules, and some scaling on chin, upper lip, and nasolabial fold, and almost exclusively affects women. There is a perioral halo of clear skin. The cause is unknown.

Adenoma Sebaceum

Rare skin condition which is often found in patients with tuberous sclerosis and is often also associated with epilepsy, mental retardation, and angiofibromas (adenoma sebaceum is a misnomer). It is characterized by 2–4 mm papules (angiofibromas) over central face without comedones, pustules, or cysts.

Drug-Induced Perioral Dermatitis

Occurs in patients receiving excessive doses or very protracted treatment with inhaled and topically applied corticosteroids (Fig. 15.3).

Pyoderma Gangrenosum or Ecthyma

Can mimic iododerma and bromoderma.

Cause of Idiopathic Acne Vulgaris

Idiopathic acne vulgaris is a condition of the sebaceous follicles. The pathogenesis of acne is not yet fully understood, but factors which promote the development of acne are: increased

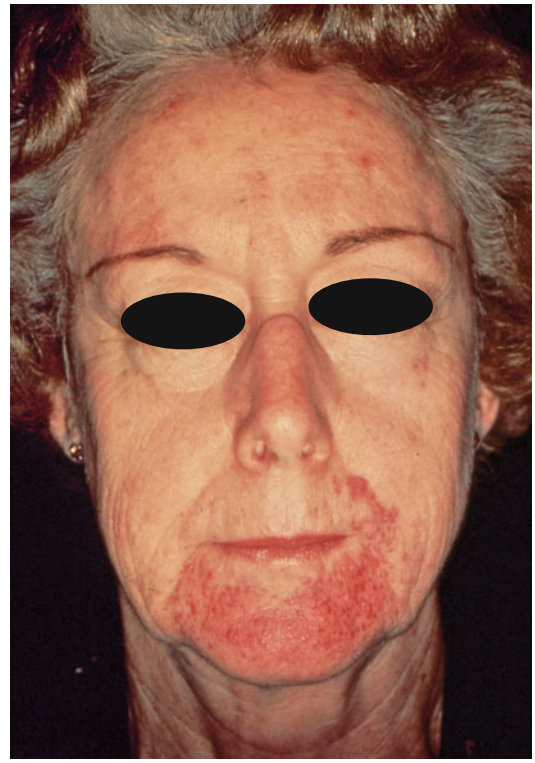

Fig. 15.3 Drug-induced perioral dermatitis on a patient using topical steroids

sebum production (which is influenced by endogenous androgens), ductal hypercornification, abnormal follicular keratinization, colonization of the pilosebaceous ducts by P. *acnes*, inflammation, and genetic predisposition. Propionibacteria are gram-positive, anaerobic, non-motile, pleomorphic rod-shaped cells. P. *acnes* commonly reside on sebaceous gland-rich areas of skin in humans and can be found on skin from birth until death. A high association between P. *acnes* levels and sebum production has been shown.

Propionibacteria is thought to be pathogenic in acne due to its production of exocellular enzymes and other bioactive exocellular products, such as proinflammatory lipids, which may act as virulence determinants, as well as its interaction with the immune system. People suffering from severe acne have shown to have increased cellular and humoral immunity to P. *acnes*, illustrating the interaction of propionibacteria with the immune

system. Acne lesions have an early infiltrate of predominantly lymphocytes (CD4+>CD8+), which later progresses to a general infiltrate of mixed cell types including HLA-DR+ Langerhans cells, HLA-DR+ basal keratinocytes, neutrophils, macrophages, and complement factors. It is believed propionibacteria activate lymphocytes via antigens and mitogens, resulting in cytokine release and the beginning of the inflammatory cascade with resulting increases in IL-1α, TNFα, HLA-DR, IL-8, and ICAM-1. The inflammatory cascade leads to disruption of the sebaceous follicle and possibly keratinocyte damage, worsening the acne.

Acneiform skin eruptions very similar to the presentation of idiopathic acne vulgaris has been reported to be caused by several drug categories including: corticosteroids, neuropsychotherapeutic drugs, antituberculosis drugs, immunomodulating drugs, and targeted therapy in the field of oncology. The mechanism by which each drug causes acneiform eruptions varies and is not always known. However, given each drug's mechanism of action or target of action, many of the drugs can be hypothesized as to why they cause acne based on their effects on natural pathways involved in idiopathic acne vulgaris. The mechanisms will be described further on in the chapter.

Differentiating Factors

There are no specific criteria established to diagnose drug-induced acne or acneiform eruptions, however there are several differentiating characteristics that can aid in diagnosing drug-induced acne versus other more common skin conditions, like idiopathic acne vulgaris. Unlike idiopathic acne, which generally affects people during teenage and young adulthood years, drug-induced acne can have an unusual onset of age in early childhood or later in adulthood (>30 years of age). Drug-induced acne can occur de novo as an abrupt onset of an acneiform eruption in the absence of a history of acne vulgaris, as an unusually severe acne flare in a patient with a past history of mild acne vulgaris, or as an aggravation of pre-existing acne. Unlike idiopathic acne vulgaris, drug-induced acne is characterized by a monomorphic, inflammatory pattern of pustules and papules with either a lack of or late appearance of comedones and cysts occurring secondary to the inflammatory lesions. While idiopathic acne vulgaris commonly occurs on the face and neck and, less commonly, on the back, chest, and arms, drug-induced acne will extend beyond the seborrheic areas, often involving the arms, trunk, lower back, and genitalia. Drug-induced acne is more resistant to conventional acne therapy than idiopathic acne. With no defined criteria and a lack of any overwhelming distinguishing features, diagnosis can be difficult, but an exhaustive search for a causative agent must be completed in all suspected cases. A time relationship between medication ingestion and development of symptoms is crucial in establishing a diagnosis of drug-induced acne. Onset of acne after drug implementation, improvement after drug withdrawal, or recurrence after drug reintroduction can establish this relationship.

Helpful hints for clinicians to differentiate drug induced acneiform eruptions from idiopathic acne vulgaris can be found in Table 15.1.

Table 15.1 Differentiating drug-induced acneiform eruptions from idiopathic acne vulgaris

Drug-induced acneiform eruption	Idiopathic acne vulgaris
Monomorphic, inflammatory pattern of papules and pustules	Polymorphic pattern of comedones, pustules, cysts, and scarring of varying severity
Lack of comedones and cysts or their late appearance secondary to inflammatory lesions	Comedones and cysts are characteristic skin lesions
Extension beyond seborrheic areas to include arms, trunk, lower back, and genitalia	Localized primarily on seborrheic areas such as the face and neck and, less commonly, on the upper back, chest, and arms
Can affect young children and adults >30 years of age	Commonly affects adolescents and young adults
Resistant to conventional acne therapy	Improves with conventional acne therapy
Onset after drug initiation, improvement after drug withdrawal, or reoccurrence after drug reintroduction	No causative relationship to drug therapy

Work-Up

When suspecting a drug-induced acneiform eruption it is important to take a thorough history, as new drugs or non-prescription drugs can cause acneiform eruptions. Physicians should always conduct an exhaustive search of possible culprit drugs when drug-induced acneiform eruptions are suspected.

A trial of drug termination should be tried in a drug-induced acneiform eruption that persists or is severe. It is recommended to start termination of drugs that have been reported to cause the reaction or any drugs that were started in the 1–2 weeks previous to the initial eruption. Clinicians must also remember to rule out idiopathic acne vulgaris and other skin conditions that present similarly.

If drug termination is not feasible due to necessity of the drug, treatment of the drug-induced acneiform eruption can be considered with benzoyl peroxide, topical or oral antibiotics, or isotretinoin in certain cases. The drug may also be temporarily terminated and then restarted after the skin lesions are cleared, along with careful monitoring.

Clinical diagnosis is used to diagnose idiopathic acne vulgaris and drug-induced acneiform eruptions.

Drugs Implicated

Drug-induced acneiform eruptions are well documented to be caused by: corticosteroids, neuropsychotherapeutic drugs, antituberculosis drugs, immunomodulating drugs, and targeted therapy in the field of oncology.

Corticosteroids and Corticotropin

Topical, oral, intravenous, or inhaled corticosteroids as well as corticotropin cause acneiform eruptions occurring within the first few weeks of treatment to several months. Dosage, duration of treatment, and individual susceptibility affect the likelihood of developing and the severity of the acneiform eruption. Classically, it will present as a monomorphic eruption of inflammatory papules and pustules on the seborrheic areas with possible extension to the upper arms. Several months after the initial phase, the inflammatory papules resolve and open and closed comedones will appear on the same areas. Low-dose corticosteroids may cause eruptions of only comedones.

Androgens and Anabolic Steroids

Androgens and anabolic steroids affect sebaceous glands because of their structural similarity with endogenous androgens, which increase sebum production and lead to the development of idiopathic acne vulgaris. Acne can occur within weeks to several months of initiating treatment and can occur de novo or as exacerbations of existing acne. Anabolic steroid usage can make treating acne more difficult, and therapy should be focused on the immediate withdrawal of the anabolic steroids followed by conventional management of acne.

Hormonal Contraceptives

Progestogens with androgenic activity or low-dose estrogens can induce acneiform eruptions or exacerbate pre-existing acne lesions. Contraceptive implants have had varying reports on inducing acneiform eruptions and are an area where further studies are needed.

Tricyclic Antidepressants

Amineptine classically can cause an abrupt onset of monomorphic lesions composed of microcysts, macrocysts, and comedones of varying size many months or years after initiation of treatment. Severity was directly related to dosage and duration of usage. Amineptine and its byproducts could be detected within the skin lesions, and histologic examination showed rare instances of involvement of the eccrine sweat glands with keratinizing syringometaplasia and areas of neutrophilic eccrine hidradenitis. Treatment included withdrawal of amineptine, surgical removal of macrocysts, and treatment with isotretinoin. Rare case reports have also associated maprotiline and imipramine with drug-induced acneiform eruptions.

Lithium

Lithium can cause an abrupt onset of inflammatory lesions on the face, axilla, groin, arms, and

buttocks. Acneiform eruptions occur more frequently in men and patients who are allergic to lithium. No dose-effect relationship has been observed, although high concentrations of lithium may be observed in the skin, suggesting the drug accumulates there, which may lead to its pathogenicity.

Vitamin B_{12}

Predominately causes acneiform eruptions in women. The lesions develop abruptly within 1–2 weeks of initiating vitamin B_{12} injections. The lesions are characteristically monomorphous, inflammatory, and voluminous papules and pustules located on the face. Vitamin B_{12} withdrawal leads to resolution of the acne. Acne is considered a clue for vitamin overload, but it is unknown why vitamin B_{12} induces acneiform eruptions. It is hypothesized that iodine particles, which are used for vitamin B_{12} extraction, are still present in commercial preparations, leading to the eruption.

Dactinomycin

Dactinomycin can cause acne, mainly in men being treated for testicular cancer. Lesions are most often inflammatory and located in seborrheic areas. Classically they appear after the fifth day of treatment and are dose-dependent. Comedones may appear later in the course. Dactinomycin has androgenic properties and a tricyclic chemical structure. These characteristics are hypothesized as reasons it induces acneiform eruptions.

Cyclosporine

Causes acne in 15 % of patients. May present as a severe nodulocystic form of acne or may occur as acne keloidalis. Treatment includes cessation of cyclosporine and use of another immunosuppressant. If cyclosporine cannot be discontinued, isotretinoin can be used, along with careful monitoring of serum lipid levels. Cyclosporine also causes sebaceous hyperplasia. Unlike idiopathic hyperplasia, these tend to be more numerous and larger than idiopathic sebaceous hyperplasia. Both types of sebaceous hyperplasia are more commonly seen on the face.

Sirolimus

Causes acne in 15–25 % of patients. It occurs predominately in male patients with a history of severe acne vulgaris. Characteristically it presents with inflammatory papulopustules on the seborrheic regions and extending to the scalp, arms, forearms, and cervical area. There is no association with the dose or blood concentrations. Treatment is the same as for cyclosporine. It is hypothesized that sirolimus induces acne because of its direct inhibition of epidermal grow factor activity by inhibiting the mammalian target of rapamycin, a protein kinase involved in growth factor and cytokine signaling pathways.

Isoniazid

Characteristically causes an abrupt, extensive eruption of open and closed comedones and inflammatory papulopustules. Acneiform eruptions can occur up to 18 months after initiating therapy and can improve with discontinuation of the drug. It is hypothesized that slow acetylating phenotypes among patients makes them more susceptible to this side effect.

Rifampin

Associated with a chronic papular acneiform eruption appearing 5 weeks after initiating treatment. The lesions occur on the face, neck, and shoulders.

Halogens

Iodide, bromide, and chloride salt-containing drugs are associated with specific eruptions called iododerma, bromoderma, and chloracne, respectively. It is hypothesized that these compounds are eliminated by sebaceous glands leading to the eruptions. Iododerma and bromoderma characteristically present as large, inflammatory, violaceous nodules or vegetating or bullous lesions. Sometimes lesions will present only as severe acne of the face and trunk, but the lesions can occur anywhere on the body. Iododermas occur most commonly in patients with renal insufficiency, as the kidneys excrete iodine. Iododermas have been reported after iodized salt consumption, intravenous injection of iodinated contrast medium, cardiac catheterization, lymphography,

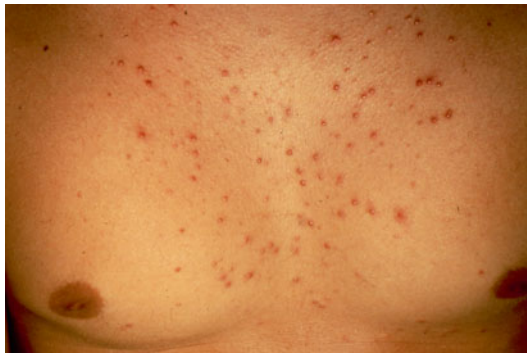

Fig. 15.4 Acneiform from iodides

urography, potassium iodide intake, and amiodarone intake. In these patients, iodine serum levels are elevated and discontinuation of iodine intake is sufficient to improve the patient's symptoms. For severe cases, local or systemic corticosteroids may be used.

Bromodermas present similarly to iododermas (Fig. 15.4) and diagnosis is confirmed by an elevated serum and urine bromide level. Withdrawal of the drug containing bromide and conventional acne treatments lead to disappearance of the lesions. Chloracne presents with comedones on the face, characteristically in the malar crescent and retroauricular folds, as well as the axilla and other parts of the body. The nose is characteristically spared by the eruption. In severe cases, cysts may appear on the face and neck, leading to the appearance of plucked chicken skin. Cutaneous lesions occur after exposure to polyhalogenated aromatic hydrocarbons or other chloracnegens from occupational or environmental exposure. Lesions can appear 2–3 months after first exposure and may last up to 15–30 years. Conventional treatment often yields no improvement.

Dantrolene

Characteristically it presents as open comedones, cysts, pustules, and abscesses on sites of chronic trauma, friction, or pressure such as the back, extensor surfaces of the forearms, axillae, buttocks, and perineum. There is no correlation with dosage, and lesions occur from 6 months to 4 years after beginning treatment. If possible, discontinuation of dantrolene with initiation of another treatment should be done. Isotretinoin should not be used with dantrolene due to hepatotoxicity.

Targeted Therapies

Acneiform eruption has become a hallmark of some targeted therapies involved in treating inflammatory or tumoral diseases. The highest incidence of eruptions occur with epidermal growth factor receptor (EGFR) inhibitors, affecting >60 % of patients. Monoclonal antibodies and tyrosine kinase inhibitors have also caused acneiform eruptions. Typically the eruptions will occur after the first course of treatment and progressively worsen over the course of the first month. Spontaneous regression or worsening after subsequent treatments can occur. Lesions are typically inflammatory papules and pustules located on the seborrheic areas of the face, but can also spread to the scalp and trunk. The papules can be pruritic. The incidence and severity of the eruptions are dose-dependent.

Case reports and studies have shown the following drugs to be associated with drug-induced acneiform eruptions: thyroid hormone, danazol, phenytoin, phenobarbital, primidone, carbamazepine, lamotrigine, aripiprazole, vitamins B_1 and B_6, azathioprine, thiourea, thiouracil, topical tacrolimus, topical pimecrolimus, ethionamide, quinidine, and antiretroviral therapy. Although these drugs, listed below, have been associated with drug-induced acneiform eruptions, more studies or case reports are needed to document the causative effects.

Drugs Implicated in Drug-Induced Acneiform Eruptions

- **Hormones**: local and systemic corticosteroids, corticotropin, androgens and anabolic steroids, hormonal contraceptives, thyroid hormone, danazol
- **Neuropsychotherapeutic drugs**: tricyclic antidepressants (amineptine, maprotiline, imipramine), lithium, phenytoin, phenobarbital, primidone, carbamazepine, lamotrigine, aripiprazole, selective serotonin reuptake inhibitors (SSRIs)

- **Vitamins**: Vitamins B_1, B_6, B_{12}
- **Cytostatic drugs**: Dactinomycin, Azathioprine, Thiourea, Thiouracil
- **Immunomodulating molecules**: cyclosporine, sirolimus, topical tacrolimus, topical pimecrolimus
- **Antituberculosis drugs**: Isoniazid, Rifampin, Ethionamide
- **Halogens**: iodine, bromine, chlorine, halothane gas, lithium
- **Targeted therapies**:
  - **Epidermal growth factor receptor (EGFR) inhibitors**: cetuximab, panitumumab
  - **Multitargeted tyrosine kinase inhibitors**: gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, imatinib
  - **Vascular endothelial growth factor (VEGF) inhibitors**: bevacizumab
  - **Proteasome inhibitor**: bortezomib
  - **Tumor necrosis factor alpha (TNF-α) inhibitors**: lenalidomide, infliximab
  - **Histone deacetylase inhibitor**: vorinostat
- **Miscellaneous**: Dantrolene, Quinidine, antiretroviral therapy

Treatment

Drug-induced acneiform eruptions are often mild and tolerable, and mimic the more common and self-limiting idiopathic disease. Physicians are compelled to check for a drug association in cases where drug-induced acneiform eruptions are suspected. The treatment includes identification and withdrawal of the drug, if possible. After cessation of the inciting drug, symptoms should abate. If the patient is unable to stop the drug, then conventional acne treatment is warranted. Drug-induced acneiform eruptions are more resistant to conventional acne treatment, however. If eruptions are mild, cosmetics may be used alone to treat the acne. If more moderate to severe cases of acneiform eruptions occur, the patient may use topical antibacterials like erythromycin, clindamycin, metronidazole, or benzoyl peroxide. Oral antibiotics such as doxycycline may also be used. In severe cases, oral isotretinoin may be used if it will not interact with other medications the patient is taking. Careful monitoring is necessary when using isotretinoin. Topical corticosteroids may also be used.

Main Points

- Medical history data often provides insight into the potential role that recently initiated drugs have in the development of acneiform eruptions.
- Physicians should always conduct an exhaustive search of possible culprit drugs when drug-induced acneiform eruptions are suspected.
- Unusual clinical features such as late age of onset, extension beyond the seborrheic areas, monomorphic inflammatory clinical pattern with lack of or late onset of comedones, and resistance to conventional therapy should prompt the clinician to suspect drug-induced acneiform eruptions.
- Discontinuation of the drug is the most effective treatment, but conventional acne treatment may be used as needed or if withdrawal of the inciting drug is not feasible.

Conclusions

Acne is seen in at least some form in most patients, usually during the adolescent age range. It presents at a time when self image is of paramount importance, and at its worst can leave disfiguring scars. Discovery of the drug that causes or exacerbates acne can help a young patient better cope with this difficult time of life.

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Collagen Vascular Diseases and Cutaneous Drug Reactions

16

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Abstract

Collagen vascular diseases (CVD) are a collection of autoimmune diseases in which a defect in the immune system causes the body to recognize its own structural proteins, primarily collagen, as foreign, resulting in self-directed immune responses. Tissues composed of various forms of collagen are often affected, including arteries, tendons, and other connective tissues. For this reason, CVD is sometimes called connective-tissue disease. Environmental triggers of CVD include infections, pollutants, radiation, and medications. This chapter identifies various medications that induce or exacerbate a particular CVD, as well as the manifestations, diagnosis, and treatment options thereof. The CVD subtypes discussed in this chapter are subacute cutaneous lupus erythematosus (SCLE), dermatomyositis, polyarteritis nodosa, and scleroderma. Other autoimmune diseases often classified as collagen vascular diseases not treated in this chapter include rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

Keywords

Connective tissue disease • Collagen vascular disease • Drug-induced • Lupus • Systemic lupus erythematosus • SLE • Subacute cutaneous lupus erythematosus • SCLE • Drug-induced lupus erythematosus • DILE • Dermatomyositis • Polyarteritis nodosa • Vasculitis • Scleroderma • CREST • Sclerosis

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_16

Introduction

Collagen vascular diseases (CVD) are a group of autoimmune diseases directed against collagen. Collagen contributes to multiple structures in the body such as tendons, ligaments, bones, and blood vessels. As in most autoimmune diseases, women are affected more than men, especially those in their 30s – 40s, although age ranges vary. When an individual with a genetic predisposition to this class of diseases is exposed to an environmental trigger, this trigger can induce the formation antibodies that recognize components of collagen. Inflammation ensues, leading to the pathognomonic signs and symptoms for each particular disease. Examples of environmental triggers include infections (viral, bacterial, fungal), environmental toxins (cigarette smoke, pesticides, pollutants), radiation, and medications.

Subacute Cutaneous Lupus Erythematosus (SCLE)

Subacute cutaneous lupus erythematosus (SCLE) is a distinct subset of systemic lupus erythematosus (SLE), in which a cutaneous eruption is the primary manifestation of the disease. The diagnostic criteria for SLE include mucocutaneous (including malar rash, discoid rash, photosensitivity, or oral ulcers) and systemic manifestations (including arthritis, serositis, pleuritis, pericarditis, renal disease, neurologic disease, hematologic disorder, immunologic disorders (including anti-deoxyribonucleic acid [DNA], anti-Sm, or anti-phospholipid antibodies) and abnormal antinuclear antibody [ANA] titers). A positive antihistone antibody is more likely to be present in lupus skin reactions secondary to a medication. Patients with SCLE frequently fulfill four or more of the SLE criteria; arthritis, photosensitivity, leukopenia, and a positive ANA being the most common. Arthralgias involving small joints are present in approximately 50 % of patients. Unlike in SLE, however, SCLE usually lacks the presentation of systemic disease; only approximately 10–20 % of patients with SCLE ever develop the systemic manifestations of SLE.

Clinical Presentation

The characteristic lesions of SCLE begin as typical erythematous papules or plaques but evolve into psoriasiform, lichenoid, or polycyclic annular lesions, often accompanied by telangiectasias and depigmentation. The inciting lesion is typically a macule or scaly papule. The psoriasiform papulosquamous lesions of SCLE are described as sharply defined, slightly delicate, and scaling evolving into confluent erythematous plaques of oval (Fig. 16.1) or polycyclic formations. The annular lesions are described as erythematous plaques with central clearing and only slight scaling. These lesions are non-scarring, non-atrophic, and photosensitive. The scales are thin and easily separated from the underlying epidermis. In general, the eruptions of SCLE predominately appear in a photodistributed pattern (Fig. 16.2), with sun-exposed areas of the face, neck, upper chest and back, and extensor surfaces of the arms being most commonly affected, although the involved areas can be more generalized as well. The axillae, flanks, and knuckles are typically spared. SCLE may occur concomitantly in patients with SLE, Sjogren syndrome, or it may be drug-induced. No significant differences in the clinical, histopathological or immunopathological features between drug-induced SCLE and idiopathic SCLE are known.

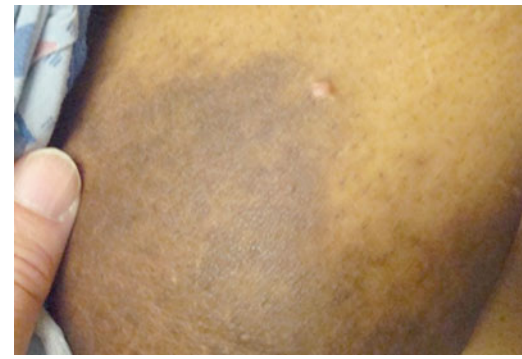

Fig. 16.1 Annular plaque on the breast of a woman who was on methyldopa. The biopsy was compatible with DLE. The patient was histone positive and improved when the drug was stopped

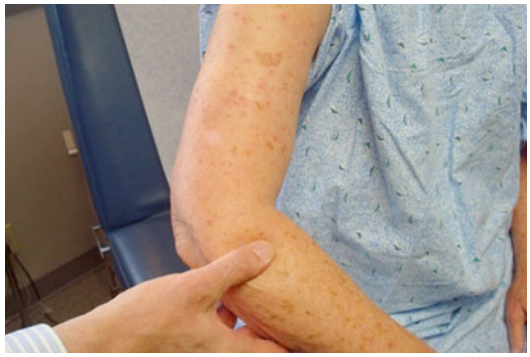

Fig. 16.2 Photodistributed oval erythematous plaques that were sun-induced in a patient on hydrochlorthiazide. She was SSA/SSB positive. The biopsy was compatible with subacute cutaneous lupus, and the patient cleared when the drug was discontinued

Drug-Induced SCLE

SCLE is an autoimmune disease that is more likely to occur among genetically predisposed individuals confronted with an environmental trigger. The inherited antigens correlating most with SCLE include human leukocyte antigen (HLA) B8, HLA-DR3, HLA-DRw52, and HLA-DQ1. Individuals with anti-Ro (SS-A) or anti-La (SS-B) autoantibodies are greatly predisposed to developing SCLE, as greater than 80 % of those with SCLE are anti-Ro antibody positive. A positive anti-histone antibody is indicative of drug induced LE.

Environmental triggers commonly involve ultraviolet light, which supports the observation that lesions are most frequently distributed on sun-exposed surfaces of the body. The exact mechanism is unknown. However, approximately 30 % of patients with SCLE are found to have a drug as the inciting agent. Drugs can either induce or exacerbate the disease. In particular, the anti-hypertensive, hydrochlorothiazide (HCTZ), has been extensively studied and is most frequently noted for its temporal relationship to drug-eruptions causing SCLE, as well as remission of disease when the agent is discontinued. Other drugs demonstrating a strong association with drug-induced SCLE include, but are not limited to, other antihypertensive medications, especially calcium channel blockers (CCB) and angiotensin-converting enzyme inhibitors (ACE-I), D-penicillamine, anti-tumor necrosis factor (TNF) agents, the antifungals griseofulvin and terbinafine, anti-epileptics, and proton-pump inhibitors (Table 16.1).

Studies have aimed to determine the time interval between drug exposure and cutaneous eruption (incubation time), as well as the time interval between drug discontinuation and resolution of cutaneous eruption (resolution phase). The incubation period between drug exposure and appearance of drug eruptions varied greatly between drugs and depended heavily on drug classes. A study published by G. Lowe in the *British Journal of Dermatology* demonstrated a mean incubation period of approximately 28 weeks. In the same study, thiazide diuretics, such as HCTZ, and calcium channel blockers (CCBs), such as verapamil and diltiazem, proved to have the largest interval of incubation, whereas antifungal medications had the shortest incubation period. The incubation period for thiazides and calcium channel blockers varied greatly, from months to years. The mean incubation time for antifungal medication was approximately 1 month. These varying incubation times emphasize the need to consider historical drug exposures as well as drugs that were started without incident when diagnosing current dermatologic findings.

Diagnosis

SCLE is a diagnosis based on clinical presentation, in conjunction with results from histopathology, immunofluorescence, and serology. Notably, drug-induced SCLE may differ from idiopathic SCLE in that drug-induced SCLE are more likely to cause malar rash accompanied by bullous erythema multiforme and vasculitic manifestations. In SCLE, histology reveals a thin epidermis, with slight lymphocytic perivascular and perifollicular inflammatory infiltrate in the superficial and deep dermis. Follicular plugging, hyper-orthokeratosis, and parakeratosis are less common than with other forms of lupus erythematosus, such as discoid lupus. The epidermis in SCLE lesions displays extensive damage of all layers, with eosinophilic necrosis and vacuolization. The

Table 16.1 Drugs reported to induce subacute cutaneous lupus erythematosus

Anti-arrhythmics/anti-hypertensives ACE inhibitors Enalapril Lisinopril Captopril Cilazapril Ramipril β-blockers Oxprenolol Acebutolol Calcium-channel blockers Diltiazem Verapamil Nifedipine Nitrendipine Class I anti-arrhythmics Quinidine	**Antibiotics/antifungals** Griseofulvin Terbinafine Amoxicillin + clavulanic acid	**Anti-cholinergics** Inhaled tiotropium
Antidepressants Buproprion	**Anti-epileptics** Carbamazepine Lamotrigine Phenytoin	**Anti-gout agents** Allopurinol
Antihistamines Ranitidine Brompheniramine Cinnarizine + thiethylperazine	**Anti-neoplastics** Docetaxel Paclitaxel Tamoxifen Capecitabine Doxorubicin Methotrexate	**Anti-thombotics** Ticlopidine
Biologics Adalimumab Bevacizumab Etanercept Efalizumab Golimumab Infliximab	**Diuretics** HCTZ HCTZ + triamterene Chlorothiazide	**Glucose control** Glyburide
Hormone-modulators Leuprorelin Anastrazole	**Immunomodulators** Leflunomide Interferon alpha and beta 1a	**NSAIDs** Piroxicam –
Proton-pump inhibitors Lansoprazole Pantoprazole Omeprazole	**Statins** Simvastatin –	**Other** D-penicillamine (chelator, rheumatoid treatment)

Adapted from Grönhagen et al. (2012)

majority of patients have a positive immunopathologic lupus band test, meaning that complement and or immunoglobulin is present along the dermal-epidermal junction. Serology in SCLE is often positive for ANA and is more likely than SLE to be associated with positive SS-A and SS-B autoantibodies. Anti-histone antibodies are present in more than 95 % of cases of drug-induced SCLE.

Treatment and Course

The average resolution time upon discontinuing the inciting drug is approximately 7 weeks. Several studies attempted treatment before discontinuing the drug, with no resolution noted until the drug was eventually terminated. Most lesions resolve without additional treatment. However, a few reported cases in the literature have required active treatment for resolution of

drug-induced SCLE to occur; the inciting drugs in these cases were terbinafine, leflunomide, anastrazole, leuprorelin, and psoralen plus ultraviolet A (PUVA) therapy. Treatment was initiated with topical steroids such as clobetasol, oral prednisone, hydroxychloroquine, topical tacrolimus, or mycophenolate mofetil. In several follow-up appointments, most patients who were originally anti–Ro or La positive did not convert to negative upon resolution. This signified that once a patient seroconverted, he or she remained positive for the antibodies associated with the disease despite treatment and resolution of symptoms.

Drug-Induced Lupus Erythematosus (DILE)

Drug-induced lupus erythematosus (DILE) can be easily confused with drug-induced SCLE; however, the key distinction is that whereas both conditions are drug-induced, SCLE is primarily *cutaneous*. While DILE can be cutaneous as well, it is more likely than SCLE to manifest systemically. Malar and discoid lesions are *rare* in DILE, as are renal or neurologic impairments. In addition, DILE has a distinct antibody profile from traditional SLE and SCLE. While both SCLE and DILE (as well as SLE) are associated with a positive ANA and anti-histone antibodies, SCLE patients are far more likely to be Anti-Ro (SS-A) or anti-La (SS-B) positive. DILE patients are more likely to have a homogenous pattern of anti-histone antibodies on immunopathology, whereas drug-induced SCLE patients most often have a speckled pattern. DILE usually has normal complement levels, whereas SCLE can be associated with complement deficiency. The inciting drugs also differ, with DILE more likely to be caused by procainamide, isoniazid, timolol, and hydralyzine.

Dermatomyositis (DM)

Dermatomyositis (DM) is a CVD that is distinguished by characteristic skin lesions and myopathy. The myopathy is usually inflammatory and can cause weakness. The skin lesions considered diagnostic of DM consist of varying forms of dermatitis and an eyelid heliotrope rash with periorbital edema, although a host of cutaneous named signs are also associated with DM. Idiopathic DM can involve a vague systemic prodrome, edema, dermatitis, interstitial pulmonary fibrosis, and inflammation of muscle tissue. The prodrome is typically characterized by intermittent fevers, malaise, anorexia, arthralgias, and marked weight loss. The muscle involvement is primarily proximal, resulting in myalgias and muscular degeneration. DM is relatively rare, and like most autoimmune diseases affects mostly women. African Americans are disproportionately affected. Although adults can be affected, there is a juvenile form of DM as well. The drugs most known to cause DM are hydroxyurea and D-penacillamine.

Clinical Presentation

Some pathognomonic skin findings of DM are the heliotrope rash, Gottron's papules, mechanic's hands (Fig. 16.3), Holster shawl, V-signs, and malar rash. The heliotrope rash (named for the purple flower) is described as an erythematous to violaceous eruption around the upper eyelids associated with swelling. The heliotrope rash is often tender to touch as it can involve the orbicularis oculi muscle. Gottron's

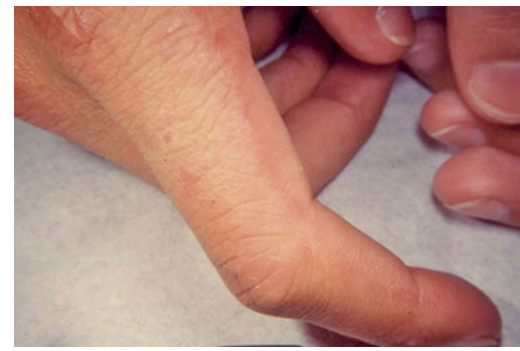

Fig. 16.3 Mechanic's hand with dermatitis along the radial edge of the index finger. It resolved when doxycycline was discontinued

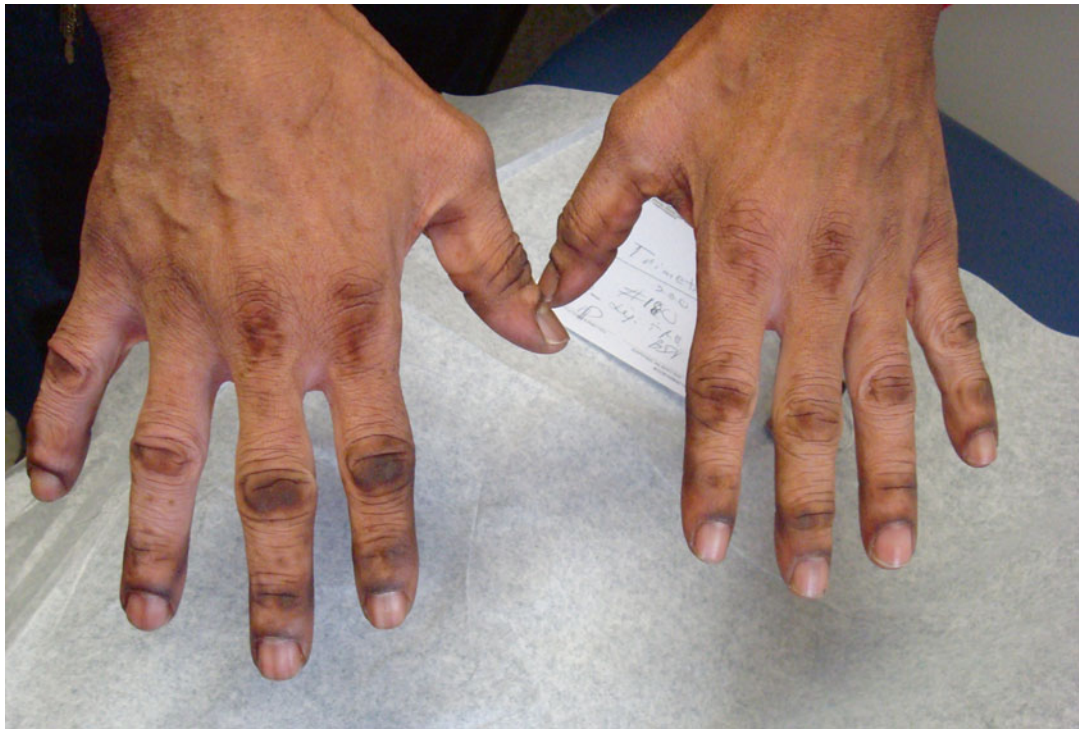

Fig. 16.4 Hyperpigmentation and dermatitis over knuckles in a patient on minocycline mimicking dermatomyositis. Note also proximal nail fold changes

papules consist of erythematous to violaceous papules that erupt symmetrically along the extensor surfaces of the metacarpophalangeal and interphalangeal joints (Fig. 16.4), although the term is sometimes used to refer to similar lesions on the medial malleoli. The papules can become scaly and ulcerate. Mechanic's hands are hands whose palms and lateral finger surfaces are thickened (hyperkeratotic). Holster sign signifies similar lesions on the hips, shawl sign is erythema of the upper back and shoulders, and V-sign is erythema of the V-area of the neck and chest. Holster sign is significant for the fact that it is outside of the typical photodistributed pattern of presentation. Poikiloderma—hyperpigmented and hypopigmented lesions that contain small telangiectasias with epidermal atrophy—may be observed along with erythema in the areas of the shawl and V-signs. The lesions are typically quite pruritic and may become thickened and palpable. Facial erythema can also be present and is similar to the characteristic malar rash of SLE; however the erythema involves the nasolabial skin folds that are typically spared in SLE and SCLE. Cuticle overgrowth and periungual changes may occur, particularly in the capillary nail beds. In addition, vascular changes can occur with areas of dilation presenting as erythematous changes elsewhere on the body.

The "myositis" element of DM consists of symmetric proximal muscle weakness with edema and myalgias. The most common locations for these findings are the deltoids and hip flexors. Classic presentations and complaints are related to patients' subsequent inability to climb stairs, comb their hair, or lift light objects over their heads. Involvement of bulbar muscles can cause difficulty swallowing, and potential involvement of respiratory muscles can make speaking and even breathing difficult. Finally, in the terminal phases of the illness, cardiac muscle involvement produces cardiac failure.

Drug-Induced DM

Many drugs have been reported to induce a DM-like eruption (Fig. 16.5). The agents most frequently implicated are hydroxyurea, penacillamine, and zoledronic acid, however other medications can cause the disease as well (Table 16.2). Case reports dominate the literature and review indicates that different drugs can induce different manifestations of DM. Humoral immunity and vasculopathy caused by complement deposition are most likely responsible for the muscular changes in DM. The causes of dermatologic findings are less clear, although it has been posited that the reaction is associated with the development of autoantibodies through the unmasking of sequestered antigens when the drug is introduced to bodily tissues.

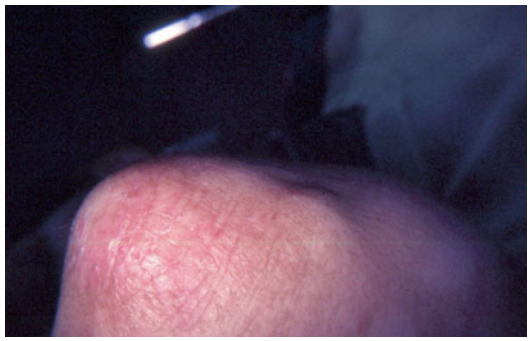

Fig. 16.5 Erythema, atrophy, and telangiectasias over elbow in a patient on hydroxyurea, with symmetric dermatitis over the other elbow mimicking dermatomyositis

Table 16.2 Drugs reported to induce dermatomyositis

Antibiotics and anti-fungals	Isoniazid Penicillin Sulfonamides Terbinafine
Anti-neoplastics	Capecitabine Cyclophosphamide Etoposide Hydroxyurea Tegafur
Bisphosphonates	Zoledronic acid
Chelators	Fibrates Statins
Lipid-lowering agents	D-penicillamine
Analgesics	NSAIDs

Hydroxyurea

An antimetabolite agent that is most commonly used for the treatment of neoplastic myeloproliferative disorders. Other common uses for hydroxyurea include the treatment of sickle cell crises and chronic myelogenous leukemia, as well as adjunct therapy for autoimmune immunodeficiency syndrome (AIDS). Many side effects can occur with the use of hydroxyurea, including several cutaneous reactions such as xerosis, ichthyosis, stomatitis, and DM-like eruptions. Several case reports have discussed hydroxyurea-induced DM, especially the appearance of Gottron's papules. Notably, these DM-like cutaneous eruptions occur with or without the systemic manifestations typically found in the disease.

D-Penicillamine

Commonly used for the treatment of rheumatoid arthritis, as it is an immunosuppressive agent that acts by reducing the number of T-cells and inhibiting macrophage functionality. It is also utilized as a copper chelator in the treatment of illnesses such as Wilson's disease. A rare adverse effect found in several patients taking D-penicillamine for rheumatoid arthritis is the development of DM. Within 2 months of therapy with this agent, patients can begin to experience the classic heliotrope rash, Gottron's papules, and erythema of the face, limbs, and chest.

Zoledronic Acid

A bisphosphonate commonly used for the treatment of osteoporosis, certain malignancies associated with fractures, as well as Paget's disease, and there are case reports of it inducing DM. A case reported in the *Australasian Journal of Dermatology* in 2012 by Tong et al. identified a patient taking bisphosphonates for the treatment of her osteoporosis. Several days following a single infusion of zoledronic acid, the patient complained of proximal muscle weakness, fatigue, and a widespread rash on her forehead, neck, upper chest, lateral thighs, and left arm. The rash was reminiscent of DM: macular and violaceous with small telangiectasias.

Terbinafine

A commonly used allylamine antifungal medication effective against dermatophyte fungi. Topical preparations are available for superficial skin infections such as tinea, commonly known as ringworm. Oral preparations are used for the treatment of diseases such as onychomycosis, a fungal infection of the nail bed, because of the deeper location of the infection and minimal penetration of topical ointments. Several case reports indicate that terbinafine administration has a temporal relationship to dermatomyositis onset. Within several weeks of beginning oral terbinafine, a characteristic photodistributed erythema involving the face, neck, chest, abdomen, and extremities, as well as Gottron's papules can erupt.

Lipid-Lowering Agents

Those such as HMG-CoA reductase inhibitors (statins, especially simvastatin) and fibrates can induce DM in previously healthy, asymptomatic individuals. The eruption occurs within several months of drug use. Symptoms such as an erythematous photodistributed rash over the chest, upper back, arms, and shoulders, as well as dysphagia to solids, weight loss, and proximal muscular weakness, can occur upon initiating treatment.

Diagnosis

Diagnosis may be primarily clinical, but a known offending drug plus laboratory findings may be helpful. Patients can present with primarily skin lesions without muscle complaints, a form of amyopathic DM. This is actually quite common because skin changes often occur several months prior to muscle changes in DM. The Bohan and Peter criteria for the diagnosis of DM include: symmetrical weakness of proximal muscles; increase in serum skeletal muscle enzymes (i.e., elevated creatine phosphokinase [CPK], transaminases, lactate dehydrogenase [LDH], aldolase); a characteristic abnormal electromyograph (EMG); myositis on muscle biopsy; and dermatologic features as previously described. For a DM diagnosis, three criteria from must be met in addition to the characteristic skin changes. Autoantibodies such as anti-synthetase and anti-Mi-2 antibodies are also present in the disease. In general, the histopathological findings of DM and drug-induced DM consist of thinning of the basement membrane, hydropic degeneration of the basal layer of the epidermis, edema of the papillary dermis, perivascular and periadnexal lymphocytic infiltrate in the superficial and deep dermis, and increased dermal mucin. In terms of hydroxyurea, histopathological findings of DM-like papules are consistent with DM and include a lichenoid inflammation with vacuolar changes in the basal layer of the epidermis and apoptotic keratinocytes. Histopathology of the D-penacillamine DM-like lesions shows an upper dermal lymphocytic infiltrate and basal cell liquefaction degeneration again consistent with dermatomyositis. Meanwhile, biopsy of zoledronic acid–induced lesions has been consistent with typical findings of DM: superficial telangiectasia, lichenoid inflammatory infiltrate, perivascular lymphocytic infiltrate, and interstitial dermal mucin deposition. When terbinafine causes DM, serum creatinine kinase levels become elevated and biopsies taken from these lesions have revealed a pattern characteristic of dermatomyositis, namely interface dermatitis, mucin deposition, basement membrane zone thickening, and denuded endothelial cells. Finally, histopathology of lesions caused by lipid lowering agents has shown perivasculitis, thinning of blood-vessel endothelium, and increased connective tissue, all findings that can be consistent with dermatomyositis. Creatinine kinase levels also increase, often to ten times the normal value.

Treatment and Course

Discontinuation of the inciting medication and, at times, introduction of oral steroids has been found to induce remission. Regarding hydroxyurea, the cessation of the drug may result in gradual resolution of the cutaneous lesions within months. In the case study regarding DM induced by a bisphosphonate, the drug was discontinued

and the patient had to be treated with prednisolone, hydroxychloroquine, and topical betamethasone for resolution of both cutaneous and myopathic symptoms, which took 1 year. While in this case the drug likely caused the DM, it is possible that the patient had DM and it manifested during zoledronic acid administration or was unmasked by it. In the case of terbinafine, within 6 months of cessation, cutaneous changes can begin to resolve, although muscular symptoms have been found to persist. The rash can also persist despite discontinuation of terbinafine, which can be attributed to the medication actually inducing an autoimmune state in such individuals. Upon discontinuation of a statin causing DM, many patients do not improve clinically, even after months. Steroid treatment with intravenous methylprednisolone or oral prednisone has been found to lower creatinine kinase levels and improve both the diminished proximal muscle strength as well as the skin rash within weeks of treatment. As with terbinafine, this persistence of a DM state even after cessation of medication use may be attributed to an autoimmune musculocutaneous pathogenesis. In sum, the duration of DM post-drug cessation may vary dramatically.

Polyarteritis Nodosa (PAN)

Polyarteritis nodosa (PAN) is a systemic vasculitis primarily affecting medium- and small-sized muscular arteries. Major vessels involved are those of the liver, heart, gastrointestinal tract, subcutaneous tissues, joints, and muscles. PAN classically spares the respiratory system. Historically PAN was subsumed under other vasculitities, such as microscopic polyarteritis, but recently the acceptance of PAN as a distinct entity has led to fewer patients with this diagnosis. The major distinction between the PAN and microscopic polyarteritis is the near absolute presence of anti-neutrophil cytoplasmic antibodies (ANCA) in the latter. The inciting event in PAN is that of an inflammatory necrotizing panarteritis of the small- and medium-sized arteries. Small aneurysms develop that can often rupture leading to hemorrhage and ecchymosis. PAN is also an obliterative arteritis that can lead to ischemia of downstream tissue and necrosis of organs. In each vasculitis, symptoms occur due to ischemic damage to the skin and internal organs. Most people who develop PAN do so around age 40. Unlike some other autoimmune diseases, PAN appears more commonly in men. Intravenous drug abuse, systemic lupus erythematosus, and hepatitis B and C are known associations with PAN.

Clinical Presentation

Cutaneous manifestations of PAN include painful, pulsating, subcutaneous nodules (Fig. 16.6) distributed along the course of blood vessels. Typically these nodules appear on the lower extremities and can often ulcerate. Overlying these nodules is slightly erythematous skin.

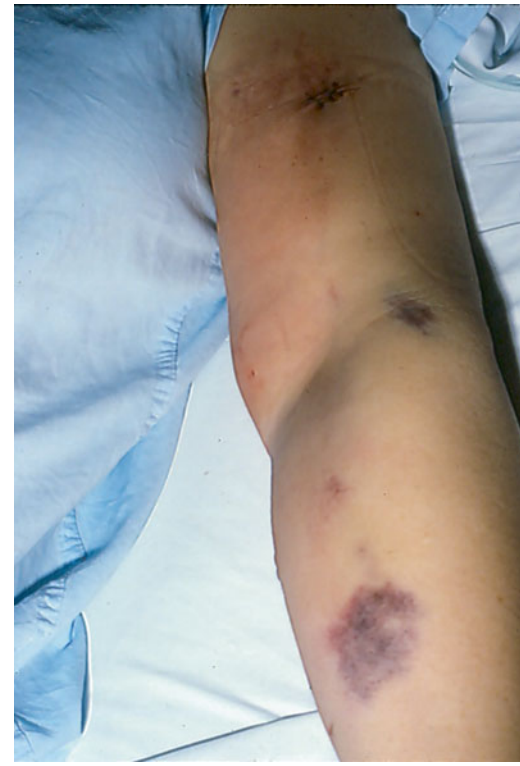

Fig. 16.6 Purpuic nodules over the arm, showing vasculitis on biopsy. ANCA negative and on the upper vs, lower extremities, so probably not polyarteritis nodosa. Drug reaction was a possibility but the history was negative

Patients may also present with livedo reticularis, a lace-like purplish discoloration of the skin caused by chronic obstruction of venules. Systemic symptoms caused by the affectation of internal organs may include tachycardia, hypertension, edema, weight loss, hepatomegaly, arthralgia, stroke, and intestinal infarctions. One of the hallmarks of the disease is a mononeuritis multiplex that leads to the unilateral foot drop often seen in PAN patients. Several medications have been linked to the eruption of cutaneous manifestations of PAN. The most common inciting drugs are gemcitabine and minocycline.

Drug-Induced PAN

Gemcitabine is an anti-neoplastic agent frequently used in the treatment of non-small–cell lung, pancreatic, bladder, colon, ovarian, and breast cancers. It is a nucleoside analog that functions in the inhibition of DNA synthesis. Recently, gemcitabine therapy was shown to induce a PAN-like cutaneous disease state in some cancer patients. Symptoms can appear within a month of initiation of the agent. Cutaneous manifestations include multiple painful subcutaneous nodules with overlying erythema concentrated in the lower extremities.

Another drug that has been associated with PAN cutaneous findings is *minocycline*. Minocycline is a synthetic derivative of tetracycline and is commonly used in the treatment of acne vulgaris, methicillin-resistant staphylococcus aureus (MRSA), and Lyme disease. It functions by inhibiting bacterial protein synthesis. The most common side effects include photosensitivity, esophagitis, diarrhea, and blue-gray skin discoloration. Minocycline use has been linked to drug-induced lupus, and several reports have also shown an induction of cutaneous PAN. Some individuals on therapy for acne reported multiple tender subcutaneous nodules with overlying violaceous skin on the lower extremities. Symptoms of joint pain and stiffness, as well as livedo reticularis, are frequently found in association with the cutaneous lesions. Otherwise, systemic manifestations of PAN are typically absent with minocycline use.

Diagnosis

Classic PAN is typically diagnosed by biopsy of a skin lesion or angiography showing aneurysms, along with supporting clinical features. Laboratory findings include leukocytosis with neutrophilia, thrombocytosis, normocytic anemia, and an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. The American College of Rheumatology criteria for the diagnosis of PAN state that a patient has PAN if three of the following ten criteria are met: weight loss greater than 4.5 kg, livedo reticularis, myalgia, testicular pain, neuritis, diastolic blood pressure greater than 90 mmHg, elevated blood urea nitrogen (BUN) and creatinine, positive hepatitis B or C viral tests, aneurysms on angiography, or biopsy showing arteritis. When an inciting medication is present, some findings are similar though a strict diagnosis may not be met.

Biopsy of the gemcitabine-induced lesions with histologic analysis has revealed findings consistent with primary PAN, namely a superficial and deep perivascular inflammatory cell infiltrate, transmural inflammation of subcutaneous tissue medium-sized arteries, and occlusion of the lumen with intimal proliferation. Laboratory findings often are unrevealing, except for an elevated ESR or white-blood-cell count. Serologic results are typically negative. Vis-à-vis minocycline, biopsy of the induced nodules reveals a necrotizing vasculitis with a vascular wall neutrophil infiltration, necrosis, and thrombi. Interestingly, perinuclear ANCA (pANCA) develop whereas the presence of pANCA in idiopathic PAN is rare. As the association between minocycline and PAN has been strongly suggested, diagnostic criteria for minocycline-induced cutaneous PAN exist and include: minocycline use for greater than 1 year, skin manifestations such as subcutaneous nodules and/or livedo reticularis, arthritis and/or myalgias and/or neuropathy in the distribution of the rash, lack of systemic organ involvement, skin biopsy with necrotizing vasculitis of small- or medium-sized vessels, pANCA positive titer, and improvement of symptoms after discontinuing the agent. Six of seven of these criteria must be met in order to diagnose minocycline-induced cutaneous PAN.

Treatment and Course

Morbidity from classic PAN is most commonly secondary to renal or cardiovascular causes. The mainstay of treatment includes prednisone and cyclophosphamide. Steroids such as prednisone are tapered after a few months of remission, and cyclophosphamide tapered later, sometimes after 1 year of remission. When PAN is caused by gemcitabine and the drug is discontinued, skin lesions start to improve. Administration of a non-steroidal anti-inflammatory drug (NSAID) can also hasten recovery. Treatment of minocycline-induced cutaneous PAN also involves discontinuing the drug, with an optional gradual steroid taper.

Scleroderma

Scleroderma is an autoimmune connective-tissue disorder characterized by chronic sclerosis of the skin. The classic disease is divided into localized or systemic forms. Localized scleroderma involves predominantly cutaneous manifestations, subdivided into morphea (localized, generalized, profunda, or pansclerotic) or linear (with or without melorheostosis, which is bone-cortex widening with increased hyperdensity or hemiatrophy). Systemic sclerosis is determined by the extent of skin involvement and the internal organs affected. It is subdivided into the CREST syndrome (calcinosis, raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias) and progressive systemic sclerosis. Cutaneous and visceral organ manifestations result from chronic inflammation, progressive tissue fibrosis, and excessive collagen production and deposition in endothelial walls of the vasculature.

Scleroderma is another autoimmune disease that disproportionately affects middle-aged African American women.

Clinical Presentation

Skin manifestations of scleroderma can include pigment alterations resulting in areas of hyperpigmentation as well as areas of hypopigmentation, telangiectasias, edema, and textural changes leading to a tight and shiny appearance of the skin (Fig. 16.7) with patches of hair loss. Occasionally patients can present with deep fibrotic lesions and ulcerations. Common organs involved are the gastrointestinal tract, lungs, heart, and kidneys. Involvement of these systems can result in gastroesophageal reflux, constipation, dyspnea, palpitations, hypertension, and renal insufficiency, among others. Like the other drug-induced diseases in this chapter, those genetically predisposed individuals who are exposed to certain environmental triggers are more prone to developing the disease. Environmental factors known to trigger scleroderma are occupational exposure to certain solvents such as vinyl chloride and carbon tetrachloride, as well as radiation. Viruses have also been implicated in the onset of scleroderma, the most studied being cytomegalovirus and parvovirus B19. Finally, a variety of drugs have been found to induce or exacerbate the disease (Table 16.3).

Drug-Induced Cutaneous Scleroderma

Anti-neoplastic agents are the most studied inducers of scleroderma. *Hydroxyurea* is DNA-

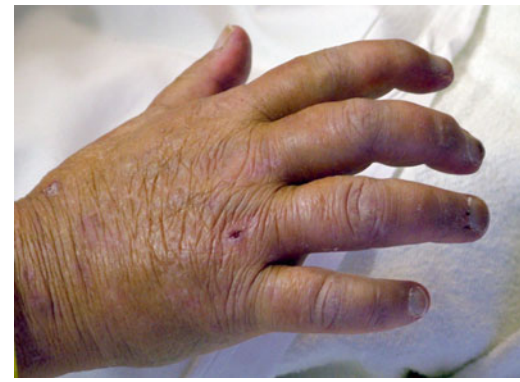

Fig. 16.7 Skin is taught and indurated over the hand, which the patient cannot completely open. Tryptopohan was the cause in a patient with nephrogenic fibrosis. This should be of historical interest only, as the inciting drug has been discontinued. Other sclerodemoid drug eruptions can look similar

Table 16.3 Drugs reported to induce cutaneous scleroderma

Biologics	Adalimumab Cathepsin K–inhibitors (e.g., balicatib)
Amino acids	L-tryptophan L-5-hydroxytryptophan (L-5 HTP)
Anti-hypertensives	β-blockers Bisoprolol ACE-I Fosinopril
Anti-neoplastics	Bleomycin Carboplatin Docetaxel Gemcitabine Hydroxyurea Paclitaxel
Anti-parasitics	Endectocide
Anti-retrovirals	Enfuviritide
Immunomodulators	Interferon
Analgesics	Ergots Ketobemidone Methysergide Morphine Pentazosine
Hormone-modulators	Bromocriptine
Neurologic agents	Carbidopa Ethosuximide
Other	D-penacillamine (chelator, rheumatoid treatment)

synthesis inhibitor often used in the treatment of myeloproliferative disorders. Its use has been associated with DM eruptions, but it has also been associated with a rare drug-induced scleroderma-like syndrome after longterm use. Patients on this therapy for many years have experienced gradual skin changes simulating those found in scleroderma. In particular, skin can become shiny and flat, with induration, a woody consistency, and loss of hair follicles.

Other chemotherapeutic drugs such as *paclitaxel* and *carboplatin* can similarly induce scleroderma. Both are frequently used for the treatment of gynecological malignancies but have been used against many cancers. Paclitaxel, a taxane, stabilizes microtubules and prevents their degradation during cellular division. Carboplatin interferes with DNA repair. Of the many side effects of chemotherapeutic medications, one is the rare adverse effect of scleroderma-like cutaneous lesions. Upon several courses of treatment, patients may develop some characteristic skin lesions of scleroderma, namely shiny, thickened epidermis with generalized edema. Furthermore, with paclitaxel and carboplatin use, the systemic visceral findings of diffuse classic scleroderma, such as pulmonary, gastrointestinal, cardiac, and renal effects, are not present.

Bleomycin is another chemotherapeutic agent and is commonly used in the treatment of Hodgkin's lymphoma and testicular cancer. It acts by inducing DNA-strand breaks, thereby preventing neoplastic proliferation. One of the most well-known adverse effects of bleomycin use is pulmonary fibrosis. Supplemental laboratory studies have resulted in the discovery that mice injected with bleomycin develop *dermal* fibrosis identical to that found in scleroderma.

Diagnosis

In classic scleroderma manifestations, antinuclear antibodies (ANA) are present in almost all patients, typically with a speckled pattern on microscopy. The antinucleolar pattern is considered highly specific for systemic scleroderma. Other antibodies present in patients affected with scleroderma are anti-topoisomerase I (also known as Scl-70), anti-centromere, anti-fibrillarin, anti-RNA polymerase I and II, anti-PM-Scl, and anti-ribonucleoprotein (RNP) antibodies. Both the systemic and localized forms of typical scleroderma show similar histological changes. Initially, perivascular T-cell lymphocytic infiltration occurs. Collagen production and deposition increase. Dermal thickness then increases substantially, while the subcutaneous fat is reduced. A severe fibroproliferative vasculopathy of the small vessels exists, which primarily affects the organs. In the advanced stages of scleroderma, there may only be minimal inflammatory infiltrate, but collagen deposition increases markedly. The dermal thickness is also greatly increased.

In cutaneous scleroderma caused by hydroxyurea, histological findings include extensive dermal fibrosis with thickening of collagen bundles within the dermis and hypodermis, similar to classic scleroderma. Mild papillary edema and

perivascular lymphohistiocytic infiltrate with eosinophils can also be present. Immunological findings, however, are typically negative for the antibodies found in primary scleroderma (such as anti-Scl-70 and anti-RNP antibodies). Paclitaxel or carboplatin–induced scleroderma's histopathological findings are consistent with primary scleroderma in that inflammatory-cell infiltration occurs around dermal vessels with increased collagen bundle deposition in the dermis. As with hydroxyurea-induced scleroderma-like syndrome, paclitaxel and carboplatin both induce a similar syndrome with negative antibody findings, and this lack of antibodies can help rule out primary systemic or localized scleroderma.

In the mouse lab study by Yamamoto (2006) involving bleomycin, dermal sclerosis manifests after dermal fibrosis, with lesions showing characteristic scleroderma-like histopathological findings such as thickened collagen bundles and dermal layers as well as lymphocytic inflammatory infiltration.

Treatment and Course

Studies indicate that within 6 months of discontinuation of hydroxyurea, resolution of scleroderma skin lesions can be seen without scarring. After administration of the antineoplastic agents paclitaxel or carboplatin has ceased, skin lesions subside and resolution can be hastened by the use of topical or systemic steroids, depending on the severity of lesions. Complete resolution is typically noted within 3 months upon medication withdrawal. Finally, some studies indicate that cessation of bleomycin injections allowed the scleroderma-like sclerosis to slowly retreat after approximately 6 weeks.

Conclusions

Collagen vascular diseases are systemic illnesses caused by circulating autoantibodies that attack multiple organs, including the skin. There are two ways that drugs can affect the skin in a way similar to these autoimmune diseases. One is to cause a reaction in the skin that mimics the disease and the other is to exacerbate the disease and have the exacerbation be manifested in the skin. In this chapter we have described both possibilities. Eliminating the offending medication may not only spare the patient further skin disease, but also avoid damage to other organs when the disease is activated.

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Fixed Drug Eruptions

17

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Abstract

Fixed Drug Eruptions (FDEs) are a localized response to medications that typically appear as well-demarcated erythematous dusky patches or plaques. They may be solitary, multiple, or generalized. The initial eruption of a FDE appears 1 week post-drug exposure, whereas subsequent exposures to the same drug lead to development of lesions within 30 min to 24 h. Despite the number of occurrences, these patches and plaques resolve within 2–3 weeks of discontinuing the offending agent, often leaving post-inflammatory hyperpigmentation. NSAIDs (non-steroidal anti-inflammatory drugs), tetracyclines, trimethoprim-sulfamethoxazole, sedatives including barbiturates, benzodiazepines and chlordiazepoxide, and anti-convulsants are the most commonly reported drugs causing FDE. Certain drugs have a predilection for causing particular subtypes of FDE, as well as mucosal involvement. Histologically, FDEs present with a vacuolar dermatitis occurring at the dermo-epidermal junction. Lymphocyte infiltration and hydropic degeneration of keratinocytes develop over the first 24 h following exposure, which can progress to separation of the dermis and epidermis with subepidermal bullae formation. The immunologic mechanism of FDE involves activation of CD8+ T cells that release interferon gamma, granzymes, and perforins, leading to recruitment of neutrophils, CD4+ T

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_17

cells, mast cells, and occasionally eosinophils. Diagnosis of FDE is largely clinical and treatment is comprised of discontinuing the offending drug and treating symptoms, such as pruritus and pain. However, if the offending agent is unclear, patch testing or oral re-challenge at sub-therapeutic doses are the preferred diagnostic tests.

Keywords

Toxic epidermal necrolysis (TEN) • Erythema multiforme (EM) • Targetoid lesions • NSAIDs • Tetracylines • Polysensitivity • Pigmentary incontinence • Vacuolar dermatitis • CD8 T-cells • Patch testing

Introduction

The fixed drug eruption was first described in 1894 by Brocq, who noted a patient developing a recurring erythematous plaque in the same location with each exposure to antipyrine. FDE is the second most common cutaneous reaction to oral medications and occurs in both sexes and in all age groups. FDEs account for 14–22 % of cutaneous drug reactions. The reaction is rarely seen with application of topical drugs. NSAIDS, tetracyclines, trimethoprim-sulfamethoxazole, sedatives, and anticonvulsants are the most commonly drugs associated with FDEs, but the list of causative agents is fairly extensive. Some areas of the body are more likely to be involved when exposed to certain drugs than others. For example, naproxen and trimethoprim-sulfamethoxazole are associated with mostly oral mucosal lesions. Unlike morbilliform rashes, vasculitides, and other cutaneous responses to drugs that present with symmetric, generalized lesions, FDE is clinically defined by its unilateral recurrence at the same site with re-exposure to the drug. This is a unique skin response to drug exposure; however, similar clinical presentation with these recurring lesions can occur following exposure to UVA and UVB light and certain foods.

FDEs are categorized based on their clinical appearance and include generalized, linear, bullous, urticarial, pigmenting, non-pigmenting, wandering, eczematous, psoriasiform, erythema dyschromicum perstans–like, vulvitis, and oral versions. Despite their differences in appearance, all types maintain the characteristic of recurring within the same area as the initial eruption. Currently, only patch testing or oral re-challenge to the suspected agents are available to make a definitive diagnosis. Although FDE is mainly a clinical diagnosis, it can often mimic other, more serious conditions, including EM, toxic epidermal necrolysis (TEN), and Stevens Johnson syndrome. When the diagnosis is unclear, a skin biopsy can often distinguish FDEs from other conditions. One exception is the severe generalized variant of FDE, which can appear histologically similar to TEN

Clinical Presentation

Fixed drug eruptions most often present as isolated or small groups of well-demarcated, round to oval dusky red macules and patches that range in size from coin-sized to lesions that cover 1–2 % of body surface area (BSA) (Fig. 17.1). As previously described, they are distinct from other cutaneous drug eruptions because they usually recur in locations that are identical to the previous eruption. Depending on the severity of the reaction, the patches may subsequently evolve into edematous plaques with a darker purple or blue target-like center (Fig. 17.2) that may eventually form a bulla (Fig. 17.3). These lesions can be distinguished from EM lesions clinically because they are usually localized and lack a white, edematous halo that appears between the center and the dark red periphery seen in classic target lesions of EM. FDEs also take a more ovoid shape than the circular papules and plaques of EM.

The first time an individual is exposed to a drug, the FDE may not appear for up to 1 week. With subsequent exposure to the same drug, the patches and plaques can develop as early as 30 min following drug exposure, with most reactions appearing within 8–24 h. Patients do not normally report constitutional symptoms; however, pruritus and pain at the site of the FDE are two commonly reported symptoms that can precede the appearance of the lesions.

FDEs have a predilection for areas with thin skin, such as the lips, genitalia, and perianal regions, although they have also been reported on the trunk, palms, soles, and web spaces of the hands and feet (Figs. 17.4 and 17.5). Mucosal involvement often leads to isolated erosions overlying the erythematous macules and patches. Despite these commonly reported sites of FDEs, lesions can appear on any area of the skin, mucosa, or mucocutaneous junction. Case reports have described a Koebner-like phenomenon in patients with FDEs, with lesions occurring over areas of previous trauma.

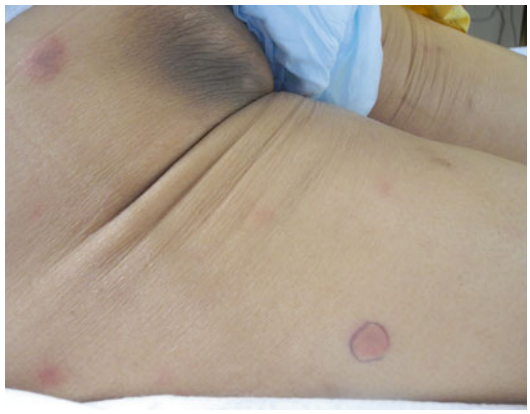


Fig. 17.1 Adult with multiple FDE due to a Cephalosporin

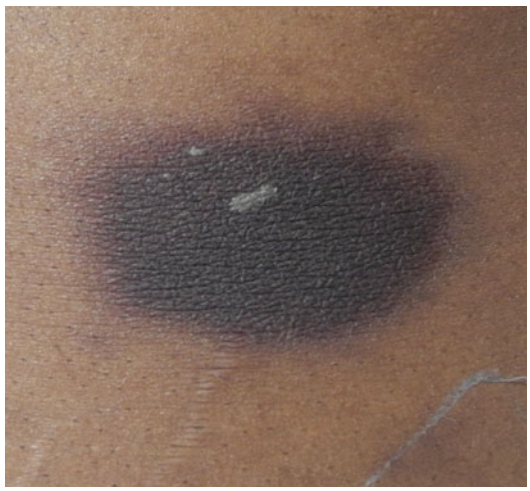


Fig. 17.2 Recurrent localized FDE. Hyperpigmented patch with surrounding violaceous erythema

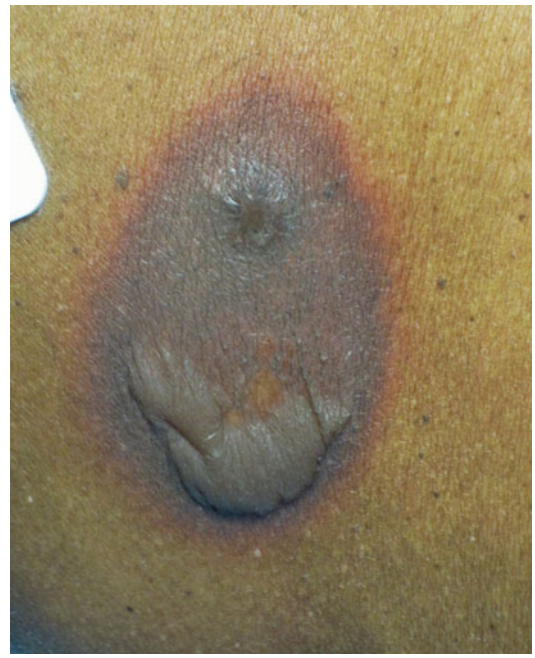
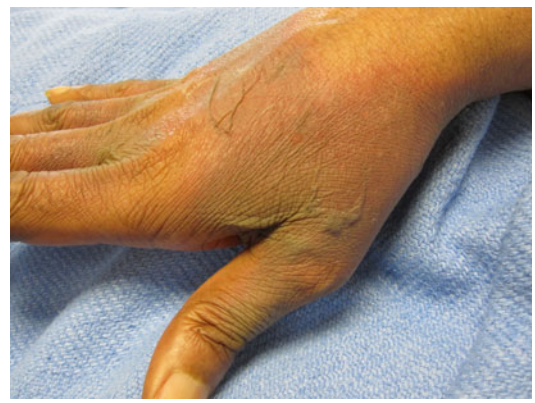
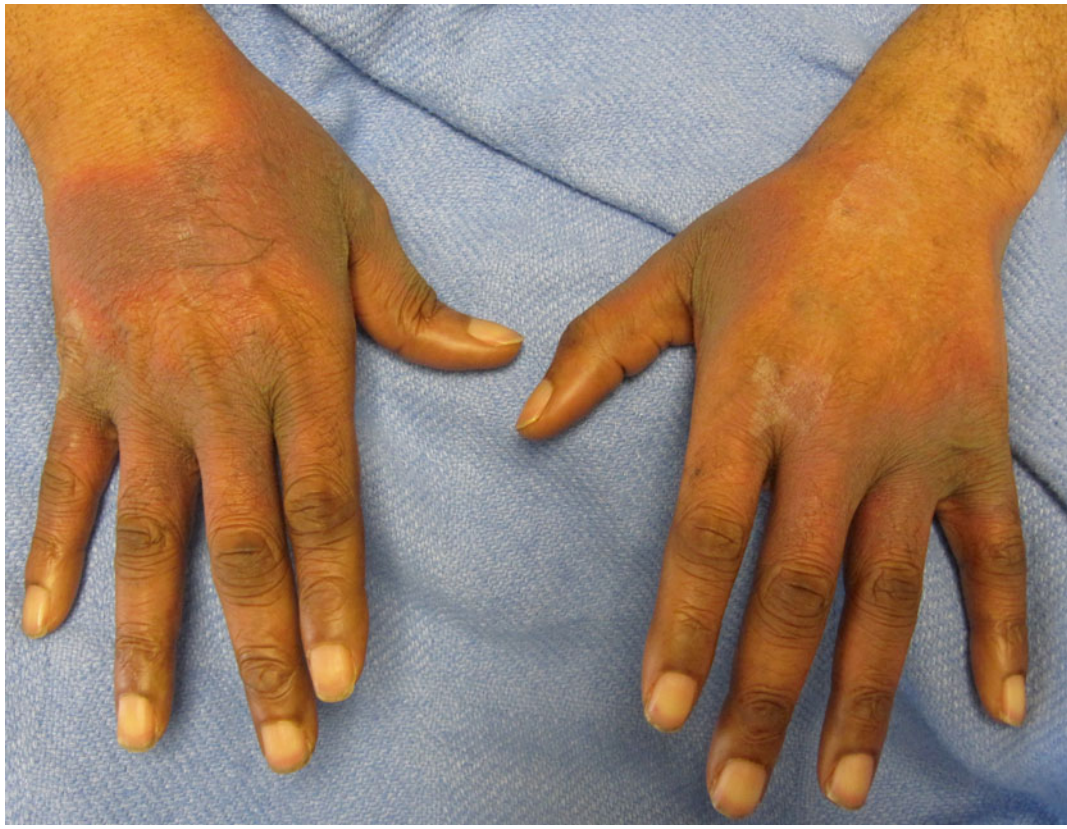


Fig. 17.3 Bulla formation in localized FDE



Figs. 17.4 and 17.5 FDE involving the bilateral hands



Figs. 17.4 and 17.5 (continued)

FDEs occur with equal prevalence among males and females, and cases have been documented in all age groups. In adults, morbilliform rashes make up around 95 % of cutaneous drug reactions, while in children FDEs account for up to 25 % of cutaneous drug reactions. The patient history will normally reveal recent introduction of a new analgesic, antibiotic, sedative, or anticonvulsant. These cases are easier to identify in the hospital setting due to better documentation of the patient's medication regimen. In outpatient clinics, patients may not be seen until the second or third FDE occurrence, especially if the lesion is not symptomatic, which makes identification of the causative drug difficult. With the introduction of new analgesics to the market, there is an increasing report of "polysensitivity." For example, a patient may report their first FDE with one analgesic and subsequently avoid that analgesic. However, upon exposure to a second analgesic, they have an FDE recurrence despite the use of a different medication. The cross-reactivity in this class of drugs has not been fully explored, although it is likely that the medications have similar ingredients to which the patient is sensitive.

Special Variants: Localized FDE (Non-pigmenting)

The non-pigmenting fixed drug eruption (NPFDE) is a variant of FDE that is more common in pediatric patients. NPFDEs evolve over the first 24 h with similar clinical and histological characteristics of FDE. The non-pigmenting term refers to the recovery phase of these lesions. Although NPFDEs will recur at the same site as

the initial presentation like an FDE, the non-pigmenting variety does not leave a well demarcated patch of hyperpigmentation characteristic of classic FDE. The original well-circumscribed patch or plaque slowly fades over 2–3 weeks. Very few cases have been described, and the mechanism by which complete resolution of the lesions between exposures occurs is not well known. In addition, while FDEs are almost always asymmetrical, occurring in an unpredictable pattern on almost any exposed skin or mucosa, NPFDEs have been described as symmetrical, well-demarcated, erythematous patches and plaques.

Fixed drug eruptions in children are not as well described in the literature in comparison to the adult population. It has been suggested that FDEs occur more frequently in the pediatric population and may possibly be one of the most common drug eruptions in children, however, often the lesions go misdiagnosed. Pediatricians commonly encounter urticarial eruptions and morbilliform rashes following ingestion of certain medications, but the well-demarcated lesions in a FDE can be missed if it is attributed to other causes after a single exposure to the offending agent, since recurrence at the same site is the hallmark of FDE. Acetaminophen and sulfonamides are the most cited drugs causing FDE in children, while pseudoephedrine is the most common inciting agent in adults. Unlike adults, tetracycline is not a well-known cause of FDE in children, likely due to the fact that this antibiotic is not regularly administered to children under 8 years of age because of its side effects.

Diagnosis and treatment in children is similar to adults. Patch testing and oral re-challenge can confirm the offending drug, and symptomatic treatment can control pain and itching, but do not expedite the healing process.

Generalized Bullous FDE

In severe generalized bullous FDE (GBFDE), the patches and plaques can cover large surface areas, mimicking toxic epidermal necrolysis and Stevens-Johnson Syndome (TEN/SJS) with development of central flaccid bullae or vesicles within the edematous plaques. GBFDE appears on both the trunk and extremities, and the patches and plaques remain well-demarcated, as in other FDE variants (Fig. 17.6). Like TEN/SJS, GBFDE may present with constitutional symptoms, although not to the same degree as the former. GBFDE is also less likely to involve mucosal surfaces and will usually resolve within 7–14 days once the drug has been discontinued. Nonetheless, the presentation can be quite severe, and a recent review noted that mortality rates may approach that of TEN/SJS.

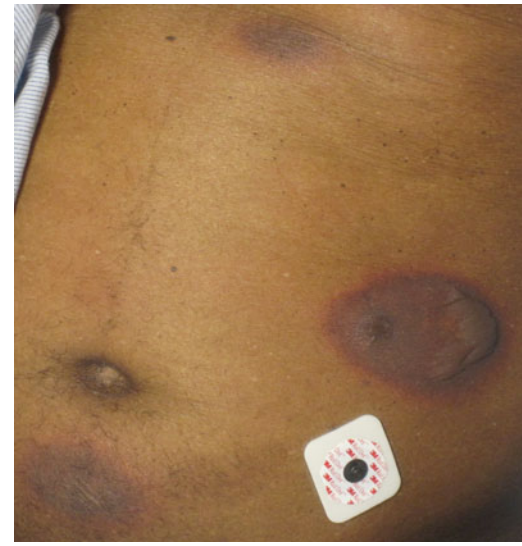
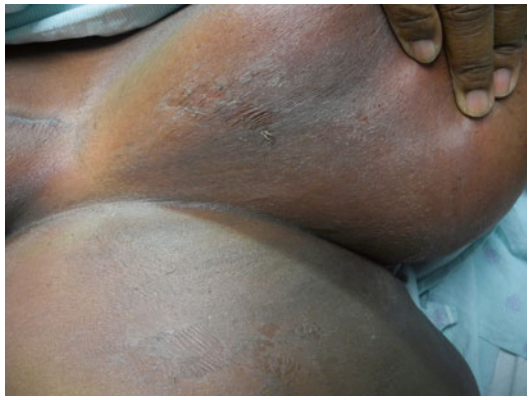
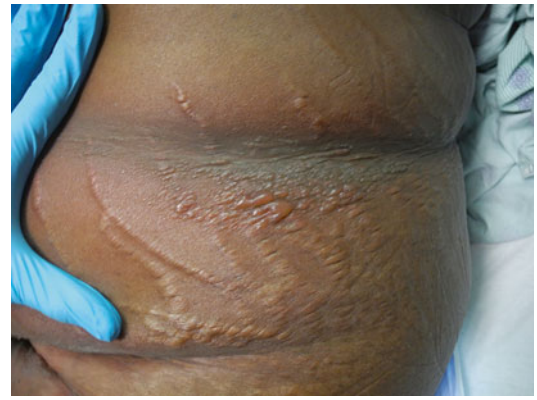


Fig. 17.6 Multiple bullous FDE due to sulfamethoxazole/trimethoprim

Inverse FDE

Fixed drug eruptions with an inverse or flexural distribution have been reported and are thought to be variants of the symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). The literature is limited regarding this presentation, but Ozkaya and Babuna described a case of a 12-year-old boy who presented with an amoxicillin-induced drug eruption who developed large, well-demarcated, erythematous symmetrical plaques in his gluteal cleft and flexor





Figs. 17.7 and 17.8 Involvement of flexural areas and skin folds in an inverse FDE or SDRIFE-FDE overlap

regions. The lesions resolved with FDE-characteristic hyperpigmentation, and the plaques reappeared with oral re-challenge of amoxicillin at a sub-therapeutic dose. The symmetry of his lesions in predominantly flexor areas, as well as the gluteal cleft involvement, was more consistent with SDRIFE; however, the well-demarcated lesions, residual hyperpigmentation, and site-specific recurrence were more consistent with FDE. It is likely that overlap between both eruptions exists, as illustrated in Figs. 17.7 and 17.8.

Oral–Genital Fixed Drug Eruptions

Oral–genital mucosal FDEs can occur as solitary lesions or in addition to lesions affecting other areas of skin. The two main offending agents are naproxen and trimethoprim-sulfamethoxazole. The latter drug has a predilection for lesions on the dorsal surface of the tongue, while the former affects the dorsum of the tongue and the hard palate with equal prevalence (Fig. 17.9). However, lesions have been reported on the mucosal lip, buccal mucosa, and gingiva as well.

FDE involving the genital mucosa is well described, and commonly presents as an itchy or painful erythematous plaque that may become bullous or eroded. The most commonly involved site in male patients is the glans penis; however, the shaft and scrotum may also be affected

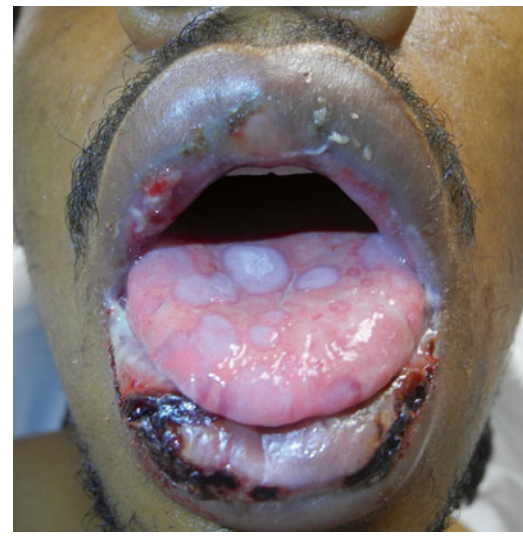


Fig. 17.9 Oral FDE due to Ibuprofen, involving the dorsal tongue

(Fig. 17.10). Previous reviews have suggested that and trimethoprim-sulfamethoxazole and tetracycline are the most common causal agents.

Multiple case series of genital FDE have included only a small number of female patients, suggesting that the entity is likely underreported in women. Female patients with genital FDE are likely to present to their primary care physician or gynecologist and are often diagnosed with another condition. Additionally, several cases of

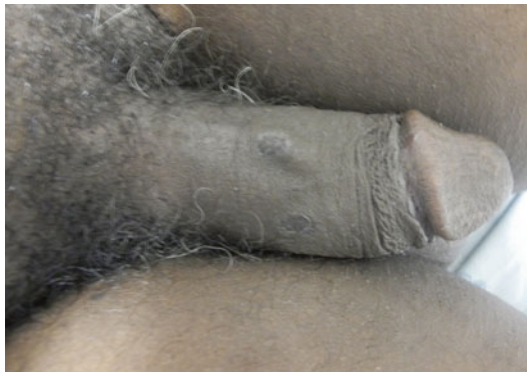


Fig. 17.10 FDE due to sulfamethoxazole/trimethoprim, involving the penile shaft

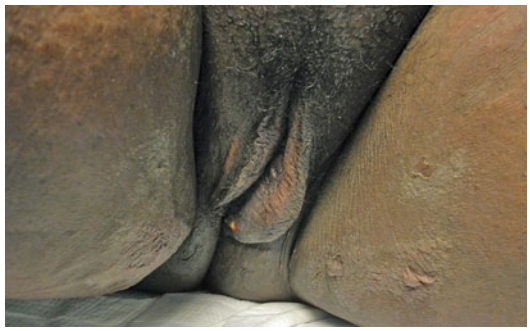


Fig. 17.11 FDE involving the labia majora, extending down the bilateral inner thighs and perineal area

genital FDE have been reported in patients who were not ingesting the drug, but whose sexual partner was taking the offending drug, with the patient being exposed to the drug through sexual contact. In a recent series of patients with vulvar FDE, the most common clinical presentation was bilaterally symmetrical erythematous vulvitis, involving the labia minora and majora and extending to the perineum (Fig. 17.11). Involvement of the inner thighs and perianal area can also occur. Chronic erosive mucositis is another presentation of genital FDE. The most common associated drugs are NSAIDs (ibuprofen, cyclo-oxygenase-2 inhibitors and 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors). Because NSAIDs are one of the most common offenders, female patients may present with a cyclical pattern of oral-mucosal lesions associated with treating dysmenorrhea. The condition is often misdiagnosed as other cyclical diseases, such as herpes simplex virus infection or Behcet's disease.

Diagnosis is difficult when lesions are not associated with classical FDE lesions on the skin because they do not leave the classic residual hyperpigmentation following their resolution. The lesions also vary in appearance, including bullous/erosive and aphthous forms or superficial erosion with an erythematous base. The bullous/erosive pattern is most frequent, especially on the aforementioned preferred mucosal locations. Patients report pain and burning as the main symptoms, which resolve with discontinuation of the offending drug.

Diagnosis

Patients should be questioned regarding all drugs they have ingested, including over-the-counter and prescribed medications. Nutritional supplements, herbal products, and diet aids are possibilities as well. Patients tend to overlook medications that they have been taking sporadically over years. Often asking a patient whether they take any medications for specific conditions or symptoms such as headache, muscle pains, constipation, urinary tract infections, and menstrual cramps may yield a more accurate history. Biopsy can be helpful in atypical cases such as in generalized or bullous FDE, for those with oral or genital involvement, and those in whom the diagnosis is unclear. The presence of systemic symptoms such as fever, arthralgia, or malaise may also be indications for biopsy.

Definitive diagnosis of FDE is obtained through oral re-challenge or patch testing. Patch testing is preferred to oral re-challenge because it avoids systemic exposure to the drug and the risk of more severe or greater number or generalized lesions. Oral re-challenge involves administration of sub-therapeutic doses of the suspected drug until a response is observed. Other obstacles to the oral challenge is the need to follow the patient closely after the drug is administered, and the need for multiple drug challenges if no

response is observed at sub-therapeutic doses. Additionally, only one medication can be tested at a time. Patients who have previously had severe generalized bullous eruptions should not have oral re-challenge testing.

Patch testing is the preferred diagnostic test for FDEs. It is safer than oral re-challenge, and is very effective in identifying NSAIDs as causative agents, as well as patients experiencing polysensitive FDEs. One drawback of patch testing is its lack of utility for FDEs caused by antibiotics. Oral re-challenge is still used to identify these classes of drugs when patch testing is not sufficient.

Treatment

Fixed drug eruptions normally resolve within 2–3 weeks of discontinuation of the offending drug. Patients may seek symptomatic management of accompanying pruritus with antihistamines, although this does not improve the appearance of the lesions. There are no currently effective therapeutic options to cause more rapid resolution of post-inflammatory hyperpigmentation from FDEs, although potent topical steroids may provide symptomatic relief. Resolved lesions often leave an area of post-inflammatory hyperpigmentation that may decrease over time, but often lasts for months. Cutaneous bullous or erosive lesions require proper wound care with nonstick dressings. In cases complicated by infection of open wounds, topical or even systemic antibiotics may be needed. Patients with generalized bullous FDE may require hospitalization and management similar to that of patients with TEN/SJS.

Mild oral involvement may be treated with supportive measures such as compounded solutions containing viscous lidocaine, topical steroids, and calcium carbonate. A petrolatum-based ointment applied every hour may be used for severe lip involvement and to prevent crust from accumulating. If significant hemorrhagic crust is present on the lips, moist compresses can be used to gently debride the affected area. Hospitalization for nutritional support, hydration, and pain control may be needed in severe cases of oral FDE. For erosive genital fixed drug eruptions, a barrier protectant containing zinc oxide paste may reduce irritation from friction due to undergarments and decrease the risk of super-infection.

Clinical Differential Diagnosis

As mentioned before, FDE is a clinical diagnosis. When FDEs were first described in the late nineteenth century, physicians noticed that patients reacting to UVA/UVB light exposure and certain foods had a presentation almost identical to patients with FDE. Biopsy of the lesions showed the same histological changes. The only means of differentiation between these diagnoses is history and re-challenge.

The localized erythematous patches and plaques can be mistaken for many other conditions with a similar appearance, including insect bites, lichen planus, contact dermatitis, cellulitis, and tinea corporis. The target-like appearance of some lesions may be confused with Lyme disease or EM. When vesicles and bullae are involved in cases of severe generalized bullous FDE, the lesions can be mistaken for other bullous drug eruptions such as TEN/SJS. Autoimmune blistering diseases, such as pemphigus vulgaris, bullous pemphigoid, and linear IgA should be considered on the differential diagnosis as well. These can be distinguished from FDE by their characteristic histologic and immunofluorescent findings when biopsied.

The target-like plaque seen in FDE can be differentiated from EM and Lyme disease because it lacks the three rings pathognomonic of target lesions (central dark macule surrounded by a lighter edematous ring with a darker-hued outermost ring) commonly seen in EM and the annular, enlarging plaque of erythema chronicum migrans seen with Lyme disease.

The clinical differential diagnosis for oral–genital mucosal fixed drug eruptions differs depending on the presence of solitary versus multiple FDE lesions. For single lesions, it is important to rule out sexually transmitted diseases, such as herpes simplex virus (HSV) infection,

primary syphilis, lymphogranuloma venereum, and *Haemophilus ducreyi*, all of which are better managed with early diagnosis and treatment. HSV typically involves only keratinized mucosa (especially when recurrent), including the cutaneous lips, gingiva, dorsal tongue, and hard palate. The differential diagnosis also includes recurrent aphthous ulcers, psoriasis, chronic contact dermatitis, lichen sclerosis, neoplasm, and candidiasis. While candidal infections are often found on the buccal mucosa, FDE on the oral mucosa is usually on the dorsum of the tongue and the hard palate. Candidiasis can also produce a white exudate that can be scraped off during physical evaluation. The aphthous ulcers seen in patients with autoimmune disorders, methotrexate ingestion, or those with certain vitamin deficiencies, can be difficult to differentiate from oral FDE lesions, especially when they appear on the lower lip mucosa. The differential diagnosis for multiple lesions includes lichen planus, psoriasis, Fuch's syndrome (chronic mucosal erythema multiforme), as well as pemphigus vulgaris, mucous membrane pemphigoid, and Linear IgA bullous dermatosis. As with FDEs on other skin surfaces, EM major and Stevens-Johnson are histologically similar to oral-mucosal FDEs, although their clinical appearance can be distinguished with a trained clinical eye. While FDEs have a sharply demarcated plaque or erosion with an erythematous base, bullous drug eruptions appear as multiple, smaller papules often coalescing into plaques and bullae with targetoid features. There is also a lack of systemic symptoms in FDEs compared to many other bullous drug eruptions.

Histology and Histological Differential Diagnosis

Histologically, fixed drug eruptions belong to the "interface" reaction pattern group of diseases confined to the epidermis and upper dermis. The predominant histological features include hydropic degeneration of basal keratinocytes and local infiltration of lymphocytes. Degeneration of the basal layer of epidermis begins within the first 8 h after drug exposure. This is followed by migration of CD8+ T lymphocytes and other inflammatory cells over the next 24–48 h. The stratum basale regenerates over the following 2–3 weeks once the drug is discontinued, leaving dermal macrophages filled with melanin in the upper dermis that contribute to post-inflammatory hyperpigmentation.

The infiltration of lymphocytes occurs at the dermo-epidermal junction, followed by migration of polymorphonuclear leukocytes, eosinophils, and mast cells to the area during evolution of the lesion. The degeneration of the basal epidermal layer leads to pigmentary incontinence, the histologic hallmark of FDEs. Pigmentary incontinence is caused by free melanin granules in the upper dermis and melanosomes that have been phagocytosed by dermal macrophages, and is a sign of damage to the stratum basale. Similar damage is observed in lupus erythematosus and lichen planus. The clinical manifestation of pigmentary incontinence is a blue-to-gray appearance of the skin. The non-pigmenting variant of FDE lacks this characteristic feature, and histologically does not show perivascular infiltrates or migration of melanophages into the reticular dermis. These lesions resolve without any evidence of post-inflammatory hyperpigmentation.

The destruction of keratinocytes leads to the formation of Civatte bodies, seen in conditions causing interface dermatitis, such as lichen planus, and discoid lupus erythematous. Civatte bodies are dense, homogenous, rounded eosinophilic bodies seen at the dermo-epidermal junction that consist predominantly of keratin intermediate filaments. Although the exact mechanism of Civatte body formation is still debated, the most favored explanation is that they are composed of debris from degenerated keratinocytes, which are phagocytized by surrounding macrophages. The keratin filaments serve as a framework to attract other inflammatory cells and antibodies.

If the degeneration in lesions of FDE extends to the entire epidermis, the biopsy changes can be mistaken for the trans-epidermal necrosis of TEN. If the FDE progresses to the severe bullous variant, histology usually shows subepidermal

Table 17.1 Clues in the histological differential diagnosis of FDE and other similar diseases

Condition	Histological features
Fixed drug eruption	Inflammation usually obscures the DE junction up to the mid-epidermis and more likely to have neutrophils and eosinophils. Significant pigment incontinence. Papillary dermal fibrosis in recurrent episodes
Erythema multiforme	Occasional spongiosis, edema of papillary dermis, individual necrotic keratinocytes. Primarily lymphoid infiltrate in acute phase. Rarely eosinophils
Toxic epidermal necrolysis/Steven Johnson Syndrome	Basket-weave stratum corneum. Individual necrotic keratinocytes. May progress to confluent epidermal necrosis. Cell death out of proportion to inflammation
Lupus/dermatomyositis	Compact hyperkeratosis. More interface change out of proportion to number of lymphocytes. Basement membrane thickening. Dermal mucin between collagen bundles. Perivascular and periadnexal lymphoid aggregagtes. Occasionally more epidermal atrophy in DM
Acute graft-vs.-host disease	"Satellite-cell necrosis" defined as apoptosis of keratinocytes with infiltrating immune cells in the vicinity of the apoptotic cell
Cutaneous T-cell lymphoma	Epidermotropism of large atypical lymphocytes. Little spongiosis. Papillary dermal fibrosis
PLC/PLEVA	More inflammatory than other vacuolar interface entities. Compact stratum corneum with ulceration or crust. Dyskeratotic keratinocytes. Erythrocyte extravasation. Purely lymphoid infiltrate
Lichen planus	Band-like lichenoid lymphohistiocytic inflammation generally pressing up against the epidermis and obscuring the dermo-epidermal junction. Generally no eosinophils. Hyperkeratosis, no parakeratosis. Wedged-shaped hypergranulosis. Saw-tooth rete ridges

edema with perivascular inflammation and exocytosis of lymphocytes, polymorphonuclear leukocytes (PMNs or neutrophils), histiocytes, mast cells and occasion eosinophils. Lesions may also mimic the Pautrier abscesses characteristic of mycosis fungoides, particularly if the lymphocyte burden at the dermo-epidermal is large. EM and FDE may both show disruption of the interface between the dermis and epidermis histologically. A band-like lymphoctyic infiltration at the dermo-epidermal junction, along with hydropic degeneration of keratinocytes, is a common histologic feature of both. Supepidermal clefting can occur in the bullous form of FDE, much like toxic epidermal necrolysis. All three of these conditions may show necrosis through the entire epidermis on histologic analysis of skin biopsies.

The histological differential diagnosis of the interface reaction pattern includes EM and TEN/SJS as discussed above, but also includes acute graft-versus-host disease (aGVHD), connective tissue disease such as lupus erythematosus and dermatomyositis, cutaneous T-cell lymphoma, and lichen planus. Clues that may be helpful in differentiating these entities are presented in Table 17.1.

