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Haur Yueh Lee
Daniel Creamer *Editors*

Drug Eruptions

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Updates in Clinical Dermatology

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Drug Eruptions

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This book is dedicated to
Prof. Jean-Claude Roujeau (1944–2021)
Dermatologist, clinician-scientist, and doyen of cutaneous adverse drug reactions

Preface

Introduction

An adverse drug reaction (ADR) is an unwanted, detrimental response to a medication which is independent of its therapeutic action. Recognition that a medicine's benefit is offset by potential side effects is a paradox all doctors must bear in mind as they write a prescription. This consideration represents an important aspect of the clinical encounter and one which informs the formulation of a treatment strategy. Indeed, concern about adverse effects can have a deep influence on prescribing practices, as physicians attempt to 'Do No Harm'. While the inherent risks of any medication need to be assessed by the clinician, the patient must have confidence that their doctor is aware of potential side effects and will advise and guide them appropriately. The study of adverse drug reactions is thus an essential theme in clinical therapeutics.

Cutaneous eruptions induced as a side effect to drugs account for 15–20% of all ADRs, with presentations which range from mild to severe. This book addresses the subject of cutaneous drug side effects and aims to summarise current knowledge in both the pathogenetic and clinical domains.

Clinical Approach to a Patient with a Cutaneous ADR

In a patient presenting with new signs and symptoms in the skin, the clinician must consider whether the dermatosis might be caused by a medication. A distinction needs to be made between the aggravation of a pre-existing skin disorder by a drug (e.g. rosacea destabilised by glucocorticoids) and the induction of a primary eruption as manifestation of a drug side effect (e.g. drug-induced exanthem). The former situation is not uncommon and is an important consideration in clinical dermatology; however it is the specific drug-induced dermatoses which constitute the field of cutaneous ADRs.

As in any medical consultation, history-taking is imperative when making an assessment of a potential cADR. There are several contextual features which heighten a clinician's concern about a drug aetiology. The incidence of cutaneous drug reactions increases with the number of drugs taken, while the prevalence of cADRs increases with advancing age. Individuals with complex medical problems and who are in-patients appear to be at greater risk for a drug reaction. The presence of an ongoing systemic infection (particularly

herpesvirus infections) may also have a permissive effect on cutaneous drug reactions, irrespective of the anti-microbial medications they are receiving. Studies have demonstrated that female patients tend to be more likely to suffer a cADR.

In many instances a cADR will present as an acute eruption, that is an inflammatory rash which develops suddenly and progresses swiftly to become widespread. These drug reactions are commonly accompanied by symptoms of pruritus or cutaneous soreness, while constitutional symptoms of systemic inflammation (such as fever and malaise) are typically a component of the severe cADRs. Drug reaction with eosinophilia and systemic symptoms (DRESS) is one of the severe cutaneous adverse reactions which is, as its name indicates, a disorder with significant systemic as well as skin involvement. However, some cADRs are not explosive in onset, do not become generalised, and are not associated with systemic features. In these disorders, the evolution of skin signs may be insidious and slowly progressive.

Many cADRs have a clinical presentation which is identical to a non-drug-induced dermatosis. The morphology and distribution of weals in drug-induced urticaria is indistinguishable from that seen in idiopathic urticaria. Therefore, assessment of the physical signs alone is not sufficient to implicate a drug aetiology. Nonetheless some cADRs do have both a specific morphology and a characteristic distribution. An example is the 'atypical' target seen in drug-induced SJS/TEN which can be differentiated morphologically from the 'classic' target of HSV-induced erythema multiforme. In drug-induced SJS/TEN, atypical target lesions tend to be concentrated on the face and central upper torso whereas in erythema multiforme the eruption favours acral skin. An understanding of disease-specific patterns is helpful in the approach to a patient suspected of having a drug hypersensitivity dermatosis.

The analysis of skin biopsies also plays a key role in the assessment of drug-induced skin disease. As with the physical signs, the dermatopathology of cADRs is rarely pathognomic but requires careful consideration in the context of the complete clinical picture. Common patterns of inflammation are seen in drug eruptions, but variations in cytology or histology can help the pathologist to implicate a drug trigger.

Drug Causality in Cutaneous ADRs

It is important to state that a cADR can only be diagnosed if the patient has taken a medicine prior to the eruption's onset. Although patently obvious, this fundamental premise lies at the heart of diagnosing a cADR and of identifying the causative medication. Moreover, the critical therapeutic manoeuvre in all these disorders is discontinuation of the offending drug, an action which almost always results in resolution. Therefore, the clinical presentation must be appraised in the context of the patient's drug history.

When identifying a culprit medication it is important to recognise that the process of attribution is, by and large, an intuitive process undertaken by the

clinician without assistance from laboratory investigations. Although there are biological assays which can be used (outlined in the following chapters) imputation of the causative agent normally involves consideration and integration of three variables: clinical phenotype of cADR, drug timelines, and relative notoriety of possible culprits.

To attribute a cADR to a certain drug one must establish that the medication under consideration is likely to cause the reaction pattern. A crucial question is: does our knowledge of this drug's toxicity profile conform with the patient's eruption? Pharmacovigilance studies have given us insight into the side effect potential of most medications. In the context of dermatology this information is refined so that we now have an understanding of the type(s) of cADR caused by a particular drug.

The temporal relationship between drug administration and onset of the cADR is central in imputation of the culprit. Has the reaction occurred following the administration of the drug (challenge)? Is there a clinical improvement with withdrawal of the drug (dechallenge)? Has the reaction recurred following re-exposure to the drug (re-challenge)? The time lag between first administration of the culprit medication and onset of the cADR is called the latency period and reflects patho-mechanisms underlying the specific drug eruption. This 'incubation' time is fairly constant for each of the cADR syndromes and helps to identify the trigger when the patient is receiving more than one medication. A drug which has been taken for longer or shorter than the typical latency period is unlikely to be the culprit. When a cADR is being considered, all the patients' medications must be noted along with the length of time each has been taken. Marrying up drug timelines with latency period of the reaction is a key task in pinpointing the guilty agent.

Along with an understanding of latency, clinicians need to be aware that every drug carries a greater or lesser potential to cause cADRs. This is the concept of relative notoriety. It sometimes stated that 'any drug can cause any reaction', an aphorism which is theoretically true but unhelpful in practice. In the clinical setting, the majority of reactions are caused by a relatively restricted number of medications. Drugs which feature as common triggers in the cADR syndromes include the aromatic anticonvulsants, antibiotics, sulfur-containing drugs, and allopurinol. While some drugs have the potential to induce many of the cADR syndromes, other fastidious agents have a propensity to trigger just one or two of the drug eruption phenotypes. Figure 1 illustrates the principles in drug causality analysis.

As new drugs are launched the scope of cutaneous side effects will expand both in terms of clinical phenotypes and in the numbers of potential culprit agents. At the present time, it is the targeted anti-cancer therapies which have been unveiled as an important new source of cutaneous toxicity. These drugs use completely new mechanisms to alter cancer biology and consequently reveal novel pathways for drug-induced skin injury. The ongoing explosion in pharmaco-therapeutics will add to the ways drugs cause rashes and in so doing will diversify the practice of clinical dermato-toxicology.

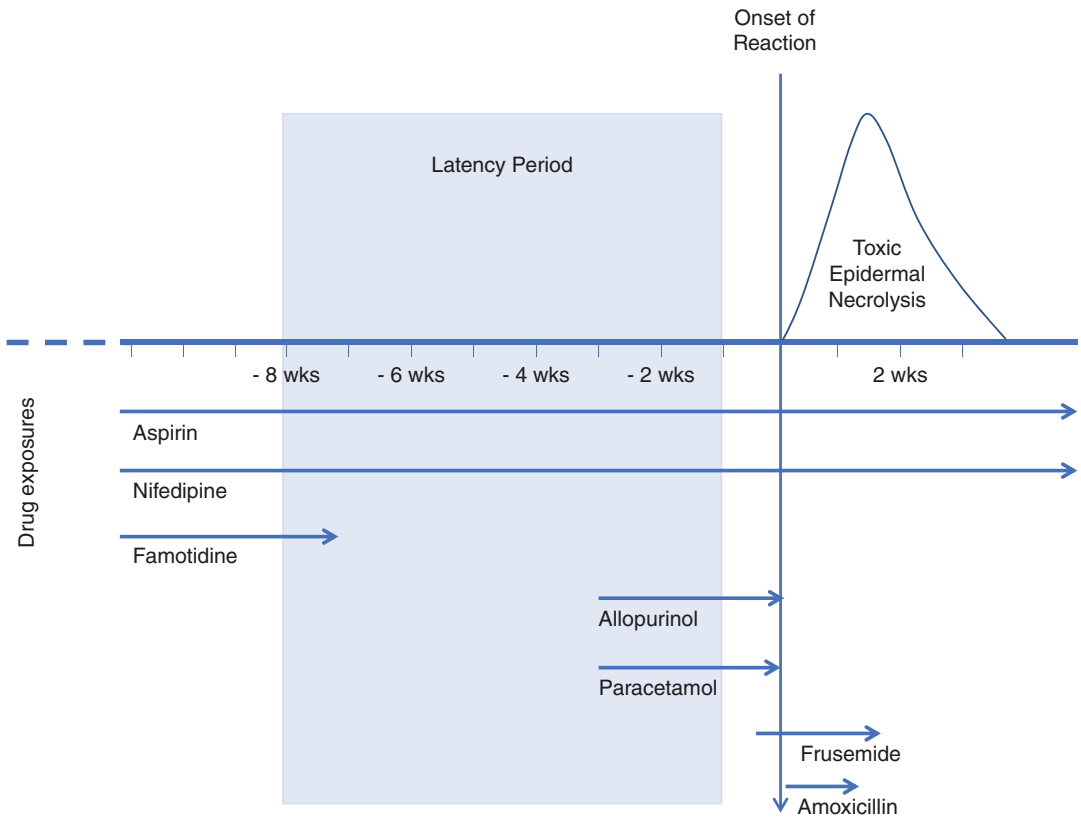

Fig. 1 Illustrates the principles in drug causality analysis. In a case of toxic epidermal necrolysis, the latency period is typically between 1 week to 8 weeks. Drugs which fall outside of this latency period, or are stopped prematurely, are unlikely to be causative. In this example, only allopurinol and paracetamol satisfy the latency, however, allopurinol is the most likely culprit drug based on its notoriety

Classification of the Cutaneous ADRs

Traditionally, adverse drug reactions have been classified as Type A or Type B reactions. Type A reactions are predictable, dose-dependent, occur in all individuals and arise out of the pharmacological activity of the drug. A typical example would be skin purpura or bleeding arising from warfarin overdose. Type B reactions, on the other hand, are thought to be idiosyncratic, unpredictable, and not dose-dependent. Drug hypersensitivity reactions are responsible for the majority of type B reactions. Whilst this is a simple and straightforward approach, improved understanding has shown that many type B reactions, though immune-mediated, may be dose-dependent and/or require a threshold dose before the reaction is initiated. Likewise, the mechanisms of various drug hypersensitivity reactions are being clarified and so are no longer considered idiosyncratic. Similarly, in certain ethnic groups, severe reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis can be predicted and prevented.

In an attempt to improve on the above categorisation, two complementary approaches to the classification of drug eruptions are proposed:

1. Mechanistic Classification.
2. Phenotypic Classification.

Mechanistic Classification

The various chapters in this book illustrate the breadth of drug-induced skin reactions. Not all of the mechanisms behind these drug reactions are known; however, they can be broadly categorised into drug hypersensitivity and non-hypersensitivity reactions (Fig. 2).

Drug Hypersensitivity Reactions

Drug hypersensitivity reactions are classified according to the underlying immune mechanisms, as described by Gell and Coombs. Type I reactions are Ig-E mediated and occur within 1–6 h after drug intake. The presentation of type I reactions includes urticaria, angioedema, and anaphylaxis. Type II

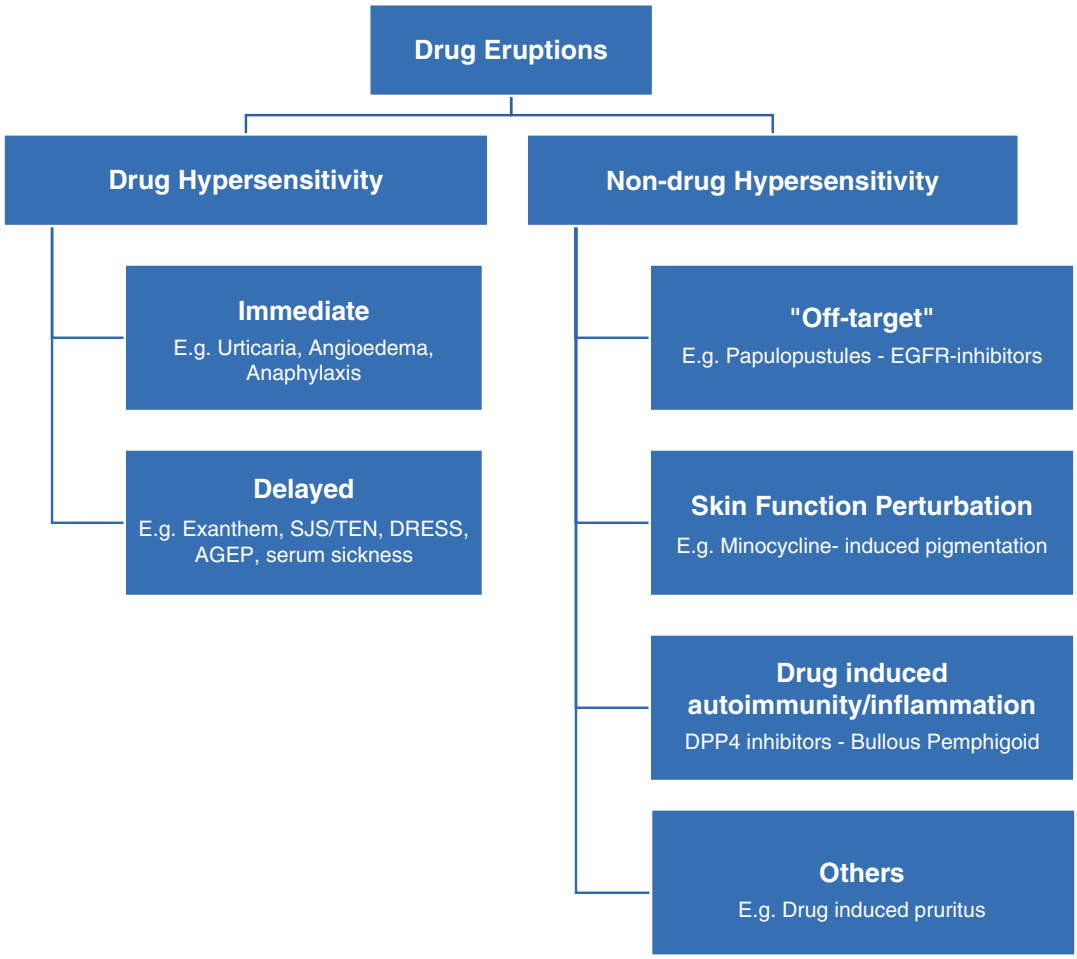

Fig. 2 Classification of cutaneous adverse drug reactions

reactions are Ig-G mediated, present typically as blood dyscrasias such as haemolytic anaemia, thrombocytopenia, or neutropenia. The skin is not involved in type II reactions. In type III reactions, the mediators are antigen-antibody complexes and may present as serum sickness or vasculitis. Lastly, type IV reactions are T cell mediated and can be further subdivided into four subtypes, a–d, depending on the cytokines and accompanying cells involved (see chapter "Mechanisms of Drug Hypersensitivity"). Type IV reactions typically affect the skin and present as exanthematous drug eruptions, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and acute generalised exanthematous pustulosis (AGEP).

Drug hypersensitivity syndromes can also be classified into immediate and non-immediate (delayed) reactions based on the time interval between drug exposure and the onset of symptoms. Type I reactions are considered immediate reactions due to their short latency from drug ingestion, typically <1–6 h whereas types II, III, and IV are considered delayed reactions due to their longer latency periods of days, or even weeks.

Non-hypersensitivity

The mechanism behind non-drug hypersensitivity reactions is not well defined. Mechanisms vary and cutaneous involvement arises from a range of drug-induced biological processes. These include 'off-target' effects of the drug (e.g. papulopustular eruption with EGFR inhibitors), perturbation of a normal skin function (e.g. drug-induced pigmentation or photosensitivity), and drug-induced inflammatory or autoimmune pathways (e.g. drug-induced cutaneous lupus erythematosus). This classification, though arbitrary, is practical since in vitro and in vivo tests (described in chapter "In Vitro Drug Allergy Testing") are less likely to be useful in determining drug causality in non-hypersensitive reactions.

Phenotypic Classification

Cutaneous adverse drug reactions can also be broadly classified into two groups according to clinical threat or severity. The severe cutaneous adverse reactions (SCAR) are categorised based on prominent systemic involvement, considerable morbidity, and a significant mortality risk, whereas benign cutaneous adverse reactions (BCAR) tend not to have a systemic component and carry a negligible morbidity/mortality. Entities classified as SCARs include (1) Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), (2) drug reaction with eosinophilia and systemic symptoms (DRESS), and (3) acute generalised exanthematous pustulosis (AGEP). The mortality risk for such reactions ranges from 1 to 5% in AGEP, 5 to 10% in DRESS, and 25% in SJS/TEN. However, the initial presentation of these SCARs may be similar to an exanthematous drug reaction; therefore serial evaluation of the patient is necessary to monitor for progression and for the appearance of red flags heralding a more severe phenotype (Table 1). These red flags include constitutional symptoms such as fever, flu-like symptoms, and lethargy. If at pre-

Table 1 Red flags which suggest a severe cutaneous adverse drug reaction

Constitutional symptoms: malaise, fever, sore throat, rhinorrhoea, odynophagia
Mucosal involvement: kerato-conjunctivitis, erosions of oral/lip/anogenital mucosae
Facial oedema
Target-like lesions, blisters, erosions, pustules
Lymphadenopathy
Organomegaly
Eosinophilia, atypical mononuclear cells, other blood dyscrasias
Deranged liver function tests, impaired renal function, other visceral dysfunction

sentation mucositis (at any site), skin tenderness, purpura, blisters, or erosions are present then an early, evolving SJS/TEN must be considered. In patients with DRESS, a widespread dermatosis and facial oedema are usually prominent, while eosinophilia and internal organ involvement should be actively sought with appropriate laboratory evaluation.

In the severe cutaneous adverse drug reactions the patient should never be re-exposed to, or re-challenged with, the causal drug since there is a substantial risk of provoking a fatal reaction. This rule need not be adhered to in benign skin reactions when an approach of 'treating-through' may be considered, a decision which should follow careful risk/benefit analysis. In particular this policy can be adopted if the culprit drug is essential to the patient's health and there is no other drug alternative available.

In the ensuing chapters of this book the diverse presentation of drug eruptions will be discussed. These range from self-limiting and benign reaction patterns to those that are severe and life-threatening. Despite advances in our understanding of the mechanisms of adverse drug reactions, the diagnosis remains clinical. Appreciation of the varied clinical presentations, typical latency, and the common putative drugs will enable clinicians to recognise and diagnose such reactions, institute timely measures such as drug withdrawal and specific treatments as well as determine if subsequent allergological evaluation is required or appropriate.

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Part I

General Considerations

Pharmacogenetics of Cutaneous Adverse Drug Reactions

Vincent Lai Ming Yip and Munir Pirmohamed

1 Introduction

Pharmacogenetics is the study of the genetic variability in drug response, either in terms of efficacy or toxicity (Nebert 1999). Pharmacogenomics is a recently introduced concept which acknowledges our ability to interrogate the whole genome. Pharmacogenetics and pharmacogenomics are terms which can be used interchangeably; there is no specific distinction in their use in this chapter.

The notion of pharmacogenetics was introduced by the German pharmacologist Friedrich Vogel in 1959 (Vogel 1959); however, a role for genetics in the causation of adverse drug reactions (ADRs) was first proposed by Motulsky in 1957 (Motulsky 1957). Today the aim of pharmacogenetics is to improve the way clinicians prescribe medicines and to enable more precision in predicting how patients will respond to drugs. The development of pharmacogenetics remained slow initially and was primarily focused on phenotype-driven assessment of variation in drug-metabolising enzyme genes, such as cytochrome P450 enzymes (CYP) (Meyer 2004). The term "pharmacogenomics" emerged in 1997 as the human genome project was nearing completion and advances in new genotyping and sequencing technologies allowed assessment of the whole genome (Meyer 2004). Despite many advances in the field of pharmacogenetics over the decades, only a few pharmacogenetic tests have found their way into the clinical arena (Roden and Tyndale 2011). Reasons cited for a lack of translation of pharmacogenetic findings into clinical practice include problems with sample sizes, clinical phenotyping, genotyping strategies, inadequate assessment of co-existing clinical and environmental determinants, lack of collaboration among groups and insufficient funding (Pirmohamed 2011).

Despite these challenges several pharmacogenetic associations with cutaneous adverse drug reactions (cADRs) have been adopted into clinical practice and have resulted in a change in the drug label or summary of product characteristics. The manifestations of cADRs can be diverse and include serious life-threatening reactions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) (also known as the hypersensitivity syndrome, or HSS) (Duong et al. 2017). Drug-induced exanthem (sometimes referred to as maculopapular exanthem), fixed drug eruption and urticaria are examples of non-life-threatening cADRs (Mockenhaupt 2017), but which can nevertheless affect patient quality of life. cADRs are

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largely considered to have immune-mediated pathophysiology and significant progress has been made in understanding the mechanisms of these reactions (Pichler and Hausmann 2016). Immune-mediated ADRs account for up to 8% of all hospital admissions that are drug related (Gomes and Demoly 2005). Due to the immune nature of cADRs strong genetic predisposing factors have been identified within the major histocompatibility complex (MHC) on chromosome 6. However, genetic factors have also been introduced outside the MHC and are likely to be identified in the future as the sample size of studies increases. This chapter covers the most important pharmacogenetic associations that have been reported with cADRs.

2 Abacavir Hypersensitivity and *HLA-B*57:01*

Abacavir is a nucleoside reverse transcriptase inhibitor with efficacy for the treatment of Human Immunodeficiency Virus (HIV). Prior to the introduction of pre-treatment pharmacogenetic screening, between 5–8% of patients prescribed abacavir would experience a hypersensitivity reaction within the first 6 weeks of treatment (Hetherington et al. 2001). Symptoms of a hypersensitivity reaction include rash, fever, gastrointestinal tract symptoms, respiratory symptoms and constitutional symptoms that become more severe with continued treatment. In this situation, abacavir should be immediately and permanently discontinued and subsequent re-challenge is contraindicated (Hetherington et al. 2001). Clinically, the symptoms of an abacavir hypersensitivity reaction are non-specific and can be difficult to distinguish from concomitant infection, reaction to other drugs or inflammatory disease (Mallal et al. 2008).

An association between the diagnosis of hypersensitivity reaction to abacavir and carriage of the MHC class I allele human leukocyte antigen (HLA) *B*57:01* was reported in 2002 by two independent research groups (Mallal et al. 2002; Hetherington et al. 2002). In an Australian cohort, 18 HIV-positive patients with a diagnosis of abacavir hypersensitivity were compared with 167 abacavir-tolerant patients. Carriage of *HLA-B*57:01* was significantly associated with the risk of abacavir hypersensitivity [odds ratio (OR) = 117; 95% CI 29–481] (Mallal et al. 2002). In the second study, *HLA-B*57:01* was significantly enriched in 84 patients with abacavir hypersensitivity compared with 113 drug tolerant controls (46% vs. 4%) (Hetherington et al. 2002). The association between abacavir hypersensitivity and *HLA-B*57:01* has subsequently been replicated in several independent studies from multiple patient populations (Table 1) (Hughes et al. 2004a, b; Martin et al. 2004; Phillips et al. 2005; Stekler et al. 2006; Rodriguez-Novoa et al. 2007; Colombo et al. 2008; Rauch et al. 2008; Saag et al. 2008; Berka et al. 2012).

A large, prospective, controlled trial recruited 1956 HIV patients and randomly assigned subjects to undergo *HLA-B*57:01* screening with exclusion of *HLA-B*57:01* positive patients from abacavir treatment or receive a standard-of-care approach without prospective *HLA-B*57:01* screening. No patients in the screening group experienced an abacavir hypersensitivity reaction compared with 2.7% in the control group ($P < 0.001$) (Mallal et al. 2008). Based on this study the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) recommended prospective pharmacogenetic screening for *HLA-B*57:01* before initiation of abacavir treatment. The diagnostic accuracy and cost-effectiveness of *HLA-B*57:01* has subsequently been confirmed in meta-analyses (Hughes et al. 2004a; Cargnin et al. 2014). Although the population frequency of *HLA-B*57:01* varies in different parts of the world, the utility of this test has been shown in several ethnic groups (Cargnin et al. 2014). Furthermore, pre-prescription genotyping for HLA-B*57:01 has also been shown to be cost-effective (Nieves Calatrava et al. 2010; Kauf et al. 2010). It is interesting to note that 45% of individuals who are HLA-B*57:01 positive can tolerate abacavir. A recent study has showed this may be related to carriage of different variants of endoplasmic reticulum aminopeptidase 1 (ERAP1), with low activity variants that inefficiently trim peptides within the MHC cleft more likely to be abacavir tolerant (Pavlos et al. 2020).

Table 1 Studies that have reported genetic variants associated with abacavir hypersensitivity

Study	Location	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Hetherington et al. (2002)	North America	Abacavir hypersensitivity	85	Abacavir-tolerant	115	*HLA-B57*	OR: 23.6 (95% CI: 8.0–70.0), $P < 0.0001$
Mallal et al. (2002)	Western Australia	Abacavir hypersensitivity	18	Abacavir-tolerant	167	*HLA-B*57:01*	OR: 117 (95% CI: 29–481), $P_c < 0.0001$
Hughes et al. (2004b)	United Kingdom	Abacavir hypersensitivity	13	Abacavir-tolerant	51	*HLA-B*57:01*	OR: 29 (95% CI: 6.4–132.3), $P < 0.0001$
Martin et al. (2004)	Western Australia	Abacavir hypersensitivity	18	Abacavir-tolerant	230	*HLA-B*57:01*	OR: 960, P_c 0.0001
Stekler et al. (2006)	United States	Abacavir hypersensitivity	9	Abacavir-tolerant	41	*HLA-B*57:01*	RR: 6.9 (95% CI: 3.5–13.6), $P = 0.03$
Rodriguez-Novoa et al. (2007)	Spain	Abacavir hypersensitivity	26	Abacavir-tolerant	27	*HLA-B*57:01*	PPV 92%, NPV 63%, sensitivity 42%, specificity 96%
Colombo et al. (2008)	Switzerland	Abacavir hypersensitivity	98	Abacavir-tolerant	1005	*HCP5* SNP as proxy for *HLA-B*57:01*	PPV 94%, NPV 100%, sensitivity 100%, specificity 99%
Rauch et al. (2008)	Switzerland	Abacavir hypersensitivity	149	Abacavir-tolerant	1728	*HLA-B*57:01*	OR: 10.3 (95% CI: 4.8–22.1), $P < 0.001$ = physician 1 OR: 10.0 (95% CI: 4.7–21.3), $P < 0.001$ = physician 2
Saag et al. (2008)	United States	Abacavir hypersensitivity	130 whites 69 blacks	Abacavir-tolerant	202 whites 206 blacks	*HLA-B*57:01*	OR: 1945 (95% CI: 110–34,352) = whites OR: 900 (95% CI: 38–21,045) = blacks
Berka et al. (2012)	Canada	Abacavir hypersensitivity	16 whites 3 others (indo-Asians and aboriginals)	Abacavir-tolerant	307 whites 163 others (blacks, aboriginals, indo-Asians, Hispanics, metis, Orientals)	*HLA-B*57:01*	OR: 6934 (95% CI: 321–149,035), $P < 0.0001$ PPV 90%, NPV 100%, sensitivity 100%, Specificity 99.6%

HLA human leukocyte antigen, *OR* odds ratio, *PPV* positive predictive value, *NPV* negative predictive value

3 Carbamazepine Hypersensitivity

Carbamazepine (CBZ) is a tricyclic anticonvulsant that was originally licensed for epilepsy in the UK in 1965 and remains one of the most frequently prescribed anticonvulsant agents (Moran et al. 2004). Over time the indications for carbamazepine have widened and it is now also prescribed for the treatment of neuropathic pain and psychiatric disorders (Bialer 2012).

Carbamazepine is generally well tolerated, but up to 10% of patients starting treatment experience a cADR (Marson et al. 2007). The majority of these patients present with an erythematous eruption after a few days which resolves spontaneously without further intervention. However, some patients present with more serious reactions that include DRESS or SJS/TEN (Yip et al. 2012). Patients should be advised to stop carbamazepine if they develop a rash as it is not possible to predict which patients will progress to more severe hypersensitivity. Early discontinuation of the culprit drug is associated with improved clinical outcomes (Garcia-Doval et al. 2000). The incidence of carbamazepine-induced DRESS has an estimated frequency of 1.0–4.1 per 10,000 exposures (Tennis and Stern 1997). The estimated incidence of carbamazepine-induced SJS/TEN in Asian populations is 25 cases per 10,000 (Chen et al. 2011) compared with 1–6 cases per 10,000 in European patients (McCormack et al. 2011).

3.1 Carbamazepine Metabolism Genes

The metabolism of carbamazepine is complex and involves multiple cytochrome P450 isoforms and detoxification pathways (Pearce et al. 2002, 2005, 2008). Generation of chemically reactive metabolites, such as epoxides and arene oxides, can cause direct toxicity or lead to generation of neo-antigens that can activate the immune system leading to hypersensitivity reactions (Yip et al. 2017). Initial pharmacogenetic studies in carbamazepine hypersensitivity focused on polymorphisms in drug metabolism enzymes which could lead to increased formation (or reduced clearance) of toxic metabolites. Microsomal epoxide hydrolase is responsible for the biotransformation of chemically reactive carbamazepine 10,11-epoxide (CBZE) to the inactive 10,11-dihydro-10,11-*trans*-dihydroxy-carbamazepine and is encoded by the gene *EPHX1* (Pearce et al. 2002). A study in a Han Chinese population reported that the single nucleotide polymorphism (SNP) c.337T>C in *EPHX1*, which encodes microsomal epoxide hydrolase, was significantly associated with the development of carbamazepine-induced SJS/TEN (He et al. 2014). In the same study, polymorphisms in *ABCB1*, *CYP3A4*, *FAS*, *SCN1A*, *MICA* and *BAG6* were not associated with susceptibility to CBZ-induced SJS/TEN in a Han Chinese population. More recently, we have detected that the SNP c.416A>G in *EPHX1* is associated with an estimated 50% reduction in the clearance of CBZE in patients prescribed CBZ for epilepsy (Yip et al. 2020). CBZE is known to modify proteins covalently, such as human serum albumin, and excessive formation of these haptens could trigger hypersensitivity reactions in susceptible individuals (Yip et al. 2017). Other studies, however, have been unable to detect an association between polymorphisms in carbamazepine metabolism enzymes (*CYP3A4*, *2B6*, *2C8*, *2C9*, *1A2* and *EPHX1*) and carbamazepine hypersensitivity (Green et al. 1995; Hung et al. 2006).

3.2 Carbamazepine and HLA Alleles

*HLA-B*15:02*

The strongest pharmacogenetic associations for carbamazepine hypersensitivity have been reported with HLAs. The first reported association was in Han Chinese patients from Taiwan. In this study carriage of *HLA-B*15:02* was very strongly associated (OR > 2000) with carbamazepine-induced SJS/TEN (Chung et al. 2004). The association was replicated in other South East Asian populations from China, Hong Kong, Thailand, Malaysia and India (Table 2). Interestingly, the association between *HLA-*

Table 2 Studies that have reported genetic variants associated with carbamazepine hypersensitivity

Study	Location	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Green et al. (1995)	UK	SJS/TEN, hepatitis, pneumonitis	10	Healthy controls	10	None	Microsomal epoxide hydrolase variation not related to hypersensitivity
Pirmohamed et al. (2001)	UK	23 serious reaction (SJS/TEN, DRESS, hepatoxicity) 36 non-serious reaction (rash)	59	63 CBZ-tolerant 250 healthy volunteers	313	*TNF2* (−308G>A)	OR 2.4 (95% CI: 1.2–4.8), $P = 0.01$ (serious reactions)
						HLA-DR3	OR 3.3 (95% CI: 1.3–9.0), $P = 0.01$ (serious reactions)
						HLA-DQ2	OR 3.2 (95% CI: 1.1–8.6), $P = 0.02$ (serious reactions)
Chung et al. (2004)	Taiwan	39 SJS 5 overlap SJS/TEN	44	101 CBZ-tolerant 93 healthy volunteers	194	*HLA-B*15:02*	OR 2504 (95% CI: 126–49,522), $P = 3.13 \times 10^{-27}$
Alfirevic et al. (2006a)	UK	Carbamazepine hypersensitivity	56	CBZ-tolerant	43	None	(*HLA-B*15:02* not detected)
Alfirevic et al. (2006b)	UK	Serious CBZ-induced hypersensitivity	61	44 CBZ-tolerant 172 healthy controls	216	*HSPA1A* (+1911C>G)	OR 0.36 (95% CI: 0.11–1.00), $P = 0.035$ (tolerant)
						HSPA1A (+438C>T)	OR 0.097 (95% CI: 0.0023–0.67), $P = 0.0063$
						HSPA1L (+2437T>C)	OR 0.24 (95% CI: 0.057–0.79), $P = 0.014$
Hung et al. (2006)	Taiwan	60 SJS/TEN 13 DRESS 18 drug exanthem	91	CBZ-tolerant	144	*HLA-B*15:02* (SJS/TEN)	OR 1357 (95% CI: 193.4–8838.3), $P = 1.6 \times 10^{-41}$
						*HLA-A*31:01* (MPE)	OR 17.5 (95% CI: 4.6–66.5). $P = 2.2 \times 10^{-3}$
Lonjou et al. (2006)	Europe/Asian	SJS/TEN	12	Healthy controls	1822	*HLA-B*15:02* (Asians)	4 Asian patients all tested positive for *HLA-B*15:02*
Man et al. (2007)	Hong Kong	4 SJS/TEN 4 drug exanthem	8	CBZ-tolerant	16	*HLA-B*15:02* (SJS/TEN)	OR 71.9 (95% CI: 3.7–1415.8), $P = 1.48 \times 10^{-4}$
Locharernkul et al. (2008)	Thailand	6 SJS 5 drug exanthem	11	CBZ-tolerant	42	*HLA-B*15:02* (SJS)	OR 25.5 (95% CI: 2.68–242.61), $P = 0.0005$
Mehta et al. (2009)	India	SJS	8	Healthy controls	10	*HLA-B*15:02*	OR 71.4 (95% CI: 3.0–1698), $P = 0.0014$

(continued)

Table 2 (continued)

Study	Location	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Tassaneeyakul et al. (2010)	Thailand	SJS/TEN	42	CBZ tolerant controls	42	*HLA-B*15:02*	OR 54.76 (95% CI: 14.62–205.13), $P = 2.89 \times 10^{-12}$
Ikeda et al. (2010)	Japan	5 SJS/TEN 10 drug exanthem	15	Healthy controls	493	*HLA-B*59:01*	RR 15.16 (SJS/TEN)
Kaniwa et al. (2010)	Japan	SJS/TEN	15	Healthy controls	82,000	*HLA-B*15:11*	OR 16.3 (95% CI: 4.76–55.6), $P = 0.0004$
Wu et al. (2010)	China	8 SJS/TEN 28 drug exanthem	36	50 CBZ-tolerant 71 healthy controls	121	*HLA-B*15:02*	OR 184 (95% CI: 33.2–1021.0) (SJS vs. tolerant controls) OR 173.3 (95% CI: 36.0–834.5) (healthy vs. healthy)
Wang et al. (2011)	China	9 SJS/TEN 39 drug exanthem	48	80 CBZ-tolerant 62 healthy controls	142	*HLA-B*15:02*	OR 114.826 (95% CI: 6.25–2111.03), $P < 0.001$ (SJS vs. tolerant) OR 85.087 (95% CI: 4.61–1569.48), $P < 0.001$ (SJS vs. healthy)
Chang et al. (2011)	Malaysia	SJS/TEN	21	Healthy controls	300	*HLA-B*15:02*	OR 16.15 (95% CI: 4.57–62.4), $P_c = 7.87 \times 10^{-6}$
Kim et al. (2011)	Korean	7 SJS, 17 DRESS	24	50 CBZ-tolerant 485 healthy controls	50	*HLA-B*15:11*	OR 18.0 (95% CI: 2.3–141.2), $P = 0.011$ (tolerant)
						*HLA-A*31:01*	OR 8.8 (95% CI: 2.5–30.7), $P_c = 0.011$ (tolerant) OR 7.3 (95% CI: 2.3–22.5), $P_c = 0.013$ (healthy)
McCormack et al. (2011)	European populations (GWAS)	12 SJS/TEN 27 DRESS 106 drug exanthem	145	257 CBZ-tolerant 3987 healthy controls	4244	*HLA-A*31:01*	OR 9.12 (95% CI: 4.03–20.65), $P = 1.0 \times 10^{-7}$ (all phenotypes vs. tolerant)
Ozeki et al. (2011)	Japan (GWAS)	CBZ-induced cADRs (SJS/TEN, DRESS)	53	Healthy controls	882	*HLA-A*31:01*	OR 10.8 (95% CI: 5.9–19.6), $P = 3.64 \times 10^{-15}$
Zhang et al. (2011)	China	SJS/TEN	17	21 CBZ-tolerant 185 healthy controls	206	*HLA-B*15:02*	OR 152 (95% CI: 12–1835), $P < 0.0001$ (tolerant) OR 158 (95% CI: 19–1266), $P < 0.0001$ (healthy)
Kulkantrakorn et al. (2012)	Thailand	SJS/TEN	34	Healthy controls	40	*HLA-B*15:02*	OR 75.4 (95% CI: 13.0–718.9), $P < 0.001$

Shi et al. (2012)	China	SJS/TEN	18	93 CBZ-tolerant 93 healthy controls	186	*HLA-B*15:02*	OR 17.55 (95% CI: 5.31–58.06), $P < 0.001$ (tolerant) OR 21.58 (95% CI: 6.36–73.27), $P < 0.001$ (healthy)
						*HLA-A*24:02*	OR 3.18 (95% CI: 1.11–9.11), $P = 0.03$ (tolerant) OR 2.34 (95% CI: 1.07–5.11), $P = 0.03$ (healthy)
He et al. (2013)	China	SJS/TEN	35	CBZ-tolerant	125	*HLA-B*15:02*	OR 18.222 (95% CI: 3.662–90.662), $P = 0.000$
Amstutz et al. (2013)	North America (paediatrics)	9 SJS/TEN 6 DRESS 26 drug exanthem 1 AGEP	42	CBZ-tolerant	91	*HLA-B*15:02*	OR 38.65 (95% CI: 2.68–2239.5), $P = 0.0022$ (SJS/TEN only)
						*HLA-A*31:01*	OR 7.85 (95% CI: 1.82–47.80), $P = 0.0016$
He et al. (2014)	China	SJS/TEN	28	CBZ-tolerant	200	*EPHX1 c.337T>C*	OR 0.478 (95% CI: 0.267–0.855), $P = 0.011$
Hsiao et al. (2014)	China	112 SJS/TEN 23 DRESS 51 drug exanthem 8 other	194	CBZ-tolerant	152	*HLA-B*15:02*	OR 97.6 (95% CI: 42.0–226.8), $P_c = 5.8 \times 10^{-43}$ (SJS/TEN)
						*HLA-B*40:01*	OR 0.22 (95% CI: 0.1–0.4), $P_c = 8.3 \times 10^{-5}$ (SJS/TEN)
						*HLA-A*31:01*	OR 6.86 (95% CI: 2.4–19.9), $P_c = 7 \times 10^{-3}$ (HSS/MPE)
						*HLA-B*51:01*	OR 4.56 (95% CI: 2.0–10.5), $P_c = 0.01$
Ksouda et al. (2017)	Africa	DRESS	7	CBZ-tolerant	25	*HLA-A*31:01*	OR 32 (95% CI: 2.6–389.2), $P = 0.004$
Khor et al. (2017)	Malaysia	SJS/TEN	28	CBZ-tolerant	227	*HLA-B*15:02*	OR 26.6 (95% CI: 12.80–55.25), $P = 2.31 \times 10^{-26}$
						*HLA-A*31:01*	OR 10.4 (95% CI: 1.64–65.79), $P = 0.023$ (Indians only)
Yuliwulandari et al. (2017)	Java Island (Javanese and Sudanese)	SJS/TEN	12	17 CBZ-tolerant 236 healthy controls	253	HLA-B75 serotype	OR 12 (95% CI: 1.90–75.72), $P = 0.0078$ (tolerant) OR 8.56 (95% CI: 1.83–40), $P = 0.0018$
Devi (2018)	India	SJS/TEN	4	CBZ-tolerant	3	NA	No significant association detected