Pathophysiology

The primary immunological mechanism responsible for FDE involves CD8+ T lymphocytes that migrate to the intraepidermal spaces. These CD8+ effector T cells release the cytotoxins perforin and granzyme B that initiate apoptosis in the basal keratinocytes. The offending drug is the antigen that serves as the activator of the CD8+ T cells; however, activation of the CD8+ T cells alone does not lead to all the damage observed in mature FDE lesions. Evolution of the lesion subsequently shows recruitment of CD4+ T cells, more CD8+ T cells, and neutrophils by cytokines and cell adhesion molecules that lead to the disruption of the dermo-epidermal junction. Mast

cells are also involved in the expansion of T-cell activation through cell adhesion factors and the release of TNF alpha. Histamine is not a primary inflammatory factor in FDE, but when mast cells are activated, they also contribute to the perivascular edema seen in the upper dermis.

Once the drug is discontinued, the inflammatory cells are no longer activated and they undergo apoptosis and are cleared from the dermo-epidermal junction over 2–3 weeks. However, the regenerating basal keratinocytes secrete IL-15, which allows some effector CD8+ T cells to become memory T cells. These immune cells remain quiescent in the upper dermis, confined to the borders of the now inactive lesion. The CD8+ T cells with memory capabilities become reactivated if the drug, or a drug with cross-reactivity, is reintroduced to the patient's system, leading to the development of another FDE in the same location previously affected.

Conclusions

Fixed drug reactions are characterized by their eruption at a localized site with recurrence after each subsequent exposure to an offending drug. Lesions appear within 8–24 h after exposure. NSAIDS, tetracyclines, trimethoprim-sulfamethoxazole, anticonvulsants, and barbiturates are the most common offenders; however, many other drugs have been reported to cause FDE and as the number of medications increase, this list will continue to expand.

FDEs most often evolve from a small macule of erythema to a dusky red patch or plaque with occasional bullae formation and, rarely, generalized whole-body involvement. History reveals introduction of a new drug, which allows distinction from other conditions with a similar appearance. Histology shows band-like lymphocytic infiltration with Civatte bodies and disruption of the dermo-epidermal junction. CD8+ T cells are the predominant cell type in lesions of FDE.

Diagnosis is usually made through clinical exam, although biopsy and drug re-challenge allow for a more definitive diagnosis. Treatment is symptomatic, and lesions usually resolve within 2–3 weeks of discontinuing the drug, after which a hyperpigmented patch may remain for weeks to months.

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Autoimmune Bullous Diseases and Drugs

18

Margaret A. Stafford, Shivani S. Patel, Lindsay N. Boyers, and Chante Karimkhani

Abstract

Drug-induced bullous disorders encompass a diverse array of clinical presentations determined by the pathology at the dermal/epidermal junction. These include bullous pemphigoid, dermatitis herpetiformis, linear IgA, and pemphigus variants. Fluid-filled blisters encompass all drug-induced bullous disorders after a latency period; however, other clinical features including mucosal involvement can vary.

In linear IgA bullous dermatosis, vancomycin is the most common offending agent. Pemphigus variants, including vulgaris and foliaceus, often present after the use of thiol, phenol, and non-thiol containing drugs. More than 50 different drugs have been associated with the onset of bullous pemphigoid, with thiols being a major group tied to drug-induced bullous pemphigoid. A few cases of drug-induced dermatitis herpetiformis have been reported in the literature. Most of these cases involve hormone-modulating or immunomodulating drugs.

Overall, drug-induced bullous dermatoses respond rapidly to cessation of the offending agent and corticosteroid therapy. It is therefore important to always have clinical suspicion for the drug-induced form of autoimmune bullous dermatoses.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_18

Keywords

Bullous pemphigoid • Dermatitis herpetiformis • Drug eruption • Drug-induced • Linear IgA • Linear IgA bullous dermatosis • Pemphigus • Pemphigus foliaceus • Pemphigus vulgaris

Drug-Induced Bullous Pemphigoid

Bullous pemphigoid is the most common autoimmune blistering disease. The clinical picture is of tense bullae corresponding to subepidermal blisters. Two proteins, BP180 and BP230, are the targets of autoantibodies. These proteins are components of the hemidesmosome and lamina lucida of the basement membrane. The majority of bullous pemphigoid cases arise with no recognizable inducing factor. Most cases of idiopathic bullous pemphigoid occur after age 60, but there have been cases reported in children. Each race and gender seems to be equally impacted.

A recognizable inducing factor is present in less than 15 % of bullous pemphigoid cases. Of this subset, medications are the most commonly identified agent. More than 50 different drugs have been associated with the onset of bullous pemphigoid (see Table 18.1 for a selection of associated drugs). Eruptions may appear up to 3 months after ingestion of the offending medication.

Table 18.1 List of drugs reported to induce bullous pemphigoid

Antibiotics	**Antiarrythmics-antihypertensives**	**Vaccines**
Actinomycin	Ca± channel blockers	Influenza
Amoxicillin	Amlodipine	Swine flu
Ampicillin	Nifedipine	Tetanus toxoid
Cephalexin	ACE inhibitors	HZV
Ciprofloxacin	Captopril	Hexavalent combined vaccines
Chloroquine	Enalapril	
Dactinomycin	Lisinopril	
Levofloxacin	β-blockers	
Penicillin	Nadolol	
Rifampin	Practolol	
	Angiotensin II antagonists	
	Losartan	
NSAID	**Salicylates**	**Other**
Azapropazone	Aspirin	Arsenic
Diclofenac (topical)	Sulphasalazine	Clonidine
Ibuprofen	Salicylazosulfapyridine	Erlotinib
Mefenamic acid		Fluoxetine
Phenacetin		Flupenthixol
Diuretics	**Antidiabetics**	Gabapentin
Furosemide	Sitagliptin	Galantamine hydrobromide
Spironolactone	Tolbutamide	Gold thiosulfate
	Vildagliptin	Interleukin-2
Anti TNF-α	**Antirheumatics**	Levetiracetam
Adalimumab	D-penicillamine	Methyldopa
Efalizumab	Tiobutarit	Terbinafine
Etanercept		Omeprazole
		Psoralens with UVA
		Placental extracts
		Potassium iodide
		Risperidone
		Sulfonamide

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Table 18.2 Suggested differences between drug-induced bullous pemphigoid and classic bullous pemphigoid

	Drug-induced bullous pemphigoid	Classic bullous pemphigoid
History:	Receives multiple therapeutic regimens	May or may not receive multiple therapeutic regimens
	Patient was treated with a new drug recently	Patient did not receive a new drug recently
Clinical picture:	Younger age of onset	Older age of onset
	Possible positive Nikolsky sign	Nikolsky sign is negative
	Appearance of lesions on normally appearing skin	Frequent appearance of lesions on an erythematous and urticarial base
	Mucosal involvement may be present	Mucosal involvement is rare
Histology findings:	Marked eosinophilic infiltrate	Eosinophilic infiltrate present
	Intraepidermal vesicles may be present	Intraepidermal vesicles are not present
	Necrotic keratinocytes may be present	Necrotic keratinocytes are rarely seen
	Thrombus formation may be seen	Thrombus formation is very rarely seen
Laboratory findings:	Marked eosinophilia in serum	Eosinophilia present
Clinical course:	Responds rapidly to treatment with oral corticosteroids	May exhibit prolonged course despite oral corticosteroid treatment
	Improves after discontinuation of inciting drug	No inciting drug is identified
–	Rarely relapses	Relapses often

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In cases of drug-induced bullous pemphigoid (DIBP), cessation of the offending agent commonly results in prompt resolution of the disease. Suspicion for an underlying drug causing the disease should therefore always be present, as treatment may be much less aggressive in drug-induced bullous pemphigoid compared to classic bullous pemphigoid.

Clinical Presentation

Like idiopathic bullous pemphigoid, the clinical picture of DIBP is heterogeneous. The varying presentations can make diagnosis difficult. Morphology ranges from classic tense bullae arising from erythematous urticarial basis that inconsistently involves the oral mucosa, to few bullous lesions with no erythematous bases, to target lesions, to scarring plaques and nodules with bullae or excoriations (papular or nodular pemphigoid). It can even mimic other diseases such as bullous erythema multiforme and pemphigus. DIBP is typically present in a younger population than idiopathic bullous pemphigoid. Other common clinical features of DIBP include positive Nikolsky sign, appearance of lesions on normal-appearing skin, target lesions on the palms and soles, involvement of the lower legs, and mucosal involvement. Nikolsky's sign involves the application of pressure to a blister, resulting in exfoliation of the superficial layers of the skin. Table 18.2 presents a summary of suggested differences between DIBP and classic bullous pemphigoid.

Offending Drugs

Because many associated drugs are commonly prescribed yet only a few patients develop DIBP, drugs likely act as triggers in patients with underlying genetic susceptibility. A number of mechanisms have been proposed regarding the pathogenesis of DIBP. These include:

1. Drugs may act as haptens, binding to proteins in the lamina lucida and changing their antigenic properties, resulting in anti-BMZ antibody production. This theory may explain the association of thiols with DIBP. This class of drugs is the most commonly associated with

DIBP. Thiols contain or release sulfhydryl groups either in their initial form or as a metabolite. The thiol group may allow the molecule to combine with proteins in the lamina lucida and act as a hapten. Thiols associated with DIBP include penicillamine, captopril, penicillin and penicillin derivatives, furosemide, and some cephalosporins.

2. Drugs may stimulate an autoimmune response by causing structural modifications in molecules that result in exposure of otherwise hidden epitopes, which are the part of an antigen molecule to which an antibody attaches itself. The immune system subsequently recognizes and targets these epitopes resulting in disease.
3. Sulfur-containing drugs may cause a biochemical, dermo-epidermal split with no immune mediation.
4. T-regulatory cells may be modulated such that they have decreased suppressor activity, resulting in increased production of autoantibodies against bullous pemphigoid antigens. Penicillamine may contribute to DIBP by this mechanism.

Vaccinations have rarely been reported to trigger bullous pemphigoid. In less than 20 cases in recent years, anti-influenza vaccine, tetanus toxoid booster, and tetracoq vaccine have been associated with the onset of bullous pemphigoid. It has been postulated that the underlying mechanism is due to inflammation in the skin at the vaccination site with disruption of the basement membrane architecture and subsequent generation of anti-basement membrane-specific antibodies. Alternatively, vaccinations may trigger an enhanced autoimmune response in patients with a predisposition to or subclinical bullous pemphigoid. In addition, cases of DIBP have also been linked to topical treatments, radiation therapy, and UV therapy.

Diagnosis

Diagnosis is confirmed by histopathological staining and immunofluorescence studies. Typical histopathological findings in DIBP include perivascular infiltrate of lymphocytes with eosinophils and neutrophils, subepidermal blisters, intraepidermal vesicles, foci of necrotic keratinocytes, and thrombi in dermal vessels. Blister cavities may contain numerous eosinophils, neutrophils, and fibrin. Of these histologic features, necrotic keratinocytes, intraepidermal vesicles, and thrombi are commonly seen in DIBP but are not associated with classic bullous pemphigoid. Notably, samples taken from normal skin do not show diagnostic findings.

Direct immunofluorescence and indirect immunofluorescence are consistent with idiopathic bullous pemphigoid. Direct immunofluorescence in bullous pemphigoid demonstrates IgG antibodies and C3 linear along the basement membrane zone in 90 % of cases. Circulating IgG antibodies are detected in 75 % of cases with indirect immunofluorescence.

Labs may show marked eosinophilia in serum and increased soluble IL-2 receptor. Other immunological markers such as macrophage migration inhibitory factor may be present. Mast cell degranulation toward the offending drug may also be present.

Treatment and Course

The course of the disease varies based on the type of DIBP. Two main types have been defined, with the most common being the pure drug eruption form of bullous pemphigoid. In this case, the disease is acute and self-limited; relapses are uncommon. It resolves with cessation of the culprit drug with or without steroid therapy (Figs. 18.1 and 18.2).

The second type is better described as drug-triggered bullous pemphigoid. Drug administration seems to precipitate the onset of a chronic form of bullous pemphigoid that evolves to have all features of the classic form of the disease. Additional therapy aside from drug withdrawal is often necessary in these cases, which can be managed similarly to idiopathic bullous pemphigoid.

Drug-Induced Pemphigus

Pemphigus is a group of intraepidermal blistering disorders caused by a disruption of desmosomes leading to acantholysis, or a loss of keratinocyte adhesion. There are five main variants of

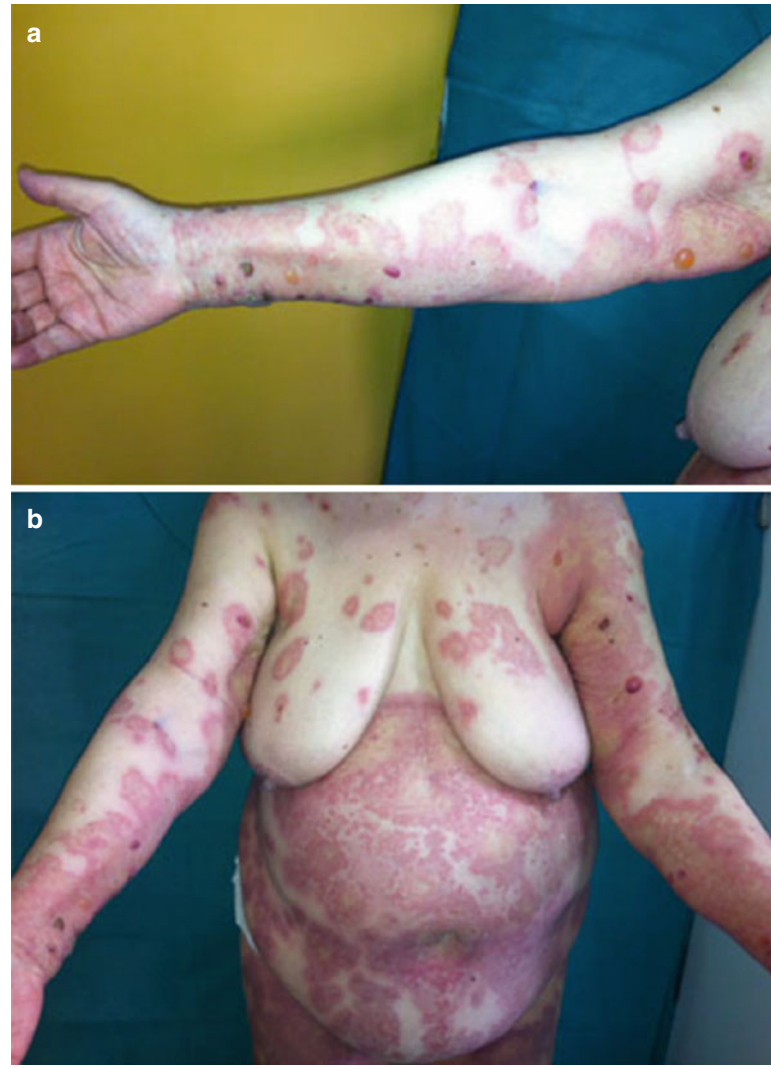

Fig. 18.1 (**a**) Tense bullae appearing on an erythematous base. The patient reported receiving antibiotic treatment (quinolone) 2 weeks prior to the appearance of the eruption. (**b**) Tense bullae on an erythematous base, accompanied by an erythema multiforme type eruption (Reproduced with permission from John Wiley and Sons, from Stavropoulos et al. (2014). Copyright © 2014)

pemphigus classified by the level of intraepidermal acantholysis: pemphigus vulgaris (PV), pemphigus foliaceus (PF), pemphigus erythematosus, drug-induced pemphigus, and paraneoplastic pemphigus. Drug-induced pemphigus is an increasingly common variant of pemphigus, accounting for approximately 10 % of all reported cases. In drug-induced pemphigus, PF is most often reported; however, PV can be seen as well. Most cases have been described in patients ranging from 30 to 90 years of age.

Desmosome disruption is attributed to various autoantibody-antigen complexes on the cell surface. In PV, the most common antigen inducing disease is desmoglein 3 (Dsg-3), which is often located deep within the mucosal layers. Desmoglein 1 (Dsg-1) is the main adhesion protein in PF that is primarily located in the upper layers of the epidermis.

Drug-induced pemphigus can be evoked via immune or biochemical mediated pathways, depending on the offending drug class. Biochemical acantholysis does not require antibody formation and usually occurs via direct drug-mediated enzyme inhibition. This process is associated with thiol-containing drug-induced pemphigus. These drugs potentially inhibit enzymes, such as keratinocyte transglutaminase, that normally cause keratinocyte adhesion. Another proposed mechanism involves the disruption of cell aggregation by

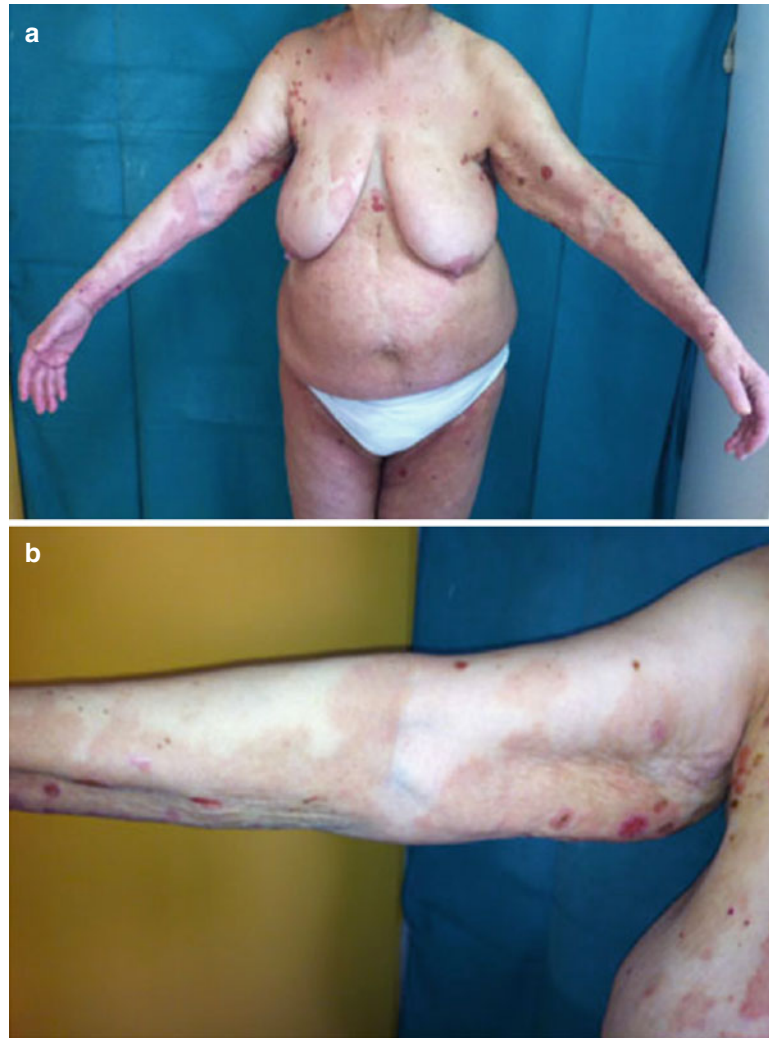

Fig. 18.2 (**a**) Marked improvement of bullous pemphigoid lesions after discontinuation of the possible inciting drug and 3 weeks of treatment with oral prednisolone. (**b**) Cessation of the appearance of new lesions and marked improvement of inflammation was observed within 3 weeks from initiation of oral corticosteroid treatment and after discontinuation of the inciting drug. Two years later the patient is still in remission and is not receiving any treatment (Reproduced with permission from John Wiley and Sons, from Stavropoulos et al. (2014). Copyright © 2014)

formation of thiol-cysteine bonds instead of cysteine-cysteine bonds. In both processes, thiol-containing drugs induce acantholysis directly without the formation of autoantibodies. The biochemical pathway can help explain why circulating autoantibodies are only present in 70 % of patients with drug-induced pemphigus.

Phenol-containing drugs can also induce pemphigus through the biochemical pathway via release of cytokines, such as TNF alpha and interleukin-1, from keratinocytes resulting in acantholysis. A third class of offending agents includes non-thiol containing drugs. These drugs induce acantholysis by evoking the immune pathway via formation of pathogenic IgG autoantibodies against Dsg-3. By attacking the mucosal antigen Dsg-3, non-thiol inducing pemphigus usually present as the vulgaris variant.

Clinical Presentation

PV and PF have differing presentations that assist in distinguishing between the two drug-inducing forms. In PV, oral erosions usually precede the development of cutaneous lesions, which can lead to a misdiagnosis of aphthous ulcers. Various mucosal sites can be involved, including but not limited to the oropharynx, esophagus, vulva, cervix, and the conjunctiva. The mucosal lesions are ill-defined, irregularly shaped erosions that are often uncomfortable, causing difficulty eating and drinking.

In PV, skin lesions tend to favor the trunk, groin, scalp, and face. Non-scarring, flaccid blisters develop at these sites, coalesce, and subsequently rupture, leaving behind painful erosions. Nikolsky's sign, if present, is frequently suggestive of vulgaris-type lesions.

In PF, small, fluid-filled blisters usually begin on the trunk. Due to fragility, the blisters rupture easily, leaving behind scaly, crusted erosions, often on an erythematous base. Contrary to the vulgaris variant, there is little to no mucosal involvement in PF. Due to the common presence of both mucosal and cutaneous involvement, PV carries a less favorable prognosis.

Drug-induced pemphigus is virtually indistinguishable from its idiopathic counterpart. However, studies have reported superficial blistering and pruritus as more common with drug-induced pemphigus.

Offending Drugs

Offending agents can be categorized into one of three groups: thiol-containing drugs, non-thiol drugs, and phenol drugs (Table 18.3). Thiol drugs contain a sulfhydryl (-SH) group. They are the most frequent culprits reported in drug-induced pemphigus, provoking the foliaceus variant most often. Thiol-containing drugs reported to cause pemphigus include d-penicillamine, lisinopril, and captopril. Of all cases in the literature, d-penicillamine is the most common culprit.

Non-thiol drugs are most likely to induce the vulgaris response by disruption of the mucosal Dsg-3 antigen. The most frequent drugs reported include cephalosporins, penicillin, and enalapril. Rifampin, aspirin, and levodopa are phenol-containing drugs linked to pemphigus.

Topical ophthalmic drops, topical imiquimod, and cutaneous ointments have also been causatively linked to pemphigus, described as "contact pemphigus" in the literature. These topical medications are absorbed through the skin and reportedly cause a neoantigen response at the site of application.

Table 18.3 Drugs reported to induce pemphigus

Drug class	Medication
Thiol drugs	D-penicillamine
	Lisinopril
	Captopril
Non-thiol drugs	Cephalosporin
	Penicillin
	Enalapril
Phenol drugs	Rifampin
	Aspirin
	Levodopa

Diagnosis

Diagnosis requires a high clinical suspicion, since a diverse array of entities are known to cause pemphigus including cancer, pesticides, stress, and hormones. When there is a high index of suspicion, a thorough history is essential and should include any over-the-counter medications. Diagnostic challenges are also present secondary to the prolonged latency period of some offending agents and potential multiple drug interactions.

When pemphigus is suspected, a perilesional biopsy should be taken within two centimeters of active blistering. Cautious technique should be maintained throughout the procedure due to fragility of the vesicles. Biopsy specimens should undergo direct immunofluorescence analysis and hematoxylin and eosin (H & E) staining to ascertain acantholysis.

Under H & E staining, acantholysis is the main histological feature present. With direct immunofluorescence, the demonstration of anti-desmoglein autoantibodies is virtually diagnostic of pemphigus. The deposition of IgG along the desmosomes resembles a "net-like" or "chicken-wire" appearance. Lesions of PF demonstrate superficial deposition, related to Dsg-1, while acantholysis of PV is detected in the suprabasal layer against Dsg-3. Overall, direct immunofluorescence has a higher sensitivity and specificity in making the diagnosis of pemphigus compared to H & E staining.

To differentiate between drug-induced and idiopathic pemphigus, novel immunostaining techniques are being studied. In normal human skin, a net-like deposition of a monoclonal

antibody, 32-2B, can be seen with immuno-labeling around the cell cytoplasm. The normal pattern can also be detected in most cases of drug-induced variants of pemphigus. Studies have demonstrated abnormal 32-2B staining with idiopathic pemphigus consisting of a "patchy pattern" of coarse deposits. However, a minority of drug-induced pemphigus cases involve an abnormal staining pattern. In these cases, mean recovery time and prognosis were worse. Therefore, normal 32-2B staining may help to differentiate between the two causes, and may also serve as a potential indicator of better prognosis within the drug-induced form.

Treatment and Course

Overall, first-line treatment involves removal of the causative agent. However, withdrawal of the drug is not 100 % effective, as more than 50 % of patients with drug-induced pemphigus continue to have symptoms despite discontinuation of the drug. Mean recovery time is approximately 3 months. Thiol-induced PF is associated with a faster recovery time after withdrawal of the offending agent, partly due to lack of mucosal involvement.

After a case of drug-induced pemphigus occurs, patients may have an increased predisposition to recurrent episodes with similar drugs. Therefore, thiol or phenol containing drugs should be avoided as much as possible to prevent subsequent occurrences.

Drug-Induced Linear IGA Bullous Dermatosis

Linear IgA Bullous Dermatosis (LABD) is a rare autoimmune blistering disease characterized by continuous linear IgA deposition along the basement membrane zone, revealed by direct immunofluorescence assay. Subsequent complement activation and neutrophil recruitment results in loss of adhesions at the dermal-epidermal junction and eventual blister formation. The majority of cases are idiopathic. However, drug-induced linear IgA has been described in over 100 case reports, with the first reported case in 1981.

The etiology of drug-induced LABD remains unclear, but it is speculated to be caused by an immune response to a drug-derived hapten-protein complex. Two protein antigens located in the lamina lucida and sublamina densa (97-kD protein and 285-kD protein) have been identified as potential targets. Some research suggests the 97-kD protein located in the lamina lucida may represent a portion of the 180-kD bullous pemphigoid antigen (BPAg2). However, other studies suggest the epitope may be uniquely distinct from BPAg2. In other cases, the antibody response has been directed toward several other antigens, including Type VII collagen. Despite variable antigenicity, these heterogeneous patients retain IgA deposition along the basement membrane, and therefore, remain under the umbrella of the same diagnosis.

Although there is no definitive inciting factor, some authors postulate infection as a cofactor in the pathogenesis of drug-induced LABD. The immunological response may be triggered by the interaction of an infection, such as an upper respiratory tract infection, with the appropriate treatment. Primary exposure to a drug usually results in an asymptomatic response. Subsequent exposure is usually necessary for a heightened autoimmune response. In patients with drug-induced LABD after primary contact, infection may increase sensitivity to the drug, causing a delayed skin reaction.

Clinical Presentation

Cutaneous findings in drug-induced LABD often mimic other bullous diseases. The most characteristic feature is tense bullous lesions organized in a "string of pearls" or "cluster of jewels" pattern. The clear bullous lesions are centered upon on a normal, erythematous, or urticarial base. However, the clinical appearance can be heterogeneous, often resembling the papulovesicular lesions in dermatitis herpetiformis. Other reported cases have demonstrated features of toxic epidermal necrolysis. Targetoid lesions, urticaria, and erythematous plaques can also represent clinical manifestations of the disease.

Mucocutaneous manifestations are found in up to one-third of drug-induced LABD cases, often

preceding the skin lesions. Oropharyngeal involvement is the most common, including vesicles, ulcerations, cheilosis, and palatine erosions. Genital and laryngeal lesions have also been documented in several cases. Ocular discharge, burning, and grittiness are frequent complaints. The most common sites of cutaneous involvement in adults include the upper and lower limbs, trunk, and face. This distribution can also make it challenging to distinguish from dermatitis herpetiformis, which affects the same sites. In children, however, there is a stronger predilection for the thighs and groin.

The presentation of drug-induced LABD shares many similarities with idiopathic LABD clinically, and its features are indistinguishable immunohistopathologically. However, large erosions and Nikolsky sign are found more frequently in patients with drug-induced LABD. The median healing time also differs between the two groups, requiring on average an extra week for the idiopathic form.

Offending Drugs

A wide range of drugs have been implicated in the development of drug-induced LABD (a partial list is below), although half of the reported cases have been associated with vancomycin. Cases of vancomycin-induced LABD demonstrated a shorter latency period of 2–21 days compared to a mean of 64 days with other drugs. The reason for shorter latency period remains unknown, but may be related to a more sensitive antigenic response.

Drugs Reported to Induce Linear IgA Bullous Dermatosis (LABD)

- Vancomycin
- Captopril
- Trimethoprim-Sulfamethoxazole
- Amiodarone
- Piroxicam
- Ceftriaxone
- Furosemide

The second and third most commonly involved drugs included captopril and trimethoprim-sulfamethoxazole, respectively. Other medications, including amiodarone, piroxicam, ceftriaxone, penicillin, cefuroxime, furosemide, and naproxen, have also been reported as causative agents of drug-induced LABD.

Diagnosis

The acute onset of widespread bullous lesions suggests the possibility of drug-induced LABD. Since the presentation of drug-induced LABD may resemble other bullous diseases, the demonstration of a linear band of IgA deposited along the basement membrane via direct immunofluorescence remains the gold standard for diagnosis. When drug-induced LABD is suspected, a punch biopsy of perilesional skin should be performed in the clinic and sent to a laboratory for testing. A thorough medication history should also be conducted to assess for potential contributors.

Conditions included in the differential diagnosis for LABD include dermatitis herpetiformis, bullous impetigo, bullous pemphigoid, and pemphigoid gestationis. Direct immunofluorescence enables these disorders to be distinguished because deposition of various antibodies and complements usually differ.

Treatment and Course

Treatment involves withdrawal of the offending agent. Resolution is variable, ranging from 1 to 5 weeks in the current literature. In approximately half of cases, additional systemic treatment is warranted. In contrast to idiopathic LABD, long-term therapy is not necessary. Dapsone alone or in combination with corticosteroids is first line treatment for severe or persistent drug-induced LABD unresponsive to medication withdrawal. Systemic therapy is required until lesions resolve and clinical remission is achieved.

Dermatitis Herpetiformis

Dermatitits herpetiformis (DH) is a chronic, pruritic, papulovesicular dermatosis that takes an annular or herpetic distribution on extensor surfaces. It is characterized by a neutrophilic

infiltrate via light microscopy and granular IgA deposition at the dermal papillae via immunofluorescence. DH is closely linked to gluten sensitivity. Interestingly, most patients with DH do not exhibit gastrointestinal symptoms, yet frequently have histological changes corresponding to celiac disease. Both DH and celiac disease respond to a gluten-free diet. DH is also associated with other autoimmune diseases, pernicious anemia, thyroid disease, and cancer. Lymphomas are the most common cancer in patients with DH. In addition to gluten, certain drugs have been implicated in exacerbating existing DH, including thyroid hormone replacement, contraceptive hormones, and chemotherapeutic drugs. Indomethacin and both topical and oral iodide have been linked to exacerbating DH.

A few cases of drug-induced DH have been reported in the literature. Most of these cases involve hormone-modulating or immunomodulatory drugs. Leuprolide acetate, a gonadotropin releasing hormone (GnRH) analog has been implicated in at least two cases of DH. In each case, re-administration of the drug or a similar drug resulted in re-emergence of skin lesions. Other drugs that have been associated with DH include the TNF-alpha monoclonal antibody infliximab and progesterone contraceptives.

Clinical Presentation

One case reported the depot form of leuprolide acetate causing recurrent flares of DH with each 3-month injection in a 68-year-old male being treated for adenocarcinoma of the prostate. The patient first developed intensely pruritic and erythematous papules and tense vesicles on his knees, elbows, and left thumb 2–3 weeks after initiation of leuprolide. These lesions decreased in intensity toward the end of the 3-month therapeutic cycle and flared within 1–3 days of the subsequent injection. The diagnosis of DH was confirmed via tissue diagnosis. The patient declined systemic therapy, choosing only topical emollients for treatment. The lesions steadily improved over the 9 months following his last leuprolide depot injection. The extended time course of symptoms was attributed to the depot nature of the leuprolide, resulting in a longer time course of effect.

Another case described a 75-year-old man who developed DH 1 month after initiating 1 mg, daily subcutaneous injections of leuprolide for prostate cancer. His past medical history included atrial fibrillation and gastrointestinal symptoms of flatulence and dumping syndrome that had been attributed to an esophagectomy and partial gastrectomy for esophageal adenocarcinoma. He had a sister with gluten-sensitive enteropathy. Clinical presentation and histopathologic features were consistent with DH. Serum gliadin IgA and IgG were elevated. His lesions cleared 3 days after discontinuation of leuprolide and treatment with dapsone 50 mg/day and initiation a gluten-free diet. Eight months later, a second GnRH analog, bicalutamide, was initiated. The patient's lesions recurred within a week.

Offending Drugs

These cases support the role of hormonal factors in DH. The emergence after administration of GnRH analog supports a role of the hypothalamic pituitary-gonadal pathway. There is evidence suggesting that this pathway plays a role in modulating immune function and that ties sex hormones to the progression and severity of autoimmune diseases. GnRH and GnRH receptors are expressed in the thymus, spleen, and peripheral immune cells. Many autoimmune diseases are less prevalent in males, and androgens have been shown to have a suppressive effect on immune activity, including decreased autoimmunity. Thus, it is plausible that the primary pathogenesis of leuprolide-induced DH is linked to the androgen-deficient state induced by this drug resulting in enhanced autoimmunity. Other implicated drugs tend to involve hormonal or inflammatory pathways, and likely also contribute to DH emergence by enhancing autoimmune reactivity.

Conclusions

Bullous diseases can be caused by a drug as part of drug allergy. The subgroup of autoimmune bullous eruptions can be mimicked by

drug reactions, and subtle differences including immunoflourescent studies, may be needed to tell an idiopathic reaction from one caused by a medication. Overall, drug-induced bullous dermatoses respond rapidly to cessation of the offending agent and corticosteroid therapy. It is therefore important to always have clinical suspicion for the drug-induced form.

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Lymphoma and Pseudolymphoma and Drug Reactions

19

Matthew Hoffmann

Abstract

Pseudolymphoma is a well-documented benign reaction to a foreign stimulus, including many systemic medications. Pseudolymphomas typically present in one of two patterns, B-cell lymphoma-like or T-cell lymphoma-like. It can be clinically indistinguishable from the malignant counterpart and therefore requires meticulous histopathologic evaluation to differentiate. Treatment is conservative, with removal of the causative medication usually leading to resolution of the lesions. Rarely, pseudolymphoma can progress to overt lymphoma, which should be treated in accordance with standards of care for the particular malignancy.

Drug-induced lymphomas arise either as progressions from pseudolymphoma or as complications related to iatrogenic immune suppression, and should be treated in accordance with standards of care for each malignancy.

Keywords

Pseudolymphoma • B-cell lymphoma • Cutaneous T-cell lymphoma • Lymphocytoma • DRESS

Introduction

Pseudolymphoma is a well-documented benign reaction to a foreign stimulus, including many systemic medications. Pseudolymphomas typically present in one of two patterns, B-cell lymphoma-like or T-cell lymphoma-like. It can be clinically indistinguishable from the malignant counterpart and therefore requires meticulous

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_19

histopathologic evaluation to differentiate. Treatment is conservative, with removal of the causative medication usually leading to resolution of the lesions. Rarely, pseudolymphoma can progress to overt lymphoma, which should be treated in accordance with standards of care for the particular malignancy.

Drug-induced lymphomas arise either as progressions from pseudolymphoma or as complications related to iatrogenic immune suppression, and should be treated in accordance with standards of care for each malignancy.

Drug-Induced Pseudolymphoma

Pseudolymphoma is a nonspecific term characterizing a collection of benign disorders incited by one of many possible stimuli, drugs being a well-documented example of one such of these stimuli. First described in the late nineteenth century, this disease appears clinically and/or histologically similar to cutaneous lymphoid malignancies including B- and T-cell lymphomas, but tends to have a benign course and portend a very good prognosis once the inciting factor is removed. However, as with many dermatologic diseases, pseudolymphoma falls within a spectrum that can range from benign to rarely eventuating into an overt B- or T-cell lymphoma. Most often witnessed in adults and with a female predilection, pseudolymphoma presents as either B-cell lymphoma-like nodules or cutaneous T-cell lymphoma-like patches, plaques, or tumors after days to many years of use of the inciting medication. It is often clinically indistinguishable from cutaneous lymphoma. Though often solitary, these lesions may range from localized to widespread, even presenting as generalized erythroderma simulating Sezary syndrome. The diagnosis of pseudolymphoma relies on histopathologic discernment from its malignant counterpart. Herein we will discuss the most common clinical presentations and accompanying histopathology, as well as potential distracters to consider in your differential, and options regarding treatment.

B-Cell Lymphoma-Like Pseudolymphoma (BPL)

Traditional description of pseudolymphoma is divided based on clinical and histologic patterns, either as B-cell lymphoma-like (BPL) or cutaneous T-cell lymphoma-like (TPL). BPL typically presents as a solitary nodule that favors the face and trunk, typically without overlying epidermal change. Systemic symptoms are not expected, with the noted exception of occasional regional lymphadenopathy. The histologic pattern of BPL tends to be dense nodular or diffuse lymphocytic infiltrate, often described as "top-heavy" with overlying Grenz zone, although this is not specific. T-lymphocytes, histiocytes, dendritic cells, plasma cells, and eosinophils may also be present. Nodal architecture may be observed with a germinal center and occasionally mantle zone formation. Numerous tingible-body macrophages are observed in the germinal centers.

While differentiating from overt B-cell lymphoma may present a diagnostic quandary, subtle distinctions can be noted to separate each entity. Features such as admixed T- and B-lymphocytes, other inflammatory cells including eosinophils and plasma cells, tingible-body macrophages, polyclonal IgH heavy chain gene rearrangement, and lack of kappa or lambda light chain restriction all suggest pseudolymphoma. Other immunohistochemical markers including BCL-6, CD10, and proliferative marker Ki-67, are often positive but limited just to germinal centers, with p53 negativity. These markers are variable in overt B-cell lymphoma depending upon the specific neoplastic cell population. In contrast to BPL, a predominantly lymphocytic infiltrate, loss of normal nodal architecture, and monoclonal heavy chain gene rearrangment or light chain restriction all favor overt B-cell lymphoma.

Differential

While BPL obviously must be differentiated from its cutaneous lymphoma counterpart, other cutaneous lymphoid infiltrates must also be clinically considered. Among these are leukemia cutis, cutaneous Hodgkin disease, non-lymphoid metastasis, lupus erythematosus tumidus, and

lymphocytic infiltrate of Jessner. It also is important to note that although we have focused on drug-induced BPL in this chapter, pseudolymphoma or, more broadly, cutaneous lymphoid hyperplasia, can arise from a number of etiologies including infection, arthropod bite, implanted foreign bodies (such as metal implants or tattoos), and vaccinations, among others. When presented with a patient with the above findings it is important to attempt to discern the etiology of the individual's lymphoid response, although this is not always possible.

T-Cell Lymphoma-Like Pseudolymphoma (TPL)

The definition of TPL has evolved along with advances in knowledge and technology in modern medicine. This evolution has led to the development of two separate considerations of the meaning of TPL. The first is of historical significance, describing TPL as a clinical diagnosis, whereas the second is by modern understanding based on both clinical and histopathological information. The historic definition based on clinical description is a systemic reaction to a medication, with signs and symptoms including fever, chills, lymphadenopathy, hepatosplenomegaly, and blood dyscrasias including eosinophilia, now considered drug reaction with eosinophilia and systemic symptoms (DRESS). Previously known as phenytoin hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome, anticonvulsant pseudolymphoma syndrome, and drug hypersensitivity syndrome among other iterations, these clinically based monikers tended to reflect a more acute disease presentation with significant and potentially acutely life-threatening systemic symptoms. This diagnosis was called pseudolymphoma in the regard that it clinically had signs and symptoms reflective of lymphoma, but tended to improve with removal of the causative medication. As implied by name, this syndrome was commonly described with use of various anticonvulsants, but scores of medications have been implicated in this syndrome. Additional information can be found within the chapter covering DRESS.

As knowledge and technology have improved, the diagnosis of TPL has shifted to a histopathologic basis. TPL by modern description often presents with a non-descript clinical appearance, but can range from a papular eruption to mycosis fungoides (MF)-like patches and plaques. Even Sezary syndrome-like erythroderma has been described. The diagnosis is based upon demonstrating an atypical T-lymphocytic infiltrate, often with a band-like dermal pattern and cerebriform nuclei, epidermotropism, and vacuolar interface change. Occasionally T-cell monoclonality is found, although a polyclonal infiltrate is the general rule. T-cell gene rearrangement by polymerase chain reaction is often relied upon to assist with identifying pseudolymphoma versus overt lymphoma. While a powerful tool, it should be used as a component of the diagnostic evaluation and not as the sole determination. It has been well documented that many benign reactive processes demonstrate monoclonality and some lymphoid malignancies, particularly early neoplasms, can also demonstrate polyclonality.

Differentiation from overt cutaneous T-cell lymphoma (CTCL) is of utmost importance and requires consideration of the patient as a whole. Simple consideration of onset and duration of lesions often can provide clues toward the correct diagnosis. MF often has a smoldering history of multiple sun-protected lesions requiring multiple biopsies to obtain a diagnosis, while relative acute, solitary, atypically located lesions, particularly within the context of use of a known inciting medication, are much more likely to represent pseudolymphoma (Figs. 19.1, 19.2 and 19.3). Although many of the histologic features of TPL mimic those of MF, the absence of marked papillary dermal fibrosis and polymorphic infiltrate are more often noted in TPL.

Immunohistochemical markers have also been evaluated as diagnostic tools, but many with disappointing results. Markers common to MF include increased CD4: 8 ratios and loss of CD7, but studies have demonstrated similar changes within TPL. Admixed B- and T-cell infiltrates with evenly scattered CD30 positivity are non-diagnostic but have been suggested to generally

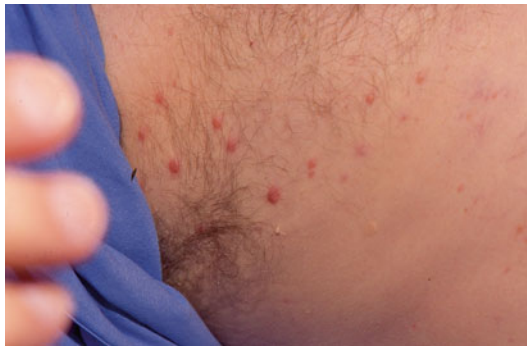

Fig. 19.1 This is true cutaneous lymphoma—erythematous papules in the groin. Clinical clues it is a true lymphoma are that the lesions are multiple, chronic, and on non-sun-exposed skin. The histology showed cutaneous T-cell lymphoma. The patient was not on drugs associated with pseudolymphoma

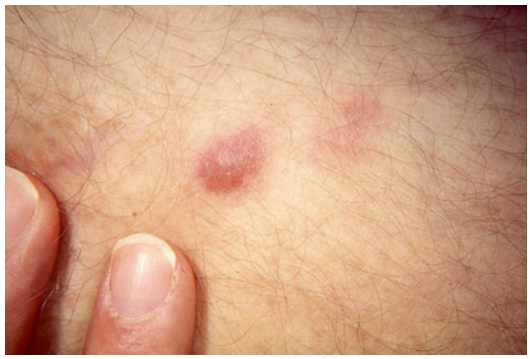

Fig. 19.2 This erythematous papule on histopathology showed pseudolymphoma. It was on the forearm. Clues it might be a pseudolymphoma were that it was acute, solitary, and on sun-exposed skin. The patient was not a medications associated with psuedolymphoma

represent benign conditions. Recent studies have evaluated the use of programmed death-1 (PD-1) as a possible marker for TPL. Results suggest there is consistent PD-1 positivity in pseudolymphoma and absence in MF. Other studies potentially supporting this assertion have found PD-1 positivity in Sezary syndrome but absence in MF and have suggested its use as a marker to differentiate Sezary syndrome from erythrodermic MF. However, the most prominent distinguishing characteristic is simply the resolution of signs and symptoms upon discontinuation of the inciting medication.

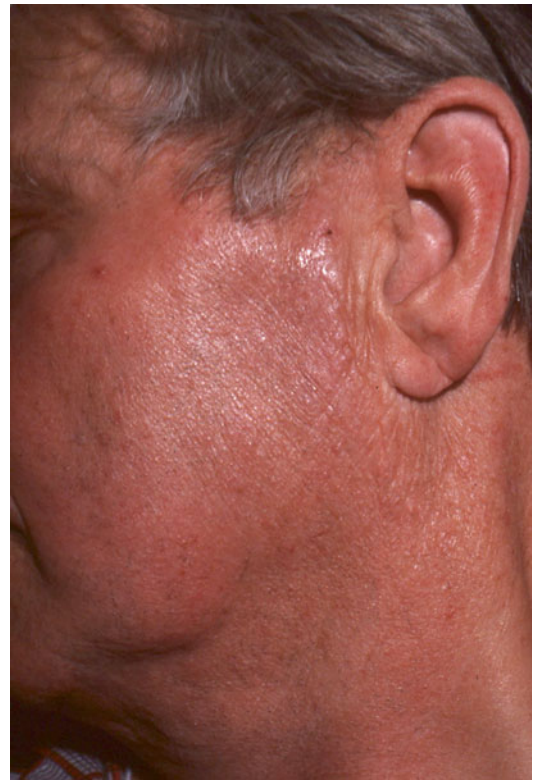

Fig. 19.3 An erythematous papule with overlying small hemorrhage was seen in an elderly man. Clinical clues of a pseudolymphoma were that it was acute, solitary, and on sun-exposed skin. The pathology showed a psuedolymphoma and the patient was on dilantin. Discontinuation of the dilantin resulted in resolution of the papule

Differential

TPL clinically may present with a wide array of non-specific cutaneous findings. Therefore the differential is of a histologic basis and, most importantly, includes CTCL as discussed above.

Treatment

Treatment of pseudolymphoma, whether B- or T-cell-like, most importantly begins with discontinuation of the causative medication, which alone may lead to resolution of the disease. While numerous medications have been implicated, some of the most commonly reported include various anticonvulsants, antidepressants, antipsychotics, antihypertensives, and antihistamines. Tables 19.1 and 19.2 contain more detailed,

Table 19.1 Medications indicted in the etiology of B-cell pseudolymphoma

Medication class	Indicted drugs
Antibiotics	Penicillin
Anticonvulsants	Carbamazepine, Lamotrigine, Phenobarbital, Phenytoin
Antidepressants	Amitriptyline, Doxipin, Fluoxetine
Antihistamines	Oxatomide
Antihypertensives	Losartan, Nifedipine, Propranolol
Antipsychotics	Thioridazine
Biologics	Ustekinumab
Bisphosphonates	Zolendronic acid,
Chemotherapeutics	Methotrexate
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)	Indomethacin
Stimulants	Methylphenidate

although not comprehensive, lists of reported medications for both subsets of pseudolymphoma. Spontaneous and complete resolution often occurs upon stopping the medication and re-exposure is documented to lead to a repeated, if not worsened, eruption. When drug removal alone is insufficient, other local therapies reported to be successful include topical and intralesional corticosteroids, PUVA, cryosurgery, laser ablation, and simple excision. Radiotherapy can be considered for persistent lesions.

In general, conservative treatment is recommended as this is typically a benign disease that often responds to discontinuation of the causative medication with non-scarring spontaneous remission. Although rare, drug-induced pseudolymphoma has been reported to progress to overt lymphoma. In the case of lack of response or disease progression despite treatment, reconsideration should be given to the diagnosis and additional

Table 19.2 Medications indicted in the etiology of T-cell pseudolymphomas, including DRESS syndrome

Medication class	Indicted medications
Antiarrhythmics	Digoxin
Antibiotics	Cefuroxime, Dapsone, Isoniazid, Levofloxacin, Minocycline, Nitrofurantoin, Penicillin, Rifampin, Trimethoprim-sulfamethoxazole, Vancomycin
Anticonvulsants	Carbamazepine, Ethosuximide, Phenobarbital, Phenytoin, Valproic acid
Antidepressants	Amitriptyline, Bupropion, Desipramine, Doxepin, Fluoxetine, Maprotiline
Antihistamines	Cimetidine, Doxepin, Diphenhydramine, Mequitazine, Ranitidine
Antihypertensives	Atenolol, Amlodipine, Clonidine, Captopril, Diltiazem, Enalapril, Furosemide, Hydralazine, Hydrochlorothiazide, Lisinopril, Losartan, Prazosin, Spironolactone, Valsartan, Verapamil
Antipsychotics	Chlorpromazine, Lithium, Phenothiazine, Thioridazine
Antirheumatics	Allopurinol, D-penicillamine, Gold, Sulfasalazine
Anti-TNF alpha agents	Adalimumab, Etanercept, Infliximab
Chemotherapeutics	Cyclosporine, Fluorouracil, Gemcitabine, Imatinib, Leucovorin, Methotrexate, Oxaliplatin
Cholesterol-lowering agents	Lovastatin
Nitrates	Isosorbide dinitrate, Nitroglycerin
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Diclofenac, Fenoprofen, Ibuprofen, Indomethacin, Lornoxicam, Naproxen
Platelet Inhibitors	Aspirin, Dipyridamole
Sedatives	Clonazepam, Lorazepam
Sex Steroids	Estrogen, Progesterone
Stimulants	Methylphenidate

treatment should be in line with current standards based on the appropriate diagnosis. Consideration should be given to long-term follow up for all patients with a diagnosis of pseudolymphoma to monitor for the possible development of a lymphoproliferative malignancy.

Drug-Induced Cutaneous Lymphoma

Cutaneous lymphoma is a term that describes a multitude of varying cutaneous malignancies. Recently a joint World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) consensus criteria was released defining primary cutaneous lymphoma as T- or B-cell lymphomas that present in skin without evidence of extracutaneous disease at the time of diagnosis. Although there are numerous subtypes of T- and B-cell cutaneous lymphomas, none are commonly described in the literature as having a directly medication-induced etiology. There are, however, reports of numerous non-melanoma skin cancers developing in immunocompromised patients. These are most commonly squamous cell and basal cell carcinomas but, rarely, cutaneous lymphomas have also been reported. Virally induced lymphomas, particularly Epstein-Barr virus-related Burkitt, Hodgkin, and non-Hodgkin lymphoma, are very well documented among immunosuppressed patients. As the iatrogenic suppression of the immune system in these allows the expression of these malignancies through dysregulation of immune surveillance mechanisms, cutaneous lymphoma could be considered "drug-induced," although not by the classic understanding of this expression.

As previously discussed, there are reports of drug-induced pseudolymphoma progressing to overt B- and T-cell cutaneous lymphomas. These are rare in the current literature and some authors raise questions regarding initial diagnosis. Interestingly, many of the documented cases of progression demonstrated monoclonality at the time of initial diagnosis. Some suggest these progressions are actually misdiagnoses of overt lymphoma. This could be due to a lack of necessary histologic criteria from the initial biopsy, or perhaps represent very early stage disease which then follows a natural progression to overt lymphoma, regardless of medication use. Direct induction of overt cutaneous lymphoma by medication is not supported by current literature. The diagnosis of such should raise the question of other possible etiologies and promote further evaluation of the case. Treatment, however, should not be delayed once the diagnosis of lymphoma is confirmed. This should include removal of all potential causative medications, when possible, and follow established treatment guidelines for the specific malignancy that has arisen.

Conclusions

Most lymphomas are a straightforward diagnoses, even in the skin. However, if a drug etiology is never considered, then it will never be diagnosed. Discontinuing the offending medications and avoiding the pitfalls of misdiagnosing lymphoma is of obvious importance.

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Part III

Drug Reactions of the Appendeges

Drug-Induced Alopecia

20

Kendra Lesiak, Jamen R. Bartlett,
and Gretchen W. Frieling

Abstract

Hair loss is a common complaint, and an understanding of the hair cycle is vital in order to interpret whether hair loss is secondary to medication use, as the use of prescription medications is widespread. When there is a temporal association between the onset of hair loss and the commencement of a medication, the medication is commonly presumed to have caused the hair loss. Drug-induced alopecia is a result of either rapid termination of the normal growth phase (anagen effluvium) or a premature conversion of actively growing hairs into the dormant, resting phase (telogen effluvium). Hair loss, in particular telogen effluvium, may, however, occur in response to a number of triggers including fever, hemorrhage, severe illness, and stress. Because hair loss is often delayed and because diffuse alopecia often begins sub-clinically, it may be challenging to determine the primary of alopecia. As a rule of thumb, adverse drug reactions are reversible provided the causative drug is avoided; however, identifying the culprit medication can be difficult. This chapter will review the normal hair cycle and discuss the major drugs that have been associated with alopecia, along with their mechanism (s) of action.

Keywords

Alopecia • Drug-induced alopecia • Hair loss • Drug-induced hair loss

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_20

Introduction

Hair loss is a common complaint, and an understanding of the hair cycle is vital in order to interpret whether hair loss is secondary to medication use, as the use of prescription medications is widespread. When there is a temporal association between the onset of hair loss and the commencement of a medication, the medications are commonly presumed to cause hair loss. Drug-induced alopecia is a result of either rapid termination of the normal growth phase (anagen effluvium) or a premature conversion of actively growing hairs into the dormant, resting phase (telogen effluvium). Hair loss, in particular telogen effluvium, may, however, occur in response to a number of triggers including fever, hemorrhage, severe illness, and stress. Because hair loss is often delayed and because diffuse alopecia often begins subclinically, it may be challenging to determine the primary cause. As a rule, adverse drug reactions are reversible provided the causative drug is avoided. This chapter will review the normal hair cycle and discuss the major drugs that have been associated with alopecia, along with their mechanisms of action.

Normal Hair Cycle

Imperative to accurately diagnosing hair-related disease processes is a fundamental understanding of the normal hair cycle. Hair on the human scalp grows at a rate of 0.3–0.4 mm/day, corresponding to 1 inch every 2 months or 6 inches per year. Each individual human hair follicle has its own cycle, which consists of three distinct and concurrent phases: anagen, catagen, and telogen, corresponding to growth, involution, and resting phases. The duration of the anagen phase determines the ultimate hair length, with the average duration in normal healthy individuals being 3 years. An understanding of this cycle is vital in order to interpret whether hair loss is secondary to medication use. The anagen, or "active," phase is when hair growth occurs. The cells in the root of the hair divide rapidly, and the longer the hair resides in the anagen phase, the faster and longer it will grow. Approximately 85 % of the hairs on one's head are in the anagen phase at any given time, and this phase can last between 2 and 6 years, the exact timeframe of which is genetically determined.

The hair on the extremities, eyelashes, and eyebrows has an extremely short active growth phase (30–45 days), justifying the short length compared to scalp hair. During this phase, the cells in the papilla divide to produce new hair fibers, and the follicle buries itself into the dermal layer of the skin to nourish the strand. The catagen phase, or "degradation" phase, is a short transitional phase between anagen and telogen. It lasts about 2 weeks and is characterized by follicular shrinkage due to apoptosis. The hair pulls away from its blood and nutrient supply in the dermal papilla, hence pausing growth. About 3 % of all scalp hairs are in this phase at any time. The follicle is 1/6 its original length, causing the hair shaft to be pushed upward. While hair is not growing during this phase, the length of the terminal fibers increases when the follicle pushes them upward. This defines formation of a club hair. During the telogen, or "resting" phase, the follicle is inactive for 1 to 4 months. Telogen typically lasts about 100 days and 6–15 % of the hairs on one's head are in this phase at any given time. The hair follicle is completely at rest and the club hair is fully formed. Pulling a hair out in this phase will reveal a solid, hard, dry, white material at the root. About 100 telogen hairs are shed normally each day. At some point, the follicle will begin re-growth, entering the active phase once again. If the old hair has not already been shed, it will be pushed out by the new emerging hair shaft.

Presentation and Characteristics

Drug-induced hair loss typically presents as a diffuse, non-scarring alopecia of the scalp with rare involvement of other areas such as the eyebrows, axillary hair, pubic hair, and total body hair. Associated symptoms and follicular or interfollicular inflammation are typically absent. Females are more commonly affected than males.

Drug-induced alopecia occurs via two major mechanisms: anagen effluvium and telogen effluvium. Anagen effluvium typically begins within 1–3 weeks of initiation of a new medication and is classically associated with anti-cancer chemotherapeutic agents. The onset of telogen effluvium, however, is delayed for 2–4 months following initiation of a new medication. Both of these conditions cause diffuse, generalized non-scarring alopecia, which are generally reversible following discontinuation of the causative agent. Drug-induced telogen effluvium is usually persistent or progressive while the medication is continued. If a particular drug is suspected, testing involves suspending its use for at least 3 months. Re-growth following discontinuation and recurrence of telogen effluvium upon re-exposure to the medication would support a conclusion of drug-induced alopecia. These two major entities will be discussed in detail below.

Anagen Effluvium

Anagen effluvium is characterized by severe diffuse reversible alopecia, generally in the setting of high-dose chemotherapy. In fact, 65 % of patients undergoing chemotherapy will experience drug-induced alopecia. Anagen effluvium typically affects the scalp most prominently, but terminal hair at other sites, including the eyebrows, eyelashes, axillary hair, and pubic hairs may also be affected. Anagen effluvium most commonly begins 1–3 weeks following initiation of high-dose chemotherapy and becomes most clinically apparent at 1–2 months. It results from direct toxicity of the chemotherapeutic agents to the rapidly dividing cells of the anagen hair matrix. Abrupt cessation of mitotic activity leads to abnormal keratinization of the hair shaft and results in Pohl-Pinkus constrictions (tapering of the hair shaft). When these narrowed areas within the hair shaft reach the surface of the skin, they break off. Telogen hairs are unaffected and thus diffuse, but incomplete hair loss is evident clinically. Within several weeks of drug cessation, the hair matrix resumes its normal activity and complete recovery generally occurs; however, alterations to hair color and texture following re-growth are commonly reported.

Anagen effluvium is most common and severe during combination chemotherapeutic regimens. All cytotoxic chemotherapeutic regimens have been implicated, but it is most common with alkylating agents, antimetabolites, vinca alkaloids, topoisomerase inhibitors, and anthracyclines. Other causes of anagen effluvium may include loose anagen syndrome (caused by a defect in the hair cuticle leading to poorly anchored hairs in young blond girls), syphilis, and exposure to isoniazid, thallium, or boron.

Telogen Effluvium

Telogen effluvium is the most common cause of diffuse hair loss secondary to medication or systemic disease. It is characterized by excess shedding of telogen hairs in the absence of clinical or histological evidence of inflammation. It may, however, be associated with scalp paresthesia or pain referred to as trichodynia. Though scalp hair is most commonly affected, diffuse thinning of pubic and axillary hair may also be noted. A specific and identifiable trigger, such as pregnancy, illness, trauma, malnutrition, or occasionally, initiation of a new medication, generally precedes acute telogen effluvium. Gradual onset and prolonged telogen effluvium may be more difficult to assess and must be differentiated from androgenetic alopecia and chronic idiopathic telogen effluvium.

Though there are several distinct mechanisms by which telogen effluvium can occur, drug-induced telogen effluvium generally occurs via immediate anagen release in which an abnormally large number of follicles are stimulated to leave the normal anagen phase and enter telogen prematurely and simultaneously. Clinically, this translates to increased hair shedding 2–3 months after starting the culpable medication.

There are several clinical tests, which may help to confirm the diagnosis of telogen effluvium. The hair pull test, in which 40–60 strands of hair are grasped firmly between the thumb and forefinger and gently pulled in three separate areas of the scalp, may suggest a diagnosis of telogen effluvium if more than 4–6 (10 %) hairs are released. This test is heavily influenced by

recent shampooing and styling of the hair, so the results may be difficult to interpret and a negative test does not exclude the diagnosis of telogen effluvium. A trichogram, in which a mixture of normal anagen and telogen hairs are forcibly plucked from the scalp, is considered diagnostic of telogen effluvium if more than 20–25 % are telogen hairs.

Telogen effluvium may be precipitated by a variety of metabolic alterations, including fever, severe infection, surgery, thyroid disease, hyperparathyroidism, chronic malnutrition or malabsorptive states, crash dieting with severe protein-caloric restriction, severe hereditary or acquired zinc deficiency, renal dialysis with secondary hypervitaminosis A, allergic contact dermatitis to hair dyes, and severe chronic illnesses such as HIV, syphilis, systemic lupus erythematosus, chronic renal failure, chronic liver failure, and advanced malignancy. Half of hyperthyroid patients and 33 % of hypothyroid patients will have diffuse hair loss, which is reversible upon return to a euthyroid state. Acrodermatitis enteropathica and acquired zinc deficiency due to long-standing parenteral nutrition can lead to severe telogen effluvium, though correction of a subclinical zinc deficiency will not stop the increased shedding of telogen effluvium. Many sources recommend iron supplementation if ferritin levels are below 40 ng/ml in patients with telogen effluvium; however, the relationship between ferritin levels and telogen effluvium remains unclear. At least one study has shown that iron replacement alone does not lead to resolution of hair shedding, but ferritin levels may act as markers of patients' overall nutritional status. Some authors suggest slow onset diffuse hair loss in low iron states may result from temporary failure of follicles to re-enter the anagen phase.

Differential Diagnosis and Work-Up

When a patient presents with a complaint of increased hair shedding or diffuse hair thinning, a thorough clinical history and physical examination is essential. Many patients can recall when the hair loss began and how long it has lasted, though quantifying hair loss can be more difficult. As it is normal to lose between 50 and 150 hairs per day, it may be difficult for patients to truly quantify increased hair shedding. It is important to remind patients that this normal hair shedding occurs during routine washing and styling. Therefore, if an individual is washing and styling every other day as opposed to daily, they may notice more hair loss during these activities and overestimate daily hair loss. In long-haired patients, a subjective clue to hair loss is the amount of times an elastic band is wrapped around a ponytail. A patient may report that this number has increased recently, indicating significant hair loss.

Associated symptoms, such as scalp pruritus, tenderness, inflammation, or scaling should be elicited. A thorough review of systems, including questions regarding recent weight loss, systemic illness or fever, and menstrual history, should be discussed. Heavy periods and amenorrhea can be associated with iron deficiency anemia and endocrine abnormalities, respectively. History of oral contraceptive use, pregnancies, miscarriages, signs of androgen excess and/or polycystic ovaries should be sought. A review of the patient's past medical history for autoimmune disease, hepatic and renal disorders, and chronic infections is indicated. Family history of premature hair loss should be elicited as androgenetic alopecia, which is often hereditary, may fall within the differential diagnosis. Dietary and medication history, including prescription and non-prescription medications, should also be reviewed. Vegetarians/vegans often have increased hair shedding, probably secondary to iron and protein deficiency.

In addition to thorough history, review of systems, and clinical examination, evaluation of a patient with alopecia may include a comprehensive metabolic panel, thyroid panel, hematocrit, ferritin, and ESR. If this workup is negative or the time course is suggestive, drug-induced alopecia should be considered.

Biopsy/Histopathology

Punch biopsy is preferred for evaluation by a dermatopathologist.

- **Telogen effluvium (TE):** Total number of hair follicles is normal with a predominance of telogen follicles, and little to no anagen or catagen follicles. Drug-induced TE induces a

Table 20.1 Differentiating factors: drug-induced vs. idiopathic alopecia

Drug-induced alopecia	Idiopathic alopecia
Temporal association of drug initiation and alopecia	No association with initiation of drug
Cessation of drug leads to recovery and restoration of hairs and reversion of histopathological changes	No recovery of hairs after cessation of drug
No evidence of thyroid dysfunction	± Thyroid dysfunction

shift to the catagen phase, and by the time a biopsy is taken, most follicles are in the telogen phase. Dermal inflammation is absent.

- **Anagen effluvium:** The total number of hair follicles is normal with a predominance of anagen follicles, and little to no catagen or telogen follicles. Dermal inflammation is minimal to absent.
- **Cicatrical alopecia:** Hair follicles and sebaceous glands are replaced by elastic fiber rich-fibrous tissue, which extends above the level of arrector pili insertion (in contrast to normal telogen hairs in which the fibrosis is only in the deeper follicle). Prominent lamellar fibroplasia is typically seen. In early lesions, a moderately dense lymphocytic infiltrate may be seen around the upper 2/3 of the follicle. The epidermis is uninvolved. In later lesions, the epidermis may show some atrophy with loss of the rete ridges.

Differentiating Factors

There are no specific criteria established to diagnose drug-induced alopecia or to distinguish drug-induced alopecia from other causes of alopecia. However, there are several differentiating characteristics that can aid in this distinction (Table 20.1).

Drugs Implicated

Anti-coagulants

Many anti-coagulants are known to cause reversible hair loss, but the exact mechanism and pathogenesis remain unclear. Systemic heparin and heparinoid therapy can cause transitory diffuse hair loss, namely telogen effluvium, in up to 50 % of patients. Animal models have demonstrated that heparin has an anti-mitotic effect on follicular epithelial cells, inhibits anagen growth, stimulates epidermal proliferation, and inhibits epithelial bulb cell proliferation. Hair re-growth characteristically occurs after drug cessation. Low-molecular-weight heparins (LMWHs) are a mixture of short-chain heparins (2,000–10,000 Da) and are safer than unfractionated heparins. Additionally, LMWHs have fewer complications, can be given in discrete doses, and do not require drug monitoring. Dalteparin was the first reported LMWH to cause rapid, diffuse, reversible alopecia. The first report was 10 weeks after dalteparin treatment for sinus thrombosis in a 9-year-old girl and the second case series reported this phenomenon in hemodialysis patients. Hair re-growth commenced nearly 6 weeks after discontinuation of dalteparin. Barnes et al. demonstrated that hair re-growth can be re-established with citrate anticoagulation. Wang et al. reported three cases of alopecia in women after initiation of enoxaparin for central venous and sinus thrombosis. In these cases, telogen effluvium was precipitated by enoxaparin-induced premature transformation of anagen-phase follicles into telogen-phase, resting follicles. Tinzaparin is another LMWH associated with reversible hair loss, which has been documented in a 66-year-old patient on hemodialysis. The effect and severity of LMWH-associated hair loss is thought to be related to the dose and not to the duration of therapy, and

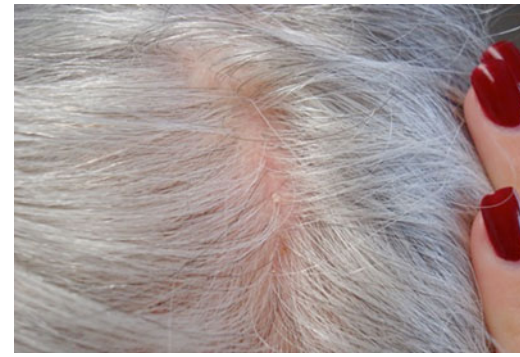

Fig. 20.1 Diffuse hair loss with over 25 % telogen hairs on trichogram that began after Coumadin therapy was initiated. Note the scalp is normal other than mild small non-adherent scaling of seborrhea

there is typically a latent period of 2 weeks from the time of drug administration to hair shedding. Warfarin is less likely to cause clinically significant alopecia, although it has been documented (Fig. 20.1). According to Flesch, the onset of warfarin-induced alopecia may be extremely delayed, often up to years. Three cases of warfarin-induced hair loss were reported by Umlas and Harken, which occurred many years after continuous warfarin therapy for heart disease. They also noted that the alopecia was dose independent and this phenomenon is likely to be under-diagnosed because of the late onset.

Antidepressants

Alopecia is a known side effect of antidepressant medications. Treatment consists of various regimens, including tricyclic or monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRI), or serotonin–norepinephrine reuptake inhibitor (SNRI). Few examples of alopecia induced by tricyclic antidepressants exist in the literature, but cases of hair loss associated with imipramine and desipramine have been reported. No cases of hair loss have been reported with use of MAOIs. Second-generation antidepressants, specifically SSRIs, have caused telogen effluvium. Sertraline, paroxetine, fluoxetine, and citalopram have all been shown to cause reversible alopecia with re-growth as early as 3 months following cessation of use; however, hair regrowth was delayed 1.5 years in a least one case report.

Antimicrobials

Antibiotics, antivirals, antifungals, antihelminthics, and antiretrovirals can all damage hair growth and induce not only telogen effluvium but, rarely, alopecia universalis. Antibiotics have not historically shown a strong predilection toward damaging the hair follicle. Hajime et al. reported a case linking gentamycin to scalp and eyebrow loss following treatment of pseudomonas in a 15-year-old male. Few case reports exist describing dose-related reversible alopecia secondary to nitrofurantoin. The anti-tuberculin drugs isoniazid, thiacetazone, and ethionamide have all been associated with alopecia in the past, but the mechanism is unclear. Hypotheses include involvement of androgen, as isoniazid has been shown to alter estrogen-androgen metabolism. Azole antifungal medications, namely fluconazole and itraconazole, as well as anidulafungin, have been associated with hair loss at high doses. The antihelminthics benzimidazole and albendazole are used for echinococcosis infections, and both have been reported to cause reversible alopecia.

Interferon-alpha (IFN-α), used in the treatment of Hepatitis C, causes dose-independent alopecia in 50 % of patients. Hair loss caused by IFN-α can be localized to an injection site or cause telogen effluvium and, in rare cases, can cause alopecia universalis. The alopecia associated with interferon-alpha therapy is transient and resolves following discontinuation of the drug (see the section on Interferon). Antiretroviral drugs carry a moderate risk for development of alopecia. Approximately 10 % of patients treated with indinavir will experience severe telogen effluvium, possibly with patchy hair loss of the legs, thighs, pubic, and axillary regions. Combined treatment with indinavir and ritonavir may increase the severity of adverse effects because ritonavir increases the plasma concentration of indinavir. A proposed mechanism of action for telogen effluvium associated with indinavir is the enhancement of retinoic acid signaling specific to indinavir. Transitioning to a new drug regimen or discontinuing indinavir will allow restoration of normal hair growth.

Busulfan

Busulfan is a chemotherapeutic agent commonly used in conditioning regimens prior to bone marrow transplant. Unlike most chemotherapeutic agents, which cause a reversible anagen effluvium, busulfan has been reported to cause permanent partial or diffuse hair loss in up to 50 % of patients. Scalp biopsies in these patients demonstrate decreased follicle density without associated inflammation or fibrosis. Reduced follicle density may be a consequence of stem cell destruction or acute damage to matrix keratinocytes.

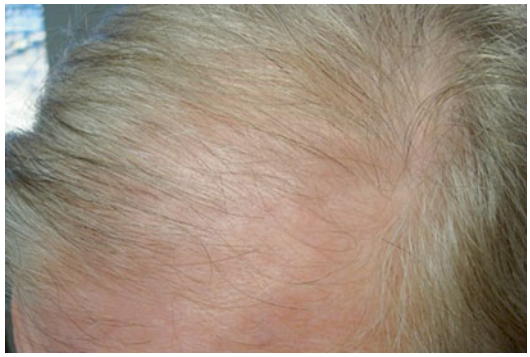

Fig. 20.2 Diffuse hair loss due to a beta blocker, which dissipated months after the drug was discontinued

Cardiovascular Drugs

Beta-blockers are commonly used to treat hypertension, but have a known side effect of alopecia (Fig. 20.2), specifically telogen effluvium. Metoprolol (Lopressor), propranolol (Inderol), and nadolol (Corgard) have been documented to cause telogen effluvium. Hair re-growth has been reported within 3 months of nadolol withdrawal. The angiotensin-converting enzyme inhibitors (ACEi), used in the treatment of hypertension and congestive heart failure, have also been associated with hair loss. In one report a combination of captopril (Capoten) and furosemide cased diffuse hair loss. Angiotensin-converting enzyme inhibitors and β-receptor blocking agents may rarely precipitate a rapidly progressive lichen planopilaris in susceptible patients. Use of these agents in patients with active lichen planopilaris should be avoided. Amiodarone, an anti-arrhythmic, is known for its numerous side effects, including alopecia. In all cases, hair re-growth was reported upon discontinuation of amiodarone.

Chemotherapy Agents

Chemotherapy-induced alopecia (CIA) is commonplace for patients receiving a cytotoxic drug regimen. Although it is a well-known side effect of therapy, the anticipated hair loss can be extremely distressing, enough so that patients consistently rank it among the worst hardships involved with chemotherapy. CIA can be seen within days of initiating treatment, followed by complete hair loss around the second cycle, 4–8 weeks following induction. The degree of hair loss is directly related to dose, schedule, rate, and route of delivery. Hair loss typically begins at the crown of the head, followed by the temporal region. The hair loss can be diffuse or patchy, depending on which individual follicles are in the anagen phase. Chemotherapeutic agents most commonly associated with hair loss include anthracyclines, antibiotics, antimetabolites, vinca alkaloids, and taxanes. The cytotoxic drugs used in chemotherapy target rapidly dividing cells; unfortunately, hair follicles are innocent bystanders and unintended targets. Due to the fact that the hair follicles affected are dividing, or in the anagen phase, the term used to describe CIA is anagen effluvium. It is known that p53 plays a large role in hair follicle apoptosis, and recent studies have shown that Fas and c-kit do play a role, but the exact molecular pathway is still not fully understood. An ongoing debate continues surrounding more hypothetical pathways. The vast majority of patients will have hair re-growth 1-3 months following the discontinuation or completion of chemotherapy, however, the hair texture, thickness, color, and waviness may be altered in up to 60 % of patients.

Dopaminergic Therapy

Levodopa, ergot, and non-ergot alkaloid dopamine receptor agonists have been associated with alopecia and generally affect women more than men. Case reports have documented telogen effluvium in patients with Parkinson's disease that were taking dopaminergic medications. Levodopa, bromocriptine, pramipexole, ropinirole, cabergoline, and pergolide have all been described in the literature as having adverse effects on hair. The pathophysiologic mechanism is unknown, but switching agents or stopping treatment has been shown to reverse the adverse effects over time.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a mechanical cardiopulmonary support device that acts as an artificial lung during cardiothoracic surgery or in patients with severe

respiratory distress. Hair loss following EMCO is extremely common and reported extensively. One study demonstrated that up to 87 % of patients will potentially lose hair following utilization of ECMO. The etiology of hair loss with ECMO is most likely multifactorial and resolves spontaneously over time.

Fluoroscopy

Rarely, the use of fluoroscopy during interventional procedures, such as neurointervention following an acute stroke or coronary angiography and angioplasty, has been associated with radiation dermatitis and alopecia in exposed areas. Some authors have termed this "square alopecia," reflecting the geometric distribution pattern frequently observed. This is commonly misdiagnosed as alopecia areata, as the patient may not readily provide a history of exposure to fluoroscopy. It most commonly occurs in the retroauricular region, as the highest dosages of radiation are frequently applied in this location. The severity is proportional to the fluoroscopy dose, the total time of the procedure, the interval between exposures, the size of the irradiated area, and individual patient characteristics, such as age, smoking status, nutritional status, skin integrity, tissue oxygenation, capillary density, hormonal status, genetic factors, obesity, and skin color.

Hormonal Therapies

The estrogen in oral contraceptive pills (OCPs) has been linked to prolonged anagen duration. An alternate hypothesis is that some OCPs contain anti-androgens (drosperidone, cyproterone acetate), which arrest androgenetic alopecia. Subsequent cessation of OCPs presumably then leads to resumption of an unrecognized androgenetic alopecia. Telogen effluvium can also be seen following cessation or interruption of OCPs. Some progesterone-based medications (levonorgestrel, norgestrel, norethisterone, tibolone) may induce or worsen androgenetic alopecia.

Human Epidermal Receptor (HER) Tyrosine Kinase Inhibitors

Tufted hair folliculitis has been reported to develop during treatment with both lapatinib (a HER1 and HER2 tyrosine kinase inhibitor) and trastuzumab (a HER2 monoclonal antibody inhibitor). In the case of trastuzumab, the patient experienced significant scaling and pruritus in association with tufted hair folliculitis. These symptoms resolved with clobetasol propionate 0.05 % topical solution applied twice daily.

The HER1 tyrosine kinase inhibitors erlotinib and gefitinib have been reported to cause a cicatricial alopecia with associated chronic folliculitis and perifolliculitis. Erlotinib has also been reported to cause folliculitis decalvans, which improved with antimicrobial and topical corticosteroid therapy despite continuation of treatment.

Interferon (IFN)

Telogen effluvium occurs in up to 50 % of patients receiving interferon therapy. This effect is not dose-related. Hair shedding is reversible after interruption of treatment and, in some cases, despite continuation of treatment. Changes in hair texture and color upon regrowth are frequently observed. For example, in one report 18 % of patients treated with low-dose IFN-α for malignant melanoma experienced hair whitening. Acquired hair straightening has also occurred in patients on combined IFN-α and ribavirin therapy for hepatitis B. Transient localized alopecia has been reported at IFN-α injection sites.

Multiple cases of localized alopecia areata, alopecia totalis, and alopecia universalis during or shortly after treatment of chronic Hepatitis C with peg-IFN-α and ribavirin have been reported in the literature. At least one case of alopecia totalis involved a patient with pre-existing alopecia areata. Alopecia was noted 3–9 months following treatment initiation, and resolution occurred irrespective of treatment in most patients 3–12 months later. There are at least two reported cases of irreversible alopecia universalis and totalis following peg IFN and ribavirin therapy.

Minoxidil

Topical minoxidil is commonly used in the treatment of alopecia, specifically androgenetic alopecia. Paradoxically, diffuse hair shedding often occurs within 4–6 weeks of initiating therapy secondary to a brief telogen effluvium. Minoxidil

induces premature termination of the telogen phase, leading to simultaneous release of many telogen hairs as responding follicles transition to anagen.

Upon discontinuation of minoxidil, all of the follicles that had prolonged anagen phases during therapy simultaneously enter the telogen phase. This results in a severe telogen effluvium approximately 2–3 months later. Minoxidil has also been reported to induce hair darkening.

Mood Stabilizers

Although uncommon, psychiatric medications can cause alopecia. Mood stabilizers such as lithium and valproic acid are two of the more common inducers of telogen effluvium, but often these symptoms are dose-related and readily reversible with modification of the amount given. It has been reported that 12–19 % of long-term users of lithium will experience hair loss or hair thinning. Alopecia may occur weeks to years into treatment with lithium, with the typical time course being 4–6 months. The adverse drug effects of lithium treatment affect females more often than males. It is essential to rule out lithium-induced thyroid disease, a common side effect of lithium treatment, in patients with hair loss or thinning. Returning the patient to a euthyroid state should readily reverse the hair loss. The incidence of alopecia caused by valproic acid is 0.5–12 %. Valproic acid-associated alopecia seems to be associated with increased valproic acid blood concentration, and dose reduction allows hair regrowth. Carbamazepine therapy can also lead to hair loss, with an incidence of 1.6–6 %. Newer mood-stabilizing compounds such as gabapentin rarely cause alopecia. Among the antipsychotic drug classes, only haldoperidol, olanzapine, and rispiridone have been reported to cause hair loss.

Mycophenolate Mofetil

In a long-term observational prospective study of mycophenolate mofetil use in patients with proliferative lupus nephritis, new onset alopecia was noted in 1 of 33 patients. Due to alopecia being a known complication of systemic lupus erythematosus, these results should be interpreted with caution. As discussed below, alopecia has also been seen in patients taking combination mycophenolate mofetil and tacrolimus therapy for long-term immunosuppression following transplant.

Radiation

Radiation for the treatment of brain tumors commonly leads to cicatricial alopecia in exposed areas of the scalp secondary to permanent destruction of hair follicles. This is most common with radiation doses over 700 Gy. Most patients are not completely bald following therapy, as hair follicles in the telogen phase at the time of the treatment are able to escape destruction.

Retinoids

Retinoids, including acitretin and isotretinoin, which are commonly used in dermatology for the treatment of psoriasis and acne, respectively, are known to cause significant telogen effluvium in up to 20 % of patients. Retinoic acid plays an important role in hair growth, with retinoic acid receptors found throughout every portion of the hair follicle. Tightly regulated control of retinoid metabolism may be required for normal function of hair follicles.

Typically, a dose-related alopecia is most notable on the scalp; however, body hair may also be affected. This side effect appears more often in patients treated with acitretin than isotretinoin. Clinical trials have shown 23 % of patients treated with 50 mg daily of acitretin and 9 % of patients treated with 25 mg daily of acitretin reported significant alopecia versus only 1 % of patients treated with placebo for psoriasis.

Retinoids cause a telogen effluvium primarily due to shortening of the telogen phase with premature detachment of club hairs and diffuse hair shedding. They also cause a decrease in the duration of the anagen phase. An observational study of 30 patients on isotretinoin demonstrated significantly decreased hairs, decreased mean hair density, and decreased numbers of anagen hairs during treatment.

Mild hair loss is also frequently seen in patients taking vitamin supplements containing vitamin A. This effect may be potentiated by concurrent administration of vitamin E. Interestingly,

vitamin A deficiency can also result in alopecia, and topical tretinoin has been successfully used to treat androgenetic alopecia in several studies.

Acitretin-induced full-body poliosis with concurrent alopecia and acquired generalized kinking of the hair (possibly secondary to altered keratinization of the inner root sheath leading to structural changes in the hair shaft), and other acitretin-induced changes in hair color and texture have been reported as well.

Tacrolimus

In a 2005 retrospective study of 59 consecutive simultaneous kidney-pancreas transplant patients, 28.9 % of the patients treated with tacrolimus and mycophenolate mofetil developed clinically significant alopecia, while none of the patients taking cyclosporine with or without mycophenolate mofetil developed alopecia. Females were much more likely than males to experience alopecia.

Alopecia areata and alopecia totalis have also been reported in three females with type 1 diabetes mellitus taking tacrolimus and mycophenolate mofetil following islet cell transplantation. Alopecia was reversible with conventional treatments for alopecia areata, including topical anthralin, salicylic acid, and intralesional cortisone injections, despite continuation of tacrolimus in two of the three cases and continuation of mycophenolate mofetil in two of the three cases. It is important to interpret these reports with caution, however, as alopecia areata is thought to be an autoimmune disease, which may cluster in families with other autoimmune diseases such as type 1 diabetes mellitus.

TNF-α Inhibitor-Induced Psoriasiform Alopecia

TNF-α inhibitors are being increasingly used in the treatment of psoriasis and inflammatory bowel disease. Paradoxically, multiple cases of psoriasiform alopecia of the scalp have been observed in patients with or without a history of psoriasis receiving TNF-α inhibitors, most commonly infliximab and adalimumab. Biopsy of affected areas demonstrates a psoriasiform dermatitis with an increased number of catagen or telogen hairs, miniaturization of hairs, and a peribulbar and superficial perivascular dermatitis with a mixed infiltrate including eosinophils and plasma cells. Cicatricial alopecia may result in protracted cases. Two cases of biopsy-proven lichen planopilaris of the scalp associated with the TNF-α inhibitor, etanercept, including one case in an 8-year-old boy and one case in a 56-year-old woman being treated for severe psoriasis have been reported. A case of lichen planopilaris of the scalp associated with infliximab has also been reported.

Management and Treatment

Iatrogenic hair loss related to medication use has been widely reported in medical literature, with a litany of drugs implicated. Proper evaluation of patients with hair loss is essential to identifying the root cause of the problem. Following a detailed physical examination, review of systems, and laboratory work-up to rule out other etiologies for the hair loss, comprehensive drug reconciliation should be performed. The drug reconciliation should cover all prescription, over-the-counter and chemotherapeutic medications, as well as vitamin supplements, herbal preparations, and adjunctive treatments. Changes in dosage or frequency of intake are to be noted. Since telogen effluvium takes 2–4 months to fully manifest, all medications started within 4 months of initial hair loss must be reviewed. The gold standard for rendering a diagnosis of drug-induced alopecia is discontinuation of the medication in question for an extended amount of time, with subsequent restoration of hair growth.

Following cessation of symptoms and hair regrowth, a second challenge to prove causation should be made if any question remains surrounding the medication's association with alopecia. Identification of the inciting drug and subsequent discontinuation is the cornerstone of treatment in this subset of patients. In a majority of cases for patients with drug-induced telogen effluvium, cessation of the medication will result in a complete recovery, usually within 4–6 months, and rarely with symptoms lasting more

than a year. Patient reassurance is imperative in management, as the concern that they will "go bald" can be overwhelming.

Though telogen effluvium is a self-limited disease, it may exacerbate or precipitate androgenetic alopecia in at-risk patients. In this subset of patients, treatment with topical minoxidil or finasteride may be indicated. As discussed previously, patients treated with chemotherapy may experience anagen effluvium, which is among the most distressing side effects of chemotherapy, potentially affecting body image. The first step in management of these patients is discussion of the anticipated hair loss and exploration of cosmetic options, including wigs, hats, hair cuts, etc.

In patients receiving chemotherapy for non-hematologic malignancies, scalp hypothermia is a proposed method to reduce hair loss. Theoretically, vasoconstriction caused by the low temperature reduces the amount of cytotoxic chemical that reaches the hair follicle. Reduced biochemical activity due to the extreme cold may also deem the hair follicle less susceptible to damage.

As stated previously, the vast majority of patients affected with anagen effluvium will regain their hair within months of cessation of the trigger drug, but it has been shown that patients using topical minoxidil recovered hair approximately 50 days sooner than those using placebo. Patients with telogen and anagen effluvium need a combination of medical intervention along with a healthy support system to fully manage and treat their disease.

Main Points

- Hair loss secondary to medications has been widely reported in medical literature, with numerous drugs implicated.
- An understanding of the hair cycle is vital in order to render a diagnosis of drug-induced alopecia.
- The two main mechanisms by which drug-induced alopecia occurs are anagen effluvium and telogen effluvium.
- Clinical presentation is typically a diffuse, non-scarring alopecia of the scalp, with rare involvement of other areas such as the eyebrows, axillary hair, pubic hair, and total body hair.
- Detailed physical examination, review of systems, laboratory work-up (comprehensive metabolic panel, thyroid panel, hematocrit, ferritin, and ESR), and a thorough drug reconciliation should be performed in all patients presenting with alopecia.
- Most adverse drug reactions are reversible, provided the causative drug is avoided. It can be quite difficult, however, to assign a culprit medication.

Conclusions

Alopecia can have a significant impact on body image. Numerous factors may be implicated, including medications. In most cases, discontinuation of the culprit drug will result in cessation of hair loss and reversal of the process. It is beneficial to identify the drug in question as soon as possible to limit associated psychological damage.

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Drug Eruptions of the Scalp

21

Wilma F. Bergfeld and Shilpi Khetarpal

Abstract

Cutaneous drug eruptions are common, compromising approximately 2 % of all drug reactions. Reaction types vary and can be skin-limited or life-threatening. Cutaneous reactions can involve any part of the skin; this section will focus on drug eruptions of the scalp. Adverse cutaneous reactions involving the scalp can be caused my many medications, including those that are topical or systemic, as well as prescription and over-the-counter. Most of the scalp drug eruptions are limited to the skin and can be treated with discontinuation of the agent or, if symptomatic, topical agents. They can be classified as psoriasiform, pustular, folliculitis, contact dermatitis, eczematous, erythematous, and hair-loss.

Keywords

Anti-tumor necrosis factor-alpha • Chemotherapy • Drug eruptions • Scalp • Eosinophilic pustular folliculitis • Erosive pustular dermatosis of the scalp

Introduction

Cutaneous drug eruptions are common, accounting for 2–3 % of all adverse drug reactions; they can range from extremely mild to erythroderma and life-threatening. They are typically dose-dependent and related to the pharmacologic action of the drug. Cutaneous reactions can be caused by a single drug or combinations of multiple drugs. Morbilliform eruptions are the most common presentation of an adverse drug eruption, and any area of skin can be affected. There are many different types of cutaneous reactions that can be caused by drugs, as listed here:

- Psoriasiform
- Pustular
- Morbilliform
- Eczematous
- Bullous

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_21

- Lichenoid
- Vasculitic
- Fixed

Various factors, including drug- and patient-based variables, contribute to the risk of an adverse reaction. Drug factors include the route of administration, dose, mechanism of action, duration, and metabolism. Patient factors include age, gender, underlying disease, and genetic variations in metabolizing enzymes. A majority of reactions are toxic reactions rather than allergic; they can also be caused by drug–drug interactions or exacerbation of a preexisting dermatologic condition. Drug eruptions of the scalp are rare, but occur more commonly with specific classes of drugs.

Drug Eruptions of the Scalp

Psoriasiform

Anti-tumor necrosis factor-alpha (anti-TNF-α) can cause psoriasiform eruptions with severe scalp involvement leading to inflammatory alopecia (Black et al. 2011). Anti-TNF-α agents are very effective therapies for both inflammatory bowel disease (IBD) and psoriasis but they can also cause psoriasiform cutaneous eruptions. The reported rate of anti-TNF-α induced psoriasiform eruptions is 1–3 per 1000 person years (Black et al. 2011). All five cases of severe scalp psoriasiform lesions with inflammatory alopecia were in patients with underlying Crohn's disease (CD) treated with anti-TNF agents. Two patients were being treated with infliximab and three with adalimumab. None of the patients had a personal or family history of psoriasis. In addition to having severe scalp involvement, patients also had flexural involvement of psoriasis. Infectious causes were ruled out in each case and skin biopsies confirmed the clinical diagnosis. Patients were treated with topical therapy including topical steroids and vitamin D derivatives. Two patients required systemic therapy with methotrexate and cyclosporin. None of the patients had to discontinue anti-TNF-α therapy. Previous similar studies showed that this reaction pattern was more common in patients with CD when compared to ulcerative colitis (UC). It is not known whether IBD patients are at an increased risk of developing scalp/inverse psoriasis or whether these disease locations are more common among all patients with anti-TNF-α induced psoriasiform eruptions regardless of their underlying disorder. It is unclear as to the mechanism by which TNF-α inhibitors cause psoriasis and whether the psorasiform eruption is a true effect of the anti-TNF-α class (Black et al. 2011).

Pustular

Chemotherapy agents can also cause various cutaneous eruptions including those involving the scalp. Bevacizumab blocks vascular endothelial growth factor, thereby inhibiting angiogenesis; it is known to cause various cutaneous eruptions including exfoliative dermatitis, ulceration, and acneiform eruptions (Fiedler and Gray 2003). Capecitabine and bevacizumab were being used in a patient to treat metastatic colon cancer, and after completing 6 months of therapy, the patient developed scalp erosions that evolved into crusted plaques (Gollnick et al. 1990). The histopathology was similar to erosive pustular dermatosis of the scalp (EPDS) with impetiginization. Tissue culture revealed a polymicrobial infection, and the patient was given antibiotics based on culture sensitivities and had significant improvement.

Eosinophilic pustular folliculitis (EPF) is a rare disorder that was described over 30 years ago. Fewer than five cases associated with medication have been reported (Guarneri and Cannavo 2013). Recently, a case of EPF was reported due to chemotherapy. A 60-year-old woman with breast cancer presented with a papulopustular scalp eruption that occurred one week after undergoing chemotherapy with cyclophosphamide, methotrexate, and 5-flurouracil (Guarneri and Cannavo 2013). The eruption was painful and lasted for 7 days, then resolved on its own. Bacterial cultures were negative. Skin biopsy was consistent with the diagnosis of EPF. The patient received additional chemotherapy with the same agents and the eruption did not recur. EPF is a rare condition that clinically presents as papulopustules

on an erythematous base in an annular configuration. Commonly affected areas include the scalp, face, and trunk. It typically has spontaneous remissions and exacerbations. It has been associated with various underlying disorders, including HIV infection, hematologic malignancies, infantile EPF, and silicone augmentation (Guarneri and Cannavo 2013). First-line therapy includes topical corticosteroids. Medications typically associated with EPF include minocycline, carbamazepine, and allopurinol.

Contact Dermatitis

Over-the-counter medications, such as minoxidil, can cause scalp eruptions. Minoxidil 2 and 5 % is FDA-approved for use in males, and 2 % is approved for use in females older than 18 years. Minoxidil works by prolonging the anagen hair cycle, which enlarges miniaturized follicles. Its precise mechanism is unknown, but is considered to be a potassium channel opener, vasodilator, and apoptosis inhibitor. A new theory is that minoxidil stimulates hair growth by activating cytoprotective prostaglandin synthase-1 (PGHS-1). Recent studies have shown that PGHS-1 is the main isoform in the dermal papillae of the human hair follicle (Hammond-Thelin 2008). Topical minoxidil solution is typically well tolerated. However, at the start of therapy pruritus, scaling, or dryness of the scalp can occur. An elderly patient with female-type androgenetic alopecia (AGA) started using 5 % minoxidil solution, twice daily, 40 days prior to itching and scaling of the scalp. These scaly plaques eventually turned into pustules and erosions of the scalp, forming crust and purulent discharge (Hammond-Thelin 2008). The patient was treated with various oral and topical antibiotics without improvement. Cultures were negative for bacterial and mycological growth. Clinical and histopathological features were consistent with EPDS (this is defined in the prior paragraph that talks about pustular eruptions as erosive pustular dermatosis of the scalp). The patient was started on 0.05 % clobetasol propionate foam for eight weeks and had significant improvement of the lesions without scarring alopecia (Hammond-Thelin 2008). EPDS is an uncommon condition that occurs in elderly white females. It classically develops in areas of atrophic, sun-exposed areas with sterile pustules and a non-specific inflammatory infiltrate. The cause is unknown, but is believed to be triggered by trauma. Various traumas have been reported to cause EPDS, including blunt trauma, surgical procedures, cryotherapy, radiotherapy, photodynamic therapy, topical tretinoin, 5-fluorouracil, and imiquimod (Kanwar and Narang 2013). The most common side effects of minoxidil include irritant contact dermatitis, allergic contact dermatitis, or exacerbation of seborrheic dermatitis. In this patient, patch testing was performed and was negative at 72 h to 5 % minoxidil in ethanol and 5 % minoxidil in propylene-glycol, so irritant/allergic etiologies were excluded. It is believed that the alcohol-containing solution of the 5 % minoxidil could represent the triggering factor (Hammond-Thelin 2008). A second patient, who was a 22-year-old male, developed papulopustules on the scalp and forehead 6 days after starting 5 % minoxidil solution for AGA. The patient reported a similar eruption 3 years prior after using minoxidil solution. The patient declined a biopsy, so based on the clinical history, a diagnosis of pustular contact dermatitis was made (Laing et al. 2006). Patch testing was performed with 5 % minoxidil in ethanol and 5 % minoxidil in propylene glycol and the patient developed positive reactions to both within 48 h. Pustular allergic contact dermatitis from minoxidil is a reported complication and has distinct histopathological features. These patients can develop pustular patch test reactions (Laing et al. 2006).

Hair Loss

Many medications have been known to cause hair loss. Medications affect hair loss via two mechanisms: telogen effluvium (TE) and anagen effluvium (AE). These can be distinguished based on time course. In TE hair loss is delayed and occurs 2–4 months after the drug is given. However, in AE hair loss occurs within 2–3 weeks of drug administration. Nevertheless, both are considered non-scarring forms of alopecia. In both cases, hair loss is typically reversible after the offending drug is discontinued.

Table. 21.1 Drugs that can cause Telogen Effluvium

Allopurinol	Beta-blockers
Androgens	Ergots
Anticholesterol agents (statins)	Hormones (OCPs, HRT)
Anticoagulants	Dopa
Anticonvulsants	Immunomodulators
Antifungals	Retinoids (vitamin A)
Antihistamines (H2)	Psychotropics
Anti-inflammatory	Minoxidil
Anti-mitotic	Heavy metals (gold)
Anti-thyroid	SERMS and phytoestrogens

Telogen Effluvium (TE)

TE is the most common hair-loss condition in both males and females that presents to the dermatologist, and it is seen in all races and ethnic groups of all ages. Patients present with increased shedding and associated diffuse alopecia. The excessive shedding is the result of alterations of the hair growth cycle, with premature conversion of anagen (growing) follicles to telogen (dormant) follicles (Mastroianni et al. 2005).

Many drugs, and fewer herbals and supplements, have been reported to induce alopecia and TE (Table. 21.1). Clinically, all drugs should be suspect in a patient with TE. Careful histories allow for documentation of the drug initiation, time of discontinuation, or change in dosage. A change in dose can initiate the TE. Like other causes of TE, once initiated, it can unmask underlying disorders such as androgenetic alopecia (Osorio et al. 2012). A brief discussion about these agents follows:

Androgens, (such as testosterone, hormonal therapies with androgenic progesterones or testosterone, DHEAS, and anabolic steroids) can induce TE and alopecia.

Anticoagulants (such as coumadin, heparin, heparinoids, and enoxaparin) can produce a TE.

Anticonvalsants (such as Carbamazepine and valproic acid) have been reported to occasionally induce a TE. The suggested mechanism is altered or reduced zinc and selenium levels.

Antidepressants (such as amphetamines, imipramine, desipramine, fluoxetine, sertaline, and dixyrazine) can produce a TE. Lithium induces hypothyroidism and can result in TE and alopecia.

Antifungal drugs (such as fluconazole and ketoconazole in high doses) have induced a reversible TE.

Antiinflammatory drugs (such as chronic NSAIDs) have induced a reversible TE.

Antimitotic drugs used in cancer or as an immunosuppressive can produce an anagen effluvium (acute loss of 80 % scalp hair) and at lower dose can induce a TE.

Angiotensin-converting enzyme inhibitors (captopril and enalapril) can induce TE. The mechanism appears to be binding of zinc, and is reversible with zinc supplements.

B-blockers (such as systemic and topical ophthalmologic proparanol, and metroprolol) can induce a chronic TE and diffuse alopecia.

Estrogen antagonist (such as tamoxifen, SERMS [selected estrogen receptor modifiers], and botanical phytoestrogens) can induce a TE and diffuse alopecia. These are estrogen competitive receptor inhibitors that inhibit estrogen action on the dermal papilla.

Heavy metals such as gold have induced severe alopecia.

Hypervitaminosis **A** can induce alopecia and TE. Vitamin A derivatives to monitor include mega multivitamins, vitamin A supplements, and the oral retinoids.

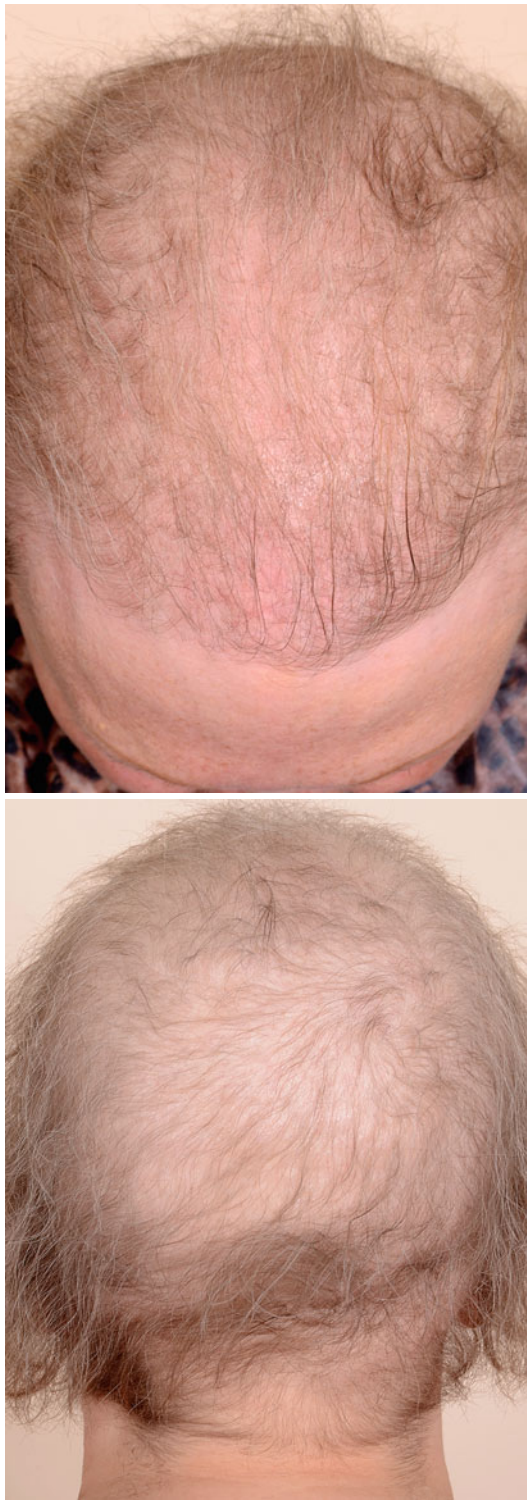
Minoxidil given orally can induce hirsutism, while when applied topically, it can initiate a TE which usually resolves in several months.

Statins to reduce cholesterol (such as clofibrfate, triparanol, and cholestyramine) can produce TE which can be dose-related.

Sulfasalizine and inflammatory bowel disease can induce a TE. At times it is difficult to separate the drug activity from the disease to determine which has induced the TE and diffuse alopecia.

Anagen Effluvium (AE)

AE is when there is an abrupt cessation of mitotic or metabolic activity of the hair follicles in the growing phase, and is one of the most common



Figs. 21.1 and 21.2 Top and back views of a 60-year-old woman with anagen effluvium after 3 weeks of chemotherapy with doxorubicin and cyclophosphamide for breast cancer

Table. 21.2 Drugs that can cause Anagen Effluvium

Commonly associated	Uncommonly associated
Doxorubicin	Vincristine
Daunorubicin	Vinblastine
Paclitaxel	5-Fluorouracil
Docetaxel	Hydroxyurea
Cyclophosphamide	Thiotepa
Ifosfamide	–
Etoposide	–
Mechlorethamine	–
Methotreaxate Bleomycin	–

chemotherapy reactions (~65 %). It is often synonymous with chemotherapy-induced alopecia (Figs. 21.1 and 21.2). The alopecia typically involves the scalp, but other areas like the eyebrows, axilla, and pubic regions can be involved (Rodriguez-Martin et al. 2007). AE is seen more commonly with combination chemotherapy than with single drug use, and the severity is dose-dependent. Various cytotoxic agents have been reported to cause AE (Table. 21.2). Although AE is typically associated with chemotherapy and radiation, exposure to toxic agents like mercury, boron, and thallium can cause AE. Other medications that have been reported to cause AE include bismuth, levodopa, colchicine, and cyclosporine (Rodriguez-Martin et al. 2007). Heavy metals can disrupt hair growth by binding with the sulfhydryl group of keratins in the hair.

Conclusions

Drug eruptions of the scalp most often manifest as alopecia. Alopecia, in our culture, is indeed a major cosmetic problem affecting quality of life. Male and female alopecia patients are difficult to treat. Finding the drug that is causing or exacerbating hair loss is a major contribution to our patients' care.

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Drug Reactions in the Nail in Cutaneous Drug Eruptions

22

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Abstract

Nail disorders can be challenging to diagnose for clinicians and difficult to endure for patients. They encompass a wide variety of pathology and sequelae from direct trauma causing cosmetic deformity and pain, to diffuse changes that may herald an underlying systemic disease, a toxic exposure, or the side effect of a drug. In the setting of drug side effects, cessation of the offending agent may sometimes be curative, however, it may not always be feasible or warranted, such as in the case of chemotherapeutics. Clinicians, who can link nail changes and the mechanism of action/targets in drugs to the appropriate affected components of the nail apparatus, are at an advantage for timely detection and intervention. Nail changes can result from destruction of the epithelium, changes in vascularity, changes in permeability, toxicities, and/or pigmentation. In this chapter we review the reactions manifested by nails in conjunction with potential culpable drugs.

Keywords

Nail plate • Nail matrix • Nail fold • Nail bed • Beau's lines • Onycholysis • Onychomadesis • Photo-onycholysis • Retinoids • Taxanes • Epidermal growth factor inhibitors

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_22

Introduction

Much like the rings in a tree or the rock layers of a cliff, nails serve as a kind of record for the chronology, severity, and type of events that have occurred in the skin and the human body. In this way, nails serve as a biomarker showing signs of disease or exposures. Nail samples can be used in forensic and post-mortem evaluations, as they can be non-invasively collected and analyzed to determine diseases, environmental or occupational exposure, poisoning, drug consumption, ingestion of illegal substances, sometimes even the timing of these events. In order to read the signs manifested by nails, one must first understand their structure, function, and physiology.

As in the case of hair, nails are not solely aesthetic and decorative structures; they serve important evolutionary functions. Some functions are shared between, and some unique to, the upper and lower extremities. The nails on all extremities provide protection to the digits. Nails are also present in other primate species, and predate the human foot. Their continued presence on the lower extremities of humans resulted in a separate adaptation from hands; assisting with the bipedal stride. On the hands, nails assist with grip and manual dexterity. The edge of the nail plate can be used for reach, or serve as a rudimentary pinching tool when combined with the thumbnail. The nails on the hand also provide counter pressure for grasp and manipulation, and improve dexterity.

Diseases of different etiologies can manifest similar nail changes. Thus a checklist of the major disease categories that could possibly affect the nail should be ever present in the mind of clinicians, including: systemic diseases, toxic exposures, nutritional deficiencies, and medications. A thorough clinical history and keen observation are of utmost importance in finding the true nature of each given presentation.

Anatomy and Histology of the Nail

What is often referred to colloquially as "the nail" is in actuality only the nail plate. The nail is a complex apparatus comprised of both anatomically prominent and unseen parts. The nail arises from the dorsal surface of the distal digits (phalanges) of the upper and lower extremities. The nail plate is a flexible yet strong structure composed of densely packed keratinocytes layered perpendicularly to the longitudinal axis of the digit. The nail plate has one free edge known as the free margin. An epidermal recess known as the nail fold surrounds the remaining three edges of the nail plate (Fig. 22.1). The cuticle, or eponychium, arises from the dorsal edge of the nail fold. The nail plate rests upon and adheres to an epithelial surface, known as the nail bed (Figs. 22.2 and 22.3), and extends along the nail bed via accumulation of layers of keratinocyte husks. Upon reaching the distal free edge, the nail plate detaches from the nail bed, forming a shelf over the distal nail bed, creating the hyponychium. The nail plate acquires its keratin from the cells in the nail matrix, a squamous epithelial layer without a stratum granulosum (Fig. 22.4) that lines the proximal third portion of the nail fold invagination (Fig. 22.5). The matrix is composed of two sides, a proximal/dorsal component and a distal/ventral aspect. As the nail fold houses the matrix cells oriented in opposing directions, nail plate production is a separate, but convergent process, whose ultimate product yields the distal/longitudinal extension vector of the nail plate. The dorsal nail matrix produces the dorsal nail plate and the ventral/distal nail matrix generates the ventral half of the plate. The distal nail matrix protrudes as an anatomically prominent, though sometimes hidden, structure known as the lunula. The lunula appears white due to keratinization and is sometimes obscured by the eponychium.

Generalized Nail Changes

Beau's Lines/Onychomadesis

The eponymously named dystrophy was first described in 1846 by Joseph Honore Simone Beau. Beau's lines can be described as a "hiccup" in the mitotic machinery of the nail, the matrix epithelium (Fig. 22.6). A pause or halt of mitotic activity manifests as a depression along the transverse axis of the nail plate. As mitotic activity

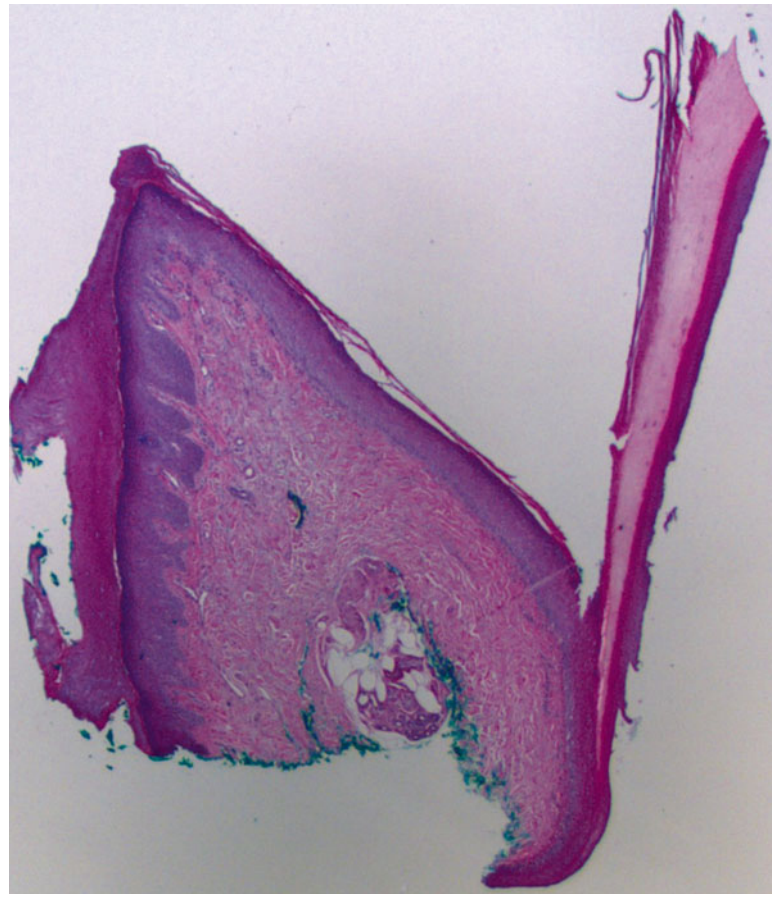


Fig. 22.1 Proximal nail fold epithelium (200×)

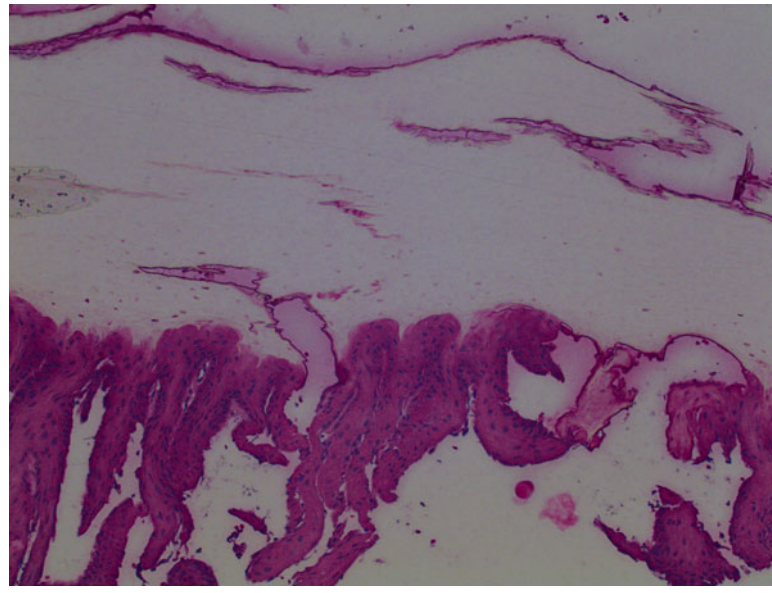


Fig. 22.2 Nail plate with nail bed epithelium (1000×)

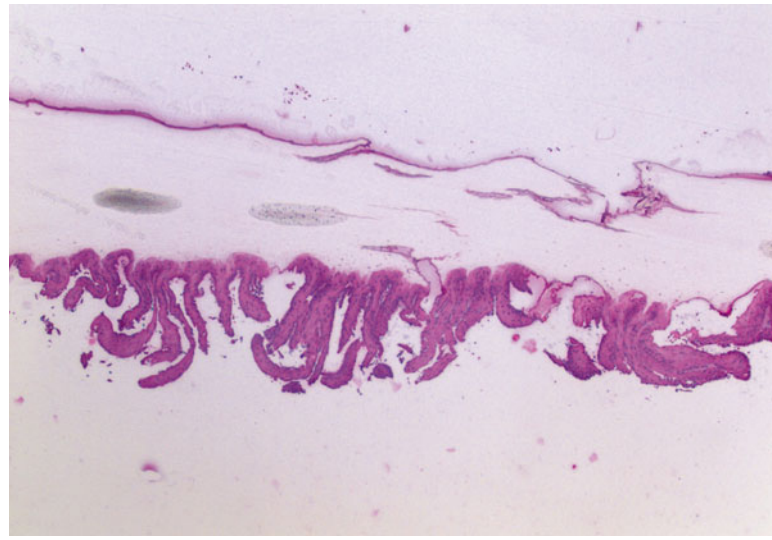


Fig. 22.3 Nail plate with nail bed epithelium (400×)

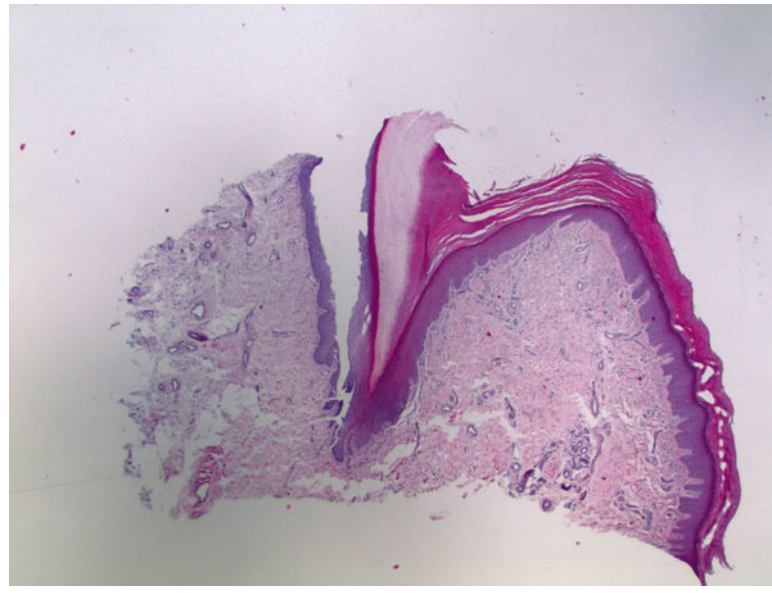


Fig. 22.4 Nail matrix lining the proximal portion of the nail fold invagination (200×)

resumes, the line will progress, as many other nail disorders such as splinter hemorrhages do, as the nail plate extends. The significance of Beau's lines is their ability to document the insult by the depth and length of the depression. Depth indicates the amount of damage to the matrix, and the length of the depression indicates the insult's duration.

Beau's lines can result singly from trauma. Suspicion for a drug-related or systemic cause should arise when Beau's lines arise in multiple, (up to all 20) nails simultaneously, or present with repeated episodes. Beau's lines are most often created by drugs that target the nail matrix epithelium or affect its highly active mitotic turnover. Therapeutic measures most commonly responsible for these events are chemoradiation therapy and retinoids. Theoretically, any chemotherapeutic drug can affect the body's highly active epithelium, such as the gastrointestinal tract or nail matrix.

Onychomadesis is detachment of the nail plate occurring at the proximal nail bed or fold and

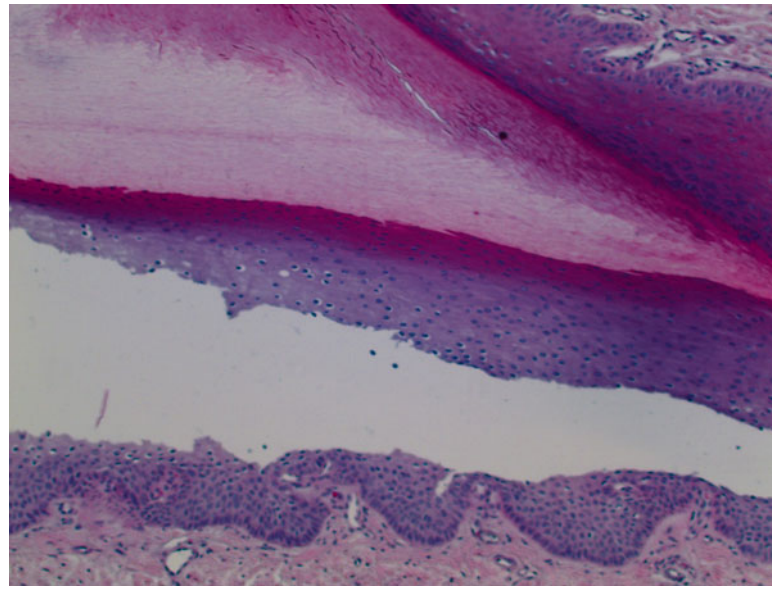


Fig. 22.5 Nail matrix epithelium (1000×)

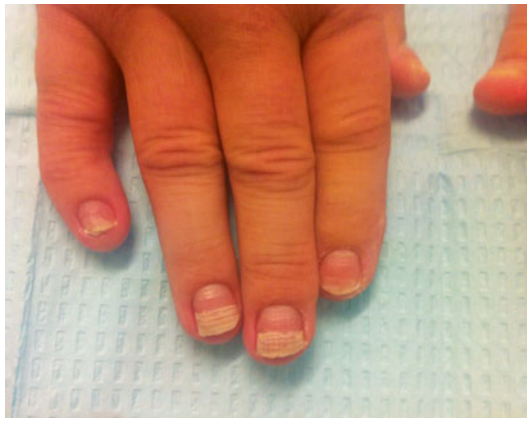


Fig. 22.6 Beau's lines bordering on onychomadesis

subsequent shedding for the nail. Onychomadesis can occur when an insult, such as one creating Beau's lines, is carried to its inevitable conclusion. In this setting, the insult creating mitotic arrest has become severe enough to result in structural instability of the nail plate, and the nail plate is detached while the new nail grows out.

Onychomadesis can occur spontaneously or after infections such as hand, foot, and mouth disease. Drug-induced onychomadesis can be due to a lengthening list of potential causes. Chemotherapeutics and retinoids inducing Beau's lines can also be a cause of onychomadesis. There have also been reports of anticonvulsants such as carbamazepine and valproic acid causing onychomadesis.

While drugs have been well documented to cause onychomadesis, the possibility exists that severe drug allergy can also induce the process via an inflammatory route. Cases have been shown to occur, such as during critical illness. There exists a documented case of onychomadesis occurring following an allergic response to penicillin.

Onycholysis

Onycholysis means the detachment of the nail plate from the nail bed. This process can occur from destruction of the nail bed's viable epithelium or destruction of cell-to-cell adhesion molecules. Onycholysis, in contrast to onychomadesis, occurs distally from the nail bed or hyponychium, rather than proximally at the nail fold and nail matrix. It manifests as transverse white discoloration of the nail and is common in psoriasis.

Onycholysis has been associated with infection, trauma, psoriasis, photo reactions, and drugs (Table. 22.1). Drugs have been shown to cause onycholysis in combination with photo exposure, or as a sole agent. Therapeutics causing onycholysis include tetracyclines, fluoroquinolones, and psoralens.

Table 22.1 Causes/manifestations of onycholysis

Cause	Nail clues
Psoriasis	**Erythematous border** Oil spots, salmon spots, pitting
Lichen planus	Nail thinning and fissuring **Pterygium (winged nails with central groove)**
Connective tissue disease	Proximal nail fold **capillary** abnormalities
Onychomycosis	**Yellow** discoloration/streaks Toenails
Pompholyx	Fingernails, most digits
Tumors	One digit, subungual mass
Drugs	All/most nails **Hemorrhagic changes**
Trauma	Usually fingernails **Transverse leukonychia**
Idiopathic	Usually fingernails Chronic paronychia frequently

Drug-induced Nail Dyspigmentation

A wide range of medications can cause pigmentary changes of the nail, affecting several to all nails. The color changes range from leukonychia (true and apparent) to brown pigmentation. Nail pigmentation may occur from deposition of the drug within either the nail plate or dermis (the latter of which may also be associated with cutaneous and mucosal pigmentation).

Leukonychia

True leukonychia (transverse) results from damage to keratinocytes in the distal nail matrix, which causes failure of maturation and retention of nuclei. Thus, transverse leukonychia occurs from the reflection of light, and is characterized by 1–2 mm transverse bands (each nail can have one or more). Affected nails will present with transverse leukonychia at the same site, indicating simultaneous damage to matrix keratinocytes (Fig. 22.7). The most common cause of transverse leukonychia is chemotherapy agents, most commonly doxorubicin, cyclophosphamide, and vincristine. Other agents include arsenic, fluorine, retinoids, cortisone, sulfonamides, pilocarpine, and trazodone. Arsenic and thallium poisoning will both present with transverse leukonychia involving the entire width of the nail plate.

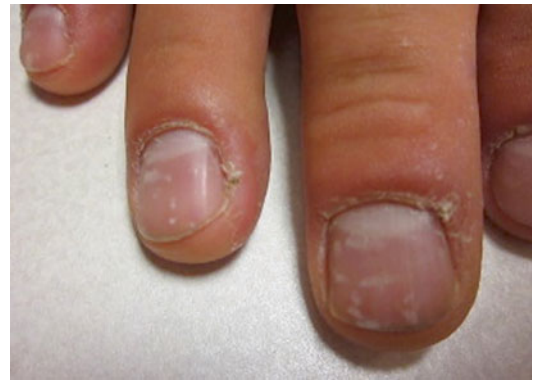


Fig. 22.7 Leukonychia bands on multiple nails

Apparent leukonychia results from drug-induced damage to the nail bed. Alterations of blood flow to the nail bed will cause changes from the normal pink color seen. Half-and-half nails show proximal white discoloration of the nail that blends with the lunula (and distal portion retains the pink color). Muehrcke's lines are transverse white bands that alternate with bands of normal pink colored nail bed (Fig. 22.8).

Muerhcke's Nails

- Multiple paired white transverse lines
- Oriented parallel to the lunula
- Associations: Chronic hypoalbuminemia, nephrotic syndrome

Both leukonychia and Muehrcke's nail changes are asymptomatic, and the mechanism is poorly understood. They occur most commonly during chemotherapy administration and resolve upon discontinuation.

Brown Nail Dyspigmentation (Melanin-Induced)

Drug-induced damage to melanocytes in the nail matrix can stimulate melanin production, particularly in darker-skinned individuals (Figs. 22.9 and 22.10). Longitudinal melanonychia results from stimulation of a small cluster of melanocytes, whereas the entire nail plate

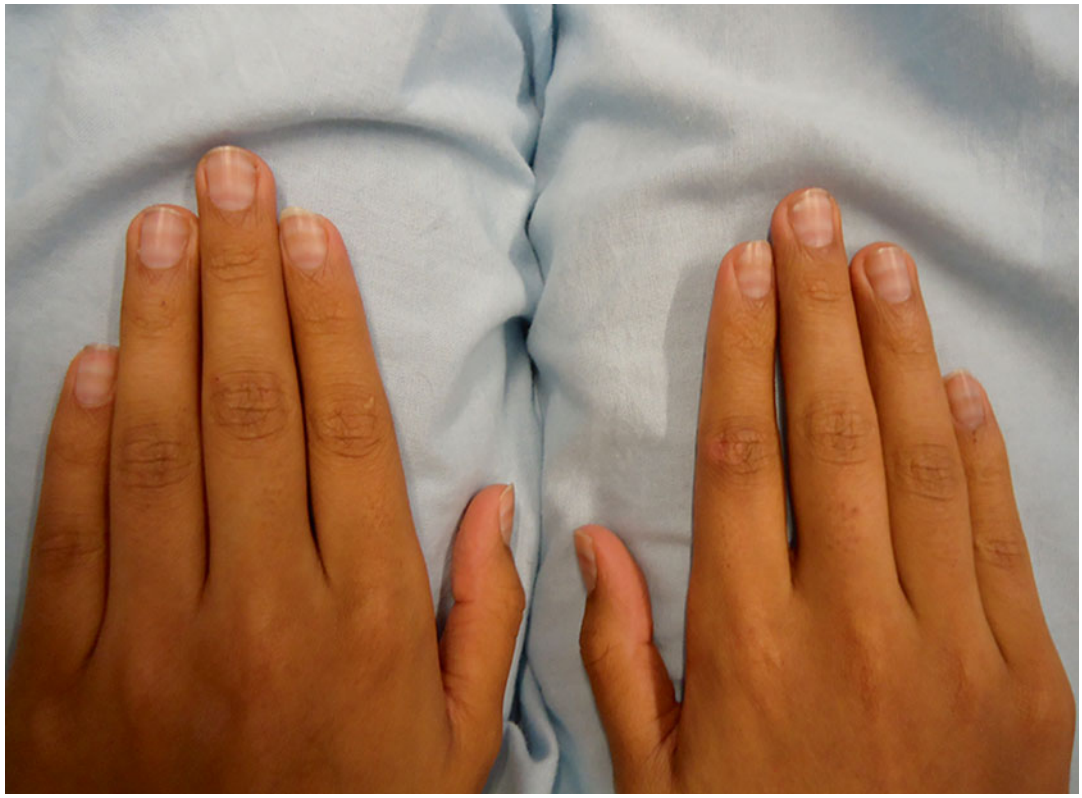
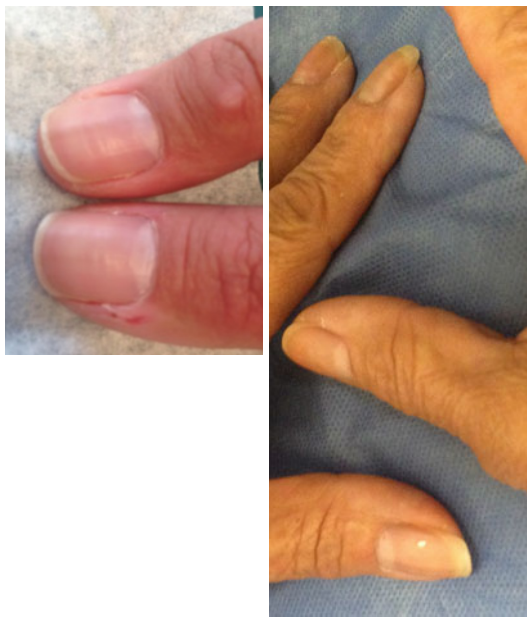


Fig. 22.8 Muehrke's nails showing transverse white bands



Figs. 22.9 and 22.10 Examples of melanonychia

develops pigmentation if there is diffuse melanocyte activation. This is a common side effect of chemotherapy; in fact, repeated cycles can produce transverse leukonychia (suggesting intermittent melanocyte stimulation corresponding to the rounds of chemotherapy). Bleomycin, cyclophosphamide, doxorubicin, daunorubicin, fluorouracil (also lunular pigmentation), and hydroxyurea (also lunular pigmentation) are most commonly associated with melanonychia. Other sources of melanonychia include psoralens, methotrexate, radiation therapy, imatinib, and zidovudine (which can present with diffuse dark brown melanonychia or blue lunula).

Drug-induced melanonychia is generally reversible, though the clinician should be aware that it can takes years after cessation of the offending drug for melanin production to stop. This has to be distinguished from melanoma of the nail unit (subungual melanoma) that also

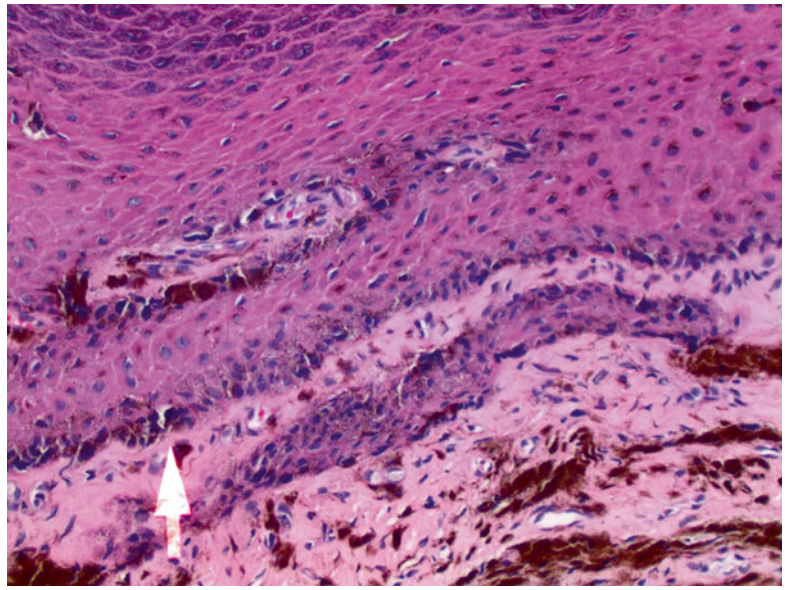


Fig. 22.11 Melanoma of the nail bed. *Arrow* shows contiguous proliferation of Hyperchromatic, enlarged melanocytes in the nail bed epithelium

presents with melanonychia (Fig. 22.11). The clinical presentation with the irregular pigmentation and involvement of the adjacent nail fold (Hutchinson sign) can help to distinguish melanoma from drug-induced pigmentation. In clinically ambiguous cases, a biopsy of the nail matrix and nail bed can be useful.

Non-Melanin-induced Nail Dyspigmentation

Drug excretion of deposition within the nail plate can cause pigmentation changes independent of melanocyte stimulation. Discoloration occurs in the nail plate and/or the nails (Tables. 22.2 and 22.3).

Table 22.2 Exogenous agents causing discoloration of the nail plate

Agent	Discoloration
Mercury products	Gray-black
Resorcinol	Brown
Vioform	Yellow
Picric acid	Yellow-brown
Nicotine	Yellow-brown
Hair dyes	Black
Photographic developer	Yellow-brown
Hydroquinone	Orange-brown

Adapted from Favaro PC. *Metrology of Nail Clippings as Trace Element Biomarkers*. Copyright © July 2013. Delft University Press. Delft, The Netherlands

- Yellow nail discoloration may be seen in patients treated with tetracycline and gold salts. Valproic acid has also been reported to cause yellow nail changes, though the mechanism is unclear.
- Dark brown dyspigmentation occurs with clofazimine deposition within the nail plate.
- Lead and silver can also deposit within the nail plate to cause diffuse nail pigmentation (or, in the case of silver, localized to the lunula).
- Dermal deposition of pigment (from the drug itself, melanin, or hemosiderin) can give the appearance of subungual dyspigmentation, which does not grow out with the nail (since the skin is affected, not the nail apparatus).
- Minocycline and other tetracyclines have been associated with blue-gray dyspigmentation of this nature (Fig. 22.12), with sparing of the lunula.
- Antimalarials are known to cause gray, blue, or brown nail pigmentation.

Paronychia/Pyogenic Granulomas

As the nail fold and nail plate create a tightly bound and adherent structure, disruption of the cells' ability to adhere, or their alignment, can

Table 22.3 Endogenous agents causing discoloration of the nail

Agent	Discoloration	Location
Tetracyclines	Yellow-brown	Nail plate
Antimalarials	Blue	Nail plate, bed
Aresenic	White bands	Nail plate
Chlorpromazine	Blue-black	Nail bed
Phenolphthalein	Gray-black	Lunula
Gold salts	Black-brown	Nail plate
Cytoxic drugs: bleomycin, doxorubicin, cyclophosphamide, melphalan, 5-fluorouracil	Horizontal or vertical brown-black bands	Nail bed and/or nail plate

Adapted from Favaro PC. *Metrology of Nail Clippings as Trace Element Biomarkers*. Copyright © July 2013. Delft University Press. Delft, The Netherlands

Fig. 22.12 Blue-gray nail discoloration due to minocycline

produce recesses and potentially exposed areas for infection to develop. Paronychia often arises concurrently with peri- or subungual pyogenic granulomas.

Pyogenic granulomas are nodular lesions consisting of excessive granulation tissue. Commonly they arise due to hormonal stimulation during pregnancy, often on the gums or nose. Pyogenic granulomas are known to arise in or along the nail. The presenting symptom for a patient can often be painful pyogenic granulomata or paronychia interfering with daily acts of living. Occasionally the morbidity of these sequelae can be severe enough to alter drug therapy. Drugs known to cause pyogenic granulomas include retinoids, epidermal growth factor receptor (EGFR) inhibitors, and taxanes.

For the clinician, the importance of distinguishing the conditions can alleviate patients' pain and help them potentially tolerate their chemotherapeutic regimen through completion. Pyogenic granulomas are not only painful, but can become friable and bleed. They are known to regress with cessation of the offending drug, but can also persist. Recurrences occur often if the culprit drug is not altered. Drainage of abscesses (with organisms cultured often being Staphylococcus aureus and Streptococcus pyogenes), antibiotics, and supportive care with soaks are the best forms of therapy. In cases of lesions secondary to EGFR inhibitors, topical or intralesional steroids as well as topical retinoids such as adapalene have been used with some success.

Alterations of Blood Flow

The potential to obstruct the blood flow feeding the nail apparatus exists with certain drugs. Nonselective beta-blockers such as propranolol can produce digital ischemia with synergistic effects of reduced cardiac output and peripheral vasoconstriction. In this setting, the entirety of the nail apparatus and potentially distal digits can suffer as a result of Raynaud's phenomenon. When this occurs, the distal tissues suffer from necrosis and may not recover or respond to withdrawal of the offending agent.

In contrast to ischemia, hemorrhages in the nails vary in severity and etiology (Fig. 22.13). Splinter hemorrhages are common, and range in cause from trauma to endocarditis. Blood thinners raise the general risk of hemorrhage, but for specific subungual hemorrhage/hematomas, the taxanes are well known to cause these phenomena, with up to 80 % of patients developing them. Similarly to the regional architectural disruption caused by pyogenic granulomas, subungual hemorrhages can affect the daily activities of 25 % of

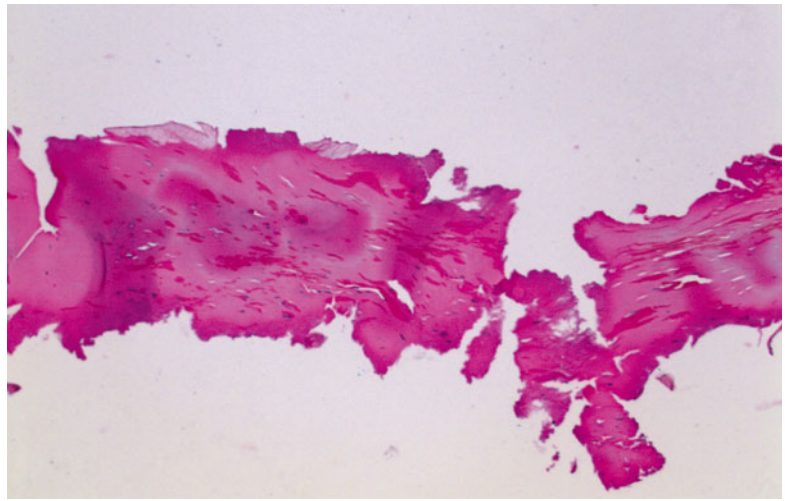


Fig. 22.13 Hemorrhage in nail plate (1000×)

Table 22.4 Types of retinoids

Natural	Synthetic
Retinol	Tazarotene
Tretinoin	Adapalene
Isotretinoin	
Retinyl-palmitate	

patients receiving taxanes through pain and in 33 % lead to infection. In the case of hemorrhages, however, they are dose- and exposure-related and abate after therapy cessation.

Common Nail-altering Drug Classes

Several drug classes exist with notoriety for commonly causing one, or potentially multiple, types of nail reactions. Significant and routine classes of drugs within this category will be discussed.

Retinoids

Retinoids are formed by manipulation of vitamin-A. Retinoids can be found as natural or synthetic varieties (Table 22.4). As a whole, they are a success in numerous respects, including therapeutic applications and formulation availability. Availability and usage of retinoids ranges from over-the-counter cosmeceuticals (usually containing retinyl-palmitate) to the prescribed tretinoin (all-*trans*-retinoic acid) and isotretinoin. The disease targets of retinoids are numerous and include recalcitrant acne, acute promyelocytic leukemia, and psoriasis.

Most retinoids' effects take place in the cell nucleus where they activate transcription through interaction with the vitamin A receptor. However, some synthetics can function outside vitamin A pathways. Vitamin A is essential to the development and maturation of epithelial and other high-turnover tissues, and especially maintains balance for the keratinizing epithelium.

Retinoids, however, prove to be a double-edged sword. While they are widely useful in their respective treatment applications, retinoids have been implicated in several types of nail disorders, such as Beau's lines and onychomadesis (discussed previously). Retinoids' mechanism of enhancing repair or differentiation results in definitive documentation of their ability to induce granulation tissue throughout the body, although the exact mechanism is not known. Nails are one tissue where pyogenic granulomas, or granulation tissue, can develop. The lesions often appear on the lateral or proximal fold. Isotretinoin reexposure to the drug results in reappearance of the lesion, linking the agent and reaction.

Chemotherapeutics

The mechanisms of chemotherapeutic agents vary widely. Epidermal growth factor receptor (EGFR) is a tyrosine kinase oncoprotein, whose

Table 22.5 Grading scale for adverse events in nails with EGFRI therapy

Adverse event	1	2	3
Nail changes	Discoloration Ridging Koilonychia Pitting	Pain in nail beds Partial or complete loss of nails	Changes interfering with activities of daily living

overexpression is implicated in malignancies of multiple tissues. EGFR is expressed on epithelial tissues, among others. Inhibition of this receptor can stymie tumor progression and when this involves a widely expressed molecule, side effects of inhibition are predictably abundant.

EGFR in skin transmits signaling for keratinocyte differentiation and survival. Thus inhibition halts differentiation and development and promotes apoptosis. In the nail, patients often develop paronychia, desquamation, xerosis, and pyogenic granulomata. Onycholysis has also been observed but as a secondary result of significant local inflammation or infection. Notable EGFRIs include cetuximab, erlotinib, panitumumab, and lapatinib.

Analyses have shown that the EGFRIs have a relative risk of nail toxicity as compared to control of 76.94. The mechanism of nail toxicity from EGFRIs is still unknown and may have more to do with the surrounding tissues affected than the nail apparatus itself. Onset of events occurs between 1–4 months following initial treatment. With this extended timeframe, secondary infection from fungal or bacterial organisms may occur. Successful treatment with minocycline has occurred however, as stated previously, the tetracyclines also have well documented nail reactions. Adverse events in nails with EGFRI therapy are prevalent enough to warrant a grading scale for changes (Table 22.5).

Taxanes present another class of chemotherapeutics widely used and also have adverse effects on nails. The original taxane synthesized from the yew trees in the genus *Taxus* is paclitaxel; its name stemming from its synthesis of the pacific yew tree bark. Docetaxel, a later semi-synthetic derivative from the European yew leaves, was developed following scarcity of tree supply. The two drugs function similarly and with comparable efficacy. Their mechanism of action is inhibiting depolymerization of microtubules and cell cycle arrest.

By the nature of their mechanism alone, the taxanes have the potential to affect the nail apparatus from multiple fronts. Paclitaxel is shown to induce onycholysis and docetaxel has been implicated additionally in Beau's lines/onychomadesis, subungual hemorrhages, and hyperpigmentation.

Elemental Toxicities and Deficiencies

The nail can serve as a window for underlying disorders of trace elements, posing complex questions for investigation for clinicians and forensic pathologists. Unlike drugs, which are hopefully documented in the medical record, elements may simply become toxic via undisclosed exposure in the environment or in a patient's diet. In the case of diet, a thorough clinical history accounting for vitamin and herbal supplements as well as medications can be helpful. Further complexity can arise, however, as some elements are essentially required in trace amounts and may present in a patient as a deficiency rather than an excess. Some investigators have employed mass fractions or concentrations of elements, e.g., cadmium, lead, mercury and arsenic, in nail and hair samples as markers for certain exposures, and of these selenium has been the most described and utilized.

Selenium is a trace element with a dietary reference intake of 55 μg per day and a tolerable upper intake level of 400 μg per day. There is a fine line between toxicity and requirement, especially in the era of vitamin supplement fads. Deficiency is less common, however, it is still sometimes seen in patients with gastrointestinal conditions that cause poor absorption. Selenium has multiple biological roles as an enzymatic cofactor and incorporation into amino acids. It is used as a cofactor for antioxidation reactions by the glutathione peroxidase family of enzymes and as a cofactor for reactions that interchange

thyroid hormone forms. Additionally, selenium can incorporate into cysteine to form selenocysteine, and in this form can be integrated in part of the cytokeratin structures such as hair and nails. This property is both a reason for the deleterious symptoms of selenium toxicity and deficiency as well as a method by which to identify and track these states and selenium levels.

Deficient and toxic states of selenium both cause damage to nails and have multiple systemic manifestations. Both states have an impact on hair and nails, and low selenium levels are thought to increase the risk of prostate cancer, while high levels have been thought to impose a risk for melanoma. Selenium deficiency, when present, is generally seen in settings of gastrointestinal disease (e.g., Crohn's or other syndromes causing impaired absorption), or in patients receiving parenteral nutrition and infants with selenium-deficient formula. For a healthy person, selenium is present in a wide range of foods, e.g., nuts, fish, meat, and eggs. The true leukonychia characteristic of the deficiency on exam has been seen in patients after bowel resections, and these cases responded to selenium supplementation. In addition to leukonychia, Terry's nails (opaque white discoloration of proximal portion of the nail obscuring the lunula), and hypopigmentation of skin and hair (pseudoalbinism) have been observed in low-selenium states.

Selenosis has become a more conceivable diagnosis with the rise of the supplement industry. A national recall of supplements occurred in the United States in 2008 due to incorrect levels of selenium found in a brand of supplements. Case reports of patients with selenium toxicity were documented at this time and shown to present with Mee's lines (classically seen in the setting of metal toxicities, e.g., arsenic or thallium as per above) and alopecia. In severe cases, nail and hair brittleness and/or loss have been accompanied by nausea, abdominal pain, diarrhea, irritability, and peripheral neuropathy. It should be noted that brittle nails can also be a sign of imbalances in multiple different nutrients including zinc, biotin, protein, and iron deficiencies, in which case nails may also take on a spoon-shape morphology known as koilonychias

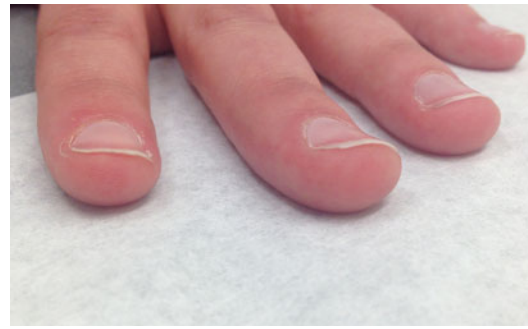


Fig. 22.14 Spoon-shaped nails signify koilonychia

(Fig. 22.14); thus brittleness of the nail is not a specific diagnostic sign, but rather an indicator that nutritional imbalances may be considered and investigated.

Determining a patient's selenium levels as well as several other elements such as mercury and arsenic depend not only on nail changes, but on nail sampling as well. While blood and urine tests may impart more immediate information on elemental levels in the body, nails can provide a long-term picture of levels and exposure. Nail clippings offer patients a less-invasive manner of specimen submission for testing.

Conclusions

Nails are a vital evolutionary adaptation for humans that tell a story of what the body has endured, and they serve as sentinels for medical diagnoses In being highly visible to patients and clinicians, and accessible for examination grossly, biochemically, or histologically, nails impart the opportunity to make a timely diagnosis of underlying problems. Their growth pattern and durable structure (even when damaged) provide a long-term assessment of a patient's history and exposures to various agents, especially drugs. Nail changes can overlap, and thus provide a difficult diagnostic picture when presented alone. Clinicians with knowledge of the potential differential diagnoses indicated by these changes can intervene more quickly, and potentially impact the course of local and systemic disease.

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Part IV

Life-Threatening Skin Drug Reactions

Drug Eruptions and Erythroderma

23

Yuri T. Jadotte, Robert A. Schwartz, Chante Karimkhani, Lindsay N. Boyers, and Shivani S. Patel

Abstract

Erythroderma, also known as generalized exfoliative dermatitis, manifests as widespread scaling and erythema of most of the body's cutaneous surface. Other than an apparent predilection for males, the disease occurs no more or less commonly in any other specific subsets of the population. Its etiology is highly variable, although the most common cause is a drug eruption, flare of a pre-existing dermatologic condition or lymphoma or other cancer. It may occur secondary to systemic use or topical application of the medication. Other causes may include infections, particularly in immunocompromised patients, excessive exposure to solar radiation while taking photosensitive drugs, and malignancy. Erythroderma is potentially life threatening, due to the severe associated hemodynamic and metabolic complications. The diagnosis of this disease is made clinically. Histological findings tend to be non-specific. Treatment of hemodynamic instability should be given precedence to reduce mortality, followed by rapid identification of the underlying cause of disease, as this relates directly to the prognosis of the condition as well as the likelihood of resolution from cessation of the offending agent or treatment of the underlying disease.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_23

Keywords

Erythroderma • Exfoliative dermatitis • Generalized erythroderma • Drug eruptions • Erythema • Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

Introduction

Erythroderma comes from the Greek words "erythro" and "derma," meaning "redness" and "skin," respectively. It is a condition that is also known as generalized exfoliative dermatitis, generalized erythroderma, or erythrodermatitis. This disease manifests as widespread scaling and erythema of 90 % or more of the body's cutaneous surface, involving substantially abnormal skin metabolism that may have major implications for morbidity and mortality. It is due to massive dilation of cutaneous capillaries throughout the body, followed by diffuse exfoliation or peeling of the epidermis. The challenge with erythroderma is twofold: first, it is a nonspecific cutaneous manifestation that is not due to any single disease, but instead may be associated with a wide variety of underlying conditions. It is usually due to a flare of a preexistent skin disorder, a drug eruption, a lymphoma or other cancer, or is classified as idiopathic. This includes cutaneous conditions and systemic diseases, as well as causes which originate from within the body and those that are external to it. Therefore, the presence of erythroderma requires the initiation of a systematic search for, and the prompt identification of, a specific causative factor. Second, treatment of hemodynamic instability resulting from erythroderma, as well as any potentially life-threatening infections, must occur simultaneously as, or even prior to, a thorough search for the identification of the underlying causative agent, in order to reduce the risk of mortality. In essence, this condition is a dermatologic emergency, and both diagnosis and management must occur simultaneously. In addition, erythroderma is commonly precipitated by a reaction to drugs taken either systemically or used topically, which is the focus of this chapter.

Epidemiology

The epidemiology of erythroderma has been examined, but the true incidence and prevalence of the disease remains unknown, as the epidemiological evidence is not robust, and no systematic reviews have been conducted on this evidence. Studies suggest that the incidence of the disease may be as low as 0.9 per 100,000 persons to as high as 35 per 100,000 persons, but there are no particular geographic patterns of distribution of the incidence of this disease. Also, there is little to no epidemiological evidence on the prevalence of erythroderma in the published literature. However, the disease is thought to occur more often in men, with male to female ratios as low as 2:1 and as high as 4:1. It also appears to be more common in adults than in children, with the typical age ranging from 40–60 years or older. The reason for the greater association of erythroderma with male gender or middle-to-older age is unclear. The epidemiological evidence on the geographical prevalence of erythroderma is unclear; however, multiple case studies and case series have documented occurrence in diverse populations spanning all continents. Also, the global burden and impact of this disease on the quality of life and survival of patients worldwide has not yet been studied.

Etiology

Erythroderma is a constellation of signs and symptoms that are highly non-specific and indicative of a number of underlying diseases, although the patterns of signs and symptoms can facilitate the identification of an etiologic agent. The most common drugs that can precipitate erythroderma are listed below. Table 23.1 presents some of the underlying conditions that may be associated with the disease. They range from dermatologic conditions limited

Table 23.1 Potential underlying diseases associated with erythroderma

Diseases commonly associated with or preceding erythroderma[a]
Dermatologic diseases
Psoriasis
Atopic dermatitis
Pityriasis rubra pilaris
Contact and other types of dermatitis
Dermatophytosis
Ichthyosis
Pemphigus foliaceus
Systemic diseases
Lymphoma: CTCL, Large cell, Hodgkin's
Leukemia
Carcinoma (of blood vessels, thyroid, lung, esophagus, colon, liver or prostate)
Dermatomyositis
Hepatitis
Renal insufficiency
Immunodeficiency (acquired or congenital)
Histoplasmosis
Toxoplasmosis
Lupus erythematosus
Thyrotoxicosis
Sarcoidosis
Graft-versus-host disease
Hyper-eosinophilic syndrome

[a]Conditions that are more commonly associated with erythroderma are in **bold** lettering

to the epidermis, to those involving the dermis and subcutaneous tissues, as well as systemic diseases for which erythroderma can be a cutaneous manifestation. Psoriasis and atopic dermatitis are often associated with erythroderma. However, it is unclear whether this association is truly reflective of an inherent pathophysiologic link between these two diseases and erythroderma, or whether it is due to the greater prevalence of these diseases in general. For example, eczema is well known to be the most common dermatologic disease in the world and has been rated as having the highest impact on patients' quality of life. In some cases of erythroderma, an underlying condition is not found and the disease remains idiopathic. In children without pre-existing dermatoses (such as atopic eczema), drugs are the most commonly responsible etiologic agents.

Drugs Commonly Associated with Erythroderma

- Antihypertensive medications: beta-blockers
- Antibiotics: bactrim (trimethoprim-sulfamethoxazole), tobramycin, vancomycin, penicillin, gentamycin, cefoxitin
- Antifungals: ketoconazole, griseofulvin
- Calcium channel blockers: nifedipine
- Proton pump inhibitors: omeprazole
- H2 blockers: cimetidine, ranitidine
- ACE inhibitors: captopril
- Anti-tuberculosis medications
- Carbamazepine
- Phenobarbital
- Paracetamol
- Lithium
- Plaquenil
- Antimalarials

Given this broad-based etiology, evaluation of a patient presenting with the signs and symptoms of erythroderma must include a systematic search for potential etiologic agents, which most often are drugs or pre-existing dermatoses. Other common categories of diseases that may manifest as erythroderma are cutaneous and internal malignancies, such as mycosis fungoides and cancers of the GI tract, respectively. Patients with pre-existing psoriasis can develop erythroderma secondary to the withdrawal of topical or systematic steroid treatments. Thus, it is important to not only identify whether the patient began a new drug regimen recently, but also to assess whether a drug has been ceased recently.

Drug reactions may initially consist of morbilliform, urticarial, or lichenoid rashes that eventually coalesce to present as generalized erythroderma. This pattern may be a tell-tale sign that a drug is the etiologic agent in those cases. Other patterns in the development of erythrodermic symptoms and signs may be telling as well. For example, patients with erythroderma due to underlying malignancy will likely present with a history of gradual onset of skin manifestations, combined with recalcitrance from standard therapeutic approaches and progressive decompensation (as opposed to the rapid decompensation

Table 23.2 Molecular mechanisms implicated in the pathogenesis of erythroderma

Marker	Mechanism of action	Associated clinical and prognostic findings
VCAM-1, ICAM-1, E- and P-selectins	Cellular adhesion	Increased expression, leading to increased dermal and epidermal inflammation
Th1 (Helper T-Cells)	Type 4 hypersensitivity reaction	Increased dermal inflammation
Interleukin 1, 2, 8	Inflammatory cytokines	Increased epidermal mitosis and turnover

which is more typical of drug-induced erythroderma). Moreover, mucosal involvement suggests the presence of toxic epidermal necrolysis (TEN), which is life-threatening and must be identified and treated immediately. It is usually due to a hypersensitivity-induced reaction to an offending drug. TEN often has cardiac, pulmonary, renal, and ocular complications, which can also help identify the etiology of the disease. Lastly, some herbal preparations or non-traditional medical treatments may cause this disease; however, the body of evidence to support this claim is unclear at this time.

Pathogenesis

The molecular pathogenesis of erythroderma remains elusive. However, a number of key changes have been noted. Table 23.2 lists some of the biochemical changes that have been documented in histologic samples from patients with erythroderma. Note that all of these histologic changes are relatively non-specific and are unlikely, at this time, to be useful for making a diagnosis of erythroderma. However, they may be useful in diagnosing an underlying dermatosis if one is present. Given the lack of evidence on their effectiveness as diagnostic or prognostic markers at this time, use of these biochemical changes in the management of erythroderma is not recommended.

Clinical and Histologic Manifestations

Erythroderma begins as erythematous and pruritic patches distributed throughout the body, which progressively or rapidly coalesce to involve 90 % or more of the cutaneous surface. The skin of these patients appears shiny, which is indicative of extensive dermal edema, and is typically bright red, suggesting widespread dilatation of dermal capillaries. The patient may complain of dryness and the feeling of having tight skin. The patient may also experience severe pruritus. Further physical examination typically reveals that the skin is warm to touch, with diffuse scaling throughout the body. Scaly patches may be present on the face, scalp, trunk, arms and legs, as well as the palms and soles. In some cases, the "nose sign" may be present, which occurs when the nasal and paranasal regions are not affected. However, this is not a diagnostic sign. Patients with drug eruption-related erythroderma may demonstrate evidence of leukonychia. Prolonged erythroderma may result in permanent hair loss throughout the body (alopecia) severe nail dystrophic changes, and coarse induration of the skin. Dark-skinned individuals may also exhibit widespread hypopigmentation.

Since the disease is commonly associated with, or precipitated by, an underlying cutaneous disorder, the above signs and symptoms may occur in confluence with evidence of the other disease. For example, patients with erythroderma associated with pre-existing psoriasis will experience the above, as well as psoriatic plaques (Fig. 23.1). Gotron's papules, muscular weakness, and the classic heliotropic rash may be seen in patients with underlying dermatomyositis. Some patients may experience erythroderma in the context of the drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (Fig. 23.2). The "red man syndrome" can present as a result of rapid intravenous infusion of antibiotics, particularly vancomycin, and consists of the acute appearance of an intensely erythematous rash that presents as erythroderma (Fig. 23.3). The erythema in red man syndrome

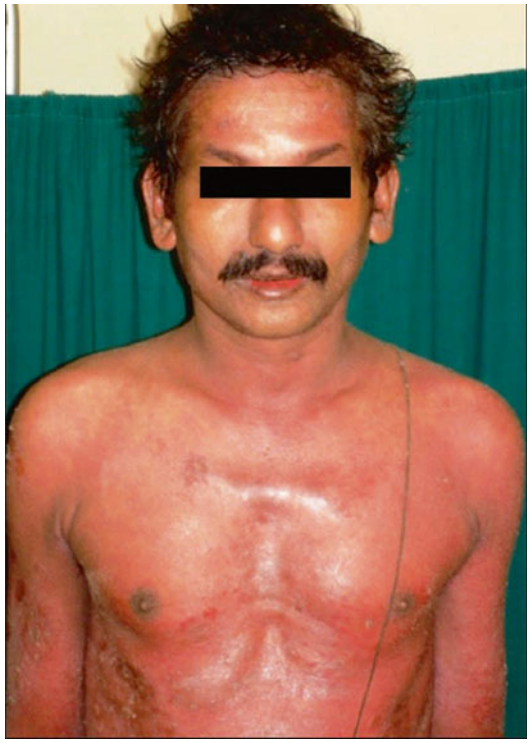

Fig. 23.1 Generalized erythema prior to exfoliation. (Hulmani M, NandaKishore B, Bhat MR, Sukumar D, Martis J, Kamath G, et al. Clinico-etiological study of 30 erythroderma cases from tertiary center in South India. *Indian Dermatol Online J*. 2014; 5(1):25–9. Figure 1, Psoriatic erythroderma, p 26. Used with permission: open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported)

tends to be continuous from the point of infusion, which is different than the appearance of the disease in other conditions, although this is certainly not a specific sign.

Histological findings are usually non-specific and can include hyperkeratosis (manifesting clinically as extensive scaling), parakeratosis and acanthosis (with lead to peeling of the epidermis), as well as a perivascular lymphocytic infiltrate. Eosinophilia can be present within the context of leukocytosis. The presence of this finding with other systemic symptoms (especially hepatic disease) is characteristic of the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. syndrome. Serum albumin may also be low, which may contribute to the hemodynamic instability of the patient.

Diagnosis and Prognosis

The diagnosis of erythroderma is clinical. Patients who present with the aforementioned clinical signs and symptoms have this disease; the appropriate management steps should be taken. However, a concerted effort must also be made to identify the underlying causative agent, which can be a drug, a pre-existing dermatosis, or both. The previous list and Table 23.1 present the most common drugs and dermatoses associated with erythroderma. The prognosis of this disease is directly correlated with the underlying etiology. Patients who develop drug-induced erythroderma experience a rapid onset of the disease, followed by prompt resolution if the offending agent is stopped. The disease may also progress fairly rapidly in patients with contact allergies or with toxic shock or scalded skin syndrome. Patients with chronic dermatoses, such as psoriasis and atopic dermatitis, may experience a slower progression, as well as greater recalcitrance.

The most common causes of death in patients with erythroderma relate to the metabolic and hemodynamic imbalances that result from capillary dilation, which include protein, electrolyte, and fluid loss. Increased and widespread vasodilation can also lead to hypothermia, which may precipitate the emergence of a compensatory hypermetabolic state in which the body increases production of energy while depleting cellular energy reserves. All of these, in turn, increase the risk of heart failure as well as septicemia, both of which are more likely to occur in elderly patients. Some patients may die of pneumonia. However, erythroderma may be linked with serious, possibly fatal visceral involvement in the DRESS syndrome. For example, a patient with erythroderma with fulminant hepatitis would be classified as DRESS syndrome.

Management

The therapeutic approach for erythroderma is twofold. First, the management of erythroderma depends on identification of the etiologic agent. However, there are some basic steps that must be initiated regardless of the suspected etiologic agent.

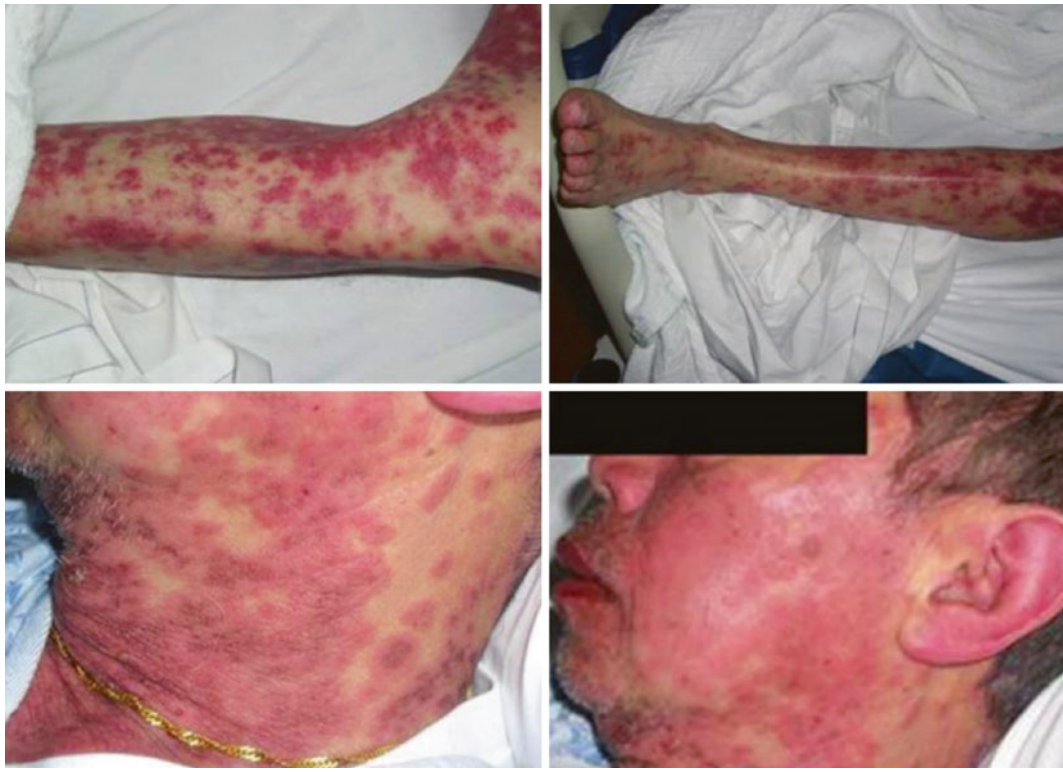

Fig. 23.2 Erythematous macules and plaques over the lower extremities in top two photos. There is more confluence of the patches and plaques on the side of the neck in the lower left image, and on the lower right the redness and desquamation are becoming more generalized. (Kaswala DH. Drug rash with eosinophilia and systemic symptoms syndrome due to anti-TB medication. *J Family Med Prim Care.* 2013;2(1):83–5. Figure 1, Rash, p 84. Used with permission: open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported)

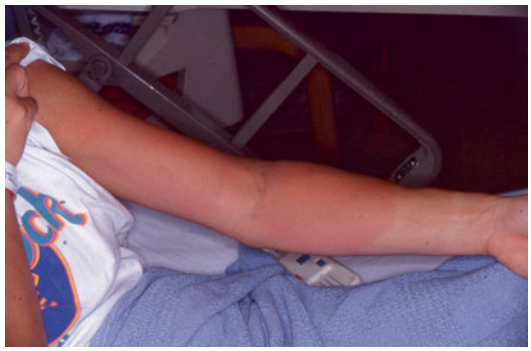

Fig. 23.3 Blanching erythema seen most often related to vancomycin infusion

These include: close monitoring of vital signs and the patient's weight and fluid intake, hepatic and renal function tests, serum electrolytes and complete blood count with lymphocytic differentiation, as well as electrocardiograms and chest X-rays. These baseline tools are used to monitor the patient's current status and provide an initial assessment of the most immediate therapeutic approaches to take. For example, a chest X-ray suggestive of pneumonia or other pulmonary or cardiac abnormalities should also be explored, particularly if potentially life-threatening (i.e., evidence of cardiomegaly which could be indicative of heart failure). Other diagnostic tools may be used selectively depending on clinical suspicion. For example, a history of gradual onset erythroderma should prompt a work-up for possible malignancy, including stool for occult blood, rectal exam, and computed tomography scan. Skin cultures or KOH prep of skin scrapings should be performed if bacterial infection or scabies are suspected, respectively. HIV testing is appropriate if the patient presents with low white blood cell count and possible evidence of opportunistic infections.

Once a diagnosis is made, treatment should be geared toward the associated disease, with the expectation that erythroderma will resolve complementarily. Given that erythroderma can be associated with dozens of underlying dermatoses and systematic diseases, all of which require a different therapeutic treatment, the management of each of these diseases is well beyond the scope of this chapter. More importantly, however, it is critical to address the patient's hemodynamic and metabolic instability immediately, as these are the most life-threatening complications of erythroderma. Preferably, the patient should be hospitalized, as this is a dermatologic emergency.

The acute treatment of erythroderma is the same regardless of etiology and consists of: maintaining normal fluid balance with intravenous fluids, promoting proper skin moisture and temperature, and applying mild topical corticosteroids to reduce inflammation and associated pruritus. Topical antimicrobials may be applied if there is suspicion of an infectious etiology. The initiation of a high-protein diet is recommended to help address protein loss from the skin. All medications that are not absolutely essential should be withdrawn during the acute phase of the management of erythroderma. Once hemodynamic and metabolic stability have been achieved, treatment for the etiologic factor may be initiated.

Conclusions

Exfoliative dermatitis is one of the potentially life-threatening skin diseases. Drugs are a frequent cause; a drug allergy should always be considered in the differential diagnosis of these patients. All medications should be initially stopped, if at all possible, especially those commonly associated with this condition. Unfortunately, good clinical judgment, patient history, drug history in the general population, and consideration of cross-reactivity are our only tools in assessing the possible drug cause. A definitive test to determine the cause of this disease is sorely needed in this group of challenging patients. One should also watch for visceral involvement, since erythroderma may be part of the DRESS syndrome with potentially fatal liver, cardiac or other visceral involvement.

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Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

24

Natasha Klimas, Josephine Quintanilla-Dieck, and Travis Vandergriff

Abstract

Erythema multiforme in its most extreme form has traditionally been divided between toxic epidermal necrolysis and Stevens-Johnson Syndrome. These two life-threatening skin diseases are now considered part of the same spectrum of disease. They can be differentiated by clinical and histological criteria. We can also now predict which patients are apt to have the most guarded prognosis. Treatment by multiple agents is imperfect, but offers a better chance of a good outcome than ever before.

Keywords

Immune memory • Histocompatibility complex • Apoptosis • "Target" lesions • "Wet paper" appearance • Asboe-Hanson sign • IVIG • Plasmapheresis

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute, life-threatening mucocutaneous reactions characterized by epidermal necrosis and detachment of differing severity, which are drug-induced in most cases. SJS is defined by <10 % body surface area (BSA) of involvement, SJS–TEN overlap by 10–30 %, and TEN by >30 %.

Epidemiology

TEN and SJS are rare disorders, with an incidence of 0.4–1.2 per million person-years for TEN and 1.2–6.0 per million person-years for SJS. Both

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_24

reactions are more common with increasing age. TEN and SJS occur more frequently in females, with a female-to-male ratio of 1.5–1.

Immunocompromise predisposes individuals to SJS and TEN. Patients with AIDS are at a 1,000-fold increased risk for TEN compared to the general population. Those with connective tissue diseases and malignancies are also more susceptible to SJS and TEN. Ninety-five percent of SJS/TEN cases are associated with medication use. Risk is highest during the initial 1–3 week(s) of therapy, but extends into the 8 week following drug exposure. In rare cases, SJS/TEN may also be induced by measles-mumps-rubella vaccination and microbial pathogens such as *Mycoplasma pneumonia*, dengue virus, and cytomegalovirus (CMV).

More than 100 drugs have been linked with SJS/TEN in the adult population. However, the following "high risk" medications trigger most cases: antimicrobial sulfonamides, sulfasalazine, allopurinol, nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, non-steroidal anti-inflammatory agents (NSAIDs), aminopenicillins, cephalosporins, and quinolones. Recently, Sassolas et al. published an algorithm for assessment of drug causality in SJS/TEN (ALDEN), which provides a structured scoring system to help identify the causative drug (please refer to Suggested Readings list for details).

Mortality rates in SJS/TEN vary widely and are contingent on multiple factors, particularly BSA of detachment and patient age. Average mortality rates in SJS are estimated at 1–5 %, and in TEN they are 25–35 %. Survival analysis conducted among SJS/TEN patients has shown that mortality risk extends far beyond the acute phase of illness, with a mortality rate of 23 % at 6 weeks and 34 % at 1 year. Factors that increase mortality risk include severe liver or kidney disorders, recent infection, and malignancy.

Pathophysiology

The mechanisms responsible for SJS/TEN development are incompletely understood. However, drug hypersensitivity is widely accepted as the *sine qua non* of SJS/TEN pathogenesis. T-cell mediated hypersensitivity triggering SJS/TEN is thought to result from an impaired capacity to detoxify reactive intermediate drug metabolites; altered drug metabolism may be attributable to both genetic and acquired causes. Antigens yielded by the reaction of metabolites with host tissues then initiate the pathogenic immune response.

Further corroborating evidence favoring an immune-mediated diathesis in SJS/TEN is provided by the timeline of development: a 1- to 3-week interval of sensitization between the onset of drug therapy and disease manifestation is typical. Immune memory is also implicated by the rapid recrudescence of SJS/TEN following drug re-challenge.

In the early phases of cutaneous lesions, cytotoxic CD8+ T cells expressing cutaneous lymphocyte-associated antigen (CLA) involved with skin-homing predominate, implicating major histocompatibility complex (MHC) class-I restricted antigen presentation and subsequent clonal expansion. Natural killer T-cells (NKT) and monocytes/macrophages are also recruited. T-cells isolated from SJS/TEN blisters have drug-specific cytotoxicity targeted to keratinocytes and B-lymphocytes.

Cytotoxicity in SJS/TEN is thought to be multifactorial, with contributions by both the Fas-Fas ligand (FasL) pathway and granulysin. Granzyme B, as well as Interleukin (IL)-6, TNF-α, interferon-γ, and IL-18 are also found within blister fluid and/or lesional epidermis. The effects of these cytokines likely gives rise to the constitutional symptoms of epidermal necrolysis. In addition, the actions of these cytokines provide a molecular basis for discrepancy between the fulminant epidermal denudation and the incongruously scant inflammatory infiltrates of SJS/TEN lesions.

Cell-mediated cytotoxicity precipitates widespread apoptosis, a characteristic feature of the initial phase of SJS/TEN, the consequence of which is the classical "necrolysis" observed histologically. As SJS/TEN progresses, the burden of apoptotic cells overcomes the capacity of phagocytes for elimination and within hours, the apoptotic cells release their intracellular contents,

triggering inflammation. Dissolution of intracellular and basement membrane adhesions occurs and epidermal viability is lost, generating the histologic picture of epidermal necrolysis.

Apoptosis in SJS/TEN is thought to be initiated by the binding of specific ligands to cell surface death receptors. In this process, the Fas (CD95, Apo-1)/ FasL (CD95L) receptor-ligand pair plays a prominent role. Following ligation, intracellular signaling machinery, namely FADD and pro-caspase-8, is activated. In turn, this generates apoptosis through autoactivation of the protease caspase-8 and activation of additional caspases responsible for cellular dissolution (caspases-3, -6, -7). Blood levels of soluble FasL are increased in patients with TEN, and blood levels correlate with BSA of involvement.

Compelling evidence also supports a prominent role in SJS/TEN induction by granulysin, a cytolytic product of NK cells and cytotoxic T-lymphocytes. In the murine model, intradermal injection of granulysin results in features mimicking SJS/TEN. Further, gene expression profiling of blister fluid demonstrates granulysin expression is two to four times greater than other cytotoxic proteins including perforin, granzyme B or soluble FasL. Depleting granulysin diminishes cytoxicity.

Strong associations exist between certain MHC allotypes and epidermal necrolysis; thus, genetic susceptibility is also thought to play a pivotal role. This feature is demonstrated by the increased incidence of TEN development among human leukocyte antigen (HLA)-B12 in individuals. In addition, the HLA-B12 haplotype is linked with heightened risk of ocular complications. Among the Han Chinese, Thai, Malaysian, and South Indian populations, HLA-B*1502 correlates with increased risk for SJS/TEN induced by aromatic antiepileptic agents such as carbamazepine, oxcarbazepine, lamotrigine, and phenytoin. In the above populations, as well as Europeans, HLA-B*5801 incurs increased risk for allopurinol-induced epidermal necrolysis. Among Europeans, HLA-B*5701 correlates with abacavir-induced hypersensitivity reactions and HLA-A*3101 with carbamazepine-induced hypersensitivity.

Clinical Presentation

It is important to note that although they share many clinical features and were previously thought to lie on a nosographic continuum of severity, erythema multiforme (EM) is currently considered a distinct clinical entity from SJS and TEN. EM is a self-limited disorder. With only minor epidermal denudation, often 1–2 % BSA involvement (<10 %), EM preferentially involves the distal extremities in a symmetric distribution. EM exhibits characteristic "target" lesions with three zones: (1) an outer erythematous zone; (2) an edematous paler zone; and (3) a dark, dusky center. "Atypical" target lesions feature ill-defined margins and/or two zones in contrast to the three of classical targets. Mucosal involvement is minimal in the EM minor and occurs in 5–60 % of EM major patients. In contrast, mucosal involvement is seen in 92–100 % of SJS and nearly 100 % of TEN patients. Moreover, EM confers minimal to no systemic symptoms. Differentiation of EM from SJS and TEN is based predominately on clinical features, particularly lesion distribution and the presence of classical target lesions. Classical target lesions must be present for a diagnosis of EM, whereas the diagnoses of SJS/TEN are to be considered for atypical targets. Histological features of EM resemble those of SJS/TEN and are therefore of limited discriminative utility.

Clinical Manifestations

Prodromal symptoms of SJS and TEN precede cutaneous manifestations by 1–3 days and include eye stinging, odynophagia, and fever. The trunk, often the pre-sternal region, is frequently the initial site of cutaneous involvement (Fig. 24.1). Lesions then spread to the face, neck, hands, feet, and proximal upper extremities. Relative sparing of the distal upper and lower extremities is typical.

Early cutaneous findings generally include irregularly shaped, erythematous, dusky red or purpuric macules that are typically tender. These lesions have the tendency to rapidly coalesce with

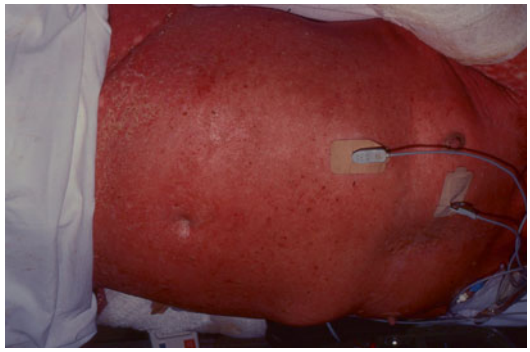

Fig. 24.1 Dusky red discoloration with trunkal involvement that is often seen early in TEN. Early desqumation is starting over lower abdominal panniculus. Reaction was to Bactrim

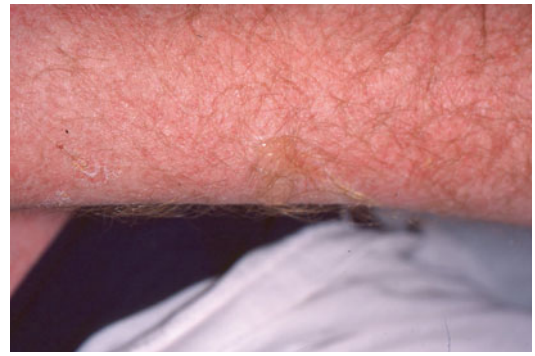

Fig. 24.2 Diffuse erythema over forearm with fragile blisters. The blisters on the left are already broken and the "wet cigarette paper" is on the lower border of arm just to the left of center

disease progression. In some cases, early lesions may be slightly infiltrated. Atypical targets with dark centers are also often seen. At this point in the evolution of SJS or TEN, lesions may mimic more benign drug-related disorders including exanthematous drug eruptions or EM major.

With progression toward full-thickness necrosis, the erythematous macules assume a grey hue over the next hours to days. Application of tangential mechanical pressure to erythematous zones in this phase may produce detachment of the epidermis from the dermis, referred to as a positive Nikolsky sign. This phenomenon is not specific to SJS/TEN, however, as it is also observed in those with autoimmune bullous diseases. At this time, the skin demonstrates a "wet cigarette paper" appearance (Fig. 24.2). Friction or pressure easily detaches the epidermis, exposing an erythematous, often bleeding or "scalded" dermis. In this second phase, large tracts of epidermal denudation develop. With epidermal cleavage, blisters arise as fluid fills the space between the dermis and epidermis. These flaccid, easily-ruptured blisters may be extended laterally by pressure of the thumb, a feature known as a positive Asboe-Hansen sign. Tense vesicles or bullae may occasionally be observed, typically only in the palmar or plantar regions as the thicker epidermal layer of these surfaces more readily resists pressure.

Epidermal cleavage progresses for 5–7 days. Thereafter, a plateau phase of re-epithelialization begins. Re-epithelialization is generally complete within 3 weeks. Healing is slower in areas of maceration, pressure, or infection. Skin grafting is not required, as keratinocytes are recruited from reservoirs such as follicles and healthy perilesional epidermis and proliferate.

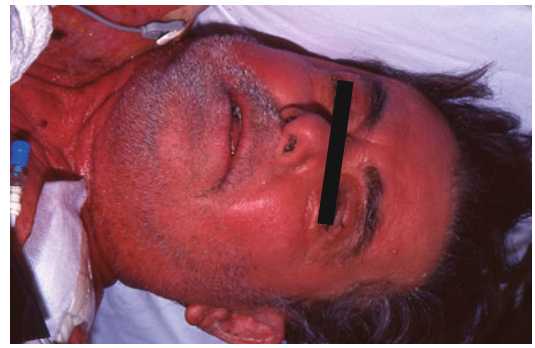

Fig. 24.3 Diffuse erythema with swelling of eyelids, especially on the patient's left side. There is some early conjunctivitis of right eye. This was due to sulfa antibiotic

Mucosal involvement presents as erythema and exquisitely painful erosions of the genital, buccal, and ocular mucosa. At least two mucosal surfaces are generally affected. Mucosal/ocular manifestations typically precede or occur simultaneously with cutaneous signs.

Ocular involvement is present in 50–78 % of cases and may include photophobia, discharge, crusting, eyelid edema (Fig. 24.3), and conjunctivitis, as well as conjunctival membrane or pseudomembrane formation. Eyelash shedding may also be observed. Oral involvement occurs in 71–100 %

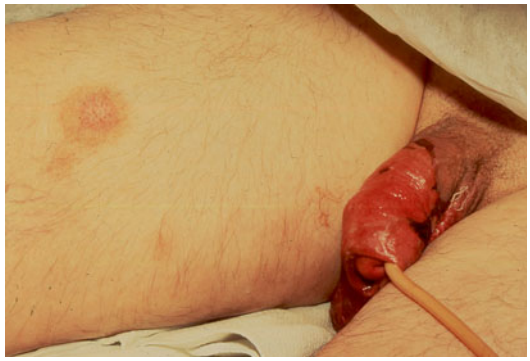

Fig. 24.4 TEN of the genitalia with dramatic stripping of epidermis of the glans and shaft of the penis. The base of the penis shows epidermal denuding, indicating a positive Nikolsky's sign. A urinary catheter has been inserted due to severe dysuria and urinary retention

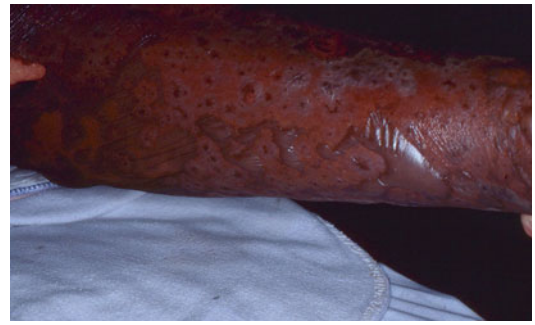

Fig. 24.5 Flaccid bullae and erosive papules over the forearm of a patient with TEN. The skin is being wiped away with a finger over the elbow, showing a positive Nikolsky's sign. The danger of not stopping the offending antibiotic early was the probable cause of end-stage pulmonary disease and death. The patient failed on high-dose intravenous corticosteroids, plasmaphoresis, and intensive topical therapy

of cases. The vermilion border of the lips and oral cavity frequently feature grey-white pseudomembranes and crusts overlying hemorrhagic erosions. Genital involvement (Fig. 24.4), often with associated dysuria, presents in 40–63 %, and may be complicated by dyspareunia, synechiae formation, and urethral or anal strictures in rare cases.

Though epidermal necrolysis has been described as "acute skin failure," multiple internal organ systems are also involved. Pulmonary complications (Fig. 24.5) include bronchiolitis obliterans, subcutaneous emphysema, and acute respiratory distress syndrome (ARDS). Renal involvement can lead to microalbuminuria or overt proteinuria, hematuria, azotemia, and acute renal failure secondary to glomerular and/or renal tubular damage. Gastrointestinal dysfunction secondary to epithelial sloughing may include esophagitis, severe abdominal pain and diarrhea, malabsorption, melena, and even hepatitis or colonic perforation. Anemia and leukopenia are common. Myocarditis and encephalopathy have also been documented.

The most frequent complication of the acute phase of SJS/TEN is sepsis. Compromised epithelial barrier function predisposes patients to infections, which represent the most common cause of mortality. *Pseudomonas* and *Staphylococcus aureus* are the most frequently identified pathogens. However, enterobacteriaceae are isolated from one-third of positive blood cultures implicating gastrointestinal translocation with mucosal involvement. Multisystem organ failure ensues in roughly one-third of cases.

Sequelae

After resolution of the acute phase, epidermal necrolysis behaves as a chronic disease; long-term complications are more common and severe than previously thought.

Sequelae of imperfect healing are frequent in SJS and TEN. Cutaneous dyschromia and nail dystrophy occur in 62.5 % and 37.5 % of patients, respectively. Diffuse hair loss may also be seen.

Ocular involvement can be severe and blinding. Surprisingly, the diagnosis of TEN does not predict more severe ocular involvement or more frequent late ophthalmological sequelae compared to SJS. Among those with ocular involvement, complications include severe dry eyes in nearly half of cases, trichiasis in 16 %, symblepharon in 14 %, entropion in 5 %, corneal ulceration in 2 %, and visual loss in 5 %.

Oral sequelae include xerostomia, increased salivary acidity, and periodontal disease, as well as gingival inflammation and synechiae.

Genital involvement may be complicated by dyspareunia with vaginal itching, dryness, and

Table. 24.1 Differential diagnosis

Diagnosis	Distinguishing features
Acute generalized exanthematous pustulosis (AGEP)	Superficial (subcorneal) pustules on an erythematous base Shorter interval between drug exposure and reaction onset
Drug-induced linear IgA bullous dermatosis (LABD)	Tense blisters predominate New blisters arise at margins of erythematous annular lesions ("string of pearls" sign)
Erythema multiforme (EM)	Typical target lesions Extremity predominance Less severe mucosal involvement
Exanthematous (morbilliform) drug eruption	Lacks mucosal involvement Less prominent skin pain
Generalized bullous fixed drug eruption (GBFDE)	More well-defined lesion borders Less prominent mucosal involvement Rapid resolution in 7 – 14 days
Graft-versus-host disease (GVHD)	Post-transplant setting
Kawasaki disease	Differences in mucosal/ocular manifestations
Paraneoplastic pemphigus	Neoplastic association Chronic course
Phototoxic eruption	Photodistribution Recent sun exposure Phototoxic medication exposure
Staphylococcal scalded skin syndrome (SSSS)	Lacks mucosal involvement

bleeding. In males, phimosis may be seen. In rare cases, synechiae and urethral or anal strictures requiring surgical intervention may form.

The differential diagnosis of SJS/TEN includes acute generalized exanthematous pustulosis (AGEP), EM, generalized bullous fixed drug eruption (GBFDE), and staphylococcal scalded skin syndrome (SSSS). These and other diagnoses to be considered in the appropriate clinical setting are detailed in Table 24.1 along with some of their distinguishing clinical features.

Diagnostic Findings

Histopathology

Scattered apoptotic keratinocytes are seen in the basal and immediate suprabasal epidermal layers in the initial phase of SJS or TEN. These findings serve as a microscopic correlate of the clinical grey or dusky coloration, which signals incipient epidermal necrolysis and cleavage.

Biopsy of later stage lesions reveals confluent epidermal necrosis, often with underlying subepidermal blisters. In such specimens, sparse perivascular infiltrates with lymphocytic predominance are observed. Cytological analysis demonstrates macrophages and lymphocytes in the epidermis, the majority of which are CD8+. Conversely, lymphocytes located in the papillary dermis are chiefly CD4+.

Laboratory Studies

In general, blood tests are of limited diagnostic utility but aid in management, prognostication, and early identification of complications. Laboratory studies reveal anemia in nearly all cases. Leukopenia, particularly lymphopenia, is likewise common and found in roughly 90 % of cases. Neutropenia portends a poor prognosis, and eosinophilia is typically not observed. In nearly one-third of patients, mild elevation of liver enzymes occurs. Urinalysis reveals proteinuria in half of cases.

Prognosis

The validated SCORTEN scoring system may be employed to assess disease severity and prognosis, as well as guide clinical decision-making. One point is assigned for each of the seven following criteria: (1) age >40 years; (2) comorbid malignancy; (3) tachycardia >120 beats per minute (bpm); (4) initial BSA of detachment >10 %; (5) blood urea nitrogen >28 mg/dL; (6) glucose >252 mg/dL; and (7) bicarbonate

>20 mEq/L. Mortality escalates from 3 % for a patient with 0 or 1 point to 35 % for a patient with 3 points. Predicted mortality for those with ≥5 points approaches 90 %. For optimal predictive value, scoring must be repeated on day 3 post-admission.

Treatment

Optimal medical management of SJS and TEN demands prompt recognition and diagnosis as well as immediate withdrawal of the causative drug(s). Even after adjustment for confounders such as patient age, BSA of involvement, and immune status, earlier discontinuation of the culprit medication correlates with a better prognosis. All nonlife-sustaining drugs should be withdrawn in cases where the offending agent is unknown, particularly those administered within 8 weeks of SJS/TEN onset.

Supportive care in the appropriate clinical setting and specific therapy where indicated are also cornerstones of management.

Management in nonspecialized wards is appropriate only for patients with limited cutaneous involvement without rapid progression and a SCORTEN score of 0 or 1. Transfer to burn centers or intensive care units is warranted for patients with a SCORTEN score of 3 or above, as these individuals require therapy that may exhaust the capabilities of general wards. Mortality is reduced with early transfer to a burn unit; such facilities are particularly well-equipped and trained in the care of patients with epidermal loss.

Debridement of blisters is not recommended, and burn centers should be reminded of this by their dermatology referral.

Supportive Care

Supportive care centers on maintaining hemodynamic stability and prompt diagnosis and intervention for life-threatening sequelae. Goals of management essentially parallel those of extensive burns.

Erosions yield sizeable insensible fluid losses and associated hypovolemia and electrolyte abnormalities, thus fluid resuscitation should be rapidly initiated and titrated as necessary. As epidermal cleavage in SJS/TEN usually affects the trunk, sites of central line placement are often involved. Consequently, these sites are predisposed to infection. For this reason, peripheral venous access is preferred.

Ideally¸ ambient temperatures should be elevated at 82.4–86 °F, or 28–30 °C. Use of aluminum survival sheets and a controlled pressure thermo-regulated bed is preferable to a traditional bed and sheets.

Aseptic precautions are critical given the significant risk of infection, and surveillance for infection should be vigilant in SJS/TEN. Blood, skin, and urine cultures should be obtained at frequent intervals. Though routine antimicrobial prophylaxis in not recommended, antimicrobial therapy should be initiated promptly when infection is suspected.

Daily wound care with enhanced focus on the face, eyes, nose, mouth, ears, interdigital spaces, axillary folds, and anogenital region, optimally with the assistance of a dermatologist (burn unit patients are frequently not seen by a dermatologist but it is recommended), is essential. Topical emollients such as petrolatum should be applied to detached sites, particularly sites under pressure. Isotonic sterile sodium chloride solution may be used to cleanse serous or serosanguinous crusts on the face. Silicone dressings may also be applied to areas of detachment. Silicone dressings may be left in place until re-epithelialization is complete, however, sterile sodium chloride should be used to cleanse the exposed surfaces of these dressings daily. Non-adherent layered dressings such as Exu-Dry™ may also be utilized. Care for areas near orifices such as the mouth, nose, or ears may include topical antibiotic application. Intact regions should remain dry. Movement may precipitate detachment, thus patient manipulation should be minimized. Debridement of the necrotic epidermis is not recommended.

Patients should undergo daily eye exams by an ophthalmologist. Eyelid cleansing with

sterile sodium chloride solution is recommended daily. Antibiotic or antiseptic eye drops to minimize corneal colonization by bacteria, as well as preservative-free ocular emollients and Vitamin A are often administered. Evolving synechiae should be mechanically disrupted. In the acute phase, transplantation of cryopreserved amniotic membrane suppresses inflammation, promotes epithelial healing, and may preclude the development of blinding cicatricial sequelae. Daily cleansing of the nostrils with isotonic sterile sodium chloride solution applied with a sterile cotton swab is advised. Subsequently, a topical antibiotic such as mupirocin should be applied.

Isotonic sterile sodium chloride solution should be used to rinse the mouth several times daily. Provided the areas are not macerated, sterile sodium chloride solution should also be applied to the interdigital spaces and anogenital region daily. If these areas are macerated, 0.5 % silver nitrate solution is suggested.

Other recommended measures include anticoagulation for venous thromboembolism prophylaxis, early initiation of alimentary support, optimally via nasogastric tube, to promote healing of the gastrointestinal tract and reduce the risk of bacterial translocation, and pain management.

Specific Therapy

Various anti-inflammatory and/or immunomodulatory therapies have been employed in light of the pathophysiological basis for TEN and SJS. However, rarity of the two conditions constrains performance of randomized controlled trials. For this reason, the majority of evidence supporting specific SJS or TEN therapies originates from small, uncontrolled trials and series or case reports. Thus no specific interventions have demonstrated compelling proof of efficacy requisite for wide implementation. Overall, the management of severe SJS echoes that of TEN, although individuals with attenuated forms of SJS without rapid progression may require only supportive therapies.

Corticosteroids

Systemic corticosteroids have anchored SJS/TEN management for decades; however use of these agents remains controversial. When administered early in the evolution of SJS/TEN, particularly via pulsed intravenous dosing, corticosteroids may reduce mortality without lengthening healing time. However, results of other studies suggest corticosteroid therapy may actually increase mortality and the incidence of adverse events, specifically sepsis. Therefore corticosteroids are no longer recommended as a mainstay of therapy.

Intravenous Immunoglobulin

Commercial preparations of Intravenous Immunoglobulin (IVIG) include antibodies targeted to Fas which abrogate ligation of FasL, impeding keratinocyte cell death in vitro. However, translation of this finding from the bench to the bedside has yielded conflicting results. Several independent studies have demonstrated improved mortality among patients with TEN managed with IVIG. With total IVIG doses of 2.7, 4, and 3.4 g/kg, survival rates were 88 %, 94 %, and 100 %, respectively. In contrast, other studies comparing total IVIG doses of 1.6 or 2.8 g/kg IVIG to supportive therapy alone report no appreciable mortality benefit. In another trial, 2 g/kg of total IVIG revealed no measurable effect on disease progression or rate of re-epithelialization, and no improvement in mortality predicted by SCORTEN. A larger, retrospective analysis conducted in the RegiSCAR cohort confirmed this lack of survival benefit, albeit at a lower IVIG dose. It has been suggested that optimal therapeutic efficacy may not be achieved by total doses of less than 2 g/kg; this may partially account for the discordant results of these trials.