(continued)

Table 2 (continued)

Study	Location	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Mockenhaupt et al. (2019)	Europe	28 SJS/TEN 10 DRESS	38	Healthy controls	8862	*HLA-B*57:01*	OR 9.0 (95% CI: 4.2–19.4), $P = 9.62 \times 10^{-7}$ (SJS/TEN)
						*HLA-A*31:01*	OR 49.9 (95% CI: 12.9–193.6), $P = 4.0 \times 10^{-18}$ (HSS)
						*HLA-B*57:01* or *HLA-A*31:01*	OR 10.0 (95% CI: 5.3–19.1), $P = 3.58 \times 10^{-11}$ (all hypersensitivity)
Nicoletti et al. (2019)	Europe	25 DRESS 10 SJS/TEN 5 SJS 1 TEN 2 AGEP	43	Healthy controls	10,701	*HLA-A*31:01*	OR 12.9 (95% CI: 5.58–29.78), $P = 2.1 \times 10^{-9}$ (HSS)
						*HLA-B*57:01*	OR 6.2 (95% CI: 2.47–15.37), $P = 9.9 \times 10^{-5}$ (SJS/TEN)
Capule et al. (2020)	Philippines	SJS/TEN	8	CBZ-tolerant	32	HLA-B75 serotype	OR 23.25 (95% CI: 2.33–232.21), $P = 0.007$)
						*HLA-B*15:02*	OR 7.33 (95% CI: 0.73–73.25), $P = 0.09$
						*HLA-B*15:21*	OR 7.53 (95% CI: 1.27–44.79), $P = 0.026$

AGEP acute generalised exanthematous pustulosis, *CBZ* carbamazepine, *DRESS* drug reaction with eosinophilia and systemic symptoms, *GWAS* genome-wide association study, *OR* odds ratio, *RR* relative risk, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

*B*15:02* and carbamazepine-induced SJS/TEN is both phenotype- and ethnicity-specific. *HLA-B*15:02* was not significantly associated with other phenotypes of carbamazepine-induced hypersensitivity (e.g. drug exanthem, DRESS) (Yip et al. 2012) and the association was not detected in Caucasian (Alfirevic et al. 2006a), Japanese (Kaniwa et al. 2010) or Korean populations (Kim et al. 2011). The carriage of *HLA-B*15:02* is highest among Asian populations such as Han Chinese (0.057–0.145), Thai (0.0.085–0.275) and Malaysians (0.12–0.157) and lowest in Europeans (0.01–0.02), Japanese (0.002) and Koreans (0.004) (Lim et al. 2008). The differences in background frequency of *HLA-B*15:02* could explain why carriage of *HLA-B*15:02* is relevant only in certain South East Asian populations.

A prospective study of *HLA-B*15:02* pharmacogenetic screening in Taiwan recruited 4877 patients and genotyped them prior to initiation of antiepileptic treatment. Those testing positive for *HLA-B*15:02* (7.7% of total population) were advised to avoid CBZ and offered alternative medication. A mild transient rash developed in 4.3% of participants and a more widespread rash, requiring hospitalisation, developed in 0.1% of subjects. SJS/TEN did not develop in any of the subjects testing negative for *HLA-B*15:02* compared with an estimated historical incidence of 10 cases among study subjects ($P < 0.001$) (Chen et al. 2011). Based on these data the EMA and FDA have included warnings in the label for CBZ about the risk of SJS/TEN with the presence of *HLA-B*15:02* (Phillips et al. 2018).

*HLA-A*31:01*

The *HLA-A*31:01* allele was first associated with CBZ-induced drug exanthem in a candidate-gene study from Taiwan (OR = 17.5; 95% CI: 4.6–66.5, $P = 0.0022$) (Hung et al. 2006). Subsequently, two independent genome-wide association studies (GWAS) reported significant associations between *HLA-A*31:01* and all phenotypes of CBZ hypersensitivity in European (McCormack et al. 2011) and Japanese patients (Ozeki et al. 2011). The association between *HLA-A*31:01* and CBZ-induced hypersensitivity was further replicated in Korean (Kim et al. 2011), Han Chinese (Hsiao et al. 2014), Tunisian (Ksouda et al. 2017) and Indian (Khor et al. 2017) populations. In a paediatric study, *HLA-A*31:01* was significantly associated with CBZ-induced DRESS (OR = 26.4; 95% CI: 2.53–307.89, $P = 0.025$) and drug exanthem (OR = 8.6, CI: 1.67–57.5, $P = 0.0037$), but not SJS/TEN (Amstutz et al. 2013).

More recently, a Japanese study has assessed the effect of prospective *HLA-A*31:01* screening on CBZ hypersensitivity (Mushiroda et al. 2018). Of the 1130 subjects included in the study, 198 (17.5%) of the population tested positive for *HLA-A*31:01* and were offered alternatives to CBZ. Twenty-three patients (2.0%) in the study experienced CBZ hypersensitivity: 3 DRESS, 9 drug exanthem, 5 erythema multiforme, 6 undetermined. There were no cases of CBZ-induced SJS/TEN. Compared with historical data from the Japan Medical Data Centre the incidence of CBZ-induced hypersensitivity was significantly decreased (historical incidence 5.1%, OR 0.60, 95% CI: 0.26–0.59, $P < 0.001$).

3.3 Carbamazepine and Other HLA Alleles

Several other HLA alleles have been associated with CBZ hypersensitivity. *HLA-B*15:11* has been significantly associated with CBZ-induced SJS/TEN in Korean (OR = 18.0, 95% CI: 2.3–141.2, $P = 0.001$) (Kim et al. 2011) and Japanese patients (OR = 16.3, 95% CI: 4.76–55.6, $P = 0.0004$) (Kaniwa et al. 2010). Both *HLA-B*15:11* and *B*15:02* are part of the HLA-B57 serotype conferring structural similarity in the peptide binding groove (Marsh et al. 2010). More recent studies in patients from Java Island and Philippines have confirmed the association between *HLA-B75* serotypes, including *HLA-B*15:21,* and CBZ-induced SJS/TEN (Yuliwulandari et al. 2017; Capule et al. 2020).

*HLA-B*57:01* has been associated with CBZ-SJS/TEN in European populations (Mockenhaupt et al. 2019; Nicoletti et al. 2019). *HLA-B*57:01* is already a well-known risk factor for abacavir

hypersensitivity syndrome (Table 1) and flucloxacillin drug-induced liver injury (Daly et al. 2009). The association of *HLA-B*57:01* with CBZ-SJS/TEN will require further replication and investigation of the functional mechanisms.

In Japanese patients, *HLA-B*59:01* was reported as a potential marker for severe hypersensitivity (relative risk 15.16) (Ikeda et al. 2010). In a Chinese study, CBZ-induced SJS/TEN was associated with carriage of *HLA-A*24:02* (OR = 3.18; 95% CI: 1.11–9.11, P = 0.03) (Shi et al. 2012). *HLA-B*51:01* was significantly associated with CBZ-induced drug exanthem or DRESS (OR = 4.56; 95% CI: 2.0–10.5, P_c = 0.01) but the allele *HLA-B*40:01* appeared to have a protective effect in Chinese patients (OR = 0.22; 95% CI: 0.1–0.4, $P_c = 8.3 \times 10^{-5}$) (Hsiao et al. 2014).

The Summary of Product Characteristics (SmPC) for carbamazepine advises that testing for *HLA-B*15:02* should be considered for populations at risk. It also advises that there is insufficient data to support a recommendation for *HLA-A*31:01* screening prior to starting carbamazepine therapy (https://www.medicines.org.uk/emc/product/1040/smpc). By contrast, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline advises the avoidance of carbamazepine in patients who are either *HLA-B*15:02* or *HLA-A*31:01* positive (Phillips et al. 2018). Health economic analyses have shown that screening for *HLA-B*15:02* in patients of Asian ancestry and for *HLA-A*31:01* in Caucasian patients is cost-effective (Dong et al. 2012; Plumpton et al. 2015; Choi and Mohit 2019).

3.4 Carbamazepine and T Cell Receptor Variation

A recent study analysing blister fluid cells and peripheral blood mononuclear cells from patients with CBZ-induced SJS/TEN identified drug-specific T cell receptor (TCR) αβ repertoires, TCRα CDR3 (third complementarity region) "VFDNTDKLI", and TCRβ CDR3 "ASSLAGELF", with its expression showing both drug and phenotype specificity and a bias for *HLA-B*15:02* (Pan et al. 2019). Adoptive transfer of the public αβTCR lymphocytes to *HLA-B*1502* transgenic mice with administration of carbamazepine induced phenotypes mimicked severe cutaneous hypersensitivity. No hypersensitivity reactions were observed in *HLA-B*15:02* mice administered only carbamazepine without transfer of the public αβTCR lymphocytes.

4 Aromatic Antiepileptics and Hypersensitivity

Aromatic antiepileptic drugs (AEDs), including carbamazepine, oxcarbazepine, phenytoin and lamotrigine, are frequently associated with cADRs and the potential for cross reactivity within this group (Romano et al. 2006). Table 3 provides a summary of studies that have investigated genetic predisposition to hypersensitivity reactions to aromatic AEDs.

Oxcarbazepine is a 10-keto analogue of carbamazepine with a modified pharmacokinetic profile to minimise the formation of reactive metabolites whilst retaining anticonvulsant activity (May et al. 2003). Due to its chemical similarity to carbamazepine three studies have investigated the association between *HLA-B*15:02* and oxcarbazepine-induced hypersensitivity reactions (Hung et al. 2010; Hu et al. 2011; Chen et al. 2017). Two studies confirmed a significant association between *HLA-B*15:02* and susceptibility to oxcarbazepine-SJS/TEN in patients from Taiwan and Thailand (Hung et al. 2010; Chen et al. 2017). The third study from China reported a significant association between *HLA-B*15:02* and oxcarbazepine-induced drug exanthem which is interesting as the *HLA-B*15:02* allele has not been associated with CBZ-induced drug exanthem (Hu et al. 2011). Two further studies in Chinese patients with oxcarbazepine-induced drug exanthem did not detect a significant association with *HLA-B*15:02* (He et al. 2012; Lv et al. 2013). *HLA-B*38:02* was reported to be associated with increased risk of oxcarbazepine-drug exanthem in a Chinese population (Lv et al. 2013).

Table 3 Studies that have reported genetic variants associated with hypersensitivity to aromatic antiepileptic drugs

Study	Location	Culprit drugs	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Man et al. (2007)	China	CBZ PHT LTG	2 TEN 4 SJS 2 DRESS 16 drug exanthem	24	AED-tolerant	48	*HLA-B*15:02*	OR 17.6 (95% CI: 2.9–105.2), $P = 0.001$ (overall) NS for drug exanthem 1 × LTG and 1xPHT (*HLA-B*15:02* positive)
Locherernkul et al. (2008)	Thailand	CBZ PHT LTG OXC CLoB	6 CBZ-SJS 4 PHT-SJS 5 CBZ-drug exanthem 9 PHT-drug exanthem 3 CBZ/PHT-drug exanthem 3 CBZ/LVT 1 LTG-drug exanthem 1 OXC-drug exanthem 1 CLB-drug exanthem	31	AED-tolerant	50	*HLA-B*15:02*	OR 25.5 (95% CI: 2.68–242.61), $P = 0.0005$ (CBZ-SJS group) OR 18.5 (95% CI: 1.82–188.40), $P = 0.005$ (PHT-SJS group) CBZ-drug exanthem and PHT-drug exanthem NS
Lonjou et al. (2008)	Europe	LTG	SJS/TEN	17	Healthy controls	1822	*HLA-B*38*	OR 6.8 (95% CI: 2.2–21), $P_c = 0.02$
Kazeem et al. (2009)	UK	LTG	10 SJS/TEN 12 DRESS	22	LTG-tolerant	43	*HLA-A*68:01* *HLA-B*58:01* *HLA-DRB1*13:01*	OR 19.22 (95% CI: 1.01–365), $P = 0.012$ OR 14.59 (95% CI: 0.74–289), $P = 0.037$ OR 8.5 (95% CI: 0.79–423), $P = 0.045$

(continued)

Table 3 (continued)

Study	Location	Culprit drugs	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Hung et al. (2010)	Taiwan	PHT, LTG, OXC	26 PHT-SJS/TEN 6 LTG-SJS 3 OXC-SJS	35	113 PHT-tolerant, 67 LTG-tolerant, 93 healthy controls	273	*HLA-B*15:02* *HLA-B*13:01* *HLA-Cw*08:01* *HLA-DRB1*16:02*	OR 5.1 (95% CI: 1.8–15.1), $P = 0.0041$ (PHT) NS (LTG-SJS) OR 80.7 (95% CI: 3.8–1714.4), $P = 8.4 \times 10^{-4}$ (OXC) OR 3.7 (95% CI: 1.4–10.0), $P = 0.0154$ (PHT) OR 3.0 (95% CI: 1.1–7.8), $P = 0.0281$ (PHT) OR 4.3 (95% CI: 1.4–12.8), $P = 0.0128$
Hu et al. (2011)	China	OXC	Drug exanthem	9	9 OXC-tolerant 72 healthy controls	81	*HLA-B*15:02*	NS against OXC-tolerant controls OR 8.8 (95% CI: 1.853–41.790), $P = 0.011$ (healthy)
Shi et al. (2011)	China	LTG	2 SJS 11 drug exanthem	13	28 LTG-tolerant 264 healthy controls	292	*HLA-B*	No significant association detected
He et al. (2012)	China	OXC	Drug exanthem	14	OXC-tolerant	35	*HLA-B*	No significant association detected
McCormack et al. (2012)	UK (GWAS)	LTG PHT	42 LTG-drug exanthem 3 LTG-DRESS 1 LTG-SJS 40 PHT-drug exanthem 4 PHT-DRESS	86	Healthy controls	1296	NA	No significant association detected
Lv et al. (2013)	China	OXC	Drug exanthem	14	28 OXC-tolerant 1236 population controls	1264	*HLA-B*38:02*	OR 6.239 (95% CI: 1.783–22.460), $P = 0.018$ (healthy controls)

Li et al. (2013)	China	CBZ LTG	40 CBZ-drug exanthem 43 LTG-drug exanthem	83	52 CBZ-tolerant 42 LTG-tolerant 72 healthy controls	166	*HLA-A*02:01* *HLA-DRB1*14:05*	$P = 0.033$ $P = 0.003$ Increased in CBZ-drug exanthem vs. CBZ-tolerant
							*HLA-B*58:01* *HLA-DRB1*03:01*	$P = 0.037$ $P = 0.024$ Reduced in CBZ-drug exanthem vs. CBZ-tolerant
							*HLA-A*30:01* *HLA-B*13:02*	$P = 0.013$ $P = 0.013$ Increased in LTG-drug exanthem vs. LTG-tolerant
							*HLA-A*33:03*	$P = 0.048$ Reduced in LTG-drug exanthem vs. LTG-tolerant
Chung et al. (2014)	Taiwan Japan Malaysia (GWAS)	PHT	61 SJS/TEN 44 DRESS 78 drug exanthem	183	130 PHT-tolerant 3655 healthy controls	3785	*CYP2C9*3*	OR 12 (95% CI: 6.6–20), $P = 1.1 \times 10^{-17}$
Manuyakorn et al. (2013)	Thailand	PB PHT CBZ	18 PB-DRESS, 2 PB-SJS/TEN 15 PHT-DRESS, 2 PHT-SJS/TEN 3 CBZ-SJS	40	PB-, PHT- and CBZ-tolerant controls	40	*CYP2C19*2*	OR 4.5 (95% CI: 1.17–17.37), $P < 0.03$ (PB) Not significant with PHT or PB No association *HLA-B*15:02*
Fricke-Galindo et al. (2014)	Mexico	CBZ PHT LTG	4 CBZ-drug exanthem 1 PHT-drug exanthem 10 LTG-drug exanthem 4 LTG-SJS 1 CBZ/PHT-drug exanthem	20	31 AED-tolerant 225 healthy volunteers	256	*HLA-A*02:01:01/ B*35:01:01/C*04:01:01*	$P_c = 0.0048$ (LTG-tolerant) $P < 0.0001$ (healthy) Increased in LTG-MPE vs. tolerant and healthy controls
							*HLA-C*08:01*	$P_c = 0.0179$ (PHT-tolerant) $P_c < 0.0001$ (healthy) Increased in PHT-MPE vs. tolerant and healthy controls

(continued)

Table 3 (continued)

Study	Location	Culprit drugs	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Wang et al. (2014)	China	CBZ OXC PHT LTG	1 CBZ-TEN 3 CBZ-drug exanthem 1 OXC--drug exanthem 3 LTG-drug exanthem 1 PHT-SJS 1 PHT-drug exanthem	10	AED-tolerant	50	*HLA-A*24:02*	OR 0.130 (95% CI: 0.015–1.108), $P = 0.04$
Sun et al. (2014)	China	CBZ OXC PB	4 CBZ-SJS 2 CBZ-DRESS 5 CBZ-drug exanthem 1 OXC-SJS 3 OXC-drug exanthem 1 PB-SJS 1 PB-drug exanthem	17 (paediatrics)	32 AED-tolerant 38 healthy volunteers	70	*HLA-B*15:02*	OR 6.25 (95% CI: 1.06–36.74), $P = 0.043$ (tolerant controls) OR 4.86 (95% CI: 1.01–23.47), $P = 0.049$ (healthy controls) Above only for patients with SJS
Suvichapanich et al. (2015)	Thailand	PHT PB	2 PHT-SJS/TEN 15 PHT-DRESS 2 PB-SJS/TEN 18 PB-DRESS	37 (paediatric)	16 PHT-tolerant 19 PB-tolerant 396 healthy volunteers	431	*CYP2C9*3*	OR 14.52 (95% CI: 1.18–∞), $P = 0.044$ (tolerant controls) OR 4.43 (95% CI 1.39–13.97), $P = 0.016$ (healthy controls)

Tassaneeyakul et al. (2016)	Thailand	PHT	39 SJS/TEN 21 DRESS	60	PHT-tolerant	92	*HLA-B*56:02*	OR 10.40 (95% CI: 1.12–96.31), $P = 0.0274$ (SJS/TEN)
							*HLA-C*14:02*	OR 6.49 (95% CI: 1.59–26.62), $P = 0.0077$ (SJS/TEN)
							*HLA-B*51:01*	OR 4.81 (95% CI: 1.32–17.54), $P = 0.0163$ (SJS/TEN) OR 5.18 (95% CI: 1.18–22.74), $P = 0.0381$ (DRESS)
							*HLA-B*38:02*	OR 3.70 (95% CI: 1.19–11.51), $P = 0.0431$ (SJS/TEN)
							*HLA-B*58:01*	OR 3.15 (95% CI: 1.11–8.91), $P = 0.0431$ (SJS/TEN)
							*HLA-A*33:03*	OR 2.70 (95% CI: 1.10–6.63), $P = 0.0495$ (SJS/TEN)
							*CYP2C9*3*	OR 4.30 (95% CI: 1.41–13.09), $P = 0.0133$ (SJS/TEN)
Yampayon et al. (2017)	Thailand	PHT	15 SJS 21 DRESS	36	PHT-tolerant	100	*CYP2C9*3*	OR 5.70 (95% CI: 1.39–23.36), $P = 0.0251$ (SJS)
							*HLA-B*13:01*	OR 6.76 (95% CI: 2.42–18.85), $P = 0.0003$ (DRESS)
							*HLA-B*56:02/04*	OR 38.03 (95% CI: 1.88–767.19), $P = 0.0046$ (DRESS)
							*CYP2C19*3*	OR 4.47 (95% CI: 1.09–18.36), $P = 0.0478$, (DRESS)
Chen et al. (2017)	Taiwan/ Thailand	OXC	20 SJS/TEN 6 DRESS 22 drug exanthem 2 bullous	50	OXC-tolerant	101	*HLA-B*15:02*	OR 27.90 (95% CI: 7.84–99.23), $P = 1.87 \times 10^{-10}$ (SJS)