Inconsistent study designs and patient-related variables in studies complicate critical evaluation of IVIG's efficacy. Moreover, the benefit of supportive therapies may confound observations. Accordingly, high doses of IVIG (e.g., 3 mg/kg total administered at 1 mg/kg per day) appear to be a safe, reasonable treatment option. Further

trials must be conducted to better characterize the efficacy of IVIG in epidermal necrolysis.

Plasmapheresis

Plasmapheresis, or plasma exchange, has been performed in SJS/TEN with the objective of rapid removal of the offending drug or its metabolites and pro-inflammatory substances, particularly cytokines. Clinical improvement has been demonstrated in a number studies evaluating the utility of plasmapheresis. In one cohort refractory to systemic corticosteroids and/or IVIG, plasma exchange halted disease progression with re-epithelialization demonstrated in all four patients. Additional studies are warranted to confirm these promising early results of plasma exchange in epidermal necrolysis.

Cyclophosphamide

The effect of cyclophosphamide (100–300 mg/day), on the course of epidermal necrolysis has been assessed in small case series. Trials of solitary cyclophosphamide therapy as well as combination therapy with cyclosporine and corticosteroids suggest a beneficial impact. However, larger trials are necessary to corroborate these findings.

Cyclosporine

Cyclosporine, a calcineurin inhibitor and T-cell antagonist, has demonstrated favorable effects in several recent trials at doses of 3–4 mg/kg/day. In one recent study conducted among 29 patients, cyclosporine resulted in cessation of disease progression. No increase in infection was found, and cyclosporine was well-tolerated. In this trial and a subsequent independent study, cyclosporine conferred 100 % survival.

Anti-TNF, G-CSF, and NAC

Antibodies directed toward tumor necrosis factor (TNF) have been used with favorable results. However, one prior randomized, blinded, controlled trial assessing the effect of thalidomide, an anti-TNF agent, was terminated due to excess mortality in the thalidomide group. In contrast, subsequent case reports have demonstrated successful outcomes of TNF blockade in the form of infliximab and etanercept. At any rate, anti-TNF therapy must be used with supreme caution. In patients with TEN and neutropenia, granulocyte colony-stimulating factor (G-CSF) has significantly accelerated re-epithelialization. Several reports have also demonstrated beneficial therapeutic effects of N-acetylcysteine (NAC) administration. Again, additional trials will be required to validate the outcomes of these interventions.

Management of Sequelae

Given the protean nature SJS/TEN complications, an interdisciplinary approach to care is imperative. Observation of vigilant sun protection practices is critical in the management of the cutaneous dyspigmentation which complicates epidermal necrolysis. Providers must also be alert in the prevention and treatment of ocular complications, with early referral to an ophthalmologist. As vaginal synechiae may not be appreciable until months after epidermal necrolysis onset, early, regular pelvic examination is recommended for female patients. In males, genitourinary manifestations such as penile and urethral erosions and phimosis warrant close urology follow-up. Special attention and prompt referral to specialists is also required for oral, gastrointestinal, and pulmonary involvement.

Conclusions

Moving forward, HLA haplotyping prior to the administration of drugs is likely to be a useful tool for primary prevention of epidermal necrolysis. This principle is illustrated by the FDA-issued recommendation of testing patients with “Asian ancestry” for HLA-B*1502 prior to initiating carbamazepine therapy.

Detailed drug histories identify the offending agent in only 70 % of patients. In cases where the identity of the culprit agent remains in doubt, ex vivo/in vitro testing, particularly via the lymphocyte transformation test (LTT)

may be helpful. This test quantifies T-cell proliferation in the presence of suspect drugs. However, this assay is limited by low sensitivity, thus the development of novel methods of culprit drug identification is key.

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Drug-Induced Delayed Multi-organ Hypersensitivity Syndrome

25

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Abstract

Drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS), also known as drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome (DIHS), or drug hypersensitivity syndrome (DHS) is a rare, potentially fatal, drug-induced hypersensitivity reaction characterized by cutaneous eruption, fever, lymphadenopathy, hematologic abnormalities, and visceral manifestations. Anticonvulsants such as carbamazepine, phenytoin, lamotrigine, and phenobarbital as well as allopurinol and sulfonamides, are the most common causes of DIDMOHS. Impaired drug detoxification and herpes virus reactivation play a key role in DIDMOHS pathogenesis. Human leukocyte antigen (HLA) haplotypes also contribute. Early cutaneous findings generally include a morbilliform eruption characterized by diffuse, erythematous, pruritic macules across the face, upper trunk, and upper extremities with later extension to the lower extremities. Rapid confluence and progression are characteristic. DIDMOHS frequently involves the lymphatic, hematologic, and hepatic systems. Renal, pulmonary, and cardiac dysfunction may also ensue.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_25

Early recognition and diagnosis with prompt withdrawal of the culprit drug is paramount. Corticosteroid therapy is widely accepted as the cornerstone of DIDMOHS management. Moving forward, haplotyping and assays such as the lymphocyte transformation test (LTT) will aid in the primary prevention and diagnosis of DIDMOHS. Novel steroid-sparing immunomodulatory agents also have significant therapeutic potential.

Keywords

Corticosteroids • Cytochrome P450 • Drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS) • Drug reaction with eosinophilia and systemic symptoms (DRESS) • Drug allergy • Drug eruption • Drug-induced hypersensitivity syndrome (DIHS) • Eosinophilia • Erythroderma herpesvirus • Human leukocyte antigen (HLA) haplotype

Introduction

Drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS) is a rare, potentially fatal, drug-induced hypersensitivity reaction characterized by cutaneous eruption, fever, lymphadenopathy, hematologic abnormalities and visceral manifestations.

A variety of other terms have been used to describe this condition, including drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome (DIHS), drug hypersensitivity syndrome (DHS), mononucleosis-like syndrome, anticonvulsant hypersensitivity syndrome (AHS), phenytoin syndrome and dapsone syndrome. The nosographic controversy surrounding DIDMOHS mirrors the absence of established diagnostic criteria for the disorder and its highly diverse clinical manifestations. We use the acronym DIDMOHS herein.

DIDMOHS was initially noted among patients treated with anti-epileptic agents in the 1930s when phenytoin was introduced. To this day, anti-epileptic agents (specifically carbamazepine, phenytoin, lamotrigine, and phenobarbital) and allopurinol are the most common causes of DIDMOHS. DIDMOHS is also induced by sulfonamides, especially sulfasalazine and dapsone, as well as vancomycin, minocycline, gold salts, and HIV medications such as abacavir.

Epidemiology

In the general population, DIDMOHS risk ranges between 1 in 1000 and 1 in 1,0000 drug exposures. Immunocompromise predisposes individuals to DIDMOHS. Although DIDMOHS may occur in the pediatric population, the majority of cases occur in adults, with roughly equal distribution among males and females. African-Americans and individuals from the Caribbean basin may be at increased risk.

DIDMOHS frequency also varies based on drug types. Carbamazepine and phenytoin induce DIDMOHS at a rate ranging from 1 to 5 in 1,0000 exposed individuals. Although relatively infrequently used, lamotrigine is associated with DIDMOHS in 1 in 300 adults undergoing treatment.

Pathophysiology

DIDMOHS pathogenesis is incompletely understood. However, it is widely accepted that immune-mediated phenomena are responsible. From a broad perspective, an immune diathesis is suggested by the increased risk with immunocompromise. Several attributes of DIDMOHS implicate a delayed-type cell mediated response in particular. These include its reproducibility with patch testing and obligatory sensitization interval between drug exposure and reaction onset. Rapid recrudescence

following drug re-challenge likewise insinuates cell-mediated immunopathogenesis.

HLA Haplotype

Strong associations exist between certain human leukocyte antigen (HLA) haplotypes and DIDMOHS. Interaction between the specific haplotype and culprit drug is thought to form a hapten. Subsequently, the hapten is presented to T-cells to generate the immune response. In the acute phase of DIDMOHS, expansion of both $CD4^+$ and $CD8^+$ T-cell populations occurs. These T-cells secrete proinflammatory cytokines such as interferon-gamma, interleukin-5 and others. In vitro and in vivo evidence in the form of lymphocyte proliferation analysis and patch testing demonstrates this response is drug-specific.

Heightened levels of interleukin-5 in conjunction with eotaxin evoke the eosinophilia of DIDMOHS. In turn, hypereosinophilia is thought to contribute to internal organ involvement, as eosinophil granule proteins are toxic to many tissues. Tumor necrosis factor is also involved, propagating tissue damage after secretion by macrophages.

The HLA-DR3, HLA-DQ2, and HLA-B*1502 haplotypes have been implicated in carbamazepine-induced DIDMOHS. Among individuals of Portuguese or Han Chinese descent, HLA-B*5801 is linked with severe allopurinol-induced drug hypersensitivity reactions, including DIDMOHS. White individuals with the HLA-B*5701 haplotype are predisposed to abacavir-induced DIDMOHS. In addition, the HLA-A*3101 haplotype is linked with higher frequency of DIDMOHS among European and Han Chinese populations.

The above associations notwithstanding, HLA haplotypes appear to be necessary but not sufficient for DIDMOHS initiation; these markers have high negative predictive value but low positive predictive value for drug hypersensitivity.

Drug Detoxification

Polymorphism of genes encoding enzymes responsible for the detoxification of drugs and intermediate metabolites also contributes to DIDMOHS development. DIDMOHS cases often occur in a familial distribution, the basis for which appears to be autosomal dominant inheritance of detoxification genes.

In most individuals, anticonvulsants such as carbamazepine, phenytoin, and phenobarbital are metabolized by the cytochrome P450 (CYP-450) system, generating intermediate toxic arene oxides. These arene oxides are detoxified by the enzymes glutathione transferase and epoxide hydroxylase. However, mutations in these enzymes impair detoxification. Thus, toxic arene oxides thought to elicit the DIDMOHS response accumulate. Among patients recovering from DIDMOHS, defective detoxification of anticonvulsants and sulfonamides has been established. In addition, other processes inhibiting or inducing CYP-450 activity also modify DIDMOHS risk.

Sulfonamide-induced DIDMOHS susceptibility varies based on sensitivity of lymphocytes to hydroxylamine, a toxic intermediate generated by CYP-450. Patients with sulfonamide-induced DIDMOHS may develop antibodies that recognize microsomal proteins to which this reactive intermediate binds. Risk is also increased by specific acetylation polymorphisms which impede the conjugation phase of drug detoxification, particularly the slow N-acetylator phenotype.

Herpes Virus Reactivation

Reactivation of herpes viruses also contributes to DIDMOHS pathogenesis, principally human herpes virus (HHV)-6. DIDMOHS is also associated with HHV-7, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) reactivation. Viral reactivation in DIDMOHS occurs sequentially. HHV-6 and EBV initiate the cascade of viral reactivation; with progression HHV-7 and finally CMV reactivation occur. Interestingly, the sequential order of viral reactivation in DIDMOHS parallels that of graft-versus-host disease (GVHD).

Approximately three out of five DIDMOHS patients demonstrate increasing anti-HHV-6 IgG antibodies and HHV-6 DNA titers in the weeks following the onset of cutaneous features. In situ

hybridization (ISH) and polymerase chain reaction (PCR) also confirm HHV-6 mRNA and DNA presence in lesional skin. In severe cases associated with hepatitis or encephalitis, HHV-6 may be detected in the liver and cerebrospinal fluid, respectively. In addition, recurrence of DIDMOHS manifestations such as fever and hepatitis appear to coincide with the presence of HHV-6 in sera.

Clinical Presentation

Prodrome

In most cases, DIDMOHS presents 2–6 weeks following exposure to the offending medication. This latency interval is substantially longer than the typical 4- to 9-day interval of exanthematous drug eruptions and 4- to 28-day interval of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). Latency varies based on the specific culprit drug; for instance, carbamazepine-induced DIDMOHS presents later than allopurinol-induced DIDMOHS. Malaise, pruritus, and pyrexia are often the initial manifestations of DIDMOHS. Typically, fever ranges between 38 and 40 °C and precedes dermatologic features by several days. In some cases, pyrexia lasts several weeks. Dysphagia may appear before skin lesions. Prodromal symptoms may also include lymphadenopathy.

Mucocutaneous Manifestations

Typically¸ DIDMOHS begins as a morbilliform eruption characterized by diffuse, erythematous, pruritic macules. The face, upper trunk, and upper extremities are often the first sites involved, with extension to the lower extremities. Follicular accentuation as well as sterile follicular or non-follicular-based pustules may be observed. Additional findings may include vesicles, bullae, and atypical target lesions.

Rapid confluence and progression of erythema is common in DIDMOHS. In half of cases, erythema encompasses over 50 % body surface area (BSA). Twenty to thirty percent of patients experience progression to exfoliative dermatitis or erythroderma, defined by generalized erythema and scale involving >90 % of BSA.

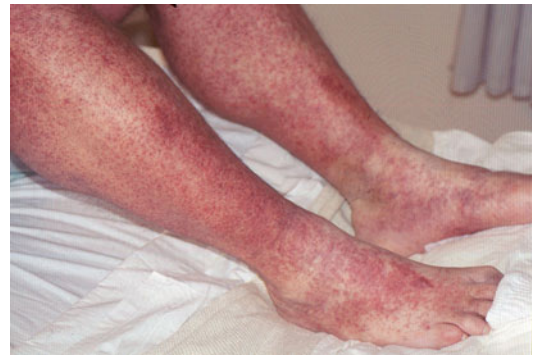

Fig. 25.1 Exanthem over legs developing a violaceous hue before scaling. This patient had been on clindamycin for many weeks and developed this skin eruption, which generalized with time. He had renal disease that resolved after months of systemic corticosteroids and discontinuing the clindamycin. He was also noted to have eosinophilia

Lesions may become infiltrated and indurated with edema. Facial edema is present in half of cases, often with characteristic erythema, symmetry, and persistence. The periorbital and midfacial regions are typically the most significantly affected. In some cases, facial edema is so prominent as to mimic angioedema.

The exanthem of DIDMOHS may assume a violaceous hue with generalized scale after initial presentation (Fig. 25.1). Even after withdrawal of the culprit drug, these findings may persist for weeks or months. Mucosal manifestations in the form of cheilitis, erosions, dysphagia, pharyngitis, pharyngeal erythema, and tonsillar enlargement may also be seen. In a recent prospective study, the oral mucosa was involved in 52 % of 117 cases.

Cutaneous Histopathology

Histopathology of skin lesions may aid in confirming the diagnosis of DIDMOHS, although the findings are relatively non-specific. There is an inflammatory infiltrate of lymphocytes, and often eosinophils in the dermis. There is also

interface dermatitis with variable degrees of spongiosis and keratinocyte dyskeratosis. In more severe cases, the dyskeratosis is widespread, and the interface vacuolization may lead to subepidermal vesiculation. These changes are evident clinically as epidermal necrosis and blistering.

Internal Manifestations

DIDMOHS may involve multiple organ systems, most commonly the lymphatic, hematologic, and hepatic systems. Renal, pulmonary, and cardiac dysfunction may also ensue. In rare cases, endocrine, gastrointestinal, musculoskeletal, and neurologic function may be impaired.

Lymphatic

Lymphadenopathy is prevalent in DIDMOHS, affecting 75 % of patients. Patients may experience limited lymph node involvement or generalized lymphadenopathy with enlargement (1–2 cm) and tenderness involving the cervical, axillary, and inguinal lymph nodal regions. Two distinct variants are present on histopathology: benign lymphoid hyperplasia and pseudolymphoma.

Hematologic

Hematologic abnormalities are common in DIDMOHS. Eosinophilia is prominent, with eosinophil counts above >700/μL in 50–90 % of cases. Patients often demonstrate leukocytosis, up to 50×10^9 leukocytes/L. During the period between drug initiation and the onset of DIDMOHS symptoms, a period of leukopenia or lymphopenia frequently precedes leukocytosis. Atypical lymphocytosis with large activated lymphocytes, lymphoblasts, or mononucleosis-like cells may be observed. Atypical lymphocytes, often regarded as characteristic for DIDMOHS, are present in roughly two-thirds of patients.

Hematology may also reveal a decrease in hemoglobin and hematocrit, as well as thrombocytopenia. In rare, severe cases, hemophagocytic syndrome has been linked with DIDMOHS approximately 2 weeks following reaction onset.

Hepatic

The liver is the most frequent site of internal organ involvement in DIDMOHS. Hepatic features are associated with phenytoin, minocycline, and dapsone-induced DIDMOHS. Hepatomegaly and jaundice may be seen, often with concurrent hepatitis of varying severity. Hepatitis associated with DIDMOHS is generally anicteric. In most cases, hepatitis is asymptomatic and detected only after laboratory studies are obtained. Approximately 70 % of patients exhibit serum alanine aminotransferase (ALT) elevation. DIDMOHS with erythema multiforme (EM)-like cutaneous findings (purpura and atypical targets) correlates with significantly greater increase of liver enzymes. Liver enzyme levels frequently remain elevated for several days following culprit drug withdrawal. In some cases, ALT elevation may persist for months.

Severe acute hepatitis, defined by ALT elevation of >10 times the upper limit of normal and/or acute hepatic failure with coagulopathy and encephalopathy, may occur in conjunction with DIDMOHS. Sulfasalazine is the most frequently implicated drug in this instance. In severe cases, generalized hepatic necrosis may be observed. Liver failure with coagulopathy and sepsis may complicate hepatic necrosis. In fact, hepatic necrosis is the leading cause of mortality in DIDMOHS. Jaundice as well as profound elevation of aspartate aminotransferase (AST) and bilirubin are prognostic markers for incipient liver transplantation or death, as cases of life-saving emergency liver transplantation have been reported.

Renal

Renal manifestations occur in 10–30 % of DIDMOHS patients; most commonly acute interstitial nephritis. Those with comorbid kidney disease and the elderly are particularly susceptible. Allopurinol is most closely linked with renal involvement, though carbamazepine and dapsone are also associated. In most cases, patients are asymptomatic, though patients may rarely report hematuria. Laboratory studies reveal serum creatinine and blood urea nitrogen (BUN) elevation consistent with impaired clearance. Proteinuria

and eosinophiluria may also be observed. Typically, renal dysfunction is mild and recovery occurs following withdrawal of the culprit drug.

Pulmonary

Pulmonary manifestations of DIDMOHS may also occur. Patients may experience dyspnea as well as nonproductive cough. Interstitial pneumonia may be observed, particularly in minocycline-induced DIDMOHS. In addition, pleuritis and impaired pulmonary function in association with DIDMOHS have been reported. DIDMOHS patients are also at risk for acute respiratory distress syndrome (ARDS) requiring emergent intubation and mechanical ventilation.

Cardiac

DIDMOHS may also involve the heart in the form of myocarditis. Minocycline and ampicillin are the most frequently implicated drugs. The onset of myocarditis is unpredictable, as it may occur early in the evolution of DIDMOHS or months following drug withdrawal.

Endocrine

Endocrine dysfunction may also be observed in association with DIDMOHS, more commonly as a long-term complication than during the acute phase of hypersensitivity. Thyroid abnormalities, most commonly thyroiditis and sick euthyroid syndrome, may be found, both of which may generate clinical hyperthyroidism, hypothyroidism, or both during their course. In addition, isolated elevation of free T4 or low thyrotropin (TSH) may be observed. Three to twelve months after DIDMOHS resolution, antithyroid antibodies may be detected. Correspondingly, symptoms of classical Graves' Disease ensue. In rare cases, overt thyrotoxicosis may develop. Hashimoto's Thyroiditis with antibodies directed to thyroid peroxidase (TPO) and thyroglobulin may also complicate DIDMOHS. Thus, routine assessment of thyroid function is recommended for at least 2 years in patients recovering from DIDMOHS.

Fulminant Type 1 diabetes mellitus (DMT1) may also present as a rare complication of DIDMOHS. Autoantibodies associated with classical DMT1 (i.e., islet cell and glutamic acid decarboxylase autoantibodies, etc.) are characteristically absent. Instead, DMT1 associated with DIDMOHS is thought to be related to HHV-6 reactivation.

Gastrointestinal

DIDMOHS may also affect the gastrointestinal system. Gastroenteritis and associated dehydration are the most frequent findings. Acute gastrointestinal bleeding may also occur as a complication of ulcers, particularly in the setting of disseminated CMV infection. Arterial bleeding demonstrated via endoscopy may require emergent clipping and blood transfusion. In addition, colitis, pancreatitis, and even chronic enteropathy have also been reported.

Musculoskeletal

Musculoskeletal involvement in the form of arthralgia and/or arthritis, in addition to myositis, may also occur in the context of DIDMOHS.

Neurological

In rare cases, neurological manifestations evolve from DIDMOHS, namely meningitis and encephalitis. These complications develop roughly 2–4 weeks following reaction onset. Associated clinical findings include speech abnormalities, headache, seizure, muscle weakness, cranial nerve palsies, and coma.

Diagnosis

The protean manifestations of DIDMOHS complicate diagnosis. The diagnosis of DIDMOHS may be delayed or progress unrecognized due to its variable findings, evolution, severity, or similarity to alternative disorders. Disparate or fragmentary clinical features, for instance hepatitis without rash, or eosinophilia and pulmonary infiltrates in isolation may be enigmatic. Presently, no single set of diagnostic criteria has been widely accepted, adding to the challenge of diagnosis.

It is critical to exclude other serious processes when DIDMOHS is suspected. Viral and bacterial infections may present similar to

DIDMOHS. Hematologic disorders including various lymphomas, particularly angioimmunoblastic T-cell lymphoma as well as idiopathic hypereosinophilic syndrome, may share numerous clinical features with DIDMOHS but are distinguished via histologic analysis. Autoimmune/vasculitic processes including systemic lupus erythematosus, polyarteritis nodosa, granulomatosis with polyangiitis, and Churg-Strauss Syndrome, may present with cutaneous eruption, eosinophilia, and multiorgan manifestations. However, immunologic traits such as antineutrophil cytoplasmic antibody (ANCA) and antinuclear antibody (ANA) patterns aid in distinguishing these conditions from DIDMOHS.

It is also critical to distinguish DIDMOHS from other potentially fatal cutaneous drug eruptions because management differs among these conditions. Compared to TEN/SJS, acute generalized exanthematous pustulosis (AGEP) and drug-induced erythroderma, in DIDMOHS, the interval between culprit drug initiation and reaction onset is longer. DIDMOHS also takes longer to resolve. Histopathology differentiates TEN/SJS by its epidermal necrolysis and AGEP by its subcorneal pustules. In addition, eosinophila, atypical lymphocytosis, and hepatitis are found with significantly greater frequency in DIDMOHS than other acute drug eruptions.

Favoring the term DRESS, Bocquet, Bagot and Roujeau proposed the first diagnostic criteria. According to Bocquet et al., the presence of three or more of the following is consistent with a diagnosis of DRESS: (1) drug rash; (2) eosinophilia $>1.5 \times 10^9$/L or atypical lymphocytes present; (3) systemic manifestations (adenopathy [>2 cm in diameter], or hepatitis [transaminase elevation of at least two times upper limit], or interstitial nephritis, or pneumonitis, or carditis).

The European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) group later refined these initial criteria. According to RegiSCAR, the following three features must be present for diagnosis: (1) acute rash; (2) clinical suspicion of drug causality; (3) and hospitalization. In addition, three of the four following systemic features must be demonstrated: (1) fever >38 °C; (2) lymphadenopathy of two or more sites; (3) involvement of at least one internal organ (liver, kidney, heart, pancreas, or other); and (4) hematologic involvement (lymphocyte count outside normal limit, eosinophil count higher than upper limit, or platelet count below lower limit). Points are allotted based on the extent of the above findings. A definite diagnosis is confirmed with a total score >5. Scores of <2, 2–3, or 4–5 are consistent with no case, a possible case, or probable case, respectively. Details of point assignment are available in prior publications.

Distinct criteria have been also proposed by the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) group; the J-SCAR group uses the term DIHS. Their criteria are the first to incorporate contribution by HHV-6. J-SCAR criteria include the following: (1) maculopapular rash developing 3 weeks after culprit drug initiation; (2) persistent symptoms after withdrawal of culprit drug; (3) fever >38 °C; (4) hepatic abnormalities (ALT > 100 units/L) or other organ involvement; (5) leukocyte abnormalities (one or more of the following: leukocytosis [$>11 \times 10^9$/L], atypical lymphocytes [>5 %], or eosinophilia [$>1.5 \times 10^9$/L]); (6) lymphadenopathy; and (7) HHV-6 reactivation. If all seven features are present, typical DIHS is confirmed. If the first five features are present, atypical DIHS is diagnosed. However, implementation of the J-SCAR criteria may be impaired by limited availability of serologies, such as HHV-6 IgG antibody titers.

No international consensus on the most suitable criteria for the diagnosis of DIDMOHS has been reached.

Treatment and Prognosis

Early recognition and diagnosis are paramount, as delay in diagnosis is detrimental to patient outcomes. Likewise, prompt withdrawal of the culprit drug is vital.

Corticosteroid therapy is widely accepted as the cornerstone of DIDMOHS management. Therapy should commence at a minimum dose of 1.0 mg/kg/day of prednisone or equivalent. In general, patients demonstrate rapid improvement

within several days of corticosteroid initiation. Further, corticosteroid therapy may preclude the development of late autoimmune sequelae. Following resolution of clinical and laboratory abnormalities, the induction dose may be gradually tapered over 3–6 months. Marked clinical deterioration may be observed with inadvertent discontinuation or overly rapid corticosteroid tapering. Immediate intervention to prevent organ failure is vital upon recognition of visceral dysfunction. The optimal approach is interdisciplinary, with involvement of specialists as indicated.

Patients with severe visceral manifestations may be treated with pulsed intravenous methylprednisolone at 30 mg/kg for 3 days. Pulsed methylprednisolone is also appropriate for patients who exhibit either no improvement or exacerbation on oral corticosteroids.

Steroid-sparing agents may provide additional treatment options, although no protocols exist. Intravenous immunoglobulin (IVIG) therapy has demonstrated therapeutic benefit in several cases. The impact of IVIG is thought to be related to its anti-inflammatory properties, support of anti-HHV-6 immunity, and repletion of immunoglobulins, which are often deficient in DIDMOHS. However, severe adverse effects or uncontrolled DIDMOHS occurred in five of six patients in one recent trial of single-agent IVIG treatment. Thus, IVIG is not recommended as monotherapy.

Treatment of DIDMOHS with cyclosporine and cyclophosphamide also appear in the literature. N-acetylcysteine (NAC) may also be a beneficial adjunct in anticonvulsant-induced DIDMOHS, as it moderates reactive intermediate toxicity and enhances drug metabolism. Antiviral interventions such as valganciclovir or ganciclovir may prevent or abrogate complications associated with HHV-6 reactivation. Consequently, a novel combination treatment regimen targeting distinct causative mechanisms has been proposed: prednisone, NAC, and valganciclovir.

Although corticosteroids have demonstrated efficacy in the acute setting, the long-term impact of corticosteroids on the course of DIDMOHS is unknown. Prolonged immunosuppression may facilitate viral reactivation. Moreover, a chronic, steroid-dependent variant of DIDMOHS has been described.

In cases without severe organ involvement, for instance those devoid of renal or pulmonary involvement and limited hepatic enzyme elevation (e.g., <3 times upper limit of normal), symptomatic or supportive treatment may be appropriate. Supportive therapy should include antipyretics. Topical steroids and emollients as well as H1-antihistamines may be used for control of cutaneous symptoms such as pruritus. Non-steroidal anti-inflammatory agents should be avoided as these may complicate or exacerbate the clinical picture due to cross-reactivity. For the same reason, routine antibiotic prophylaxis is not recommended.

Transfer to a specialized intensive care or burn unit is appropriate for patients presenting with erythroderma. Similar to patients with extensive burns, individuals with erythroderma may require fluid resuscitation, correction of electrolyte abnormalities, elevated environmental temperatures, nutritional support, and vigilant skin care with emollient dressings. These patients are also at heightened risk for infection due to compromised epidermal barrier function. Erythroderma is particularly precarious in those with comorbid heart disease or the elderly, as the high-output state generated by cutaneous vasodilation may precipitate heart failure.

The consensus group of the French Society of Dermatology has proposed a decision tree for the management of DIDMOHS adapted to case-specific clinical manifestations. The foremost step is immediate withdrawal of the offending agent. They recommend supportive therapy for patients without signs of severity (hepatic enzymes <5 times normal, renal involvement, pneumonia, hemophagocytosis, cardiac involvement, etc.). Recommended supportive therapies include topical corticosteroids, emollients, and H1-antihistamines. One mg/kg/day of prednisone or equivalent as well as evaluation by appropriate specialists is advised for patients with the above signs of severity. In the presence of life-threatening conditions such as hemophagocytosis with bone marrow failure, encephalitis, renal failure, respiratory failure, or severe hepatitis,

combination therapy via addition of IVIG (2 g/kg over 5 days) is recommended. Patients with severe DIDMOHS and confirmed viral reactivation may be given antivirals such as ganciclovir in addition to steroids and/or IVIG.

Most patients experience full recovery from DIDMOHS, though symptoms may take many weeks to resolve; dermatologic sequelae such as dyschromia often persist for longer intervals. As in the acute setting, an interdisciplinary approach to follow-up is imperative for those with visceral involvement.

Retrospective studies have reported a mortality rate for DIDMOHS of 5–10 %, with most fatalities occurring outside the acute phase of illness. Children recover more readily from DIDMOHS, while the prognosis is more guarded in the elderly population.

Liver failure, multi-organ failure, fulminant myocarditis, hemophagocytosis, and sepsis are responsible for the majority of DIDMOHS-related deaths. Systemic inflammatory response syndrome (SIRS), tachycardia, tachypnea, leukocytosis, gastrointestinal bleeding, and coagulopathy portend heightened mortality risk in DIDMOHS.

Conclusions

Moving forward, DIDMOHS may prove an ideal setting for the practice of personalized medicine. For primary prevention of DIDMOHS, HLA haplotyping prior to drug administration will be beneficial. The FDA now recommends testing patients with Asian ancestry for HLA-B*1502 prior to initiating carbamazepine therapy.

The lymphocyte transformation test (LTT) will likely aid in determining the causative drug in DIDMOHS. The LTT quantifies T-cell proliferation in the presence of suspect drug(s). This test detects cross-reactivity and may also be used to distinguish reactions with distinct immunopathologic mechanisms. Accordingly, it may be used to select safe medication alternatives following adverse reactions such as DIDMOHS. However, the false-negative rate of LTT is elevated during the acute phase of DIDMOHS. Thus, it is recommended that LTT be deferred until 5–8 weeks after DIDMOHS onset.

Novel immunomodulatory agents may be effective in the therapy of DIDMOHS, sparing patients the considerable morbidity of systemic corticosteroids. However, additional trials will be necessary to characterize the impact of these interventions on the course of DIDMOHS.

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Acute Generalized Exanthematous Pustulosis

26

Jonathan J. Lee, Daniela Kroshinsky, and Mai P. Hoang

Abstract

Acute generalized exanthematous pustulosis (AGEP) is an acute, self-limited, widespread cutaneous eruption characterized by the development of numerous, non-follicular, sterile pustules on a background of erythematous, edematous skin. The eruption usually develops within hours to days of exposure to medications (antibiotics, antifungals, calcium channel blockers, and carbamazepine most commonly), but it has also been documented to be associated with various infections (mostly viral), spider bites, and herbal medications. After the inciting medication is removed or precipitant infection clears, the skin reaction resolves spontaneously within 1–2 weeks. The histologic hallmark of AGEP is spongiform subcorneal and/or intraepidermal pustules with marked papillary edema, polymorphous perivascular infiltrates with neutrophils, and exocytosis of some eosinophils. AGEP is immunologically mediated by a T cell-orchestrated neutrophil response through the expression of neutrophilotactic chemokines such as CXCL8.

Keywords

Pustule • Pustular psoriasis • DRESS • Sneddon-Wilkinson disease • Pustular psoriasis of Von-Zumbush • Nikolsky's sign • TEN • Leukocytoclastic vasculitis • CXCL • RANTES • Subcorneal

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_26

Introduction

Acute generalized exanthematous pustulosis (AGEP) is an uncommon condition previously considered to be within the spectrum of pustular psoriasis (von Zumbusch type). In their classic 1968 series of 104 cases of generalized pustular psoriasis, Baker and Ryan (1968) isolated five atypical cases wherein a single, short-lived, sterile, exanthematous, and pustular eruption occurred *de novo* in patients with no history of psoriasis and was usually associated with a precipitant infection or medication. Beylot et al. (1980) later introduced the term *pustuloses exanthématiques aiguës généralisées*, or acute generalized exanthematous pustulosis, to describe such self-limited eruptions and put forth the following diagnostic criteria: (1) acute onset after a bout of infection or drugs in subjects without a history of psoriasis, (2) spontaneous healing after a single attack, and (3) dermal vasculitis and/or non-follicular subcorneal pustules on dermatopathologic examination. It is now known that AGEP is a distinct condition but can also occur in patients with psoriasis.

Clinical Presentation

AGEP often presents with the sudden onset of high fever occurring just before, after, or simultaneously with, a widespread pruritic or burning, edematous, erythematous rash (Fig. 26.1) atop which quickly develops numerous (often hundreds), non-follicular, sterile, pustules (usually pinhead-sized to <5 mm) that can become confluent into lakes of pus (Fig. 26.2). This micropustular rash typically begins on the face or intertriginous areas and extends to the trunk and limbs over a period of hours. Most patients have more than 100 pustules, and the mean duration of the pustules in one clinical series was 9.7 days (range, 4–30 days). Flexural prominence is characteristic, while diffuse, patchy, and more localized patterns have also been described. The pustules can also coalesce, resulting in superficial erosions that mimic a positive Nikolsky's sign and a clinical picture resembling toxic epidermal necrolysis. Mucous membranes may also be involved in up to 20 % of cases, causing erosions in the mouth, the tongue, and the lip. The pustular rash may be accompanied by additional skin findings including atypical targetoid lesions resembling erythema multiforme, blisters, and vesicles, as well as other physical exam findings, including localized edema of the hand and face (Fig. 26.3) and purpura of the lower extremities.

In addition to the cutaneous symptoms, fever greater than 100.4 °F and a neutrophilic (>70 %)

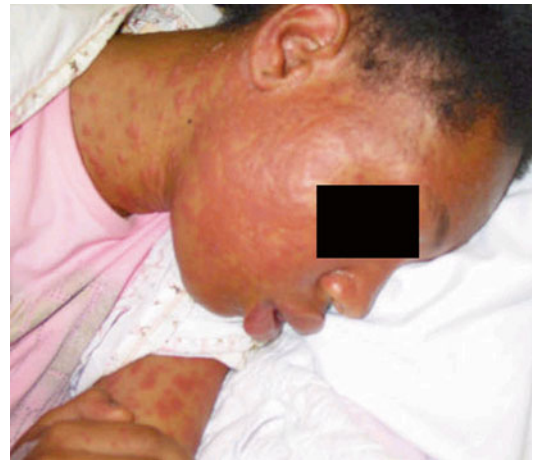


Fig. 26.1 Generalized edematous, erythematous rash preceding pustule presentation.

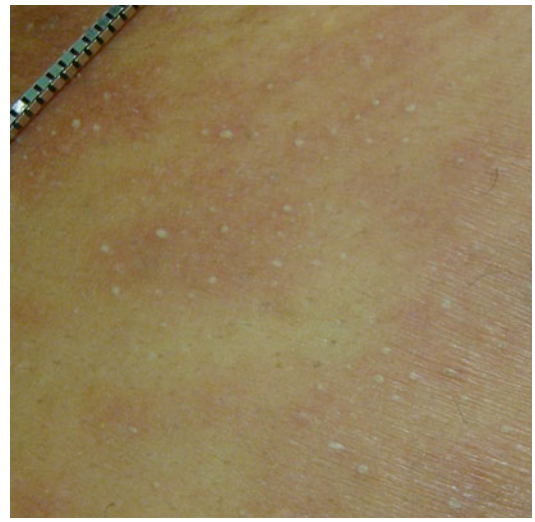


Fig. 26.2 Non-follicular, sterile, pinpoint pustules characteristic of acute generalized exanthematous pustulosis

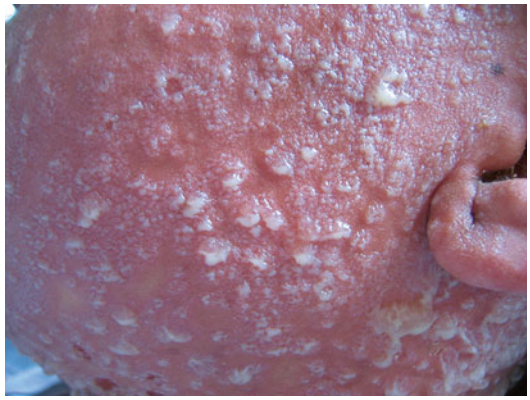


Fig. 26.3 Bullous lesions and lakes of pus

leukocytosis (>10,000/mL) is often present. Lymphadenopathy has also been reported in some cases. Possible laboratory abnormalities can include eosinophilia (>700/mL), mild transaminitis (up to twice normal range), and reversible reduction in creatinine clearance. Hypocalcemia may also be present but is often related to hypoalbuminemia. Although *Staphylococcus aureus* may be present in a few cases, the pustules are most often, and by definition, amicrobial.

AGEP typically occurs anywhere from a few hours to a few days after the administration of the offending drug. In a multinational case–control study of 97 validated cases of AGEP, Sideroff et al. (2007) found that the median time between drug exposure and symptom development was 1 day for antibiotics and 11 days for all other drugs. The pustular eruption typically lasts for 7–10 days and is followed by superficial desquamation lasting several days, characterized at times by collarettes of scale (Fig. 26.3). In most cases, AGEP is self-limited and resolves without treatment 1–2 weeks after removing the offending drug. Courses lasting longer than 2 weeks are rare. AGEP typically has a favorable prognosis, with a reported mortality rate of less than 5 %, usually due to infections in the elderly or immunocompromised, secondary comorbidities, or hemodynamic instability followed by formation of bullae resulting from confluent pustules.

The estimated incidence of AGEP is one to five cases per million per year, most often occurring in adults. It affects both sexes but appears to occur in females more often. One study has found associations with HLA types B51, DR11, and DQ3.

Treatment for AGEP is chiefly symptomatic and supportive. Immediate withdrawal of the presumed causative agent is the mainstay of therapy. Antibiotics are not to be given unless there is a well-documented associated infection. When a patient is taking multiple medications, those frequently associated with AGEP should be stopped. Older or immunocompromised patients with significant fever or widespread eruption may require hospitalization for fluids, electrolyte repletion, and nutritional support. Symptomatic treatment involves moist dressings during the pustular phase to relieve pruritus and prevent superinfection. Emollients may support skin barrier function restoration during the desquamation phase. The use of topical corticosteroids and oral antihistamines has been proposed for symptomatic relief, but their efficacy has not been evaluated in clinical trials. To date, there is limited evidence to support the use of systemic corticosteroids.

Clinical Differential Diagnosis

The clinical differential diagnosis for acute generalized exanthematous pustulosis (AGEP) includes generalized acute pustular psoriasis (von Zumbusch type), subcorneal pustular dermatosis (Sneddon-Wilkinson disease), bullous impetigo, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), erythema multiforme, Sweet syndrome (neutrophilic dermatosis of the skin), subcorneal immunoglobulin A dermatosis, viral exanthema with secondary pustulation, and infectious folliculitis.

Without additional historical, laboratory, or histologic data, generalized acute pustular psoriasis and AGEP may be difficult to distinguish both clinically and histologically. Factors that support the diagnosis of generalized acute pustular psoriasis include a history of psoriasis, absence of drug exposure, and histologic findings of subcorneal pustules, papillary dermal edema, and dermal eosinophils. Longer duration of symptoms,

mainly fever and pustular eruption, also supports this diagnosis. Although pustular psoriasis can be caused by drugs, the spectrum of associated medications (mainly beta-blockers and lithium) is very different from those associated with AGEP. Furthermore, a more abrupt-onset, short duration (2 weeks), association with recently introduced drugs, spontaneous resolution after withdrawal of culprit drugs, and a non-recurrent tendency supports the diagnosis of AGEP.

Histopathology and Histologic Differential Diagnosis

Roujeau et al. (1991) described the main histologic findings of AGEP to be subcorneal and/or intraepidermal pustules (66 %), papillary dermal edema (61 %), a polymorphous perivascular infiltrate with eosinophils (34 %), necrotic keratinocytes (25 %), and leukocytoclastic vasculitis with fibrinoid necrosis (20 %). In most cases, the epidermis was uninvolved or exhibited spongiosis without psoriasiform hyperplasia (61 %). Additional findings include pustular or dermal eosinophilic exocytosis, leukocytoclastic vasculitis with fibrinoid deposits, and erythrocyte extravasation. Hyperplastic epidermal changes, such as acanthosis and papillomatosis, as well as follicular pustules, are rare.

The histologic differential diagnosis of AGEP includes pustular psoriasis, subcorneal pustular dermatosis, pustular contact dermatitis, bullous leukocytoclastic vasculitis, drug hypersensitivity syndrome, and IgA pemphigus. The main differential diagnosis is pustular psoriasis. Features that are more characteristic of AGEP include the presence of papillary dermal edema, necrotic keratinocytes, and dermal eosinophils (Fig. 26.4a–c). Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) exhibits only subcorneal pustules; whereas intraepidermal pustules are often noted in AGEP. A few cases of pustular contact dermatitis exhibiting subcorneal pustules have been reported in the literature and, thus, can be difficult to distinguish from AGEP. While pustular lesions may arise in some cases of leukocytoclastic vasculitis, vasculitis is an uncommon feature of AGEP. Drug hypersensitivity syndrome, or DRESS (drug rash with eosinophilia and systemic syndrome), may present with pustules, but these typically are less pronounced than those seen in AGEP. In addition, patients with drug hypersensitivity syndrome often have lymphadenopathy, eosinophilia, mononucleosis, and significant visceral involvement, such as hepatitis, nephritis, pneumonitis, and/or myocarditis. Mild acanthosis would usually be noted in cases of IgA pemphigus. In addition, direct immunofluorescence would demonstrate intercellular IgA deposition.

Etiology

It appears that greater than 90 % of all reported cases of AGEP are drug-related, with a wide variety of medications suspected to cause this reaction pattern. In 2001, Sidoroff and colleagues put forth a comprehensive list of medications that had been published in case reports and larger series of AGEP. Among the medications, antibacterials of the β-Lactam, macrolide, and cephalosporin drug classes were most commonly implicated. In addition, antimycotics, calcium channel blockers, hydroxychloroquine, antalgics and antipyretics, antiparasitics, antiarrhythmics, tricyclic antidepressants, anxiolytics, and others have been found to cause AGEP. Of note, there have been cases reported of AGEP caused by aspirin. According to a EuroSCAR study, pristinamycin, aminopenicillins, quinolones, (hydroxy) chloroquine, sulfonamides, terbinafine, and diltiazem were the drugs that conferred the highest risk. Lower risk etiologic medications include corticosteroids, macrolides, non-steroidal anti-inflammatory drugs, and antiepileptic drugs. Others include terazosin, omeprazole, sennoside, and anti-retroviral protease inhibitors. Topical medications, including bufexamac and other mercury products, have also been linked to AGEP through contact sensitivity. A more recent review of the literature by Speeckaert et al. (2010) identified case reports of AGEP caused by anticonvulsants such as phenytoin, low-molecular weight heparin, and many others.

AGEP has also been associated with viral infections, such as with Adenovirus, Coxsackie B4 virus, Cytomegalovirus, E. coli, Echovirus, Enterovirus, Epstein-Barr virus, Hepatitis B virus, and Human Parvovirus B19. Case reports of AGEP associated with bacterial and parasitic infections, such as with *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Echinococcosis*, have also been documented. Exposure to mercury was a suspected cause for 8 of 63 patients reported by Roujeau et al. (1991). Vaccinations, illicit drug use, herbal medications, spider bites, intravenous contrast media, lacquer chicken, and progesterone have also been associated with AGEP. However, given the preponderance of evidence behind medications and other supplements as causing AGEP and the rather limited, weaker evidence supporting infectious causes, such cases are best considered as *parainfectious* causes of AGEP until proven otherwise.

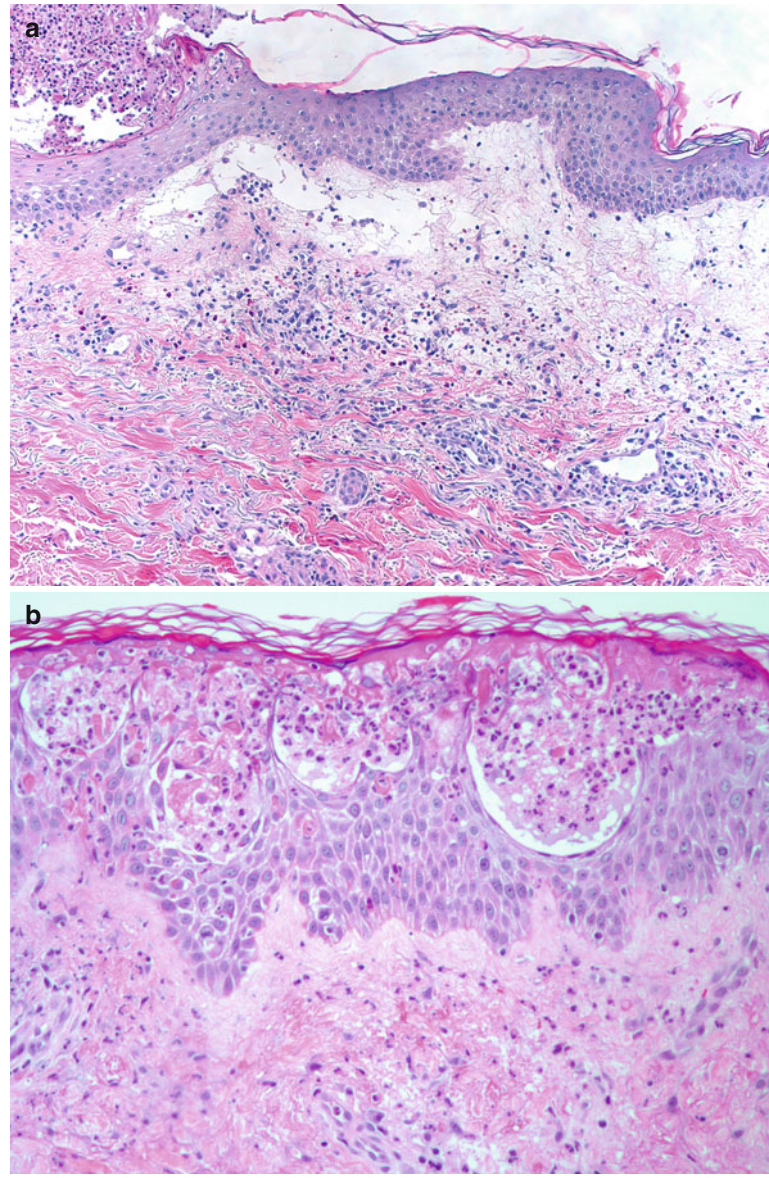
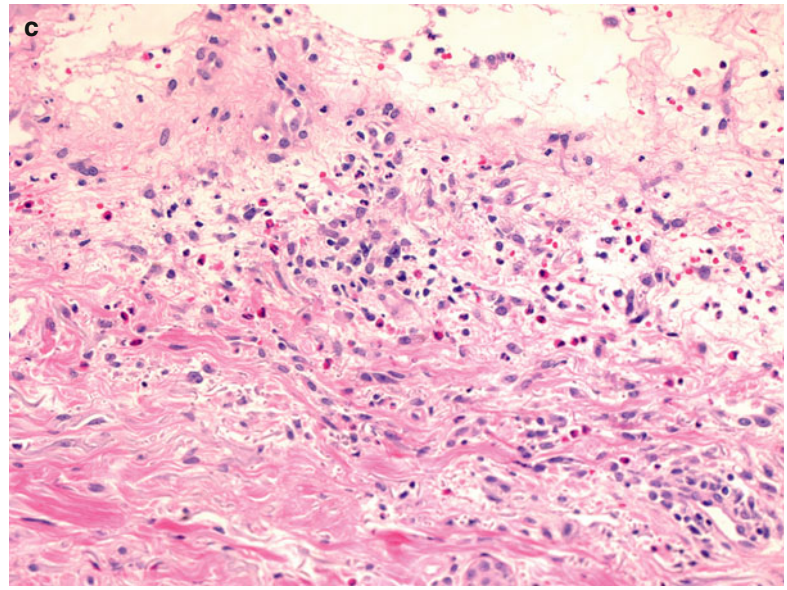


Fig. 26.4 Salient histologic features of acute generalized exanthematous pustulosis include (**a**) papillary dermal edema, (**b**) necrotic keratinocytes, and (**c**) a prominent dermal infiltrate of eosinophils

Fig. 26.4 (continued)



Pathophysiology

Our understanding of the pathogenic mechanisms underlying AGEP is incomplete. However, immunohistologic investigation of patch test studies as well as direct immunologic study of immune cells generated from these patch tests and from the peripheral blood of patients with drug-induced AGEP have demonstrated the crucial role of CXCL (chemokine (C-X-C motif) ligand)-8 producing, drug-specific T cells in orchestrating the neutrophil response.

Based on these studies, Britschgi and Pichler (2002) have proposed a three-phase model for the regulation of T-cell/keratinocyte-orchestrated neutrophil-rich inflammation in AGEP. Phase 1 involves the activation and expansion of drug-specific T cells with subsequent migration to the skin. After exposure to the offending drug, professional antigen-presenting cells activate drug-specific T cells by presenting the drug on major histocompatibility complex (MHC) class I (for CD8+) and class II (for CD4+) in the lymph nodes. These drug-specific T-cells then expand and subsequently migrate into the dermis and epidermis.

Phase 2 is characterized by the functional, orchestrating activity of drug-specific T-cells in the skin as well as drug presentation by Langerhans' cells and keratinocytes. The principal role of infiltrating CD4+ T-cells is the massive secretion of the neutrophil recruiting factors CXCL8 and granulocyte macrophage colony-stimulating factor (GM-CSF), as well as of other factors (interferon-γ, interleukin-4, interleukin-5, and RANTES (regulated on activation, normal T expressed and secreted). On the other hand, CD8+ T-cells produce interferon-γ and destroy tissue/keratinocytes through cytotoxic mechanisms including perforin/granzyme B and the Fas/Fas-L apoptotic system. These T-cells are further stimulated by drug-presenting keratinocytes (MHC class I) and by Langerhans' cells (MHC class I and II). It is thought that the release of inflammatory cytokines such as interferon-γ may stimulate the keratinocytes to secrete CXCL8. At this point, CD4+ and CD8+ cells are scattered throughout the epidermis, but the subcorneal vesicles are populated mainly by CD4+ cells. Very few neutrophils and eosinophils are present at this stage.

In Phase 3, neutrophils are recruited to the skin in increasing numbers by attachment to the site of inflammation via adhesion molecules (e.g., intercellular adhesion molecule-1), expressed on activated endothelial cells. They migrate through

the dermis into the epidermis along an increasing CXCL8 gradient, and eventually fill the vesicles, transforming them into pustules. At this point, T-cells are mainly gathered in the dermis (CD4+ more so than CD8+) and around blood vessels (where CD4+ and CD8+ are more similar in number).

This final phase may proceed as long as the drug is present. Resident antigen-presenting cells and keratinocytes may continue to present the drug to and stimulate T-cells, which will continue to orchestrate the inflammation by activation and destruction of the tissue and by recruitment of more neutrophils to the skin. The release of interleukin-5 and RANTES may contribute to the eosinophilia seen in some patients.

Conclusions

AGEP is a rare, dramatic drug reaction. It mimics generalized pustular psoriasis, and some authors consider it a variant of that disease. It is usually self-limited but the offending medication must be identified and discontinued. Clinicians need to be alert to this illness so early recognition can lead to discontinuation of the offending medication as quickly as possible.

Suggested Reading

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Part V

Skin Drug Reactions of Specific Drug Groups

Cutaneous Drug Reactions to Anticoagulants

27

Sarah A. Fantus

Abstract

Warfarin-induced skin necrosis is caused by a nonimmune-mediated transient hypercoagulable state at the initiation of therapy. Grossly and histopathologically it is very hard to differentiate from heparin-induced skin necrosis (HISN). HISN is a manifestation of heparin-induced thrombocytopenia and thrombosis syndrome (HITT); it is a type II antibody-mediated hypersensitivity reaction. It is clinically important because the rapidly progressive cutaneous necrosis heralds a life-threatening systemic reaction to heparin. Delayed-type hypersensitivity to heparin is a far more common cutaneous reaction to heparin and can look quite similar to HISN at the outset. It is critical to differentiate between the two because of the clinical management implications.

Keywords

Anticoagulant • Warfarin-induced skin necrosis • Heparin-induced skin necrosis • Delayed-type hypersensitivity

Introduction

Anticoagulants are widely used medications for both prophylaxis and treatment of thromboembolic disease with a unique set of serious cutaneous adverse effects, some of which signal life-threatening conditions. This chapter will focus on three important cutaneous drug reactions: warfarin-induced skin necrosis (WISN), heparin-induced skin necrosis (HISN), and delayed-type hypersensitivity to heparin (DTH-heparin) (Table 27.1). Of note, there have been reports of immediate-type hypersensitivity reactions to heparin, mostly attributed to impurities in heparin preparations. Cutaneous manifestations are as would be expected, with an anaphylactoid reaction with cutaneous manifestations such as urticaria and angioedema.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_27

Table 27.1 Comparison of anticoagulant-associated skin lesions

	Warfarin-induced skin necrosis	Heparin-induced skin necrosis	Heparin delayed-type hypersensitivity
Incidence	0.01–0.1 %	UFH: <3 % LMWH: <0.1 %	7.5 %
Onset	90 % day 3–6 Almost all by day 10	Day 5–10 If previous sensitization (within 3 months), day 1–5	Day 7–14 If previous sensitization (within 100 days), day 1–5
Gross appearance	Necrosis at sites with increased subcutaneous fat	Necrosis at injection sites but can be at distant sites. Can be caused by IV heparin.	Erythematous plaques at injection sites but can be at distant sites. Can be caused by IV heparin.
Histopathology	Fibrin thrombi (red clots) in dermal vessels Necrosis RBC extravasation	Platelet thrombi (white clots) in dermal vessels Necrosis RBC extravasation	Perivascular lymphocytic infiltrate ± Spongiosis
Associated features	Protein C deficiency Obesity Female sex VTE	Pain HITT	Pruritis Pregnancy
Course	Self-limiting	Life-threatening With continued course, new and extensive skin necrosis	Self-limiting With continued course, may generalize
Management	Discontinue warfarin Start vitamin K, FFP Start alternative anticoagulation	Discontinue heparin Start heparinoid or direct thrombin inhibitor	Discontinue heparin ± Allergy testing
Ability to restart	Yes (at low dose and slow taper)	No (with exception of specific surgical situations)	No SQ UFH or LMWH. IV heparin and fondaparinux often tolerated

Abbreviations: *VTE* venous thromboembolism, *FFP* fresh frozen plasma, *UFH* unfractionated heparin, *LMWH* low-molecular-weight heparin, *SQ* subcutaneous, *RBC* red blood cell, *IV* intravenous

Warfarin-Induced Skin Necrosis (WISN)

Warfarin is one of the coumarin congeners, which also include bishydroxycoumarin, phenprocoumon, acenocoumarol. These medications anticoagulate by inhibiting the enzyme that reduces oxidized vitamin K back to its active state, thereby inhibiting vitamin K-dependent coagulation factors. Warfarin is the most widely used oral anticoagulant worldwide.

Epidemiology and Pathophysiology

WISN affects 0.01–0.1 % of treated patients. It occurs more frequently in obese middle-aged women, with a female-to-male ratio of 4:1. The majority of patients are ill and hospitalized; DVT, pulmonary embolism, and thrombophlebitis are the most common indications for anticoagulation in these patients.

The pathophysiology of WISN involves the balance of anticoagulation and coagulation forces, perturbed by the initiation of warfarin.

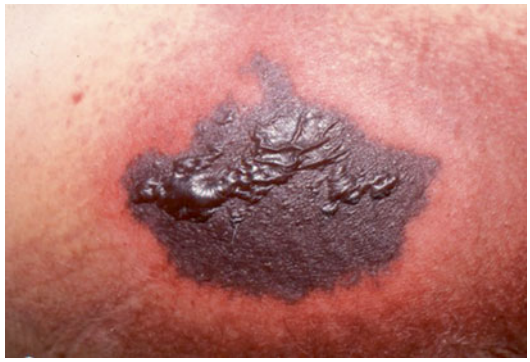

Fig. 27.1 Necrotic tissue measuring 15 cm over the left buttock of a patient on day 3 of coumadin therapy. At least 90 % of patients are on days 3–5 of coumadin therapy. Bullae formation is seen over the surface and dramatic surrounding erythema. Pain is usually severe

Factors inhibited by warfarin, due to their vitamin K-dependence, include factors II, VII, IX, and X as well as anticoagulation proteins C and S. Protein C and factor VII have short half-lives (5–8 h) relative to factors II, IX, and X (2–3 days), leading to a more rapid decrease in the former relative to the latter. This causes a transient hypercoagulable state during the initiation of therapy. This also explains why protein C deficiency (acquired or inherited) is a significant risk factor for development of WISN. Less frequently, protein S deficiency, antithrombin III deficiency, factor V Leiden mutation, and antiphospholipid antibody syndrome have been associated with WISN. Other proposed mechanisms of WISN include the direct toxic effect of warfarin on vessel walls and immunologic hypersensitivity to warfarin.

Presentation

Early symptoms are localized paresthesia and edema with progression to livedo macules, petechiae, and ecchymosis; hemorrhagic bullae form within 24 h (Fig. 27.1). After days, lesions are characterized by full-thickness necrosis and painful subcutaneous ulcerations. 90 % of cases occur between days 3 and 6 after treatment initiation; almost all occur by day 10. There have been reports of WISN occurring up to 15 years after treatment initiation as well as several days after cessation of therapy. Areas with more subcutaneous fat are more susceptible, such as the abdomen, buttocks, thighs, and breast tissue. One-third of patients have multiple sites of involvement. Of note, the cutaneous appearance of warfarin necrosis is difficult to distinguish from that of heparin necrosis.

Histopathology

- Diffuse microthrombi in dermal and subcutaneous vessels
- Necrosis of epidermis and dermis
- Erythrocyte extravasation
- No evidence of inflammation or vasculitis

Differential Diagnosis

- HISN: history of heparin use, lesion at injection site, heparin-induced thrombocytopenia and thrombosis syndrome (HITT) manifestations
- Catastrophic antiphospholipid syndrome (Asherson's syndrome): multiorgan dysfunction, positive antiphospholipid antibodies, histopathologic evidence of small vessel thromboses
- Calciphylaxis (Fig. 27.2): end-stage renal disease, characteristic histopathology, predominant lower extremity involvement
- Microemboli (septic, cholesterol): "purple toe syndrome"
- Disseminated intravascular coagulation (Fig. 27.3—symmetrical peripheral gangrene and purpura fulminans are both probably the same disease): associated clinical condition (sepsis, hemolytic transfusion reaction, severe head injury, amniotic or fat embolism, etc.), multiple organ ischemic necrosis, consistent labs (schistocytes on blood smear, thrombocytopenia, prolonged coagulation studies,

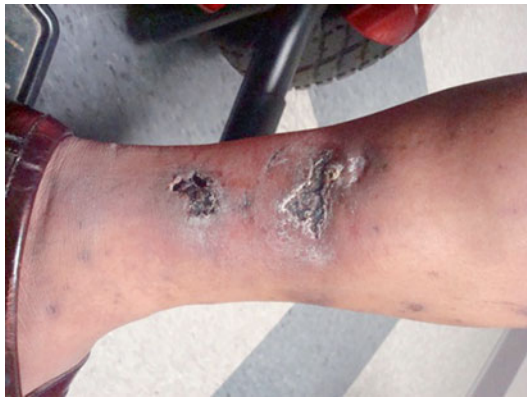

Fig. 27.2 Multiple sites of necrosis over the ankle of a dialysis patient with surrounding erythema and induration. Histopathology on biopsy was compatible with calciphylaxis. The pain was exquisite and response to sodium thiosulfate was rapid. There was no history of anticoagulation

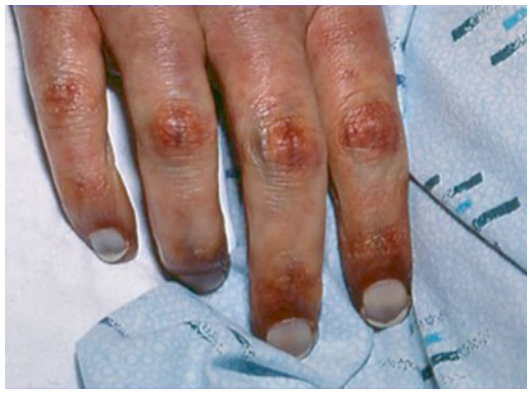

Fig. 27.3 Purpuric necrotic changes in fingers in a patient with disseminated intravascular coagulation syndrome. In purpura fulminans the necrosis is often symmetric and peripheral. The patient had E coli sepsis. Sepsis is the commonest cause of purpura fulminans

increased D-dimer and fibrin degradation products, reduced coagulation factor levels)

- Purpura fulminans (Fig. 27.3): diffuse non-thrombocytopenic purpura, recent serious infection
- Necrotizing fasciitis: positive wound culture and tissue Gram stain
- Cryoglobulinemia: palpable purpura, Raynaud phenomenon, elevated cryocrit, leukocytoclastic vasculitis, hepatitis C, decreased C4 out of proportion to C3

Diagnosis and Management

Diagnosis is made based on clinical suspicion, biopsy, and ruling out other diagnoses. First steps in management include cessation of warfarin, administration of fresh frozen plasma and vitamin K, and initiation of an alternative anticoagulant such as heparin. Local treatment includes topical bactericidal agents. Surgical debridement, skin grafting, or amputation is required in more than 50 % of cases. Treatment with recombinant protein C has been shown to be beneficial in patients with documented protein C deficiency, but cost is prohibitive. An important distinction between warfarin-induced and heparin-induced skin necrosis is that warfarin can be reintroduced after an episode while heparin cannot, in most circumstances. It is important to start warfarin at a low dose, with slow increase to therapeutic level; loading doses should be avoided, and heparin bridging considered. The lesions are self-limited and generally resolve over several weeks.

Heparin-Induced Skin Necrosis

Heparins work by activating antithrombin and thereby inhibiting thrombin, or factor IIa, in the coagulation cascade. Unfractionated heparin (UFH) is a large negatively charged polysaccharide that forms a complex with antithrombin and the coagulation factor to be inhibited: either factor IIa (thrombin) or Xa. Low-molecular-weight heparin (LMWH) is fractionated into shorter polysaccharides with a higher concentration of the relevant pentasaccharide binding sequence. Examples include enoxaparin and dalteparin. Fondaparinux is a synthesized sulfated pentasaccharide that specifically inhibits factor Xa. The heparinoids (e.g., danaparoid) have similar antithrombotic effects.

Epidemiology and Pathophysiology

Heparin-induced skin necrosis (HISN) occurs in association with heparin-induced thrombocytopenia (HIT), a type II antibody-mediated

hypersensitivity reaction in which the heparin polysaccharide forms a complex with platelet factor 4 (PF4) and an IgG antibody. This complex binds to platelet receptors causing platelet activation and release of procoagulant substances, resulting in venous and arterial thrombosis. Incidence is estimated to be between 0.1 and 5 % of those treated with UFH or LMWH. The incidence of HIT is ten times higher with the use of UFH compared to LMWH. The fall in platelet count (either below 150×10^9/L or a decrease by 30–50 %) that signals HIT occurs 5–10 days after treatment initiation, though it can occur within 24 h in patients with preformed antibodies due to recent exposure (within 3 months). There are also reports of delayed-onset HIT up to 3 weeks after treatment discontinuation.

Cutaneous HIT manifestations occur due to intradermal microvascular thrombosis. Interestingly, the same receptor that the heparin-PF4-IgG complex binds to on platelets (FcγRIIa) exists in microvascular endothelial cells only in the superficial dermal vascular plexus, which may explain the distribution of pathology. The incidence of skin lesions in patients with HIT is 10–20 %, though this is an overestimate of the actual incidence of HISN given misidentification of DTH-heparin as HISN. Subcutaneous and intravascular UFH, as well as LMWH, can cause HISN.

Presentation

Briefly, systemic manifestations of HIT include thrombocytopenia (85–90 % of patients), venous thrombosis (17–55 %), and arterial thrombosis (3–10 %). When HIT is associated with thrombosis it is termed HIT and thrombosis syndrome, or HITT. Interestingly, many HIT patients with cutaneous findings do not have absolute thrombocytopenia. Platelet counts may be artificially elevated due to critical illness. In the case of subcutaneous UFH or LMWH, lesions are most commonly found at injections sites, though they can also occur at distant sites. In cases of HISN associated with IV UFH, lesions tend to occur overlying fatty tissues. The earliest finding in HISN is a painful erythematous lesion around the injection site with progression to hemorrhagic bullae, and eventually cutaneous necrosis with central black eschar (Fig. 27.4) and surrounding induration and erythema. The pain and erythema resolves within 5 days, leaving black necrotic tissue with a well-defined border; irregular branching margins are sometimes seen.

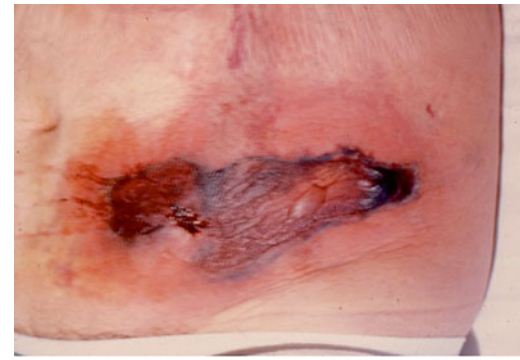

Fig. 27.4 Heparin necrosis at the site of subcutaneous heparin injection, with a large hemorrhagic area of necrosis covering left lower abdomen with surrounding erythema. Heparin was discontinued and the patient survived after multiple plastic surgery procedures

Histopathology

- Platelet "white clots" in dermal microvasculature
- Epidermal and dermal necrosis
- ± subepidermal blister
- Extravasation of erythrocytes into dermis
- No evidence of inflammation or vasculitis

Differential Diagnosis

- Heparin-DTH: absence of necrosis, pruritis, scaling, papules, suggestive histopathology, negative HIT labs
- WISN: history of warfarin use within 3–6 days, negative HIT labs
- Catastrophic antiphospholipid syndrome
- Purpura fulminans
- Necrotizing fasciitis
- Calciphylaxis

- Disseminated intravascular coagulation
- Microemboli (cholesterol, septic)
- Cryoglobulinemia

Diagnosis and Management

If HISN is suspected, platelet count should be monitored and laboratory HIT diagnostics completed. These include functional platelet activation assays (serotonin release assay or platelet activation assay) as well as PF4 antigen assay (ELISA). Heparin (UFH or LMWH) treatment should be stopped and alternative anticoagulation with a heparanoid (danaparoid) or direct thrombin inhibitor (lepirudin or argatroban) should be initiated. There are specific guidelines for future anticoagulation for HIT patients; heparins should be avoided with the exception of short-term use for surgery in patients in whom heparin antibodies are confirmed to be absent. As expected, surgical debridement and skin grafting may be needed to treat HISN depending on severity.

Delayed-Type Hypersensitivity (DTH) to Heparin

DTH to heparin is far more common and less severe than HISN. While both are immune mediated they are caused by fundamentally different immune mechanisms: DTH is a type IV, T-cell mediated hypersensitivity, while HISN is a type II, antibody-mediated hypersensitivity. It is critically important to distinguish between these two cutaneous reactions, as the management and prognosis are quite different.

Epidemiology and Pathophysiology

Because UFH is composed of a complex mixture of polysaccharide chains, there are a number of non-specific binding reactions that may occur. Both UFH and LMWH are naturally derived from porcine gut or bovine lung, which also may contribute to immune reactivity. The specific antigen that causes this type IV hypersensitivity reaction is unknown.

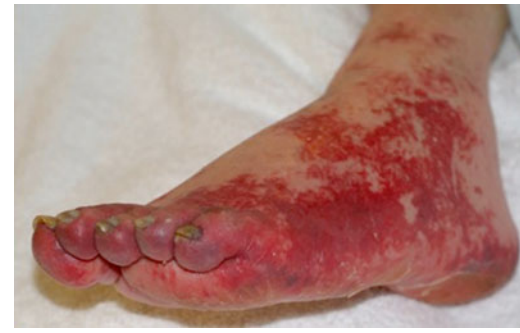

Fig. 27.5 Delayed hypersensitivity reaction to heparin without necrosis, but a erythematous plaque covering the entire foot. Heparin was stopped. No surgery was necessary. Platelets and other laboratory tests were negative for HIT

A wide range of values for the incidence of heparin-DTH has been reported: 0.2–40 %. A 2009 prospective trial found the incidence of heparin-DTH to be 7.5 % in hospitalized patients using LMWH. Risk factors are older age, female sex, pregnancy, obesity, long duration of treatment, and use of UFH. 92.5 % of all 212 patients reported (with sex specified) in the literature as of 2006 were female. DTH-heparin occurs after administration of both UFH and LMWH. There are seldom reports of this reaction with fondaparinux and heparinoids. A large 2010 prospective trial found the incidence of cutaneous DTH reactions to fondaparinux to be 0.4 %, 20 times lower than the incidence with commonly used heparins.

Presentation

These lesions initially appear similar to HISN with erythema at the injection site. There is a spectrum of cutaneous manifestations from mild erythema to infiltrated plaques (Fig. 27.5) with papulovesicles. Lesions are associated with itching and generally start within two weeks of treatment initiation. Patients who have been sensitized to heparin within the previous 100 days can present as early the day after treatment initiation. Delayed presentations up to 5 months after treatment initiation have been reported. Generalized eczema or exanthema occurs in 3–10 % of

patients after use of subcutaneous heparin. IV administration of heparin can rarely cause a maculopapular exanthema.

Histopathology

- Perivascular lymphocytic infiltrate, CD4+
- Spongiosis

Differential Diagnosis

- Local infection
- Irritant contact dermatitis to skin disinfectants or tape
- HISN

Diagnosis and Management

If a patient has a cutaneous reaction while on heparin therapy, the first step is to rule out life-threatening HIT with HISN (see HISN section). In some patients a skin biopsy will be necessary for diagnosis. When diagnosis is established, subcutaneous heparin therapy should be stopped and an alternative nonheparin anticoagulant initiated if clinically necessary. Topical corticosteroid treatment is generally sufficient for localized lesions.

The utility of allergy testing in cases of suspected DTH-heparin is limited. In most cases, biopsy and clinical presentation alone should be sufficient to make the diagnosis. Concerns regarding allergy testing are lack of specificity and sensitivity, possible sensitization to new antigens, contraindication in cases of HIT, and infeasibility of completion during clinical decision making (must be done 6 weeks after clearance of all lesions).

Reasons to complete allergy testing include unclear diagnosis, no histology available, or need to identify alternative anticoagulants. In those cases, a skin test and/or a subcutaneous challenge test should be done; if both are negative, DTH-heparin is excluded. If either is positive, an intravenous heparin challenge should completed to determine if the patient can tolerate IV heparin in the future. If the IV challenge is negative, IV heparin is a safe alternative for anticoagulation in these patients. In a prospective trial of 28 patients with skin or subcutaneous challenge-proven DTH-heparin after subcutaneous administration, all patients had a negative IV challenge. IV heparin can be administered in urgent cases without prior testing. Typically there is extensive cross-reactivity among all subcutaneous preparations of UFH and LMWH. Unfortunately, heparinoids also exhibit considerable cross-reactivity with heparin in the case of DTH. Fondaparinux is a potential alternative treatment for these patients, though there have been reports of cross-reactivity. Up to 50 % of patients with past episodes of heparin-DTH do not tolerate fondaparinux.

Conclusions

Anticoagulants have two significant skin reactions. One is immune in nature and is seen with heparin and its derivatives. It presents most often with distal cutaneous necrosis. The second is seen with warfarin and its derivatives, and is also manifested mainly by necrosis. It is not immune in nature and tends to be more proximal over areas of fat deposition. Since the same patient is often on these drugs, differentiation is crucial. Biopsy, timing, and laboratory tests help to allow this differentiation.

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Antiepileptic Medications and Cutaneous Drug Reactions

28

Sarah A. Fantus

Abstract

Antiepileptic drugs (AEDs) have long been associated with a high incidence of cutaneous reactions, none of which are specific to these drugs. This chapter will address three clinically distinct serious cutaneous reactions seen most characteristically with AEDs. Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), is most commonly associated with AEDs. Issues unique to AED-induced DRESS/DIHS include specific clinical manifestations, the contribution of AED metabolism to theories of pathogenesis, and cross-reactivity among AEDs. AEDs are an important cause of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN); in some populations carbamazepine is the most commonly associated drug, especially in those with a genetic predisposition. The great majority of drug-induced cutaneous pseudolymphoma cases are associated with phenytoin.

Keywords

Antiepileptic drugs • DRESS • DIHS • SJS/TEN • HHV-6 • Pseudolymphoma

Introduction

Antiepileptic drugs (AEDs) are also referred to as anticonvulsants and antiseizure medications. They are used in the treatment of epileptic seizures and, increasingly, in the treatment of psychiatric disorders and neuropathic pain. The general mechanism of action is to inhibit excitatory neurotransmission via sodium and calcium channels or to enhance inhibitory neurotransmission via GABA receptors. AEDs can be categorized as aromatic or non-aromatic based on the presence and metabolism of aromatic rings in their chemical structure; this distinction is relevant in the discussion of cutaneous drug reactions. Selected aromatic AEDs include carbamazepine, phenytoin, phenobarbital, and

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_28

primidone. Valproic acid, lamotrigine, and levetiracetam are non-aromatic.

Cutaneous reactions to AEDs are quite common: one large retrospective study of 1,875 patients taking AEDs found the incidence of "rash" to be 14.3 %. Another important issue with AEDs and cutaneous reactions is that the cross-reactivity is high. The same study investigated cross-reactivity and found rates to be as high as 70 % for some drug pairs: the most cross-reactive pairs were phenytoin/carbamazepine and phenobarbital/carbamazepine.

Finally, there has been longstanding debate in the literature as to how cutaneous reactions to AEDs should be categorized. Historically, reactions to specific drugs were named (e.g., phenytoin syndrome). Once a similar reaction was recognized among many AEDs and other medications, the constellation was identified as a more general "hypersensitivity" syndrome. Some authors have lumped Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) into this category. This chapter will discuss the following clinically distinct serious AED-induced cutaneous reactions: drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug-induced cutaneous pseudolymphoma (CPL).

AEDs and DRESS/DIHS

AED "hypersensitivity" reactions have been recognized by various names since the 1950s. In the late 1990s, there was an effort to place all of these hypersensitivity reactions under the same umbrella: drug reaction with eosinophilia and systemic symptoms, or DRESS. More recently, the term "drug-induced hypersensitivity syndrome" (DIHS) has been proposed. DRESS/DIHS has been associated with myriad drugs, including AEDs, antimicrobials, nonsteroidal anti-inflammatories, antidepressants, sulfonamides, angiotensin-converting enzyme inhibitors, beta-blockers, and allopurinol. Far and away the majority of reported DRESS/DIHS occurrences are associated with aromatic AEDs.

This section will focus on AED-induced DRESS/DIHS; please see Part IV for a more general discussion of life-threatening skin drug reactions.

Epidemiology and Pathophysiology

The estimated incidence of AED-associated DRESS/DIHS is between 1 per 1,000 and 1 per 10,000 exposures to AEDs. Classically, DRESS/DIHS has been associated with three aromatic AEDs: carbamazepine, phenytoin, and phenobarbital. Carbamazepine is the most common medication implicated in DRESS/DIHS. While DRESS/DHS is more common with aromatic AEDs, there are also reports with valproic acid, levetiracetam, zonisamide, and lamotrigine (especially in combination with valproic acid). In fact, the FDA issued a warning of severe skin rashes (not always DRESS/DIHS) with lamotrigine use, citing an incidence of 8 per 1,000 pediatric patients and 3 per 1,000 adult patients receiving therapy for epilepsy.

DRESS/DIHS can occur at any age; there are two peaks between 21 and 40 years and between 61 and 70 years. There is no sex predilection. The majority of reported cases are in African-American patients, but this may be due solely to the higher incidence of epilepsy in these patients.

The mechanism of DRESS/DHS probably involves a combination of genetic, immune, and metabolic factors. In the case of aromatic AEDs, differences in drug detoxification and metabolism seem to be key in the pathogenesis of DRESS/DHS. The aromatic rings of these medications are metabolized by cytochrome P450 enzymes to toxic arene oxides, which are in turn detoxified by epoxide hydrolase. This enzyme may be deficient in patients prone to DRESS/DHS. The arene oxides bind to cellular macromolecules and both have a direct cytotoxic effect and form haptens that elicit an immune response.

There also may be a viral component to the pathophysiology. Reactivation of latent human herpes virus-6 (HHV-6) as well as cytomegalovirus, Epstein-Barr virus, and human herpes virus-7, has been reported in cases of DRESS/DIHS. The clinical manifestations of DRESS/

DIHS may be mediated by antiviral T-cells that cross-react with drugs. This helps explain the delayed onset, the continued systemic manifestations after drug withdrawal, and the waxing and waning nature of the clinical manifestations.

Presentation

DRESS/DIHS is characterized by the triad of skin reaction, fever, and systemic involvement occurring 2–8 weeks after drug initiation. Fatigue, low-grade fever, lymphadenopathy, and pharyngitis can precede cutaneous manifestations by several days. The most commonly cited scenario is a symmetric morbilliform eruption appearing over the trunk and face and subsequently spreading to the extremities. Facial edema, especially periorbital edema, is a hallmark of DRESS/DIHS. Small, sterile pustules may be present. Purpura can develop, especially on the lower extremities. The rash may develop into severe diffuse erythroderma and exfoliative dermatitis. Mucosal involvement is infrequent.

Liver involvement is the most frequent systemic manifestation (34–94 % of patients); other systemic manifestations include lymphadenopathy, pneumonitis, nephritis, colitis, myocarditis, encephalitis, diabetes mellitus, and thyroiditis. Liver involvement ranges from transient derangement of liver enzymes to liver necrosis with fulminant hepatic failure, which is the most frequent cause of death. The overall mortality rate of DRESS/DIHS is 10 %. Hematologic manifestations include eosinophilia (approximately 60 %), hypogammaglobulinemia, and atypical lymphocytosis. There is often a flare of clinical symptoms several weeks after the withdrawal of the causative drug.

Of note, some clinical manifestations are more common with specific AEDs. Kidney involvement is more frequently observed in phenytoin-induced DRESS/DIHS compared to carbamazepine and phenobarbital. Atypical lymphocytosis occurs more frequently with phenobarbital. Lamotrigine-induced DRESS/DIHS is typically characterized by a more severe rash and a lower frequency of eosinophilia and lymphadenopathy.

Histopathology

- Dense dermal lymphocytic infiltrate, diffuse or superficial perivascular
- May have atypical lymphocytes in band-like formations
- Presence of eosinophils

Differential Diagnosis

- Other cutaneous drug reactions:
  - SJS/TEN: mucosal involvement
  - AGEP: acute generalized erythematous pustulosis
  - Drug-induced pseudolymphoma
- Acute viral reactions (e.g., measles, infectious mononucleosis, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus)
- Hypereosinophilic syndrome
- Staphylococcal scalded skin syndrome
- Serum sickness-like reaction
- Kawasaki disease: pediatric patient

Diagnosis and Management

Diagnosis of DRESS/DIHS depends on clinical recognition. The following list of clinical findings may aid in diagnosis:

- Morbilliform rash developing 2–8 weeks after drug initiation (Fig. 28.1)
- Drug is high risk, such as an aromatic AED
- Fever
- Liver abnormalities or other organ involvement
- Leukocyte abnormalities: eosinophilia, atypical lymphocytosis, leukocytosis
- Lymphadenopathy

Potential diagnostic testing includes patch testing and lymphocyte toxicity assay/lymphocyte transformation test. Patch testing is not useful for immediate diagnostic purposes because it must be done at least 6 weeks after complete recovery; in addition, its diagnostic accuracy in

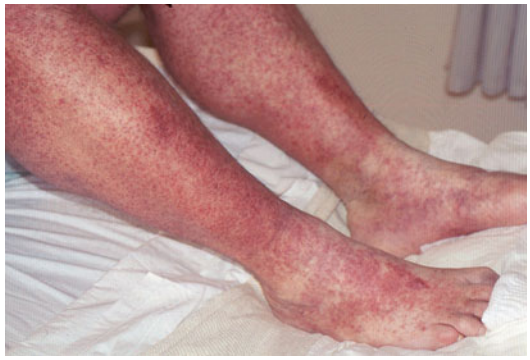

Fig. 28.1 Symmetric, erythematous morbilliform drug reaction in a patient with DRESS syndrome

the case of DRESS/DIHS is not well established. The lymphocyte toxicity assay is used to predict susceptibility of patients to DRESS/DIHS; the transformation test is used to confirm diagnosis by detection of peripherally circulating drug-specific T-cells. Neither of these tests has been established as appropriate and valid in the diagnosis of DRESS/DIHS at this stage.

Testing for HHV-6 reactivation through detection of a rise in anti-HHV-6 IgG titers and/or HHV-6 DNA levels 2–3 weeks after the onset of the cutaneous reaction may be considered. HHV-6 reactivation is not detected in all DRESS/DIHS patients; this may be due to the complex interplay of immune suppression by AEDs and the anti-viral response. In a study of 100 patients, a rise in HHV-6 IgG titers was detected in 62. HHV-6 reactivation seems to be more common in more severe cases, so it may be used as a marker of prognosis.

The first step in suspected AED-induced DRESS/DIHS is to create a medication timeline to confirm timing after drug initiation and to identify any other potential culprits. The implicated drug should be stopped immediately. If the implicated drug is an aromatic AED, other aromatic AEDs should also be avoided even if they have been tolerated in the past. Cross-reactivity among aromatic AEDs is 80 %. Valproic acid, gabapentin, benzodiazepines, and levetiracetam have been suggested as safer alternatives. Cross-reactivity between aromatic and non-aromatic AEDs is less commonly reported (e.g., carbamazepine and valproic acid). Note that cross-reactivity among aromatic AEDs occurs in DRESS/DIHS, but not necessarily in other serious adverse cutaneous reactions such as SJS/TEN.

Systemic corticosteroids are often used to treat DRESS/DIHS, but efficacy has not been demonstrated by randomized controlled trials. Supportive treatment includes antipyretics, antihistamines, and topical corticosteroids and moisturizers. Symptoms may persist for weeks after drug withdrawal. Because of the possible genetic component of DRESS/DIHS, the patient should be encouraged to notify first-degree relatives.

AEDs and SJS/TEN

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening cutaneous reactions, most often drug-induced. They differ in the percent of the body surface area involved: SJS <10 %, SJS/TEN overlap 10–30 %, and TEN >30 %. More than 100 drugs have been associated with SJS/TEN; 80–95 % of cases are caused by a medication. The medications most strongly associated with SJS/TEN are AEDs, antibiotics, and xanthine oxidase inhibitors. The overall incidence of SJS, SJS/TEN overlap, and TEN is estimated to be 2–7 per million people per year; SJS is approximately three times more common than TEN. The mortality rate is substantial: approximately 1–10 % for SJS and 25–30 % for TEN.

This section will focus on AED-induced SJS/TEN; please see Chap. 24 for a discussion of SJS/TEN in more detail.

Epidemiology and Pathophysiology

AEDs considered high risk for SJS/TEN include carbamazepine, phenytoin, phenobarbital, valproic acid, and lamotrigine. Combining AEDs, in particular lamotrigine and valproic acid, increases the risk of SJS/TEN. The incidence of SJS/TEN caused by various AEDs varies significantly according to the population being studied. For example, Asian populations have a higher

incidence of carbamazepine-induced SJS/TEN than non-Asian populations.

The pathophysiology of SJS/TEN is a CD8+ T-cell mediated immune reaction directed at keratinocytes. Either the offending drug induces this immune response or its metabolite binds to cellular peptides, forming an immunogenic hapten. The activation of CD8+ and other immune cells induces keratinocyte apoptosis. Particular human leukocyte antigen (HLA) allotypes confer a higher risk in some populations, and so may be involved in the pathogenesis.

There is a relationship between the HLA-B*1502 allele and carbamazepine-induced SJS/TEN in patients of Asian ancestry (specifically, Han-Chinese, Thai, Korean and Malaysian populations). The risk of carbamazepine-induced SJS/TEN is 25–220 times greater in these populations than in users with non-Asian ancestry. There have been reports of SJS/TEN induced by other AEDs in patients with the HLA-B*1502 allele, such as lamotrigine and phenytoin, but the number of cases is not high enough to demonstrate a clear risk association. The HLA-B*1502 association is only seen with carbamazepine-induced SJS/TEN, not other carbamazepine-induced cutaneous reactions (e.g., DRESS).

Presentation

There are no defining features of AED-induced SJS/TEN compared to all-cause SJS/TEN. Briefly, the presentation of SJS/TEN begins with a flu-like prodrome lasting for several days. Onset is usually 1–3 weeks after drug initiation. The cutaneous manifestations are sudden onset in a symmetric generalized distribution, predominantly on the face and trunk (Fig. 28.2). Lesions are ill-defined erythematous or purpuric macules, sometimes with central duskiness. Lesions coalesce to form large patches, which progress to necrotic, sloughing epidermis, often detaching in sheets, particularly at sites of friction. The dermoepidermal separation also manifests as flaccid bullae. Mucous membranes are prominently involved early in the course of the disease; involvement of at least two mucosal sites is included in the diagnostic criteria.

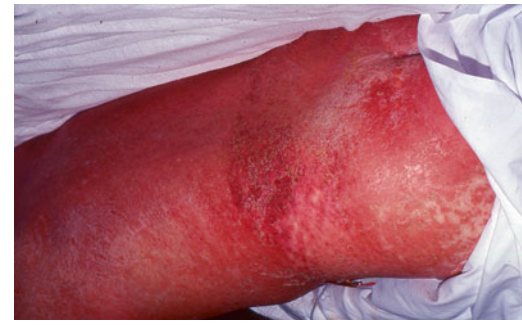

Fig. 28.2 Erythematous drug eruption in a patient with TEN. Note positive Nikolsky's sign developing on the inner edge of the thigh with erosive epidermal peeling

There are significant systemic manifestations of TEN due to extensive sloughing of both internal and external mucocutaneous membranes. These include, but are not limited to, renal, pulmonary, cardiovascular, and gastrointestinal dysfunction. Depending on the severity, SJS/TEN may progress to involve anywhere from <10 to 100 % of the body surface area. Progression lasts for 4–5 days but may be longer if the half-life of the offending drug is long. The leading cause of death in TEN is sepsis leading to multi-organ failure. Those who survive the acute phase of TEN experience significant morbidity, including ocular dysfunction, dyspigmentation and scarring, alopecia, xerostomia, genitourinary dysfunction, and onychodystrophy.

Histopathology

- Dermoepidermal separation
- Full-thickness epidermal necrosis
- Sparse CD4+ lymphocytic infiltrate in dermis
- CD8+ lymphocytic infiltrate in epidermis
- Endothelial apoptosis

Differential Diagnosis

- DRESS/DHS: facial edema, lack of epidermal sloughing, prominent inflammatory infiltrate
- Erythema multiforme: typical targetoid lesions predominantly located on extremities

- Generalized morbilliform eruption: lack of mucous membrane involvement, nonspecific histology
- Staphylococcal scalded skin syndrome: lack of mucosal involvement, child, full thickness epidermal necrosis, association with staphylococcus aureus infection
- Acute graft versus host disease: appropriate history, distal to proximal spread, folliculocentric initial distribution
- Drug-induced linear immunoglobulin A dermatosis: tense bullae, IgA positive direct immunofluorescence, exposure to vancomycin

Diagnosis and Management

The diagnosis of SJS/TEN is made on the basis of clinical and histological findings. There are no laboratory tests with established diagnostic efficacy.

Management of SJS/TEN starts with withdrawal of the offending medication (this is the most crucial and sometimes overlooked part of a successful outcome) and transfer to the intensive care unit for supportive treatment. A careful history and drug timeline should be utilized to identify drugs that have been newly administered in the last 4 weeks and are known to cause SJS/TEN. Supportive treatment should focus on reconstitution of the barrier function of the skin, correcting fluid balance, and monitoring for infection. Barrier function can be restored with paraffin gauze, grafts, skin substitutes, and moisture-retaining dressings. Lesions should not be actively debrided. Skin cultures should be taken at short intervals. Antibiotic prophylaxis is not recommended.

A number of systemic treatments for SJS/TEN have been proposed, though there are not controlled trials to support any of these modalities. Historically, systemic corticosteroids have been the mainstay of treatment, but this has been the subject of significant controversy in recent years. At issue is the balance between the benefit of halting inflammation during the progression phase and the detrimental impact of these medications on healing as well as risk of infection. Alternative treatments include intravenous immunoglobulin, plasmapheresis, TNF-alpha inhibitors, cyclophosphamide, N-acetylcysteine, and cyclosporine.

The offending medication should be avoided in the future. The extent of cross-reactivity among AEDs in the case of SJS/TEN is not clearly elucidated. Patients with a history of SJS/TEN to an aromatic anticonvulsant (e.g., carbamazepine, phenytoin, phenobarbital) should avoid this class of medications. Lamotrigine may be a safe alternative for these patients.

AEDs and Drug-Induced Cutaneous Pseudolymphoma

Cutaneous pseudolymphoma (CPL) is a benign T- or B-cell lymphoproliferative process that mimics cutaneous lymphoma clinically and/or histologically. It was first identified in 1891 by Kaposi under the term “sarcomatosis cutis;” it has been identified by several other names over the years (e.g., lymphocytoma cutis, lymphadenosis benigna cutis, cutaneous lymphoid hyperplasia). There are two major subtypes of CPL: cutaneous T-cell pseudolymphoma and cutaneous B-cell pseudolymphoma; these are further subdivided by histology, immunophenotype, and etiology. This section will focus on drug-induced CPL; for a general discussion of CPL please see Chap. 19.

Epidemiology and Pathophysiology

Drug-induced CPL is generally the T-cell subtype, but cases of drug-induced B-cell CPL have been reported. It is far less common than DRESS/DIHS. The great majority of cases are reported in association with phenytoin; there have been an estimated 200 reported cases. There are also reports with other AEDs (carbamazepine, phenobarbital, primidone, phenytoin, lamotrigine, ethosuximide) and non-AEDs (angiotensin converting enzyme inhibitors, antipsychotics, beta-blockers, antihistamines, antidepressants, antibiotics, diuretics, etc.).

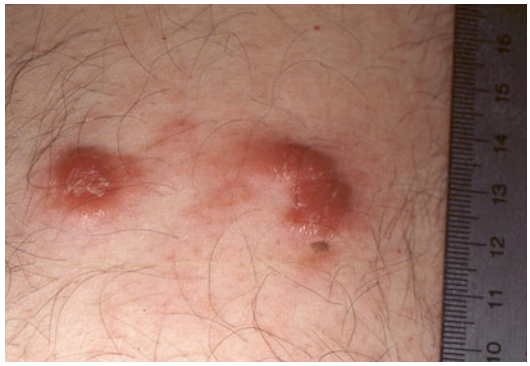

Fig. 28.3 Pseudolymphomatous look on histopathology as well as clinically in this patient on Dilantin. Indurated erythematous nodules over the extensor forearm

The proposed mechanism is drug-induced depression of the immune system leading to impaired immunosurveillance, abnormal lymphocyte proliferation, and increased suppressor T-cell activity. These patients have increased levels of peripheral T lymphocytes and increased blastic transformation of lymphocytes.

Presentation

Drug-induced CPL presents insidiously weeks to years after drug initiation. Cutaneous manifestations are widely variable: localized or widespread firm, erythematous papules, nodules, or plaques. It can also present as mycosis fungoides-like erythroderma. Systemic involvement is limited, differentiating CPL from DRESS/DIHS. Lymphadenopathy may be present. There are generally no hematologic abnormalities, though circulating Sézary cells may be detected. Lesions resolve with withdrawal of the medication.

Histopathology

- Mimics cutaneous lymphoma (Fig. 28.3)
- Drug-induced CPL more likely to be T-cell subtype:
  - Superficial band-like lymphocytic infiltrate in papillary dermis
  - Blurring of dermoepidermal junction
  - Papillary dermal edema, red cell extravasation
  - Variable epidermal changes: acanthosis, epidermotropism, occasional Pautrier microabcsess-like collections
- B-cell subtypes more often have a nodular pattern
- May also have histological findings in lymph nodes

Differential Diagnosis

- Cutaneous lymphoma
- Non-lymphoid metastatic disease
- DRESS/DIHS

Diagnosis and Management

A cutaneous biopsy should be obtained for histopathology and immunohistochemistry. Similar to cutaneous T-cell lymphoma, most cases of drug-induced CPL contain CD4+ lymphocytes.

Differentiating between CPL and lymphoma is difficult. There are factors that can help differentiate between cutaneous T-cell pseudolymphoma and cutaneous T-cell lymphoma (CTCL). Key clinical features of CPL are localized presentation and spontaneous remission after withdrawal of medication. Histological studies can help in that epidermotropism is more mild in CPL than CTCL; presence of Pautrier microabscesses is less likely; lymphocytes are smaller and more benign-appearing; presence of CD2; CD3; and CD5 markers is more frequent; loss of CD7 marker is rare; and TCR gene rearrangements are far less common.

Withdrawal of the AED or other causative medication is an important first step in management of drug-induced pseudolymphoma. Most lesions will resolve spontaneously after several months. For persistent lesions, topical or intralesional corticosteroids, cryotherapy, interferon alpha, local irradiation, and surgical excision may be considered. There have been rare reports of transformation to malignant lymphoma with the long-term use of phenytoin.

Conclusions

Anti-seizure medications remain a mainstay in the control of seizures and are also used for pain relief as well as numerous psychiatric conditions. As their use continues, so does the risk of one of their most challenging side effects—skin reactions. This group can frequently cause mild to moderate drug eruptions. They are also a leading cause of severe, life-threatening drug reactions. Another curious and difficult problem is their ability to cross-react. Constant vigilance for skin reactions is mandatory, since the best early therapy for a good prognosis is discontinuation of the offending drug.

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Chemotherapy and Cutaneous Drug Reactions

29

Gabriella Fabbrocini, Luigia Panariello, Gemma Caro, and Giuseppe Monfrecola

Abstract

Over the last two decades, new chemotherapeutic agents have been used for the treatment of cancer with remarkable efficacy. Despite these positive effects, several dermatologic adverse events have emerged such as xerosis, alopecia, papulo-pustular rash, nail damage, trichomegaly, hand–foot syndrome, EMPACT syndrome, and oral mucositis, affecting the quality of life of these patients.

The dermatologist plays a critical role in the management of these adverse effects, through pharmacological and dermocosmetological treatment, to cure them and to prevent avoiding the interruption of these therapies for skin toxicity. To better standardize these reactions and their management is an important tool for the dermatologist.

Keywords

Chemotherapy • Skin reaction • Target therapy • Dermocosmetological treatment • Papulo-pustular rash • Paronychia • Oral mucositis

Introduction

The use of systemic chemotherapy dates to the 1940s, with the first use of nitrogen mustards for lymphomas studied by Goodman and Gilman. Over the last two decades, a number of new chemotherapeutic agents have been developed for the treatment of cancer. These drugs may be classified according to their mechanism of action in:

- Signal transduction inhibitors (epidermal growth factor receptor inhibitors [EGFRi] and multikinase inhibitors [MKi]
- Proteasome inhibitors
- Spindle inhibitors (taxanes and vinca alkaloids)
- Antimetabolites (purine and pyrimidine analogs)
- Genotoxic agents (alkylating agents, intercalating agents, enzyme inhibitors)

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_29

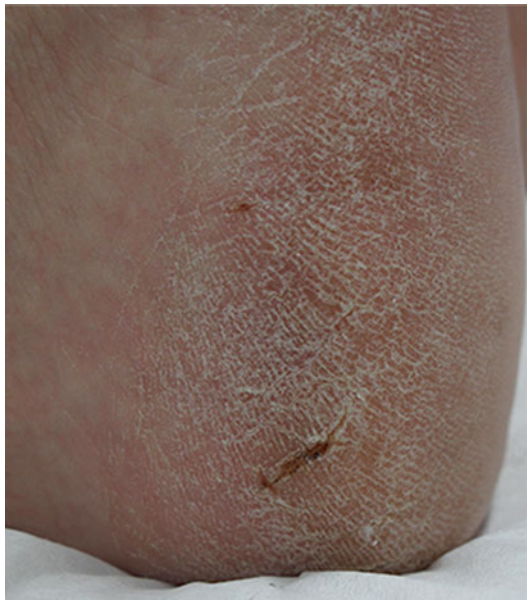

Fig. 29.1 Xerosis: significant dryness of the skin of the foot

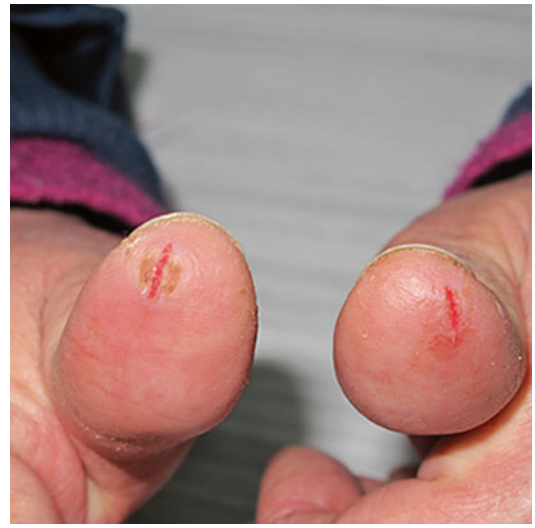

Fig. 29.2 Xerosis: fissures of the hands

Cancer therapies have led to remarkable results as a consequence of improved toxicity profiles and effects on survival. Yet despite these positive effects, several dermatologic adverse events have emerged. These skin reactions can decrease the quality of life of these patients. The dermatologist plays a critical role in the management of these adverse effects, avoiding the interruption of cancer treatments.

Nowadays the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is the most commonly system used to evaluate the severity of these adverse effects. The aim of this chapter is to examine the most frequent skin reactions due to these chemotherapeutic regimens.

Xerosis

Xerosis is a very common effect of several chemotherapeutic drugs such as EGFR inhibitors, MKi, hormonal agents and retinoids. In a variable range (5–35 %) of patients treated with signal transduction inhibitors, significant dryness of the skin (Fig. 29.1), frequently associated with pruritus, occurs, generally 30–60 days or more after the start of chemotherapy. In severe cases, fissures of the hands (Fig. 29.2) and dryness of the vaginal or perianal area may also occur. Risk factors for xerosis are: age, preexisting eczema, and prior treatment with cytotoxics.

Dry skin can be attributed to abnormal keratinocyte differentiation, which leads to a modification of stratum corneum and to an interference with sebaceous gland function, resulting into a loss of the water-retaining function of the epidermis. The development of chronic xerotic dermatitis can occur, exposing the skin to secondary infection with *S. aureus* and, rarely, herpes simplex virus.

Pharmacological Treatment

Short-term, low-dose topical steroids may be necessary for severe xerosis associated with inflammation. In case of infection with *S. aureus*, topical or systemic antibiotics should be used (clindamycin gel 1 % and flucloxacillin 500 mg three times daily for 7 days, or Doxycycline 100 mgs twice a day for 7 days). In cases of herpes simplex virus, antiviral drugs should be prescribed (valaciclovir 500 mg twice daily for 5 days).

Fissures can be treated with propylene glycol 50 % solution under plastic occlusion, salicylic

acid 10 % ointment, hydrocolloid dressing, flurandrenolone tape, or liquid cyanoacrylate glue.

Dermocosmetological Treatment

Treatment of mild or moderate xerosis consists of thick moisturizing creams without fragrances or potential irritants. Specific creams can include urea, colloidal oatmeal, and petroleum-based creams. It is preferable to use unsaponifiable substance, aloe, niacinamide, tocopherols and tocotrienols, ceramides, gamma oryzanol, and cosmetic formulations with little or no presence of petrolatum and silicones, in order to avoid the maceration of the stratum corneum. Alcohol-containing lotions, retinoids, or benzoyl peroxide are not recommended. For scaly areas of xerosis, ammonium lactate or lactic acid creams can be utilized. For skin fissures, thick moisturizers or zinc oxide creams can be applied.

Patients should be instructed to avoid long-lasting baths and to use tepid water, to prefer detergents without surfactants and foaming substances, and bath oil or mild moisturizing soaps that are free from fragrances or perfumes.

Antimicrobial silk clothing can be an adjuvant strategy. This kind of fabric has extremely low frictional properties. The protein structure of fibroin is similar to stratum corneum of the human skin, able to absorb a high percentage of moisture without becoming damp, maintaining a stable heat, and constant skin temperature. It also has antimicrobial action, which could help to avoid secondary infections.

Alopecia

The overall incidence of chemotherapy-induced hair loss is estimated to be 65 %. The prevalence and severity are related to the chemotherapeutic agent: >80 % for anti-microtubule agents, 60–100 % for topoisomerase inhibitors, >60 % for alkylators, and 10–50 % for antimetabolites. Higher incidences are registered with poly-chemotherapy respect to monotherapy.

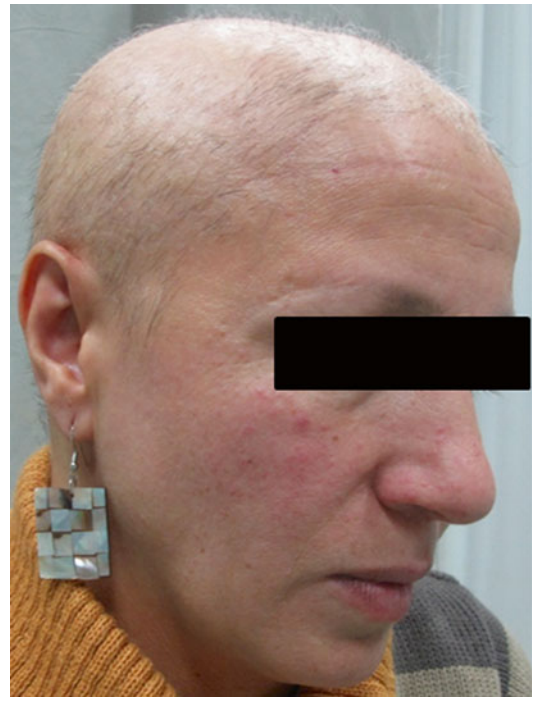

Fig. 29.3 Alopecia of the scalp in a patient treated with EGFRi

Chemotherapy-induced hair loss is considered to be one of the most traumatic aspects for oncological patients. It can negatively impact body image, sexuality, and self-esteem. 8 % of patients refuse to use chemotherapy for the anxiety of hair loss. Risk factors for hair loss are: drug dose, administration regimen, exposure to X-rays, age, comorbidities, the presence of androgenetic alopecia, and nutritional and hormonal status.

Hair-shaft shedding can occur days or weeks after the initiation of chemotherapy. Both shedding patterns, dystrophic anagen effluvium and telogen effluvium, can be observed. The affected areas seem to be selective, with a more frequent involvement of scalp regions that show low total hair densities, such as the frontal or occipital hairlines (Fig. 29.3). The mitotic activity of the hair follicle at the moment of the insult is one of the factors that may influence the shedding pattern.

The highly proliferative matrix keratinocytes of anagen hair follicles, located in the hair bulb,

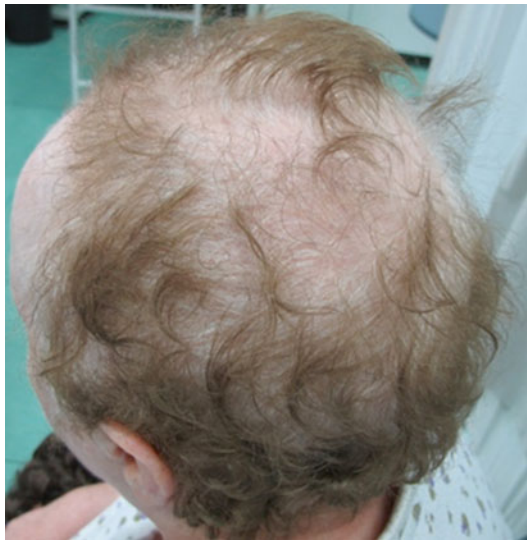

Fig. 29.4 Permanent alopecia in a patient treated with cyclophosphamide

and their pigmentary system are the main targets of chemotherapeutic drugs. They are very sensitive to toxins and drugs and can easily undergo rapid apoptosis. Sometimes, a damage of hair-follicle stem cells occurs; it can lead to permanent alopecia (Fig. 29.4).

Normally, up to 90 % of scalp hairs are in the anagen phase, for this reason the scalp is the most frequently affected area. Hairs of the beard, eyebrows, and eyelashes, as well as axillary and pubic regions, may be also affected, depending on the percentage of hairs in anagen. When hair is in late anagen phase, during which the mitotic rate is low, chemotherapy accelerates the normal transition to telogen, while catagen and telogen are not affected because they are mitotically inactive phases.

Generally, the hair loss is reversible, with hair regrowth typically occurring after a delay of 3–6 months. In some patients, the new growth shows changes in color and/or texture, but these differences can be temporary. Although rare, cases of permanent alopecia, in which hair regrowth is severely retarded or does not occur at all, are reported. This kind of alopecia is frequently associated with high-dose chemotherapy or with busulfan and cyclophosphamide administration.

Pharmacological Treatment

A solution of 2 % topical minoxidil is the best treatment for accelerating regrowth after chemotherapy. It must be applied twice a day on the involved areas for at least 1 month. Even if this type of alopecia is often reversible, it has been demonstrated that minoxidil reduces its severity and duration.

Dermocosmetological Treatment

A tetrapeptide composed of lysine, aspartic acid, valina, and tyrosine could be considered as an additional treatment. It is an analogue of P substance, a neuropeptide, which prolongs the anagen and retards the catagen phases, and acts as a releasing grow factor. It can be used in association with minoxidil, to improve its effect on hair regrowth, or it can also be used alone as maintenance treatment.

Implementation of gentle hair care strategies should be done not only throughout chemotherapy but also after. In order to avoid additional traumas, patients should use a soft brush, wash hair only as often as necessary, and use a gentle shampoo. Cutting hair short or shaving hair is not necessary, but it could be more comfortable.

A silk wig, glue-free, is the best way to make the patient feel better, avoiding additional irritation of the scalp (due to the glue and synthetic materials). This could help patients to deal with their condition and, at the same time, protect the scalp from sun and cold exposure.

Scalp cooling has been proposed as preventive therapy for alopecia. It is an effective method and patients' compliance is good, except for some cases of headache and uncomfortable feelings reported. Some references indicate scalp cooling as a risk for scalp skin metastasis in hematological malignancies.

Papulo-Pustular Rash

A papulo-pustular rash is the most common cutaneous toxicity of EGFRi, affecting up to 90 % of patients. It is less frequent (30–40 %) and milder, with the MKi sorafenib and sunitinib.

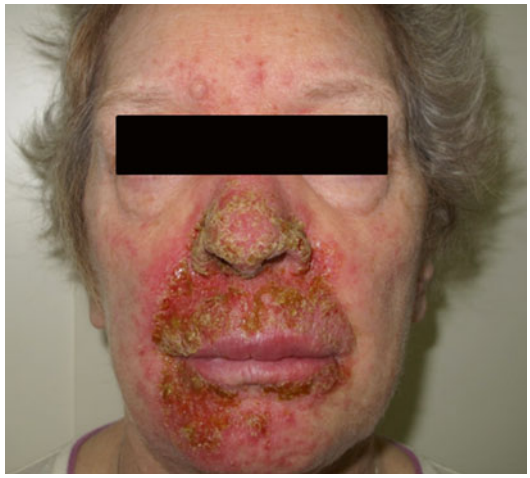

Fig. 29.5 Papulo-pustular rash of the face in a patient under treatment with panitumumab

The most frequently affected areas are sebaceous gland–bearing regions of the body, i.e., the scalp, face (Fig. 29.5), chest (Fig. 29.6), and upper aspect of the back, but the eruption can extend over the entire body except for the palms, soles, and mucosa. The rash commonly starts as a sensory disturbance characterized by erythema, edema, and dysesthesia (weeks 0–1), followed by a progression to inflammatory papules with central pustule formation (weeks 1–3), which result in the formation of crusts (weeks 3–5). The final phase is characterized by post-inflammatory pink or hyperpigmented macules and telangiectatic changes (weeks 5–8).

The pathogenesis of the acneiform eruption is not well understood. EGFR is expressed on epidermal keratinocytes, hair follicle epithelium, and the sweat gland apparatus. Its activation plays a crucial role in keratinocyte proliferation and differentiation, and in keratinization. Its inhibition induces growth arrest and apoptosis, decreasing cell migration, increasing cell attachment and differentiation, and stimulating inflammation.

Although the rash has been defined "acneiform" some differences have to be underlined. The EGFRI-induced papulopustular eruption does not present comedones, and differences in pathology and etiology from acne vulgaris exist. In acne, in fact, the primary process is sebaceous hyperplasia and lipid release into the follicular lumen; it leads to comedo formation and overgrowth of *Propionibacterium acnes* that results in follicular wall rupture, stimulating neutrophil chemotaxis and pustule formation. On the other hand, in EGFRi rash, the primary event is the damage to sebaceous glands and follicular epithelium, which leads to alteration in keratinocytes growth and differentiation. This causes the release of cytokines and the infiltration of mononuclear leucocytes ("sterile folliculitis"). The severity of the papulo-pustular rash is dose dependent and correlates with an improved tumor response and survival.

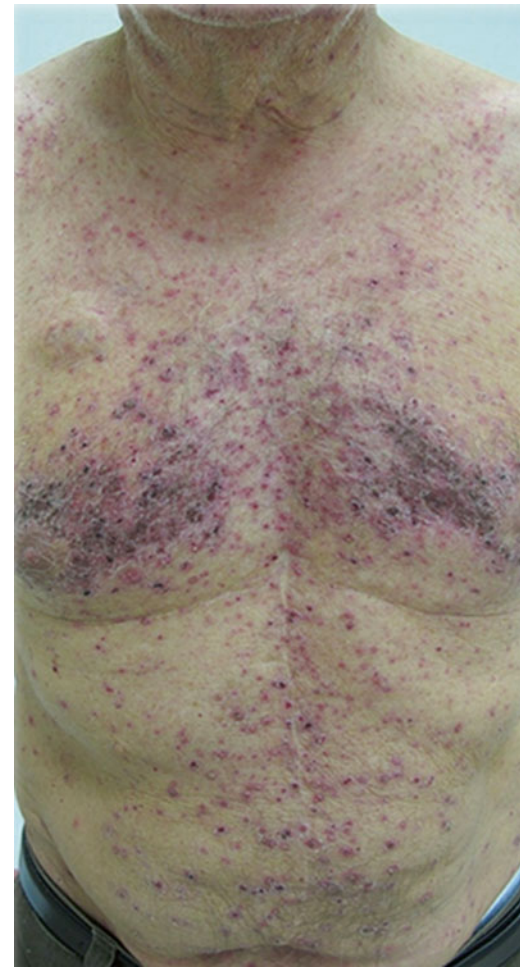

Fig. 29.6 Papulo-pustular rash of the trunk in a patient under treatment with panitumumab

Even though it is never fatal, it has a negative impact on quality of life because of its visible

characteristics and related symptoms, such as pain, burning, and skin sensitivity. Its main aggravating factors are sun exposure, concomitant radiotherapy, and inadequate moisture levels in the skin.

Pharmacological Treatment

The current guidelines for management of the EGFRi- associated papulo-pustular eruption include the following:

- **Grade 1 (mild):** continue EGFRi; no treatment is required for rash; in some cases initiation of topical hydrocortisone 1 or 2.5 % cream and/or clindamycin 1 % gel could be necessary
- **Grade 2 (moderate):** continue EGFRi; topical therapy plus systemic antibiotic therapy, such as doxycycline 100 mg twice daily, or oral minocycline 100 mg twice daily
- **Grade 3 (severe):** reduce EGFRi dose; topical therapy plus oral antibiotic plus oral methylprednisolone from dose pack.

In uncontrolled trials, topical pimecrolimus and tacrolimus, and corticosteroids, showed clinical benefit. Advantages of choosing calcineurin inhibitors rather than corticosteroids include the absence of side effects such as skin fragility and the development of rosacea. Moreover, cyclosporine analogues could also theoretically partially reverse EGFR inhibition through their known ability to stimulate EGFR autophosphorylation, as shown in epidermoid cells, is well known. The potential role for retinoids (isotretinoin at low dose 20–30 mg/day) needs further investigation.

The beneficial effects of tetracyclines can be attributed to their anti-inflammatory and tissue-protective properties, through the inhibition of neutrophil and eosinophil chemotaxis; mitogen-induced lymphocyte proliferation; collagenases; and gelatinases.

Drugs used for the therapy of acne, including benzoyl peroxide and topical retinoids such as tretinoin, adapalene or tazarotene, are contraindicated because of irritation of the skin. Moreover, they haven't shown clinical benefit in the treatment of the EGFRi rash.

Dermocosmetological Treatment

The patient should be instructed to:

- use a thick alcohol-free highly occlusive moisturizing agent
- favor tepid water and avoid prolonged, hot showers to minimize xerosis
- use a broad-spectrum sunscreen

Non-occlusive make-up has been suggested to cover grade 1 and 2 rash, and it is well tolerated by patients. Recommended cosmetic formulations should contain fatty acids and ceramides, which are essential components of the stratum corneum barrier, and lactic acid that disrupts tightly adherent corneocytes, leading to the homogenization of the permeability barrier, although it should be used with caution because of the risk of irritation.

Nail Damage

Nail abnormalities are not uncommon during chemotherapy. The most frequent manifestations include Beau's lines/onychomadesis, melanonychia, onycholysis (Fig. 29.7), and periungual pyogenic granulomas. It has been reported that taxanes cause nail changes more frequently than other drugs.

Some nail abnormalities, such as dark pigmentations, Mees' lines and Beau's lines, are asymptomatic. After the end of chemotherapy, they migrate distally as the nail grows, and usually no new stripes develop. However, other changes such as sub-ungual hemorrhage, paronychia, and onycholysis (loss of the nail plate) can negatively affect the quality of life of the patient, causing pain and impairment to activities of daily life.

Paronychia and periungual pyogenic granuloma-like lesions are observed in 10–30 % of patients receiving EGFRi, developing after 2–3 months after drug exposure (Fig. 29.8).

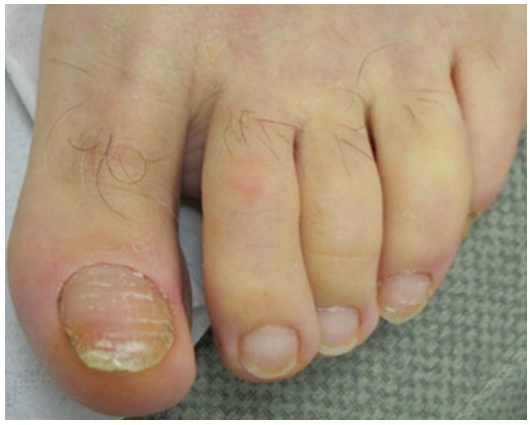

Fig. 29.7 Taxane-induced onycholysis

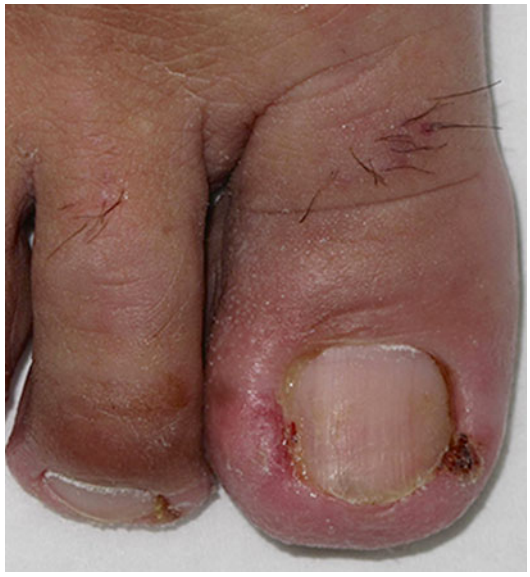

Fig. 29.8 Lapatinib-induced paronychia of the great toe

Paronychia is characterized by edematous inflammation of the nail folds and usually affects the first digit. Periungual pyogenic granuloma-like lesions are characterized by easily bleeding, friable vascular tissue overgrowth on lateral nail folds.

The pathogenesis of paronychia could be explained by the presence of a traumatic conflict between the thin tissues around the nail and nail itself. In fact, changes in growth and differentiation of the nail are responsible for the retention of squamous epithelium in the nail folds, which act as foreign bodies, causing an inflammatory reaction.

Pharmacological Treatment

Treatment of paronychia can be difficult, consisting of symptomatic relief with soaks, such as aluminum acetate or Burow's solution, and cushioning of the affected areas, in addition to treatment with topical or systemic antibiotics. For granulomas, the use of silver nitrate sticks can also be useful. In severe cases, the affected nail may need to be removed.

A new proposal treatment is represented by 8 % phenol cauterization. It has the advantages to be a conservative, effective, simple approach that can be performed without a previous anesthesia. These aspects increase the compliance with the therapy. Cessation of therapy with EGFRi may be required in severe cases to allow healing.

Dermocosmetological Treatment

The patient should be instructed to avoid tight shoes, frequent water immersion, and contact with chemicals. As for xerosis, a useful adjuvant instrument is antimicrobial silk gloves and soaks.

Trichomegaly

Trichomegaly of the eyelashes is characterized by a paradoxical overgrowth of eyelashes. It is a rare adverse effect of EGFRi, which usually occurs 2–5 months after the start of treatment and may resolve in several weeks or months after its discontinuation. The pathogenesis is not completely understood. EGFR is expressed in the keratinocytes of the outer sheath of the hair follicle. Its inhibition arrests the progression from anagen to telogen phase, leading to an aberrant anagen phase and, subsequently, to abnormal hair growth and to the formation of a disorganized hair follicle (Figs. 29.9 and 29.10).

It is not well understood why these drugs can cause both hair shedding and eyelash elongation. This adverse effect tends to persist for the duration

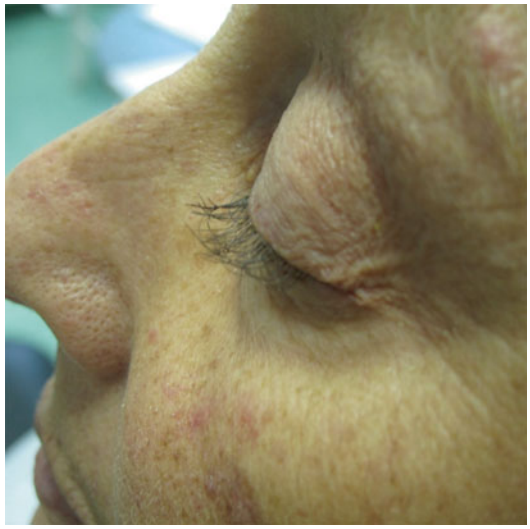

Fig. 29.9 Trichomegaly: patient in treatment with erlotinib

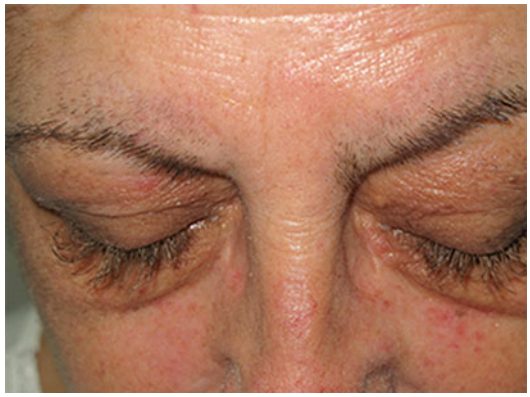

Fig. 29.10 Trichomegaly: patient in treatment with panitumumab

of the treatment with EGFRi, and it could last for a long period after drug discontinuation.

Pharmacological Treatment

Periodical trimming is highly recommended. Sometimes, the elongation of eyelashes can be complicated by trichiasis and secondary corneal ulceration. For this reason, patients affected by trichomegaly should have ophthalmologic consultation.

Hand–Foot Syndrome

Hand–foot syndrome (HFS), also known as palmar plantar erythrodysesthesia, acral erythema, or Burgdorf reaction, was first described in the literature in 1974 in a patient taking mitotane therapy for hypernephroma. It is a distinctive cutaneous side effect of chemotherapeutic agents, such as 5-flurouracil, capecitabine, vinorelbine, docetaxel, liposomal doxorubicin, hydroxyurea, mercaptopurine, intravenous cyclosporine, methotrexate, cyclophosphamide, cytosine arabinoside, sunitinib, pazopanib and sorafenib.

HFS caused by MKI typically begins after 1–4 weeks; HFS caused by cytotoxic chemotherapy can occur anywhere from 1 to 21 days, and up to several months later with continuous low-dose therapies. All-grade and grade 3 HFS is observed respectively in 34 % and 9 % of sorafenib-, 19 % and 6 % of sunitinib-, and 4.5 % and 1.9 % of pazopanib-treated patients.

Localized dysesthesia or paresthesia, and erythema of the palms and soles accompanied by swelling and discomfort are early symptoms. In severe cases, it progresses to blistering, ulceration, desquamation, and pain (Figs. 29.11 and 29.12). MKi produces hyperkeratotic plaques and blisters in contrast to diffuse erythema and edema resulting from cytotoxic agents. Lesions tend to be localized to pressure or flexure areas (tips of fingers and toes, heels, metatarsophalangeal skin, and skin overlying metacarpophalangeal or interphalangeal joints). Palms of the hands are more frequently affected than soles of the feet; sometimes they can be the only area affected.

Patients find it difficult to wear shoes and to walk when feet are involved. This can cause inability to perform activities of daily life, producing a significant financial burden. It can also cause therapy interruptions, with a negative impact on the efficacy of the treatment regimen. Symptoms are dose-dependent and resolve within weeks of discontinuing the causative drug.

Although the underlying mechanism of HFSR remains to be fully elucidated, some potential causes have been proposed for each drug. Local delivery of high drug concentrations though

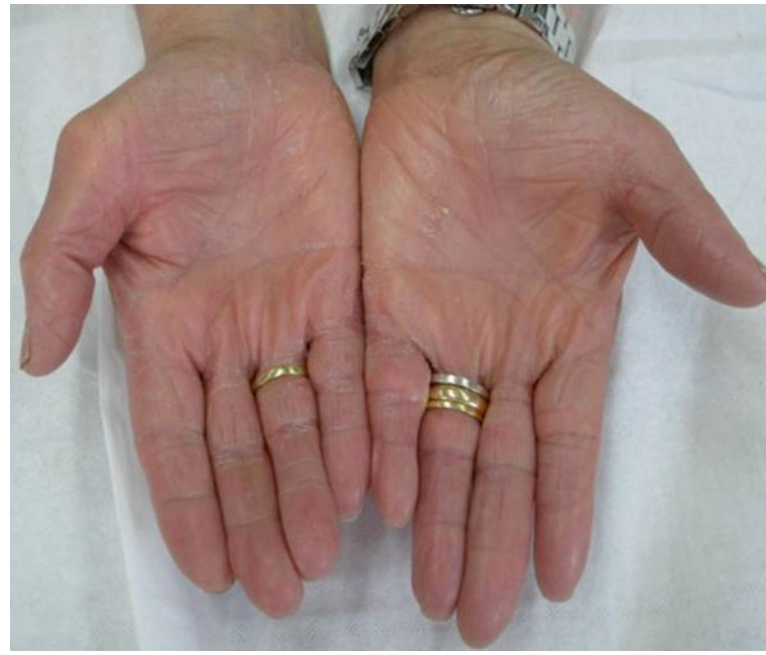

Fig. 29.11 Hand-foot syndrome: desquamation of the palm in a patient in treatment with capecitabine

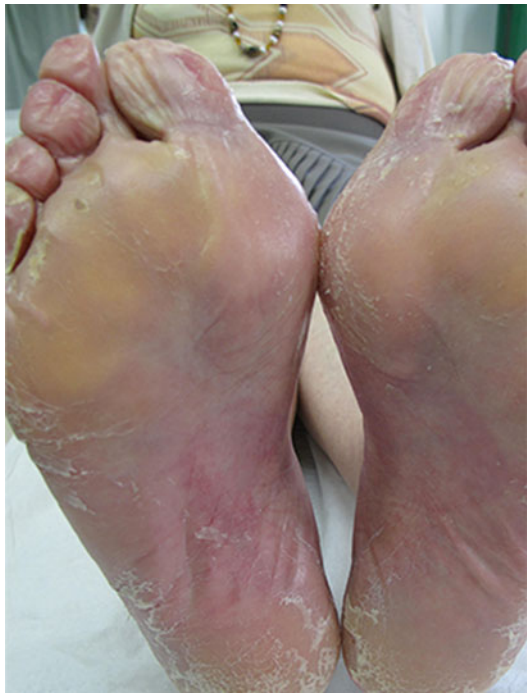

Fig. 29.12 Hand-foot syndrome: desquamation of the sole in a patient in treatment with capecitabine

eccrine glands with direct toxic effect and inhibition of target receptors has been suggested in the etiology of HFS induced by doxorubicin or sorafenib. For 5FU, HFS is dose-dependent and is possibly related to the accumulation of 5FU or its metabolites in the skin. TP-facilitated local production of 5FU from capecitabine could explain the occurrence of HFS during the administration of this drug.

Pharmacological Treatment

Prevention of traumatic activity and rest are recommended during the first weeks of therapy. Patients should avoid constrictive footwear, excessive friction of the skin, and hot water.

For treatment of HFS, no published randomized controlled trials exist. Treatment guidelines depend on severity, and include application of emollients, topical corticosteroids, and topical anesthetics. For hyperkeratotic plaques, urea 40 % cream, tazarotene 0.1 % cream, and fluorouracil 5 % cream have been used with anecdotal success. In severe cases, chemotherapy interruption, reduction, or discontinuation may be necessary.

Pyridoxine (vitamin B6) has been found beneficial as therapy (50–150 mg/day) in some patients, while in other cases it had no effect. Its mechanism of action is still unknown.

Cyclooxygenase (COX)-2 inhibition has also been shown effective as a systemic approach for prophylaxis of chemotherapy-associated HFS.

Antimicrobial silk clothing such as gloves and socks seem to be an useful adjuvant instrument for the management of patients with HFS because this kind of fabric has extremely low frictional properties and it is able to absorb a high quantity of moisture; in addition it contains antimicrobial agents that help to avoid infections.

Before starting chemotherapy, a qualified healthcare professional should conduct a baseline skin check for predisposing factors. Hyperkeratotic areas should be removed. Feet and hands should be examined for areas under excessive friction, and the cushioning of these areas is recommended.

Empact Syndrome

EMPACT (erythema multiforme associated with phenytoin/phenobarbital and cranial radiation therapy) syndrome is a rare clinical entity first described in 2004 by Ahmed et al. Over the past two decades, more than 30 patients have been described. It is characterized by erythematous macular eruption on the scalp within the radiation field in patients under phenytoin or phenobarbital therapy that usually dramatically extends after a few days to involve extensive areas of the face, trunk (Fig. 29.13), and extremities. Significant mucocutaneous blistering (Fig. 29.14) and desquamation with conjunctival suffusion can also develop. The pathogenesis of the EMPACT syndrome is still unclear.

Studies in mice have shown that brain radiation can induce the increase of TNF-α, TNF-β, ICAM-1, and cytokines that could induce cellular autoimmunity. Moreover, radiation can alter phenytoin and anticonvulsant drugs' metabolism. Normally, phenytoin and other anticonvulsants induce microsomal cytochrome 450(CYP)3A and produce oxidative intermediates that are later detoxified by epoxide hydrolase. In the case of therapy with phenytoin/phenobarbital and radiation therapy, a deficiency of this enzyme can develop. Oxidative intermediates, which cannot be metabolized, have direct toxicity for cells, and/or they can bind cell macromolecules and behave as haptens. These mechanisms can stimulate a new immune response and be responsible of skin manifestations.

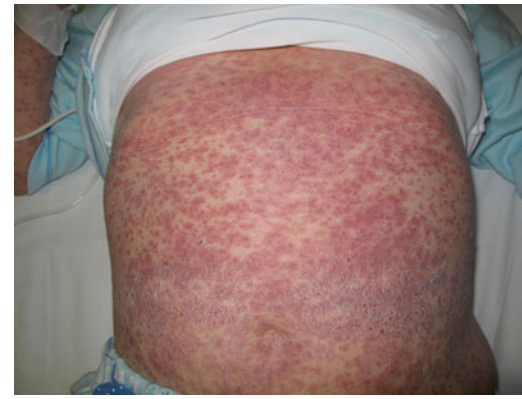

Fig. 29.13 EMPACT Syndrome: erythematous macular eruption of the trunk

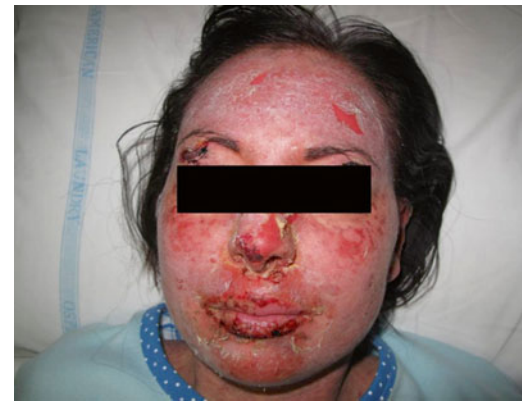

Fig. 29.14 EMPACT syndrome: blistering lesions of the face

Pharmacological Treatment

High doses of intravenous steroids (prednisone 1 mg/Kg/day) managed to reach complete resolution of the disease in 4–6 weeks.

Oral Mucositis

Mucositis and xerostomia are the most common oral complications during chemotherapy. It is a form of mucosal barrier injury (MBI) and

describes a clinical condition characterized by oral erythema, ulceration, and pain.

At least 40 %, and up to 70 %, of patients treated with standard chemotherapy regimens can have mucositis. The chemotherapeutic agents mainly associated to this reaction are: cisplatin (90 %), etoposide, melphalan, doxorubicin, vinblastine, taxanes, and methotrexate. In contrast, mucositis is uncommon with asparaginase and carmustine. The polychemotherapy drugs can increase the risk of mucositis.

EGFRi (gefitinib, erlotinib, and panitumumab) have found an incidence rate of 2–36 % for development of mild to moderate mucositis, but the mechanisms of mucosal injury induced by these kinds of drugs need to be investigated. Sirolimus (an mTOR inhibitors) is associated with a particular type of oral lesions that have been defined "aphthous-like."

Mucositis affects quality of life because of pain, inability to eat, and talk. Sometimes, symptoms are so severe as to require the delay of chemotherapy.

About pathogenesis of mucositis, once it was considered to be a reflection of direct epithelial damage caused by cytotoxic therapy. Actually, it is thought to be a complex phenomenon that also affects the connective tissue. Five overlapping stages been described:

1. initiation
2. upregulation
3. message generation
4. ulceration
5. healing

The initiation phase is characterized by the release of reactive oxygen species that damage cells, tissues, and blood vessels. This positive feedback mechanisms leads to the amplification of the process, with ulceration. Oral bacteria colonize the exposed connective tissues and activate macrophages, which produce additional inflammatory cytokines. All these events result in pain and, in neutropenic patients, bacteremia and sepsis may develop (*Streptococcus oralis* and *S. Mitis* are the most common responsible). Mycoses caused by *Candida albicans*, *C. krusei*, *C. tropicalis*, *C. parapsilosis, C. glabrata*, and aspergillus and mucor may also occur.

Patient-associated risk factors are: age, body mass index, gender, co-morbidities, alterations in salivary production, poor oral health, and mucosal trauma. Oral microflora seems to play a secondary role in the pathogenesis of mucositis and it may contribute to increase healing duration.

From a clinical point of view, mucositis typically begins within 4–5 days after chemotherapy, with a peak day between 7 and 10 days, and spontaneously resolves. Lesions are characterized by a non-uniform shape, a fibrinous pseudomembrane with cellular remains, but no peripheral erythema is visible. On the other hand "aphthous-like" lesions associated with sirolimus appear ovoid and shallow, and present a characteristic erythematous margin.

Oral Mucositis Assessment Scale (OMAS) represents the only validated mucositis scale that divides mucosal damage from symptoms and oral function.

Pharmacological Treatment

Avoidance of Mucosal Irritation. In general, mucositis should be treated conservatively to avoid the damage to the remaining cells that are necessary for the epithelium regeneration. Oral hygiene should be maintained, but the efficacy of chlorhexidine in adjunct is questionable. Patients should be instructed to have a soft bland diet, avoiding irritants such as spices, tobacco, and alcohol. Nutrition should be maintained, but sometimes supplements are needed. Orthodontic bands should be removed before starting chemotherapy.

Active Treatment of Mucositis. Cryotherapy ice chips placed in the mouth for 5 min before a bolus of 5-FU, and then for a further 25 min is useful to reduce 5-FU-induced mucositis. Benzydamine HCl, seems to be effective. Subcutaneous Granulocyte-macrophage colony-stimulating factor from days 5 to 14 of chemotherapy might have an effect on the severity and the duration of mucositis.

Control of Pain. Systemic analgesics, physical therapy, and psychologic therapy are frequently

requires. Nonsteroidal agents and other nonopioids are used first or in combination with morphine or hydromorphone if pain is severe.

Treatment of Oral Infections. Antifungal prophylaxis is recommended, and systemic fluconazole for Candida albicans can be used. Chlorhexidine mouthwashes might also be useful. For HSV or VZV infection, acyclovir and valacyclovir are the most commonly employed antiviral agents, but brivudin, famciclovir, penciclovir, bravavir, or foscarnet might be needed in case of resistance. Local antimicrobials containing amphotericin, polymyxin, mupirocin, and tobramycin may be used in bacterial infections.

Conclusions

Cancer patients now face a future with new medications that have fewer side effects and more efficacy. Many of the new, as well as older, of these medications affect the skin as a major group of side effects. As our armamentarium has changed, so have the cutaneous reactions. The most troublesome and common of these reactions has been delineated in this chapter.

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Tyrosine Kinase Medications and the Skin

30

Emily Y. Chu

Abstract

In recent years, numerous targeted therapy medications have been developed and utilized for the treatment of solid and hematologic malignancies. While these medications often demonstrate better anti-tumor efficacy than conventional chemotherapeutics, they frequently lead to a range of non-immunologic cutaneous adverse effects. Skin reactions associated with tyrosine kinase inhibitors include inflammatory eruptions such as acneiform folliculitis and hand foot skin reaction, and new onset of benign and malignant neoplasms. Tyrosine kinase medications and their associated skin reactions will be reviewed here.

Keywords

Targeted therapy • Kinase inhibitor • Keratoacanthoma • Squamous cell carcinoma • Hand–foot skin reaction • Acneiform eruption • Folliculitis

Introduction

Tyrosine kinase inhibitors represent an ever-expanding class of medications, which have been developed to target specific proteins within signal transduction cascades that control cellular processes including proliferation, differential, and survival. As such, tyrosine kinase inhibitors are now commonly used to treat solid and hematologic malignancies. Because tyrosine kinases are commonly expressed in the skin, a high rate of cutaneous adverse effects is observed. In contrast to traditional cytotoxic chemotherapeutic medications, tyrosine kinase inhibitors are associated with characteristic, reproducible skin side effects that are linked to their underlying mechanism of action. We will discuss some of the more commonly used medications and their associated cutaneous effects in this chapter.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_30

Imatinib and Dasatinib

The prototypic tyrosine kinase inhibitor is imatinib, which was approved by the U.S. Food and Drug Administration in 2001 for treatment of Philadelphia chromosome positive chronic myelogenous leukemia (CML), and in 2002 for gastrointestinal stromal tumor (GIST). It is also indicated to treat mastocytosis without or an unknown D816V c-kit mutation, hypereosinophilic syndrome, advanced or metastatic dermatofibrosarcoma protuberans (DFSP). Imatinib inhibits the *bcr-abl* tyrosine kinase, c-kit, and platelet-derived growth factor receptor (PDGFR).

A frequently observed adverse effect of imatinib is periorbital edema, which is usually asymptomatic, and therefore not problematic. Cases of more severe periorbital edema leading to vision obstruction have been reported in the literature. PDGFR is expressed on dermal dendrocytes in the skin, and it has been postulated that inhibition of PDGFR by imatinib leads to periorbital edema. This is based on observations from mouse models, in which it has been shown that signaling through PDGF receptors help control interstitial fluid homeostasis, and that inhibition of this activity leads to increased soft tissue swelling.

Pigmentary changes are also commonly observed to occur, both hypopigmentation and less often hyperpigmentation. Hypopigmentation occurs in up to 40 % of patients treated with imatinib, but may be less noticeable in those with fair skin types. Pigmentary alterations are typically reversible upon discontinuation or dose reduction of the medication. Inhibition of the c-kit receptor by imatinib is the likely cause of the hypopigmentation, as c-kit and its ligand stem cell factor (SCF) play a role in melanocyte development and survival. The occurrence of hyperpigmentation is less easily explained, and appears to be paradoxical. Leukotrichia has also been documented to occur in patients treated with imatinib and the second-generation tyrosine kinase inhibitor dasatinib. We recently examined hair bulbs from a patient treated with dasatinib and found absent melanocytes, as compared to control patients, thereby accounting for the clinical finding of leukotrichia.

Other cutaneous effects reported with use of imatinib and dasatinib include xerosis and morbilliform eruptions. Squamous cell carcinomas have also been reported to occur. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, erythroderma, and acute generalized exanthematous pustulosis have been documented.

Epidermal Growth Factor Receptor Inhibitors

The epidermal growth factor receptors (EGFRs) are expressed on the tumor cells of various types of cancers, including colon, lung, and breast. Signaling through EGFR regulates cell proliferation and survival, and increased signaling promotes metastasis. There is a relationship between EGFR expression and more aggressive cancers, a high rate of recurrence, and overall poor prognosis. Moreover, expression of EGFR may indicate resistance of a tumor to traditional chemotherapy or radiation therapy. EGFR blockade is achieved through small molecule inhibitors, including erlotinib and gefitnib, as well the monoclonal antibodies cetuximab and panitumumab.

The most common cutaneous reaction seen with use of EGFR inhibitors is acneiform folliculitis (Fig. 30.1), which is composed of

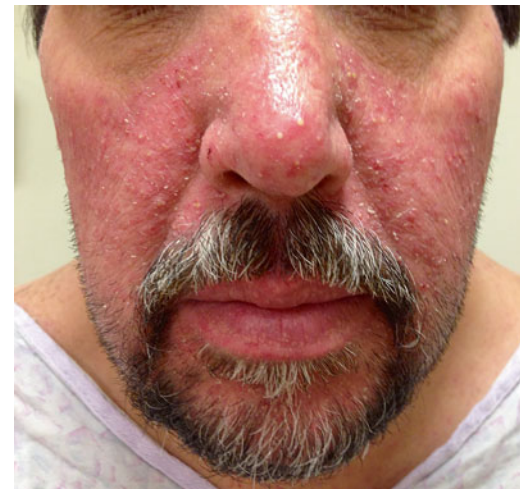

Fig. 30.1 Acneiform eruption on the face arising shortly after initiation of EGFR inhibitor therapy

inflammatory papules and pustules arising on the T-zone of the facial area, chin, upper chest, and back. In severe cases, the eruption affects the entire body. This reaction is distinguished from true acne by the lack of comedones. Cetuximab and panitumumab more commonly cause the folliculitis than erlotinib and gefinib. Overall, the eruption is seen in 50–90 % of treated patients. The eruption usually occurs within 7–10 days of starting therapy, and may resolve spontaneously while continuing the causative medication, or with dose reduction or discontinuation. It is worth noting that the appearance of EGFR inhibitor-induced folliculitis has been positively correlated to tumor response to therapy, a reassuring finding for affected patients.

Treatment of the folliculitis depends on the severity and any associated symptoms. In asymptomatic, relatively mild cases, patients may prefer no treatment at all. Topical steroids and, occasionally, antihistamines are employed for cases of limited severity. More widespread and intense eruptions warrant consideration of doxycycline or minocycline therapy (at doses of 100 mg daily or 100 mg twice daily), or tetracycline 500 mg twice daily. Finally, for the most severe cases, dose discontinuation or reduction should be considered, in addition to topical steroids and systemic antibiotics.

Paronychia and pyogenic granuloma-like lesions around the nail plate are also frequently observed in association with EGFR inhibitor therapy, and typically arise within 4 weeks after beginning treatment. Paronychia is thought to result from retention of nail plate fragment and abnormal desquamation of periungual tissue. While this reaction is non-infectious, secondary bacterial infection may occur. Treatment strategies include avoidance of trauma and use of silver nitrate sticks for pyogenic granuloma-like lesions. Topical steroids, tetracycline antibiotics, and antiseptic soaks may also be helpful to reduce inflammation. This reaction resolves upon discontinuation of the medication.

Several hair changes have been observed to affect EGFR inhibitor-treated patients, usually 2–3 months after beginning therapy. This includes trichomegaly of the eyelashes, which is thought to result from EGFR inhibitor-mediated disruption of the hair cycle, preventing exit from anagen to the catagen phase. Many patients report changes in the hair texture, specifically finer hair and curlier hair, than they had prior to therapy. Alopecia, sometimes with decreased frontal hairline growth, is observed in approximately 20 % of those treated with EGFR inhibitors.

VEGF and VEGFR Inhibitors

Vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) inhibitors are designed to block the process of angiogenesis, which is a critical process during tumorigenesis that provides sufficient blood supply to allow a tumor to grow beyond a certain size. Bevacizumab is a monoclonal antibody that targets VEGF-A, and was approved by the FDA in 2004 for the treatment of metastatic colon cancer; it is now indicated for a number of solid malignancies. Regorafenib has dual activity against VEGFR2 as well as the angiopoeitin receptor TIE2, and was approved in 2012 for the treatment of advanced colorectal cancer.

Hand–foot skin reaction (Fig. 30.2), which is focal hyperkeratosis of the palms and soles with associated mild to moderate erythema, is a commonly seen cutaneous adverse effect of VEGF and VEGFR inhibitors. Typically, this reaction occurs within the first 2–6 weeks after starting the causative medication. It should be noted that this reaction is distinct from the similar sounding hand–foot syndrome, or palmar-plantar erythrodysesthesia, which occurs in patients treated with traditional chemotherapeutic medications such as 5-fluorouracil or capecitabine and manifests with more diffuse and severe erythema and edema. Minimization of friction and trauma is recommended for hand–foot skin reaction, as are keratolytics and emollients. Ice packs and cool water immersion may also be beneficial.

An expected adverse effect of anti-angiogenesis therapy is impaired wound healing, and indeed it has been reported that 1.3–13 % of patients treated with bevacizumab display poor wound healing. Ulcerated striae distensae have

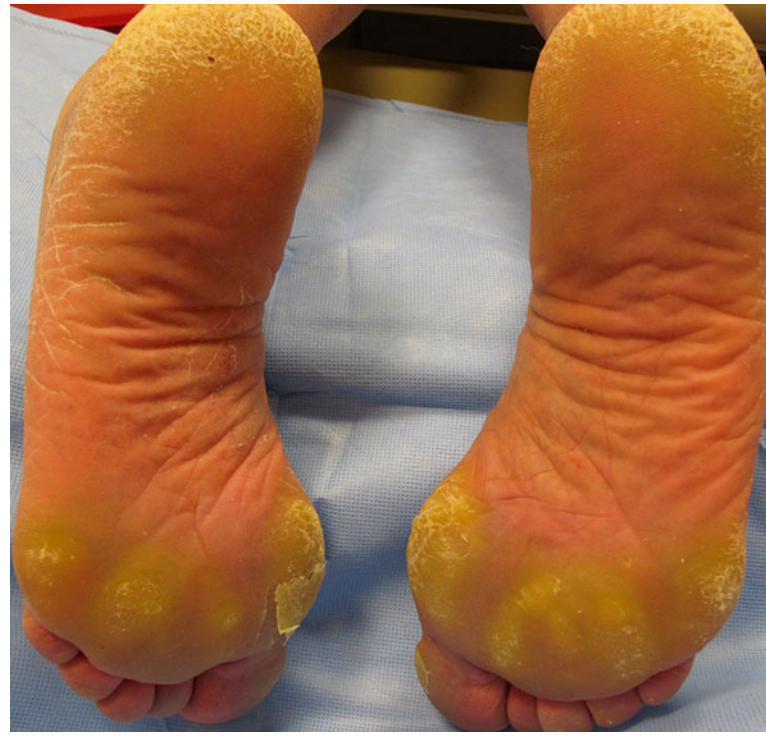

Fig. 30.2 Hand–foot skin reaction of the feet, with prominent hyperkeratosis noted over pressure points

also been observed in those taking bevacizumab. Splinter hemorrhages of the nail beds occur commonly. Finally, stomatitis and morbilliform eruptions have been well-documented to occur secondary to anti-VEGF therapy.

Multikinase Inhibitors: Sorafenib, Sunitinib, and Vandetanib

Multikinase inhibitors harbor activity against multiple tyrosine kinases. Two prototypic medications in this class are sorafenib and sunitinib. Sorafenib targets VEGFR2, 3, PDGFR, c-kit, FLT3, RET, and RAF; while sunitinib targets VEGFR1, 2, and 3, PDGFR, c-kit, FLT3, RET, and CSF-1R. Both are utilized to treat advanced renal cell carcinomas, among other tumor types.

Given its anti-c-kit activity, it is not surprising that sunitinib is associated with hair depigmentation and hypopigmentation of the skin (similar to imatinib and dasatinib). Hand–foot skin reaction and alopecia are also observed in patients treated with sunitinib. Yellow pigmentation is a distinctive finding attributed to sunitinib, and is likely related to the color of the drug itself.

Sorafenib is associated with a diverse group of skin adverse effects. Facial and scalp erythema and dysesthesias occur in approximately 60 % of patients treated with sorafenib. Hand–foot skin reaction and splinter hemorrhages also occur frequently. The so-called sorafenib dermatitis presents as a dusky erythema, and may mimic erythema multiforme clinically, but typically has an indolent course. Keratosis pilaris-like eruptions and keratoacanthomas are observed, similar to patients treated with selective BRAF inhibitors.

The multikinase inhibitors offer an intriguing opportunity to correlate specific skin adverse effects with inhibition of a specific receptor tyrosine kinase. Vandetanib is a multikinase inhibitor which targets EGFR, VEGFR2, and the RET tyrosine kinase. It holds FDA orphan drug status for the treatment of medullary thyroid cancer, which commonly harbors RET mutations. Patients treated with vandetanib developed several cutaneous adverse effects, including photosensitivity and diffuse xerosis and eczematous

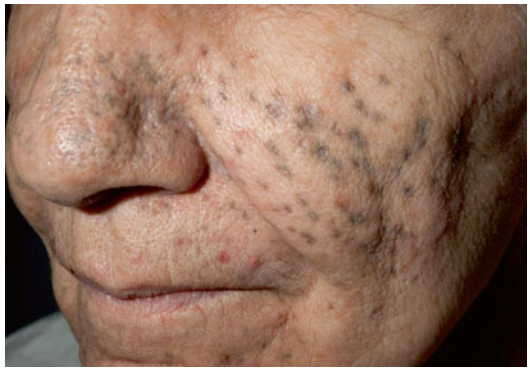

Fig. 30.3 Gray folliculocentric macules on the face, which developed after use of vandetanib. Several acneiform papules and pustules are also seen

dermatitis. In addition, acneiform eruptions are observed frequently, which is attributable to vandetanib's activity against EFGR. Those treated with vandetanib also commonly harbor splinter hemorrhages, related to the anti-VEGFR activity of the medication.

A unique side effect of vandetanib is the development of darkly pigmented macules, which are typically folliculocentric in distribution and are often preceded by photosensitivity as well as the characteristic EGFR-related acneiform eruption (Fig. 30.3). They typically occur on the face and neck, trunk, and upper extremities. The macules are typically blue-gray in appearance, and may appear within scars as well. On histopathology, there are many pigmented macrophages in the dermis. The pigmentation is highlighted by Fontana Masson stains, and variably by Prussian blue iron stains. The dyspigmentation may resolve spontaneously while the patient continues therapy, with use of sunscreen and sun avoidance measures. Improvement is also seen slowly after the medication is discontinued or reduced in dose. Finally, it has been shown that Q-switched alexandrite laser therapy yields significant benefit.

Selective BRAF Inhibitors

The selective BRAF serine/threonine kinase inhibitor vemurafenib was approved by the FDA in 2011 for the treatment of patients with advanced, unresectable, V600E-mutated melanoma. A similar agent, dabrafenib, was approved as a single-agent treatment for late-stage V600E melanoma in 2013. The selective BRAF inhibitors are also being utilized for several other types of advanced malignancies harboring V600E mutations, including papillary thyroid cancer and colon cancer. In melanoma patients, use of vemurafenib or dabrafenib has been documented to result in rapid tumor involution, within weeks of initiation of therapy. However, development of resistance to BRAF inhibitors several months after beginning therapy is a common problem. To circumvent tumor resistance, combination regimens such as those using concurrent BRAF and MEK inhibitor therapy have been developed, with the goal of prolonging survival in advanced melanoma patients.

Use of BRAF inhibitors leads to development of several inflammatory eruptions, including generalized morbilliform reactions. Such reactions are particularly prominent in patients treated sequentially with ipilimumab and then BRAF inhibitors, likely because ipilimumab enhances patients' immune responses to vemurafenib or dabrafenib. Harding et al. reported a series of 13 patients, of whom 4 patients developed grade 3 reactions 6–8 days after starting vemurafenib, after previously having received ipilimumab therapy. On histology, the rash shows a spongiotic dermatitis with perivascular inflammation composed of lymphocytes and eosinophils, typical of a medication hypersensitivity reaction. The rash can be successfully treated by dose interruption and/or reduction. It is notably relatively resistant to treatment with systemic steroids.

Photosensitivity occurs commonly in patients treated with vemurafenib, which results in severe sunburn reactions, often with blistering, in sun-exposed areas of the skin. Erythema may occur with limited sun exposure. Dummer and colleagues found that patients with this type of photosensitivity demonstrated reduced minimal erythema dose (MED) testing to UVA spectrum irradiation, while the UVB MED remained within normal limits. More recently, it has been suggested that a metabolite of vemurafenib, rather than the medication itself, is the photosensitizing

agent. As a result of these observations, it is necessary to counsel patients treated with BRAF inhibitors about the high incidence of photosensitivity, and advise them to use sunscreens with broad-spectrum UVA and UVB activity and sun-protective clothing, in addition to practicing sun avoidance when possible.

Panniculitis is a well-documented adverse effect of BRAF inhibitor treatment, occurring in patients treated with vemurafenib or dabrafenib monotherapy and BRAF inhibitor and MEK inhibitor combination therapy (vemurafenib and cobimetinib, dabrafenib and trametinib), but not affecting those treated with MEK inhibitors alone. Painful red nodules develop on the trunk and extremities, often associated with fever, chills, and arthralgias. On histopathology, there is a lobular and sometimes septal inflammatory infiltrate in the subcutaneous fat. This infiltrate may be neutrophil predominant, lymphocyte predominant, or mixed in nature. Occasionally, leukocytoclastic vasculitis is observed on biopsy specimens. Dose interruption and/or reduction of BRAF inhibitors, systemic steroids, and non-steroidal anti-inflammatory medications have been used to effectively treat panniculitis.

Sweet's syndrome has also been described in patients treated with BRAF inhibitors. On biopsy, the lesions feature a dense neutrophilic infiltrate in the dermis associated with papillary dermal edema. Sweet's syndrome and the neutrophilic panniculitis described above may represent slightly different manifestations on the same spectrum of BRAF inhibitor adverse effects.

Similar to the multikinase inhibitor sorafenib (which is a non-selective RAF inhibitor), vemurafenib and dabrafenib induce keratoacanthomas and keratoacanthoma-type squamous cell carcinomas (referred to here collectively as cuSCCs, Fig. 30.4). Approximately 20–30 % of patients treated with BRAF inhibitors develop one or more cuSCCs. Lesions tend to develop in patients with a history of extensive sun exposure, and/or clinical evidence of sun damage. Moreover, there is typically histologic evidence of at least moderate solar elastosis in biopsy specimens of cuSCCs. BRAF inhibitor-induced cuSCCs may arise within 1–2 weeks of initiation of therapy. The

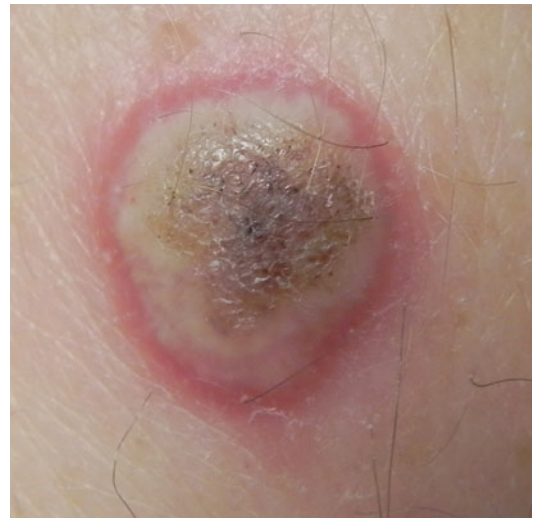

Fig. 30.4 Keratoacanthoma-type squamous cell carcinoma arising in the setting of selective BRAF inhibitor therapy

squamous cell carcinomas are typically well differentiated, often with keratoacanthoma-like features histologically including cup-shaped architecture with a keratin-filled central crater. They often lack another typical feature of classic keratoacanthomas, that of microabscesses composed of neutrophils and/or eosinophils within keratin-filled nests. To our knowledge, to date, there have been no reports of cuSCCs arising from BRAF inhibitors that have gone on to metastasize. Cohen et al. however reported a cuSCC with spindle cell morphology associated with BRAF inhibitor therapy.

Paradoxical activation of MAP kinase signaling appears to account for the development of cuSCCs in patients treated with BRAF inhibitors. In tumor cells harboring activating BRAF V600E or the less frequent V600K mutation, vemurafenib and dabrafenib work by inhibiting downstream signaling the MAP kinase signaling cascade, thereby blocking tumor cell proliferation and survival. However, in cells harboring wild-type BRAF, another RAF family kinase, CRAF, is able to form CRAF-CRAF homodimers and BRAF-CRAF heterodimers, and ultimately promotes increased signaling through the downstream MAP kinase signaling components MEK and ERK. This promotes increased cell

proliferation and survival. In the setting of pre-existing mutations in Ras, which may occur as a result of UV-induced sun damage), this paradoxical MAP kinase signaling is sufficient to promote development of cuSCCs. For this reason, it has been suggested that combination therapy with a BRAF inhibitor and a MEK inhibitor (± ERK inhibitor) lead to reduction of cuSCC development compared to BRAF inhibitor use alone. Based on recent evidence this appears to be the case, as a randomized phase 3 study evaluating vemurafenib and cobimetinib combination therapy versus vemurafenib and placebo demonstrated that in the latter group 47 patients developed cuSCCs, compared to only 7 patients in the former group.

Because cuSCCs are typically well-differentiated and are often multiple in number, they may be treated conservatively. Cryotherapy and scoop shave removal followed by electrodessication and curettage are frequently employed. Full thickness excision is recommended for larger cuSCCs, or those with moderate to poor differentiation on histology. Topical 5-fluorouracil has been reported to induce resolution of cuSCCs in several patients, even as they continued therapy with BRAF inhibitors. Photodynamic therapy (reported in by Alloo et al. using aminolevulinic acid and red light) may be helpful when a patient presents with upward of 10 lesions simultaneously. The systemic retinoid acitretin has been suggested as a means of chemoprevention of cuSCCs, although in practice, patients who are already taking a BRAF inhibitor may be reluctant to take another systemic agent unless their burden of cuSCC development has already been proven to be high. Dose reduction or discontinuation of BRAF inhibitors may be considered, as cuSCCs have been found to regress within several weeks after stopping the medication.

In addition to cuSCCs, benign keratoses also occur frequently in the setting of BRAF inhibitor therapy. Verrucous keratoses are wart-like growths that occur on the face, trunk, and extremities, arising within weeks of initiating BRAF inhibitor therapy. Histopathology of verrucous keratoses reveal epidermal hyperkeratosis, acanthosis and papillomatosis. While these lesions often display hypergranulosis with features suspicious for viral cytopathic change, to date definitive evidence of human papillomavirus (HPV) infection has not been detected within these lesions, even using polymerase chain reaction (PCR) testing to detect viral sequences. HPV immunohistochemical stains are negative in these lesions.

Another type of benign keratosis which arises in the setting of BRAF inhibitor therapy is the warty dyskeratoma. They appear as pink papules, often on the scalp, face, neck, and trunk. Histologically, there is a cup-shaped lesion with associated acantholytic dykeratosis. Patients who are treated with BRAF inhibitors are also prone to developing widespread eruptions on the trunk that show acantholytic dyskeratosis, and therefore resemble Grover's and Darier's disease. The mechanism underlying the development of such eruptions may be directly tied to paradoxical activation of MAP kinase pathway signaling (similar to BRAF inhibitor-induced cuSCCs), as it has been shown in tissue culture that rat cardiac myocytes transfected with constitutively active Ras and Raf demonstrate decreased expression of sarco/endoplasmic reticulum Ca2+-ATPase type 2 isoform (SERCA2), the protein deficient in Darier's disease.

The spectrum of BRAF inhibitor-induced cutaneous effects can further be tied to paradoxical activation the MAP kinase signaling pathway by observing parallels with the so-called RASopathies, a group of genetic diseases including Costello syndrome and cardiofaciocutaneous (CFC) syndrome which are caused by germline activating mutations in the RAS/RAF/MEK/ERK signaling pathway. Patients affected with these conditions therefore exhibit clinical manifestations that are a consequence of increased signaling through the MAP kinase signaling pathway. In the case of Costello syndrome (caused by activating *HRAS* mutations) and CFC syndrome (caused by activating mutations in *KRAS*, *BRAF*, *MEK1,* or *MEK2*), common cutaneous findings include the presence of benign wart-like papillomas, increased melanocytic nevi compared to the general population, palmoplantar keratoderma, and curly hair. The papillomas

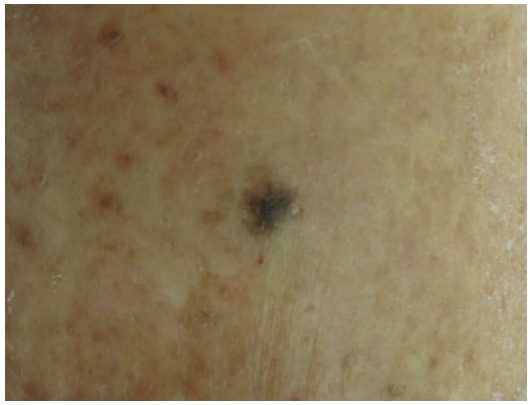

Fig. 30.5 Newly noted dysplastic nevus arising after the initiation of BRAF inhibitor therapy

of both syndromes bear a strong clinical and histologic resemblance to the verrucous keratoses of BRAF inhibitor-treated patients. Moreover, patients treated with BRAF inhibitors have been observed to develop eruptive or darkening nevi after starting therapy, curly hair, and palmoplantar keratoderma/hand foot skin reaction. Of note, palmoplantar keratoderma/hand–foot skin reaction is observed to resolve with cessation of BRAF inhibitor therapy, and is also ameliorated by dose reduction.

A concerning adverse effect of BRAF inhibitor therapy is the development of *de novo* melanomas, as well as atypical nevi (Fig. 30.5). Zimmer and colleagues described 12 new primary melanomas that arose in 11 patients within 27 weeks of beginning vemurafenib or dabrafenib. Newly noted dysplastic nevi were also demonstrated to occur. The new melanocytic lesions that arose were all BRAF wild type, and three melanomas and dysplastic nevi were found to harbor NRAS Q61R or N61K mutations. Given the risk of developing new atypical melanocytic proliferations, regular clinical examinations are recommended for patients who begin vemurafenib or dabrafenib therapy, and sun-protection measures should be emphasized.

One means of circumventing BRAF inhibitor adverse effects is by employing combination BRAF and MEK inhibitor therapy. A recent case report detailed the resolution of vemurafenib-induced keratoacanthoma-type squamous cell carcinomas, keratosis pilaris-like eruption, and hand–foot skin reaction in a patient following initiation of BRAF and MEK inhibitor combination therapy to treat progressive advanced melanoma. Similarly, it has been reported that combination vemurafenib and cobimetinib therapy in a melanoma patient previously treated with vemurafenib alone resulted in the involution of vemurafenib-induced eruptive nevi.

MEK Inhibitors

Selective MEK inhibitors have been developed for the treatment of various solid malignancies. Trametinib, which inhibits MEK1 and MEK2, was approved in 2013 for the treatment of metastatic melanoma. Several dermatologic toxicities develop in the setting of MEK inhibitor therapy. A study of 11 patients treated with the MEK inhibitor selumetinib found that acneiform papulopustular eruptions (similar to those seen with EGFR inhibitors and, to a lesser extent, selective BRAF inhibitors) occurred in all cases. Pruritus and xerosis were also common, occurring 45 % and 36 % of the patients studied, respectively. Skin hyperpigmentation, paronychia, angular cheilitis, worsening alopecia, and cutaneous fissures (Fig. 30.6) can occur. It is worth noting that many of the cutaneous adverse effects associated with MEK inhibitor therapy are also observed in patients treated with EGFR inhibitors, perhaps not surprisingly, given that EGFR and MEK lie within the same MAP kinase signaling pathway.

Conclusions

Tyrosine kinase inhibitors are now commonly used to treat solid and hematologic malignancies. Because tyrosine kinases are commonly expressed in the skin, a high rate of cutaneous adverse effects is observed. Recognition and control of these side effects is a major part of the care of these patients.

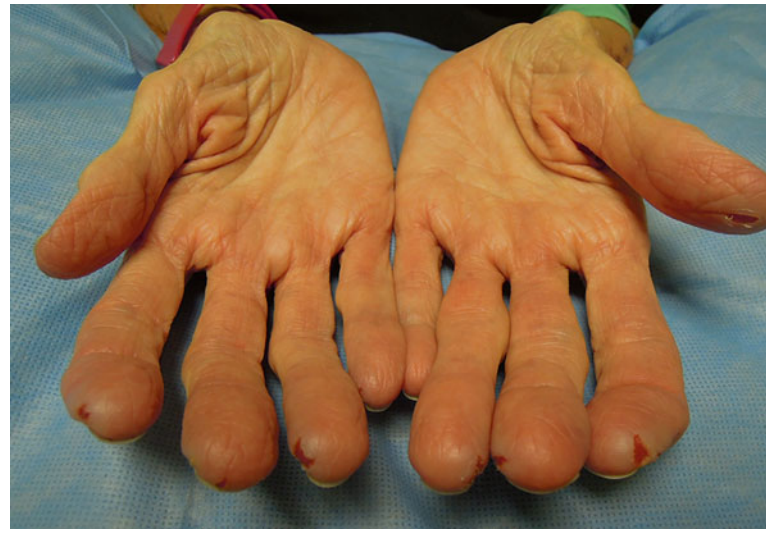

Fig. 30.6 MEK inhibitor-induced fissures on the distal fingers

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Medical Therapies and Their Effects on Skin Cancer

31

Man Kin D. Ho and Noah S. Scheinfeld

Abstract

Patients with fair skin, sun damage, and genetic predisposition to skin cancer need to be followed closely for the development of skin cancer. There are therapies that are additional risk factors in these patients, and some of these will be discussed in this chapter.

Keywords

PUVA • Keratoacanthoma • Merkel cell tumor • Nonmelanoma skin cancer • Thiopurines • Calcineruin inhibitors • Cyclosporine • 6-mercaptopurines • Mycophenolate mofetil • Retinoids • Narrow-band UVB

Introduction

Non-melanoma skin cancer (NMSC), which includes squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), has increased incidence rates and bears a detrimental cost to healthcare expenditure. There were an estimated 3.5 million cases of NMSC in the U.S. from 1992 to 2006 in the Medicare population alone. The established risk factors include high levels of sun exposure, age, male gender, skin phototype, and familial genetic predispositions. We will not discuss rarer tumors, such as merkel cell carcinoma.

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Non-melanoma Skin Cancer

Cumulative ultraviolet (UV) radiation and sun exposure are the most important risk factors for predicting the likelihood of developing NMSC. Drug-induced NMSCs have become more common since the usage of immunosuppressants (Fig. 31.1) and DNA-modifying agents as medical therapies. Post-transplant patients on immunosuppressive regimens are 65–250 times more likely to develop SCC than the general population. Not only do they have higher chances of developing NMSCs, the disease course and prognosis are

J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_31

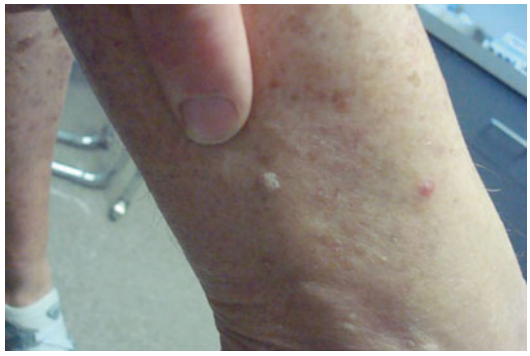

Fig. 31.1 Keratotic area on the inner ankle of a patient with lupus erythematosus with a 20-year history of immune suppression with numerous medications. The biopsy showed a squamous cell carcinoma. The important feature is the benign appearance, indicating the importance of being highly suspicious of tumors in this group of immune-suppressed patients

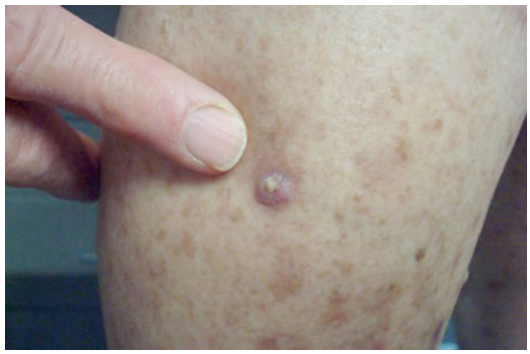

Fig. 31.2 Keratoacanthoma on the inner calf, with a rapidly growing pink tumor. It is a symmetric, circular, pink tumor with a central keratotic core. The patient had been on azathioprine for decades

often worse than the immunocompetent population, with higher mortality rates from metastatic lesions. A review on the major causes of medically induced NMSCs are discussed here, as well as agents that may help delay or inhibit the onset of adverse skin malignancies.

NMSCs that are increased include squamous cell carcinoma (10-to-1 basal-to-squamous cell cancer is reversed in long-term immunosuppressed patients), keratoacanthoma (Fig. 31.2), basal carcinoma, and merkel cell carcinoma. Precancerous tumors that are increased are porokeratosis (Fig. 31.3), actinic keratosis (Fig. 31.4), Bowen's disease, and warts in both genital and non-genital (Fig. 31.5) locations.

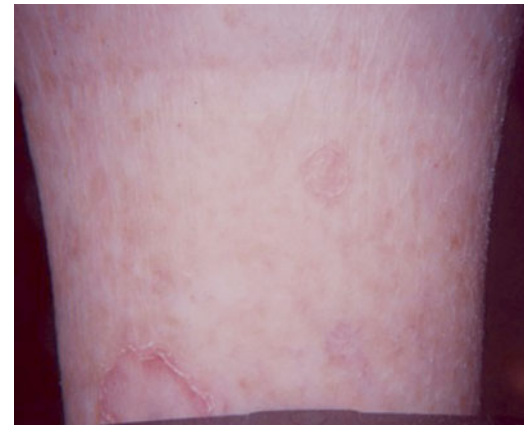

Fig. 31.3 Porokeratosis on the pretibial area in center of figure (smaller lesion) and located in the lower left of the photo (larger lesion that is cut off). The thin linear keratotic rim around the tumor is the diagnostic sign. The commonest type of porokeratosis is disseminated actinic porokeratosis. In the immune-suppressed the porokeratosis tend to be asymmetric in distribution, thicker, less common, and more likely to become a squamous cell carcinoma

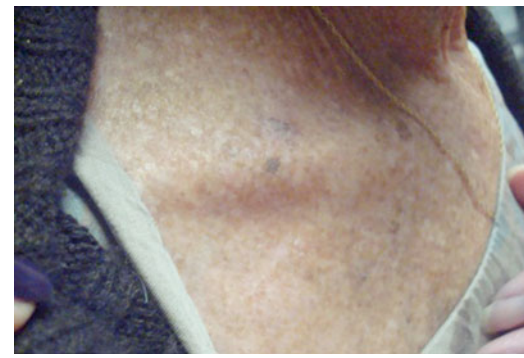

Fig. 31.4 Keratotic brown tumor on right supraclavicular area that is ill-defined, with a subtle pink base that was an actinic keratosis; in a patient who was immune-suppressed from scleroderma. There is a brown well-demarcated stuck-on tumor below the actinic keratosis and to the right of the actinic keratosis, near the patient's necklace. These two tumors are seborrheic keratoses

PUVA

A landmark paper published in 1974 supported the use of psoralen plus ultraviolet A (PUVA) as an effective treatment for psoriasis, as well as more recently for cutaneous T-cell lymphoma stage IA and IB, eczema, vitiligo, graft-versus-host disease, and atopic dermatitis. Psoralen is a naturally occurring phototoxic compound that

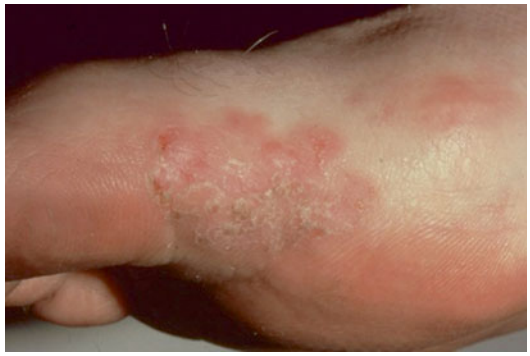

Fig. 31.5 An eczematous plaque on the inner edge of the base of the great toe. Bowen's disease often mimics a dermatitis such as eczema or psoriasis

absorbs light photons and alters DNA and cell components. It may be applied topically or taken orally 1–2 h before UVA application. Psoralen initially penetrates into the cell between DNA, and upon activation via UVA radiation, DNA base pairs are cross-linked, leading to cell apoptosis, mutagenesis, and photocarcinogenesis. More than just inhibiting cell proliferation, PUVA has immunomodulatory properties, such as changing cytokine expressions and functionality of antigen presenting cells.

Since PUVA is mutagenic and exhibits immunosuppressive properties in the skin, it has always been considered a human carcinogen. From 1975 to 2005, a major clinical trial of 1380 psoriatic patients on PUVA was initiated to study the long-term safety profile of PUVA. Results showed that there is a dose-dependent increase in the risk of SCC and moderate increase in risk of BCC at increasing PUVA radiation, which persisted even after cessation of treatments. Patients who had 350+ PUVA treatments had a six-fold increased risk of developing SCC compared with patients who had fewer than 50 treatments. High UVB was associated with an increased risk of BCC. The locations of PUVA-induced SCC also differs from UV-induced SCC, with over half the lesions on the lower extremities versus the more common sun-exposed regions on the head and neck. Men exposed to PUVA treatments are also 53 times more likely to develop invasive scrotal or penile squamous cell carcinomas than the general Caucasian population. A Swedish retrospective study with a 16-year follow-up found that patients who used PUVA have increased risks for developing cutaneous SCC with a relative risk of 5.6 for men and 3.6 for women.

Prior to the 1990s, many retrospective reviews did not appreciate the increased risk of skin cancer with PUVA therapy. This may be due to short follow-up periods (skin cancer changes take years) or because many psoriatic patients had previously received additional carcinogenic treatments including coal tar, radiotherapy, and arsenic. Interestingly, it has been observed that the increased risk of skin cancer after PUVA treatments is higher in U.S. patients than in European patients. This may be related to skin phototype differences (I–II in US vs. III–IV in Europe) or differences with the treatment approach in which Europe is more aggressive with higher single-dose treatments versus the U.S., which is more conservative, with a lower dose but longer exposure time. PUVA is an effective psoriatic treatment, but its effectiveness must be weighed against the increased risk of developing SCC.

Immunomodulatory Drugs—Thiopurines

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are steroid-sparing agents that are commonly used for inducing and maintaining remission in Crohn's disease, ulcerative colitis, and autoimmune diseases such as lupus erythematosus. These have been used in solid-organ transplant patients in the past, but now less commonly used. AZA is a prodrug that is converted nonenzymatically to 6-MP in the body. 6-MP is then metabolized by the liver and gut via one of three enzymes: thiopurine-S-methyltransferase (TPMT), xanthine oxidase, and hypoxanthine-guanine-phosphoribosyltransferase. The active metabolite, 6-thioguanine (6-TG) nucleotides, inhibits purine synthesis and eventually down-regulates DNA and RNA synthesis. It also inhibits T- and B- lymphocytes proliferation, decreasing their production and causing apoptosis of T-cells.

Many retrospective studies showed causal relationships between uses of thiopurine and increased risk of NMSCs. It is thought that 6-TG

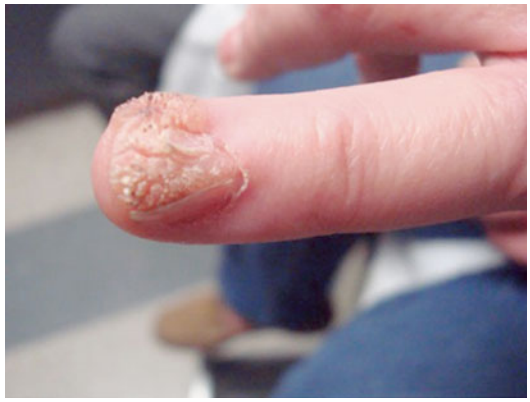

Fig. 31.6 Severe verrucae with destruction of the nail plate on the digit of a leukemia patient undergoing chemotherapy. Subungual warts can become squamous cell carcinomas in the immune-suppressed patient and a biopsy, as was done in this patient, is necessary to rule out transformation to a squamous cell carcinoma

inserts into the skin's DNA and lowers the minimal erythema dose for UVA, but not UVB, light. DNA with 6-TG is extremely photosensitive (Fig. 31.6), in contrast to normal DNA bases that do not absorb UVA light to a significant degree, which promotes DNA misregulations including DNA breakage, crosslinking, and oxidation of nucleotides. This advances to formation of reactive oxygen species (ROS) and increased risk of developing skin cancer.

A recent study showed an association between thiopurine usage in IBD patients and NMSC carry a relative risk of 4.9. Patients who may be more genetically susceptible, including those with a TPMT deficiency, should monitor their skin changes more frequently. A decreased level of TPMT may reduce metabolic clearance of thiopurines, leading to prolonged exposures inside the body and increased risks for NMSC. The patient's past and family history are important, and it may be worthwhile to test for this gene's commonly inherited polymorphisms, considering that as many as 10 % of the population carries a low-activity variant allele.

AZA is also widely used as an immunosuppressant in solid-organ transplant patients. Previous studies demonstrated post-transplant patients on multiple immunosuppressants have a 200-fold increased risk of developing NMSC. Data have suggested that transplant patients who continuously develop NMSC may switch from AZA to a possible lower-risk drug, such as mycophenolate mofetil or sirolimus.

The risk of developing NMSC with thiopurine usage is highest among Caucasian patients. There is an addictive effect, with previous UV light exposure combined with thiopurine and increased NMSC risk. Good sun-protective techniques should begin in childhood, including using sunscreen SPF 45+ and wearing protective headgear with a large brim.

DMARDs—Methotrexate, Biologic agents

Methotrexate (MTX) is a commonly prescribed disease-modifying antirheumatic drug (DMARD) for treating rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, atrophic dermatitis, and other inflammatory conditions. MTX inhibits folic acid synthesis and alters the building blocks for DNA and RNA production. Early studies showed that psoriatic patients over 65 years old have a threefold increased risk for developing lymphomas. A follow-up large retrospective study with more than 150,000 patients showed that psoriasis is associated with increased risks for Hodgkin's lymphoma (HL) and cutaneous T-cell lymphoma (CTCL). Those that have more severe psoriatic conditions have the strongest relative risks for developing CTCL. The pathophysiology of abnormal T-cell proliferation and signaling in psoriasis may explain the increased risk to CTCL, but immunomodulating treatments may also provoke lymphoma development. Given the positive association between psoriasis and lymphoma, the absolute risk of lymphoma is still relatively low, such that it only affects a small subset of psoriatic patients.

As for biologic agents—including TNF-α inhibitors, etanercept, infliximab and alefacept—there is no sufficient data to rule out any causal relationships between treatments and lymphoma. Case reports and large cohort studies with RA and inflammatory bowel disease (IBD) patients have not shown any increased rate of lymphomas

with treatments; however these studies are hard to generalize, due to multiple drug regimens and short exposure times. A short-term treatment up to 4 years is considered safe, with no apparent lymphoma risk.

Immunomodulatory Drugs—Cyclosporine, Tacrolimus

Immunosuppressive regimens are frequently used for post solid-organ transplant patients. Cyclosporine and tacrolimus are commonly used because of their long-studied pharmacokinetics and strong potency. Cyclosporine decreases the activity of T-cells by binding to a cytosolic protein cyclophilin of lymphocytes, which inhibits calcineurin that is responsible for increasing IL-2 synthesis. Tacrolimus inhibits T-lymphocyte signaling and IL-2 production by inhibiting calcineurin via binding to an immunophilin FKBP12.

A study with 161 liver transplant recipients showed 18 % and 9 % of patients presented with precancerous lesions (actinic keratoses) and malignancies, respectively, during their 19 years of cohort follow-up. It demonstrated that a cyclosporine-based regimen, old age, and skin phototype II–III are main risk factors for cutaneous complications in liver transplant recipients. Viral warts have been frequently observed in these patients, and it has been suggested that this may be an indicator of over-immunosuppression. This study demonstrated a lower rate of cutaneous malignancies when compared to heart and kidney transplant recipients (20 %). Risk factors that were previously known to predict dermatological complications include long-term immunosuppressive regimen, age, sex, phototype, and sun exposure.

Renal transplant patients have been reported to bear a 250-fold increased risk of developing SCC and BCC. These NMSCs are usually more aggressive, have a higher tumor proliferation rate, and higher invasiveness when compared to the immunocompetent population. A 2009 study showed that the cumulative incidence of skin malignancies at 10 and 20 years post-renal transplantation was 24.2 % and 54.4 %, respectively, which is in agreement with previous studies. The two most important factors include age at presentation and amount of sun exposure.

All transplant recipients need to be on immunosuppressive therapies to prevent graft rejections, and it is extremely important to do more good than harm with these drugs. There is a difference with NMSCs when comparing the immunocompromised versus the immunocompetent. The ratio of SCC: BCC is 1: 4–6 in the immunocompetent, while it is close to 1:1 in post-transplant recipients. A proposed theory is that SCC develops opportunistically under favorable (immunocompromised) conditions, while BCC develops regardless of the immune status. SCC in renal transplant patients also metastasize ten-fold higher than in the general population. Immunosuppressants will continuously be under close scrutiny to minimize adverse side effects while maintaining therapeutic purposes to keep the donor-graft functional and long lasting.

Maintenance on a single calcineurin inhibitor has shown to be superior to bi- or tri-therapy in a study with 166 patients. The incidence of SCC was 15.9 per 1000 patients for monotherapy versus 26.2 per 1000 patients for bi-/tritherapy. It was statistically significant for patients who were over 40 years old, and monotherapy kept the incidence of SCC: BCC to a ratio near that of the general population's. Monotherapy can be considered for patients who are more susceptible to develop drug-induced skin malignancies, or for those who may not need to be on multiple immunosuppressants.

New-Generation Immunosuppressants

Immunosuppressants have done wonders for post-transplant patients because they greatly reduce the risk of graft rejections. However, with a better prognosis due to improved medical treatment, patients begin to experience the long-term side effects from these drugs, which weren't a major consideration when these immuno-regimens were first introduced. A newer group of drugs, mycophenolate mofetil (MMF) and rapamycin (Rapa), were introduced as alternatives with more favorable profiles. Classical immunosuppressants

including AZA and cyclosporine were found to increase UV carcinogenesis because they have local and direct effects on keratinocytes as well as a systemic immunosuppression. MMF acts by interfering with purine synthesis but differs from thiopurines in that it does not incorporate 6-TG into DNA bases. Rapamycin inhibits the response of IL-2 and decreases activation of T- and B- cells by blocking mTOR.

A mice study successfully demonstrated that MMF and Rapa did not enhance UV carcinogenesis. Rapa even impaired the development of large tumors (>2 mm), which is in direct contrast to the previous concept that immunosuppressants should increase UV carcinogenesis from their innate toxic properties. MMF inhibits tumor growth and angiogenesis, but its effects are not as consistent as Rapa's.

One study showed that switching from calcineurin inhibitors to sirolimus (Rapa) may reduce the peritumoral vascularization and thickness of post-transplant-related SCC. The decreased tumor neovascularization is likely from the inhibitory effects of sirolimus on the VEGF pathway, as well as unknown regulations on endothelial cell growth and apoptotic signals. Another study described switching to sirolimus from cyclosporine reduced the number of skin malignancies, from 3.2 to 0.7. Sirolimus was shown to reduce the chances of acute graft rejection and lack nephrotoxicity and exacerbation of hypertension as side effects, which makes it an attractive drug of choice. There are certain downfalls with sirolimus, including acneiform eruptions, edematous complaints, and aphthous ulcerations. Sirolimus is not recommended initially after transplantation because of possible surgical complications and delayed wound healing, but it has been documented to be safe as early as 3 months post-transplant for patients who carry high risks for skin malignancies.

Retinoids

Retinoids are structurally related to vitamin A, and can be found in various food products including butter, eggs, grains, and richly colored fruits and vegetables. They have been shown to inhibit the proliferation of certain tumor cells such as skin, breast, lung, and ovarian, by interacting with DNA complexes. Retinoids are known for modulating T-helper cell differentiation because a deficiency leads to increased production of IL-12 and IFN-gamma with decreased IL-4 and IL-5, while an abundance results in the opposite scenario. This suggests that vitamin A deficiency leads to a Th1 dominance response while vitamin A excess leads to a Th2 dominance response.

Acitretin, a second-generation retinoid, has been shown to reduce the number of PUVA- and cyclosporine-induced SCC in case reports. A psoriatic patient who developed a total of 34 SCCs during his PUVA and cyclosporine treatments showed marked inhibition of new tumors while he was on a 60 mg/day dose of acitretin. Another case of a psoriatic patient who developed two SCCs within 2 months of cyclosporine treatment showed improvement when he switched to acitretin. Acitretin was titrated from 10 to 35 mg daily while cyclosporine was reduced and completely stopped when 10 SCCs had developed. He continued on acitretin for 4 years on 25 mg every other day, and only developed one additional SCC.

A recent review on strategies for chemoprevention confirmed a decreased risk of developing actinic keratoses and NMSC when post-transplant recipients are started on acitretin. Although the dosing regimen varied among different case reports and case series, acitretin showed beneficial effects and its efficacy is increased in patients who previously had NMSC. An optimal dose has not yet been identified, but a low dose of 10–20 mg/day can be started and slowly titrated up, barring any major side effects.

Narrow-Band UVB

Narrow-band ultraviolet-B (nbUVB) is a new alterative treatment to PUVA for treating psoriasis using a focus wavelength at 290–320 mm. It is a much narrower spectrum compared to conventional PUVA therapy, and the risk of unnecessary UV exposure is substantially reduced. A randomized trial of 60 patients, with 30 each on nbUVB

and PUVA bi-weekly for 3 months, showed that both groups scored a >75 % reduction in psoriasis area severity index (PSAI) score, but the cumulative clearance dose for those on nbUVB was significantly lower than the PUVA group. Adverse effects such as headache, pruritus, and diffuse hair loss also occurred less often in the nbUVB group. The PUVA group did showed benefits in requiring fewer numbers of treatments and faster times for clearing psoriasis compared to nbUVB group. One of the main concerns with PUVA is its increased risk of SCC, and it is important to know if nbUVB carries a similar risk. A large study was carried out in Scotland with a follow-up of 22 years, and showed no increased association between nbUVB and NMSC. Thus, treatment length and cumulative UV exposure continue to be important factors for psoriasis treatment considerations.

Conclusions

Many current available therapies have been extremely helpful and hopeful for our patients. However, these drugs are often double-edged in that they may address one aspect of the medical symptoms but may aggravate or initiate a new malignant transformation. Future research for a better understanding of our drugs' side effect profiles, and techniques to minimize harm caused to patients, cannot be underestimated.

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Cutaneous Reactions to BRAF Inhibitors

32

Holly H. McCoppin

Abstract

BRAF inhibitors, specifically vemurafenib and dabrafenib, are emerging as first-line treatment for unresectable and/or metastatic BRAF mutated melanoma due to their superior efficacy and improved survival statistics. While better tolerated than previously used treatment options, they carry high rates of cutaneous reactions, with most BRAF-inhibitor treated patients experiencing at least one cutaneous adverse effect.

Photosensitivity, various skin rashes, skin papillomas, hyperkeratosis, verrucal keratoses, and cutaneous squamous cell carcinomas (SCCs) are some of the more common cutaneous toxicities reported to date. These are typically managed symptomatically without need for dose reduction or discontinuation of the BRAF inhibitor. MEK inhibitors are now being used in combination with BRAF inhibitors to improve efficacy, prevent drug resistance, and lower the rate of cutaneous reactions. This chapter focuses on the cutaneous reactions associated with the RAF inhibitor sorafenib and the BRAF inhibitors vemurafenib and dabrafenib.

Keywords

BRAF inhibitor • RAF inhibitor • Metastatic melanoma • Vemurafenib • Dabrafenib

Introduction

Rapidly accelerated fibrosarcoma kinase B (BRAF), an upstream activator of mitogen-activated protein kinase (MAPK), is the most frequently mutated protein kinase found in human cancers. Activating mutations of BRAF occur in many tumor types, such as cutaneous melanoma (40–60 %), papillary thyroid cancer (46 %),

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_32

borderline ovarian tumors (34 %), biliary tract cancer (11 %), colorectal cancer (10 %), non-small-cell lung cancer (2 %), and hairy cell leukemia (100 %). Between 40 and 60 % of cutaneous melanomas carry mutations in BRAF codon 600. The BRAF mutation destabilizes the inactive conformation of the BRAF kinase, leading to the constitutively active state and subsequent downstream signaling through the MAPK pathway. The MAPK pathway is involved in regulating cellular proliferation, survival, and differentiation. The result is cell proliferation and melanoma survival advantage. The most prevalent BRAF mutations in melanoma are $BRAF^{V600E}$ (~80 %) and $BRAF^{V600K}$ (5–30 %). BRAF inhibitors have been developed to competitively bind to the ATP binding site to inhibit the action of the BRAF kinase.

RAF is a non-selective rapidly accelerated fibrosarcoma kinase. RAF inhibitors affect multiple kinases and are not BRAF specific. RAF inhibitors can be divided into two types depending on their mode of action. Type 1 RAF inhibitors bind and inhibit the active conformation of the kinase, whereas type 2 RAF (BRAF) inhibitors bind to the inactive conformation of the kinase.

Sorafenib was initially thought to be a BRAF inhibitor, but is now known to be a type 2 RAF inhibitor. It inhibits multiple other kinases, including vascular endothelial growth factor receptors 2 and 3 (VEGFR-2 and VEGFR-3), platelet-derived growth factor receptor (PDGFR)-β, FMS-like tyrosine kinase 3 (FLT-3), c-Kit protein (c-Kit), RET receptor tyrosine kinase, RAF1, mutant BRAF, and wild-type BRAF. In clinical trials, sorafenib did not improve clinical outcomes for patients with metastatic melanoma when added to chemotherapy, even in patients with BRAF-mutation-positive disease.