(continued)

Table 3 (continued)

Study	Location	Culprit drugs	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Shi et al. (2017)	China	CBZ LTG PHT	56 CBZ-SJS/TEN 22 LTG-SJS/TEN 13 PHT-SJS/TEN	81	AED-tolerant	322	*HLA-B*15:02*	OR 12.37 (95% CI 6.16–24.86), $P = 5.63 \times 10^{15}$ (CBZ only)
							*HLA-A*24:02*	OR 3.15 (95% CI: 1.86–5.32), $P = 1.02 \times 10^{-5}$ (pooled analysis—CBZ, LTG and PHT)
Ramírez et al. (2017)	Spain	CBZ LTG PHT PB	2 CBZ-SJS/TEN 4 CBZ-DRESS 3 LTG-SJS/TEN 3 LTG-DRESS 9 PHT-SJS/TEN 5 PHT-DRESS	26	61 AED-tolerant 253 healthy volunteers	314	*HLA-A*02:01/Cw15:02*	OR 14.75 (95% CI: 1.54–167.00), $P = 0.009$ (PHT-SJS/TEN vs. tolerant controls)
							*HLA-B*38:01*	OR 13.81 (95% CI: 2.18–98.04), $P = 0.002$ (PHT/LTG-SJS/TEN vs. tolerant controls) OR 115.0.0 (95% CI: 4.68–81.09), <0.001 (LTG-SJS/TEN vs. tolerant controls)
							*HLA-A*11:01*	OR 36.33 (95% CI: 1.54–24.72), $P = 0.005$ (CBZ-SJS/TEN vs. tolerant controls)
							*HLA-A*24:02*	OR 23.50 (95% CI: 2.49–553.98), $P = 0.001$ (PHT/LTG-DRESS vs. tolerant controls) OR 27.77 (95% CI: 1.5–17.33), $P = 0.005$ (LTG-DRESS vs. tolerant controls)
							*HLA-A*31:01*	OR 29.50 (95% CI: 1.73–747.87), $P = 0.033$, (CBZ-induced DRESS vs. tolerant controls)

Chang et al. (2017)	Malaysia	PHT	13 SJS/TEN 3 DRESS	16	32 PHT-tolerant 300 healthy volunteers	332	*HLA-B*15:13*	OR 11.28 (95% CI: 2.25–56.60), $P = 0.003$ (SJS/TEN vs. tolerant controls) OR 59.00 (95% CI: 2.49–1395.74), $P = 0.003$ (DRESS vs. tolerant controls)
							*HLA-B*15:02*	OR 5.71 (95% CI: 1.41–23.10), $P = 0.016$ (SJS/TEN vs. tolerant controls)
Devi (2018)	India	PHT	SJS/TEN	8	PHT-tolerant	11	*HLA-B*15:02*	Not significant
McCormack et al. (2018)	Europe/ China (GWAS)	CBZ LTG PHT	180 CBZ-drug exanthem 134 LTG-drug exanthem 74 PHT-drug exanthem	323	1066 CBZ-tolerant 844 LTG-tolerant 530 PHT-tolerant	1321	*CHFR4 (rs78239784)*	OR 7 (95% CI: 3.2–16), $P = 4.5 \times 10^{-11}$ (PHT-MPE)
							*HLA-A*31:01*	OR 8.0 (95% CI: 4.10–15.80), $P = 1.2 \times 10^{-9}$) (CBZ-SCAR)
Manuyakorn et al. (2020)	Thailand (paediatric)	PHT	17 DRESS 5 SJS/TEN	22	60 PHT-tolerant 649 healthy volunteers	709	*HLA-B*51:01*	OR 5.83 (95% CI: 1.36–25.00), $P = 0.022$ (DRESS)
							*HLA-C*14:02*	OR 5.85 (95% CI: 1.16–29.35), $P = 0.039$ (DRESS)
							*HLA-B*38:02*	OR 12.67 (95% CI: 1.50–106.89), $P = 0.044$ (SJS/TEN)

AED antiepileptic drug, *CBZ* carbamazepine, *DRESS* drug reaction with eosinophils and systemic symptoms, *GWAS* genome-wide association study, *LTG* lamotrigine, *OXC* oxcarbazepine, *OR* odds ratio, *PB* phenobarbitone, *PHT* phenytoin, *SCAR* severe cutaneous adverse reaction, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

In European patients, two studies have reported significant association between *HLA-B*38:01* and lamotrigine-induced SJS/TEN (Lonjou et al. 2008; Ramírez et al. 2017). However, the numbers of patients in both studies were relatively small with 17 (Lonjou et al. 2008) and 3 cases (Ramírez et al. 2017) of lamotrigine-induced SJS/TEN, respectively. A GWAS in Europeans was unable to detect any significant associations in patients presenting mainly with lamotrigine-induced drug exanthem (McCormack et al. 2012). A study from the UK with 22 patients presenting with either lamotrigine-induced SJS/TEN (n = 10) or DRESS (n = 12) did not detect any significant HLA associations (Kazeem et al. 2009). Several studies in patients from Taiwan (Hung et al. 2010) and China (Shi et al. 2011, 2017) were also unable to detect an association between lamotrigine hypersensitivity and *HLA-B*15:02*. Given the small numbers studied, and the contradictory data, there is no good evidence to suggest that genetic screening should be carried out before the use of lamotrigine. The only factor that has been shown to reduce the incidence of lamotrigine cADRs is to start at a low dose and escalate slowly, especially in patients on concomitant sodium valproate.

The association between *HLA-B*15:02* and susceptibility to phenytoin-induced SJS/TEN is unclear. One study in Thai patients and a second study from Taiwan detected a significant association between *HLA-B*15:02* and phenytoin-SJS/TEN (Locharernkul et al. 2008; Hung et al. 2010). Subsequent studies in Thai (Tassaneeyakul et al. 2016), Chinese (Shi et al. 2017) and Indian (Devi 2018) patients were unable to replicate the association. Phenytoin is primarily metabolised by CYP2C9, and loss-of-function mutations (e.g. *CYP2C9*2/*3*) reduce metabolism by 25–50% and have been associated with increased adverse events, since phenytoin has a narrow therapeutic range and a nonlinear pharmacokinetic profile (Silvado et al. 2018). A GWAS in 183 Taiwanese, Japanese and Malaysian patients with phenytoin-induced SJS/TEN, DRESS and drug exanthem reported a significant association with carriage of *CYP2C9*3* (Chung et al. 2014). Interestingly, the authors were able to detect delayed clearance of plasma phenytoin in patients with severe cADR providing a mechanistic link to the manifestation of hypersensitivity. The association between *CYP2C9*3* and phenytoin hypersensitivity was replicated in a cohort of paediatric patients with phenytoin-SJS/TEN and two further cohorts of Thai patients with phenytoin-induced DRESS and SJS/TEN (Tassaneeyakul et al. 2016; Suvichapanich et al. 2015; Yampayon et al. 2017). The association was not detected in a GWAS of 44 European patients presenting primarily with phenytoin-induced drug exanthem (n = 40) (McCormack et al. 2012). A more recent GWAS in both European and Han Chinese patients reported that an intronic variant in the complement factor H-related 4 gene (*CFHR4*), rs78239784, was associated with phenytoin-induced drug exanthem (McCormack et al. 2018). These results suggest that aberrant complement activation may play a role as a potential causal mechanism in a subset of phenytoin-sensitive patients. The genetic predisposition to phenytoin hypersensitivity thus presents a much more complex picture than carbamazepine, with a possibility of an association with *HLA-B*15:02*, *CYP2C9*3* and *CFH*. Given the low use of phenytoin now, any further studies will have to combine forces worldwide to have adequate statistical power to detect genetic variants of low effect size.

The CPIC recommends consideration of genotyping for *HLA-B*15:02* in patients considering phenytoin therapy regardless of ethnicity. If patients are positive for *HLA-B*15:02,* alternative AEDs should be considered. Where available, genotyping for *CYP2C9* should also be considered for patients who are *HLA-B*15:02* negative. The CPIC also make recommendations for dose adjustments depending on *CYP2C9* genotype (Caudle et al. 2014). Screening for *HLA-B*15:02* prior to phenytoin therapy was found to be cost-effective in a population from Singapore as part of screening for both phenytoin and carbamazepine (Dong et al. 2012). However, it was not cost-effective based on patient data from Hong Kong (Chen et al. 2016).

5 Allopurinol Hypersensitivity and *HLA-B*58:01*

Allopurinol is a xanthine oxidase inhibitor used in the treatment of gout (Ramasamy et al. 2013). Allopurinol hypersensitivity can manifest as severe cADRs including SJS/TEN and DRESS with an incidence of 0.69 per 1000 person years (Kim et al. 2013). The *HLA-B*58:01* allele has been significantly associated with susceptibility to multiple phenotypes of allopurinol hypersensitivity in populations globally (Table 4).

The association between *HLA-B*58:01* and allopurinol hypersensitivity was first reported in a Taiwanese population (Hung et al. 2005). Patients with severe cutaneous adverse reactions (SJS/TEN and DRESS) were included in this cohort. Subsequent studies in Korean (Kang et al. 2011), Japanese (Niihara et al. 2013), Portuguese (Gonçalo et al. 2013) and Chinese patients (Cheng et al. 2015) replicated the association between carriage of *HLA-B*58:01* and susceptibility to severe cutaneous manifestations of allopurinol hypersensitivity. Several authors have

Table 4 Studies that have reported genetic variants associated with allopurinol hypersensitivity

Study	Location	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Hung et al. (2005)	Taiwan	3 TEN 5 SJS/TEN 13 SJS 30 DRESS	51	135 allopurinol tolerant 93 healthy subjects	228	*HLA-B*58:01*	OR 580.3 (95% CI: 34.4–9780.9), $P_c = 4.7 \times 10^{-24}$ (tolerant) OR 393.51 (95% CI: 23.23–6665.26), $P_c = 8.1 \times 10^{-18}$ (healthy)
Lonjou et al. (2008)	Europe	SJS/TEN	31	Healthy controls	1822	*HLA-B*58:01*	OR 61 (95% CI: 32–118), $P < 10^{-8}$
Kaniwa et al. (2008)	Japan	SJS/TEN	10	Healthy controls	493	*HLA-B*58:01*	OR 40.8 (95% CI: 10.5–158.9), $P < 0.0001$
Tassaneeyakul et al. (2009)	Thailand	SJS/TEN	27	Allopurinol tolerant	54	*HLA-B*58:01*	OR 348.3 (95% CI: 19.2–633.6), $P = 1.6 \times 10^{-13}$
Kang et al. (2011)	Korea	20 DRESS 5 SJS/TEN	25	Allopurinol tolerant	57	*HLA-B*58:01*	OR 97.8, $P_c = 2.45 \times 10^{-11}$
						*HLA-Cw*03:02*	OR 82.1, $P_c = 9.39 \times 10^{-11}$
						*HLA-A*33:03*	OR 20.5, $P_c = 3.31 \times 10^{-6}$
Cao et al. (2012)	China	13 SJS/TEN 3 DRESS 22 drug exanthem	38	63 allopurinol tolerant 572 healthy controls	635	*HLA-B*58:01*	OR 580.07 (95% CI: 32.18–10,456.8), $P = 7.01 \times 10^{-18}$ (tolerant) OR 471.09 (95% CI: 28.66–7744.39), $P = 3.15 \times 10^{-38}$ (healthy)
Tohkin et al. (2013)	Japan (GWAS)	SJS/TEN	14	Healthy controls	991	*HLA-B*58:01*	OR 66.8 (95% CI: 19.8–225.0), $P = 2.44 \times 10^{-8}$
Niihara et al. (2013)	Japan	3 SJS 4 erythema multiforme	7	Allopurinol tolerant	25	*HLA-B*58:01*	OR 65.6 (95% CI: 2.9–1497.0), $P = 9.733 \times 10^{-4}$

(continued)

Table 4 (continued)

Study	Location	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Gonçalo et al. (2013)	Portugal	6 SJS 9 DRESS 6 drug exanthem	31	Allopurinol tolerant	23	*HLA-B*58:01*	OR 99.59 (95% CI 17.91–553.72) (SJS) OR 85.36 (95% CI: 32.52–224.04) (HSS) Not significant for drug exanthem
Cheng et al. (2015)	China	11 TEN 7 SJS/TEN 33 SJS 41 DRESS	92	75 allopurinol tolerant 99 healthy controls	174	*HLA-B*58:01*	OR 127.6 (95% CI: 40.85–398.61), $P = 3.49 \times 10^{-30}$ (tolerant) OR 154.86 (95% CI: 50.86–471.53). $P = 5.06 \times 10^{-36}$ (healthy)
Sukasem et al. (2016)	Thailand	13 SJS/TEN 10 DRESS 7 drug exanthem	30	100 allopurinol tolerant 1095 healthy controls	1195	*HLA-B*58:01*	OR 696.00 (95% CI: 74.81–6475.01), $P < 0.001$ (all phenotypes vs. tolerant) OR 579.00 (95% CI: 29.50–11362.67), $P < 0.001$ (SJS/TEN vs. tolerant) OR 430.33 (95% CI: 22.64–8958.88), $P < 0.001$ (HSS vs. tolerant) OR 144.00 (95% CI: 13.85–1497.03), $P < 0.001$ (drug exanthem vs. tolerant)

DRESS drug reaction with eosinophilia and systemic symptoms, *GWA* genome-wide association study, *OR* odds ratio, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

reported associations between allopurinol-induced SJS/TEN and presence of *HLA-B*58:01* in European (Lonjou et al. 2008), Japanese (Kaniwa et al. 2008) and Thai patients (Tassaneeyakul et al. 2009). A GWAS in 14 Japanese patients with allopurinol-induced SJS/TEN reported a significant association with *HLA-B*58:01* when compared with healthy volunteers (Tohkin et al. 2013).

A study in 38 Chinese patients with allopurinol hypersensitivity included 22 subjects presenting with allopurinol-induced drug exanthem and detected a significant association between *HLA-B*58:01* and all phenotypes of allopurinol hypersensitivity (Cao et al. 2012). The association with drug exanthem was replicated in a Thai cohort of 30 patients with 7 subjects in the study presenting with allopurinol-induced drug exanthem (Sukasem et al. 2016). However, a separate study in Portuguese patients with 6 allopurinol-induced drug exanthem patients was unable to detect a significant association with *HLA-B*58:01* (Gonçalo et al. 2013). Taken together the association between allopurinol-induced drug exanthem and *HLA-B*58:01* requires further investigation.

A large prospective study in 2926 Taiwanese patients screened patients for carriage of *HLA-B*58:01* prior to treatment with allopurinol (Ko et al. 2015). Subjects who tested positive for *HLA-B*58:01* were prescribed alternative treatment: no subjects in the study developed a serious cADR to allopurinol. A significant difference was detected as 7 cases of serious cADRs would

have been predicted based on historical incidence (0.3% per year, 95% CI: 0.28–0.31%; $P = 0.026$). A second prospective study in Korea genotyped 542 patients with chronic renal insufficiency for carriage of *HLA-B*58:01* before commencing allopurinol (Park et al. 2019). 39 patients (7.2%) were positive for *HLA-B*58:01* and received febuxostat as an alternative to allopurinol. There were no episodes of serious cADRs in the study and when compared with historical controls (0.95%), the reduction was statistically significant ($P = 0.029$).

In Europe the label for allopurinol advises prescribers to consider screening for *HLA-B*58:01* before starting treatment in patient subgroups where the prevalence of the allele is known to be high with specific reference to Han Chinese, Thai and Korean patients (https://www.medicines.org.uk/emc/product/6007/smpc). Prospective screening for *HLA-B*58:01* was reported to be cost-effective in Taiwan (Ke et al. 2017) and for African-Americans and Asians in the US (Jutkowitz et al. 2017). It was not cost-effective in the UK due to the costs of genetic testing versus the cost of alternative urate-lowering medicines (Plumpton et al. 2017). Screening for *HLA-B*58:01* was also not cost-effective in a Malaysian population as 556 tests would need to be conducted to avoid one case of SJS/TEN and the alternative treatment (probenecid) was associated with lower efficacy (Chong et al. 2018).

6 Dapsone Hypersensitivity

Dapsone is a sulfone drug with both antimicrobial and anti-inflammatory properties used in the treatment of a range of conditions including leprosy, dermatitis herpetiformis and linear IgA dermatosis (Ghaoui et al. 2020). Its use is complicated by serious idiosyncratic cutaneous adverse effects including SJS/TEN and dapsone hypersensitivity syndrome (the term used to indicate a dapsone-induced DRESS) (Tangamornsuksan and Lohitnavy 2018). Dapsone hypersensitivity syndrome occurs in 0.5–3.6% of patients up to 6 weeks after starting treatment and its clinical presentation includes fever and systemic inflammation (Liu et al. 2019). The mortality associated with dapsone hypersensitivity syndrome has been reported to be between 9.9–11.1% (Lorenz et al. 2012; Tian et al. 2012).

Four studies have reported a significant association between carriage of *HLA-B*13:01* and severe dapsone-induced cutaneous reactions (Table 5). A GWAS in Chinese patients reported a significant association between *HLA-B*13:01*

Table 5 Studies that have reported genetic variants associated with dapsone hypersensitivity

Study	Location	Case phenotype	Cases (*n*)	Control phenotype	Controls (*n*)	Significant associations	Statistical analyses
Wang et al. (2013)	China	DHS	20	102 Dapsone tolerant 96 healthy controls	198	*HLA-B*13:01*	OR 122.1 (95% CI: 23.5–636.2), $P_c = 6.038 \times 10^{-12}$ (tolerant) OR 69.6 (95% CI: 14.2–341.0), $P_c = 1.961 \times 10^{-11}$ (healthy)
Zhang et al. (2013)	China (GWAS)	DHS	76	Dapsone tolerant	1034	*HLA-B*13:01*	OR 20.53 (95% CI: 11.55–36.48), $P = 6.84 \times 10^{-25}$
Tempark et al. (2017)	Thailand	4 SJS/TEN 11 DRESS	15	29 Dapsone tolerant 986 healthy controls	1015	*HLA-B*13:01*	OR 54 (95% CI: 7.96–366), $P = 0.0001$ (tolerant) OR 26.11 (95% CI: 7.27–93.75), $P = 0.0001$ (healthy)
Chen et al. (2018)	Taiwan Malaysia	7 HSS 1 Drug exanthem	8	Healthy controls	677	*HLA-B*13:01*	OR 24.82 (95% CI: 4.92–125.26), $P_c = 1.05 \times 10^{-3}$

DRESS drug reaction with eosinophilia and systemic symptoms, *DHS* drug hypersensitivity syndrome, *GWAS* genome-wide association study, *OR* odds ratio, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

and dapsone hypersensitivity syndrome (Zhang et al. 2013). A second study confirmed the association in a Chinese population (Wang et al. 2013). More recently, a study in Thai patients reported the association between *HLA-B*13:01* and dapsone-induced SJS/TEN and DRESS (Tempark et al. 2017). *HLA-B*13:01* was significantly associated with dapsone-induced DRESS in patients prescribed dapsone for inflammatory dermatoses (Chen et al. 2018). This study also provided evidence for the functional role of *HLA-B*13:01* in the pathogenesis of dapsone hypersensitivity syndrome.

Three of the studies also investigated the role of polymorphisms in CYP2C9 and NAT2 patients with dapsone hypersensitivity syndrome (Zhang et al. 2013; Wang et al. 2013; Chen et al. 2018). Altered clearance of dapsone has been hypothesised as a potential mechanism with CYP2C9 and NAT2 reported as the two main phase I enzymes responsible for dapsone metabolism (Hutzler et al. 2001). None of the studies were able to detect a significant association between polymorphisms in metabolism enzyme and susceptibility to dapsone hypersensitivity syndrome.

A prospective screening study in China screened 1512 patients with leprosy for *HLA-B*13:01* prior to commencing dapsone (Liu et al. 2019). Patients who were carriers for *HLA-B*13:01* did not receive dapsone. No patients in the *HLA-B*13:01* negative group developed dapsone hypersensitivity syndrome which was significantly lower than the expected 13 cases according to the historical incidence of 1% per year ($P = 2.05 \times 10^{-5}$). At present there are no cost-effectiveness studies for prospective genotyping of *HLA-B*13:01* in dapsone therapy.

7 Other Drugs

Pharmacogenetic associations have been reported with other drugs but the evidence for these associations is not as comprehensive as the examples outlined above. Trimethoprim–sulfamethoxazole is an anti-infective combination drug frequently prescribed for prophylaxis of opportunistic infections in patients with HIV (Suthar et al. 2015). Hypersensitivity to sulfamethoxazole has been hypothesised to result from reactive metabolites which form tissue haptens and stimulate drug-specific cytotoxic T cells (Naisbitt et al. 2001). Several studies have focused on polymorphisms in metabolism pathways including *NAT2* (Wolkenstein et al. 1995; Zielinska et al. 1998; Pirmohamed et al. 2000; O'Neil et al. 2002; Alfirevic et al. 2003), *GCLC* (Wang et al. 2012), *GSTM1* (Deloménie et al. 1997) and *GSTT1* (Deloménie et al. 1997), but results have been conflicting. Two studies have examined the relationship between HLA and susceptibility to trimethoprim–sulfamethoxazole hypersensitivity and reported potential associations with *HLA-B*38:01* and *HLA-B*38:02* in Europeans (Lonjou et al. 2008) and *HLA-B*15:02-C*08:01* in a Thai population (Kongpan et al. 2015). More recently, a case control study of 30 Thai patients with trimethoprim–sulfamethoxazole hypersensitivity (18 SJS/TEN and 12 DRESS) reported phenotype-specific associations with HLA alleles compared with tolerant controls (Sukasem et al. 2020). Carriage of *HLA-B*15:02* and *HLA-C*08:01* was significantly associated with trimethoprim–sulfamethoxazole-induced SJS/TEN, whereas *HLA-B*13:01* was significantly associated with trimethoprim–sulfamethoxazole-induced DRESS.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor used in the treatment of HIV (Podzamczer and Fumero 2001). Hypersensitivity to nevirapine has been associated with several HLA alleles. The most reliable association has been reported with *HLA-C*04:01* and nevirapine-SJS/TEN in a Malawian cohort (Carr et al. 2013). This association was replicated in a GWAS from sub-Saharan Africa (Carr et al. 2017). The study also suggested that ERAP2, but not ERAP1, may protect against the development of nevirapine-induced SJS/TEN. This finding requires replication but it is biologically plausible since ERAP enzymes are involved in immune activation, inflammation and antigenic peptide repertoire shaping (Saveanu et al. 2005). *HLA-Cw*04* has been associated with nevirapine-cADR in patients from Thailand (Likanonsakul et al. 2009)

and Han Chinese (Gao et al. 2012). *HLA-B*35:05* was significantly associated with nevirapine hypersensitivity in Thai (Chantarangsu et al. 2009), Indian (Umapathy et al. 2011) and Asian patients (Yuan et al. 2011). The *HLA-B*35:05* association appears to be ethnicity specific as it was not detected in black or white ethnicities (Yuan et al. 2011). In a large multi-ethnic study a SNP in CYP2B6 (516G>T) was associated with increased susceptibility to nevirapine hypersensitivity across all patient ethnicities (Yuan et al. 2011) but it was not replicated in a French study (Gozalo et al. 2011).

Vancomycin is an antibiotic that is active against gram positive microbes (including methicillin-resistant *S. aureus*) and accounts for nearly 40% of cases of drug-induced DRESS as part of an analysis of electronic health records (Wolfson et al. 2019). A study of 23 patients of predominantly European ancestry reported a significant association between carriage of *HLA-A*32:01* and vancomycin-induced DRESS (Konvinse et al. 2019). This association requires replication.

8 Discussion

Over the last 20 years there have been significant advances in our understanding of hypersensitivity reactions to drugs and the role of genetic susceptibility. The strongest genetic associations have been reported with HLA alleles leading to the development and recommendation of pharmacogenetic screening prior to commencing several medications. Prospective genotyping for *HLA-B*57:01* prior to commencing abacavir therapy was mandated for all patients with HIV by the EMA and FDA, a policy which has significantly reduced the incidence of abacavir hypersensitivity and been shown to be cost-effective (Hughes et al. 2004a; Cargnin et al. 2014).

Two strong HLA associations have been reported with susceptibility to carbamazepine (CBZ) hypersensitivity. *HLA-B*15:02* is both ethnicity and phenotype specific affecting only South East Asian populations and relevant only for CBZ-induced SJS/TEN. The second association, *HLA-A*31:01*, is a genetic marker in European, Japanese and Korean patients and is associated with all phenotypes of CBZ hypersensitivity including drug exanthem, DRESS and SJS/TEN (Yip et al. 2012). The variability in ethnic susceptibility is most likely to be secondary to variable carrier frequencies of risk HLA alleles in different populations. For example, the frequency of *HLA-B*15:02* in a prospective screening study from Taiwan was 7.7% (Chen et al. 2011) compared with < 1% in Caucasians and Japanese patients (www.allelefrequencies.net). In contrast the frequency of *HLA-A*31:01* in Europeans is around 3.9% (Genin et al. 2014) and 17.5% in a prospective Japanese study (Mushiroda et al. 2018). Prospective pharmacogenetic screening studies have demonstrated the clinical utility of *HLA-B*15:02* for reducing the incidence of CBZ-SJS/TEN (Chen et al. 2011) and *HLA-A*31:01* in decreasing overall rates of CBZ hypersensitivity (Mushiroda et al. 2018). The label for CBZ in the UK recommends screening for *HLA-B*15:02* in Han Chinese, Thai and other Asian populations whenever possible before starting treatment. The label mentions *HLA-A*31:01* but does not recommend *HLA-A*31:01* screening at present (https://www.medicines.org.uk/emc/product/1040/smpc). However, the label is out of date and does not take into account more recent studies including the prospective study in Japan. Therefore, the most recent guideline from the Clinical Pharmacogenetics Implementation Consortium (CPIC) has recommended prospective genotyping for both *HLA-B*15:02* and *HLA-A*31:01* prior to starting carbamazepine. If patients are positive for *HLA-B*15:02* or *HLA-A*31:01* alternative aromatic antiepileptic drugs (AEDs) should be considered.

Due to the potential for cross-reactivity among structurally similar AEDs (e.g. oxcarbazepine, lamotrigine and phenytoin) studies have attempted to determine if specific HLA alleles can predict cross reactivity. Two studies in patients from Taiwan and Thailand reported a significant association between carriage of *HLA-B*15:02* and susceptibility to oxcarbazepine-SJS/TEN although the total number of cases is

small (n = 23) (Hung et al. 2010; Chen et al. 2017). The CPIC recommend *HLA-B*15:02* positive patients should avoid oxcarbazepine where alternatives are available (Phillips et al. 2018).

Phenytoin is another aromatic anticonvulsant associated with serious cutaneous hypersensitivity reactions. Studies in Han Chinese (n = 26) and Thai (n = 5) patients have reported significant association between *HLA-B*15:02* and susceptibility to phenytoin-induced SJS/TEN (Locharernkul et al. 2008; Hung et al. 2010). The CPIC guideline recommends that patients positive for *HLA-B*15:02* should avoid phenytoin (Caudle et al. 2014). Several studies have been unable to detect an association between carriage of *HLA-B*15:02* and lamotrigine-induced hypersensitivity (Table 3). Taken together, patients who are carriers for *HLA-B*15:02* should avoid carbamazepine, oxcarbazepine and phenytoin.

Serious cutaneous adverse reactions to allopurinol are significantly associated with carriage of the *HLA-B*58:01* allele among multiple ethnicities (Table 4). A prospective study in Taiwanese patients has demonstrated that prospective screening can significantly reduce severe allopurinol-induced hypersensitivity (Ko et al. 2015). The label for allopurinol in the UK recommends that screening should be considered before starting treatment in patients with Han Chinese, Thai or Korean descent (https://www.medicines.org.uk/emc/product/5693/smpc).

Serious hypersensitivity reactions to dapsone have been significantly associated with carriage of *HLA-B*13:01* in patients from Taiwan, China, Thailand and Malaysia (Table 5). A prospective screening study in China demonstrated a significant reduction in dapsone hypersensitivity if patients testing positive for *HLA-B*13:01* avoided dapsone (Liu et al. 2019). At present there is no mention of HLA testing in the dapsone drug label or recommendation from the CPIC.

HLAs are the most common genetic variants to be associated with drug hypersensitivity reactions. HLAs are highly polymorphic proteins that initiate immunity by presenting antigen-derived peptides to T cells (McCluskey and Peh 1999). Three models have been proposed to explain the role of MHC, T cell receptor and small molecule drugs: the hapten/prohapten model, the pharmacological interaction (p–i) model, and the altered peptide repertoire model. In the hapten model, the drug or metabolite binds irreversibly to self-proteins leading to the generation of chemically modified peptides that are presented in association with major histocompatibility antigens to T cell receptors leading to activation of the immune system (Park et al. 2001). The p–i concept hypothesises that drugs are able to bind non-covalently to either the MHC or T cell receptor activating the immune system (Pichler et al. 2006). Finally, in the altered peptide repertoire model drugs can bind to the antigen binding groove of HLA molecules leading to alteration of the repertoire of peptides that are presented, which may now include self-peptides (Illing et al. 2012). However, it is important to remember that carriage of the risk HLA allele is a necessary but insufficient factor to initiate the immunopathogenesis cascade as illustrated by patients who carry the risk allele but do not develop hypersensitivity reactions when treated with the offending drug. Other factors such as modifier genetic variants (e.g. ERAP), drug metabolism, viral reactivation and heterologous immunity could play a role (White et al. 2015).

Variation in drug metabolism has been hypothesised to predispose to hypersensitivity reactions through excess generation or reduced clearance of reactive metabolites. Interestingly, two reduced activity variants of CYP2C9 (*CYP2C9*2* and *CYP2C9*3*) have been associated with susceptibility to phenytoin hypersensitivity (Table 3). If patients are negative for *HLA-B*15:02* and intermediate or poor CYP2C9 metabolisers, the CPIC guideline recommends that clinicians should consider a reduction in the recommended starting dose by 25% and 50%, respectively (Caudle et al. 2014). A meta-analysis has reported a significant association between *CYP2C9*3* and phenytoin-induced SJS/TEN compared with tolerant controls (Wu et al. 2017).

There is emerging evidence to suggest that susceptibility to allopurinol hypersensitivity is not dependent just on carriage of *HLA-B*58:01* but also on plasma levels of oxypurinol (an active metabolite of allopurinol) and impaired renal

function (Chung et al. 2015). Similarly, in carbamazepine-induced SJS/TEN there is evidence to suggest that it is the major drug metabolite, carbamazepine epoxide, which is responsible for pathogenesis rather than the parent compound. In vitro studies have shown that both carbamazepine and carbamazepine epoxide can bind to *HLA-B*15:02* but only the epoxide leads to alteration of the peptide binding motif (Simper et al. 2018). Epoxide hydrolase is responsible for detoxification of carbamazepine epoxide and one study detected a SNP (c.337T>C) in *EPHX1* as being significantly associated with susceptibility to carbamazepine-SJS/TEN (He et al. 2014). These data suggest that susceptibility to drug hypersensitivity may involve a complex interplay between genetic variation in HLA and drug metabolism pathways as well as dose, drug interactions and unidentified physiological factors.

Despite substantial evidence and guidelines from organisations such as CPIC the clinical implementation of pharmacogenetic screening tests has been slow. A frequently cited reason for delayed uptake has been the lack of evidence from randomised control trials (RCTs). However, RCTs may not be practicable and can overlook important pharmacogenetic interactions (Huddart et al. 2019). A sample size of 1657 patients would be required to detect a drug-gene interaction at 80% power with an odds ratio of 2.0 and a minor allele frequency of 0.10 in control participants (Ross et al. 2012). It would be extremely difficult to conduct a study of this size in one centre and there is little financial incentive for pharmaceutical companies to revisit pharmacogenetic studies as many of the drugs with actionable pharmacogenetics are off patent. The level of evidence required for pharmacogenetic interventions is substantially different when compared with non-genetic tests. For example, modifications in drug exposure and dosages in patients secondary to hepatic or renal impairment do not require supporting evidence from RCTs to be added to a drug label. However, regulators typically require RCT data for pharmacogenetic variability (Pirmohamed and Hughes 2013) indicating a degree of genetic exceptionalism. To this end, guidelines from organisations such as CPIC and the Dutch Pharmacogenetics working group are evaluating all data and are beginning to recommend more wider use of genetic testing prior to starting some drugs.

We are also heading to an era where patients may already have pre-existing genomic data. For example, individuals may have been part of genome sequencing projects, such as the 100,000 Genomes Project in the UK, or may have paid for a personal genomic analysis from a commercial genetic testing company. Some hospitals especially in the US are undertaking pharmacogenomic panel tests in their patients, and including these data in electronic records, so that genetic data is available at the point of prescribing. This is termed pre-emptive genotyping and is likely to become more common practice in the future, as the costs of testing goes down and their availability increases.

In conclusion, genetic variability in drug metabolism pathways and HLAs have been significantly associated with susceptibility to drug hypersensitivity reactions. Pharmacogenetic screening has been successfully implemented into clinical practice for some associations leading to significant reduction in patient morbidity and mortality (e.g. abacavir and *HLA-B*57:01*). However, many of the pharmacogenetic associations which are present in guidelines are not mandated in drug labels leading to confusion. The advent of pre-emptive genetic approaches is likely to increase implementation of pharmacogenetic testing in clinical practice but will require better education and knowledge in prescribers and deployment of clinical decision support systems. For future studies and new drugs, researchers, clinicians, the pharmaceutical industry and regulators all need to work together to embed pharmacogenetics into the drug development process and harmonise evidence standards for drug choice and dosage recommendations. The clinical aspects of this work relies on accurate diagnosis of drug hypersensitivity syndromes with rigorous protocols for phenotyping cases. Integration of pharmacogenetics into the process which takes a drug from medicinal chemistry to prescription will inevitably improve patient outcomes.

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Mechanisms of Drug Hypersensitivity

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Abbreviations

ADR	Adverse drug reactions
APC	Antigen-presenting cells
CBZ	Carbamazepine
CCL	Chemokine (C–C motif) ligand
CTL	Cytotoxic T lymphocytes
CXCL8	Chemotactic chemokine (C–X–C motif) ligand 8
CYP2C	Cytochrome P450 2C
DH	Drug hypersensitivity
DRESS	Drug reaction with eosinophilia and systemic symptoms
FADD	Fas-associated death domain
GM-CSF	Granulocyte–macrophage colony-stimulating factor
HLA	Human leukocyte antigen
IFN	Interferon
IL	Interleukin
LTG	Lamotrigine
MCP	Monocyte chemotactic protein
MPE	Mild maculopapular exanthema
NK	Nature killer
NSAIDs	Nonsteroidal anti-inflammatory drugs
OXC	Oxcarbazepine
OXP	Oxypurinol
PHT	Phenytoin
RANTES	Regulated upon activation, normal T-cell expressed, and secreted
SAPLIP	Saposin-like protein
SCAR	Severe cutaneous adverse reactions
sFASL	Soluble Fas ligand
SJS	Stevens–Johnson syndrome
TCR	T-cell receptors
TEN	Toxic epidermal necrolysis
TNF-α	Tumor necrosis factor-α

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1 Introduction

Drug hypersensitivity reactions (DH) is a growing problem worldwide. These reactions are immune-mediated and are traditionally classified according to Gell and Coombs's criteria (Fig. 1) (Johansson et al. 2001). Type I reactions are immunoglobulin-E (IgE) mediated and their clinical presentations include urticaria, angioedema, bronchospasm, gastrointestinal symptoms, giddiness, and anaphylactic shock. They typically occur within the first hour of drug administration; hence, they are also known as immediate reactions (Montanez et al. 2017). Such reactions are

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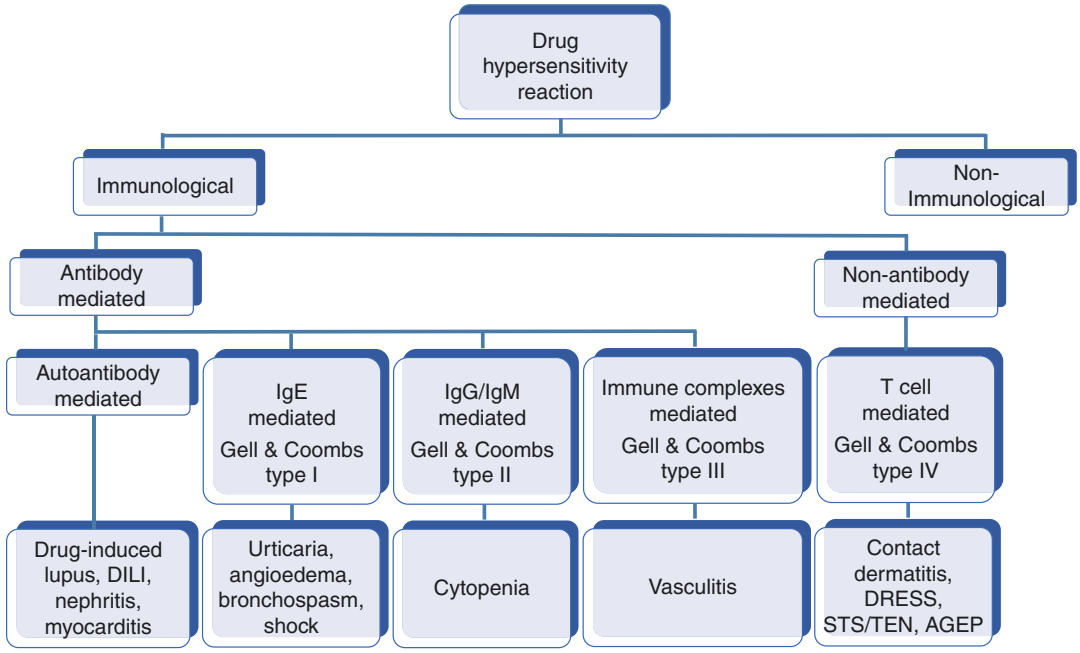

Fig. 1 Classification of pathomechanisms in drug hypersensitivity

more likely to be caused by small antigens (e.g., drug haptens), proteins, and high-molecular-weight peptides. Type II reactions, on the other hand, are usually IgG- and IgM-mediated. Drugs acting as antigens interact with membrane-bound IgG or IgM and the subsequent clearance by macrophages result in further cell destruction. Red blood cells, platelets, and neutrophils may also be involved in type II reaction. The incidence of type II reaction is relatively rare as the drug exposure needs to be of significant duration and dose in order for drug-specific antibodies to be produced. Type III reactions are mediated by antigen–antibody complexes. Circulating immune complexes formed by the binding of IgG (occasionally IgM) to the drug are deposited in various tissues, such as the blood vessels, joints, and renal glomeruli. These immune complexes activate the complement cascade and induce local inflammation, causing fever, urticaria, vasculitis, arthralgia, and serum sickness (Wedi 2010). Similar to type II reaction, type III reactions are less common and usually occur with prolonged drug usage. Lastly, type IV reactions are CD 4+ and CD8+ T-cell-mediated and these reactions usually take several days or even weeks to manifest following drug exposure. Recent studies have highlighted significant association between class I and/or II HLA alleles and T cell-mediated SCARs and this serves as a platform for screening and prevention of such reactions (Pichler 2002). The clinical presentation of type IV reactions ranges from maculopapular exanthem (MPE) to life-threatening SCARs (severe cutaneous adverse drug reactions), including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) (Valeyrie-Allanore et al. 2007).