Sorafenib is used in unresectable hepatocellular carcinoma and metastatic renal-cell carcinoma. Similarly, the type 2 RAF inhibitor RAF265, which inhibits RAF1, Val600Glu mutant BRAF, wild-type BRAF, PDGFRB, KIT, and VEGFR2, showed little specific activity in mutant-metastatic melanoma in a phase I study, but unlike sorafenib, skin toxicities have not been reported.

The new-generation type 1 BRAF inhibitors, vemurafenib and dabrafenib, are the emerging standard of care for BRAF-mutant metastatic melanoma. Vemurafenib and dabrafenib are potent inhibitors of mutated BRAF. They are orally administered and have shown significant impact on both progression-free and overall survival in patients with stage IIIc or IV BRAF mutated melanoma in clinical trials. Patients treated with vemurafenib showed a median overall survival of 13.2 months compared with 9.6 months for patients treated with dacarbazine. Median progression-free survival was 5.1 months with dabrafenib and 2.7 months with dacarbazine. More than 90 % of patients with BRAF-mutant metastatic melanoma demonstrate a clinical benefit with these drugs. The improvement in overall survival and progression-free survival is seen irrespective of whether the patient carries the $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation. LGX818 is another type 1 BRAF inhibitor under investigation in phase 1 clinical trials in metastatic melanoma. The drugs are well tolerated, but cutaneous reactions are very common because of paradoxical activation of the MAPK pathway in wild-type BRAF cells.

BMS908662 (previously XL281) is a RAF inhibitor of unknown type. Cutaneous toxicities caused by paradoxical activation of the MAPK pathway occur at rates similar to those of type 1 RAF inhibitors. Other RAF inhibitors of unknown type that have been investigated in preclinical models include GDC0879, AZ628, PF04880594, and ARQ736. ARQ736 is under investigation in a clinical trial, but data regarding cutaneous reactions are not available.

Cutaneous reactions are some of the most significant adverse events associated with BRAF inhibitors, with over 90 % of patients treated demonstrating cutaneous toxicities. This chapter summarizes the cutaneous reactions associated with type 1 and 2 RAF/BRAF inhibitors, with focus on the RAF inhibitor sorafenib and the new-generation BRAF inhibitors vemurafenib and dabrafenib.

Cutaneous Side Effects of Sorafenib

Cutaneous reactions occur in up to 93 % of patients treated with sorafenib. The most common cutaneous toxicities reported are an

erythematous eruption in 35 % of patients, hand–foot skin reaction (also known as palmar-plantar erythrodysesthesia syndrome) in up to 77 % of patients, and androgenic-like alopecia (27 %), curly hair, subungual hemorrhage (60–70 %), and facial erythema (63 %). A possible increase in cutaneous squamous-cell carcinoma with the use of sorafenib has also been reported in 6–7 % of patients.

Hand–foot skin reaction usually occurs within 45 days of sorafenib initiation, and presents as painful bilateral erythematous lesions, with or without blisters, on the palms and soles. The mechanism by which sorafenib causes hand–foot skin reaction is unknown, but its presence and severity seem to be dose-related. Biopsy samples in cases of hand–foot skin reaction have shown layered keratinocyte necrosis corresponding to the length of time the patient was receiving sorafenib. Dose reduction or cessation of sorafenib has been necessary in severe cases because of the effect on the patient's quality of life.

Cutaneous squamous cell carcinoma in patients receiving sorafenib presents as hyperkeratotic papules and/or plaques on both sun-exposed and non-sun-exposed sites, with diagnostic features on histology of keratoacanthomas or well-differentiated cutaneous squamous cell carcinomas. On cessation of the drug, development of cutaneous squamous cell carcinomas and keratoacanthomas cease, thus implicating sorafenib as the causative agent. No cutaneous reactions were reported in 76 patients with metastatic melanoma in the phase 1 study of the type 2 RAF inhibitor, RAF265.

Cutaneous Side Effects of Vemurafenib and Dabrafenib

Pruritus

Pruritus has been reported in up to 29 % of patients given vemurafenib. Pruritus was self-limited in most cases. Pruritus on its own is yet to be reported with the use of dabrafenib, but itch can be seen with Grover's disease (see Rash section below).

Photosensitivity

A UVA-induced photosensitivity has been observed in 30–57 % of patients taking vemurafenib. In most cases, the photosensitivity presented during the early phase of therapy. The UVA-induced erythema has been demonstrated to appear immediately during UVA exposure. Some patients also reported burning and pain during UVA exposure. The UV-irradiated fields showed pronounced erythema. Patients on vemurafenib have been shown to have a significant decrease in the minimal erythema dose (MED) with UVA exposure after 10 min and 24 h. When a UVA sunscreen was applied before exposure, the MED returned to normal. Ultraviolet B exposure was associated with a normal MED. Photosensitivity has not been reported in studies of dabrafenib.

A significant increase in erythrocyte porphyria concentrations has been demonstrated in patients who exhibit vemurafenib-induced photosensitivity. The photosensitivity induced by vemurafenib seems to be a property of the chemical structure of the drug, which is independent of BRAF inhibition.

This common adverse event should be prevented by regular broad-spectrum sunscreen applications with a high UVA photoprotection, in association with protective hats and clothing, and sun avoidance (even through windows) when possible.

Erythema

Facial erythema, unrelated to sun exposure, has been reported. The erythema usually involves the mediofacial area and spares the periorbital area, as previously described with sorafenib. The erythema responded to application of hydrocortisone 1 % cream in one study.

Panniculitis

Panniculitis, with a predominantly neutrophilic infiltrate, has been reported with both vemurafenib and dabrafenib. In a study of 42 patients on vemurafenib, six (14 %) developed panniculitis of the

lower extremities, with a mean time to onset of 78 days. Alpha-1 antitrypsin deficiency and Weber-Christian disease were ruled out due to normal alpha-1 antitrypsin and pancreatic enzyme levels. A case series reported three patients with biopsy-proven panniculitis with concurrent arthralgias. One patient was receiving vemurafenib and two were receiving dabrafenib. Analgesics and anti-inflammatory medications provided some relief of symptoms, however, one patient temporarily stopped taking the BRAF inhibitor. In another study, all three patients (3/41) who developed panniculitis on dabrafenib had improvement in symptoms without treatment or changes in the trial medication.

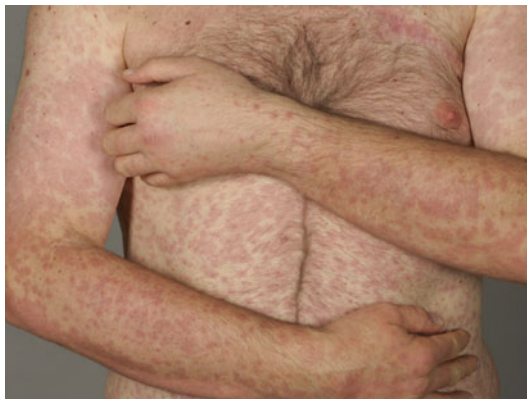

Fig. 32.1 Clinical presentation of the maculopapular rash after 2 weeks of therapy with vemurafenib (Courtesy of Rinderknecht et al. (2013))

Skin Rashes

A non-specific rash has been reported with both vemurafenib and dabrafenib, with 3–52 % of patients affected. No descriptive terms were given in the reports of the trials. In a study of 28 patients on vemurafenib, 50 % developed a disseminated pale erythematous maculopapular rash on the trunk and extremities, less frequently on the face (Fig. 32.1). The eruption commonly appeared in the first 4 weeks of treatment. Histologically, most of these were characterized by a vacuolar alteration of the epidermal-dermal junction with a mild perivascular and lichenoid lymphohistiocytic infiltrate with few admixed eosinophils (Fig. 32.2). Mild inflammatory infiltrates around adnexal structures such as hair follicles and sebaceous and eccrine glands were seen in most patients.

Grover's disease (transient acantholytic dermatosis) is a benign acantholytic disorder. It presents as several scattered erythematous papules, some eroded, with or without crusting. It typically affects the extremities and trunk, and is

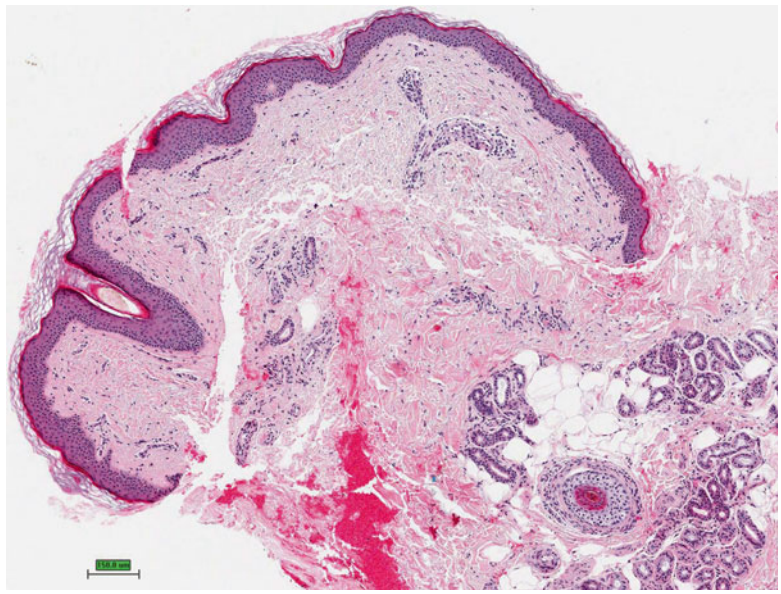

Fig. 32.2 Histology of the maculopapular rash demonstrates a lichenoid lymphohistiocytic infiltrate with interface changes, hematoxylin and eosin stain (Courtesy of Rinderknecht et al. (2013))

usually asymptomatic or only slightly pruritic. It has been reported in up to 27 % of patients receiving dabrafenib, and is similar to idiopathic Grover's disease both clinically and histologically. Median time to presentation in one study of patients on dabrafenib was 79 days. Grover's disease and eruptions resembling Darier's disease have been seen in patients taking vemurafenib, as well.

Dry Skin

Xerosis has been reported to occur in 14–33 % of patients receiving vemurafenib. Mean time to onset was 57 days in one study. The xerosis was sometimes associated with mild pruritus.

Hair Follicle Changes

Several changes affecting the hair follicle have been reported with the type 1 BRAF inhibitors, including slower and thinner growth of scalp hair (up to 29 %), alopecia (8–36 %), changes in the structure of the hair (i.e., from straight to curly, 17 %), folliculitis (9 %), and keratosis pilaris. Dabrafenib has also been associated with a change in the color (turned grey) of hair during treatment, but this has not been reported with vemurafenib. Interestingly, the alopecia has been reported to spontaneously reverse despite continued treatment.

Both vemurafenib and dabrafenib have been associated with keratosis pilaris-like eruptions and folliculocentric erythematous exanthems. In a study on vemurafenib, 43 % (12/28) of patients developed disseminated small hyperkeratotic follicular papules consistent with keratosis pilaris. This occurred often on the face, proximal upper, or lower extremities and was observed more frequently at early treatment time points. In other studies, a follicular eruption was described in 18–55 % of the patients.

Milia have been seen in 31 % of patients on vemurafenib, and occurred after a mean time to onset of 48 days in one study. Epidermoid cysts have been reported to occur in 33 % of patients, with a mean time to onset of 108 days in the same study. In a dabrafenib study, 20 % of patients developed epidermal cysts, usually small milia type, on the face, and less frequently on the trunk. Seven percent developed acneiform lesions on the face and trunk.

Nail Changes

Crumbly nails and nail color changes were encountered in 7 % (2/28) after 2 weeks and 6 weeks, respectively, of treatment with vemurafenib in one study.

Hyperkeratosis

Hyperkeratosis has been reported with both vemurafenib and dabrafenib (6–51 %). Common hyperkeratotic lesions described include verruca vulgaris, seborrheic keratoses, and plantar and palmar hyperkeratosis. A universal clinicohistopathological classification of keratotic lesions induced by BRAF inhibitors is needed to ensure consistent nomenclature and accurate comparisons between BRAF inhibitors.

Plantar hyperkeratosis (Fig. 32.3) has been reported with use of vemurafenib (9–60 %) and dabrafenib (8–22 %). The hyperkeratosis typically presents as yellowish, painful, hyperkeratotic plaques localized to the pressure points on the sole of the foot (i.e., heels and metatarsals). Unlike hand–foot skin reaction reported in patients receiving sorafenib, or palmar-plantar erythrodysesthesia syndrome seen with some chemotherapy, patients on type 1 BRAF inhibitors present with lesions only at points of pressure or friction, blisters are infrequent, and the hands are seldom involved.

Squamoproliferative Lesions

Skin papillomas are benign acanthotic lesions without signs of malignancy and have been reported in 15–46 % of patients treated with vemurafenib. They have been reported on the

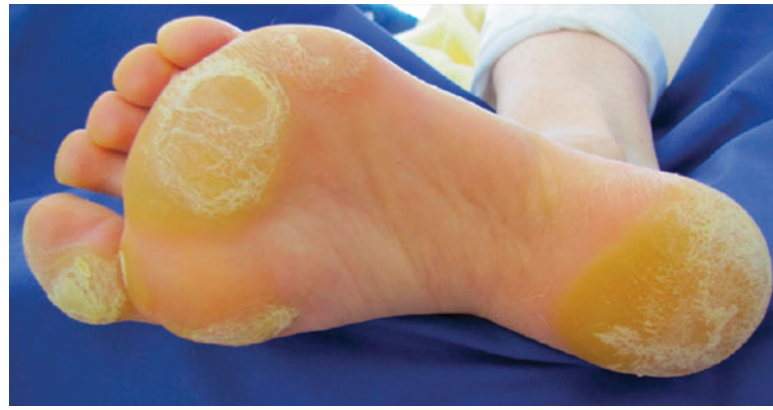

Fig. 32.3 Plantar hyperkeratosis developed after 4 weeks of therapy with vemurafenib (Courtesy of Rinderknecht et al. (2013))

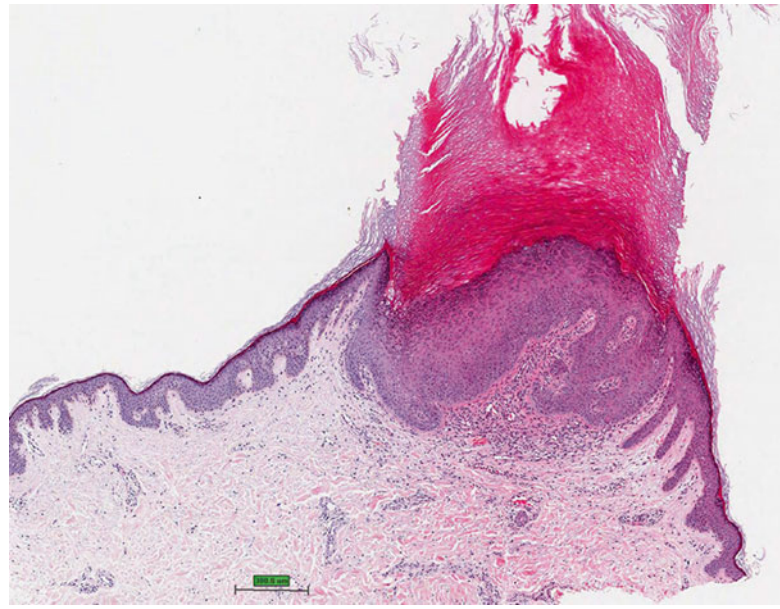

Fig. 32.4 Acanthopapilloma with marked hyperkeratosis and acanthosis, hematoxylin and eosin stain (Courtesy of Rinderknecht et al. (2013))

head, neck, and trunk. Histological evaluation of these lesions revealed marked hyperkeratosis and acanthosis and hypergranulosis, koilocytes, mitosis, and arborization of the peripheral rete ridges, suggesting viral association (Fig. 32.4). Consistent clinicohistopathological classification of skin papillomas induced by BRAF inhibitors is needed for accurate comparisons between studies.

Verruca vulgaris has been reported in 46.7 % of patients treated with vemurafenib and 5 % of patients on dabrafenib. Seborrheic keratoses were found to occur in 34 % of patients on dabrafenib. In dabrafenib trials, hyperkeratotic actinic keratoses have been noted in 10 % of patients. In a retrospective review of 15 patients treated with vemurafenib, 6 (40 %) developed actinic keratoses.

Verrucal keratoses are hyperkeratotic papules clinically similar to keratocanthomas (Fig. 32.5), warts, or nonspecific hyperkeratotic papules. Histologically, they demonstrate papillomatosis, hyperkeratosis, acanthosis, preserved granular cell layer, and various degrees of epidermal dysplasia (most commonly mild to moderate atypia) with absence of koilocytes and keratohyaline granules. Verrucal keratoses have been reported to occur on both sun-damaged

and non-sun-damaged skin in various anatomical locations in up to 49 % of patients on BRAF inhibitors. Peak time to presentation is reported to be 6–12 weeks; however there does not appear to be a relationship between the length of time on treatment and the appearance of these lesions or the degree of atypia. These lesions have not been shown to be malignant, but the noted variation in epidermal dysplasia could suggest they are premalignant variants of cutaneous squamous cell carcinomas.

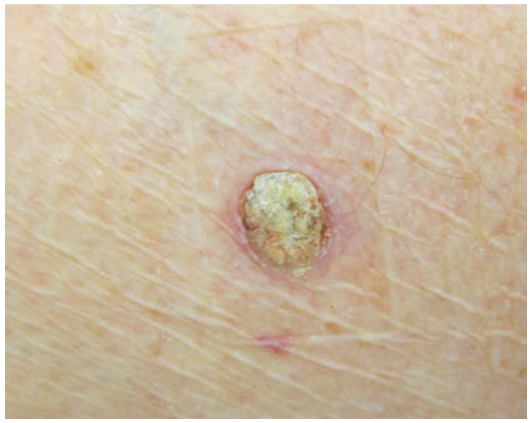

Fig. 32.5 Clinical picture of the kerathoacanthoma, appeared after 5 weeks of treatment with vemurafenib (Courtesy of Rinderknecht et al. (2013))

Squamous Cell Carcinomas

The most common malignant tumor documented in melanoma patients receiving BRAF inhibitors is cutaneous squamous cell carcinomas (SCCs) (Fig. 32.6), reported in 4–31 % of patients receiving vemurafenib and 6–20 % of patients given dabrafenib. These cutaneous SCCs are typically well differentiated or keratoacanthoma-type, however a few less well-differentiated SCCs have been reported. The cutaneous SCCs associated with use of type 1 BRAF inhibitors have occurred on both sun-exposed and non-sun-exposed skin. The median time to first incidence of cutaneous SCC was 8 weeks in vemurafenib and 16 weeks in dabrafenib. In a prospective study of patients taking dabrafenib, SCCs were located on the upper arm, chest, back and/or thigh in 67 %; and on the head, neck, forearm, hand and/or lower leg in 33 %. This is in contrast to the locations commonly seen for cutaneous SCCs. In the same study, 88 % of patients who developed a SCC also developed a verrucal keratosis, suggesting a relationship between verrucal keratosis and SCC development.

Well-differentiated and keratoacanthoma-type cutaneous SCCs were also reported in 8 % of 48 patients enrolled in the phase 1 study of

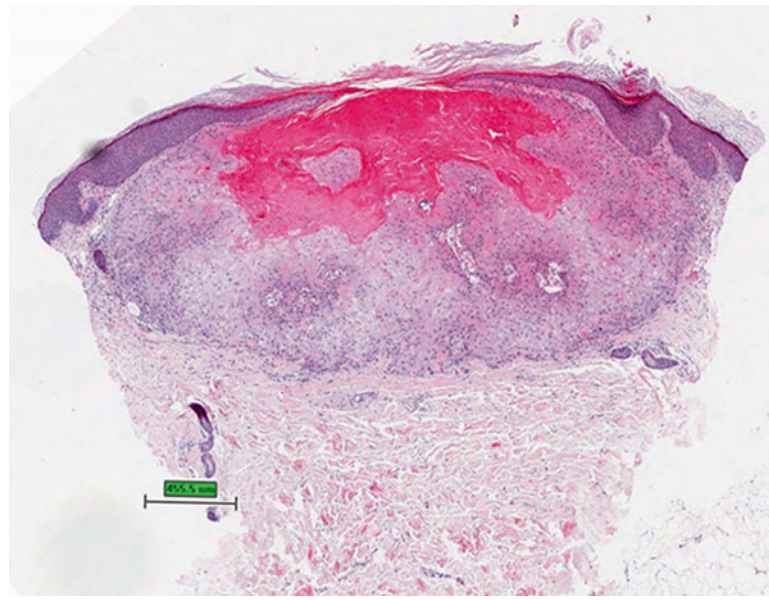

Fig. 32.6 Invagination of keratinizing, squamous epithelium with central keratin-filled crater characterizing a keratoacanthoma, hematoxylin and eosin stain (Courtesy of Rinderknecht et al. (2013))

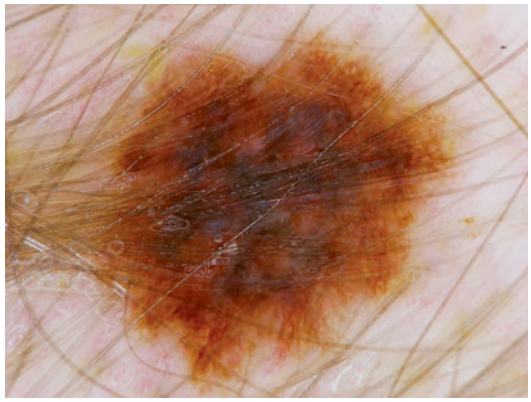

Fig. 32.7 Dermoscopic picture of a melanoma that appeared after more than 4 months of therapy with vemurafenib (Courtesy of Rinderknecht et al. (2013))

XL281 (now BMS908662), a RAF inhibitor of unknown type, and in all three patients with melanoma given BMS908662 combined with ipilimumab.

Cutaneous SCCs have been treated with excision, and dose adjustment of vemurafenib and dabrafenib has not been necessary for management of cutaneous SCC in any of the studies thus far. No metastasis of cutaneous SCC has yet been reported with use of the type 1 BRAF inhibitors. In a prospective study of dabrafenib, most SCCs were detected between weeks 6 and 24 of treatment, suggesting that close monitoring in the first 6 months of treatment is important.

Melanocytic Nevi and Melanoma

New melanocytic nevi and new primary melanomas (Figs. 32.7 and 32.8) have been noted in patients receiving BRAF inhibitors. New primary melanomas were reported in the phase 3 trials of vemurafenib (in 8 of 337 patients) and dabrafenib (3 of 187). Many studies and reports note that the new primary melanomas appearing in patients receiving BRAF inhibitors, although in a small number of patients, are wild-type BRAF lesions. BRAF wild-type melanomas might develop during BRAF blockade as a result of BRAF inhibitor-induced tumor progression via the stimulation of MAPK signaling.

Mechanisms of Keratinocyte Activation

The clinical findings associated with BRAF inhibitors suggest that they facilitate proliferation of keratinocytes. The addition of a BRAF inhibitor to wild-type BRAF keratinocytes leads to the paradoxical activation of the MAPK pathway in these cells. However, in order for this pathway to be activated, there must first be upstream activation of RAS proteins to trigger signaling through the MAPK pathway. This could occur via a pre-existing or new mutation in RAS or an upstream component that activates RAS.

Activating mutations in genes encoding the RAS proteins have been reported in 30–70 % of cutaneous SCCs in patients taking type I BRAF inhibitors. In one study, the incidence of RAS mutations was significantly higher in cutaneous squamous cell carcinomas taken from patients receiving vemurafenib (30 %) than in cutaneous squamous cell carcinomas from those not given a BRAF inhibitor (3.2 %). The presence of verrucal keratoses and SCCs on both sun-damaged and non-sun-damaged skin makes UV radiation unlikely to be the sole trigger. The presence of plantar keratosis suggests that pressure or friction should be considered as a trigger in some cases. Thus far, the limited numbers of tested cases and conflicting results in studies have resulted in a questionable role of HPV in the development of SCCs and verrucal keratoses in patients receiving BRAF inhibitors.

Combination BRAF and MEK Inhibitors

Anti-MEK drugs block the MAPK pathway downstream of BRAF in keratinocytes. The combination of MEK inhibitors with BRAF inhibitors, therefore, results in fewer cutaneous side effects and may be useful in circumventing at least some forms of resistance to BRAF inhibitors that develop in melanomas. Combinations of dabrafenib (type I BRAF inhibitor) with trametinib (MEK inhibitor) have shown improved progression-free survival and overall survival

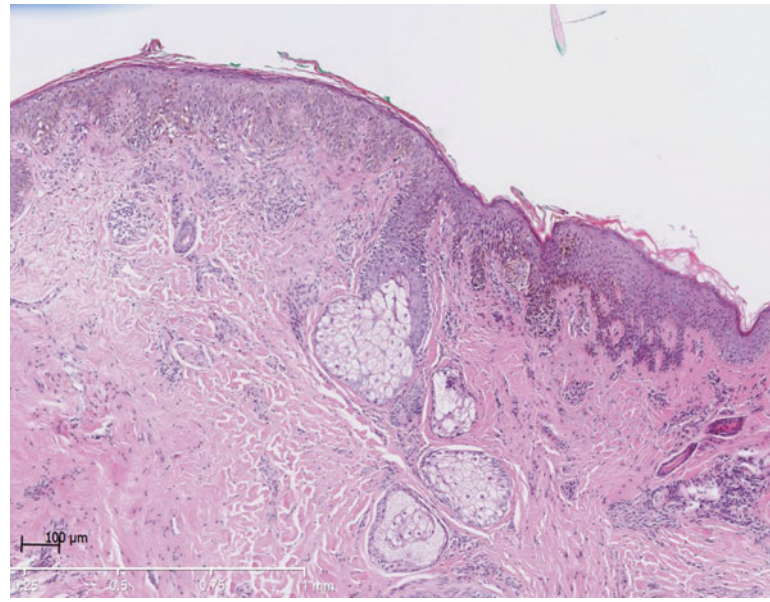

Fig. 32.8 Asymmetric, not well circumcised, melanocytic proliferation revealing a melanoma with a breslow index of 0.45 mm, hematoxylin and eosin stain (Courtesy of Rinderknecht et al. (2013))

compared with BRAF inhibitors alone. Approval by the US Food and Drug Administration has been given for treatment with the combination.

Similarly, in the phase 1 study of RO5126766 (a single agent with combined RAF and MEK inhibitor activity), no cutaneous SCCs were reported in 53 patients, although other skin reactions were common. Preliminary data from a phase 1/2 study of dabrafenib in combination with trametinib (NCT01072175) demonstrated a nonspecific rash in 13–20 % of patients and cutaneous SCC in 3 %. Many of the side effects described in patients receiving dabrafenib or vemurafenib alone have not been demonstrated to occur with combination therapy, including hyperkeratosis of palms and soles, verrucal keratosis, Grover's disease, or hair changes.

These results support the hypothesis regarding paradoxical activation of the MAPK pathway in wild-type BRAF cells (e.g., keratinocytes) by BRAF inhibitors as the cause for hyperkeratosis and cutaneous squamous cell carcinoma. The model predicts that paradoxical activation of the MAPK pathway with BRAF inhibition could be prevented by concurrent inhibition of the MAPK pathway downstream of BRAF (e.g., with a MEK inhibitor). Thus, the anti-BRAF and anti-MEK combination could not only increase the treatment efficacy, but also prevent the cutaneous reactions associated with BRAF inhibitor therapy.

Management of Cutaneous Reactions

Patients should be informed about the side effects of BRAF inhibitors and should be advised regarding effective photoprotection prior to initiation of therapy. Patients should undergo a dermatological evaluation every 8 weeks during treatment, with consideration for monthly evaluations in the first 6 months of treatment. This recommendation takes into consideration the high frequency of hyperkeratotic lesions within the first 24 weeks of treatment and allows for their early identification and management.

A low threshold for skin biopsy of new keratotic lesions and new or changing pigmented lesions is recommended. All clinically or histologically diagnosed cutaneous squamous cell carcinomas should be treated surgically. Large, tender, rapidly growing, aggressive SCCs and/or SCCs in critical anatomic locations should be excised or removed via Mohs micrographic surgery. For small, superficial SCCs, destructive modalities such as curettage and electrodessication may be sufficient. So

far, no metastatic SCCs have been associated with the use of BRAF inhibitor therapy. For patients who develop many cutaneous SCCs, the use of acitretin as a chemopreventive drug has been reported to reduce the number of hyperkeratotic lesions, both benign and malignant. The interaction of acitretin with BRAF inhibitor therapy has not yet been studied.

All other cutaneous reactions should be treated symptomatically. Grover's disease is commonly managed with moisturizers, topical steroids, oral antihistamines, lifestyle changes to avoid overheating, and with intermittent use of oral prednisone or long-term acitretin in severe cases. Keratosis pilaris-like reactions have been treated with mild keratolytics such as urea creams or moisturizers containing lactic acid or salicylic acid. Plantar hyperkeratosis can be managed with rest, elevation, regular use of urea creams, and avoidance of friction. Folliculitis can be controlled with topical antiseptics and topical and oral antibiotics. Panniculitis responds to non-steroidal anti-inflammatory drugs. Photosensitivity is best prevented by strict sun avoidance and sun protection with protective clothing and hats, and daily use of sunscreens that cover the UVA spectrum. Patients should be reminded that the reaction can be triggered behind windows.

The management of verrucal keratoses is controversial. Although these are benign lesions by definition, the occurrence of similar mutations present in cutaneous squamous cell carcinoma suggest that they should be closely monitored for changes such as rapid growth, pain, and erythema (indicative of evolution into cutaneous squamous cell carcinoma). Cryotherapy can be useful for small lesions, and there are reports that suggest a benefit for the use of acitretin.

Future

LgX818 (a type 1 BRAF inhibitor), from Novartis, is in trials currently. Although at an early stage of assessment, it seems to have a favorable toxicity profile and some activity in patients in whom vemurafenib was not successful. Trials of vemurafenib plus GDC-0983 (cobimetanib) (MEK1 inhibitor) are also in progress. Clinical trials of the BRAF inhibitor LGX818 (Encorafenib) alone and in combination with the MEK inhibitor MEK162 are also underway (Novartis). These developments, plus attempts to prolong duration of responses induced by BRAF inhibitors with immunotherapy, indicates the speed with which changes in treatment of metastatic melanoma are occurring. The days of monotherapy with vemurafenib seem to be dwindling.

Conclusions

The type I BRAF inhibitors, vemurafenib and dabrafenib, are first-line agents in BRAF-mutated metastatic melanoma and demonstrate improved overall survival and progression-free survival compared to previous agents. The most common adverse events occurring with BRAF-inhibitor treatment are skin reactions, which occur in a majority of patients treated with these drugs. Most of these can be managed without the need to cease or modify the dose of the BRAF inhibitor.

The association of cutaneous squamous cell carcinoma and possible link to the formation of wild-type BRAF primary melanomas suggests that all patients taking a BRAF inhibitor should undergo regular dermatological assessments to identify and remove such lesions.

As the number of patients treated with BRAF inhibitors increases, more detailed dermatological and histopathological description is needed, as well as an international consensus on the classification of the cutaneous manifestations of BRAF inhibitors. The combination therapy of BRAF inhibitors with MEK inhibitors appears to not only increase the treatment efficacy, but also prevent the development of many of the cutaneous reactions noted with anti-BRAF monotherapy.

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Cutaneous Reactions to Corticosteroids

33

Eleanor J. Feldman

Abstract

Corticosteroids have been used for decades. Their anti-inflammatory properties have been shown to be highly effective in a variety of autoimmune conditions as well as those with an increased inflammatory response. The undesirable effects of corticosteroids include the decrease in production of dermal infrastructure cells such as fibroblasts and mast cells, with increased development of structural proteins and complexes. This, in turn, leads to the development of a variety of skin maladies including striae, milia, telangiectasias, purpura, striae distensae, stellate tears of the skin, and atrophy. Its vasodilatory effects contribute to the development of rosacea, acne, folliculitis, and perioral dermatitis. It promotes bacterial and fungal (especially candididiasis) superinfection while introducing a foreign substance capable of inducing a hypersensitive response. Ultimately, the practictioner should be cognizant of these complications, especially in patients with long-term use, and should taper and supplement with adjunctive medications whenever possible.

Keywords

Atrophy • Striae • Telangiectasias • Perioral dermatitis • Tachyphylaxis

Introduction

Corticosteroids were introduced to the field of medicine in the 1940s after it was found that an extract of adrenocortical tissue could counteract kidney failure. Edward Kendall and Phillip Hench and their work on the adrenal cortex not only won the Nobel prize for physiology and medicine in 1950, but also led to the introduction of cortisone. Since then dozens of variations of the initial corticosteroid came into development. Whether natural or synthetic, they all have a four-ring carbon skeleton. Corticosteroids can be further divided into two main categories with two very different functions. The mineralocorticoids, such as aldosterone, are named as such due to their ability to control the maintenance of sodium and potassium, two

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_33

minerals. Differing primarily in particular hydroxylation or oxidations of specific carbons in the skeleton, the glucocorticoids control carbohydrate, protein and lipid metabolism while demonstrating a unique anti-inflammatory effect at multiple stages in a multitude of inflammatory cascades.

Not surprisingly, glucocorticoids have found substantial use within the field of dermatology, particularly in counteracting conditions with an overactive inflammatory response. This chapter will focus on the specific cutaneous reactions to corticosteroids; oral, intravenous, and topical.

Superinfection

Glucocorticoids are well known for their anti-inflammatory properties. However, with a suppressed immune response, steroids provide an ideal medium for bacterial and fungal superinfection. Studies have shown ranges of 10–25 % superinfection rate, with corticosteroid use ranging from days to months. Of the noted pathogens, fungi are more common (Fig. 33.1), as is often the case with prolonged immunosuppression. A multitude of species including tinea, candida, and trichophyton have been implicated. Of bacterial superinfection, streptococcus group A and staphylococcus are the most common. The physician should be very cognizant of superinfection, as it has a potentially fatal outcome. One study found a 10 % rate of necrotizing fasciitis in patients treated topically for bullous pemphigoid.

In infants, granuloma gluteale infantum is a rare condition in the diaper area that often develops following the use of corticosteroid treatment of diaper rash. The literature, however, is unclear as to the true etiology. Fungal cultures have not demonstrated a superinfection with *Candida sp*. In fact, preexisting candidal dermatitis has been implicated as a possible contributing factor.

Steroid Rosacea and Acne

One common complication of topical steroid use is a worsening of rosacea. Oftentimes this is found in patients of fair skin with preexisting

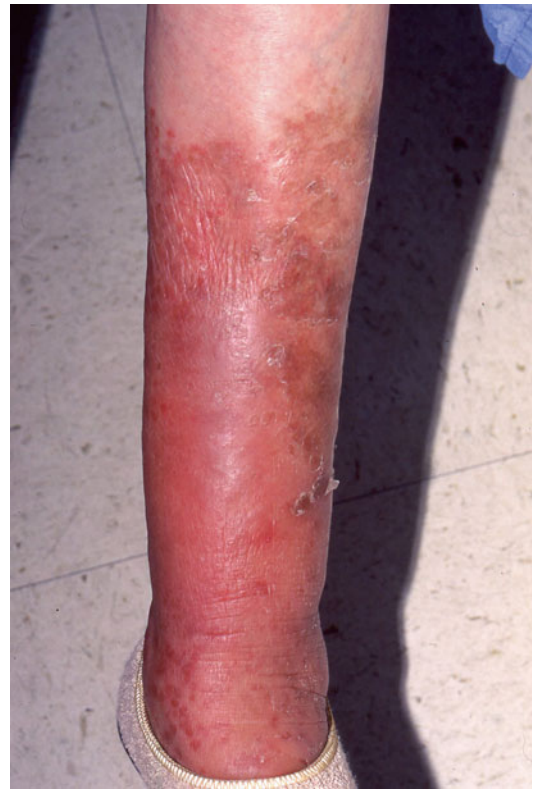

Fig. 33.1 Severe tinea corporis of the leg due to trichophytun rubrum. It started out much less prominent, but topical and systemic corticosteroid use caused the leg to swell and the erythema and some induratio to spread up the leg from the foot

disease. This typically occurs on the face in chronic users of topical cortciosteroids. A patient would often apply a low-dose topical corticosteroid to treat the initial malady. With judicious use of steroid, tachyphylaxis can develop, which subsequently can lead to increased frequency of application. With tachyphylaxis comes the risk of rebound recurrence. Patients often demonstrate a diffuse pruritic erythematous rash with papules and pustules. Possible mechanisms include dilation of blood vessels, rebound release of proinflammatory cytokines, and an accumulation of nitric oxide.

Treatment of steroid-induced rosacea is challenging. Ideally, cessation of steroid use is the treatment of choice, however, patients often have difficulty with the rebound tachyphylaxis. Many adjunctive treatments have been used, including

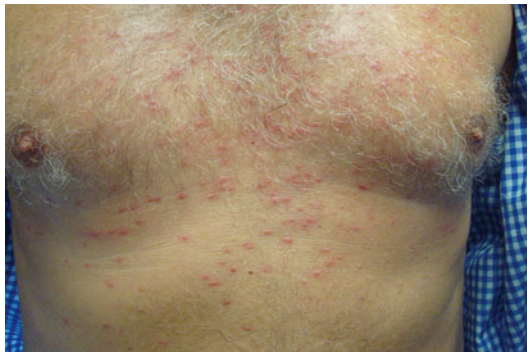

Fig. 33.2 Erythematous, monotonous papules in a symmetrical distribution over the chest in a man treated for months with triamcinilone cream. As with steroid acne, there are no comedones or cysts

the addition of topical immunomodulators such as tacrolimus, as well as topical and oral antibiotic treatment.

Interestingly, studies have shown that the presumed effect of tachyphylaxis is, in fact, a misnomer. In fact, physician and patient both often presume the presence of tachyphylaxis when in fact there was improvement or no change in the clinical condition. This may be related to the therapeutic efficacy of the topical corticosteroid, where perhaps physicians and patients expected a greater response from a weaker strength of medication.

Steroid-induced acne tends to have monotonous symmetric papules without comedones or cysts. Steroid-induced folliculitis (Fig. 33.2) is indistinguishable clinically, except often in an age group not prone to acne, and often more symptomatic with pruritis and a flare with heat.

Perioral Dermatitis

In a similar vein to steroid-induced acne and rosacea is that of perioral dermatitis. This is most commonly found in women, although men have been shown to demonstrate it as well. The typical picture is once again a chronic topical corticosteroid user who develops perioral pruritis, erythema, and papules. The papules may be pinhead-sized and can coalesce into plaques. There is often a perioral halo of clear skin, and

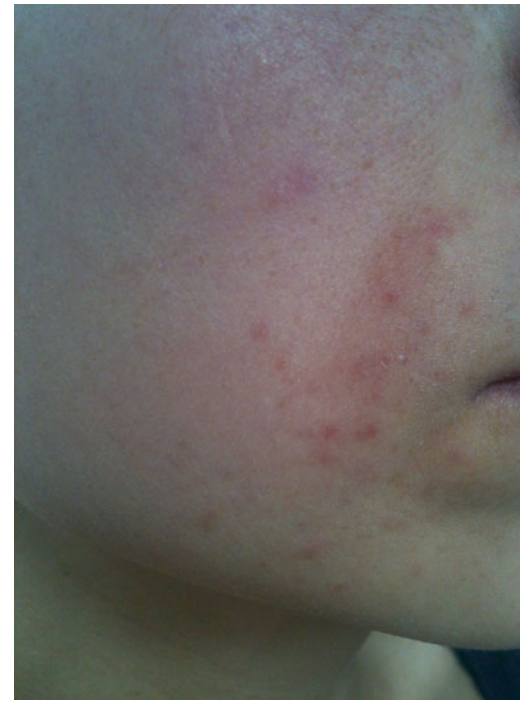

Fig. 33.3 Peroral dermatits on the left cheek, with tiny papules becoming plaque-like in places. Upper border is the corner of lip where the dermatits barely reaches. Hydrocortisone cream had been used for weeks for an unknown skin ailment when this acneiform problem appeared

the disease will only reach the lips in the corners (Fig. 33.3). Treatment once again is tapering the steroids, with possible adjunctive immunomodulators. Some authors refer to it as periorificial since it can occur around the nose and genital area when topical steroids are used there.

Alterations to Pigment and Hair

As mentioned previously, corticosteroids affect a plethora of cell types. An additional postulated cell type is the melanocyte. Steroids have been postulated to potentially decrease the synthesis of melanin from melanocytes. As a result, patients with intralesional injection of glucocorticoids have been shown to develop hypopigmentation along the distribution of the steroid. Additionally, specifically with patients of darker complexions, long-term use of topical glucocorticoids have

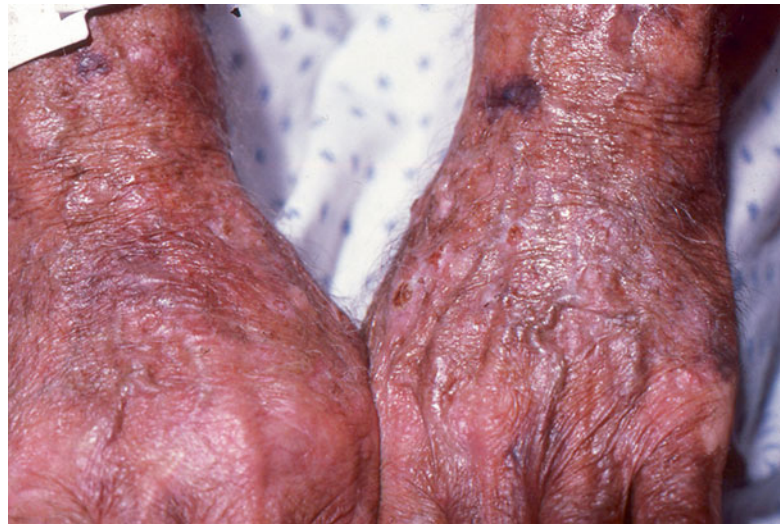

Fig. 33.4 Increased skin transparency over the backs of hands with patchy areas of hypopigmentation, purport, and small erosions. Theses changes were the result of prolonged use of desoximetasone cream for an unknown skin disease

been shown to produce patchy hypopigmentation (Fig. 33.4). The hypopigmentation typically resolves with discontinued use of the steroid.

Glucocorticoids have also been shown to promote the development of hirsutism and hypertrichosis. Studies have shown that children with long-term overuse of glucocorticoids have developed diffuse hypertrichosis. These same children have also been found to exhibit other adverse effects of prolonged corticosteroid use including growth retardation and adrenal suppression.

Hypertrichosis is a relatively rare phenomenon and is typically demonstrated in patients with prolonged use of glucocorticoids. The presence of hypertrichosis is an ominous sign and should be a clue to the physician to look for other sequelae of prolonged steroid use.

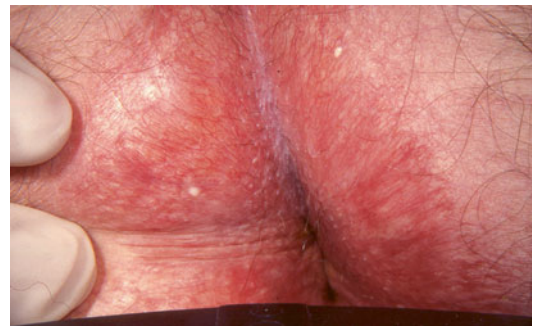

Fig. 33.5 Dramatic telangiectasias, milia, and atrophy in a patient using a fluorinated corticosteroid ointment for months for itching in the rectal area

Skin Atrophy

Perhaps one of the more widely studied complications of prolonged topical steroid use is dermal atrophy. In fact, some studies have demonstrated that all topical steroids cause skin atrophy at varying degrees. This is due to a multitude of contributing factors. First, glucocorticoid activity has been shown to suppress cell division in the basal skin layer. Additionally, it has been shown to prevent fibroblast mitoses as well as decreases in collagen synthesis, as well as the creation of mucopolysaccharides. Pathological studies have also shown a significant decrease in mast cells.

Clinically, patients present with a thinning of the skin, increasing its transparency, as shown in Fig. 33.4. Age, location, and potency of steroid all contribute to the atrophic affect. Areas of the thinnest skin, such as intertriginous areas, are more susceptible.

Often concurrently seen with skin atrophy are the presence of telangiectasias (Fig. 33.5). These typically develop due to the stimulation of dermal vascular endothelial cells by glucocorticoids.

Currently, the best treatment for steroid-induced skin atrophy is prevention. All topical steroids should be immediately discontinued. Ideally, potent steroids should be avoided in areas of thin

skin and given for the shortest period whenever possible. Topical tretinoin has shown promise, however, studies have had conflicting results. Its potential efficacy is related to in vitro studies, which have demonstrated the opposite effect of tretinoin on the skin, including an increase in mast cell count and collagen synthesis.

Striae

A well-known complication of steroids is the development of striae within the skin. One case report showed the development of diffuse red striae throughout the back, abdomen, breasts, and buttocks of a 17-year-old female after several months of topical betamethasone treatment for psoriasis vulgaris. A likely explanation is related to the co-development of skin atrophy. As the framework of the dermal tissue is altered, the skin becomes thinner. With decreased collagen synthesis, collagen cross-links, the skin is less likely to tolerate stretching, and ruptures within the framework lead to linear striae. These striae are often pruritic, necessitating the use of additional low-potency steroids for their anti-pruritic effect. As with skin atrophy, prevention is essential, and steroids should be given at low potencies and short durations whenever possible. Plastic surgery has been utilized for excision of striae.

Intramuscular Steroid Atrophy

This can be seen after intramuscular, intravenous, subcutaneous, subacromial or intra-articular steroids injection with deep atrophy of skin, subcutaneous tissue, and even muscle (Fig. 33.6). In its most severe form, Nicolau syndrome, livedo reticularis, severe pain (often immediate), and deep-tissue necrosis and gangrene occur.

Ulcerations

Glucocorticoids have also been shown to increase the tendency of skin to ulcerate. This is similarly related to the weakened infrastructure within the dermis and exacerbated by minimal trauma. These ulcers are worsened by the decrease in wound healing caused by steroids, and often persist for months until an adequate steroid taper can be achieved. Until steroids are tapered, treatment typically involves local wound care with agents such as zinc oxide and collagenase.

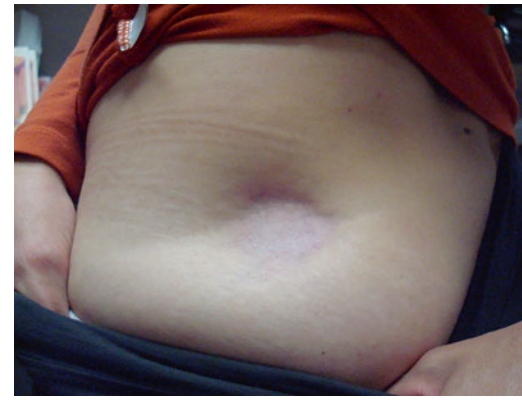

Fig. 33.6 Triamcinilone was given in this girl's buttock in dose of 80 mg for chronic arthritis. This improved over 6 months but did not completely resolve

Steroid Allergy

Though glucocorticoids are frequently used for their anti-inflammatory affect, they have been shown to paradoxically induce hypersensitivity. The prevalence of corticosteroid allergy is low relative to their widespread use. Topical reactions have been found to be prevalent in anywhere from 3 to 9 % of the general population. The first causative agent was found to be hydrocortisone. Typically responsible corticosteroids are those that are non-fluorinated, such as hydrocortisone and budesonide.

The exact pathophysiology for the steroid allergy remains unclear. A commonly described mechanism was introduced by Bundgaard in 1980. He postulated that non-fluorinated compounds degraded more rapidly than their fluorinated counterparts. The degraded product would then react with arginine and thus produce an antigen capable of inducing hypersensitivity.

The most common dermatologic manifestation to steroid allergy is a patchy eczematous-like rash, which did not respond to additional topical glucocorticoid. Systemic reactions are similar to systemic hypersensitivity to other antigens, consisting mainly of diffuse widespread urticaria or maculopapular rash in addition to other respiratory and vasogenic responses.

Steroid allergy can be diagnosed with patch testing which has been found to be 90 % sensitive. There is, however, a significant false-negative rate, which is contributed to by the anti-inflammatory properties of corticosteroids. Intradermal injections have been found to be more accurate, although they are less widely used. Determining cross-reactivity is difficult and not entirely delineated. Coopman in 1989 created a four-category system based on immunogenic potential. Type A- hydrocortisone type, Type B-triamcinolone type, Type C betamethasone type, and type D hydrocortisone-17-butyrate type. This classification was subsequently adjusted, however, and the classification scheme has not been consistently reproducible. Some have studied the potential of succinate esters in drastically increasing hypersensitive potential.

Conclusions

Corticosteroids have been widely used in the field of dermatology for decades. However, their anti-inflammatory properties serve as a double-edged sword. On one hand, they can effectively treat dermatologic maladies involving an overreactive inflammatory response. On the other hand, they affect a multitude of cells, including fibroblasts, mast cells, and endothelial cells; weaken the infrastructure of the dermis; and lead to a variety of reactions. Additionally, their anti-inflammatory effects promote bacterial and fungal growth and superinfection, resulting in potentially fatal conditions. Lastly, steroids have been shown to produce a substantial allergic response.

An attempt should be made to be cognizant of these complications, particularly in those patients with long-term use of steroids. Try to use the lowest potency possible, for the shortest possible duration, and to taper whenever possible.

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Cutaneous Reactions to Retinoids

34

Gretchen W. Frieling and Andrew R. Tegeder

Abstract

Since their introduction in the 1980s, retinoids have been increasingly used for both the topical and systemic treatment of many disorders including, but not limited, to hyper- and parakeratotic cutaneous diseases, severe acne, keratotic genodermatoses, and chemoprevention of skin cancer. Retinoids affect epidermal cell growth and differentiation, sebaceous gland function, epidermal lipids, and display anti-inflammatory properties. Retinoids have been used both topically and systemically. Today, three generations of synthetic retinoids are available:

1. First-generation (nonaromatic): tretinoin (all-trans-RA), isotretinoin (13-cis-RA), and alitretinoin (9-cis-RA)
2. Second-generation (monoaromatic): aromatic retinoids including etretinate, acitretin
3. Third-generation (polyaromatic): tazarotene, adapalene, and bexarotene.

The topical retinoids used at present have marked therapeutic effects on epidermal cell production and desquamation and, although they can only be applied to small areas of skin, they harbor reduced systemic toxicity compared to systemic retinoid therapy.

Teratogenicity is the most *significant* adverse effect of retinoid therapy; however, adverse cutaneous reactions are common, including itching, burning, erythema, and severe skin dryness with a potential dermatitis-like

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_34

reaction sometimes referred to as "retinoid dermatitis." Topical retinoids are rapidly developing at present and seem promising for the future. Novel development of receptor-specific retinoids for topical treatment of psoriasis and/or acne may lead to promising new therapeutics. Due to the minimal nature of the side effects associated with topical retinoid use, they should be used as needed, but responsibly, and with the awareness that rare severe reactions have been reported in the literature. At this time, controversy remains as to whether topical retinoids should be available over the counter. In this chapter, we will discuss the potential cutaneous side effects of retinoid therapy.

Keywords
Topical retinoids • Systemic retinoids • Cutaneous reactions • Retinoid dermatitis

Introduction

The significance of retinoids was first noted 100 years ago, but their introduction into the treatment and management of skin diseases wasn't appreciated until approximately 70 years later. Retinoids affect epidermal cell growth and differentiation, sebaceous gland function, epidermal lipids, and display anti-inflammatory properties. Vitamin A was first administered in 1930 for the treatment of phrynoderma, but severe vitaminosis A and side effects were observed. Vitamin A is stored in the liver for long periods, and therefore its prolonged use at therapeutic doses is severely limited. Thus, synthetic retinoids were subsequently developed, with more than 1500 investigated so far. Today, three generations of synthetic retinoids are available:

1. First-generation (nonaromatic): tretinoin (all-trans-RA), isotretinoin (13-cis-RA), and alitretinoin (9-cis-RA)
2. Second-generation (monoaromatic): etretinate, acitretin
3. Third-generation (polyaromatic): tazarotene, adapalene, and bexarotene.

Retinoids have become an integral part of the treatment plan for many skin diseases, including severe acne and acne-related dermatoses, psoriasis, hyperkeratotic disorders, genodermatoses, hypovitaminosis A, aging, photodamage, keloids, pseudofolliculitis barbae, and disorders of skin pigmentation including melasma and post-inflammatory pigmentation. They have also been approved for the chemoprevention of cancers, including epithelial neoplasms, AIDS-associated Kaposi sarcoma, acute promyelocytic leukemia, and cutaneous T-cell lymphoma. Less commonly, retinoids have been used for the management of eosinophilic folliculitis, lichen planus, lichen sclerosus et atrophicus, and condyloma acuminatum. Teratogenicity remains the most *significant* adverse effect of retinoid therapy and, although there are many potential systemic side effects from retinoid use, this chapter focuses on those involving the skin.

Cutaneous reactions are common, including itching, burning, erythema, and severe skin dryness, with a potential dermatitis-like reaction sometimes referred to as "retinoid dermatitis." Although irritation tends to subside as the skin acclimates to the medication effects, the main contributing factors include frequency and quantity of topical treatment, skin type, and superimposed irritation from washing or environmental factors. Retinoid dermatitis is an erythematous papular rash with a shiny, smooth presentation, sometimes referred to as "sticky skin." This is due to the flattened horny layer with erythema and hyperhidrosis, imparting a "shiny" appearance. Retinoid dermatitis can have different presentations and may mimic psoriasis, mycosis fungoides, eczematous dermatitis, and pityriasis

rosea. It is typically dose-dependent and inadequate to cause termination of the drug.

Topical retinoids are in rapid development and seem promising for the future. Novel development of receptor-specific retinoids for topical treatment of psoriasis and/or acne may lead to promising new therapeutics. Due to the minimal nature of the side effects associated with topical retinoid use, they should be used as needed, but responsibly, and with the awareness that rare severe reactions have been reported in the literature. Controversy still exists as to whether topical retinoids should be available over the counter.

The exact mechanism by which oral retinoids positively affect skin cancers is still unknown. Actinic keratoses were the first pre-cancerous lesions to be successfully treated with topical retinoids, specifically tretinoin. Oral leukoplakia and keratoacanthoma are also responsive to retinoids; however, the latter recurs after treatment is stopped, and therefore, retinoids are not first-line treatment. We do know that promotion of differentiation and apoptosis may lead to tumor dissolution. This control may be mediated by interactions with nuclear retinoid receptors. Patients with both xeroderma pigmentosum and basal cell nevus syndrome that were actively making new skin cancers (squamous cell and basal cell carcinomas, respectively) have been treated with isotretinoin, which has shown to decrease development of new skin cancers. However, neither fully-developed squamous cell carcinomas nor melanomas respond positively to retinoids.

Pharmacodynamics

Biological retinoids, including vitamin A and its derivatives retinaldehyde and retinoic acid, are present in low concentrations (0.35–0.75 mg/L) in the peripheral blood and have important roles in vision, reproduction, cell proliferation, bone growth, immune functions, and activation of tumor suppressor genes. As vitamins, they must be acquired from the diet. They are also hormones, which act through the binding of nuclear receptors and are ultimately degraded.

Synthetic retinoids were developed in the search for less toxic compounds. It was determined that modifying the carboxylic end group would maintain the biological activity while harboring reduced toxicity. Substitutions for the aromatic rings also showed less toxicity and interestingly, an increase in biologic activity.

After administration, oral retinoids can be detected for 30–60 min in the plasma. Maximum concentrations are reached approximately 2–4 h later, and clinical monitoring is recommended every 3–4 weeks.

Mechanism of Action

Retinoid concentrations vary in skin and adipose tissue, with the former having a slightly lower concentration. Once inside the cell, retinoids follow a signaling pathway that includes cytosolic proteins and two specific classes of nuclear receptors, RAR and RXR. In the skin, the specific receptors are RAR-γ and RXR-α. Retinoids bind and activate their ligands in the form of dimers. They also have complex interactions with other hormonal receptors.

Retinoids affect epidermal cell growth and differentiation, sebaceous gland function, epidermal lipids, angiogenesis, and display anti-inflammatory properties. Notably, isotretinoin decreases both sebaceous gland size and lipid synthesis. Keratinocyte proliferation is stimulated by expression of cyclic adenosine monophosphate (cAMP), epidermal growth factor receptor (EGFR), protein kinase C and transforming growth factor α (TGF-α). They are also known to affect differentiation of cells toward metaplastic and mucosal-type epithelium.

Retinoids have been shown to inhibit angiogenesis, which presumably is the foundation for their utility as anti-neoplastic agents, as well as both stimulate and inhibit the immune system. Antibody production and T-helper cells are increased. Inhibition of neutrophil migration into the epidermis is one of the commonly reported anti-inflammatory properties. Keratinocytic nitric oxide and tumor necrosis factor-α are inhibited by tretinoin and isotretinoin. Topical tretinoin has

been shown to prevent a decrease in Langerhan cells after UV exposure. Along these lines, systemic etretinate has been shown to normalize epidermal Langerhan cells in psoriatic skin. In vitro, surface antigens of T cells are increased after retinoid therapy. Forefront research is highlighting the development of receptor-selective retinoids for altering and/or improving their therapeutic profile.

Drugs

Isotretinoin

Many dermatological diseases are controlled through medications, but are not truly cured. In contrast, isotretinoin provides the closest thing to a cure, or at least a long-lasting response that a physician can utilize for acne management and treatment.

Isotretinoin is most commonly used to treat severe nodulocystic acne, but has other indications that include psoriasis, disorders of cornification, hidradenitis suppurativa, rosacea, pityrosporum folliculitis, gram-negative bacterial infections, and chemoprevention of skin cancers. Because isotretinoin is a significant teratogen, the iPledge system was introduced as an effort to reduce the number of pregnancies occurring while taking isotretinoin. The medication must be stopped should a patient become pregnant, and stringent monitoring must take place while a female patient takes isotretinoin.

Typically, dosage of isotretinoin is based on a patient's body weight, with a traditional cumulative treatment dose goal of 120–150 mg/kg. However, there is growing evidence that higher cumulative treatment doses can lead to fewer relapses. One recent study found a significant decrease in the number of relapses when cumulative treatment doses of 220 mg/kg and greater were used. These higher doses were associated with expected side effects of xerosis and cheilitis, which resolved after completion of the treatment course.

There are several common and expected cutaneous reactions to isotretinoin. These occur concurrently with the medication course, appear dose-dependent, and resolve after discontinuation

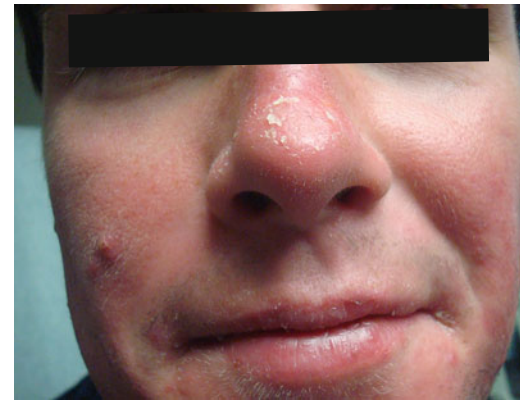

Fig. 34.1 Severe dryness and fissuring of lips and nose in a patient on isotretinoin

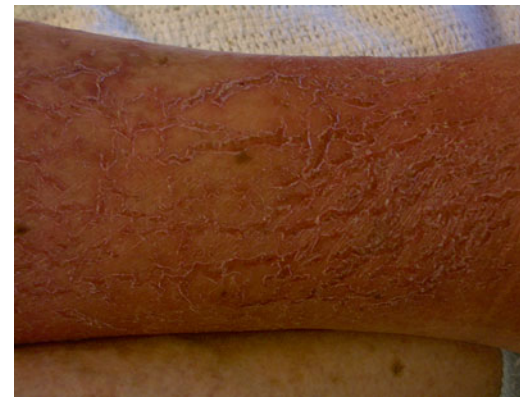

Fig. 34.2 Xerotic skin with reticulate fissuring seen in asteatotic dermatitis over the ankle in a patient on isotretinoin

or completion of the treatment. The most commonly reported adverse effects are mucocutaneous. These are a consequence of alterations in the skin barrier function due to decreased sebum production, change in lipid composition in the skin, and thinning of the stratum corneum.

Cheilitis, and eye, mouth, nose, and skin dryness are the most common mucocutaneous adverse effects. In fact, cheilitis (Fig. 34.1) is nearly universal, and its absence could suggest non-compliance or treatment failure. Many patients notice dryness of the face and acral skin. Generalized xerosis (Fig. 34.2) is a common complaint and might occur in half of patients treated. Though acral erythema and desquamation are uncommon adverse effects, they have

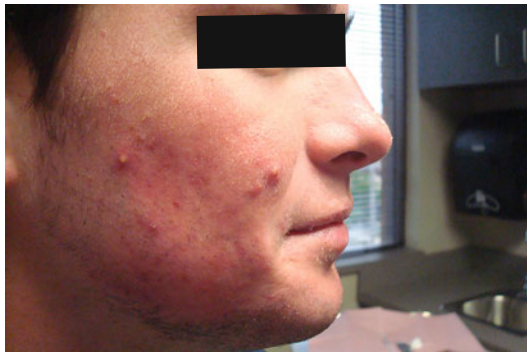

Fig. 34.3 Increased redness and inflammation of pustules after 1 month of isotretinoin therapy

been reported in the literature and the authors have seen it firsthand. Some patients might complain of pruritus, but this appears to be fairly uncommon. Along with dry skin and mucous membranes, epistaxis occurs relatively frequently. One series looked at 100 patients taking isotretinoin and showed 31 out of the 100 patients experienced epistaxis at some point in time. Most patients are able to manage these side effects with supportive measures such as frequent emollient use and reassurance.

There are many other rare, but reported, cutaneous side effects of isotretinoin therapy. Some patients experience an increase in *Staphylococcus aureus* colonization on the skin. Lip abscesses have formed as a result of bacterial colonization in patients with severe cheilitis. Some patients can experience the unfortunate event of worsening acne (Fig. 34.3) with isotretinoin. There have been case reports of patients developing acne fulminans during a course of isotretinoin, requiring cessation of therapy. Pyogenic granuloma formation is an uncommon but significantly distressing adverse effect for some patients taking isotretinoin. Normally the complication resolves after discontinuation of the medication. There are case reports of periungual pyogenic granulomas, though they can occur anywhere on the body. The mechanism by which isotretinoin causes pyogenic granuloma formation remains unclear.

Isotretinoin also has the ability to adversely affect the fingernails and toenails. Some reported adverse effects include nail fragility, median nail dystrophy, and nail brittleness. These are also transient and resolve after completion of isotretinoin course. Ingrown nails have been reported, but are rare. There are isolated reports of facial edema caused by isotretinoin, though other reports have lauded isotretinoin as a potential treatment for this type of edema.

Other rare adverse effects include increased sweating, bruising, hair abnormalities such as alopecia and telogen effluvium, flushing, excess granulation tissue, sun sensitivity, rectal bleeding with anal fissures, pseudoporphyria, and acute generalized exanthematous pustulosis.

The most common ocular side effect of isotretinoin is conjunctivitis, occurring in 20–50 % of patients during therapy. Other common complaints include hordeolum, chalazion, and blepharitis. Meibomian gland dysfunction is one mechanism that can lead to dry eye symptoms. Isotretinoin alters gene expression and cell proliferation in the meibomian glands, which could, in part, lead to dry eye symptoms. There are reports of sub-conjunctival hemorrhage associated with isotretinoin, but this does not appear to be a common finding, is asymptomatic, and self-resolves. Other more serious, but less common, ocular side effects include corneal opacities and decreased night vision.

Tretinoin (Retin-A®)

Topical tretinoin (13-cis-retinoic acid) has become the standard agent in the treatment of acne vulgaris, primarily due to its action on the initial part of the pathological process, the microcomedone. Tretinoin has shown to dramatically reduce lesion counts. One of the other most common usages of topical tretinoin is for photoaging, with many studies showing improvements in fine and coarse wrinkling, roughness, and redness. More rarely, oral tretinoin has been used systemically for acute promyelocytic leukemia (APML).

Tretinoin, like other topical retinoids, has predictable adverse effects, including dryness and skin irritation, likely from the hydroalcoholic ingredients. These are dose-dependent and resolve after cessation of therapy. Pyogenic granulomas have been reported following tretinoin

therapy, developing after initiation and disappearing after cessation of the drug. Many studies have shown that tretinoin is a photosensitizer; however, neither phototoxic nor photoallergic reactions are generally observed. This "photosensitivity" is most likely secondary to thinning of the stratum corneum with enhanced ultraviolet light susceptibility.

Acitretin (Soriatane®)

Previously known as etretin, acitretin is the active metabolite of etretinate and has basically supplanted etretin due to a better safety profile. Acitretin is most commonly used to treat psoriasis and has been found to be particularly effective in treating the pustular, nail, and erythrodermic variants. It is currently the only non-immunomodulatory FDA-approved systemic psoriasis treatment. Other indications include Darier's disease and chemoprevention of non-melanoma skin cancers in organ transplant and immunosuppressed patients, hidradenitis suppurativa, and treatment of congenital disorders of keratinization.

Acitretin specifically inhibits the migration of polymorphonuclear cells into the epidermis by preventing release of toxic oxygen species, decreasing proliferation of lymphocytes, and decreasing antigen presentation of keratinocytes in vitro.

Pharmacologically, acitretin has a half-life of 1–2 days and is much less lipophilic than etreinate, allowing more rapid elimination from the body. Dosing for psoriasis and other disorders normally starts at 10–25 mg daily and is then escalated as tolerated and as needed, often reaching doses of 40–50 mg daily depending on disease control and patient tolerance.

Acitretin shares many of the same adverse effects of oral isotretinoin. Mucocutaneous adverse effects are common and include cheilitis, xerosis, nail dystrophy, and pyogenic granuloma. These mucocutaneous side effects respond to supportive measures, are mostly dose-dependent, and resolve once the medication is discontinued. Similar to isotretinoin, it is a significant teratogen and prescribers need to use caution when treating women of child-bearing age. Some authors recommend monthly pregnancy testing for those women taking acitretin. Indeed, the elimination time for acitretin is prolonged, meaning patients should not give blood or become pregnant for 3 years after treatment. Even when acitretin falls to undetectable levels in the blood, there is the potential for it to re-esterify into etretinate. Alcohol consumption appears to contribute to this re-esterification.

Etretinate

Etretinate (Tegison) is an aromatic retinoid known for its successful treatment of extensive plaque-like, pustular and erythrodermic psoriasis, Darier's disease, lichen planus, oral leukoplakia, porokeratosis of Mibelli, lichen planus, and hereditary ichthyoses, with less success in the treatment of acne. Etretinate is deposited in the epidermis in 7–10 days and subsequently prevents epidermal accumulation. Peak plasma concentrations occur approximately 4 hours after administration, with a half-life of 10 days. After long-term administration, it is stored in adipose tissue, which is then eliminated slowly from the body, sometimes taking 2 years. Although elimination can be prolonged, toxicity after chronic administration is rare with a dose between 10 and 50 mg/day. Case reports have been published with harlequin ichthyosis infants who have survived on etretinate. A prophylactic effect was reported in patients with malignant degeneration of porokeratosis of Mibelli. In one patient, no new epithelial tumors developed while on a 2-year course of retinoids. Etretinate has also been useful in the treatment of epidermodysplasia verruciformis. Lichen planus is often self-remitting; however, chronic forms of the skin and mucous membranes can be severe and painful. Etretinate has been useful in the treatment of chronic lichen planus, with the best results in the erosive-atrophic form.

The most commonly reported side effects of etretinate include mucocutaneous dryness, and liver and triglyceride abnormalities. Colonization of the nares with *Staphylococcus aureus* has been reported. Patients on etretinate may feel excessively cold, presumably due to excessive heat loss through the erythematous skin. An increased photosensitivity has been reported with etretinate use in less than 13 % of patients. However, the

combination of PUVA and etretinate has demonstrated success in the treatment of psoriasis, and due to the lack of evidence supporting this so-called photosensitivity when patients are subjected to phototesting, many patients are still encouraged to seek some sunlight in management of their psoriasis. Palmoplantar pustular and papular lesions have been reported in patients on etretinate therapy. Saurat et al. showed this was due to etretinate-induced miliaria in hyperhydrotic patients, and the papules could be early psoriatic lesions. Erythema multiforme was reported in two patients after etretinate therapy, with confirmation by re-challenge in one of the patients. Etretinate has also been reported to cause diffuse alopecia, specifically telogen effluvium, in 10–75 % of patients, and this is the most common cause of discontinuation of the medication, especially in women. This is directly proportional to the dose, with the scalp being the most commonly affected site, and eyebrows and eyelashes rarely affected. The hair shafts may be different upon re-growth, with curly, kinky, or twisted hairs replacing formerly straight hair shafts. Two cases of pyogenic granuloma formation have been reported. Nail changes can vary, with decreased shine, thinning, fragility, and/or loosening/loss of the nail entirely. These changes can occur alone or in combination with redness and edema of the nail bed as well as excess granulation tissue deposition.

Adapalene (Differin®)

Adapalene is a receptor-selective retinoid analog that binds with the highest affinity to members of the RAR family. Like topical tretinoin, adapalene is used as a topical treatment for acne vulgaris. The medication is available in 0.1 and 0.3 % gel and cream forms and is used daily for control of acne and some cases of pustular rosacea.

Numerous studies have compared adapalene with tretinoin regarding their respective efficacy in treating acne. A large meta-analysis concluded that topical adapalene 0.1 % was more effective than topical tretinoin 0.025 % and was better tolerated by patients. Other subsequent studies have mixed results, some demonstrating better efficacy with higher concentrations of tretinoin than 0.025 % but also suggesting that adapalene is better tolerated by patients, with less incidence of irritant dermatitis. In any case, it is an effective and sometimes better-tolerated alternative to tretinoin.

Adverse effects of adapalene are somewhat similar to tretinoin though, as discussed above, can be better tolerated. The most common side effects include skin irritation, xerosis, and mild exfoliation. These are controlled via supportive measures, with one study finding daily moisturizer use an effective means of considerably reducing skin irritation and dryness. Rarely, pyogenic granulomas have been associated with topical adapalene therapy.

Tazarotene (Tazorac®)

Tazarotene is available in concentrations of 0.05 and 0.1 % in gel and cream forms. A foam form is currently being evaluated in clinical trials. An oral form is not currently available in the United States and has not been approved by the FDA.

Tazarotene is indicated for use in patients with plaque-type psoriasis, acne vulgaris, and photoaged skin. Studies have found that tazarotene performed favorably compared to all strengths of tretinoin in controlling inflammatory acne lesions. Studies inconsistently find tazarotene may be slightly more irritating than tretinoin.

As with other topical retinoids, the most common adverse effects include cheilitis and irritant dermatitis at the site of application. Similarly, the adverse effects are normally dose-dependent and resolve after discontinuation. As with other topical and systemic retinoids, there are cases of pyogenic granuloma formation after topical application of tazarotene, though this seems to be a rare adverse effect.

Oral tazarotene is atypical in that it is not associated with the adverse events typical for other systemic retinoids (hyperlipidemia, etc.). It is considered pregnancy category X and may be associated with more severe skeletal abnormalities.

Bexarotene

Bexarotene (Targretin®) is the first synthetic retinoid X receptor–selective retinoid that is FDA-approved (1999) for cutaneous T-cell lymphoma (CTCL) treatment, with a response rate of 50 % in all stages of the disease. The mechanism of

action in CTCL is presumably via apoptosis, but remains largely unknown. Safety and effectiveness of bexarotene have been shown when used as both monotherapy and combination therapy, but therapeutic monitoring is still recommended. It is very expensive.

Although generally well tolerated, adverse cutaneous side effects have been reported, such as pruritus and rash. These effects are proportional to the bexarotene dose. Bagazgoitia et al. reported a 55-year-old woman with Sézary syndrome who developed a progressive generalized exfoliative erythroderma after initiation of bexarotene. Similarly, Ruiz-de-Casas et al. reported granulomatous papules and nodules on the face and left arm in a 39-year-old woman with Sézary syndrome after treatment with bexarotene. In both of these cases, the cutaneous reactions and lesions disappeared when bexarotene was discontinued.

Alitretinoin (Panretin®)

Alitretinoin (9-cis-retinoic acid,) is an isomer of tretinoin with significant anti-inflammatory and immunomodulatory activity. Alitretinoin can bind to all six known intracellular retinoid receptors (RAR-α, -β, -γ, and RXR-α, -β, -γ), with a slightly higher affinity for RAR receptors. Thus, alitretinoin can inhibit cellular proliferation, induce terminal cellular differentiation, and induce apoptosis (the latter of which is regulated by RXRs). Although priced over ten times higher than tretinoin and tazarotene, alitretinoin is currently the only licensed product for moderate to severe chronic hand eczema that is otherwise unresponsive to potent topical corticosteroids. Other indications for topical alitretinoin include photoaging, cutaneous T-cell lymphoma, pyogenic granulomas, and Kaposi sarcoma.

Alitretinoin is generally safe and well-tolerated. However, few mild-to-moderately severe cutaneous adverse events have been reported that are limited to the site of application. These include rash, erythema, pruritus, pain, exfoliative dermatitis, tingling, and edema, with rash and erythema being the most common. Walmesely et al. reported one patient who developed cellulitis and bacteremia after scratching a lesion that was treated with alitretinoin. These reactions were reversible on reduction in frequency or suspension of application. Although retinoids as a class have been associated with photosensitivity, alitretinoin has not been associated with this side effect. In vitro studies have demonstrated that alitretinoin exhibits a minimal photosensitizing effect; however, it is still recommended that patients minimize sun exposure during use. Due to the success of other retinoids (tazarotene and tretinoin) in the treatment of photoaging, Baumann et al. evaluated the efficacy of alitretinoin for this indication. Aliretinoin 0.1 % topical get was well-tolerated by 20 patients and both benign and precancerous skin lesions showed improvement.

Alitretinoin 0.1 % gel has shown significant anti-tumor activity in cutaneous AIDS-related Kaposi sarcoma (KS) lesions and decrease in disease progression. Patients with AIDS-related KS received multiple daily dose applications of alitretinoin 0.1 % gel for ≤60 weeks and had no extensive systemic exposure. Initially, alitretinoin should be applied topically twice daily to lesional areas. If irritation occurs, the frequency can be decreased. If severe irritation occurs, the medication should be discontinued until symptoms resolve. Complete cure of KS with alitretinoin has not been observed. Also, this drug is very expensive.

Motretinide (Tasmaderm®)

Motretinide is the ethylamide of tretinoin and is reported to be effective in the local treatment of papulopustular acne. In a study of 15 patients treated with topical 0.1 % motretinide vanishing cream daily for 8 weeks, only 1 patient experienced severe cutaneous adverse effects, which included a "severe flare-up reaction with crust formation" in the first week of treatment. The reaction disappeared with discontinuation of the treatment. However, in all other patients treated, motretinide was well-tolerated and had positive treatment effects.

Monitoring and Recommendations During Systemic Retinoid Therapy

In contrast to topical retinoids, systemic retinoids should be monitored regularly. Laboratory tests should be performed before and during therapy

(every 2 months), including a CBC, liver function tests, lipid panel (cholesterol and triglycerides), and pregnancy test. If elevations in liver enzymes or lipids occur, or if there are CBC abnormalities, the retinoid dose should be decreased by half. Four-month clinic visits must include a complete examination. Radiographic studies of the skeletal system and an ocular examination should be performed annually. Muscle studies and EMG should be done in the case of muscular pain and weakness. Alcohol, smoking, and other drugs with a propensity to cause liver damage (methotrexate) or hyperlipidemia should be actively avoided at all times during treatment.

Monitoring of retinoid blood concentrations can be important, especially in determining those patients who are non-responders. High-pressure liquid chromatography (HPLC) is the detection method of choice.

Treatment of Retinoid-Induced Cutaneous Drug Reactions

Veraldi et al. reported the successful, tolerated use of 0.2 % Myrtacine and 4 % vitamin PP in the treatment of retinoid dermatitis in patients with mild-to-moderate acne, and significantly improved acne severity and overall clinical outcome. Retinoid dermatitis can induce post-inflammatory hyperpigmentation, and attempts should be made to reduce its occurrence by modifying treatment plans in patients with pigmented skin. Topical treatments including Vaseline, emollients, and sun-blocking agents are very useful agents for symptomatic relief. Specifically, accumulation of excess granulation tissue seen with etretinate therapy can be managed with topical trichloroacetic acid or silver nitrate with surgical removal. The use of keratolytics and other drying agents that impair barrier function and enhance evaporation from the skin should be avoided, and moisturizers with ultraviolet light protection should be applied religiously. Hot showers should be avoided or minimized. Frequent eye drops and use of eyeglasses rather than contact lenses can help with xerophthalmia. Decreased night vision can occur and patients should be cautious when driving in dark conditions.

Main Points

- Retinoids are biological-response modifiers that are regulators of differentiation, proliferation, apoptosis, and immune response.
- Topical application of retinoids avoids systemic toxicity and has led to extensive use for acne, actinic keratoses, and photodamage.
- The most common acute cutaneous side effects include excessive dryness of the skin with associated pruritis, erythema, skin fragility and desquamation, particularly affecting the palms and soles. Dryness of the lips potentially with desquamation and fissuring and mucous membranes is also prominent. All of these should respond positively to topical lubricants and/or dose adjustments.
- While most side effects of topical retinoids are not life-threatening, they pose discomfort to the patients, can affect quality of life, and adherence to the treatment.
- Retinoids have shown value in the prevention and treatment of pre-malignant and malignant skin conditions.

Conclusions

The first major contribution of the retinoids to medical care was in skin disease, first for cystic acne and then for the keratinzing disorders. This has now expanded to myeloproliferative diseases both in the skin and elsewhere. The side effects of these medications is toxic in nature, so lowering the dose whenever possible will contribute to the lessening of the many muccocutaneous side effects. These medications are often indicated for long periods of time, so controlling these drug-related problems has become an important consideration when caring for this group of patients.

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Part VI

Cutaneous Reactions with Specific Pathology

Neutrophilic Dermatoses

35

Cassondra M. Andreychik and Dirk M. Elston

Abstract

Neutrophilic dermatoses are a group of skin conditions that involve dermal inflammation by neutrophils without an identified infectious agent. The neutrophilic dermatoses featured in this chapter are Sweet's syndrome, bowel-associated dermatosis/arthritis syndrome, pyoderma gangrenosum, juvenile idiopathic arthritis/Still's disease, erythema marginatum, neutrophilic eccrine hidradinitis, and rheumatoid neutrophilic dermatosis. Many of these conditions have systemic associations as well as drug-induced forms. Sweet's syndrome is the prototypical neutrophilic dermatosis and is most widely associated with a recent upper respiratory tract infection, although an almost identical eruption is associated with the use of granulocyte-colony stimulating factor. Bowel-associated dermatosis-arthritis syndrome is associated with bowel bypass surgery and inflammatory bowel disease. Pyoderma gangrenosum is associated with inflammatory bowel disease, but has also been observed after treatment with propylthiouracil and granulocyte-colony stimulating factor. Still's disease involves fevers, arthritis and arthralgia, and a transient evanescent rash. Erythema elevatum diutinum is a chronic fibrosing form of cutaneous leukocytoclastic vasculitis. Cases of generalized pustular psoriasis have been observed after treatment with salicylates, iodides, and biologic tumor necrosis factor inhibitors. Neutrophrophilic-associated syndromes

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_35

in patients with rheumatoid arthritis have been associated with use of certain medications, particularly in the case of palisaded neutrophilic granulomatous dermatitis.

Keywords
Neutrophilic dermatoses • Sweet's syndrome • Pyoderma gangrenosum • Still's disease • Neutrophilic eccrine hidradenitis • Rheumatoid neutrophilic dermatosis • Drug-induced neutrophilic dermatoses

Introduction

The neutrophilic dermatoses are characterized by dermal inflammation consisting primarily of neutrophils without an identifiable infectious cause and usually without the presence of leukocytoclastic vasculitis. These conditions include Sweet's syndrome, bowel-associated dermatosis/arthritis syndrome, pyoderma gangrenosum, juvenile idiopathic arthritis/Still's disease, erythema marginatum, neutrophilic eccrine hidradinitis, and rheumatoid neutrophilic dermatosis (Table 35.1). Erythema elevatum diutinum will also be discussed in this chapter. It differs from the other conditions in that it represents a chronic fibrosing form of leukocytoclastic vasculitis. Generalized pustular psoriasis is discussed as its manifestations are mediated by neutrophils.

Sweet's Syndrome

Sweet's syndrome (acute febrile neutrophilic dermatosis) is the prototype of the neutrophilic dermatoses. There are three clinical subtypes of Sweet's syndrome based upon pathophysiology: classical (or idiopathic), malignancy-associated, and drug-induced. Classical Sweet's syndrome comprises the majority of cases. Malignancy-associated Sweet's syndrome most commonly occurs in association with hematologic malignancies (85 % of cases), predominantly acute myelogenous leukemia. Solid tumor associations, while less common, include carcinomas of the gastrointestinal tract, breast, and genito-urinary organs.

Clinically, Sweet's syndrome presents abruptly with pyrexia, neutrophilia, and tender, erythematous papules that may progress into plaques or nodules (Fig. 35.1a–c). Cutaneous symptoms of the disease may be preceded by a period of several days or weeks of febrile illness, and fever may persist throughout the episode of dermatosis. Fever may also be absent in some cases. The cutaneous lesions may acquire a pseudovesicular appearance due to marked edema in the upper dermis. Dusky (Fig. 35.2) and bullous variants are more commonly associated with malignancy and may present similarly to features of pyoderma gangrenosum. Sweet's syndrome lesions are often distributed asymmetrically and may be observed anywhere on the body, however, there is an increased observation of lesions on the head, neck, and upper extremities. Lesions typically resolve without scarring. Episodes of classic disease are commonly preceded by an upper respiratory or gastrointestinal infection, or vaccination. Extracutaneous manifestations include arthritis, arthralgias, conjunctivitis, episcleritis, and neutrophilic alveolitis. Granulocyte colony stimulating factor can produce similar cutaneous lesions (Fig. 35.3). Neutrophilic dermatosis of the dorsum of the hand is a variant of Sweet's syndrome that exhibits a spectrum of manifestations from Sweet's syndrome-like lesions to lesions more closely resembling pyoderma gangrenosum (Fig. 35.4). Histologically, it demonstrates a diffuse dermal neutrophilic infiltrate with karyorrhexis, variable ulceration, and subepidermal edema (Figs. 35.5 and 35.6).

Table 35.1 Summary of drug-induced neutrophilic dermatoses

Condition	Appearance	Location	Histopathology	Associations
Sweet's syndrome	Papules, plaques, nodules	Head, neck, upper extremity	Massive papillary dermal edema, nodular and diffuse neutrophilic infiltration with karyorrhexis	Fever, leukocytosis, arthralgias
Pyoderma gangrenosum	Pustule/vesiculopustule, ulcer	Lower extremity (pretibial); also breast, hand, trunk, head, neck, peristomal	Suppurative folliculitis, dense neutrophilic infiltrate; 50 % show leukocytoclastic vasculitis	50 % have underlying systemic disorder (Crohn's, ulcerative colitis)
Erythema elevatum diutinum	Red-purple papules, plaques, nodules	Extensor surfaces of extremities	Leukocytoclastic vasculitis, polymorphonuclear neutrophils, onion-skin fibrosis	Associated with infection, neoplasia, and medications
Neutrophilic eccrine hidradenitis	Erythematous edematous plaques	Can be localized or widespread	Infiltration of neutrophils within eccrine ducts, secretory coils + edema	Fever, neutropenia; malignancy, chemotherapy association
Generalized pustular psoriasis	Sheets of coalescing pustules on erythematous base	Flexural, crural, acral surfaces	Spongiform pustules	Fever, chills, malaise, arthralgias
Palisaded neutrophilic granulomatous dermatitis	Pink to violaceous papules, plaques, nodules	Extensor surfaces of extremities (elbows, fingers)	Small vessel leukocytoclastic vasculitis, neutrophilic infiltrate	Arthritis

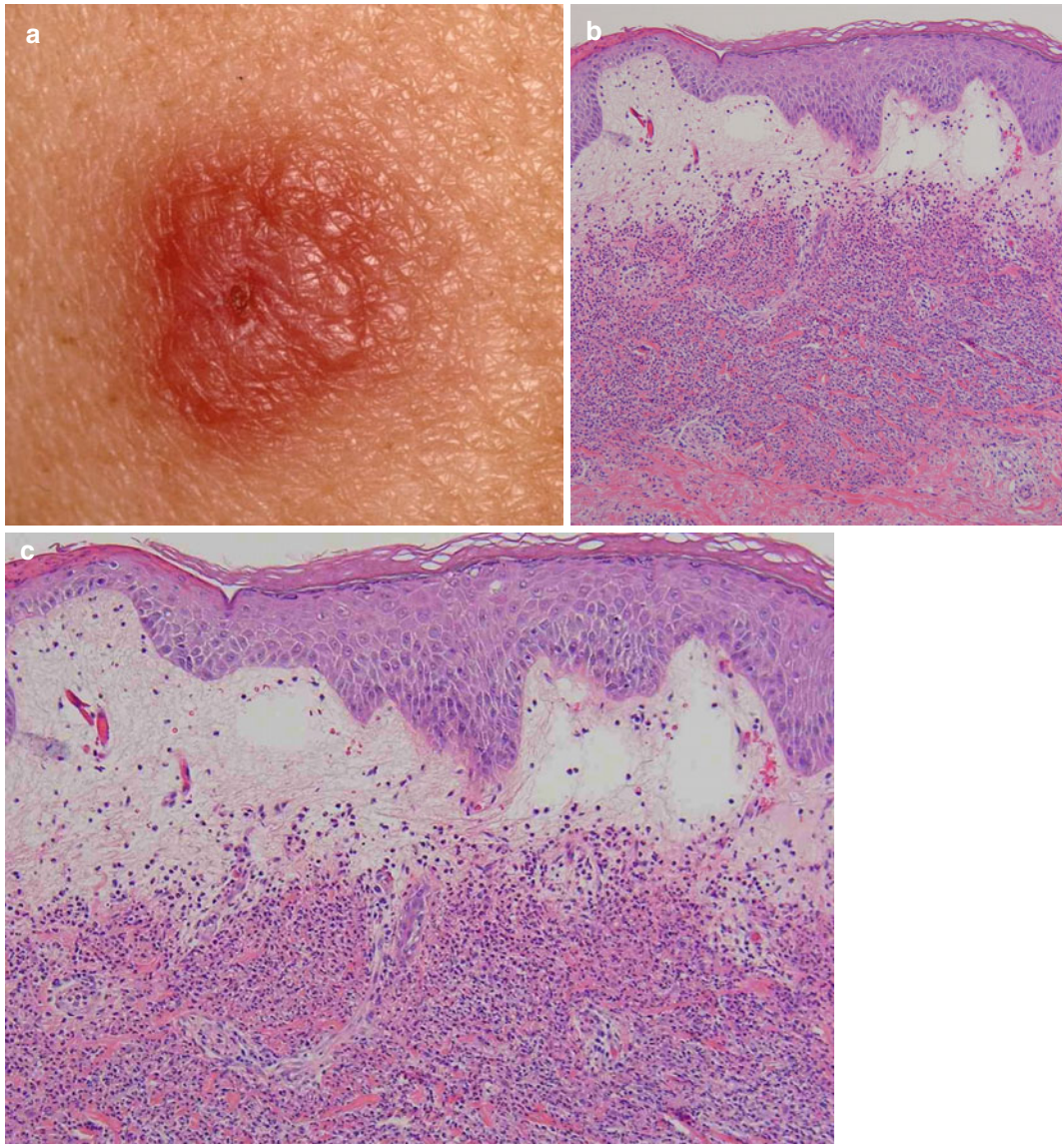

Fig. 35.1 (**a**–**c**) Sweet's syndrome: (**a**) erythematous, edematous, tender plaque; (**b**) note massive papillary dermal edema; (**c**) diffuse neutrophilic infiltrate with karyorrhexis

The pathogenesis of Sweet's syndrome has not been fully elucidated. Granulocyte colony-stimulating factor may be involved, and involvement of interleukins (IL)-1, -3, -6, and -8 has also been postulated. Histopathologic changes include massive edema of the dermal papillae and dermal infiltration of mature neutrophils with karyorrhexis. Leukocytoclastic vasculitis may be present focally. Eosinophils, lymphocytes, and histiocytes may be present within the inflammatory infiltrate.

Many drugs have been implicated as causes of Sweet's syndrome (Table 35.2). Early reports of drug-induced Sweet's syndrome involved trimethoprim-sulfamethoxazole, however, the most widely implicated medication reported in association with this condition is granulocyte-colony stimulating factor (G-CSF). The syndrome typically develops approximately 2 weeks after exposure of the offending drug. The syndrome is also known to recur with re-administration of the agent, which

can be a useful diagnostic characteristic. Further, discontinuation of the causative agent causes improvement of disease manifestations. Other medications that have been reported to induce Sweet's syndrome include tretinoin, specific vaccines (e.g. pneumococcal), lithium, furosemide, hydralazine, oral contraceptives, minocycline, azathioprine, imatinib, and bortezomib.

The differential diagnosis for Sweet's syndrome includes infection, reactive erythemas, and vasculitides. Infections to be excluded include bacterial pyoderma, deep fungal infection, atypical mycobacterial infection, and leishmaniasis. In patients with leukemia, it is important to distinguish paraneoplastic Sweet's syndrome from leukemia cutis. This may be difficult in some patients, as Sweet's syndrome may recruit neoplastic as well as benign granulocytes. The evaluation of patients with Sweet's syndrome involves a thorough history and physical examination to rule out underlying diseases. Appropriate laboratory studies include a complete blood count with differential, comprehensive metabolic panel, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, urine analysis, and serum immunofixation electrophoresis. A skin biopsy should be performed for histopathologic analysis. If infection is suspected, tissue cultures may be necessary.

First-line therapy for Sweet's syndrome is systemic corticosteroids at a dose of 0.5–1 mg/kg/day with a taper over 2–6 weeks. Some patients may require treatment for 2–3 months with tapering doses, but when prolonged courses are needed alternative therapy should be considered. Systemic potassium iodine and colchicine are also considered first-line agents and may be more suitable for patients with chronic disease.

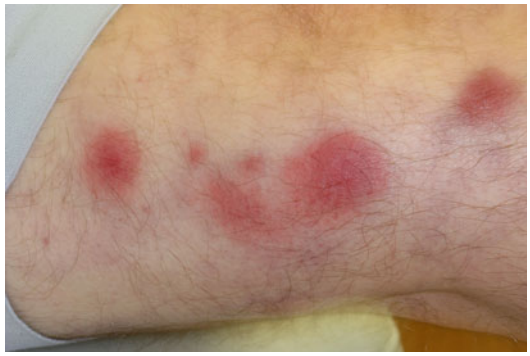

Fig. 35.2 Dusky lesions of Sweet's syndrome in a patient with leukemia

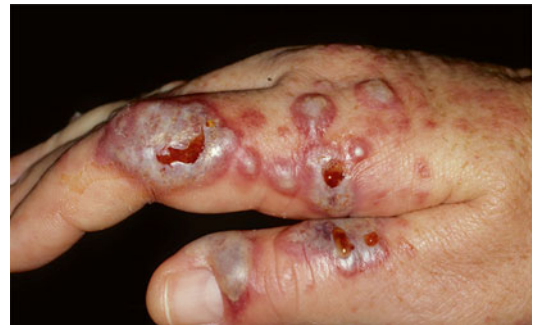

Fig. 35.4 Neutrophilic dermatosis of the dorsal hands

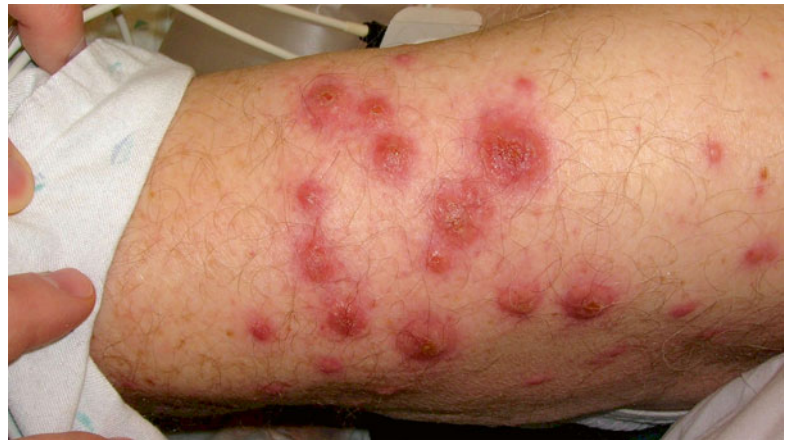

Fig. 35.3 Sweet's-like reaction associated with GCSF therapy

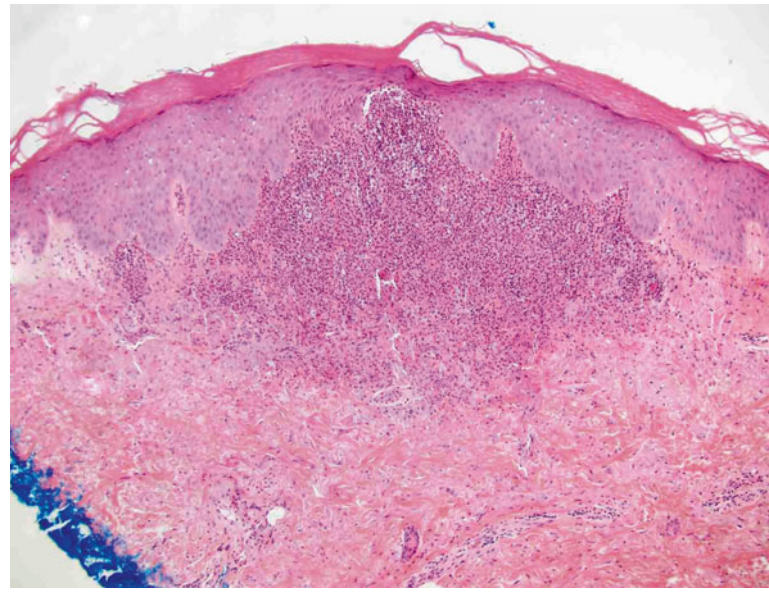

Fig. 35.5 Neutrophilic dermatosis of the dorsal hands: Papillary dermal edema and neutrophilic infiltrate

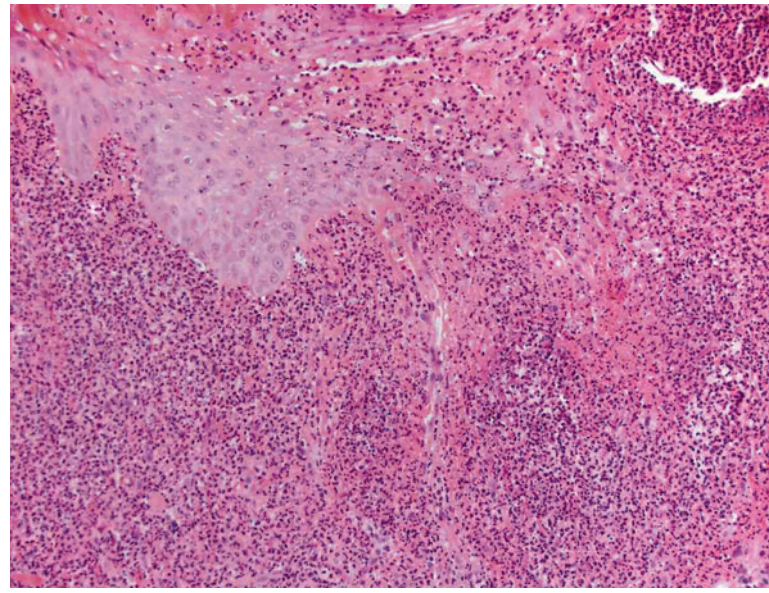

Fig. 35.6 Neutrophilic dermatosis of the dorsal hands: Ulceration, pseudoepitheliomatous hyperplasia of the epidermis and neutrophilic infiltrate

Approximately one-third of patients experience recurrence and require the addition of a steroid-sparing agent. These second-line agents include dapsone, tumor necrosis factor (TNF)-alpha antagonists, indomethacin, and cyclosporine. In regard to drug-induced Sweet's syndrome, discontinuation of the offending medication results in spontaneous improvement and resolution of the syndrome.