2 Models of Drug Antigen Presentation

There are four hypotheses that have been proposed to explain the interactions between drug, HLA, and T cells (Fig. 2): (1) the "hapten–prohapten" theory, (2) the "p–i concept," (3) the "altered peptide repertoire" model, and (4) the

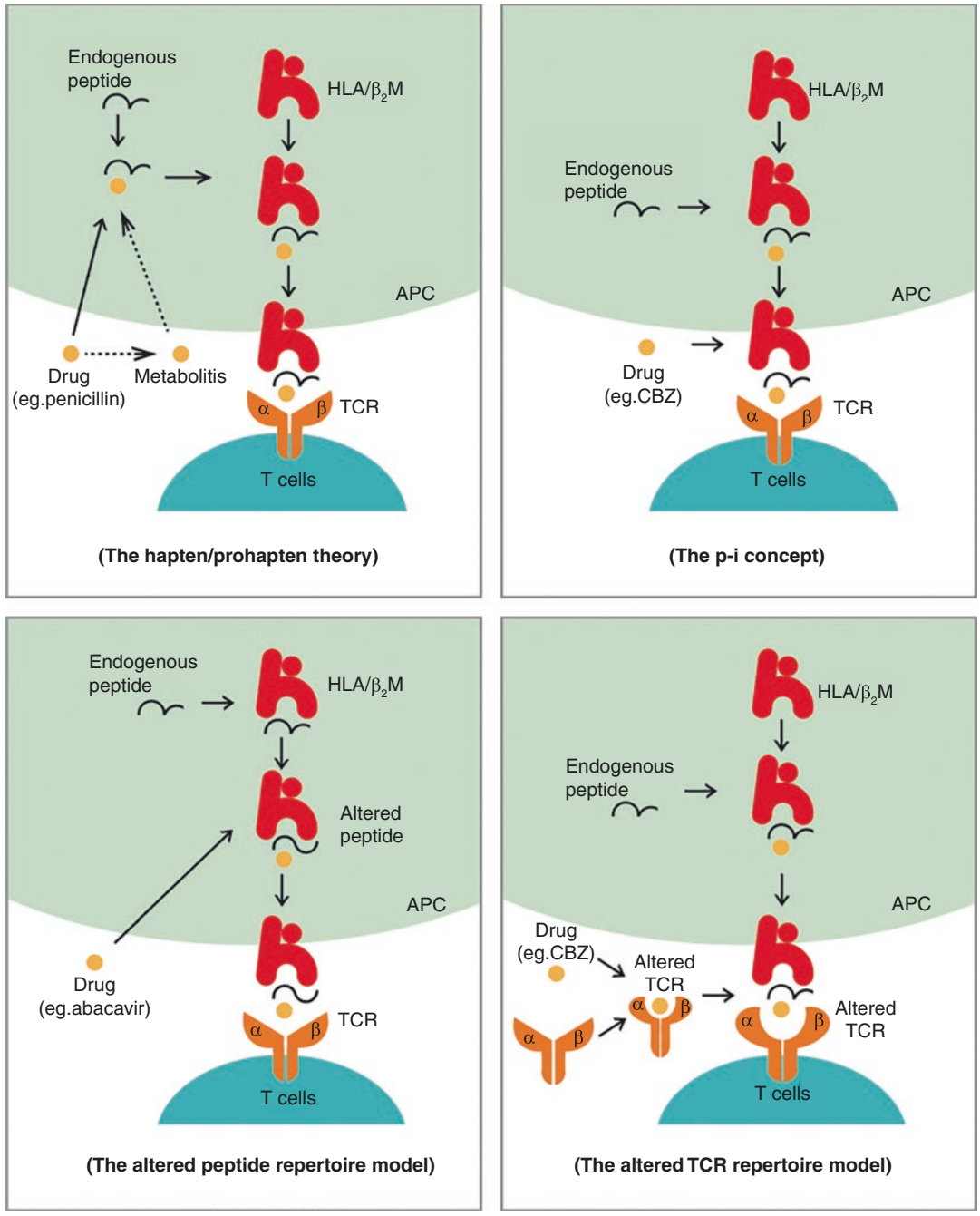

Fig. 2 Models of the interaction of human leukocyte antigen (HLA), drug, and T-cell receptor (TCR). (1) The "hapten–prohapten" theory. Drugs/metabolites bind covalently with the endogenous peptides that are processed conventionally in antigen-presenting cells (APC) to form the drug–HLA–TCR complex. (2) The "p–i" model theory. Drugs directly bind to the HLA–peptide complex or TCR, this response is independent on process in APC. (3) The "altered peptide repertoire" theory. Drugs bind to a specific altered peptide repertoire but may not directly bind to HLA, and thus interact with TCR to promote the drug-specific T-cell activation. (4) The "altered TCR repertoire" model. Drugs bind to TCR directly cause conformational change of TCR. This modified drug–TCR structure has the potential to bind HLA–self-peptide complex

"altered TCR repertoire" model (Valeyrie-Allanore et al. 2007; Watkins and Pichler 2013). In the hapten–prohapten theory, a drug or its metabolite interacts with endogenous peptide covalently to form an antigenic hapten complex. In this model, the recognition of the hapten complex by T cells results in T cell activation and downstream responses (Padovan et al. 1997). In the "p–i" model, the drug can directly bind to the self-peptide when the peptide is presented by the antigen-presenting cells (APC). For example, carbamazepine (CBZ) can directly interact with HLA-B*15:02 protein. Appropriate loading of endogenous peptides to HLA-B*15:02 is required for the stability of the HLA complex to present CBZ to T cells. Unlike the hapten model, this binding occurs without intracellular antigen presentation or drug metabolism (Wei et al. 2012). In the "altered peptide repertoire" model, binding of the drug (e.g., abacavir) to HLA protein results in a conformational change, thereby altering peptide specificity of HLA binding (Ostrov et al. 2012). Finally, in the "altered TCR repertoire" model, binding of the drug to the specific TCR results in a secondary structural alteration of the TCR, which results in the interaction with HLA-self-peptides (Watkins and Pichler 2013). For example, upon specific drug binding, the drug–TCR complex will trigger activation and expansion of cytotoxic T lymphocytes (CTL) (Naisbitt et al. 2003) with downstream production of cytotoxic proteins (Chung et al. 2008).

3 Genetic Factors in Drug Hypersensitivity

Most cases of drug hypersensitivity are unpredictable. However, recent publications have shown that in some reactions, genetic variants, particularly those involved in HLAs and drug-metabolizing enzymes may play a role. Screening for these at-risk variants is a potential preventive strategy. The genetic factors involved in both immediate and delayed type reactions are summarized below.

3.1 Genetic Factor in Immediate-Type Drug Hypersensitivity

Immediate-type drug hypersensitivity reactions arising from the use of β-lactams, aspirin, and other NSAIDs have been shown to have pharmacogenetics association. HLA genes such as HLA-DR4, HLA-DR9, HLA-DR14.1, and HLA-DR17 have been linked to penicillin-induced immediate hypersensitivity reactions in Chinese (Yang et al. 2006), whereas HLA-DRA rs7192 and HLA-DRA rs8084 are associated with penicillin/amoxicillin-induced immediate hypersensitivity reactions in Spanish and Italians (Gueant et al. 2015). The association between *DRB1*13:02* and *HLA-DRB1*06:09* with aspirin-induced urticaria and angioedema has been reported (Kim et al. 2006). In addition, DRB1∗11 has been shown to be associated with aspirin/NSAIDs-induced urticaria/angioedema and hypotension/laryngeal edema (Quiralte et al. 1999). Interestingly, both aspirin/NSAID-induced chronic idiopathic urticaria and aspirin/NSAID-induced hypersensitivity reactions are associated with HLA-B44 and HLA-Cw5 (Pacor et al. 2006). Besides HLA genes, genetic variants of cytokines (such as TGFB1, TNF, and IL18) have also been shown to mediate β-lactams and aspirin-induced hypersensitivity (Kim et al. 2011a; Choi et al. 2009; Qiao et al. 2005; Yang et al. 2005). The genes belonging to arachidonic acid pathway (ALOX15, ALOX5, ALOX5AP, CYSLTR1, PTGDR, and TBXAS1) are also involved in NSAIDs-mediated hypersensitivity (Cornejo-Garcia et al. 2012; Oussalah et al. 2016).

3.2 Genetic Factor in Delayed-Type Drug Hypersensitivity

As shown in Fig. 3, following exposure to an offending drug, a drug–peptide complex is formed and this interacts with a specific HLA of an antigen-presenting cells. This is subsequently recognized by the TCR of T cells, resulting in the initiation of delayed-type drug hypersensitivity.

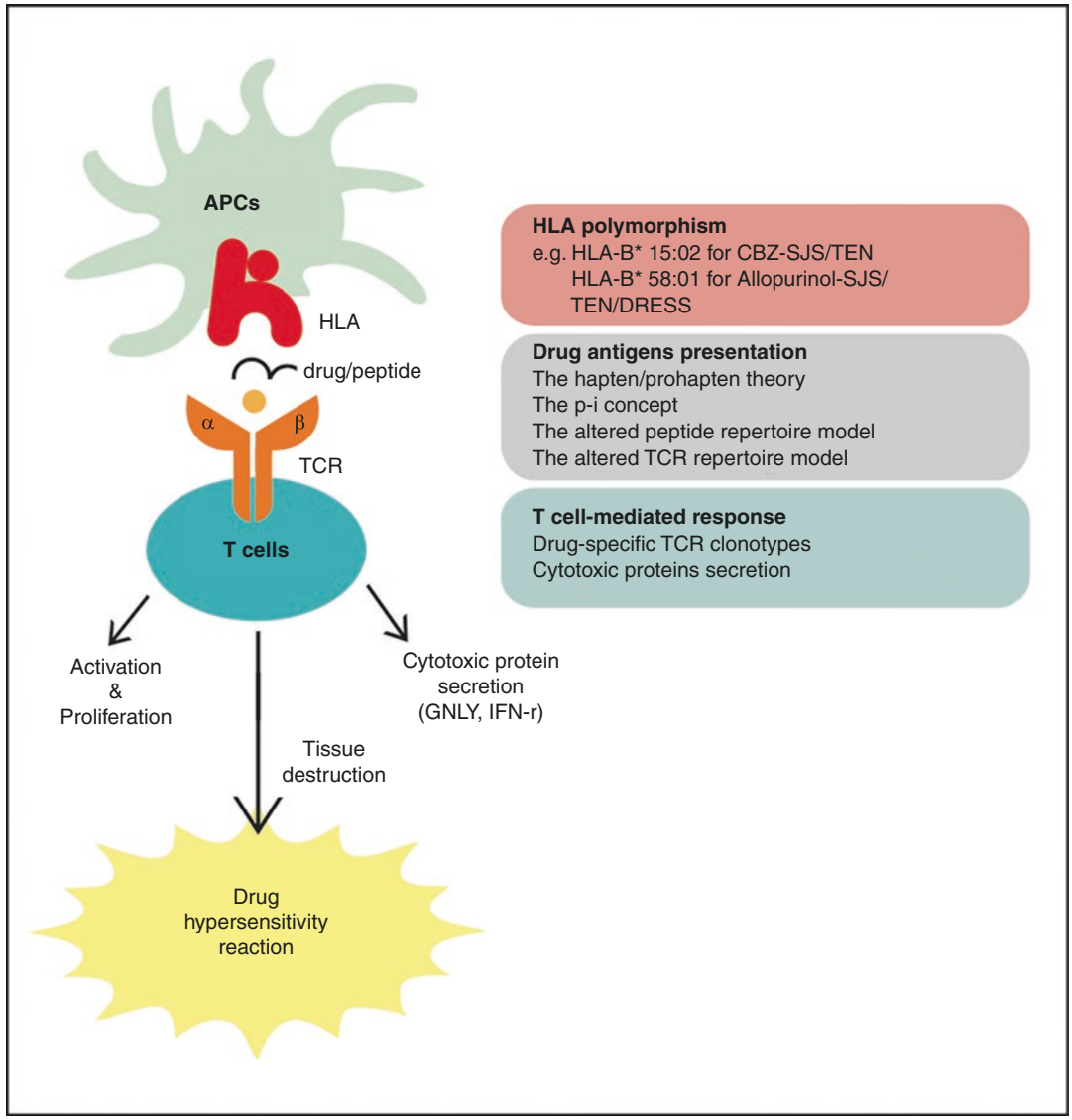

Fig. 3 The pathogenic factors involved in drug hypersensitivity. Different drug-antigen presentation mechanisms and pathogenic factors influence the development of drug hypersensitivity. These include genetic polymorphisms in human leukocyte antigen (HLA), drug antigen presentation of specific HLA/drug/TCR complex and T cell-mediated immune responses such as cytotoxic protein secretion cause tissue destruction

Various HLA alleles have been reported in association with SJS/TEN. Such associations are drug and ethnicity-specific and are summarized in Table 1 (Yang et al. 2006; Gueant et al. 2015; Kim et al. 2006; Quiralte et al. 1999; Pacor et al. 2006; Romano et al. 1998; Mallal et al. 2002; Hung et al. 2005; Martin et al. 2005; Littera et al. 2006; Gatanaga et al. 2007; Locharernkul et al. 2008; Lonjou et al. 2008; Saag et al. 2008; Chantarangsu et al. 2009; Kazeem et al. 2009; Hung et al. 2010; Ikeda et al. 2010; Kaniwa et al. 2010; Kim et al. 2010; Kim et al. 2011b; McCormack et al. 2011; Ozeki et al. 2011; Somkrua et al. 2011; Chung and Hung 2012;

Table 1 HLA association between drugs and ADR in different ethnicities

Drug	HLA allele	ADR	Ethnicity	References
Immediate type				
Aspirin	*DRB1*13:02, DRB1*06:09*	Urticaria/angioedema	Korean	Kim et al. (2006)
Aspirin and other NSAIDs	*DRB1*11*	Urticaria/angioedema and hypotension/ laryngeal edema	Spanish	Quiralte et al. (1999)
Aspirin and other NSAIDs	*B*44, Cw*5*	Chronic idiopathic urticaria	Italian	Pacor et al. (2006)
Penicillins	DR4, DR9, DR14.1, DR17	Immediate hypersensitive reaction and with urticaria	Chinese	Yang et al. (2006)
Penicillins and amoxicillin	DRA rs7192, DRA rs8084	Immediate hypersensitive reaction	Spanish and Italians	Gueant et al. (2015)
Delayed type				
Abacavir	B*57:01	HSS	Caucasians African	Mallal et al. (2002) and Saag et al. (2008)
Allopurinol	B*58:01	SJS/TEN/DRESS	Asians Caucasian	Somkrua et al. (2011), Hung et al. (2005) and Lonjou et al. (2008)
Aminopenicillins	A*2 DRW52	DRESS	Italian	Romano et al. (1998)
Carbamazepine	B*15:02	SJS/TEN	Han Chinese Thai Malaysians Indians	Tangamornsuksan et al. (2013)
	B*15:08	SJS/TEN	Indians	Chung and Hung (2012)
	B*15:11	SJS/TEN	Japanese Koreans	Kaniwa et al. (2010) and Kim et al. (2011)
	B*15:18	SJS/TEN	Japanese	Ikeda et al. (2010)
	B*57:01	SJS/TEN	European	Mockenhaupt et al. (2019)
	B*59:01	SJS/TEN	Japanese	Kaniwa et al. (2010)
	A*31:01	DRESS	European Han Chinese Japanese Korean	Kim et al. (2011), Genin et al. (2014), McCormack et al. (2011) and Ozeki et al. (2011)
		SJS/TEN	European, Japanese	Genin et al. (2014), McCormack et al. (2011) and Ozeki et al. (2011)
Dapsone	B*13:01	DRESS	Han Chinese	Zhang et al. (2013)
Lamotrigine	B*15:02 B*58:01 Cw*07:18 DQB1*06:09	SJS/TEN	Han Chinese	Lonjou et al. (2008), Cheung et al. (2013), Hung et al. (2010) and Kazeem et al. (2009)
–	B*38	SJS/TEN	Caucasians	Lonjou et al. (2008)
Methazolamide	B*59:01 Cw*01:02	SJS/TEN	Korean, Japanese Han Chinese	Kim et al. (2010) and Tangamornsuksan and Lohitnavy (2019)
Nevirapine	DRB1*01:01	DRESS/MPE	Australians	Martin et al. (2005)
	B*14:02	DRESS/MPE	Caucasians in Sardinians	Littera et al. (2006)
	B*35:05	DRESS/MPE	Thai	Chantarangsu et al. (2009)
	Cw8	DRESS/MPE	Caucasians in Sardinians Japanese	Littera et al. (2006) and Gatanaga et al. (2007)

Table 1 (continued)

Drug	HLA allele	ADR	Ethnicity	References
Oxcarbazepine	B*15:02	SJS/TEN	Han Chinese	Chen et al. (2017)
Oxicam	B*73:01	SJS/TEN	Caucasians	Lonjou et al. (2008)
Phenytoin	B*15:02	SJS/TEN	Han Chinese Thai Malaysians	Cheung et al. (2013), Hung et al. (2010), Locharernkul et al. (2008), Chang et al. (2017)
	B*13:01 Cw*08:01 DRB1*16:02	SJS/TEN	Han Chinese	Hung et al. (2010)
	B*15:13	SJS/TEN	Malaysians	Chang et al. (2017)
	CYP2C9*3	SJS/TEN/DRESS	Han Chinese Japanese Malaysians Thai	Chung et al. (2014) and Tassaneeyakul et al. (2016)
Sulfamethoxazole	B*38	SJS/TEN	Caucasians	Lonjou et al. (2008)
Vancomycin	A*32:01	DRESS	Caucasians	Konvinse et al. (2019)

HLA human leukocyte antigen, *HSS* hypersensitivity syndrome, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis, *DRESS* drug reaction with eosinophilia and systemic symptoms, *MPE* maculopapular exanthema

Cheung et al. 2013; Tangamornsuksan et al. 2013; Zhang et al. 2013; Chung et al. 2014; Genin et al. 2014; Tassaneeyakul et al. 2016; Chang et al. 2017; Chen et al. 2017; Konvinse et al. 2019; Mockenhaupt et al. 2019; Tangamornsuksan and Lohitnavy 2019).

Allopurinol

Allopurinol is a xanthine oxidase inhibitor that is frequently prescribed for the treatment of gout. Initial comparison between cases of allopurinol-induced SCARs and tolerant controls showed a strong association of HLA-B*58:01, with this HLA being present in all cases of allopurinol SCARs (Hung et al. 2005). This strong association was subsequently reproduced in different ethnicities, including Han Chinese, Thai populations (Lonjou et al. 2008; Somkrua et al. 2011) as well as in Korean, Japanese, and European populations, thereby validating HLA-B*58:01 as a useful predictive biomarker for allopurinol induced SCARs. It is therefore reasonable for allopurinol to be contraindicated in patients who are positive for HLA-B∗58:01 (Hung et al. 2005). However, in our follow-up study, only 84%, and not 100%, of Chinese patients with allopurinol hypersensitivity carried the HLA-B∗58:01 allele. The low positive predictive value and variable negative predictive value of HLA-B∗58:01 for allopurinol-induced SCARs suggest that other factors may contribute to the pathogenesis of allopurinol-induced SCARs (Ng et al. 2016).

Aromatic Anticonvulsants

Aromatic anticonvulsants such as CBZ, oxcarbazepine (OXC), phenytoin (PHT), and lamotrigine (LTG) are high-risk drugs for drug hypersensitivity reactions. We first reported a strong association between CBZ and HLA-B∗15:02 in patients who developed SJS/TEN in Taiwan in 2004 (Chung et al. 2004). Since then, other aromatic antiepileptic drugs, such as PHT (Locharernkul et al. 2008), OXC (Chen et al. 2017), and LTG (Shi et al. 2011), have also been shown to have a positive association with HLA-B*15:02 allele for SJS/TEN. This allele has been further validated in different populations from Thailand, Malaysia, Singapore, and India (Locharernkul et al. 2008; Tangamornsuksan et al. 2013). Based on these results, the genetic screening of HLA-B∗15:02 prior to the initiation of CBZ has been recommended in some Asian populations (Ferrell Jr. and McLeod 2008). On the other hand, HLA-A*31:01 allele has been identified as a risk factor for CBZ-induced DRESS, but not of CBZ-induced SJS/TEN in Europeans, Han Chinese, and Koreans (Kim et al. 2011b; Genin et al. 2014; Hung et al. 2006).

HLA-A*31:01 was also shown to be associated with CBZ-induced cutaneous adverse drug reactions (ADR) across the spectrum, from MPR to DRESS, and SJS/TEN in the Japanese (McCormack et al. 2011; Ozeki et al. 2011). For CBZ-induced SJS/TEN in Europeans, a recent study from RegiSCAR group showed that HLA-B*57:01, instead of HLA-A*31:01, was a risk factor (Mockenhaupt et al. 2019). Lastly, HLA-B∗15:11 allele was shown to be associated with carbamazepine-induced SJS/TEN in Japanese and Korean populations as well (Kaniwa et al. 2010; Kim et al. 2011b).

Abacavir

Abacavir is used in the treatment of HIV infection and is also a high notoriety drug for drug hypersensitivity reactions. In 2002, two studies demonstrated that HLA-B*57:01 was a risk factor for abacavir-related hypersensitivity (Mallal et al. 2002; Hetherington et al. 2002). In addition, it has been shown that 44% of white study participants and 100% of black participants with the HLA-B*57:01 allele experienced abacavir-induced hypersensitivity (Saag et al. 2008). A further randomized trial confirmed that screening for HLA-B*57:01 as an effective measure for the prevention of abacavir induced hypersensitivity (Mallal et al. 2008).

Other Drugs

Several other antibiotic-induced hypersensitivity reactions and pharmacogenomic associations have been reported. These include *HLA-B*38 and* sulfamethoxazole (Lonjou et al. 2008), *HLA-B*13:01* and dapsone-induced hypersensitivity syndrome (Zhang et al. 2013), *HLA*-A*32:01 and vancomycin-induced DRESS (Konvinse et al. 2019) as well as HLA-A*2 and DRW52 in aminopenicillins-induced DRESS (Romano et al. 1998). Nevirapine-induced MPE or DRESS is associated with *HLA-DRB1*01:01* in Western Australia (Shepherd et al. 2005), B*14:02 in Caucasians in Sardinians (Littera et al. 2006), *HLA-B*35:05* in Thailand (Chantarangsu et al. 2009), and *HLA-Cw8* in Japan (Gatanaga et al. 2007). Other associations include *HLA-B*59:01* and methazolamide-induced SJS/TEN (Kim et al. 2010; Tangamornsuksan and Lohitnavy 2019), *HLA-B*73:01* and oxicam-induced SJS/TEN (Lonjou et al. 2008).

4 Drug Metabolism in SCARs

In addition to pharmacogenetic associations, individual drug metabolism and clearance are also critical factors that influence susceptibility and prognosis of SCARs. Individuals with rapid drug clearance may be at a lower risk of developing SCARs. This is illustrated in genetic variants of CYP2C9*3 and PHT-related SCAR (Chung et al. 2014). CYP2C9*3 attenuates the clearance of PHT and patients with phenytoin-associated SCAR patients who carried the CYP2C9*3 showed a delayed clearance of plasma PHT, resulting in an increase of PHT toxicity and a higher likelihood of hypersensitivity reactions (Chung et al. 2014). Other examples include the strong association between CYP3A5*3 and antiepileptics-induced hypersensitivity reactions (Tanno et al. 2015) as well as CYP2B6, with nevirapine-induced SJS/TEN (Ciccacci et al. 2013).

Another example illustrating the role of drug metabolism and dosage is in allopurinol SCARS. High starting doses of allopurinol and renal impairment are known risk factors. Renal impairment or chronic kidney disease impacts the clearance of oxypurinol (the metabolite of allopurinol). This leads to elevated plasma concentrations and a higher risk of SCARs (Chung et al. 2015a). In addition, the coexistence of renal impairment and HLA-B*58:01 increase the risk of allopurinol-induced cutaneous adverse drug reactions (heterozygous HLA-B*58:01 and normal renal function: OR: 15.25, specificity: 82%; homozygous HLA-B*58:01 and severe renal impairment: OR: 1269.45, specificity: 100%) (Ng et al. 2016). These results suggests that allopurinol should be avoided in patients with coexisting HLA-B*58:01 and renal impairment.

5 Immune Mechanisms in DH

5.1 Immediate-Type: IgE-Mediated DH

Type I DH reactions are mainly mediated by mast cells and basophils activation via allergic (IgE-mediated) or nonallergic (non-IgE-mediated) mechanisms (Fig. 4). Type I DH response can be systemic or local in nature and generally arises due to the cross-linking of membrane-bound IgE antibodies on the basophil/mast cell with antigens. The cross-linkage of drug antigens to Ig-E bound high-affinity Fc receptor (FcεRI) located on mast cells/basophils results in degranulation and the release of mediators. These mediators include histamine, leukotrienes, and prostaglandins which are responsible for the clinical features of urticaria, angioedema, or anaphylaxis (Moon et al. 2014; Schnyder and Pichler 2009). In contrast, NSAIDs (except pyrazolones) are believed to cause anaphylaxis via an aberrant arachidonic acid metabolism pathway or selective T cell-mediated mechanism instead of the classical IgE-mediated pathway (Blanca-Lopez et al. 2016; Canto et al. 2009; Brockow et al. 2013). Other non-IgE mechanisms include those mediated by IgG antibodies, complement or via contact system activation. The clinical presentation of these alternative pathways is indistinguishable from IgE-mediated anaphylaxis (Munoz-Cano et al. 2016; Finkelman et al. 2016). The cross linkage of drugs with drug-specific IgG bound to FcγRIII stimulates the release of platelet activation factor (PAF) from basophils, macrophages, or neutrophils (Finkelman et al. 2016). This IgG immune-complex can trigger further complement activation. Another non-Ig E mechanism is via the contact system activation of complements. Upon activation, bradykinin formation is initiated and this may play a role in anaphylaxis (Finkelman et al. 2016). Reactions to radiocontrast media, dextran, and some NSAIDs are postulated to occur via these non-Ig E pathways (Wedi 2010; Dona et al. 2016; Laroche et al. 1999; Kishimoto et al. 2008). Finally, nonimmunologic mechanisms may be involved in anaphylaxis: Direct mast cell degranulation via MAS-related G protein-coupled receptor-X2 (MRGPRX2) has been shown. This pathway may mediate reactions that are caused by quinolones, vancomycin, and neuromuscular blocking drugs (Subramanian et al. 2016).

5.2 Delayed-Type: T Cells Mediated DH

Delayed reactions vary in severity. MPEs are generally benign, whereas SCARs such as DRESS, SJS/TEN, and AGEP are associated with significant morbidity and/or mortality. The mechanisms differ across diseases and are summarized below.

MPE (Type Iva)

In MPE, the activation of CD4+ T cells through drug presentation by antigen presenting cells leads to the release of inflammatory cytokines such as interferon-gamma (IFN-γ). IFN-γ further activates macrophages and amplifies the release of cytokines and chemokines that recruit additional monocytes (Pichler 2003).

DRESS Syndrome (Type IVb)

DRESS is characterized by peripheral blood eosinophil activation (Rive et al. 2013) and high serum levels of cytokines and chemokines, such as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), and thymus and activation-regulated chemokine (TARC)/CC chemokine ligand 17 (Choquet-Kastylevsky et al. 1998; Teraki and Fukuda 2017). This profile suggests a Th2-type immune response as the dominant pathway. As the disease progresses from acute to subacute and resolution phases, there is a corresponding transition from an initial Treg expansion to Th17 cell expansion (Hashizume et al. 2016; Fujiyama et al. 2014; Olteanu et al. 2019). In addition, it has recently been shown that type 2 innate lymphoid cells were increased both in the skin and serum of patients with DRESS. These were associated with high levels of serum ST-2, IL-5 and TSLP as well as increased expression of IL-33/ST-2 expression in type 2 innate lymphoid cells. These markers may

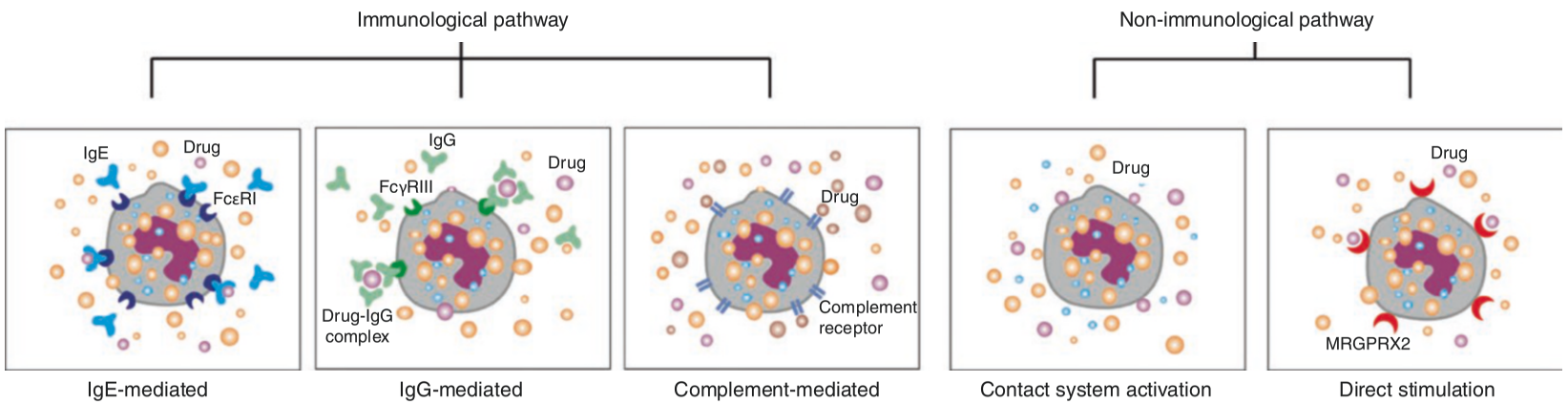

Fig. 4 Multiple mechanisms and pathways involved in anaphylaxis. The pathways of anaphylaxis can be classified into immunological and nonimmunological depending on the underlying mechanism. Immunological anaphylaxis can be mediated by an IgE, IgG, and complement mechanism, whereas nonimmunological anaphylaxis involves contact system activation and direct stimulation

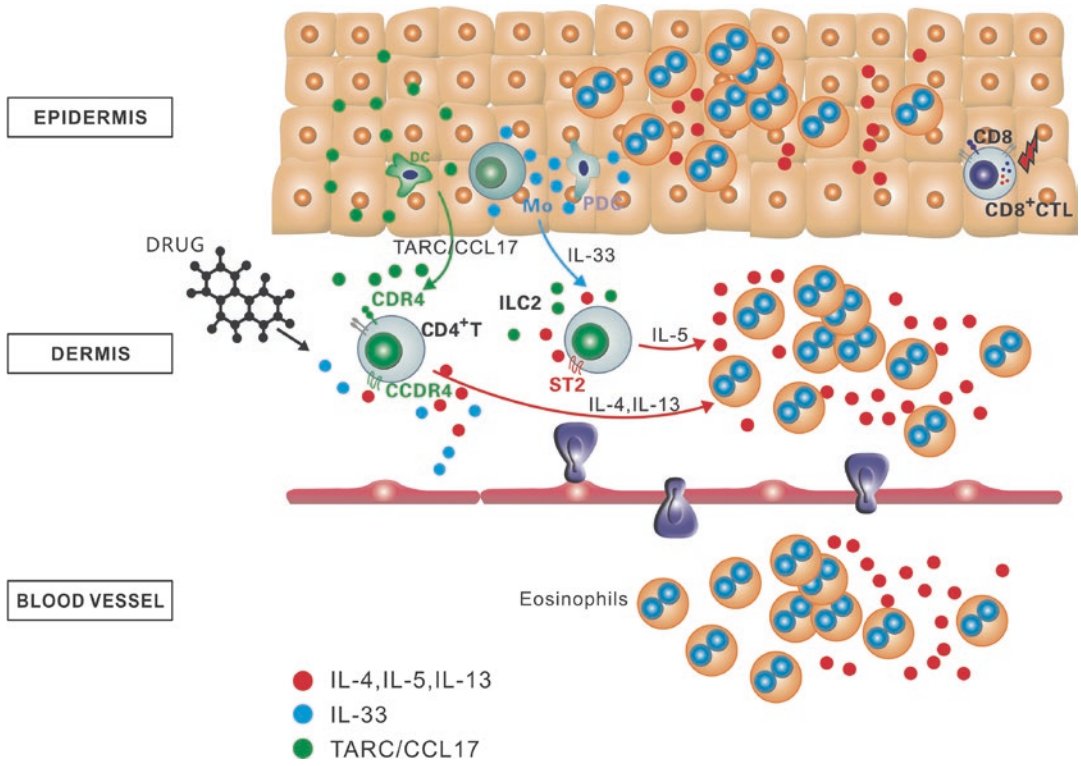

Fig. 5 The pathomechanisms in DRESS. Th2 and ST2 membrane-bound ILC2 are activated by TARC/CCL17 and IL-33 which is released from dendritic cells and monocytes. Subsequently, activated T cells produce various cytokine including IL-4, IL-5 and IL-13 as chemoattractant to cause recruitment of eosinophils. In addition, CD8 T cells may observed in skin lesion

mediate the skin inflammation in DRESS and serum ST2 may be a biomarker for liver involvement in DRESS (Tsai et al. 2019). The CXCL3/CXCR10 axis has also been found to be associated with the development of long-term sequelae and HHV-6 reactivation in DRESS (Yang et al. 2020; Chen et al. 2015). More recently, the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway has been recently shown to be a possible disease pathway in DRESS. In a patient with severe DRESS, the use of tofacitinib (JAK1 and JAK3 inhibitor) brought about control of disease (Kim et al. 2020). The mechanisms in DRESS are summarized in Fig. 5.

SJS/TEN (Type IVc)

The central hypothesis to explain SJS/TEN is the activation of CTLs/nature killer (NK) cells and the release of cytotoxic proteins. Three cytotoxic proteins, granulysin, perforin/granzyme B, and Fas–FasL, are thought to be the major mediators responsible for the extensive skin necrosis in SJS/TEN (Fig. 6).

Granulysin

Granulysin belongs to the saposin-like protein (SAPLIP) family. It is expressed on activated CTL and NK cells and is involved in cell cytotoxicity. The transcription and expression of granulysin is much higher compared to perforin, granzyme B, and soluble Fas ligand (sFasL) in blister fluids, suggesting it is the most important mediator for necrolysis. This is further supported in mice studies, whereby SJS/TEN-like lesions were replicated following granulysin injections (Chung et al. 2008). Serum granulysin is elevated during the early stage of SJS/TEN, suggesting its role as an early diagnostic marker of SJS/TEN (Abe et al. 2009). Moreover, granulysin is a chemoattractant and is involved in the recruitment of

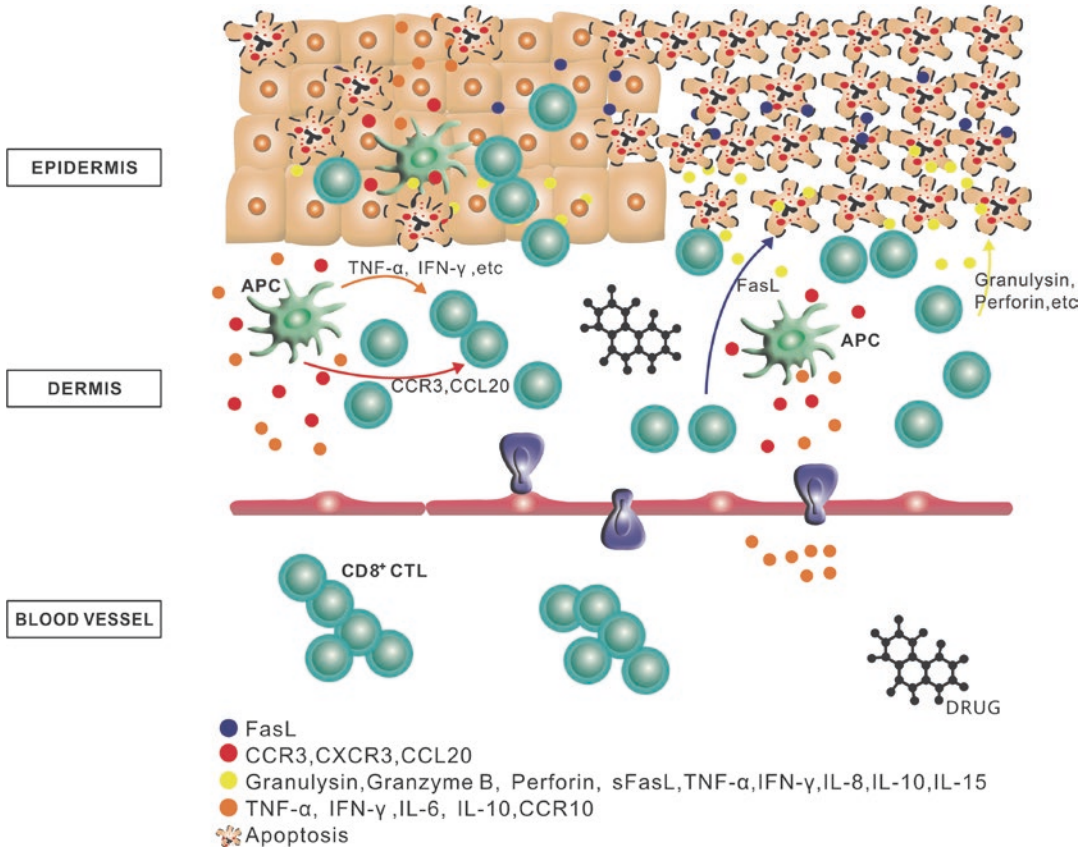

Fig. 6 The pathomechanisms involved in SJS/TEN. CTLs are activated through the antigen (drug) presentation by the antigen presenting cell (APC) and subsequently carry out the cellular immune reactions directed at keratinocytes. Upon activation, CTLs release various cytotoxic proteins, including granulysin, perforin/granzyme B, Fas/Fas ligand, and other cytokines/chemokines resulting in disseminated keratinocyte death in skin lesions. These toxic signals in turn regulate trafficking, proliferation, and activation of T cells and other immune cells to amplify the reaction

antigen-presenting cells (APCs) thereby amplifying the specific immune response. Pro-inflammatory cytokines released from these inflammatory cells include Regulated upon Activation, Normal T-cell Expressed, and Secreted (RANTES), chemokine (C–C motif) ligand (CCL)5, monocyte chemotactic protein (MCP)-1, MCP-3, macrophage inflammatory protein-1a, CCL3, interleukin (IL)-10, IL-1, IL-6, and interferon (IFN)-α (Deng et al. 2005).

Perforin/Granzyme B Pathway

Perforin and granzyme B are stored within the cytotoxic granules of activated CTL and NK cells (Bots and Medema 2006). When activated, perforin would punch a pore on the membrane of keratinocytes, promoting the entry of granzyme B which induces apoptosis via caspase pathways (Pinkoski et al. 2001; Nassif et al. 2002). Prior studies have shown that blister lymphocytes were cytotoxic in nature and these cytotoxic effects were abrogated by blocking the perforin/granzyme pathway and not with anti-Fas monoclonal antibody (Nassif et al. 2002).

NK Cells

NK cells are found in the blister fluid of SJS/TEN patients (Chung et al. 2008) suggesting that NK cells are important immune effectors for epidermal detachment in SJS/TEN. The cytotoxicity of

NK cells is regulated by activation and inhibitory signals through the surface NK receptors (Lanier 2005). It has been reported that the activation receptor CD94/NKG2C is found in NK cells and the expression of its soluble ligand HLA-E is increased in the keratinocytes of SJS/TEN patients (Morel et al. 2010).

Fas–FasL Interaction

It is first reported that the activated Fas–Fas ligand (FasL) binding may play a role in the apoptosis of keratinocytes in SJS/TEN (Viard et al. 1998). In TEN patients, FasL was reported to be found on both the keratinocyte surface and also in high levels within the circulation (Viard et al. 1998). However, the exact role of Fas–FasL remains controversial as a later study was unable to demonstrate the expression of membrane-bound FasL on keratinocytes in either patients with TEN or healthy controls even though elevated levels of sFasL in SJS/TEN were detected (Abe et al. 2003).

Annexin A1–FPR1 Interaction

Annexin A1 was identified in the supernatants of specific drug-stimulated PBMCs of SJS/TEN patients by mass spectrometric analysis (Saito et al. 2014). In a fraction of keratinocytes in the SJS/TEN, cell death was shown to be mediated through programmed cell necrosis or necroptosis. This process is initiated by annexin-1 binding to FPR1 (the receptor for annexin A1) which is expressed on keratinocytes (Saito et al. 2014). Also, high levels of RIP3 expression in the epidermis of patients with SJS/TEN were also found (Saito et al. 2014; Kim et al. 2015). RIP3-mediated phosphorylation and activation of MLKL (a key downstream component of RIP3) was detected in the necrotic keratinocytes, supporting the hypothesis of necroptosis as one of the cell death mechanisms in SJS/TEN (Kim et al. 2015).