Bowel-Associated Dermatosis-Arthritis Syndrome

Bowel-associated dermatosis-arthritis syndrome is a neutrophilic dermatosis that closely resembles Sweet's syndrome clinically and histologically. It presents with fever, flu-like symptoms, and inflammatory cutaneous eruptions. The condition is associated with bowel bypass surgery

and inflammatory bowel disease. It is thought to be caused by an immune response to bacterial antigens in the blind loop of bowel with subsequent immune complex formation. Clinically, this syndrome presents with sterile erythematous macules which may evolve into papular, vesicular, and pustular lesions. Lesions are frequently observed on the upper extremities and chest. Histopathological evaluation exhibits infiltration of mature neutrophils in the dermis with karyorrhexis and prominent papillary dermal edema, just as in Sweet's syndrome. Acute treatment involves corticosteroids, however antibiotic therapy and elimination of the blind loop of bowel may be necessary.

Table 35.2 Drugs causing Sweet's syndrome

Antibiotics	Minocycline[a] Nitrofurantoin Fluoroquinolones Trimethoprim-sulfamethoxazole
Antiepileptics	Carbemazepine Diazepam
Antineoplastics	Bortezomib Imatinib mesylate Lenalidomide
Colony stimulating factors	Granulocyte-colony stimulating factor (G-CSF) Granulocyte-macrophage-colony stimulating factor (GM-CSF)
Contraceptives	Levonorgestrel/ethinyl estradiol (Triphasil) Levonorgestrel-releasing intrauterine system (Mirena)
Nonsteroidal antiinflammatory agents	Celecoxib Diclofenac
Retinoids	All-trans retinoic acid 13-cis-retinoic acid
Vaccines	H1N1 Influenza Pneumoccocal
Others	Abacavir Azacitidine Azathioprine Clozapine Furosemide[a] Hydralazine[a] Lithium Propylthiouracil

[a]Do not fully meet criteria for drug-induced Sweet's syndrome, but reports have attributed these drugs to the condition

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a cutaneous disease that presents initially as a pustule or vesiculopustule and progresses to an ulcer with an undermined border (Fig. 35.7). Ulcers are recurrent, painful, and commonly demonstrate a cribriform pattern of pitted necrosis. There are four major clinical subtypes of pyoderma gangrenosum: ulcerative, pustular, bullous, and vegetative (Table 35.3). Peak incidence occurs between 20 and 50 years, with women more frequently affected than men. It most often occurs on the lower legs, with predominance on the pretibial area. It is also observed on the breast, hand, trunk, head, neck, and peristomal areas. Notably, PG exhibits pathergy, occurring in sites of trauma such as needle sticks. Another manifestation of pathergy is that debridement typically exacerbates the condition. As many as 50 % of affected patients have an underlying systemic disorder such as ulcerative colitis (10–15 % of cases), Crohn's disease, hepatitis C, seronegative rheumatoid arthritis, spondylitis, and various lymphoproliferative disorders. Of importance, PG can also be attributed to drug therapies, with reported causative agents such as propylthiouracil, pegfilgastrim (G-CSF), gefinib (an epidermal growth factor receptor inhibitor), sunitinib, adalimumab, infliximab, and isotretinoin.

The pathogenesis is not fully understood, but it is hypothesized that aberrant integrin oscillations and increased expression of interleukin-23

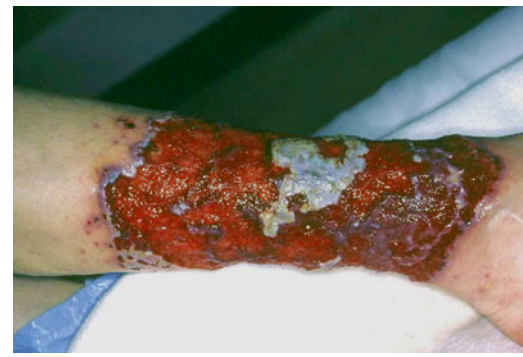

Fig. 35.7 Pyoderma gangrenosum: cribriform pitting and necrotic undermined border

Table 35.3 Subtypes of pyoderma gangrenosum

Variant	Clinical findings	Area of involvement	Association
Ulcerative (classic) PG	Painful papule, pustule, or vesicle that expands peripherally, degenerates centrally leading to ulcer formation	Lower extremities and trunk	–
Bullous (atypical) PG	Rapid development of blue-gray, inflammatory bullae	Arms and face	Hematologic disease
Pustular PG	Rapid development of painful pustules surrounded by erythema	Extremities	Inflammatory bowel disease
Vegetative PG	Solitary, superficial indolent nodule, plaque, or ulcer	Head and neck	–

may be involved. Patients respond to anti-tumor necrosis alpha therapy with infliximab, suggesting that this cytokine plays an important role. Protein deposition on skin vessels in PG lesions suggests the involvement of a type III hypersensitivity reaction. Also, it is hypothesized that the pathogenesis of PG may involve a cross-reaction between antigens in the bowel and the skin, due to the strong association with inflammatory bowel disease.

Eruptions of pyoderma gangrenosum have been reported in association with therapy of various drugs. Specifically, ANCA-positive propylthiouracil (PTU)-induced PG has been reported involving symptoms of fever, fatigue, arthralgia, and skin ulceration. This often affects women taking the medication to treat Grave's disease and appears 2–3 years after initiation of PTU therapy. Of note, ANCAs have been shown to play a role in the activation of neutrophils. Pathogenesis of PTU-induced PG is postulated to involve the selective accumulation of PTU in neutrophils and binding to myeloperoxidase, ultimately leading to stimulation and degranulation of other neutrophils. Interestingly, some targeted biological therapies used to treat inflammatory conditions have been shown to result in complex pathways that may cause a response that is paradoxical to the treatment goal. For example, drugs such as infliximab and TNF-alpha inhibitors have been reported as a cause of PG, while both can also be quite effective as treatments of this condition.

The differential diagnosis for pyoderma gangrenosum involves six disease categories: vascular occlusive or venous diseases, vasculitides, neoplastic diseases, infections (such as ecthyma and deep mycoses), exogenous tissue injury, and drug reactions. Evaluation relies on clinical manifestation with support from histopathological analysis. There are no specific diagnostic laboratory tests for PG, therefore blood work is typically done to rule out other causes. Colonoscopy may be necessary to evaluate underlying inflammatory bowel disease. Histopathology is variable throughout the course of the lesion. Initially, a deep suppurative folliculitis with a dense neutrophilic infiltrate is observed. Multiple foci of folliculitis correspond to the pitted necrosis seen in evolving lesions. The histological features of fully developed ulcers include epidermal and dermal necrosis, neutrophils, and karyorrhexis. Forty percent of cases show a leukocytoclastic vasculitis.

In addition to medical therapy, management involves gentle wound care to create an ideal environment for healing. Moist dressings that will not adhere to the wound base, such as Vaseline-impregnated gauze, can help protect from trauma. Due to the observed pathergy phenomenon in PG, wound debridement should be avoided to prevent disease progression. For limited disease, local treatment may be efficacious and enable avoidance of systemic medications. This therapy includes high-potency topical or intralesional corticosteroids and calcineurin

inhibitors (i.e., tacrolimus), focusing on the inflamed periphery. Intralesional therapy should proceed cautiously, due to risk of pathergy. Extensive disease requires systemic therapy. Systemic corticosteroids are first-line agents. If more prolonged treatment is needed or the patient fails to respond to initial therapy, cyclosporine may be given. Other treatment options include infliximab as well as other TNF-alpha inhibitors, mycophenolate mofetil, methotrexate, azathioprine, dapsone, and minocycline. With treatment, 50 % of patients report complete wound healing within 1 year. Drug-induced PG therapy involves discontinuation of the offending agent and systemic corticosteroid therapy. In paradoxical PG caused by infliximab or TNF-alpha inhibitors, it may be effective to switch from one TNF-alpha inhibitor to another.

Juvenile Idiopathic Arthritis (Still's Disease)

Still's disease is an inflammatory condition featuring high spiking fevers, arthritis and arthralgia, lymphadenopathy, and a transient evanescent rash. Fevers are typically greater than 39 °C that spike daily, with highest temperatures observed late afternoon to early evening. Joint pains occur in 64–100 % of patients with this condition. Cutaneous eruptions occur in about 80 % of patients, characterized by salmon-pink or erythematous macules and papules that often arise during febrile episodes. The distribution of the eruption commonly involves the proximal limbs and trunk. The rash is transient and evolving and may change depending on the course of the illness.

The cause and pathogenesis of this condition is not fully described, but involves interactions between genetic predisposition, immune pathways, and environmental pathogens. Genetic predisposition involves major histocompatibility complex loci, particularly human leukocyte antigens (HLA) of DR and DP alleles. Environmental exposures include infection (rubella virus, Epstein-Barr virus, influenza A, chlamydia, parvovirus B19, and mycoplasma pneumonia), breastfeeding, sun/vitamin D exposure, and maternal smoking.

Diagnosis involves laboratory tests reflecting systemic inflammation; however, these findings are not specific for Still's disease. Increased white blood cell count (20,000–30,000/mm^3) and sedimentation rate are typically observed with negative rheumatoid factor and anti-nuclear antibodies. Histopathologic analysis shows a normal epidermis overlying a perivascular inflammation involving the superficial dermis. The infiltrating inflammatory mediators observed are lymphocytes and neutrophils. For patients who exhibit urticarial lesions, histology shows a marked perivascular neutrophilic infiltrate as well as interstitial involvement.

Effective treatment typically involves nonsteroidal anti-inflammatory drugs (NSAIDs). However, glucocorticoids or methotrexate may be used instead of NSAIDs for refractory disease. Also, biologic agents have shown good results in trials for these situations. Optimally, if NSAIDs are ineffective, glucocorticoid therapy should be initiated with prompt addition of a disease-modifying agent to prevent the need for long-term glucocorticoid use.

Erythema Marginatum

Erythema marginatum is primarily a cutaneous manifestation of acute rheumatic fever. It presents as a macular, blanching, serpiginous, and erythematous rash with a sharply demarcated and irregular border. Lesions are typically observed on the trunk and extremities and may vary in size. Histologically, they demonstrate perivascular neutrophils, typically without karyorrhexis.

Erythema Elevatum Diutinum

Erythema elevatum diutinum (EED) is a rare condition that represents a chronic form of cutaneous leukocytoclastic vasculitis that produces characteristic onion-skin fibrosis. Clinically, it presents with persistent red-purple papules, plaques, and nodules distributed symmetrically

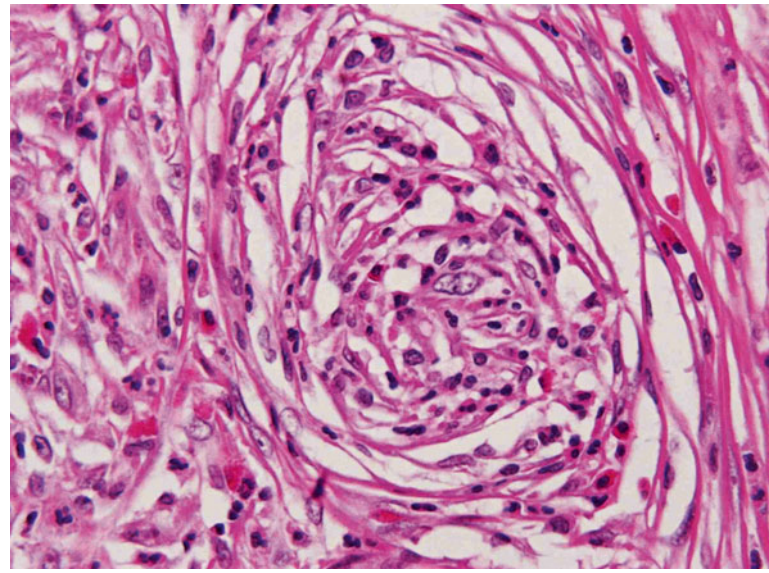

Fig. 35.8 Erythema elevatum diutinum: Onion-skin fibrosis with neutrophils and karyorrhexis

over the extensors of extremities, with predominance over joints, the dorsum of hands and feet, knees, elbows, buttocks, and Achilles tendon. Lesions are typically asymptomatic, with occasional pain. Histopathologically, EED presents as a leukocytoclastic vasculitis with polymorphonuclear neutrophils, extravasated red blood cells, and concentric perivascular eosinophilic fibrosis (Fig. 35.8). Direct immunofluorescence shows deposits of IgG and C3 in vessels located in the upper dermis. Chronic lesions may produce plywood patterns of lamellar fibrosis and well as prominent deposition of cholesterol crystals derived from the membranes of extravasated erythrocytes.

The pathogenesis of EED is postulated to involve an Arthus-like type-III hypersensitivity reaction. It has been associated with isolated paraproteinemia, and several autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, and celiac disease. EED has also been associated with infections (hepatitis, HIV, streptococcus, syphilis) and malignancies such as multiple myeloma, B-cell lymphoma, myelodysplasia, and breast carcinoma.

The differential diagnosis for EDD includes granuloma annulare, Sweet's syndrome, sarcoidosis, pseudolymphoma, Kaposi's sarcoma, and bacterial or fungal infections.

Dapsone remains a valuable treatment for EED. However, recurrence is common upon discontinuation. Alternative treatments include sulfapyridine and colchicine. Systemic corticosteroids are typically ineffective; however, high-potency topical or intralesional corticosteroids have been proven effective in limited disease.

Neutrophilic Eccrine Hidradinitis

Neutrophilic eccrine hidradenitis (NEH) is a benign, self-limited disorder found to be associated with malignancy, certain medications, and infections (Table 35.4). Specifically, NEH is associated with malignancies such as myelogenous leukemia, Hodgkin's lymphoma, and solid tumors including osteogenic sarcoma, testicular carcinoma, metastatic breast cancer, and Wilms tumor. NEH lesions have been reported in association with these malignancies in the absence of chemotherapy; however, certain chemotherapy agents have been associated with the development of these cutaneous findings. Most frequently, NEH has been described in patients receiving cytarabine-containing induction therapy for acute myelogenous leukemia (AML). Specific infectious pathogens associated with NEH include *Serratia marcescens*, *Enterobacter*

cloacae, *Staphylococcus aureus*, and human immunodeficiency virus (HIV).

Clinically, NEH presents as erythematous edematous plaques that can cause pain or pruritus. Lesions are most frequently located on the extremities, trunk, face, palms, and around the eyes. The distribution of skin involvement can either be localized or widespread, with variable morphology. Concomitant systemic manifestations include pyrexia and neutropenia.

Etiology of NEH involves toxic injury to sweat glands, causing inflammatory neutrophilic infiltration. Due to the association of NEH with AML, two pathogenic theories have been proposed. One theory involves primary neutrophilic inflammation directly associated with leukemia, while the other involves the concentration of toxic metabolites of chemotherapy that causes necrosis of eccrine epithelium and subsequent neutrophilic inflammation.

Specific drug associations with this condition include chemotherapeutic agents (cytarabine, doxorubicin, mitoxantrone, cyclophosphamide, bleomycin); acetaminophen; zidovudine; stavudine; granulocyte-colony stimulation factor; and minocycline. Cytarabine is the most widely reported drug causing NEH. In patients receiving chemotherapy, the cutaneous eruption typically begins 8–15 days after the initiation of therapy and lasts for 6–33 days.

NEH must be distinguished from pseumomonas hot foot (wet sneaker) syndrome, disseminated infection, drug hypersensitivity syndrome, leukemia cutis, Sweet's syndrome, pyoderma gangrenosum, vasculitis, erythema multiforme, and bullous pyoderma. Histopathological evaluation reveals infiltration of neutrophils in eccrine ducts and secretory coils in addition to edema. Abscess formation and necrosis of secretory cells may occur. Occasionally, syringosquamous metaplasia of the damaged eccrine ductal epithelium is observed.

Episodes of neutrophilic eccrine hidradenitis typically resolve spontaneously without treatment. If lesions are widespread or painful, treatment involves NSAIDs, systemic corticosteroids, or dapsone. Chemotherapy-induced NEH resolves with discontinuation of the inciting agent. Dapsone may prevent relapse upon exposure to the same chemotherapeutic agent, which has been observed at a rate of 60 %.

Table 35.4 Causes of neutrophilic eccrine hidradenitis (NEH)

Chemotherapeutic agents	Bleomycin Chlorambucil Cychlophosphamide Cytarabine Doxorubicin Mitoxantrone
Other drugs	Zidovudine Granulocyte colony-stimulating factor Minocycline
Malignancy	Acute myelogenous leukemia Hodgkin's lymphoma Solid tumors
Infection	Serratia marcescens Enterobacter cloacae Staphylococcus aureus Human immunodeficiency virus (HIV)

Generalized Pustular Psoriasis

Generalized pustular psoriasis (GPP) is an acute, sterile, pustular dermatosis (Fig. 35.9). It presents with systemic symptoms such as fever, chills, malaise, myalgias, and arthralgias. There are several possible evoking factors for this condition including pregnancy, infections,

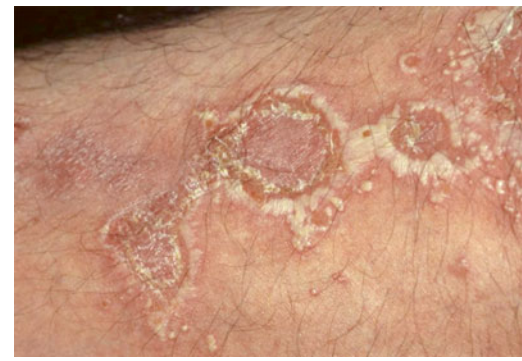

Fig. 35.9 Pustular psoriasis: Annular and serpiginous arrays of spongiform pustules

hypocalcemia, certain medications, emotional stress, and withdrawal of systemic corticosteroids. There is also a genetic component to the etiology of this condition involving mutations in the IL36RN gene. Clinically, patients present with sheets of discrete pustules that may coalesce forming broad areas of pus on an erythematous base. Commonly affected areas include flexural, crural, and acral surfaces of the body. This condition occurs in both patients with a medical history of psoriasis and those without. Patients with a psoriatic history commonly present following corticosteroid withdrawal. In patients with no history of psoriasis, infections are a common precipitating factor. Histologically, GPP exhibits subcorneal spongiform pustules.

Medications associated with pustular psoriasis include salicylates, iodides, gold therapy, lithium, hydroxychloroquine, biologic tumor necrosis factor inhibitors, and reduction or withdrawal of systemic or local corticosteroid therapy.

The differential diagnosis for GPP includes acute generalized eruptive pustulosis (AGEP), which can also be medication-induced; bullous impetigo; superficial candidiasis; acrodermatitis enteropathica (zinc deficiency); pemphigus; varicella; and drug eruption. Systemic therapy may include acitretin, methotrexate, mycophenolate mofetil, cyclosporine, and tumor necrosis factor alpha inhibitors, which can both treat and trigger pustular eruptions in psoriatic patients.

Neutrophilic-Associated Syndromes in Patients with Rheumatoid Arthritis

There are two types of neutrophilic dermatoses that may develop in patients with rheumatoid arthritis: rheumatoid neutrophilic dermatitis (RND) and palisaded neutrophilic granulomatous dermatitis (PNGD). RND presents with nontender erythematous papules, plaques, or nodules most commonly observed on the lower legs. Urticarial or vesicular appearance may be noted on rare occasions. Histopathology shows a neutrophilic infiltrate diffused through the dermis, and vasculitis is typically not observed. RND involves continuous activation of neutrophils along with the overproduction of immune complexes, causing a neutrophilic cutaneous eruption. PNGD has been reported in connection with arthritis and several drug therapies, including methotrexate, leflunomide, calcium channel blockers, beta-blockers, azathioprine, angiotensin-converting enzyme inhibitors, lipid-lowering medications, anticonvulsants, antidepressants, and antihistamines. There are also recent reports of cases of PNGD in association with TNF-alpha inhibitor therapy. Clinically, PNGD presents as pink to violaceous papules, plaques, or nodules that may appear urticarial or annular in conformation with a distribution involving the extensor surfaces of the extremities in favor of the elbows and fingers. Histopathological analysis shows palisading granulomas with central neutrophilic debris.

Other Neutrophilic Dermatoses without Known Drug Associations

Behçet's disease is a neutrophilic dermatosis characterized predominantly by recurrent oral aphthous ulcers with systemic manifestations including, genital ulcers, uveitis, and cutaneous manifestations. Systemic involvement of the central nervous system and gastrointestinal tract has also been observed. Lesions are round, with an erythematous border and a white-to-yellow fibrinous pseudomembrane. As in pyoderma gangrenosum, Behçet's disease exhibits the pathergy phenomenon, which can be a useful diagnostic feature. Individual lesions typically heal without scarring, although this is variable. Localized disease may respond to topical or intralesional corticosteroids. Widespread involvement of the disease requires systemic corticosteroids or immunosuppressants.

Conclusions

Neutrophilic dermatoses are defined by the dense infiltrate of neutrophilic white blood cells seen in the skin. Drug reactions can be a significant contributor to these illnesses, and identifying the offending agent(s) is an important step toward resolution.

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Granulomatous Drug Reactions

36

Kathleen A. Long

Abstract

One approach to classification of drug-induced cutaneous manifestations involves the histopathology identified in a biopsy of affected skin. Certain pharmaceutical agents may induce a variety of clinical lesions with the common histologic feature of granuloma formation, showing collections of inflammatory cells with predominant histiocytes. Drug-associated granulomatous dermatitis is a relatively infrequently described occurrence. Two distinct conditions with granulomatous inflammation on biopsy are methotrexate-induced accelerated nodulosis (MIAN) and interstitial granulomatous drug reaction (IGDR). MIAN is most often characterized by the rapid development of cutaneous rheumatoid nodules in rheumatoid arthritis patients treated with methotrexate. IGDR generally appears as plaques, with affinity for the skin folds, after the administration of a wide assortment of different pharmaceutical agents.

Keywords

Accelerated nodulosis • Methotrexate • Granuloma • Rheumatoid arthritis • Annular rash

Introduction

One approach to classification of drug-induced cutaneous manifestations involves the histopathology identified in a biopsy of affected skin. Certain pharmaceutical agents may induce a variety of clinical lesions with the common histologic feature of granuloma formation, showing collections of inflammatory cells with

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_36

predominant histiocytes. Drug-associated granulomatous dermatitis is a relatively infrequently described occurrence. Two distinct conditions with granulomatous inflammation on biopsy are methotrexate-induced accelerated nodulosis (MIAN) and interstitial granulomatous drug reaction (IGDR). MIAN is most often characterized by the rapid development of cutaneous rheumatoid nodules in rheumatoid arthritis patients treated with methotrexate. IGDR generally appears as plaques with affinity for the skin folds after the administration of a wide assortment of different pharmaceutical agents.

Methotrexate Nodulosis

Methotrexate is a folic acid antagonist with many indications, including treatment of rheumatoid arthritis, psoriasis, dermatomyositis, and solid and hematologic cancers. The drug is not without a multitude of possible side effects, with the ability to affect the gastrointestinal, bone marrow, lung, hematologic, immunologic, renal, respiratory, and central nervous systems. One less common side effect observed in patients treated with low-dose methotrexate for certain dermatologic and collagen vascular diseases is the development of cutaneous nodules.

Clinical Presentation

Most commonly, methotrexate-induced accelerated nodulosis (MIAN) presents in patients with rheumatoid arthritis as the accelerated development of rheumatoid nodules. The nodules are clinically identical to traditional rheumatoid nodules other than their acute and abrupt onset. They appear as flesh-colored or erythematous nodules, which may be painful or painless, and are often of smaller size than the classical version (Fig. 36.1). Nodules may develop while other symptoms of the patient's rheumatoid arthritis are in remission, which may also help differentiate from classic nodules that often manifest during severe active disease.

Common sites of involvement include fingers, elbows, hands, ears, chest, trunk, knees, and feet. Internal organs may also be affected, including the larynx, lungs, heart, and Achilles tendon. Nodules on the fingers may be seen in a disproportionally large percentage of patients with methotrexate nodulosis compared to those with simple rheumatoid nodules, and can help suggest one diagnosis over the other. Internal methotrexate nodulosis without visible external manifestations presents a potential diagnostic problem for physicians, although fortunately this entity is rare.

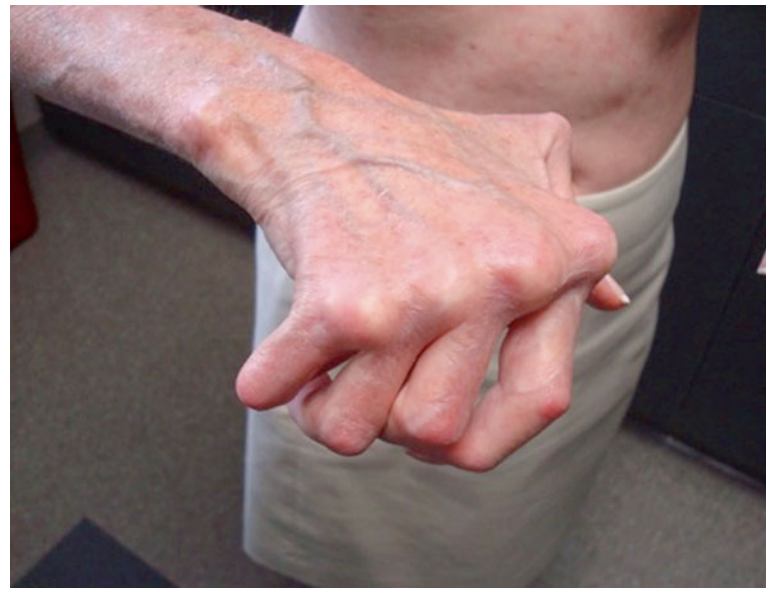

Fig. 36.1 Methotrexate nodulosis in a patient with severe long-standing rheumatoid arthritis on methotrexate for years. The nodules are seen over the proximal interphalangeal joints. They are smaller than the usual rheumatoid nodules. Unlike rheumatoid nodules, they were abrupt in onset and seen when the rheumatoid arthritis was in relative remission

Epidemiology

The majority of patients who develop methotrexate nodulosis are over age 50, although much younger individuals may be affected as well. Predilection for sex is unclear. Nodules have developed in patients on a wide range of doses of methotrexate, as well as after various durations of therapy; thus, it is difficult to determine whether a dose-dependent phenomenon or a minimum cumulative dose exists.

The frequency of rheumatoid arthritis-associated methotrexate nodulosis has been estimated at 2–11 % in rheumatoid arthritis patients treated with methotrexate. In comparison, about 20 % of all patients with rheumatoid arthritis develop rheumatoid nodules, and they tend to be associated with increased disease severity. Approximately 90 % of rheumatoid arthritis patients with rheumatoid nodules are seropositive for rheumatoid factor; most patients (78 % in one study) with methotrexate-induced accelerated nodulosis have also been found to be seropositive.

Controversy exists regarding the incidence of methotrexate nodulosis with simultaneous vasculitis. Some theories suggest that the two occur more frequently in combination, while other studies have found a low proportion of patients who developed methotrexate nodulosis with concomitant vasculitis.

Histopathology

The nodules appear histologically like those of classical rheumatoid nodules or vasculitis. They contain multinodular foci of necrobiosis and collagen degeneration, neutrophils, and fibrin deposits with surrounding palisading histiocytes. Scarring in adjacent soft tissue or subcutaneous fat is present. In the reticular dermis, histiocytes often form rosettes around collagen bundles. Multinucleated giant cells may be noted.

Accelerated Nodulosis with Diseases Other than Rheumatoid Arthritis

Although much less common, accelerated development of nodules may also develop after administering methotrexate to treat diseases other than rheumatoid arthritis. For this reason, some authors prefer the term "methotrexate nodulosis" over "methotrexate-induced accelerated nodulosis." For example, the nodules have appeared in patients treated with methotrexate for dermatomyositis, psoriatic arthritis, juvenile idiopathic arthritis, and mixed connective tissue disease. In these diseases, histopathology of the nodules may differ from traditional rheumatoid nodules, including variations such as septal panniculitis. However, the onset of lesions after initiation of methotrexate and resolution with its cessation are still characteristic.

Mechanism

The exact mechanism of the expedited development of rheumatoid nodules has not yet been elicited. However, the stimulation of adenosine receptors by methotrexate may play a role. Methotrexate is an agonist at the A1 and A2 adenosine receptors. In vitro binding to the A2 receptor produces anti-inflammatory effects. Activation of the A1 receptors, however, results in formation of giant cells and spindle-shaped arrangements of monocytes, congruent with those seen in nodules.

Genetics may play a factor in the accelerated development of rheumatoid nodules. The DRB1*0401 allele has been recognized as an HLA-class II gene linked with formation of nodules in Caucasian patients. Furthermore, methionine synthase reductase gene polymorphism has been discovered to be increased in rheumatoid arthritis patients compared to the population overall. The polymorphism was also associated with methotrexate nodulosis.

Causative Agents

While classically occurring after methotrexate administration, accelerated rheumatoid nodule development has also been observed in patients treated with etanercept, infliximab, and azathioprine. Etanercept and infliximab are both tumor necrosis factor inhibitors, while azathioprine

blocks purine synthesis using a different mechanism. Some have suggested that "therapy-induced accelerated rheumatoid nodulosis" may be a more accurate term in describing the condition, as these newer agents exhibit a similar phenomenon to methotrexate.

Management and Prognosis

In some instances, patients have continued taking methotrexate and experienced regression of nodules after the addition of drugs such as hydroxychloroquine, colchicine, sulfasalazine, azathioprine, cyclosporine, or D-penicillamine. Consensus has not been established regarding whether methotrexate should be discontinued with the development of accelerated nodulosis. Some recommend stopping the drug and others recommend adding hydroxychloroquine or another agent. Reducing the dose or discontinuing methotrexate, or adding hydroxychloroquine, generally results in the clearing of nodules in 1 week to 2 years. If methotrexate therapy is initiated again, the nodules tend to reappear.

Of note, hydroxychloroquine may decrease the likelihood of accelerated nodulosis in patients with the DRB1*0401 allele. Observing the patient while continuing methotrexate is an option if the lesions are mild and tolerable, as is the case in the majority of patients. Some patients may even experience disappearance of nodules while continuing methotrexate therapy at the same or lower doses.

Methotrexate-Induced Papular Eruption

Another reaction to distinguish from methotrexate nodulosis is methotrexate-induced papular eruption, which has been observed in patients with acute flares of collagen vascular diseases who received low-dose methotrexate. These lesions appear as clusters of erythematous papules to patches, similar in appearance to insect bites. Distribution most commonly involves proximal extremities and buttocks. Histologically, biopsy shows histiocytes and collagen bundles in the dermis, with smaller rosettes of thick collagen bundles and surrounding histiocytes in the deeper reticular dermis. Onset is after initiation of methotrexate therapy (usually within 12–24 h), and resolution generally occurs quickly after tapering methotrexate and increasing doses of corticosteroids.

Interstitial Granulomatous Drug Reaction

Initially described by Magro et al. in 1998, interstitial granulomatous drug reaction (IGDR) encompasses a typical clinical presentation associated with distinctive histopathology noted in patients taking a variety of classes of drugs. The lesions of IGDR characteristically appear after the drug is initiated and resolve upon its discontinuation.

Clinical Presentation

Clinically, the lesions of interstitial granulomatous drug reaction (IGDR) most often present as annular plaques with indurated borders, erythematous to violaceous in color, and generally nonpruritic and asymptomatic. They are often more evident after the patient takes a hot shower. Distribution most commonly involves the inner arms, medial thighs, and intertriginous zones. Rarely, patients with histolopathological findings of IGDR may exhibit generalized erythematous macules or papules, DRESS, erythroderma, or erythema nodosum-like lesions.

Histopathology

Histologically, biopsy of the lesions reveals diffuse granuloma formation; atypical lymphocyte infiltrate may or may not be present. Lymphocytes and histiocytes infiltrate into the interstitium. Degeneration of collagen and elastic fibers ("piecemeal fragmentation") is present, which may appear similar to early granuloma annulare

lesions. Vacuolar interface dermatitis is evident in nearly all cases. Most cases of interstitial granulomatous drug reaction will demonstrate tissue eosinophilia. There are usually minimal to no mucin deposits, and necrobiosis and vasculitis are absent. Neutrophils are also characteristically absent, a feature that histologically distinguishes interstitial granulomatous drug reaction from other etiologies of interstitial granulomatous dermatitis.

Causative Agents

Interstitial granulomatous drug reaction has been attributed to multiple classes of drugs, and the list continues to expand as more patients are identified to have IGDR after treatment with different agents. Angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, beta-blockers, and lipid-lowering drugs are among the most common. Often, patients may be taking agents from more than one of these classes before developing the reaction.

Drugs that may induce IGDR:

- ACE inhibitors
- Allopurinol
- Anticonvulsants
- Antidepressants
- Antihistamines
- Anti-tumor necrosis factor α (TNF-α) agents (infliximab, etanercept, adalimumab, lenalidomide)
- Antivirals (ganciclovir, entecavir)
- Benzodiazepines
- Beta-blockers
- Bowel stimulants
- Calcium channel blockers
- Chinese herbal medication
- Diuretics
- Febuxostat
- Interleukin-1 antagonists
- Lipid-lowering drugs
- Oral hypoglycemics
- Strontium
- Thalidomide
- Trastuzumab

Differential Diagnosis

The lesions of IGDR may be mistaken for cutaneous T-cell lymphoma, especially if the plaques are pruritic. The differential diagnosis also includes erythema annulare centrifugum, granuloma annulare, erythema multiforme, subacute lupus erythematosus, pigmentary purpura, granulomatous slack skin, and other dermatologic conditions that present with similar lesions.

The duration of time between initiation of the drug and appearance of lesions ranges from a few weeks to over 20 years. Thus, clinicians may not initially consider a drug reaction high on their differential, especially if the patient has already been on the agent for an extended time.

Clinically and histopathologically, granuloma annulare is the main differential diagnosis for IGDR. Granuloma annulare is a self-limited condition of annular plaques on the dorsal extremities, often seen in younger people. It is generally not related to use of specific drugs.

Interstitial granulomatous drug reaction should be distinguished from interstitial granulomatous dermatitis (IGD) associated with systemic conditions including rheumatoid arthritis, vasculitis, lupus erythematosus, and lymphoproliferative diseases. The presence of neutrophils on histology can help distinguish IGD from IGDR, as well as clinical context and history of medication administration.

Management and Prognosis

Treatment is discontinuation of the offending drug. Upon cessation, lesions resolve or significantly improve in the vast majority of patients. Resolution may take from 1 week to several months, with an average of 8 weeks. This duration is longer than the time to improvement seen with most drug reactions. If lesions persist, consideration should be given to conditions such as T-cell dyscrasia, granulomatous slack skin, or other disorders on the differential.

Conclusions

Granulomatous disease in the United States is seen most commonly due to sarcoidosis, granuloma annulare, and as a secondary reaction in many other conditions. Leprosy and tuberculosis would surely be added to this list worldwide. Drug reactions are very rarely granulomatous, but we have delineated those conditions in this chapter and they should be considered whenever more common causes of granulomas seem unlikely.

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Part VII

Drug Reactions in Specific Populations

Cutaneous Drug Reactions in Patients Infected with Human Immunodeficiency Virus

37

James F. Stanford

Abstract

Cutaneous adverse drug reactions (cADRs) are commonly seen in HIV-infected patients and must be carefully and expertly managed for the best possible outcomes to be realized. Although skin disorders have decreased in the highly active antiretroviral therapy (HAART) era, and newer pharmacogenetic tests have lessened the impact of at least one serious cutaneous adverse reaction (SCAR)—the abacavir hypersensitivity reaction—cADRs remain very important and challenging. Most cADRs are delayed hypersensitivity (Type IV) reactions. Lipoatrophy, lipohypertrophy, and retinoic acid metabolism-related dermal effects seen with some HIV-1 protease inhibitors are often stigmatizing and may lead to antiretroviral nonadherence or discontinuation. Stevens-Johnson syndrome/toxic epidermal necrolysis remain rare but have been described with most antiretroviral agents and especially with neviripine and trimethoprim-sulfamethoxazole (TMP-SMX). The ability to differentiate between the more common mild to moderate benign cADRs for which the implicated medication may often be safely continued or reintroduced from SCARs including drug-induced hypersensitivity syndromes (DIHS) such as those seen with TMP-SMX, abacavir, and non-nucleoside reverse transcriptase inhibitors, is critical as these cause significant morbidity and can worsen or be fatal on rechallenge.

Keywords

Adverse drug reaction • Dose escalation • Exanthematous eruption • Graded challenge • Hypersensitivity reaction • Lipodystrophy • Morbilliform rash • Pharmacogenomic • Stevens-Johnson syndrome • Tolerance induction • Toxic epidermal necrolysis

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_37

HIV and the Skin: A Historical Perspective

Skin problems are extremely common in HIV, especially as cell-mediated immunity declines. HIV-infected patients experience a higher frequency of common cutaneous diseases (seborrheic dermatitis, psoriasis, atopic dermatitis), drug rashes, and hypersensitivity reactions than are seen in those without HIV infection. Skin problems and reactions were especially evident in the pre-HAART era (prior to 1997/1998) but have continued to be prominent and important in the HAART era.

Highly active antiretroviral therapy (HAART), which debuted in the mid-1990s in clinical trials and was widely applied in the resource-plenty (developed) world in the later 1990s, led to rapidly declining mortality and a great reduction in the incidence and prevalence of opportunistic infections (OIs). While skin manifestations associated with immunosuppression and immune dysregulation/chronic inflammation and the skin manifestations of OIs became less frequent, skin problems have continued to be quite prominent. In some cases, for example with the non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine, higher CD4 T cell counts are, in fact, a risk factor for cutaneous drug reactions. This is partly because many of the key mechanisms underlying cutaneous drug eruptions in HIV are less related to immunosuppression than to immune dysregulation, which persists during HAART, and chronic inflammation, which is down regulated by HAART but not eliminated. Rash associated with acute retroviral syndrome (primary HIV infection) (Fig. 37.1) remains common.

Despite the current (2015) availability of 26 antiretroviral drugs (with an additional 10 fixed-dose combination [FDC] ARV pills), and currently preferred/recommended HAART consisting of low complexity (most taken once daily) and low daily pill burden (1–3 pills per day) regimens comprised from less toxic, more tolerable medications than were available in the past, managing HIV infection/AIDS remains extremely challenging.

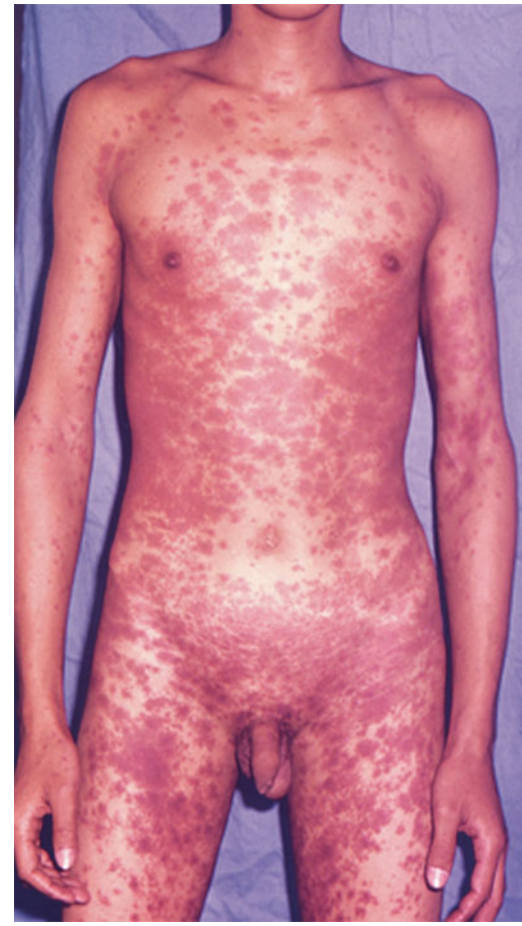

Fig 37.1 Acute retroviral syndrome includes a diffuse maculopapular eruption in 70–80 % patients (Image content provider: CDC Public Health Image Library, donated by Brian Hill, New Zealand.)

Only 25–28 % of HIV-infected patient in the United States are consistently meeting the treatment goal of fully suppressing HIV replication which allows for immune system recovery (or stability if treatment is begun prior to clinically significant immune system depression) and a near normal life expectancy. Reasons for this are multifaceted, but include: an estimated 18 % of patients who are HIV-infected are yet to be diagnosed and are unaware of their condition. Of those who are diagnosed, a significant number fail to engage in care and/or remain engaged in care due to denial, depression, shame, stigma, problems with access to care, and issues compet-

ing for the individual's attention (especially mental illness and substance abuse). Not all who are engaged in care are prescribed and/or start a HAART regimen, and of those prescribed ARVs, not all are able to adequately tolerate and/or adhere well enough to their HAART regimen to achieve full viral suppression and continued regimen viability.

Maintaining perfect or near-perfect adherence day-in-day-out, year after year is clearly a major challenge for many of our patients, as it is for all patients. The factors that influence medication-taking behavior and the ways we can effectively encourage and foster the near-perfect adherence level necessary for success are beginning to be better understood.

For those who are able to successfully engage in care and navigate the above-mentioned barriers to receiving and being fully adherent to a potentially suppressive ARV regimen, three of the largest remaining roadblocks to successful long-term viral suppression include:

1. Adverse drug reactions (ADRs) which are primarily immune-related (Fig. 37.2) and involve the skin (exclusively cutaneous or cutaneous combined with systemic symptoms and multi-organ system manifestations (Figs. 37.3 and 37.4).

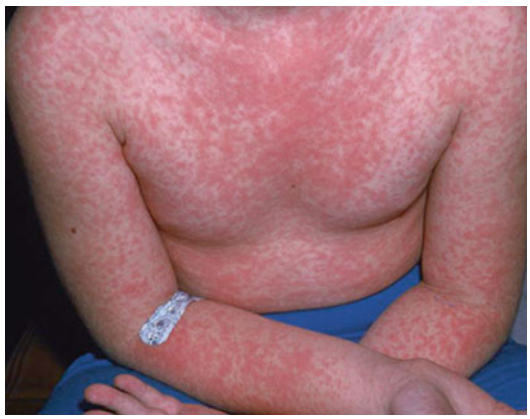

Fig 37.2 Typical morbilliform (maculopapular or exanthematous) rash seen with TMP/SMX, NNRTIs, and other medications utilized in the treatment of HIV-1-infected patients (Photo courtesy of HIV Web Study at the University of Washington)

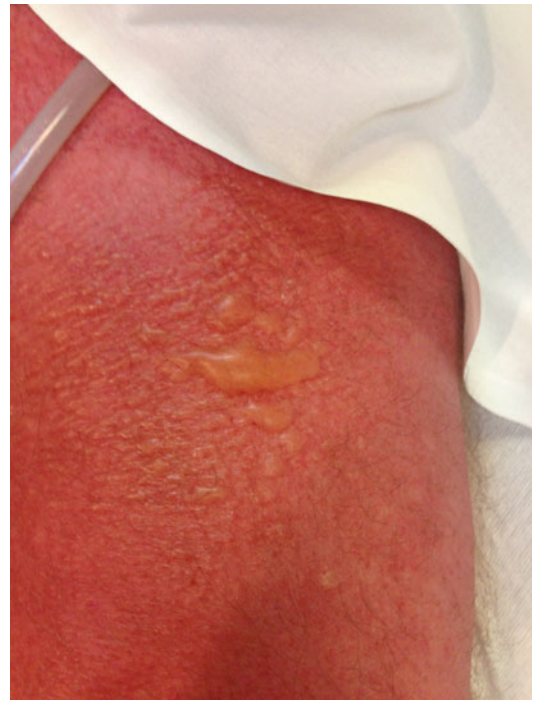

Fig. 37.3 Morbilliform eruption evolving to a diffuse erythroderma with edematous, infiltrated, blistering lesions in a patient with DiHS/DRESS

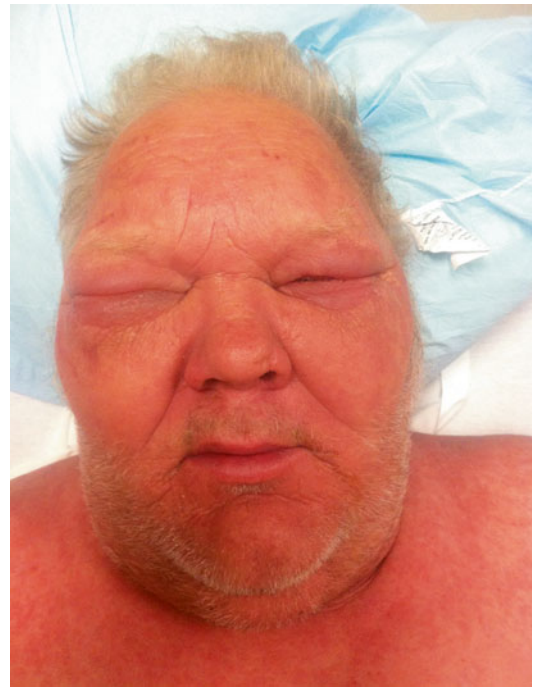

Fig. 37.4 Facial edema including periorbital swelling in a patient with DiHS/DRESS

2. Lipodystrophy and other appearance-related AEs/side effects which many patients worry will "out" them (i.e., bring *out* the fact that they are living with HIV/AIDS). These appearance-related AEs or fear of them developing may therefore lead to non-engagement in care in the first place and/or depression, despondency, HAART discontinuation, non-adherence with HAART, and/or the patient "falling out of care".
3. Immune response inflammatory syndrome (IRIS), a paradoxical worsening in the patient's condition during suppressive HAART where the awakening, increasingly competent cell-mediated (T-cell) immune system recognizes and appropriately and vigorously responds to the antigenic stimuli present on cells from previously disseminated (and occasionally localized) foreign microbial (mostly opportunistic) pathogens.

These will be all discussed in greater detail in this chapter.

Epidemiology/Risk Factors

HIV predisposes patients to drug hypersensitivity reactions, with an estimated 100-fold increase in the risk of drug rashes compared with the general population.

ADRs are the 4th to 6th leading causes of death in the developed world. In a meta-analysis of inpatient ADR prospective studies, 15.1 % of patients sustained ADRs during their hospitalizations, 6.7 % experienced serious ADRs, and 0.32 % fatal ADRs. ADRs result in death in 0.1 % of medical and 0.01 % surgical inpatients, adversely affect surviving patients' quality-of-life (QOL), and cause patients to lose confidence in their providers. They also often mimic other diseases, resulting in unnecessary investigations and delays in treatment.

Cutaneous adverse drug reactions (cADRs) are the most frequent ADRs comprising 10–30 % of all ADRs. cADRs account for 1 % of outpatient antibiotic prescription and 1–3 % of inpatient admissions. These range from mildly discomforting to life-threatening. Prior to the recognition of HIV infection and AIDS in the early 1980s and continuing into the HIV era cADRs were/are most commonly associated with anti-infective and anticonvulsant drugs, especially the aromatic anticonvulsants (phenytoin, phenobarbital, carbemazepam) but in the AIDS era have been joined by several ARV agents (Tables 37.1 and 37.2).

Adverse drug reactions can be classified by mechanism of the reactions (or by their clinical manifestations (Tables 37.3 and 37.4).

The most common cADRs are mild to moderate maculopapular (morbilliform) eruptions without systemic/other organ system involvement. These can frequently be managed without drug discontinuation or with later drug reintroduction (graded challenge/test dosing/direct rechallenge) while tolerance induction procedures such as dose escalation and true desensitization are sometimes indicated and performed. Patients with more severe, potentially life-threatening, systemic drug hypersensitivity reactions (with multi-system/multi-organ involvement) as in DIHS/DRESS and those with SJS/TEN should never undergo graded challenge or direct rechallenge and rarely, if ever, should tolerance induction procedures be attempted.

Risk factors for cADRs include being on multiple medications (polypharmacy), HIV infection, other viral infections (Epstein Barr virus [EBV]/cytomegalovirus [CMV] mono, human herpesvirus 6 [HHV-6], parvovirus B19, viral hepatitis viruses [in some but not all studies]), female sex, and age (especially age <3 years), immune status, and the presence of various genetic polymorphisms.

Pathogenesis, Pharmacogenetics/Genomics and Resulting Heterogeneity in Cutaneous Drug Eruptions

Most cADRs occurring in those living with HIV are Type B (idiosyncratic) reactions and of these, the vast majority are immunologically mediated Type IV (delayed, T-cell-mediated) hypersensitivity (allergic) reactions, although basically all categories of the immunologic reactions within the Gell and Coombs classification have been described. Clinically, reactions

Table 37.1 Rash and hypersensitivity with HIV drugs I: older drugs

Drug	Rash (%)	Severe rash (%)	Rx D/C (%)	Reports[a] (#[1]/#[2]/#[3])	Reaction
TMP/SMP	–	4	–	125/16/61	Exanthema, SJS, TEN, DiHS
PCP Rx	27–64	10–28	15–25	–	–
PCP Prophy	3–34	–	–	–	–
Sulfadiazine	10–40	0.6	3	6/5/4	Exanthema, SJS, TEN, DiHS,
Dapsone	–	–	–	43/43/10	Exanthema, Sulfone Rxn
PCP Rx	17–53	–	–	–	–
PCP Prophy	5–10	–	–	–	–
Abacavir	5–8	Rare	5	15/44/3	Exanthema, DiHS, anaphylaxis
Zidovudine	17	Rare	–	16/1/5	Exanthema
Delavirdine	14–18	4	4	13/1/3	Exanthema
Nevirapine	9–16	6–8; hepatic rxn -5; SJS/TEN 0.3	7	23/13/29	Exanthema, SJS, TEN, DiHS
Amprenavir	20–27	3	3	6/0/1	Rash, DiHS, TEN
Fosamprenavir	2–16	<1	<1	2/2/1	Rash, DiHS
Lopinavir/ritonavir	<5	NR		5/2/0	Rash
Tripanavir	2–14	rare	0.5	-/-/-	Rash, dyslipidemia

Data compiled from Carr (1995), Phillips (2007), Luther (2007), and Chaponda (2010)
rxn reaction, *NR* not reported
[a]#[1]- published reports of rash +/– exanthems +/– erythroderma +/– FDE +/– photosensitivity +/– urticaria +/– other benign rashes / #[2]- hypersensitivity reactions +/– AGEP / #[3]- SJS +/– TEN +/– anaphylaxis from Litt's D.E.R.M., 2012 @ www.drugeruptiondata.com accessed 6/15/2014

Table 37.2 Rash and hypersensitivity with HIV drugs II: newer preferred drugs

Drug	Rash (%)	Severe rash (%)	Rx D/C (%)	Reports[b] (#[1]/#[2]/#[3])	Reaction
Efavirenz	10	0.1–0.7	2	13/3/1	Exanthema, DIHS, SJS, TEN
Etravirine	12	3 cases	2	7/1/1	Rash, SJS, TEN
Rilpivirine	3–8	<0.1	0.1	0/0/0	–
Tenofovir	1–6	–	–	–	–
Atazanavir	1–6	–	0.4	9/0/3	Rash
Darunavir	7	<1	0.3	4/0/2	Rash, DiHS
Raltegravir	0	–	–	–	–
Elvitegravir	–	–	–	NR	–
Dolutegravir	1	–	<1	NR	–
Enfuvirtide	98[a]	<1	–	–	ISR[a], DIHS
Maraviroc	5/100 pt-years	–	–	–	Exanthem

Data compiled from Carr (1995), Phillips (2007), Luther and Glesby (2007), and Chaponda (2010)
[a]*ISR* injection site reaction, *NR* not reported; see text for other abbreviations
[b]#[1]- published reports of rash +/– exanthems +/– erythroderma +/– FDE +/– photosensitivity +/– urticaria +/– other benign rashes / #[2]- hypersensitivity reactions +/– AGEP / #[3]- SJS +/– TEN +/– anaphylaxis from Litt's D.E.R.M., 2012 @ www.drugeruptiondata.com accessed 6/15/2014

involving T-lymphocytes are characterized by prominent skin findings because the skin is a repository for an enormous number of T-cells.

It is unclear why HIV patients are so prone to adverse drug reactions, but the underlying reasons are likely multifactorial. Mechanisms include altered metabolism affecting the rate of inactivation and behavior of toxic metabolites, enhanced sensitivity of HIV-infected cells to cytotoxicity, immune system dysregulation, and activation including activation of T-cells via increased antigen presentation by major histocompatibility complex molecules or direct activation by parent drugs or metabolites. The "danger signal" hypothesis endorses the idea that HIV infection itself induces cytokine release and inflammatory signals, alerting the immune system to danger and promoting hyperactivity.

Heterogeneity in the reactions seen with individual ARV and OI agents and between agents can be explained by preferential recruitment and activation of various effector cells, distinct and varied T-cell recruitment and cytokine profiles, as well as host genetic predisposition influences.

Further research into the mechanism of hypersensitivity to commonly used medications in HIV infected patients is vital to improving tolerability and adherence to these therapies. Further identification and characterization of specific genetic risk profiles and additional specific risk factors/scores for more common as well as the rare severe cADRs should help to mitigate these burdensome and potentially dangerous reactions.

Table 37.3 Prototypical drug reactions involving the skin/skin structures in patients with HIV infection

Drug manifestation	Drug/drug class
Maculopapular (morbilliform)	Sulfamethoxazole Nevirapine/(NNRTIs) Amprenavir, fosamprenavir
SJS/TEN	Nevirapine Sulfamethoxazole
DIHS/DRESS	Abacavir Nevirapine Sulfamethoxazole Fosamprenavir Darunavir Enfuvirtide
Retinoid effects (ingrown nails/ alopecia/xerosis/ cheilosis)	Indinavir
Injection site reactions	Enfuvirtide

Spectrum of Reactions Seen in Patients with HIV

Adverse cutaneous drug reactions in HIV-infected patients include severe cutaneous adverse drug (SCAR) reactions including DiHS/DRESS, SJS/TEN, angioedema/anaphylaxis, and acute generalized exanthematous pustulosis (AGEP) (Fig. 37.5) which are potentially life-threatening, and bullous fixed drug eruption [bFDE] which is not; non-SCAR reactions including the very common exanthematous

Table 37.4 Severe cutaneous adverse reactions (SCAR) in patients with HIV infection

Type of Rxn	Drug/drug class[a]	Incidence (%)	Mortality (%)
DIHS/DRESS[b]	TMP/SMX Neviripine Efavirenz Enfuvirtide	4 6–8 Rare (1 case)	10
SJS/TEN[b]	Neviripine TMP/SMX Etravirine	0.3	10 (SJS) 30–50 (TEN)
Acute generalized, exanthematous pustulosis (AGEP)	Clindamycin Lopinavir/r	Rare Rare[c]	5

[a]Morbilliform rash and DiHS are both class effects for NNRTIs

[b]*DIHS/DRESS* Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, *SJS/TEN* Stevens-Johnson syndrome/toxic epidermal necrolysis, *PEP* post-exposure prophylaxis, *Lopinavir/r* lopinavir + ritonavir FDC pill

[c]One case reported in an HIV- *negative* patient receiving lopinavir/ritonavir as PEP[b]

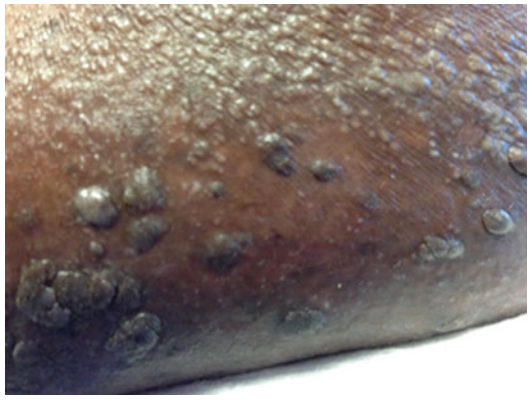

Fig. 37.5 Acute generalized exanthematous pustulosis in a patient treated with clindamycin

(morbilliform, maculopapular) eruptions (which can frequently be managed without drug discontinuation or with later drug reintroduction), other less common reactions and manifestations, and non-immune ADRs such as lipodystrophy (Fig. 37.6). Prototypical drug reactions involving the skin and/or skin structures in patients with HIV infection are discussed further below.

HIV-Related Issues Which Make Diagnosis of Cutaneous Drug Eruptions Particularly Challenging

The diagnosis of cADRs is mostly clinical. The medical history regarding the reaction is extremely important as it helps determine if the patient has had or is having a cADR versus another clinical condition in the differential diagnosis (see Table 37.5), guide choice of diagnostic tests, determine which medicine is the likely culprit drug and determine whether it might be safe to continue or reintroduce the medication. If possible, the original medical record that describes the reaction should be reviewed. Expertise is essential to optimizing the outcomes for our patients with cADRs. Consultation should be sought early and urgently in order to safely and effectively manage both the reaction and the patient's ARV and other HIV-specific needs.

Table 37.5 Differential diagnosis of cutaneous exanthems

Reaction type	Differential diagnosis[a]
Exanthematous (maculopapular, morbilliform)	Viral (EBV, CMV, HIV [ARS rash], HHV6, parvovirus B19, rubella, rubeola, enteroviruses [Echo, Coxsackie], arbovirus, hepatitis viruses), bacterial (secondary syphilis, scarlet fever, typhoid fever, rheumatic fever, rat-bite fever, leptospirosis, erysipeloid, toxic shock syndrome, Lyme disease, ehrlichiosis), RMSF (early), murine (endemic) typhus, scrub typhus, trichinosis, toxoplasmosis, pityriasis rosea, acute graft-vs-host reaction, Kawasaki disease, Adult Onset Still's Disease, SLE
Acute Generalized Exanthematous Pustulosis (AGEP)	Generalized acute pustular psoriasis (von Zumbusch type); SJS/TEN; DRESS; bullous impetigo; subcorneal pustular dermatosis (Sneddon-Wilkinson disease)
DRESS/DiHS	Acute viral infections (incl. HHV6), idiopathic hypereosinophilic syndrome, , angioimmunoblastic T cell lymphoma, Sezary syndrome, acute cutaneous lupus erythematosus, AGEP
SJS/TEN	Exfoliative dermatitis, staphylococcal scalded skin syndrome, AGEP, paraneoplastic pemphigus

[a]Cutaneous manifestations of various immune reconstitution inflammatory syndromes and the acute retroviral syndrome could mimic any of these cutaneous and cutaneous/systemic drug reactions

Components of a drug allergy history are contained within the "RASHES ITCH" mnemonic device:

- **R** xn description
- **A** ction taken
- **S** ystems involved
- **H** x – when given (date of the reaction)
- **E** xposed before or since the reaction (tolerated re-exposure/continuation)
- **S** imilar symtoms while not taking medication?
- **I** ndication – for the medication
- **T** iming – when the reaction occurred relative to the initial dose

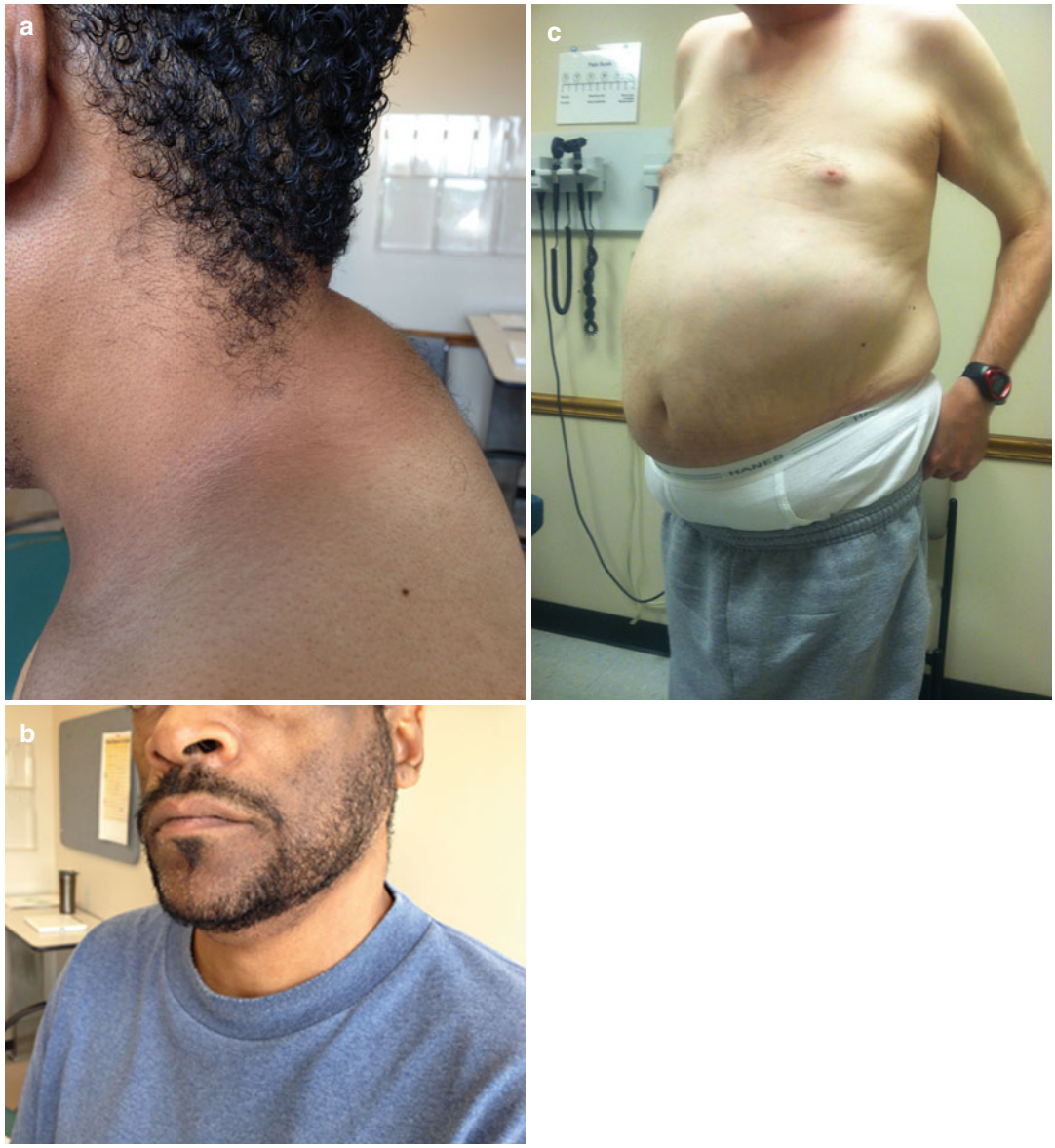

Fig. 37.6 (**a**–**c**)—Lipodystrophy associated with antiretroviral therapy (**a**) dorsocervical lipohypertrophy; (**b**) facial lipoatrophy; (**c**) abdominal lipohypertrophy (HIV-associated adipose Redistribution Syndrome [HAARS] with visceral adiposity confirmed by abdominal computed tomography [CT] scan)

- **C** oncomittant meds
- **H** x – does the patient have predisposing underlying conditions?

Additional history details are described below:

R eaction description: onset, timing, severity, evolution, manifestations; IgE – mediated phenomena, hypotension?

A ctions taken: what treatment was needed? Was the drug continued or discontinued? Was intensive care unit care, vasopressors, or intubation needed? Were other treatment needed?

S ystems involved? Rash only versus rash plus fever versus rash plus systemic manifestations (other organ systems involved—hepatic, renal, pulmonary, cardiovascular, hematologic?)

H istory: How long ago did the reaction occur? What date?

E xposed before or since the reaction? (Was the patient previously on this medication and if so when? Has the medication or a similar medication been given since the reaction and if so how was it tolerated?)

S imilar symptoms occurring when not on the medication? If this is the case perhaps this was not a drug eruption. If the reaction was urticarial does the patient have idiopathic chronic recurrent urticaria or hereditary angioedema, or a polyserositis syndrome (systemic lupus erythematosis, Familial Mediteranean fever)?

I ndication: Why was the patient on the medication ? Is it still needed or are there reasonable alternatives?

T iming – When in relation to the first dose (in hours if possible) did the reaction occur? If patient was rechallenged or had been on the medication previously how soon after re-initiation did the reaction occur?

C oncomitant meds – What other medications was the patient receiving at the time of or within a few days of the reaction?

H x – Does the patient have underlying diseases or conditions (systemic lupus erythematosus, HIV, other) which may predispose them to hypersensitivity reactions?

HIV-Related Issues Which Make Management and Prevention of Cutaneous Drug Eruptions Particularly Challenging

With the need to simultaneously suppress HIV as well as prevent and/or treat opportunistic infections, and the multiple comorbidities often encountered in these patients, it is important to anticipate and manage drug–drug interactions and avoid, if possible, initiating at the same time more than one medication with higher chances of a cutaneous drug eruption. For example, if you anticipate the need for *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia (PCP) and/or toxoplasmosis prophylaxis and a neviripine-containing or an abacavir-containing HAART regimen (in an HLA-B*5701 non-screening setting), consider either avoiding TMP/SMX DS (i.e. use either atovaquone or dapsone for PJP prophylaxis with concomitant pyrimethamine if *Toxoplasma gondii* prophylaxis is also needed [i.e., Toxoplasma IgG antibody positive and CD4 <100]) or staggering these by starting the TMP/SMX DS first and then starting HAART 1–3 months later. Use of both abacavir (in an HLA-B*5701 non-screening setting) and neviripine in the same HAART regimen is not recommended and neither drug is recommended for PEP, sPEP, or PrEP.

The use of fixed-dose combination (FDC) agents, while decreasing pill burden, improving patient quality of life (QOL) and adherence to ARV therapy, can prove to be challenging and problematic in the setting an adverse drug reaction. First the culprit medication is not always clear. HIV suppression requires combination, multi-drug regimens. HIV replication is incredibly dynamic and this, along with differential intracellular half-lives of component drugs, the risk of resistance mutations occurring during "management" of drug reactions is quite real.

Discontinuing a fixed-dose combination ARV drug when the component medications within the FDC-ARV have vastly different half-lives entails a large concern for resistance development to the agent with the longer half-life due to "virtual monotherapy," which occurs as the shorter half-life component drugs dissipate and are cleared. This is made even more difficult when in a severe reaction stopping the culprit medication early on can be critically important. Stopping one drug at a time or alternatively discontinuing all potential medication causes of a hypersensitivity reaction and reintroduction of one agent at a time is often not tenable, due to resistance concerns even when the current or proposed new regimen is comprised of agents which all have similar half-lives.

Drug-Related Lipodystrophy

Both lipodystrophy and immune reconstitution inflammatory syndrome (IRIS) have cutaneous manifestations and affect the patient's appearance, which is often of great concern as these

appearance-related adverse effects (AEs) can be quite stigma-inducing, and therefore hold the potential to lead to drug discontinuation and/or poor adherence both of which causes loss of viral control, potential for HIV drug resistance, and concomitant clinical and immune system deterioration.

Even prior to the HAART era, nucleoside analog-induced lipodystophy (also called HIV-associated adipose redistribution syndrome [HAARS] and HIV-associated metabolic and morphological abnormality syndrome [HAMMAS]) consisting of increasing visceral adiposity with concomitant facial and extremity fat wasting/lipoatrophy with or without trunchal fat accumulation/lipohypertrophy were seen and described.

Lipoatrophy is considered a consequence of mitochondrial toxicity seen especially with earlier nucleoside analogue reverse transcriptase inhibitors, didanosine (ddI), zalcitabine (ddc), and stavudine (D4T), collectively referred to as "D drugs" and somewhat with zidovudine (ZDV, also initially know as "AZT" for azidothymidine).

Lipohypertrophy and cardiometabolic syndrome/insulin resistance subdivisions of lipodystrophy are more associated with protease inhibitor-based HAART. Carr et al. identified lipodystrophy in 83 % of 113 HIV-infected patients treated with protease inhibitors (PIs) compared with 4 % of controls (HIV-infected, not using PIs). The lipodystrophy occurred after a mean of 21 months of therapy and failed to resolve following cessation of treatment.

Treatment strategies for lipodystrophy are limited and until now have had only a modest impact on those already affected. The incidence of HIV lipodystrophy appears to be declining as a result of the use of newer antiretroviral drugs. Recent studies confirm that stavudine and zidovudine are the nucleoside analogues responsible for most lipoatrophy, but also suggest that different protease inhibitors have opposing effects on lipoatrophy. Antiretroviral regimens excluding stavudine and zidovudine offer substantial protection against lipoatrophy. Established lipoatrophy improves gradually with the cessation of these drugs.

Thiazolidinediones, uridine, and pravastatin may also improve lipoatrophy, although their effects have not been shown to be sustained. Metformin and growth hormone and its analogues are effective in reducing abdominal fat accumulation, although they aggravate lipoatrophy and generally have only transient effects. Tesamorelin, a synthetic growth hormone releasing hormone, which is FDA approved for lipodystrophy was shown after 6 months of treatment to decrease substantially both visceral adipose tissue and hepatic lipid measurements. No medical intervention has been shown to have a sustained and substantial benefit on either lipoatrophy or visceral fat accumulation, so results with this agent at longer follow up are eagerly awaited. Cosmetic surgery can modestly improve facial lipoatrophy.

Cutaneous Manifestations of Immune Response Inflammatory Syndrome (IRIS)

IRIS reveals itself in paradoxical deterioration in clinical status/worsening of a preexisting infectious process occurring after initiation of *effective* HAART. It is caused by inflammation (localized or systemic) related to a reconstituting cell-mediated immune response to a preexisting infection which may have been previously diagnosed and treated or may be subclinical and unmasked by the host's regained capacity to mount an inflammatory response.

The immune reconstitution inflammatory syndrome (IRIS) has also been variably referred to as immune recovery disease, immune reconstitution disease, immune reconstitution syndrome, immune restoration disease, immune rebound illness, steroid withdrawal disease, immunorestitution disease, and immune response reaction.

Up to 25 % of patients started on HAART will experience some manifestations of IRIS, most of which include cutaneous findings. Ratnum and colleagues undertook a retrospective study of all patients starting HAART during a 2-year period. Of the 199 patients studied, 50 % were male, 59 % were black African, 29 %

were white, and 10.5 % were black Caribbean. Fourty-four (22.7 %) of these patients experienced an IRIS event at a median of 12 weeks after HAART initiation; 22 events (50 %) involved genital herpes, 10 (23 %) involved genital warts, 4 (9 %) mollusscum contagiosum, and 4 (9 %) involved varicella zoster virus infection. Five patients had mycobacterial infections, four had hepatitis, one had *Pneumocystis jiroveci* infection, and one had Kaposi sarcoma. The strongest independent predictors of IRIS were younger age at HAART initiation (P = .003), baseline CD4 cell percentage of <10 % (OR, 2.97) and CD4+ %/CD8+ % of <0.15 (OR, 3.45 95 % CI, 1.27–9.1).

IRIS is usually self-limited, however it may cause significant morbidity and is rarely fatal. IRIS is important as it may lead to HAART interruption/failure, tests/procedures, and require medical or surgical management. Early examples of immune reconstitution inflammatory syndrome targeting disseminated extrapulmonary tuberculosis with angry, hot, swollen, tender, and pointing anterior cervical lymph nodes with dual NRTI ARV clinical therapy and "hepatic IRIS" versus hepatitis B and C from blinded zidovudine plus neviripine versus zidovudine plus placebo clinical trial protocol-based therapy (leading to a temporary international halting of the trial) were seen in the early 1990s by this author.

IRIS is not unique to AIDS and HAART. It is well described as "paradoxical rxns" during tuberculosis treatment in patients without HIV/AIDS. Localized and disseminated infections with mycobacteria other than TB (MOTT) worsening during steroid withdrawal is another example.

IRIS is characterized by clinical features which are not particularly typical of naturally occurring AIDS-related OIs yet the similarities are close enough to sometimes cause confusion especially if IRIS is not initially suspected or considered. IRIS must be differentiated from drug reaction/toxicity, especially DIHS (Table 37.6)—e.g., neviripine HSR, efavirenz HSR, abacavir HSR in HLA-B*5701 negative patients or non-screening settings—OI progression due to drug resistant pathogen, non-adherence with OI prophylactic treatment with a lack of immune system restoration due to nonadherence with HAART or HIV resistance, and other non-immune/non-inflammatory processes.

Table 37.6 Delayed cutaneous hypersensitivity RXNs: warning signs and management

Red Swollen (edematous or infiltrated) lesions	
Sign	**Action**
Edema of central face	Stop drug and treat as required
Diffuse erythematous swelling	Stop drug and treat as required
Involvement of extended body surface	Stop drug and treat as required
Erythroderma	Stop drug and treat as required
Atypical targets	Stop drug and treat as required
Infiltrated plaques	Stop drug and treat as required
Hemorrhagic "Bloody" Lesions	
Sign	**Action**
Necrotic lesions	Stop and treat as required
Hemorrhagic lesions	Stop and treat as required
Palpable purpura	Stop as early as possible, treat as required
Vesiculobullous lesions	
Sign	**Action**
Painful "Skin" (early initial symptom)	Immediately stop drug and treat
Positive Nikolsky's sign	Immediately stop drug and treat
Epidermolysis	Immediately stop drug and treat
Vesicles, bullae	Stop drug and treat as required
Mucosal erosions	Stop drug and treat as required

Adapted from: Toxicology, Vol. 209/Issue 2. Pichler WJ, Shiohara T, Shear N, Andreas J. Bircher. Symptoms and danger signs in acute drug hypersensitivity. 201–207; 15 April 2005. With permission from Elsevier

It is important to understand that IRIS will resolve in most individuals with continued HAART, continued OI coverage, with or without the institution of anti-inflammatory medications (with fairly rapid resolution). However, IRIS causing significant morbidity including that due to perforation, obstructive phenomena, and mass effect, has been described.

The most common IRIS entities described include: mycobacterium avium complex lymphadenitis, pulmonary infiltrates and nodules, paradoxical exacerbation of pulmonary and central nervous system CNS) *M. tuberculosis* disease (with potential for serious CNS sequelae), IRIS-related dermatomal zoster (varicella zoster infection), *Pneumocystis jiroveci* (formerly *P.carinii*) pneumonia/respiratory failure, paradoxical worsening of viral hepatitis (HBV, HCV), progressive multifocal leukoencephalopathy (PML) worsening (including contrast enhancing PML and fatal PML), paradoxical exacerbation of cryptococcal disease (meningitis; pulmonary disease, necrotizing mediastinal lymphadenopathy), cytomegalovirus (CMV) uveitis, optic nerve neovascularization, cutananeous ulcers, and pneumonitis.

The antigenic target in IRIS, when known, is often but not always a component of an opportunistic microorganism or a more common cutaneous viral condition such as genital herpes and warts (human papilloma virus) and includes abscess formation with or without fluctuance and sinus tract formation, nodules, pustules, vesicles, exanthema, plaques, ulcers, verucous lesions, inflamed tender elevation of tattoos, and alopecia universalis.

Other less common variants include: IRIS-induced pre-eclampsia, IRIS-related sarcoidosis (new-onset or recurrent/relapsing), relapsing Guillian Barre syndrome, Reiter's syndrome, tuberculoid leprosy with "reversal reactions" and autoimmune thyroid disease (AITD).

When IRIS is considered and recognized it is important to continue HAART attempting to "treat through" the IRIS. When recognized one can often defer/avoid diagnostic evaluation procedures and their attendant risks. Exceptions to this strategy include serious, life-threatening manifestions or non-IRIS conditions which are not easily differentiated from IRIS which may be occurring and/or prove difficult to manage and the results of the diagnostic procedure would likely result in a major change in therapy.

Usual IRIS management measures include reassurance, NSAIDs, corticosteroids, and, less commonly, IVIG, thalidomide, and TNF alpha drugs. Surgery is occasionally needed for MAC/Mtb lymphadenopathy that is threatening spontaneous suppuration and drainage/sinus formation, and other situations where there is uncontrolled inflammation in a closed space causing mass effect or other serious sequelae. Continued or renewed treatment directed at the pathogen is indicated when a live antigenic stimulus for IRIS is suspected while specific pathogen directed treatment would not be indicated or helpful (and in fact might be detrimental) when the IRIS is directed against non-viable, dead microbial antigenic products. It is unknown whether treatment which leads to lysis of the organism compared with non-lytic therapies (as in cell wall active bactericidal bacterial meningitis treatment and Jarish-Herxheimer reactions with syphilis treatment) are of importance in OI treatment or prevention in the setting of IRIS.

Another strategy which has been employed successfully in some cases of IRIS is that of staggered therapy, for example 1–4 months of directed or empiric pathogen-specific therapy to decrease "antigen load" of the implicated pathogen, providing the antigenic stimulus against which the IRIS is directed, *then* after this interval treatment period adding HAART with the hope and expectation that the intensity of IRIS signs and symptoms would be less severe and more easily tolerated.

Reactions Seen with Drugs Used to Treat and Prevent Opportunistic Infections

Trimethoprim – Sulfamethoxazole

One drawback in the use of TMP/SMX is the high rate of ADRs (mostly cADRs) in HIV-infected patients. Besides penicillins, sulfonamide antibiotics are the most common cause of drug-induced allergic reactions, most commonly delayed maculopapular/morbilliform eruptions, and are the most common cause of SJS/TEN. The incidence of SCARs is estimated to be between 1:1000 and 1:100,000. IgE-mediated reactions (urticaria/angioedema, anaphylaxis) are infrequent.

Sulfonamide antibiotic ADRs are greatly increased in HIV-infected patients occurring in 40–80 % in HIV patients given TMP/SMX versus 3–5 % of healthy subjects given the drug. In patients receiving high (treatment)-dose TMP-SMX for PCP, the rate of cADRs in HIV-infected patients is reported to be 5.4 times higher than in those immunocompromising conditions other than HIV/AIDS.

In published studies, the rate of AEs requiring discontinuation of TMP-SMX varied from 9.4 to 54 %. Although the rate of drug discontinuation is lower for patients receiving PCP prophylaxis than treatment, patients receiving secondary prophylaxis have developed reactions, despite previously successful acute treatment with TMP-SMX.

Reported adverse event rates after rechallenge for persons with a history of TMP-SMX reactions ranged from 13 to 47 %, which are similar to the rates reported for patients with primary adverse events. Although severe reactions have been described, the type of adverse events are similar, regardless of previous reaction history, and most commonly include skin rash, fever, flu-like symptoms, and gastrointestinal disturbances. Two trials have reported that reactions to high-dose TMP-SMX used for PCP treatment resolved in ~ 80 % of patients, despite continuation of therapy.

Eliaszewicz and colleagues of the Epitox Study group prospectively evaluated risk factors for cutaneous drug reactions to sulfonamides in patients with AIDS using a case-controlled and multivariate analysis in 136 patients (48 [36 %] with and 88 [64 %] without a drug eruption) who were hospitalized for acute pneumocystosis or toxoplasmosis. A high CD8+ cell count and age less than 36 years indicated risk of drug eruption (respective odds ratios: 3.5 [95 % CI 1.6–7.8], P = .002, and 2.1 [95 % CI 1.0–4.6], P = .06) while markers of viral replication for HIV, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, and parvovirus B19, slow acetylation phenotype or genotype, and glutathione level were not associated with risk.

Administration of corticosteroids in the Epitox Study did not appear to have any preventive effect for cADRs. This is in contrast to other studies which have shown benefit to the early concomitant administration of steroids. Several retrospective analyses have shown a potential prevention (of cADR) benefit. Wamsley and the Canadian HIV Trials Network performed a multicenter, prospective, placebo-controlled trail of adjuctive corticosteroids (within the first 24 h after presentation) in P*neumocystis carinii* pneumonia (PCP).

The primary endpoint was a composite of death, need for mechanical ventilation for >6 days, or a partial PO_2 <70 mmHg while breathing room air 10 days after initiation of treatment. The study, in opposition to the prevailing concensus group guidelines, found no beneficial effect on PCP pneumonia/respiratory failure course/death. Superinfections or other opportunistic infections did not differ between the groups however more patients in the placebo group (11/38, 28 %) had to discontinue treatment with TMP/SMX due to developing a hypersensitivity reaction than those randomized to corticosteroids (4/40, 10 %) (P = 0.039).

Some uncommon serious TMP/SMX reactions which have been described in both HIV-infected and HIV negative individuals include IgE-mediated anaphylaxis, sudden severe (non-IgE-mediated) "anaphylactoid" reaction (mimicking hyperdynamic [early] sepsis syndrome/septic shock sometimes mimicking anaphylaxis), Stevens-Johnson Syndrome/toxic epidermal necrolysis, serum sickness, acute delirium, drug-induced aseptic meningitis, severe, protracted hypoglycemia, methemoglobinemia, and rhabdomyolysis.

The pathogenesis of sulfamethoxazole hypersensitivity is not completely understood. The N4 aromatic amine is critical for the development of delayed reactions to sulfonamide antimicrobials. Most drugs, like SMX, are too small to be effective (immunogenic) antigens in their native state. Sulfamethoxazole acts as a *prohapten,* a drug that cannot directly haptenate proteins but which can be metabolized to "reactive metabolites" which can covelently bind to (haptenate) proteins. SMX (in TMP-SMX) is partly acetylated giving rise to harmless compounds and partly oxidized by cytochrome P450 to sulfamethoxazole-hydroxylamine

(SMX-NHOH). SMX-NHOH can be secreted in the urine but is also oxidized to a nitroso compound (SMX-NO), which is highly reactive with proteins.

Reactive metabolites, like SMX-NO, are usually neutralized by glutathione-utilizing elimination pathways, but may escape neutralization and lead to immunogenic hapten-protein complexes which can stimulate both T and B cell responses including direct cellular cytotoxicity. This necrotic cell death may provide a "danger signal" to sensitized T-cells leading to the cascade of immune responses and cytokine release.

Glutathione deficiency, common in HIV infection, can potentially decrease inactivation of toxic metabolites that may lead to a higher risk of hypersensitivity. Wang et al. showed that a polymorphism in the enzyme involved in glutathione biosynthesis (glutamate cysteine ligase catalytic subunit) is significantly associated with SMX-induced hypersensitivity. A randomized controlled trial in the Canadian HIV Trials Network of N-acetylcysteine supplementation in 238 subjects 1 h before each TMP/SMX dose failed however to prevent TMP/SMX hypersensitivity reactions.

Sulfonamides are defined as drugs with an SO_2-NH_2 moiety. Antimicrobial sulfonamides (sulfonylarylamines) also contain an aromatic amine at the N_4 position and a substituted ring at the N_1 position, whereas non-antibiotic sulfonamides (nonsulfonylarylamines) do not. The putative mechanism by which hypersensitivity to sulfonamide antimicrobials (sulfonylarylamines) occurs is by generation of cytotoxic and immunogenic reactive hydroxylamine and nitrosamine metabolites. Oxidative formation of reactive metabolites is cytochrome P450- mediated and occurs at the N4 arylamine group that sulfonylarylamine drugs share whereas the N1 substituted ring appears to be important for IgE-mediated reactions.

The HIV-1 protease inhibitors, amprenavir, its prodrug, fosamprenavir, and darunavir are sulfonylarylamines and therefore, at least in theory, there is a risk of cross-allergenicity/cross-reactivity between these drugs and sulfamethoxazole. Cross-reactivity between drugs which share the sulfonylarylamine structure is largely unknown and would be difficult to measure since reactions to sulfonamide antimicrobials, such as TMP/SMX, may not be reproducible within the same patient across time as shown by Leoung, Carr, Shafer, and others.

Tripanavir, on the other hand, is a sulfonamide derivative without the aromatic amine ring and therefore cross-reactivity would not be expected. The risk of cross-reactivity between sulfonylarylamines and nonsulfonylarylamines appears to be low and more related to factors of host predisposition to drug reactions in general rather than chemical structure.

It is because nonantibiotic sulfonamides (e.g., celecoxib, acetazolamide, furosemide, hydrochlorothiazide, glipizide, sotalol, topiramate) lack these structural components that they would not be expected to cross-react with sulfonamide antibiotics. This was confirmed by a study by Strom et al. which demonstrated no increased reactions to nonantibiotic sulfonamides in patients with a history of allergy to sulfonylarylamines.

Dapsone, Sulfadiazine, Atovaquone

Dapsone is used in both the treatment of mild PCP (with trimethoprim) as well as primary and secondary prophylaxis of PCP in patients not deficient in G6PD and who are intolerant of trimethoprim-sulfamethoxazole. In patients with HIV infection (presumed) cross-allergenicity for patients who have are intolerant or allergic to TMP-SMX is as high as 40 % for dapsone intolerance. Hemolytic anemia, methemoglobinemia, and leukopenia (<1 %) may be seen and peripheral neuropathy is more common with dapsone doses >100 mg per day.

Sulfadiazine is used for toxoplasmosis treatment and secondary prophylaxis/chronic suppression of toxoplasmosis. Over a 3.5 years period at San Franscisco General Hospital sufadiazine was implicated in 3 of 8 (37 %) of SJS/TEN cases (all three would be classified as TEN by current definitions). Other cADRs include: morbilliform, rash, pruritis, urticaria, erythema nodosum, erythema multiforme, and photosensitivity.

A mild to moderate maculopapular, erythrodema, or bullous rash has been described in up to 39 % of patients in clinical trials and treated with atovaquone. Elevated LFTs may be seen in 4–6 % of patients as an isolated issue or in the presence of fever and rash.

Vancomycin

Linear IgA bullous dermatosis (LABD), also known as linear IgA disease, is a rare, idiopathic or drug-induced autoimmune blistering disease characterized by the linear deposition of IgA at the dermoepidermal junction.

Cutaneous ADRs Seen in HIV-Negative Individuals Receiving ARVs in Occupational and Non-occupational PEP and PrEP

Individuals who do not have HIV infections have been exposed to ARVs as volunteers in Phase I clinical trials, as healthy volunteers are often called upon for first in human trials where monotherapy optimal dose finding in regards to pharmacokinetic/pharmacodynamics parameters, drug toleration and an initial determination of side effects/adverse effects (AEs) in a setting where there are obviously no concerns for HIV resistance development. In contrast, HIV-infected study subject testing allows determination of the optimal clinically relevant ARV dose where there is the best pairing of anti-viral efficacy and acceptable AEs.

Besides Phase I clinical trials ARVs are also regularly prescribed for occupational and non-occupational (unprotected sex, needle sharing) post-exposure prophylaxis (PEP, nPEP) and as pre-exposure prophylaxis (PrEP) in some settings including serodiscordant partners and in both the developed and resource-constrained settings where transmission continues despite safer sex counseling and the availability of barrier precautions and/or antiviral microbicides.

There are reasons to expect that patients who do not have HIV infection may have adverse response profiles that differ from patients who are HIV infected. As a viral infection similar to EBV and CMV, HIV is a risk factor for the development of cADRs therefore one might expect cADRs to be worse or more common in HIV-infected patients. As already stated, they are indeed more common. However in some cases it appears that uninfected patients may have more severe or at least as severe cADRs than patients with HIV infection.

Since the huge majority of individuals offered PEP will not become HIV infected even if they did nothing (no PEP), the DHHS and other PEP guideline expert panels have carefully chosen the ARVs recommended for a PEP regimen to counterbalance the high number needed to treat (NNT) to prevent one occupational transmission (the lower the NNT, the better) with medications having an excellent safety profile (with a high number needed to harm, NNH). ARV combinations which have been shown to have a relatively high incidence of cADR and other ADRs in both infected and uninfected populations, such as nevirapine and abacavir are therefore not recommended for PEP or PrEP.

For those sustaining a neddlestick or sharps injury from a known HIV positive "donor source" the risk of HIV transmission varies depending on the mechanism of injury, and the source's known or presumed (from stage of disease, treatment and adherence status) viral load. Most of the time the risk is fairly low, with risk ranging from 1 in 300 from a hollow-bore needlestick to 1 in 1000 or more for mucous membrane exposures—mostly non-bloody saliva—, and needles and sharps going through latex glove in route of the percutaneous injury, to even less risk where the source patient's identity is unknown or where the mechanism of injury make it unclear but possibly a nonexposure.

As most of these scenarios carry a fairly high NNT (~300–1000 or higher to prevent one infection) one desires PEP regimens which are effective but also safe with a high number needed to harm (NNH). PEP would usually be given in an occupational health or infectious diseases clinic or in an emergency department setting while sPEP is more likely to be found in a community-based HIV care clinic specializing in care, prevention services (offering HIV prevention

counseling and the full menu of proven options) and possibly access to clinical trials or an academic hospital-based HIV care clinic setting offering care, prevention services, and an active research and clinical training program.

The only study of occupational PEP, a retrospective case control study by Cardo done in the pre-HAART sequential monotherapy era, revealed a relative risk of 0.19 (81 % reduction) in HIV transmission among those who took post-exposure zidovudine for 28–30 days. PEP currently is provided with three drug HAART regimens with minimal toxicity. Although ADRs and cADRs can never be entirely eliminated, cADRs from currently recommended regimens, an integrase strand transfer inhibitor (ISTI) plus Truvada (emtricitabine plus tenofovir) appears to fit the bill where ADRs are possible but unlikely to occur in most for whom these medications are prescribed.

Differentiating cADR from the Rash of Acute Retroviral Syndrome (ARS)

When a patient taking post-exposure prophylaxis (PEP) or pre-exposure prophylaxis develops a rash with or without other systemic symptoms one must attempt to differentiate between a morbiliform drug eruption or DiHS due to one of the ARV agents comprising the PEP or PrEP regimen and the acute retroviral syndrome (ARS) (which would also signify PEP or PrEP failure), and other disease entities in the differential diagnosis of DiHS/DRESS all of which could also be confused with ARS.

The risk of PEP or sPEP failure increases in rare injuries including large volumes of blood (transfusion of HIV-infected blood which screened seronegative but which was in the ever-shrinking "seronegative window"), injuries from a source patient having an extremely high viral load, or primary acquired but unknown drug-resistant virus or secondary drug resistance, and in cases when there is a delay in PEP institution or poor healthcare worker adherence to PEP (usually due to poor tolerance of common "start up" non-cutaneous ARV ADRs).

The efficacy of a combination prevention portfolio which includes non-occupational PEP (nPEP which includes sPEP) and PrEP is an extremely complex topic and well beyond the scope of this chapter. The risk, however, varies based on a wide variety of factors. As expected, PrEP efficacy depends on the level of adherence to the regimen. Post-sexual exposure PEP (sPEP) and PrEP, on average, are likely less efficacious than PEP and therefore constitutes a setting/patient population where a rash may have a higher chance of being due to ARS than in the PEP setting.

ARV syndrome is a mononucleosis-like, flu-like syndrome which occurs after primary HIV infection in up to 75 % of cases. In a retrospective study involving 563 serum samples from patients with suspected mono-like syndrome who were heterophile Ab negative, 11 (2 %) were positive for HIV-1 RNA (including four with >100,000 copies/mL HIV-1 RNA consistent with ARV syndrome).

The rash, a generalized skin eruption most often involving the upper thorax, neck, and face, typically occurs 48–72 h after the onset of fever and persists for 5–8 days. Scalp and extremities (including palms and soles) may be affected. The skin lesions are characteristically small (5–10 mm), well-circumscribed, oval or round, pink to deeply red colored macules or maculopapules. Vesicular, pustular, and urticarial eruptions have been reported but are less common, and oropharyngeal enanthems and ulcerations are occasionally seen. Pruritis is unusual and only mild when present. Other extracutaneous signs and symptoms include fever, night sweats, fatigue, malaise, generalized lymphadenopathy, sore throat, arthralgias, myalgias, headache, nausea/vomiting, and diarrhea.

Reactions Seen with Specific Older ARV Agents Commonly Used in Resource-Constrained/Limited Countries

Zidovudine

Zidovudine (ZVD) was the first antiretroviral agent available in clinical trials and then FDA-approved in 1987. It is available alone (Retrovir®)

or as part of two fixed-dose combination pills co-formulated with other nucleoside reverse transcriptase inhibitors (NRTIs), zidovudine plus lamivudine (3TC), trade name Combivir®, and ZDV plus 3TC plus abacavir (ABC), trade name Trizavir®. Initial early reactions may have been related to the initial higher doses utilized (1200 mg/day vs 600 mg/day).

Reactions involving skin/skin structures/appearance include lipodystrophy, nail (Fig. 37.7) and cutaneous hyperpigmentation, and Type B cADRs, including generalized exanthems (maculopapular/morbilliform eruptions), urticaria/"anaphylaxis," TEN, and leukocytoclastic vasculitis manifesting as palpable purpura. SCARs occurred in <1 % of patients while cADRs requiring drug discontinuation occurred but was not common.

Other reactions reported have included alopecia areata, and hypertrichosis of the eyelashes. Zidovudine-induced lichenoid reactions have also been described. Ficarra et al. described eight patients with white reticular atrophic buccal mucosal changes which were consistent with lichenoid reactions histologically.

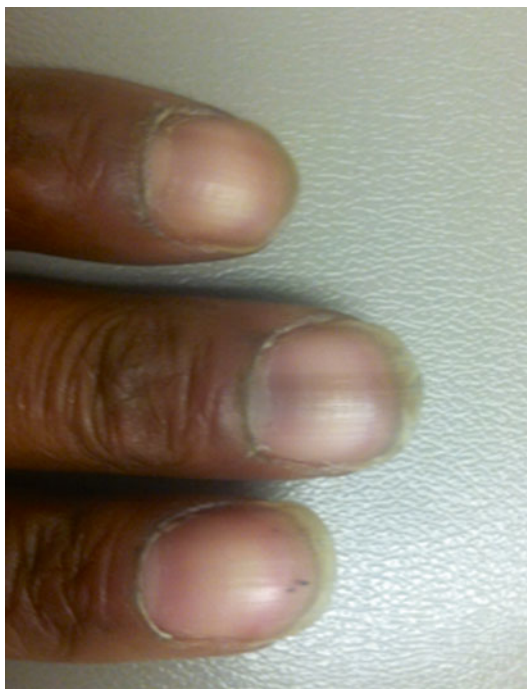

Fig. 37.7 Zidovudine-induced nail hyperpigmentation

Nail and cutaneous hyperpigmentation have been attributed to zidovudine. These typically manifest as brown or blue longitudinal bands or diffuse discoloration of fingernails and/or toenails. Nails changes alone are most common, however, occasionally these are associated with skin and/or mucous membrane hyperpigmentation. Intensity generally correlates with patient's own level of pigmentation (darker skin individuals having the more intense hyperpigmentation). Increased melanin is found in the epidermis and dermis histologically. Stopping or lowering the dose results in gradual resolution in most individuals. Fewer reports have appeared in recent years, suggesting a lesser occurrence with the FDA-approved lower doses which came into common usage in the early 1990s. Confounding the association is that hyperpigmentation identical to that described with ZDV has also been described and attributed to HIV itself in ARV – treatment naïve HIV-infected patients.

Didanosine

Didanosine (also known as ddI or Videx®) was FDA approved in 1991. A mild maculopapular/morbilliform rash may be seen typically beginning after around 7–10 days into therapy. Xerostomia was seen in around one-third of patients treated with ddI monotherapy in the late 1980s. As one of three "D drugs" along with stavudine and zalcitabine [ddc] (which was taken off the market), didanosine was strongly implicated in causing mitochrondrial toxicity-associated ADRs, especially painful peripheral neuropathy, pancreatitis, less commonly lactic acidosis/hepatic steatosis and the mitochondrial toxicity-associated cADR, lipoatrophy which is one of the manifestations of HIV-associated lipodystrophy. Didanosine has been reported in primarily case reports to cause SJS, cutaneous (leukocytoclastic) vasculitis, "anaphylactoid" reactions, and alopecia.

One case of Papuloerythroderma of Ofuji, a pruritic chronic dermatosis which can be associated with cutaneous T-cell lymphoma, has been reported in a patient who was treated with didanosine. The rash began symmetrically with erythema and hyperkeratosis on the palms and soles

progressing over a period of 5 months to red, flat papules that were granulomatous with a perivascular and periadenexal lymphohistiocytic infiltrate of CD8+ T cells, eosinophils, multinucleated giant cell, and Langerhans cells on histologic exam. Mucous membranes were not involved. After 2 months of topical psoralen followed by ultraviolet A light therapy, complete clearing occurred.

Stavudine

Stavudine (also known as D4T or Zerit™) was FDA approved 1994 and is one of two thymidine (nucleoside) analog reverse transcriptase inhibitors (NRTI), the other being zidovudine. Stavudine is most strongly related to mitochondrial toxicity and lipodystrophy (especially lipoatrophy of the face and limbs). Other manifestations of mitochondrial toxicity include peripheral neuropathy, and less commonly pancreatitis and the more serious to fatal lactic acidosis syndromes sometimes with hepatic steatosis.

Cutaneous eruptions associated with stavudine are relatively minor morbilliform reactions for which treatment discontinuation is not usually required. Introcaso characterized the cADRs of stavudine as "not significant." In one controlled clinical trial rash of any severity was seen in 18 % randomized to stavudine/lamivudine/indinavir randomized subjects compared with 13 % of those randomized and treated with zidovudine/lamivudine/indinavir.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): General Comments and Key Points

The drugs include first generation NNRTIs neviripine (Viramune®), delavirdine (Rescriptor®), and efavirenz (Sustiva®; also in Atripla® combined with tenofovir and emtricitabine) and second generation NNRTIs – etravirine (Intelence®), and rilpivirine (Endurant®; also in Complera® combined with tenofovir and emtricitabine).

The NNRTI class of drugs as a whole is characterized by a high incidence of morbilliform (maculopapular) exanthems however these and more severe hypersensitivity reactions (HSR), DiHS/DRESS are most common with neviripine. Many mild to moderate exanthematous reactions (in the absence of fever or with mild fever and no other systemic findings) resolve despite drug continuation. NNRTI rechallenge or reintroduction is possible however several important precautions must be considered and well understood. If a morbilliform drug eruption occurs in the setting of high fever, hepatitis, other systemic symptoms/manifestations, or there are cutaneous warning ("danger") signs (Table 37.6), discontinue the NNRTI and do not consider rechallenge.

Nevirapine

While neviripine is the prototype for mild to moderate morbilliform rash, an NNRTI class effect which occurred in 13–19 % of neviripine-treated patients in Phase 3 clinical trials and in 28 % of a Thai population receiving the drug, DiHS/DRESS or severe rash (i.e., SJS/TEN) appeared to occur more commonly with neviripine (8 %) than with other ARVs including other first generation NNRTIs, delavirdine and efavirenz. Since its introduction, neviripine has been directly responsible for at least 23 cases of SJS and TEN and at least three deaths. In the four major developmental/registrational trials of neviripine 6.6 % of patients experienced a severe or life-threatening eruption.

The risk for neviripine reactions is greatest in the first 6 weeks of therapy and is associated with female gender and with higher CD4 cell counts (>250 cells/mm^3 in women and >400 cells/mm^3 in men). Hepatotoxicity also occurs both as an isolated finding, perhaps an early form of IRIS (as hepatotoxicity was especially prevalent in HIV-HBV and HIV-HCV coinfected patients), and as part of a neviripine DiHS where it is seen in 50 % of cases. The drug carries a Black Box Warning for potentially fatal hepatotoxicity. Liver involvement in the neviripine morbilliform rash may be asymptomatic therefore always check liver function tests (LFTs) in this setting.

Because the risk of SCAR including SJS/TEN (Table 37.7) appears to be greatest within the first several weeks of treatment, standard recommendations are to start neviripine at half-dose

Table 37.7 Criteria of SCORTEN[a] and Auxiliary Score[b] (for prediction of in-hospital death in SJS/TEN)

SCORTEN	
Variables	**Weight**
Age ≥ 40 years	1
Involved BSA @ day 1 ≥ 10 %	1
Presence of cancer or malignancy	1
Heart rate ≥ 120 beats per minute	1
Serum urea level ≥ 120 beats per minute	1
Serum bicarbonate level < 20 mmol/L	1
Serum glucose level ≥ 14 mmol/L	1
Range of score	0–7
Auxiliary Score	
Variables	**Weight**
Age 31–55 years	1
56–75 years	2
>75 years	3
Ten (involved BSA > 30 %)	1
Presence of cancer or malignancy	1
Range of score	0–5

Adapted from Sekula P, Liss Y, Davidovici B, et al. Journal of Burn Care & Research. 2011;32:237–245. With permission from Wolters Kluwer Health, Inc.

[a]Expected probability of in-hospital death = $e^{logit}/(1+c^{logit})$
logit = !4.448 + 1.237H SCORTEN value

[b]Expected probability of in-hospital death = $e^{logit}/(1+c^{logit})$
logit = !3.1364 + 0.9129H AS value

(200 mg) for the first 2 weeks. Anton et al. compared this regimen with an even more gradual escalating schedule (100 mg × 1 week, 200 mg × 1 week, 300 mg × 1 week, then full dose 400 mg (as 200 mg twice daily) and found that 8.5 % of 166 patients on the standard schedule had to discontinue treatment due to rash compared with 2.1 % of 97 patients using the more gradual does escalation schedule. Blood levels of neviripine were appropriately monitored and remained above the inhibitory concentration (IC)-90 of the patient's viruses during the entire dose escalation period.

Risk Factors for Neviripine Rash and/or DIHS Include:

- Higher CD4 counts: ≥250 in women; ≥400 in men
- Female sex (for isolated rash, i.e. rash without DiHS) (Antinori, 2001; Ananoranich, 2005)
- Being HIV negative (in PEP situations)
- Pregnancy
- HLA-DRB1*01
- Hepatitis (B/C) infection

Higher serum concentrations were not found to be associated with neviripine cADRs in the 2NN trial.

Delavirdine

Delavirdine therapy is associated with an 18–50 % incidence of rash, the onset of which is usually in the first 2 months of treatment. Almost all of the rashes are mild to moderate. Topical and/or oral corticosteroids and antihistamines are often used to "treat through" the rash. Rash requiring/leading to drug discontinuation occurred in a low number (<10 %) of patients. Delavirdine is now rarely used in clinical practice due to a perception of lower efficacy, its thrice daily dosing schedule, and an abundance of cytochrome P450 cyp3A4-related drug interactions.

Older Protease Inhibitors

Indinavir

Indinavir is also the prototype for protease-induced lipodystrophy (also called HIV-associated adipose redistribution syndrome [HAARS] or HIV-associated morphological and metabolic abnormality syndrome [HAMMAS]) causing especially lipohypertrophy/fat redistribution in the dorsocervical area, the so-called "buffalo hump," breast enlargement, and/or anterior abdominal lipohypertrophy or the "Crix Belly" (after indinavir brand name, "Crixivan").

Indinavir is also the prototype for protease inhibitor-related retinoic acid-like effects including paronychia, chelitis, xerosis, alopecia, ingrown toenails, and curling of straight hair. According to Garcia-Silva et al. ~ 30 % of patients taking indinavir exhibit at least two of these retinoid manifestations. Hyperlipidemia is also considered by some to be a retinoid-like adverse drug effect.

Similarities in amino acid sequences near the catalytic site between cytoplasmic retinoic

acid-binding protein type 1 (CRABP-1) and indinavir has been proposed as an important factor in the retinoid-like adverse drug reactions seen with indinavir. In addition to indinavir-related interference with retinoid metabolism, cleavage of retinoid-binding proteins by indinavir is also put forth as an explanation for this association. Carr proposed that indinavir increases retinoid signaling pathway by decreasing the metabolism of retinoic acid (altering CRABP-1 mediated synthesis of 9-*cis* retinoic acid from all-*trans* retinoic acid resulting in decreased retinoic acid levels ultimately affecting retinoid-X receptor activity).

It was subsequently shown, however, that indinavir and several other ARV agents increase retinal aldehyde dehydrogenase (RALDH) activity and thereby stimulate (increase) naturally occurring all *trans*-retinoic acid blood levels. Retinol blood levels, however, are decreased and retinol-binding proteins increased in HIV-infected patients on ARV therapy compared to HIV-infected patients who are not being treated with ARVs. Reduced retinol levels may be due to increased utilization of retinol via retinoic acids (retinol is oxidized to retinal by alcohol and short chain dehydrogenases then retinal is oxidized to retinoic acid by RALDH).

Although other protease inhibitors, specifically ritonavir and saquinavir, increase retinal aldehyde dehydrogenase (RALDH) activity to an extent similar to that seen with indinavir (24, 17, and 17 % for ritonavir, saquinavir, and indinavir, respectively) only indinavir has been shown to induce RALDH gene (mRNA) expression. An increase in retinoic acid levels in the absence of increased RALDH levels via suppression of P4503A isoenzymes (by HIV protease inhibitors) has been also proposed however the main effects of HIV-1 PIs are on P450 3A4 and not on other isoenzymes (such as 1A1, 1A2, Cyp 26, 2D1) that mostly affect retinoic acid metabolism.

Taking all of this into consideration retinoid-like AEs of indinavir appear to result from increased retinoic acid levels which stem from enhanced RALDH activity or/and gene expression. On the other hand, retinoic acid activation of retinoid receptors that act as ligand-dependent transcription factors affecting retinoid responsive genes might also play a role.

The most common manifestation of indinavir, which is now rarely used in developed countries, is cutaneous xerosis, which presents as scaling and roughness of the skin with excoriations due to associated pruritis. Paronychia severity ranges from mild to granulomatous and most commonly affects the great toe. Because of its negative impact on self-image, alopecia is the most common cADR leading to discontinuation of indinavir. Patterns of hair loss include diffuse scalp alopecia, alopecia areata, and localized hair loss (limbs, chest, pubis). These effects can be countered with emollients, topical steroids, and paronychia surgery, however recurrences of paronychia after surgery have been described.

The retinoid-like effects, other fairly common and less common ADRs (HIV-associated adipose redistribution syndrome [HAARS]/lipodystrophy [especially lipohypertrophy] and nephrolithiasis/renal insufficiency), coupled with a strict every-8-h dosing requirement and the availability of effective, less toxic, and once and twice daily PIs, eventually made indinavir a little-used alternative ARV agent. Switching from indinavir to another less-toxic, more user-friendly protease inhibitor, if one with antiretroviral activity exists, is the usual management strategy.

There have been rare reports (three cases) of DIHS/DRESS with indinavir which appear indistinguishable from the abacavir hypersensitivity reaction (ABC-HSR) including the rechallenge reaction.

Amprenavir/Fosamprenavir/Tripanavir

Amprenavir and its pro-drug, fosamprenavir were at one point in time said to be more associated with cADRs than any of the other older protease inhibitors. They became available in 1999 and 2004, respectively. Tripanavir, a non-peptidomimetic PI, was FDA-approved in 2006 for salvage therapy. Fosamprenavir replaced amprenavir due to its more favorable safety profile (which includes a lower incidence of cADRs) and its less frequent dosing requirements and reduced pill burden. In treatment-naïve patients and treatment-experienced patients without amprenavir-specific resistance mutations, once-daily dosing in conjunction with ritonavir boosting is possible. Importantly, 1 % of

patients treated with amprenavir developed SJS, while this is quite rare with fosamprenavir.

Amprenavir and fosamprenavir contain the sulfonylarylamine moiety common to antimicrobial sulfonamides. The relation of this fact to their propensity to cADRs remains unclear and, in fact, a history of a previous reaction to sulfonamide antibiotics was not an exclusion criterium in most clinical trials. Both drugs are used in conjunction with ritonavir (for boosting).

Rashes occurred in 20–28 % of patients receiving the drug in phase II and III clinical trials of amprenavir and in 2–7 % fosamprenavir-treated patients. Most of the reactions were mild to moderate maculopapular eruptions in the first few weeks of treatment, discontinuation due to rash was fairly uncommon, and drug reintroduction was usually successful. A successful desensitization protocol has been published.

In the NEAT and SOLO trials in which fosamprenavir and fosamprenavir/ritonavir were compared with the prevailing protease of choice, nelfinavir, both the investigational PI and comparator PI arms included the nucleoside analog RTIs, abacavir and lamivudine. As this was in the pre-HLA-B*5701 screening era, hypersensitivity reactions occurred in both arms in both studies (9 % vs 5 % in the fosamprenavir and nefinavir arms, respectively in NEAT; 7 % vs 6 % in the Q daily fosamprenavir/ritonavir and nelfinavir arms, respectively in SOLO) yet all HSRs were attributed in both trials to abacavir. Isolated rash attributed to protease inhibitor occurred in 7 % vs 2 % in the fosamprenavir and nefinavir arms, respectively in NEAT; and 2 % vs 2 % in the q daily fosamprenavir/ritonavir and nelfinavir arms, respectively in SOLO).

Saquinavir

Maculopapular exanthems and hypersensitivity reactions are distinctly uncommon with saquinavir (hard gel formulation, Invirase®) which is currently only used with twice daily ritonavir boosting. Invirase®, FDA-approved 1995, was the first protease inhibitor available.

Invirase was poorly absorbed and treatment required patients to ingest a huge number of pills daily, but despite this heroic effort, saquinavir hard gel's antiviral effect was often short-lived as resistance soon developed in many who had this drug added to their old dual therapy-era ARVs. While this happened less often with treatment-naïve patients receiving an Invirase-based HAART regimen, a soft-gel formulation of saquinavir (Fortavase®), which had better oral bioavailability, was developed (FDA-approved in 1997) to replace Invirase.

Fortavase, although more potent and effective in the recommended prescribed regimen, also had a very high pill burden (18 pill/day not including the NRTIs in the HAART regimen) and was plagued somewhat by frequent diarrhea, sometimes severe, in those for whom it was prescribed. Eventually Fortavase was abandoned and saquinavir hard gel (Invirase) was again studied and eventually recommended but this time around with ritonavir *boosting* allowing for a twice-daily regimen and overall lower pill burden along with more optimal antiviral and immune system reconstitution effects (than unboosted Invirase or boosted or unboosted Fortavase).

Two cases of fixed-drug eruption (FDE) related to saquinavir have been reported. In these cases the eruption resolved despite continuation of saquinavir. Topical steroids were employed. In one trial of 141 HIV-infected adults randomized to various ritonavir-boosted saquinavir arms no skin-related reactions of a moderate or severe grade were reported.

Firm attribution in three cases of possible HSR in saquinavir-treated patients is difficult and questionable. In one case attribution to saquinavir is complicated by an indinavir-related purpuric rash only 8 days prior to the possible saquinavir rash, the second rash prompting a skin biopsy which showed a vasculitic rash with infiltration of both neutrophils and eosinophils and positive IgA immunoflourescent staining. In another case three protease inhibitors were employed simultaneously, making attribution difficult.

Nelfinavir

Nelfinavir (trade name, Viracept®) was FDA-approved in 1997. Rash due to nelfinavir is uncommon (<5 % in clinical trials). Hypersensitivity reactions have been reported. Most rashes have

been self-limited maculopapular rashes occasionally with some vesicular or bullous features. Onset of the rash ranges between 5 days and 2 weeks. Three cases of urticaria have also been described. Two of these cases had a positive rechallenge but were successfully "desensitized" and able to continue nelfinavir therapy.

One-day desensitization protocols with dose escalation from 25 or 500 μg to 750–1000 mg have been utilized and urticarial reactions have been seen during these procedures. Porphyria cutanea tarda has occurred temporally related to nelfinavir use although the relationship to the drug was unclear.

Lopinavir/Ritonavir

Maculopapular rash occurs in 2–4 % of patients treated with this protease inhibitor. Case reports have described systemic hypersensitivity reactions that have included morbilliform exanthema, fever, transaminitis, and mucocutaneous involvement in patients treated with lopinavir/ritonavir who then went on to tolerate ritonavir in combination with other PIs. Cases of AGEP and DiHS with multiorgan involvement have been described.

The AGEP occurred in a previously healthy, HIV-negative healthcare worker who was given lopinavir/ritonavir FDC-pills as part of a post-exposure prophylaxis regimen (with zidovudine and lamivudine). Within 24 h of initiating the PEP regimen, the patient developed a typical AGEP rash with tiny nonfollicular pustules on a diffuse erythematous skin background and a fever. The rash and fever dramatically improved within 48 h of lopinavir-ritonavir withdrawal (discontinuation). This was followed by a diffuse and marked desquamation.

Reactions Seen with Specific ARVs Currently in Common Use

Tenofovir

Tenofovir disoproxil fumarate (TDF) is a *nucleotide* analogue similar to adefovir and cidofovir. It was FDA approved in 2001 and has become an integral part of preferred/recommended HAART regimens. Rash, including maculopapular pruritic rash, vesiculobullous rash, pustular rash, and urticarial rash has been reported in 4–7 % of patients treated with TDF in the original clinical trials. Lockhart et. al. reported a series of nine patients seen in their clinics seven of whom consented to rechallenge. Five were maculopapular while four had vesiculobullus rashes including one patient with urticaria, angioedema and respiratory distress (shortness of breath). Eight of the nine patients reported the development of pruritis or a rash beginning on the face or in the hairline, a finding not typical of most other HIV medication cADRs, in the author's opinion. Rash was the most common clinical manifestation with a mean onset of 15 days (range 24 h to 6 weeks). It involved the trunk and the extremities in addition to the face in seven of the nine subjects.

The signs and symptoms of the rechallenge reactions were similar to the initial episode in manifestations, location, and intensity, but with an average time to onset of 3.7 days. The rechallenge was sequential in five patients and simultaneous due to the use of the triple FDC agent, Atripla, in two patients. One patient restarted and subsequently tolerated tenofovir despite rash redevelopment and another elected to continue or "treat through" the initial reaction.

Although the drug was not continued after positive rechallenge, the authors concluded that as initial and rechallenge reactions were mild to moderate they would currently be "more inclined to continue tenofovir in patients who develop mild-to-moderate reactions, and are considered more reliable in maintaining continuity of care, provided other severity indicators are absent."

Lamivudine/Emticitabine

Patients treated with emtricitabine may experience (mild) discoloration of their skin, nails, and/or tongue. These reactions were not severe and did not result in treatment discontinuation in any of the study subjects. The pathogenesis of the discoloration is unknown.

When compared with lamivudine in a randomized trial, the rash event rate was 17 % for emtricitabine versus 14 % for lamivudine. However, examining this evidence reveals one of the difficulties inherent in cADR attribution in patients

with HIV infection. In the same study patients were also randomized to receive either stavudine or zidovudine and also received either a protease inhibitor or a NNRTI. A second randomized, double-blind study of either emticitabine or lamivudine with didanosine and efavirenz (n=286) revealed a rash rate of 30 % in the emtricitabine arm and a 3 % skin discoloration rate.

Abacavir

Abacavir entered clinical trials around 1992 and was thought to be a promising new HIV-1 NRTI with less nausea and anemia than zidovudine (AZT or ZDV) and the potential for less mitochondrial toxicity than the "D drugs" (ddI, D4T) and zidovudine. Early in pre-approval development, a hypersensitivity reaction (HSR) was noted which was poorly understood at first but did not appear to be IgE-mediated.

Alarmingly, the symptoms could be fairly nonspecific and subtle and did not always include a rash (34 % without rash) but usually had fever and/or rash (92 %). Sixty-six percent had *both fever and rash.* A severe life-threatening hypersensitivity syndrome with multisystem manifestations sometimes requiring vasopressor support and/or mechanical ventilator support developed within hours of drug rechallenge. Fever (P=0.014), hypotension (P=0.001), edema (P=0.040), and tachycardia (P=0.001) were more often seen on rechallenge than on initial presentation. Death occurred in clinical trials at a rate of 0.03 % (3/10,000) where definitive cases were defined as those whose reaction returned on rechallenge after initial post-withdrawal symptom resolution. Hypotension occurred in 25 % of those who were rechallenged. Twenty-eight percent of patients had a respiratory tract symptom (dyspnea [12 %], cough [10 %], and pharyngitis [6 %]) during the initial or rechallenge presentation, and it should be noted that 11 of 19 (57.9 %) patients who died had respiratory symptoms at the time of initial presentation. Possible misattribution of HSR symptoms to an acute respiratory tract infection delayed the withdrawal of abacavir in four fatal cases and may have led to the decision to rechallenge patients in two additional fatal cases.

Abacavir hypersensitivity reaction (ABC HSR) is more common in U.S. caucasians (8 %) than U.S. Hispanics (2 %), and African-Americans (2.5 %). Presence of the allele conferring risk (i.e. HLA-B*5701) varies among populations worldwide. The initial reaction can be difficult to recognize/diagnose especially when not accompanied by rash however fever is a near constant finding.

In fact, rash alone without fever does not constitute HSR, and many with rash alone can continue receiving the drug and thus be "treated through" the reaction, similar to other mild to moderate ARV-associated morbilliform reactions and OI medication reactions, which are especially common with the NNRTIs and TMP/SMX, respectively.

The case definition for abacavir (ABC) hypersensitivity reaction (HSR) or syndrome (Mallal et al., Lancet 2002; 359:727–32) is the onset of at least two of the following symptoms within 6 weeks of abacavir initiation: Fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), constitutional symptoms (lethargy, malaise, arthralgia, myalgia), respiratory symptoms (dyspnea, sore throat, or cough) with resolution of symptoms within 72 h of discontinuation of abacavir and absence of an alternative likely explanation for the symptoms.

The ABC HSR occurring within clinical trails was initially reported on by Hetherington. Ninety percent of ABC HSR occurred within the first 6 weeks after beginning treatment with the drug (but may occur at any time), with the median time of onset being 9–11 days. At various points in time its incidence was reported to occur in 4.3 % of clinical trial and expanded access trial subjects, approximately 8 % of patient in nine clinical trials (range 2–9 %) and later across a series of 34 clinical trials at a frequency of 5 %. In ABC HSR fever and other symptoms worsen temporally associated with continued dosing and usually resolve (within 1–3 days) upon discontinuation of abacavir (note that rechallenge reactions last much longer).

Despite the HSR, abacavir was FDA-approved in 1998 as Ziagen and was also co-formulated as a fixed-dose dual and triple nucleoside analog

reverse transcriptase combination pills, abacavir-lamivudine (Epzicom®) and zidovudine-lamivudine-abacavir (Trizavir®), respectively. The triple nucleoside analogue RTI proved to be inferior to ritonavir-boosted protease inhibitor-based and non-nucleoside reverse trascriptase inhibitor (NNRTI)-based regimens for patients with higher (>100,000 copies) viral loads. Most recently abacavir-lamivudine has been studied as a backbone for ISTIs and is now coformulated with dolutegravir as the FDC pill Triumeq® which was FDA-approved in August, 2014.

The pharmacogenetic basis for the hypersensitivity reaction (HSR) was intensively studied by Mallal et al and Hetherington, et al. A test for the ancestral haplotype HLA B*5701 allele was developed, tested, and shown effective in reducing HSRs in two prospective cohort strategy trials leading to the approval of the test. In these studies pretreatment HLA-B*5701 screening (withholding abacavir in those positive for the allele) was compared with standard of care treatment and monitoring for reactions (without knowledge of the B*5701 results).

Genetic susceptibility to abacavir hypersensitivity is carried on the 57.1 ancestral haplotype (HLA-B*5701/DR7/DQ3). The susceptibility loci are bounded by C4A6 and HLA-C which may provide sufficient conditions for hypersensitivity. Genes which are in the susceptibility region and therefore may play a role in ABC HSR include the C4 gene encoding the fourth component of the complement cascade, the Hsp70.1 and Hsp70.2 genes encoding heat shock proteins, which serve as chaparones for peptides in the innate immune system, and the gene for the cytokine tumor necrosis factor alpha (TNF- α). Heat shock protein 70 (HSP 70) is a protein that binds peptides to facilitate protein folding. It also "kick starts" the immune system by inducing CD4-independent antigen responses. Inhibition of Hsp70 function by geldanamycin blocks the effects of numerous cytokines. Miles hypothesizes that polymorphism in Hsp70 allows binding of abacavir or a derivative causing a release of bound peptides and thereby mimics a "cytokine storm."

Clinically suspected cases do not actually all have HSR, but overdiagnosis is preferred over underdiagnosis. Rechallenge with abacavir is absolutely contraindicated as the manifestations after rechallenge often appear within a few hours, are more severe, and often include multi-system derangement including multi-system organ dysfunction/failure (respiratory failure, acute kidney injury, hepatitis, etc.) with hypotension occurring in about 25 % of patients, and rarely may be fatal.

Utility of HLA-B*5701 Allele Screening in the Prevention of Abacavir HSR

Factors which favor the implementation of a pharmacogenetic test into clinical practice include the following: application of test improves clinical outcome; the test and test results are readily and rapidly availability and low cost; the test has a high predictive value; clinical parameters that determine usefulness have been identified; the test is easily incorporated into routine management. HLA-B*5701 satisfies all of these parameters.

In the Western Australian HIV Cohort Study withholding abacavir in patients with this haplotype reduced the prevalence of hypersensitivity from 9 to 2.5 %. Two prospective cohort studies (Rauch, 2006; Waters, 2007) demonstrate that screening for HLA-B*5701 allele significantly reduces the incidence of ABC HSR. The Prospective Randomized Evaluation of DNA Screening In a Clinical Trial (PREDICT)-1 trial revealed that absence of HLA-B*5701 allele had a negative predictive value (NPV) of 100 % for skin patch-test confirmed ABC HSR and a NPV of 96 % for clinically suspected ABC HSR.

Use of the patch test in this trial showed that fever with both rash and constitutional symptoms was most predictive of an immunologically confirmed ABC HSR. HLA-B*5701 should be used to pre-screen potential patients, not as a test to confirm a reaction. It is useful in both whites and blacks.

Do not rechallenge patients with possible HSRs regardless of HLA-B*5701 test results. Not all ABC drug reactions occur as classic DiHS/HSR and can occur irrespective of

HLA-B*5701 status therefore clinical vigilance must continue to be an essential part of management of patients commencing abacavir-containing HAART.

Cutaneous adverse drug reactions described *in HLA-B*5701 test negative patients* have included several atypical manifestations (initial fever, nausea, abdominal pain then prolonged high-grade fever alone; fever, rash, diarrhea with severe rhabdomyolysis; muscle rigidity; and extrapyramidal findings; and disulfiram-like reaction) but can be severe. In one of the reports the reaction was confirmed to be skin patch-test negative.

Non-nucleotide Reverse Transcriptase Inhibitors

Efavirenz

A morbilliform rash was seen in 5–34 % of subjects in clinical trials, however <1 % experienced (WHO) Grade 3 or Grade 4 rash or SJS. The rash typically starts after 1–3 weeks of treatment and usually resolves within 2–3 weeks without the cessation of efavirenz treatment. Severe rash (as a component of DiHS or SJS/TEN) is rare (0.1–0.7 %).

Switching from efavirenz to neviripine as a management strategy for efavirenz rashes is NOT recommended. Mehta reported in a retrospective analysis that 12.6 % of those with prior neviripine rash develop rash when switched to efavirenz, however 50 % of those with prior efavirenz rash will develop rash if switched to neviripine. Therefore supportive care (topical steroids, antihistamines) and careful monitoring for signs and symptoms of systemic toxicity/hypersensitivity reaction is indicated while waiting for the efavirenz reaction to resolve.

Other mucocutaneous ADRs reported for efavirenz include annular erythema and photosensitivity, photodermatitis, leukocytoclastic vasculitis, SJS, DiHS and the "burning mouth syndrome." Vitezica and colleagues found the HLA-DRB1*01 allele was associated with cutaneous hypersensitivity induced by nevirapine and efavirenz.

Etravirine

Post-marketing ADR surveillance revealed rare cases of SJS/TEN and DRESS, one of which was fatal, prompting a "Dear Healthcare Professional" letter issued on October, 2009 in agreement with the European Medicines Agency. Reported cases of these SCARs developed between 3 and 6 weeks after etravirine treatment was started. In 2009, the prescribing information for etravirine was modified to include: "postmarketing reports of cases of Stevens–Johnson syndrome, toxic epidermal necrolysis and erythema multiforme, as well as hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. Intelence therapy should be immediately discontinued when signs and symptoms of severe skin or hypersensitivity reactions develop."

Rilpivirine

The safety and efficacy of rilpivirine was compared in Phase III clinical trials to efavirenz. The majority of rashes in both groups were ACTG Grade 1 or 2 severity. Rashes of ≥ ACTG Grade 2 (which occurred in ≥2 % of patients in either group) occurred in 7 (1 %) and 56 (8 %) of patients randomized to rilipivirine and efavirenz, respectively while rash of ACTG Grade 2–4 (and occurring in ≥10 % of patients in either group) occurred in 21 (3 %) and 93 (14 %) of patients randomized to rilpivirine and efavirenz, respectively. There were no ACTG Grade 4 rashes in either group and there was less rash leading to treatment discontinuation in the rilpiverine-treated subjects (0.1 % RPV vs. 1.8 % EFV). As of 2012 Litt's D.E.R.M. documents no post-marketing reports of rash or hypersensitivity with rilpivirine.

Protease Inhibitors

Ritonavir

Ritonavir is uncommonly implicated in cADRs. It has, however, been reported to potentially cause AGEP in its booster role with lopinavir/r FDC and in a patient treated with boosted indinavir as part of a sPEP regimen.

Atazanavir

Rash has been reported in 0.9–6 % of patients treated with atazanavir, an azapeptide protease inhibitor FDA-approved in 2003, which is one of two recommended/preferred PIs. Only four descriptive case reports of rash in patients taking atazanavir have been reported in the literature. In three of the four, causality was not firmly determined, including one patient on dual PI therapy (atazananvir plus lopinavir-ritonavir) plus lamivudine. Onset was 10 days in three patients and on Day 12 in the fourth patient. In two of the four cases the medication was continued with resolution despite continued therapy. In the one case most likely attributable to atazanavir, a 35-year-old man developed (on Day 12) a generalized, blanching, nonpruritic, maculopapular erythema with no fever. The rash resolved 2 days after discontinuation and the patient subsequently tolerated a lopinavir-ritonavir-based HAART regimen.

Darunavir

Rash has been reported with this preferred/recommended protease inhibitor in ~ 6–7 % of patients while severe reactions (DIHS) are seen in less than 1 % of those treated with darunavir-based regimens. Darunavir contains a sulfonamide moiety, however allergy to sulfonamides is not a contraindication to darunavir therapy.

Entry Blockers: Fusion Inhibitors

Efuvirtide

Given by subcutaneous injection twice daily, the route of administration and an informed discussion regarding the almost universal occurrence of injection site reactions (ISRs) lead many patients to decline even salvage use of the agent, while others survived their deep salvage period of treatment to later benefit and enjoy newer, less toxic, and fully suppressive HAART regimens which eventually emerged from Phase III registrational trials, allowing them to "graduate from" and discontinue enfuvirtide therapy.

Hypersensitivity reactions also have been described with efuvirtide but are rare. Enfuvirtide desensitization has allowed some who need the drug to tolerate it again after an initial exanthematous reaction.

Injection site reactions occur in almost all patients (Fig. 37.8) treated with the drug, being seen in 97.9 % of Phase III study subjects receiving the drug. This usually (85.6 %) became evident in the first week of treatment, with individual reactions having an average duration of 7 days. ISRs generally do not worsen over time and lead to treatment discontinuation in 3 % of patients, with <1 % discontinuations being for difficulty in self-administration. About 1–3 % have severe pain limiting normal activities and requiring analgesics. A Bioinjector (needleless) device, special needles, and rotating sites all help. Comparable pharmacokinetic and absorption was found in arm, abdomen, and thigh of study subjects.

Clinical (macroscopic) ISR patterns described by Maggi include: (1) no reaction; (2) transient infiltrative lesions which auto-resolved within 24 h; (3) transient nodular lesions which auto-resolved within 7–15 days; and (4) stable (after >30 days) scleroderma-like lesions. In clinical trials pain and/discomfort was seen in 94.6 %, site induration in 89.3 %, erythema 89 % while nodules or cysts occurred in 75.9 %.

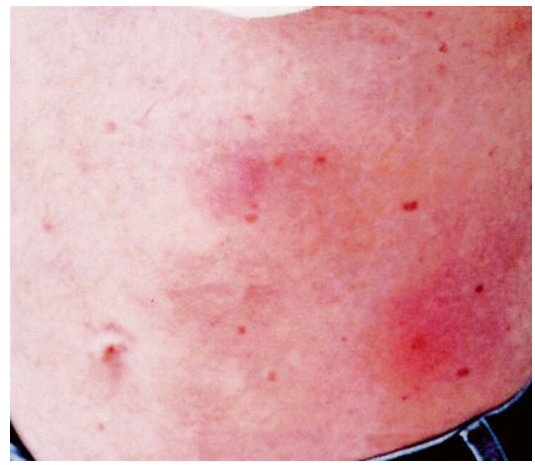

Fig. 37.8 Enfuvirtide injection site reactions on patient's abdomen (Reprinted from the Journal of the American Academy of Dermatology, Vol 49–5. Ball RA, Kinchelow T, ISR Substudy Group. Injection site reactions with the HIV-1 fusion inhibitor enfuvirtide; 826–31. Copyright © 2003; with permission from Elsevier)

Histologic ISR patterns demonstrated in a study where patients had their ISRs biopsied after they had been on efuvirtide treatment for 80 or more weeks showed the following patterns:

- Acute urticarial/vasculitis-like pattern with inflammation of fat tissue
- Subacute pattern with an initial dermal sclerosis
- Chronic scleroderma-like pattern
- Infiltration with lymphocytes +/− eosinophils; perivascular and diffuse

Immunohistochemical studies show mostly T-lymphocytes and a moderate neoangiogenesis.

As cross-resistance and optimal sequencing issues of newer ARVs became better understood in the mid 2000s and raltegravir, the first integrase strand transfer inhibitor (ISTI), and subsequently elvitegravir and dolutegravir, were approved (in 2007, 2012, and 2013 , respectively) the need for enfuvirtide for so-called "deep salvage" greatly decreased. It remains to be seen if enfuvirtide will be needed or supplanted by another agent for patients in the future should resistance and another lull in pipeline drugs (within the drug approval process) leave a future generation of HIV-infected patients to again need deep-salvage options.

Entry Blockers: Chemokine Receptor Blockers

Maraviroc

Considering all exposure in clinical trials, rash is reported to occur in 9.6 % of patients. Litt's D.E.R.M. documents the following: "dermatitis" (5 %); folliculitis (5 %); hypersensitivity rash (17 %) yet only one published report; and stomatitis (4 %).

Integrase Strand Transfer Inhibitors

Raltegravir

Integrase inhibitors (II) or integrase strand transfer inhibitors (ISTI) act by selectively inhibiting the strand transfer activity of HIV-1 and its integration into human DNA. As raltegravir [and probably other ISTIs] plus Truvada are currently recommended as post-exposure prophylaxis (PEP) agents of choice one must realize that rashes associated with the acute retroviral syndrome (ARS), which would signify PEP failure, must be differentiated from a tenofovir, emtricitabine, or raltegravir-/dolutegravir-associated cADR.

Raltegravir (Isentress®), the first approved drug in this class (2007), is rarely reported to cause hypersensitivity reactions. The rash is typically generalized and maculopapular, mild to moderate in intensity, and did not cause drug discontinuation. Published rates of cADRs are difficult to find.

Elvitegravir

Elvitegravir is only available co-formulated with cobisistat, emtricitabine, and tenofovir disproxil fumarate as Stribild®, which was FDA-approved in 2012. In an integrated analysis of double-blind, randomized, placebo-controlled phase 2 and phase 3 clinical trials where all patients received emtricitabine-tenofovir and comparator groups received either efavirenz or ritonavir-boosted atazanavir, grade 2–4 rash events (EVG 4 %, EFV 9 %, ATV/r 4 %) and rash leading to treatment discontinuation (EVG 0.1 %, EFV 1.1 %, ATV/r 1.1 %) were somewhat less common in the elvitegravir-treated subjects.

Dolutegravir

Dolutegravir (Tivacay) (DLG) which was FDA-approved in 2013, has a low incidence of rash, however in some cases patients had in addition to rash constitutional findings, and sometimes organ involvement/dysfunction, including liver injury in less than 1 % of trial subjects. In a study by Wamsley et al. the incidence of rash and discontinuation of study drug due to a skin/SQ disorder was 1 % and less than 1 % respectively in the dolutegravir–abacavir–lamivudine arm compared with 5 and 2 % in the comparator efavirenz–tenofovi–emtricitabine arm.

Management Strategies

The ability to differentiate between more benign cutaneous adverse drug reactions (cADR) for which the implicated medication may often be safely continued or reintroduced from more severe cutaneous adverse reactions (SCARs), including drug-induced hypersensitivity reactions (DIHS), also known as drug reaction with eosinophila and systemic symptoms (DRESS), and SJS/TEN is critical as these cause significant morbidity, mortality, and often long-term serious sequelae in survivors. Cutaneous ADRs, regardless of their severity, must be carefully and expertly managed for the best possible outcomes to be realized.

The patient's HIV clinician or primary care provider, if he or she is not experienced and confident in their ability to diagnose and manage these reactions along with associated implications for ongoing HAART and/or OI treatment and/or prevention, must immediately arrange for consultation and care assistance from someone or a team of experts in the area who is/are experienced and competent in these critically important issues. Physician and/or other competent clinicians/practitioners practicing dermatology, infectious diseases, HIV primary care, and/or allergy/immunology are among those most frequently called upon to provide advice, direction, and expert care.

It is essential that those involved and helping to make the tough management decisions understand the safest way to attempt to induce drug tolerance in the situations where this is feasible. Knowledge of when drug rechallenge or tolerance induction procedures are reasonable and when they should not be attempted, as well as management principles which have the highest chance of preserving future ARV treatment options, are also important qualifications for providing/assisting in the provision of this care for the patient experiencing a cADR.

Screening/Prevention

As the old adage goes it is always easier and better to prevent a problem, in this case a cADR or SCAR, than it is to treat one. HLA-B*5701 screening has clearly been shown to decrease the incidence of abacavir hypersensitivity reaction and has done so in three separate prospective studies involving several countries and settings. Screening prior to abacavir treatment has been included in international HIV treatment guidelines since around 2009/2010.

Hypersensitivity with neviripine is increased at higher CD4 levels. Current guidelines recommend to only start neviripine in ARV naïve men and women with CD4 counts of less than 400 and 250 cells microL^{-1}, respectively. Patients who are ARV-experienced who are virologically suppressed and who had a low CD4 (under the recommended threshold) when they initially began an ARV regimen/HAART who are currently above the CD4 thresholds mentioned above do not necessarily have a greater risk of hypersensitivity as shown by the ATHENA Cohort Study. The same is not true for individuals who do *not* have viral control in this subset of patients (initially low, now high CD4 cell counts) and therefore they are not candidates for treatment with neviripine.

Patient education and guidance regarding NOT escalating the neviripine dose at the 2-week point from 200 mg daily to 200 mg BID in the presence of rash and/or fever or other early warning/danger signs for impending DIHS/DRESS is extremely important and potentially life-saving. Unfortunately, some deaths have been attributed to patients not understanding, or asking for, or obtaining guidance and/or physician or nurse recommendations to stay at the starting dose and seek help from the HIV clinic or emergency department regarding the best individualized management for their neviripine rash/possible early DIHS.

Patients who are HCV-HIV coinfected should probably avoid treatment with neviripine, as it has been shown that HSR acts as an effect modifier of the association between HCV infection and mortality in a cohort of ARV drug naïve HIV-positive patients. The use of neviripine in women with a low (<18.5) BMI is also to be discouraged given the results of a study of men and non-pregnant women in South Africa where early

hepatotoxicity and some death (two women from fulminant hepatic failure) occurred more in the neviripine group than the efavirenz-treated group (17 % vs 0 % with Grade 3 or higher increase in ALT, respectively).

HIV-uninfected candidates for PEP, sPEP, or PrEP should also avoid neviripine treatment, while women who would like to conceive or who are not on reliable methods of contraception should avoid treatment with efavirenz, a known teratogen.

TMP/SMX reactions appear to occur less frequently with lower doses, therefore rates of reactions are higher with full-dose treatment than prophylaxis, and although not well reported, rashes seemed to occur more often with initial PCP treatment doses of 20 mg/kg of the TMP component compared with subsequent recommendations or 18 mg/kg and then 15–18 mg/ kg. Also, there is some evidence that less cADRs occur with low-dose PCP prophylaxis (one DS pill TIW [Monday, Wednesday, Friday] or one SS pill daily) than usual dose prophylaxis (one DS pill daily). Following this logic, avoiding high IV dosing (i.e. treatment-dose TMP-SMX) by following DHHS OI prevention guidelines and effectively preventing the need for PCP treatment may also help prevent TMP-SMX cADRs.

Considerations for using low-dose PCP prophylaxis were addressed to some degree by a NIH-sponsored CPCRA trial which compared daily with TIW TMP-SMX DS where they found equivalence in the two arms for PCP primary and secondary prevention and primary toxoplasmosis prevention but superiority for the daily regimen in secondary toxoplasmosis prophylaxis and a decrease in bacterial infections and mortality in the daily TMP-SMX-DS regimen in patients enrolled from their sites. CPCRA sites were chosen partly based on their ability to enroll difficult to treat and follow populations, including women and injection drug users, which may explain the survival benefit (i.e. by reducing IDU-associated bacterial infections).

ACTG protocol 268 demonstrated that fewer patients needed to discontinue TMP/SMX DS primary PCP prophylaxis by 12 weeks of therapy when TMP/SMX was gradually initiated (17 %) compared with the usual initiation of one TMP/SMX DS tablet from the outset (33 %) ($p = .0002$). The randomized, double blind, controlled two arm study enrolled 372 HIV-1-infected patients with a CD4 count $<250 \times 10$ cells/mm^3 who had not previously received TMP/SMX for PCP prophylaxis. Subjects were randomized to either receive daily TMP/SMX DS tablets or a gradually increasing dose of TMP/SMX suspension (to reach the equivalent of a DS tablet by study Day 13), both groups also receiving matching placebo tablet/suspension.

While this study demonstrated that gradual initiation of TMP/SMX prophylaxis reduces the incidence of treatment limiting AEs, its use has not become widespread, and it has not been endorsed in DHHS or other OI treatment and prevention guidelines, probably as it is not widely known, requires two prescriptions, the majority of patients will tolerate usual prophylaxis dosing initiation without incident, and management options exist for those who do develop mild to moderate morbilliform rash without systemic manifestations.

Symptomatic/Supportive Treatment

Management of cADRs in general, and especially SCARs, must be timely and decisive, with an early accurate diagnosis and prompt withdrawal of the medication at the earliest warning/danger sign or sign of internal organ involvement. For patients with mild symptoms, supportive care is all that is indicated. The effectiveness of antipyretics and medications for pruritis is unclear, however these are commonly utilized. Topical medium-potency (group 4) corticosteroids applied twice daily for 1 week are recommended for AGEP patients, while higher-dose steroids and sometime systemic corticosteroids (although efficacy is unproven) are often used for patients with DIHS/DRESS. SJS/TEN requires intensive supportive care, often in the ICU or with transfer to a burn or other unit with experience and expertise in treating these patients.

Treating Through Versus Discontinuing the Implicated Drug (Dechallenge)

Patients who have mild to moderate rash in the absence of constitutional symptoms can be manage by attempting to "treat through" their reaction with close supervision, even when the culprit drug is abacavir, neviripine, or TMP/SMX. About 50 % of ARV hypersensitivity mild-to-moderate morbilliform rash cases will resolve spontaneously despite continuation of therapy.

Stop therapy if there is mucosal involvement, exfoliation, blistering, an elevation in alanine aminotransferase (ALT) > five times the upper limit of normal, or symptomatic elevation of transaminases (jaundice, upper abdominal pain, fever greater than 39 °C), or intolerable pruritis. Table 37.6 provides further management details.

Note that with medications with long half-lives, such as neviripine and efavirenz cADRs may not be detected until many days after drug discontinuation and that cADRs may worsen temporarily after cessation of drug therapy. Drug resistance may develop as these drugs "outlast" the other discontinued drugs in the combination therapy leading to a "virtual monotherapy" period of time. This is especially the case in patients treated with efavirenz who happen to have the cytochrome P450 2B6 gene (CYP2B6) position 516 TT (516G→T) polymorphism. When warning/danger signs occur in patients on medications with long half lives early drug discontinuation (dechallenge) is especially critical as prompt discontinuation in this setting is associated with less morbidity and mortality in those who end up developing SJS/TEN. It is also important to remember that 34 % of abacavir hypersensitivity reactions rash may be a late or absent feature, therefore discontinuation should be based on progressive constitutional symptoms.

Table 37.8 Desensitization protocol for Efavirenz

Day	Dose (mg)	Day	Dose (mg)
1	0.5	8	64
1	1	9	128
3	2	10	200
4	4	11	300
5	8	12	400
6	16	13	500
7	32	14	600

Adapted from: Phillips EJ, Kuriakose B, Knowles SR. Efavirenz-Induced Skin Eruption and Successful Desensitization. The Annals of Pharmacotherapy; 36: 430–2. © 2002 SAGE Publications. Reprinted with permission of SAGE Publications

Table 37.9 TMP/SMX[a] desensitization protocol

Day	% of Single-Strength dose	Volume[b]	Frequency	Total amount of TMP/SMX
1	12.5	1.25 ml	Once	10 mg/50 mg
2	25	1.25 ml	Twice	20 mg/100 mg
3	37.5	1.25 ml	Three times	30 mg/150 mg
4	50	2.5 ml	Twice	40 mg/200 mg
5	75	2.5 ml	Three times	60 mg/300 mg
6	100	1 tablet	Once	80 mg/400 mg

Adapted from: Gifford S. Leoung, James F. Stanford, Michael F. Giordano, Allan Stein, Ramon A. Torres, Carol A. Giffen, Margaret Wesley, Tricia Sarracco, Ellen C. Cooper, Valerie Dratter, Jeffery J. Smith, Kevin R. Frost, American Foundation for AIDS Research (amfAR) Community-Based Clinical Trials Network. Trimethoprim-sufamethoxazole (TMP-SMX) dose escalation versus direct rechallenge for *Pneumomocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMX. Journal of Infectious Diseases 2001; 184(8):992–7; by permission of Oxford University Press

[a]*TMP/SMX* trimethoprim/sulfamethoxazole

[b]This protocol uses a standard strength TMP/SMX suspension (TMP 40 mg/SMX 200 mg per 5 ml) that can be prepared by a pharmacist

Induction of Drug Tolerance Procedures and Graded Drug Challenges ("Densensitization"/Dose Escalation and Direct Rechallenge)

Induction of drug tolerance is proposed as a more appropriate term (than desensitization) to encompass not only IgE-mediated desensitization procedures, but other non-IgE-mediated "desensitization" procedures as well. These procedures can involve IgE immune mechanisms, non-IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms A validated dose escalation strategy for TMP-SMX reintroduction/maintenance (Leoung et al) and an efavirenz "desensitization" protocol reported to be successfully utilized (case report from E. Phillips, a highly experienced expert in this field) are shown in Table 37.8 and 37.9, respectively.

Drug tolerance is defined as a state in which a patient with a drug allergy will tolerate a drug without an adverse drug reaction. It does not indicate a permanent state of tolerance, nor does this imply that the mechanism is necessarily immunologic tolerance. Also, drug tolerance is a temporary state. Induction of drug tolerance will have to be repeated in the future if the patient requires the drug again after finishing a course of treatment.

On the other hand a ***graded challenge*** (or test dosing) is a procedure to determine whether a patient will have an adverse reaction to a particular drug by administering lower-than-therapeutic doses over a period of time with observations for reactions. The rationale for doing this is that a smaller dose of "allergen" will result in a less severe and more easily treated reaction. A graded challenge does not modify a patient's immunologic or nonimmunologic response to a given drug, and is intended for patients who, after a full evaluation, are unlikely to be allergic to a given drug. Additionally, the benefit of treatment with the drug should outweigh the risk of performing the graded challenge.

A graded challenge or an induction of drug tolerance procedure should almost never be performed if the reaction history is consistent with a severe non-IgE-mediated reaction, such as SJS, TEN, DIHS/DRESS, hepatitis, or hemolytic anemia.

An allergy/immunologist colleague or HIV clinician with special interest and experience in these procedures should be involved in the decision of whether or not to undertake drug reintroduction. If proceeding with reintroduction, then they can help to decide which procedure is best in a given situation, ensuring that (truly) informed consent has been provided and sought to/from the patient or DPOA or guardian, and finally guiding the specific details of the procedure(s), including the provision of a monitoring plan and availability for urgent management should reactions occur during either a graded challenge (test dosing/direct rechallenge) or induction of drug tolerance (dose escalation/desensitization) procedures.

After a successful graded challenge and therapeutic course of Rx, future courses of the drug can be started without another challenge. One should be advised, however, that a graded challenge consisting of more than four to five steps might inadvertently induce modifications of immune effector cells and therefore *induce drug tolerance* in the patient. In this case, future drug administration must me made cautiously.

Specific Treatments

NNRTI and TMP/SMX-Induced Morbilliform Rash

The typical non-life-threatening TMP/SMX reaction is a morbilliform/maculopapular rash which can become confluent. Fever is absent or present in the mild to moderate range, with no mucous membrane involvement or vesicle formation. The onset is typically after 7–10 days of treatment (especially when 15–20 mg/kg/d dosing is used for PCP treatment). This rash typically resolves while "treating through" if mild, or upon discontinuation in 3–12 days. No additional systemic symptoms or clearly abnormal organ-specific laboratory abnormalities are seen.

Severe, sepsis-like (or anaphylactoid) TMP-SMX rechallenge reactions are fortunately rare but appear to occur regardless of the severity of

the index (prior reaction) and regardless of whether TMP/SMX re-introduction occurs via direct reintroduction, a graded challenge (test-dosing), or by induction of tolerance procedures (dose escalation/"desensitization"). While the pathogenesis and risk factors for these rare reactions are largely unknown the only apparent fairly constant variable found when examining published information is that they all appear to occur after relatively recent reactions (ie reactions occurring in the previous 6-8 weeks with most in the previous 2-3 weeks). Systematic study of the timing of successful dose escalations/desensitizations is needed and might shed some needed light on the relative importance of this observation. The possibility that publication bias could be confounding this observation is also to be considered.

There is a strong rationale for preferring to use TMP-SMX rather than alternative agents in both the prevention and treatment of PCP. TMP/SMX is clearly the preferred agent for opportunistic infection prophylaxis and treatment for the commonly encountered fungus, *Pneumocystis jiroveci* (formerly *P. carinii*), the causative agent of *Pneumocystis carinii* pneumonia (PCP). It has been shown to superior to other prophylactic drug options in PCP primary prophylaxis for those who can tolerate the drug.

TMP/SMX also provides optimal primary and secondary prophylaxis for CNS toxoplasmosis and is active against and effective in the treatment of isosporiasis, salmonella and shigella gastroenteritis, nocardiosis, bacterial pathogens in injection drug users, and paracoccidiomycosis and in the prevention of Toxoplasma gondii encephalitis.

Leoung and colleagues (from the American Foundation for AIDS Research [amfAR] Community-Based Clinical Trials Network) showed in a prospective, double-blind, placebo controlled trial of dose-escalation versus direct rechallenge in patients having previous mild to moderate ADR to TMP-SMX that if patients are carefully selected both direct rechallenge and dose escalation are potentially viable options. The study excluded those with recent reactions (ie those occurring within the than 8 weeks) and utilized a single strength (SS) TMP-SMX tablet daily as the prophylactic dose (Table 37.9). Several previous trials have shown a SS tablet to be as efficacious as a double strength (DS) tablet for PCP prophylaxis. The primary endpoint was the ability to take one SS TMP-SMX daily for 6 months. While a higher percent of participants in the dose escalation group (75%) than the direct rechallenge group (57%) were able to successful restart and remain on TMP-SMX for 6 months (p=.014) all of the reactions leading to drug discontinuation were mild and non-serious (mostly mild rash and/or fever) with the no significant difference in rash incidence/severity between the two groups. Bonfanti and colleagues studied TMP-SMX DS dose escalation vs direct rechallenge with the primary endpoint being the presence of a hypersensitivity reaction during the six month follow up using an intention-to-treat analysis. Carr and Shafer had previously shown the safety of direct rechallenge with a double strength tablet. This trial found no difference between the reintroduction strategies. A Cochrane meta-analysis of these two clinical trials plus a third smaller trial by Straatmann found a beneficial effect of a desensitization protocol over a rechallenge protocol at six months follow up for preventing discontinuation of cotrimoxazole (TMP-SMX) with number needed to treat (NNT) 7.14, (95% confidence interval (CI) 4.0-33.0) and for lower incidence of overall hypersensitivity (NNT 4.55, 95% CI 3.03-9.09) but did not show a difference between the two strategies in terms of cADRs, serious adverse reactions, or reactions requiring hospitalization (Lin, 2009).

Nevirapine-Induced Hypersensitivity Syndrome

In the HIV setting neviripine-induced DiHS/DRESS is a major concern. The time of onset since drug exposure (two to six weeks) is considerably later in DiHS/DRESS than in most drug eruptions (4 to 9 days for morbilliform eruptions and 4 to 28 days for SJS/TEN). Medications taken for more than three months or initiated less than two weeks before the onset of

DRESS are unlikely to be the causative drugs. In patients with neviripine-induced DiHS/DRESS neviripine should be discontinued and reintroduction should not be attempted in the future.

Wit in a prospective trial showed that neither the use of prednisolone nor cetirizine prevented neviripine HSR; in fact, corticosteroids have been shown in several studies (Wit, 2001; Montaner, 2003; Barreiro, 2000) to increase the risk of developing rash/HSR in those taking neviripine.

Nevirapine-Related SJS/TEN

Severe cutaneous adverse reactions which include Stevens-Johnson syndrome and toxic epidermal necrosis have been described with most medications used in HIV care. These are fortunately rare but are still greatly increased (100 – 1000 fold higher) over that seen in the general population. With the exception of the NNRTI, neviripine, the rates are similar to other culprit drugs which are not specific to HIV care.

Other HIV-specific drugs which have caused SJS/TEN include TMP/SMX, sulfadiazine, amprenavir, efavirenz, and etravirine.

Although uncontrolled case reports and case series have suggested possible benefit from the use of corticosteroids and other measures including IVIG, a prospective noncomparative study of IVIG showed no benefit in regards to mortality and disease progression (skin detachment or speed of reepitheliation). A retrospective study of patients in the prospective cohort/registry that comprised EuroSCAR also found no benefit for any specific treatment including IVIG and corticosteroid treatment. Early withdrawal of implicated medications appears to improve survival and this may be especially important in drugs with long half-lives such as neviripine, efavirenz, and other NNRTIs.

Regarding prognosis, death occurs in approximately 10% of SJS case but is greater than 30% in TEN. The SCORTEN and auxiliary scores (AS) have been prospectively studied and validated and are of use in predicting mortality in SJS / TEN (Table 37.7).

Editor's Conclusions

The cutaneous manifestations of AIDS are protean and have been instructive in defining the disease, following its progress, controlling the illness, and causing much of its socioeconomic impact. Drug reactions to AIDS drugs as well as to drugs used to control the horrendous burden of infectious diseases seen in these patients is a basic issue when caring for this group of patients. It is probably the most complex set of drug-related problems and skin diseases of any subgroup. Ferreting out all of this information is a daunting task, but this chapter has attempted to summarize it in the most meaningful way possible.

Acknowledgments The author wishes to acknowledge and thank:

Carol A. Stanford, MD, for her steadfast support and encouragement and for her thoughtful comments upon reviewing the chapter manuscript.

Ian M. Stanford, for assisting in computer and other research for factual content, informatics problem solving, and technical graphics arts support including expert help with the tables and figures, and general advice and encouragement.

Ms. Chrystal Head, for her excellent help in searching the literature, obtaining access to key but difficult to obtain references, and copyright issues.

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Pediatric Drug Eruptions of the Skin

38

Gretchen W. Frieling

Abstract

Cutaneous adverse cutaneous drug reactions (CADRs) are common among the pediatric population. Although they are rarely considered serious, CADRs account for approximately 35 % of all adverse drug reactions. Because viral exanthems are extremely common in children, clinicians are often faced with a diagnostic dilemma when children are taking many medications and present with a rash. If a child is taking numerous medications, establishing causality to a specific drug can be multifaceted and difficult. We discuss the most common pediatric drug eruptions according to the pattern of the cutaneous eruption: urticarial, exanthematous, pustular, and vesicobullous. We also include a miscellaneous group for completeness. Proper management of a CADR requires an efficient method of accurately estimating the probability of a drug association, determining the likelihood of a relapse with drug re-challenge, and relaying this information to patients and their families. A hasty diagnosis of a drug "allergy" will follow a child through his or her life, and possibly increase their exposure to more toxic medications unnecessarily. Unless a re-challenge is performed, the vast majority of CADRs in children can only be considered as possibly associated with a drug.

Keywords

Pediatric cutaneous drug eruption • Drug reaction • Cutaneous adverse drug reactions (CADRs) • Urticarial • Exanthematous • Pustular • Vesicobullous

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7_38

Introduction

Cutaneous adverse drug reactions (CADRs) occur commonly in the pediatric population. They are diagnostically challenging as they can simulate other skin diseases in children, especially viral exanthems. Children are particularly susceptible to drug overdoses due to their small body surface area, and if a patient is taking numerous medications, establishing the specific culprit can be very challenging. A prospective observational study conducted by Gallagher et al. gave an approximate ADR incidence of 2.9 %, and another larger study with 24,000 pediatric patients over 1 year showed an incidence of 15.1 ADRs per 1,000 patients, with cutaneous manifestations being the second most frequently encountered (36 %) to gastrointestinal symptoms. Naranjo et al. classifies a drug reaction as "definite" when (1) there is a reasonable time sequence after a drug concentration has been established in body fluids, (2) followed by a recognized response to the suspected drug, (3) confirmed by improvement after drug termination, and (4) the reaction returned on re-challenge. A "probable" reaction, follows conditions 1 and 3, cannot be explained by the patient's condition, and was not confirmed by a re-challenge of the drug. A "possible" reaction follows condition 1, but involves an unpredictable reaction that could be otherwise explained by the patient's condition. The quick detection and treatment of CADRs with identification of the causative agent(s) are essential to prevent continuation of the reaction, additional exposures (which could be more severe than the initial reaction) and to ensure the appropriate use of medications for both the current condition and others throughout the patient's life. Proper management of a CADR requires an efficient method of accurately estimating the probability of a drug association, determining the likelihood of a relapse with drug re-challenge, and relaying this information to patients and their families. A hasty diagnosis of a drug "allergy" will follow a child through his or her life, and possibly increase their exposure to more toxic medications unnecessarily. Unless a re-challenge is performed, the vast majority of CADRs in children can only be considered as possibly associated with a drug.

Epidemiology

Drug-induced skin eruptions are a significant health problem in the pediatric population, representing approximately 35 % of all drug reactions in children. Few epidemiologic studies have analyzed or addressed the incidence of common, non-life-threatening, drug-related skin reactions, including delayed and immediate hypersensitivity reactions, such as maculopapular exanthems, fixed drug eruptions, and urticaria. In 2000, Menniti-Ippolito et al. reported an incidence of 15.1 CADRs per 1000 children in a study of more than 24,000 children.

Clinical Presentation and Histopathological Features

Urticarial Reactions

Urticaria is considered a type I hypersensitivity reaction characterized by IgE-directed mast cell degranulation. Although common in both kids and adults, the main cause in the pediatric population is infection; however, drug-induced urticaria represents 5 % of all cutaneous drug reactions. In many cases, antibiotics are typically administered at the onset of urticaria, so it is often hard to distinguish the culprit (i.e. an infectious agent or the antibiotic). Drug-associated urticaria has a latency period of 2 weeks, whereas urticaria of other etiologies has an abrupt onset and lasts only up to 24 h by definition. The most commonly implicated medications include sulfonamides, beta-lactams, opioids, and NSAIDs (listed below). NSAIDs can act both immunologically and non-immunologically, starting immediately and approximately 24 h after drug ingestion, respectively. Urticarial vasculitis has been reported in association with selective serotonin reuptake inhibitors (SSRIs).

Drug-Induced Urticaria/Urticarial Vasculitis

- NSAIDs
- Opiods
- Penicillin
- SSRIs
- Sulfonamides

Urticaria alone is usually benign and non-lethal. Anaphylaxis, which is urticaria plus systemic symptoms including, but not limited to, weakness, hypotension, abdominal pain, and circulatory collapse, is life-threatening. Approximately 9 % of drug-induced anaphylaxis cases are in children under 18 years of age, with the very rare circumstance secondary to vaccination.

Clinically, urticaria consists of asymmetric, pruritic red-to-pick edematous patches with central clearing, some coalescing into plaques. Size varies from pinpoint to larger lesions measuring several centimeters. By definition, these lesions are self-limited and last less than 24–36 h. In children, pruritus is not always evident and angioedema is more common than in adults, with subcutaneous swellings of hands, feet, mucous membranes, eyelids, and genitals (Fig. 38.1). Angioedema can occur in isolation or with urticarial wheals. Evidence of systemic involvement should be documented, including but not limited to hypotension, tachycardia, syncope, or bronchospasm.

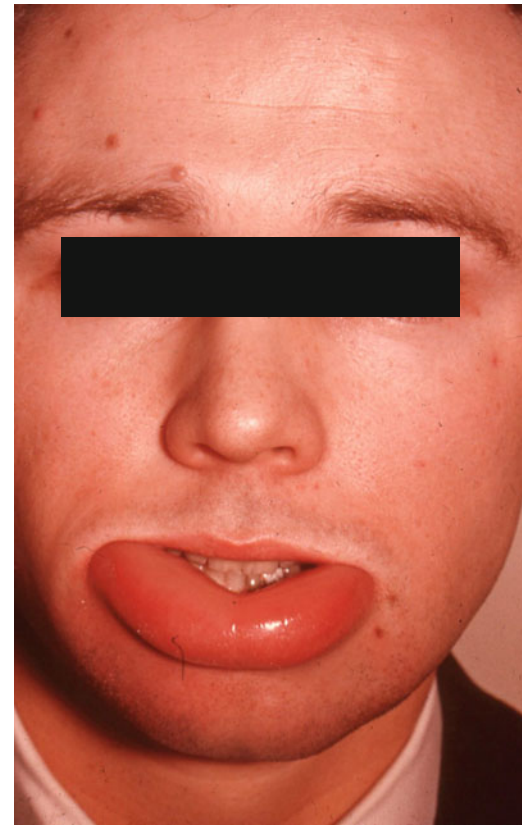

Fig. 38.1 Angioedema in a young boy. Drugs should always be considered as an underlying etiology

Histopathology

Acute urticaria consists of interstitial edema, dilated venules with endothelial swelling, and minimal inflammatory cells. *Chronic urticaria* consists of interstitial edema of the dermis and a perivascular and interstitial inflammatory infiltrate with lymphocytes, neutrophils, and eosinophils.

Management

Antihistamines and cessation of the suspected agent(s) is necessary. Oral steroids and antihistamines can be administered for symptomatic relief as needed.

Serum Sickness-Like Reaction (SSLR)

SSLR is a type III hypersensitivity reaction that is more common in infants and children than adults. It is due to the deposition of antigen-antibody complexes in the tissue with subsequent activation of the complement pathway. In contrast to true serum sickness reactions, these lack immune complex deposition, vasculitis, renal lesions, and hypocomplementemia. SSLR presents as an urticarial, ecchymotic, or morbilliform eruption accompanied by fever, lymphadenopathy, arthralgia, eosinophilia, proteinuria, and splenomegaly. This reaction typically occurs within 3 weeks of drug initiation.

SSLR is associated with a variety of medications, including but not limited to penicillins, tetracyclines, sulfonamides, cefprozil, macrolides, itraconazole, griseofulvin, and biological agents (listed below). Studies have suggested that the risk is greater with cefaclor than other antibiotics. Although SSLRs are self-limited, the lesions persist more than 24–36 h and resolve 1–6 weeks after drug cessation.

Drug-Induced Serum Sickness-Like Reaction

- Buproprion
- Cefazolin
- Cefprozil
- Cefuroxime
- Ciprofloxacin
- Clopidogrel
- Efalizumab
- Fluoxetine
- Griseofulvin
- Immunoglobulin
- Infliximab
- Insulin
- Itraconazole
- Macrolides
- Meropenem
- Mesalamine
- Minocycline
- Omalizumab
- Penicillin
- Rifampicin
- Rituximab
- Streptokinase
- Sulfonamide
- Tetracycline

Histopathology

A superficial-to-mid dermal edema with superficial perivascular lymphocytic infiltrate is present without evidence of vasculitis.

Management

Treatment is symptomatic, with removal of the offending drug, antihistamines, and NSAIDs (for arthralgias). Oral prednisone can also be used. Cross-reactivity of cefaclor or cefprozil with other cephalosporins or beta-lactams is rare, and other cephalosporins do not need to be avoided. This is controversial, however, and some clinicians will strongly dissuade the use of any beta-lactam after a cephalosporin-induced SSLR.

Exanthematous Reactions

Maculopapular Exanthems

Also know as morbilliform, simple exanthematous, or scarlatiniform exanthems, these drug reactions are very common, arguably the most common reaction in children, occurring in 1–5 % of first-time drug users. Thought to be a type IV T-cell mediated hypersensitivity reaction, these eruptions frequently occur with penicillin intake and concomitant Epstein-Barr virus (EBV) infection. Patients with HIV and/or bone marrow transplantation are at increased risk. Associated drugs include penicillins, cephalosporins, sulfonamides, and anti-seizure medications, as listed here:

Drug-Induced Maculopapular Reaction

- Antiepileptics
- Cephalosporin
- Penicillins
- Sulfonamides

Cutaneous manifestations may occur 6–12 h after drug intake, but typically begin within 1–2 weeks. The maculopapular exanthem is pruritic and morbilliform in nature, with symmetric macules and papules, starting on the trunk and spreading to the face and extremities. No pustules or blisters are present. Erythroderma, palmoplantar involvement, and fever may occur. Mucous membranes are typically spared. Before resolving, the rash becomes hyperpigmented and red-brown, and then ultimately desquamates after approximately 2 weeks.

Histopathology

The findings are relatively non-specific, with a superficial perivascular lymphocytic.

Differential Diagnosis

Viral exanthems can be practically identical in presentation and histopathologically and viral titers can be helpful. Clinical features can aid in the exclusion of acute graft-versus-host disease, toxic shock syndrome, scarlet fever, Kawasaki disease, and juvenile arthritis.

Management

Symptomatic treatment is indicated, as the reaction is typically self-limited. The risks and benefits of continuing or discontinuing the medication(s) should be weighed carefully. If the drug cannot be stopped, close monitoring is best.

Reactions can dissipate even when the causative drug is continued. For the pruritus, antihistamines, emollients, and topical corticosteroids can help. These reactions do not progress to more severe, life-threatening reactions, but it is best to assess the likelihood of an early evolving severe reaction. Worrisome signs include bullae, facial edema, fever, mucosal involvement, and positive Nikolsky sign. With re-challenge of the offending medication(s), a reaction may appear quickly, often within 72 h.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Also known as Drug-Induced Hypersensitivity Syndrome (DIHS) or drug-induced delayed multiorgan hypersensitivity (DIDMOHS; see separate chapter on Drug-induced Delayed Multiorgan Hypersensitivity), DRESS syndrome is a drug reaction that begins several weeks (median time 22 days) after drug exposure and can be life-threatening. Diagnosis is based on the presence of fever, rash, systemic symptoms, and blood eosinophilia. DRESS typically occurs on the first drug exposure, within 1–6 weeks, and has an incidence of 1:3000 exposures. DRESS can lead to mortality in 10 % of affected patients. There is a genetic predisposition in individuals with certain HLA types, and first-degree relatives have a higher risk of developing similar drug reactions.

According to the European Registry of Severe Cutaneous Adverse Reaction study group, antiepileptics were involved 35 % of the time, allopurinol 18 %, sulfonamides 12 %, dapsone 12 %, and other miscellaneous antibiotics 11 % of the time (see the list below). Of the antiepileptics, the most commonly implicated drugs are the aromatic compounds, including carbamazepine, phenytoin, and phenobarbital. Minocycline also has a high reported incidence.

Drug-Induced DRESS Syndrome

- Abacavir
- Allopurinol
- Atenolol
- Azathioprine
- Captoril
- Carbamazepine
- Clomipramine
- Dapsone
- Diltiazem
- Gold salts
- Isoniazid
- Lamotrigine
- Mexiletine
- Minocycline
- NSAIDs
- Oxicam
- Phenobarbitone
- Phenytoin
- Sulfonamides
- Trimethoprim

High fever is the first manifestation of disease (>38 °C), quickly followed by a violaceous rash, cervical lymphadenopathy and pharyngitis. The rash is present in 95 % of patients with DRESS and may last several weeks. It begins on the face, often peri-orbitally, and upper trunk, and subsequently spreads caudally. The rash can have varied presentations including a morbilliform exanthem (80 % of cases), erythroderma (10 % of cases), exfoliative dermatitis, vesicobullous eruption, pustular eruption, or targetoid lesions. Mucosal sites are involved in approximately 25 % of cases, including the mouth, lips, throat, and genitalia. Facial edema is present in 25 % of cases. Systemic involvement includes lymphadenopathy, hepatomegaly (50 % of cases), myocarditis, lung disease, gastrointestinal symptoms, and endocrine abnormalities. Thyroiditis is a delayed manifestation, often presenting several months after disease onset.

DRESS is thought to be due to a delayed T-cell mediated hypersensitivity reaction, but the exact cause remains unknown. Re-challenge with the offending medication causes return of fever and erythroderma within hours. Of note, the antiepileptics can have significant cross-reactivity; therefore, if there is a reaction to carbamazepine, phenobarbital, or phenytoin, the patient should avoid all three.

Laboratory Evaluation

A complete blood count often shows an atypical lymphocytosis and eosinophilia. Other recommended tests include coagulation panel, viral

serologies (hepatitis B, C, EBV, HHV-6), liver and renal function tests, muscle enzymes, thyroid function tests, and/or glucose levels.

Histopathology

A sparse perivascular inflammatory infiltrate with lymphocytes and eosinophils typifies the morbilliform rash. Eosinophils may be absent. Vacuolization of the basal layer and rare apoptotic keratinocytes may be seen. These features are all relatively non-specific, as the histology of DRESS syndrome is not pathognomonic.

Differential Diagnosis

Viral exanthem, erythema multiforme, fixed drug eruption, TEN.

Management

Timely withdrawal of the medication(s) is crucial. In patients with systemic involvement, prednisone (1–2 mg/kg/day) is usually indicated. For symptomatic relief, antihistamines and topical corticosteroids are beneficial.

Pustular Reactions

Acneiform Reactions

Drug-induced acneiform reactions are characterized by monomorphic follicular pustules and papules that affect both acne- and non-acne-prone areas (extremities) and heal sans scarring (Fig. 38.2). Mucosal changes are not present. Medications that have been shown to cause this type of reaction include corticosteroids, lithium, androgens, iodides, bromides, adrenocorticotropic hormone, androgens, actinomycin D, phenytoin, and isoniazid. Newer medications such as epidermal growth factor receptor inhibitors (EGFR/HER1) cetuximab, erlotinib, and panitumumab, also have a high frequency of acneiform eruptions, as listed below. The dose and length of therapy with corticosteroids is directly proportional to the risk of developing an acneiform reaction and those with a history of severe acne are at increased risk.

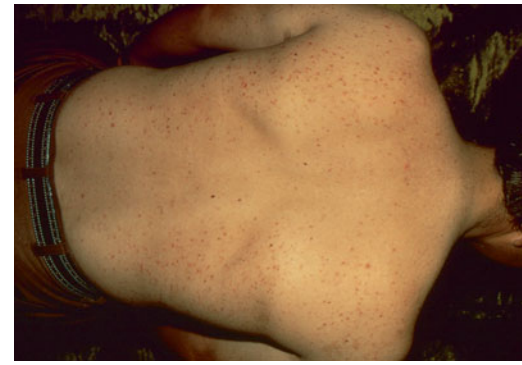

Fig. 38.2 Inflammatory acneiform papules over the back of a teenage boy who had been on long-term systemic corticosteroids

Drug-Induced Acneiform Eruptions

- Actinomycin D
- Adrenocorticotropic hormone
- Androgens
- Bromides
- Corticosteroids
- EGFR receptor inhibitors (cetuximab, erlotinib, panitumumab)
- Iodides
- Isoniazid
- Lithium
- Phenytoin

Management

Benzoyl peroxide, in addition to topical or oral antibiotics, as well as topical tretinoin cream, can be helpful as well as discontinuation of the offending medication(s).

Acute Generalized Exanthematous Pustulosis

AGEP is a serious cutaneous reaction with a reported incidence of one to five cases per million persons per year (also see the chapter on AGEP). AGEP rarely affects children, but when so, it is associated with viral (Coxsackie, parvovirus B19, cytomegalovirus, enterovirus) and bacterial (*Mycoplasma pneumonia*, *Chlamydia pneumoniae*) infections, as well as vaccinations.

The most commonly implicated drugs include penicillin, cephalosporins (cefixime), vancomycin,

clindamycin, acetominophen, paracetamol, bufexamac, cytarabine, and labetalol. Mercury exposure has also been a reported cause of AGEP, as shown here:

Drug-Induced AGEP

- Acetominophen
- Alphonamides
- Amoxicillin
- Ampicillin
- Bufexamac
- Cefixime
- Clindamycin
- Cytarabine
- Diltiazem
- Hydroxychloroquine
- Labetalol
- Mercury
- Paracetamol
- Penicillin
- Quinolones
- Terbinafine
- Vancomycin

Clinically, AGEP presents with diffuse mildly pruritic and edematous erythema of the intertriginous areas. Subsequently, numerous sterile nonfollicular pustules develop. This reaction occurs within hours of drug intake. Fever is usually present but afebrile cases have been reported. Mucous membranes are involved in 20 % of cases and extracutaneous involvement is rare.

Studies have demonstrated AGEP is a drug-specific process mediated by CD4 T-cells, which release GM-CSF and IL-8/CXCL8 cytokines, the latter of which is a potent neutrophil chemoattractant.

Laboratory Evaluation

Peripheral leukocytosis is common, with a neutrophil count over 7000/μL.

Histopathology

Subcorneal or intraepidermal pustules, superficial papillary edema, and a lymphohistiocytic perivascular inflammatory infiltrate are present. Scattered eosinophils and neutrophils can be seen. Single-cell keratinocyte necrosis or vasculitis may be seen.

Differential Diagnosis

DRESS syndrome, pustular psoriasis, leukocytoclastic vasculitis, and subcorneal pustular dermatosis. Differentiation histopathologically may be impossible.

Management

After the offending agent(s) are removed, the reaction should resolve within a couple of weeks. Fine desquamation without scarring may occur. Anti-histamines and a short course of oral corticosteroids (1–2 mg/kg/day) can be used for symptomatic relief of pruritus.

Vesicobullous Eruptions

Fixed Drug Eruption

Fixed drug eruption (FDE) is a drug reaction that classically occurs in the same location with every re-administration of a particular drug (also see the Fixed Drug Eruption chapter). FDEs are relatively common in children, accounting for 10–14 % of ADRs. It may be very difficult to determine the causative drug. The most common drugs implicated in fixed drug eruptions are listed here:

Fixed Drug Eruptions

- Acetylsalicylic acid
- Amoxicillin
- Barbiturates
- Co-trimoxazole
- Methylphenidate
- NSAIDs
- Paracetamol
- Phenylbutazone
- Phenytoin
- Pseudoephedrine
- Sulfamethoxasole
- Teicoplanin
- Tetracycline
- Trimethoprim
- Vancomycin

Clinically, there is a mucocutaneous distribution of pruritic or painful, well-circumscribed and edematous, round red-to-purple patches. They can be solitary or multiple. Vesicles and blisters are variably present. Lesions heal with pigmentary alteration, often darkly hyperpigmented. The most common sites of involvement include lips, trunk, legs, arms, and genitals. Lesions occur within 14 days of original medication assault, and the latency period decreases with subsequent administrations.

The pathogenesis is unclear, but intraepidermal cytotoxic CD8+ T cells most likely release proinflammatory cytokines with drug administration. Expression of intercellular adhesion molecules (ICAM) is seen specifically in lesional epidermis, which may explain the sharp localization and circumscription of the lesions. With drug re-challenge, a flare is usually noticed within 1–8 h.

Histopathology

Hydropic degeneration of basal layer keratinocytes, lymphocytic lichenoid infiltrate, and superficial dermal melanophages are present. Scattered necrotic keratinocytes are also seen. Bullae can be seen, as well as extensive confluent epidermal necrosis. Detachment of the epidermis does not have to occur for necrosis to be present. Histologic distinction from erythema multiforme and TEN is not always achievable.

Management

Mostly supportive, but topical corticosteroids may be helpful.

Pseudoporphyria

Pseudoporphyria is a photosensitive bullous skin disease clinically and histopathologically indistinguishable from porphyria cutanea tarda (PCT), but lacks a biochemical porphyrin abnormality. Excessive sunlight, UVA exposure, and certain drugs are supposed to be etiological factors of pseudoporphyria. These drugs include ciprofloxacin, furosemide, tetracycline, dapsone, pyridoxine, NSAIDs (especially naproxen), and oral contraceptives.

Clinically, pseudoporphyria presents with skin erythema, fragility, blistering, and scarring on photo-exposed areas, with a predilection for the face, dorsal hands, and extensor surfaces of the legs. Milia, waxy skin, and hypertrichosis, which are seen in erythropoetic porphyria (EPP) and PCT, are absent in drug-induced porphyria. Lang et al. reported that 12 % of children taking naproxen for juvenile arthritis developed pseudoporphyria. Unlike PCT, no abnormality in porphyrin metabolism has been identified in these cases.

Histopathology

Cell-poor blisters with festooning are present and resemble PCT histologically.

Management

In drug-induced pseudoporphyria, discontinuation of the suspected drug is recommended and necessary. It can take months after discontinuation of the offending drug for resolution of blister formation. Sun protection is advised for all patients.

Drug-Induced Linear IgA Bullous Dermatosis (LABD)

Although rare in children, reports suggest that almost two-thirds of LABD cases may be drug induced. In these cases, LABD presents as an idiopathic autoimmune subepidermal blistering disease. Implicated drugs include antibiotics (frequently vancomycin), NSAIDs, and diuretics. Other drugs include penicillin, cephalosporins, ACE inhibitors, phenytoin, sulfonamides, and rarely amiodarone, atorvastatin, carbamazepine, cyclosporine, furoseminde, gemcitabine, glyburide, GCSF, influenza vaccination, lithium, rifampin, PUVA, somatostatin, verapamil and vigabatrin. In children, most cases are secondary to infections and/or drugs. After the drug is discontinued, the prognosis is excellent. Of note, there have been few reports of increased morbidity secondary to pruritus.

Acutely, vesicobullous lesions develop in normal-appearing skin in an annular pattern, and often in groups of small clusters, giving rise to the so-called “cluster of jewels” sign clinically. As lesions resolve, new bullae form at the periphery of these resolving lesions (giving rise to the

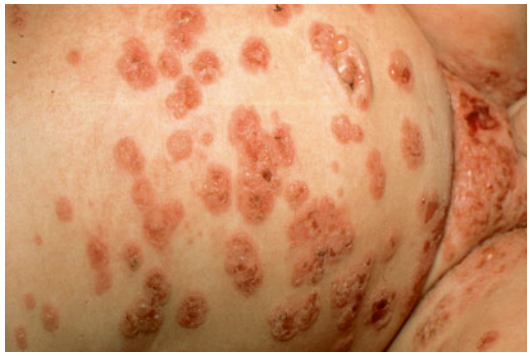

Fig. 38.3 Linear IgA bullous eruption in a 6-year-old male. Drug eruption is not infrequently the cause

so-called "string of beads" sign), forming rosette-like plaques. These plaques diffusely involve the face, trunk, and extremities, particularly around the genitals and perioral areas (Fig. 38.3).

Histopathology

Subepidermal vesicle formation is present with numerous neutrophils. In early lesions, the neutrophils are aligned along the basement membrane zone. In later lesions, the neutrophils extend into the dermis with or without eosinophils. Immunofluorescence shows linear IgA deposition along the basement membrane.

Management

Cessation of the offending drug is necessary and drug-induced LABD will typically resolve within 2–6 weeks.

Drug-Induced Pemphigus

Pemphigus vulgaris is an autoimmune mucocutaneous blistering condition. Clinically, there are flaccid blisters on a normal or erythematous base, which rupture easily and lead to erosion and crusting. In children, this is extremely rare. Cetkovska et al. attributed drug-induced pemphigus to montelukast therapy.

Drug-Induced Bullous Pemphigoid

Bullous pemphigoid (BP) is also rare in the pediatric setting, with about 50 cases reported. The cause in some of these cases has been medications. Drug-induced BP occurs in a younger population than idiopathic BP. Reported cases include after vaccinations, including hepatitis B, DTAP, and polio.

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered to be on a spectrum and are both severe mucocutaneous eruptions that are medical emergencies (also see the Chap. 24). The distinguishing feature of SJS versus TEN is the percentage of body surface area (BSA) involved; less than 10 % of BSA is SJS and greater than 30 % is TEN.

The main cause of SJS/TEN in the pediatric population is infection, with *mycoplasma pneumoniae* and herpes simplex virus commonly reported. In the pediatric population, the key medications are antibiotics. Antiepileptics (phenobarbital, valproic acid), benzodiazepines, sulfonamides, lamotrigine, and NSAIDs are less common (see the list below). The most rarely associated drugs are corticosteroids, vaccines, vitamins, antihistamines, and mucolytics. Finkelstein et al. reported 55 cases of SJS or SJS/TEN in children and found that drugs were the cause in 53 % of them. In that study, antiepileptics were the most common cause followed by sulfonamides, followed by chemotherapeutics. Mycoplasma was found in 22 % of cases. There is a strong genetic predisposition, with certain HLA haplotypes having a predisposition for certain drugs to cause SJS/TEN. This could be useful to know before beginning certain treatments in these individuals. Chung et al. reported that a predisposition exists in Han Chinese individuals given carbamazepine who specifically have HLAB*1502.

Drug-Induced SJS/TEN

- Antiepileptics
- Antihistamines
- Benzodiazapenes
- Cephalosporins
- Corticosteroids
- Mucolytics
- NSAIDs
- Penicillin

- Sulfonamides
- Vaccines
- Vitamins

Disease onset is usually within 4–24 h of the drug intake and can be non-specific, with fever and dysphagia as initial symptoms. Within a couple of days, symmetric, purpuric, annular, dusky, macules and erythema develop on the face and spread to the trunk. Hemorrhagic erosions, blisters, and areas of skin denudation appear (Fig. 38.4). Nikolsky sign is positive. There may be conjunctival involvement. Systemic symptoms such as hypotension, hypothermia, dehydration, and sepsis can occur. Lesions may heal with pigmentary alteration and scarring.

Histopathology

Greater inflammation and keratinocyte necrosis, with apoptotic cells at all layers of the epidermis, is evident. These apoptoses may coalesce to form full thickness epidermal necrosis. Mild inflammation is present. Eventually, subepidermal bullae potentially form. If eosinophils are present in the dermal inflammatory infiltrate, a possible drug etiology should also be proposed.

Management

Management is based on the scoring system SCORTEN, which includes age, BSA involved by bullous lesions, malignancy, tachycardia, serum glucose, bicarbonate, and urea. Diagnosis ultimately depends on clinical and laboratory findings at 24 h and 3 days after onset of symptoms. These patients should be treated in the pediatric burn unit or ICU. No specific treatment protocol has been shown to significantly reduce overall survival or speed/increase skin rejuvenation. Hydration, wound care, and nutritional support are necessary. Antibiotics should be given if cultures are positive. Potential systemic treatments include IVIG, corticosteroids, plasmapheresis, cyclosporine, tumor necrosis factor-alpha antagonists, and others. Potential cutaneous treatments with varying success rates include: (1) debridement with silver-impregnated gauze; (2) biosynthetic skin substitutes (Biobrane); (3) let the natural skin act as a protective layer by piercing bulla with sterile needle and leaving in place; and (4) medications (IVIG, steroids, cyclosporine). Many patients have long-term sequelae from the disease, especially dry eyes, visual loss, and corneal ulceration.

Miscellaneous Pediatric Drug-Induced Reactions

There are several other less common and less severe pediatric drug eruptions that are worth mentioning. These include: neutophilic eccrine hidradenitis, drug-induced lupus, psoriasiform

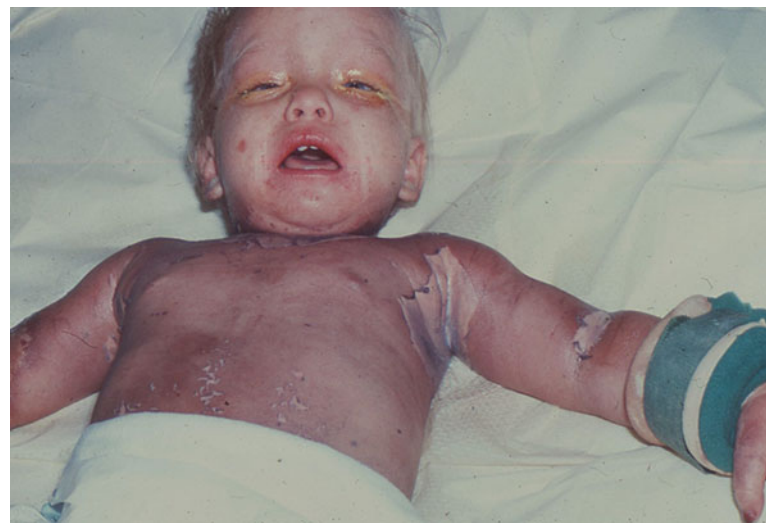

Fig. 38.4 Erosions of skin and mucous membranes in a child with toxic epidermal necrolysis (TEN). As is normally the case, this was due to staphylococcus; however, a drug should always be considered, even though drugs are the more likely culprit in adults

reactions, lichenoid drug reactions, vasculitis, dyschromatosis, phototoxic and photoallergic reactions, nail abnormalities, gingival hypertrophy, cutaneous lymphoid hyperplasia, warfarin-induced necrosis, and heparin-induced necrosis.

Neutrophlic Eccrine Hidradenitis (NEH)

NEH typically begins after chemotherapy regimens and presents with red, edematous papules, patches, and plaques on the face, trunk and extremities. Lesions resolve spontaneously, so treatment typically isn't indicated. Prophylactic dapsone has been shown to decrease recurrences.

Biologic Agents

Agents such as epidermal growth factor receptor inhibitors (EGFRI) are used in the treatment of pediatric brain tumors. EGFRIs cause folliculitis, rash, acneiform eruptions and pruritus. Other biologic agents that could potentially cause adverse skin reactions include rituximab, tyrosine kinase inhibitors, TNF-α antagonists, and sirolimus.

Drug-Induced Lupus

In children lupus this has been associated with minocycline and zafirlukast. In adults, associated medications include hydralazine, procainamide, methyldopa, isoniazid, chlorpromazine, quinidine, anti-thyroid medications, and antiepileptics.

Pediatric Malignancies

Children with malignancies are exposed to numerous medications, and thus are at a relatively increased risk of adverse skin reactions. Clinical presentations can vary from anagen effluvium to pigmentary alterations to mucositis. Reactions can also be life-threatening, including severe and generalized acneiform reactions, AGEP, DRESS, or SJS/TEN (previously discussed).

Approach and Evaluation

A thorough history and skin examination is critical before initiating recommendations and/or treatment. Due to the complexity of these cases, a systematic approach is necessary and required for accurate and timely diagnosis. A recommended approach by Nigen et al. includes: clinical impression and initial physical examination, construction of differential diagnoses, analysis of drug exposure(s), laboratory testing, and literature search. The clinical presentation begins with an immediate assessment of the patient's overall medical status. Physical examination should allow classification of the primary lesion(s) (urticarial, blistering, etc.) and presence or absence of systemic signs should be noted (fever, malaise, tachycardia, hypotension, Nikolsky sign, lymphadenopathy, hepatosplenomegaly, arthritis, mucous membranes, etc.). A systemic evaluation to rule out internal organ involvement should also be performed.

A methodical analysis of *all* drug exposures should be undertaken, including prescriptions, over-the-counter medications, herbal supplements, oral contraceptives, laxatives, and vitamins. Documentation of the dose and duration of each medication is vital. The timing of the eruption should be exactly determined and documented.

The history should include the following pertinent findings: personal history of allergies, previous medical conditions or drug reactions, family history of allergies, previous viral prodromes, and/or presence of arthralgias.

Laboratory evaluation should include a complete blood count, basic metabolic panel (analysis of liver and kidney function), and urinalysis for proteinuria. Radiographic studies are indicated if the reaction is severe, such as in DRESS syndrome, to evaluate for interstitial pneumonitis or pleural effusion.

Skin biopsy can be useful, but is not critical or indicated in all cases. Additionally, biopsies cannot distinguish between different causative drugs. In urticarial and maculopapular reactions, histopathological findings are relatively non-specific, and are not routinely recommended. However, if DRESS syndrome, SJS/TEN, or AGEP is suspected, a skin biopsy must be performed immediately.

In vitro testing can be done and includes, but is not limited to, histamine release assay, basophil degranulation test, lymphocyte transformation test, radioallergosorbent test (RAST), and lymphocyte toxicity test. In vivo tests such as patch testing and oral re-challenge can be useful to determine the culprit medication. Also, genetic

testing can predict those patients with an increased susceptibility to adverse drug reactions.

A literature search can often provide useful information for the ultimate goal of rendering a final diagnosis. If this is not possible with the information available, the likelihood of a reaction must be scored, such as highly probable, probable, possible, unlikely, or nearly excluded.

Management/Treatment

It is imperative to confirm and record any self-reported drug reactions. Withdrawal of the potentially offending drug(s) is the mainstay of immediate therapy. Antihistamines can be used for pruritus and a short course of oral corticosteroids may be useful (specifically for AGEP). Identification of the culprit drug can limit possible life-threatening re-exposure and will also prevent avoidance of harmless drugs that can be life-saving.

Prognosis

Although most cutaneous adverse drug reactions are mild and resolve with termination of treatment, a spectrum does exist, with reactions of varying intensities. The most common manifestations have excellent outcomes, including urticaria and maculopapular rashes. More severe reactions such as DRESS syndrome, Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), are less frequent.

Conclusions

Adverse drug reactions in the pediatric population are particularly challenging, as they can mimic many other eruptions, particularly viral reactions. A high index of suspicion is necessary to make timely treatment decisions and a rapid diagnosis. Testing performed after resolution of the eruption should help identify the causative agent to prevent a repeat reaction with re-exposure.

Follow-up treatment and management is crucial, with clear information given regarding the nature of the drug reaction. The name of the medication, as well as medications that could cross-react, should be provided.

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J.C. Hall, B.J. Hall (eds.), *Cutaneous Drug Eruptions: Diagnosis, Histopathology and Therapy*,
DOI 10.1007/978-1-4471-6729-7

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