Cytokines/Chemokines Involved in the Cell Immunity of SJS/TEN

Several studies have shown increased expression of certain cytokines/chemokines in the blister fluid, plasma, blister cells, or peripheral mononuclear cells of patients with SCARs. TNF-α, which induces cell apoptosis, activation, differentiation and inflammation, is increased in lesional skin of TEN patients (Chavez-Galan et al. 2009; Paquet et al. 1994). Increased serum levels of TNF-α and IFN-γ as well as inducible FasL expression have been demonstrated in TEN (Viard-Leveugle et al. 2013). Interleukin-15 (IL-15) is a cytokine which is able to induce the proliferation of natural killer cells as well as other leukocytes. In SJS/TEN, the levels of IL-15 and granulysin showed positive correlation with disease severity. Furthermore, IL-15 was associated with mortality of SJS/TEN and shown to enhance cytotoxicity of cultured natural killer cells and blister cells from patients with TEN (Su et al. 2017). In addition to TNF-α, IFN-γ, and IL-15, other cytokines such as IL-5, IL-6, IL-10, IL-12, IL-13, IL-18, CCR3, CXCR3, CXCR4, and CCR10 may be responsible for the trafficking, proliferation, regulation or activation of T cells and other leukocytes involved in SJS/TEN (Paquet et al. 2000; Correia et al. 2002; Nassif et al. 2004; Tapia et al. 2004; Caproni et al. 2006).

AGEP (Type IVd)

The activation, proliferation, and migration of drug-specific CD4+ and CD8+ T cells play an important role in the development of AGEP (Choi et al. 2010; Belhadjali et al. 2008). Drug-specific T cells produces chemotactic chemokine (C–X–C motif) ligand 8 (CXCL8)/IL-8 which contributes to the recruitment of neutrophils in AGEP (Schaerli et al. 2004). In AGEP, high levels of circulating Th17 cells and the elevated serum IL-17 and IL-22 may stimulate keratinocytes to produce IL-8 (Kabashima et al. 2011). This increase in the levels of IL-17 and IL-22 as well as granulocyte–macrophage colony-stimulating factor (GM-CSF) works synergistically with CXCL8/IL-8–induced neutrophilic activity and prevents apoptosis of neutrophils (Kabashima et al. 2011). Mutations in IL-36 receptor antagonist gene (IL36RN) contribute to recruitment of neutrophils via production of pro-inflammatory cytokines, such as IL-1, IL-6, and IL-8 (Navarini et al. 2013). In AGEP, dysregulation of IL-36 sig-

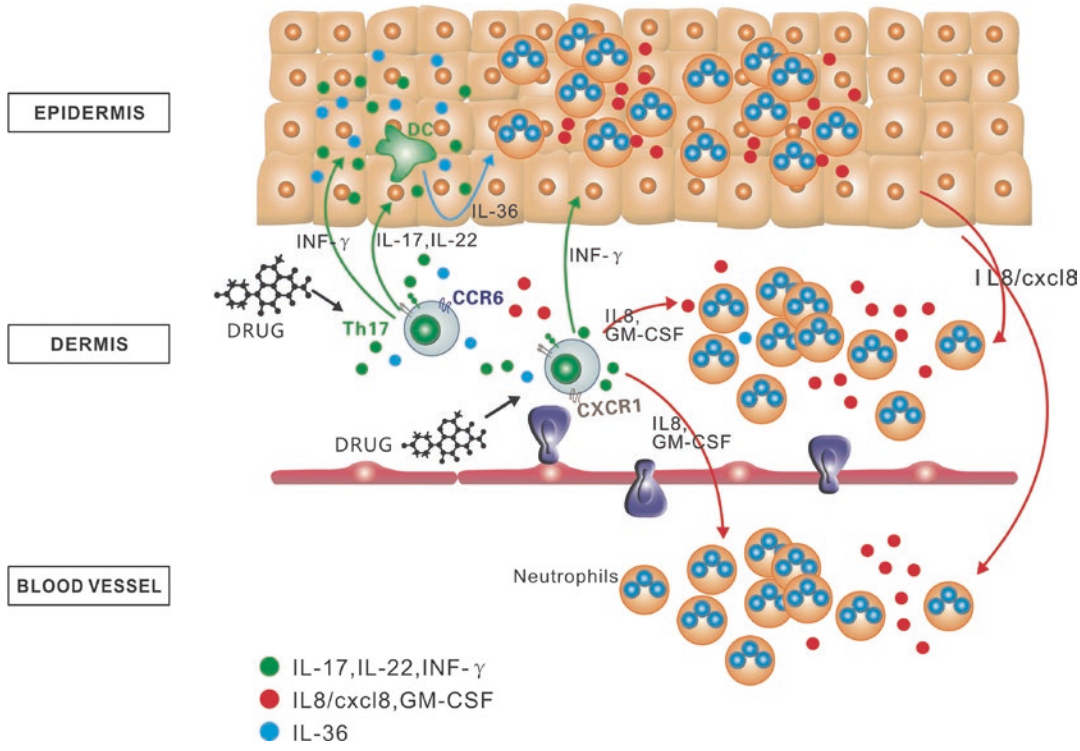

Fig. 7 The summarized mechanism in AGEP development. Drug-specific CD4 and CD8 T cells play an important role in the development of AGEP. T cells and keratinocytes release various chemokines and cytokines such as CXCL8/IL-8, IL-17, IL-22, GM-CSF, and IL-36 which recruits and activates neutrophils. Cellular damage is mediated through neutrophils and their mediators

naling pathway is postulated to drive the neutrophilic process; IL-36 production derived from blood monocytes and keratinocytes triggers the release of IL-8 from peripheral blood mononuclear cells (Meier-Schiesser et al. 2019). The immune mechanisms for AGEP are summarized in Fig. 7.

6 T Cell Receptor (TCR) Repertoire in Drug Hypersensitivity

In allopurinol-induced SCAR, preferential TCR-V-β usage and clonal expansion of specific CDR3 (third complementarity-determining region) were found in the blister cells of allopurinol induced SCAR (Chung et al. 2015b). These data suggest that, in addition to HLA-B*58:01, clonotype-specific T cells expressing granulysin upon oxypurinol induction are involved in the pathogenesis of allopurinol-induced SCAR.

In CBZ-induced SJS/TEN, CBZ-specific T cells are restricted by HLA-B*15:02 and only a few heavy chain residues allow for CBZ presentation. A restricted TCR clonotype has been identified, and is responsible for the recognition of carbamazepine within the context of HLA-B*15:02 (Wei et al. 2012). Recently, the role of TCR repertoire was further validated in the demonstration of public αβTCR of CTL being involved in immune synapses mediating SCARs (Pan et al. 2019). Furthermore, adoptive transfer of T cells expressing this public αβTCR to HLA-B*15:02 transgenic mice receiving CBZ resulted in multiorgan injuries similar to SCARs (Pan et al. 2019). These findings suggest potential clinical applications of TCR in therapeutics (Pan et al. 2019). In addition, expanded clones and a less diverse TCR repertoire have been found to be

associated with clinical severity of disease in patients with SJS/TEN by systematic sequence analysis for TCRβ (Xiong et al. 2019).

In the "altered TCR repertoire" model, drugs (such as sulfamethoxazole) alter the conformation of a specific TCR, thereby facilitating the binding of HLA–self-peptide complex (Watkins and Pichler 2013). In this model, the causative drug directly interacts with this specific TCR, but not with the peptides or HLA molecules.

In contrast, in the "altered peptide repertoire" model, binding of the drug (e.g., Abacavir) to HLA protein results in a conformational change, thereby altering peptide specificity of HLA binding (Ostrov et al. 2012; Illing et al. 2012). This was demonstrated in the abacavir model, whereby the binding of abacavir to the F-pocket of HLA-B*57:01, altered the shape and chemistry of the antigen-binding cleft. The binding of self-peptides to these antigen-binding clefts result in "polyclonal" T cell activation and autoimmune-like systemic reaction manifestations. An abacavir-stimulated patch test–positive skin in a patient 14 years after abacavir-induced DH was also shown to have "polyclonal" memory T-cell responses, adding further support for the altered peptide model (Redwood et al. 2019).

7 Conclusion

The mechanism of drug hypersensitivity is complex and not entirely understood. In this chapter, we summarize the genetic factors and different immune mechanism that are involved in drug specific allergic and nonallergic responses. Although the optimal therapeutic strategies for drug hypersensitivity remain unclear, an understanding of these mechanisms would pave the way for novel therapeutic approaches.

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Histopathology of Cutaneous Adverse Drug Reactions

Nicolas Ortonne

1 Introduction

This chapter focuses on the histopathological manifestations of cutaneous adverse drug reactions (CADRs) driven by immune-mediated lymphocyte reactivity. These disorders are triggered by T lymphocytes reactive to the culprit drug and subsequently recruited into the skin: CADRs thus represent a model of delayed hypersensitivity (Zanni et al. 1998). Although the pathophysiology of CADR is complex, studies focusing on genetic predisposition to drug allergy, T-cell functioning and keratinocyte apoptosis have informed our understanding of the biology which underpins these reactions. In particular, the development of epidermal necrolysis is influenced by a genetic risk linked to the presence of a particular HLA variant (Hung et al. 2005; Chessman et al. 2008), while the disorder is mediated through the action of cytotoxic proteins produced by effector T-cells and factors which can activate apoptosis and necroptosis pathways in target keratinocytes (Nassif et al. 2004; de Araujo et al. 2011; Chung et al. 2008).

2 Inflammatory Patterns in CADR

As described by Ackerman, the two main histopathological presentations encountered in CADRs are the spongiotic and interface dermatitis patterns (Ackerman 1997). The psoriasiform pattern is usually not seen in classical CADRs.

2.1 Spongiotic Reaction Pattern

From a histological point of view, the spongiotic reaction pattern in CADRs is similar to that seen in other eczematous dermatoses, such as atopic eczema, contact dermatitis and viral maculopapular rashes. In the acute phase there is confluent spongiosis which forms vesicles containing exocytosed lymphocytes and Langerhans cells (Fig. 1). The spongiotic pattern is frequent in maculopapular drug rashes and drug reaction with eosinophilia and systemic symptoms (DRESS). Chronic and sometimes widespread eczematous reactions have been described in older patients taking commonly prescribed medicines, such as anti-hypertensive drugs (especially calcium channel blockers, angiotensin-converting enzyme inhibitors) (Joly et al. 2007).

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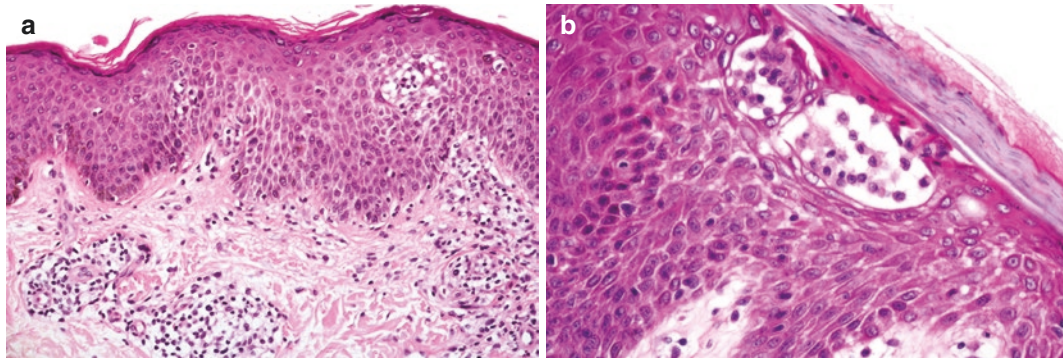

Fig. 1 Eczematous reaction pattern. (**a**) Acute phase eczema showing foci of spongiosis, characterized by the enlargement of inter-keratinocyte spaces and vesicles containing mononuclear inflammatory cells. There is a dermal perivascular infiltrate composed of lymphocytes. Haematoxylin and eosin ×200. (**b**) Vesicle at high magnification containing numerous Langerhans' cells which are recognized by their clear and irregularly shaped nuclei and moderately abundant eosinophilic cytoplasm. Haematoxylin and eosin ×400

2.2 Interface Dermatitis Pattern

The characteristic feature of the interface dermatitis pattern is epidermal attack by lymphocytes. Other cytotoxic cell populations, such as dendritic plasmacytoid cells, can also be involved in this epidermal assault. The classical inflammatory dermatosis associated with an interface dermatitis histological pattern is lichen planus (Wenzel et al. 2006).

The interface dermatitis pattern is variably associated with the following features:

- Infiltration of the deep layers of the epidermis by lymphocytes and other mononuclear cells (macrophages/dendritic plasmacytoid cells).
- Keratinocyte death producing apoptotic bodies (Civatte or colloid bodies) with the release of melanin pigment from their cytoplasm into the epidermis and dermis.
- Vacuolization of the dermoepidermal junction due to cell death and mononuclear cell exocytosis.

Two main types of interface dermatitis pattern can be identified morphologically: the vacuolar form and the classical form (Ackerman 1997). The vacuolar form is characterized by vacuolization of the basal layer of the epidermis with occasional apoptotic keratinocytes and a scanty lymphocytic infiltrate (Fig. 2a). This pattern is encountered in acute cutaneous lupus erythematosus and acute graft-versus-host disease. The classical form, which occurs most commonly in lichen planus, is typified by an abundant lymphocytic infiltrate with more marked keratinocyte apoptosis (Fig. 2b).

A third variant of the interface dermatitis pattern can be considered, one which occurs in the most severe form of CADR: Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (Fig. 2c). In this entity, keratinocyte apoptosis is predominant, in the form of confluent clusters of dead cells. Keratinocyte apoptosis explains the skin detachment in SJS/TEN, referred to as epidermal necrolysis (EN), and is caused by loss of cellular junctions between neighbouring apoptotic cells. The lymphocyte infiltrate can be quite moderate or even minimal in SJS/TEN reflecting the concept that direct contact with cytotoxic effector lymphocytes is not necessary to kill keratinocytes. However, soluble pro-apoptotic mediators, such as Fas ligand, granulysin, interferon and TNF-alpha may be involved, along with phenotypic modifications of keratinocytes, leading to death ligand expression (Arnold et al. 1999). Certain pro-inflammatory cytokines promote keratinocyte expression of pro-apoptotic ligands, such as Fas ligand (Abe et al. 2003), and induces the death of neighbouring cells. The role of the necroptosis process, recently identified in SJS/TEN, may

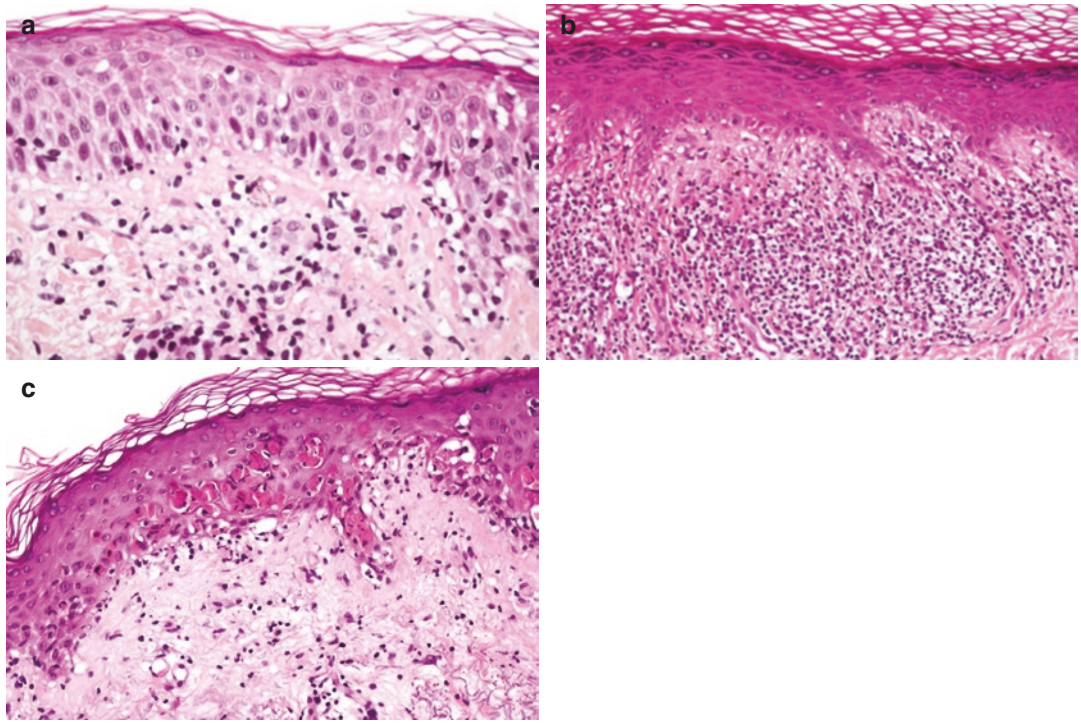

Fig. 2 Interface dermatitis reaction pattern. (**a**) Vacuolar interface dermatitis with lymphocyte exocytosis, vacuolization of the epidermal basal layer, occasional apoptotic bodies and scattered lymphocytes in the superficial dermis. Haematoxylin and eosin ×200. (**b**) Classical lichenoid interface dermatitis with a dense lymphocytic infiltrate occupying the superficial dermis and extending to the dermal–epidermal junction with numerous apoptotic bodies. Haematoxylin and eosin ×100. (**c**) Aggressive ID, illustrating "acute syndrome of apoptotic pan-epidermolysis" (ASAP), with confluent apoptotic keratinocytes and scattered lymphocytes in the superficial dermis and basal layers of the epidermis. Haematoxylin and eosin ×200

also partly explain pathomechanisms of the disorder (Saito et al. 2014). Necroptosis is characterized by a breakdown of the integrity of cell membranes with release of alarmins, which in turn induce the death of other cells and recruitment of effector T-cells.

The term "acute syndrome of apoptotic pan-epidermolysis" (ASAP) was first introduced in 2004 by Ting et al. to describe an aggressive form of lupus erythematosus showing an EN-like pattern on histology (Ting et al. 2004). We, and others, have shown that other skin diseases can present histologically with an EN pattern, including DRESS (Ortonne et al. 2015), erythema multiforme (Amode et al. 2018), lupus erythematosus (Ting et al. 2004), acute graft-versus-host disease and contact reactions with *Nigella sativa* oil (Gaudin et al. 2018). A similar cytotoxic pathway may characterize all the above entities, in which common cellular and/or molecular effectors occur downstream of drug, auto-immune, allo-immune and infectious triggers, respectively.

3 Non-specific Histological Aspects of Cutaneous ADRs

Pathologists with a reductionist vision of CADR histopathology are inclined to limit their diagnoses by the presence of eosinophils and/or apoptotic keratinocytes. These two elements are neither constant nor specific for a drug-induced dermatosis. In many forms of CADR eosinophils are absent, as are apoptotic keratinocytes. Conversely, numerous non-drug rashes are distinguished by one or other of these features.

Thus, histology is not usually considered as a major diagnostic criterion for CADR. As an example, a "non-suggestive" histology as a negative criterion for DRESS is the sole histological feature mentioned in the DRESS diagnostic system published by Kardaun et al. (2013). However, dermatopathology is an extremely important tool in discriminating severe CADRs from non-drug dermatoses. In a patient with extensive skin detachment, histology will distinguish TEN from staphylococcal scalded skin syndrome or from an autoimmune bullous disorder.

The following sections outline the major histopathological features found in classical CADR entities. It remains uncertain whether individual manifestations represent distinct clinical-pathological entities or different aspects of a disease spectrum. In a retrospective study of 216 cases of CADRs overlap cases were rare, suggesting the validity of separate, discrete drug-induced disorders (Bouvresse et al. 2012).

4 Drug-Induced Exanthem

The drug-induced exanthem, also known as a maculo-papular rash, is the commonest form of CADR and tends to show non-specific histological features (Hunziker et al. 1997). The dermatopathology may reveal only a perivascular lymphocytic infiltrate in the upper part of the dermis (Fig. 3a), and for this reason a skin biopsy is often not performed. Nonetheless, histopathological assessment may help to differentiate a drug-induced exanthem from other conditions presenting with an exanthem and a modest dermal lymphocytic infiltrate, such as cutaneous angioimmunoblastic T-cell lymphoma (AITL), secondary syphilis, or autoimmune disorders (lupus erythematosus, dermatomyositis). Of note is the similarity, at the histological level, between a viral exanthem and a drug-induced exanthem. A drug aetiology is more likely with a spongiotic reaction pattern and/or a multi-focal interface

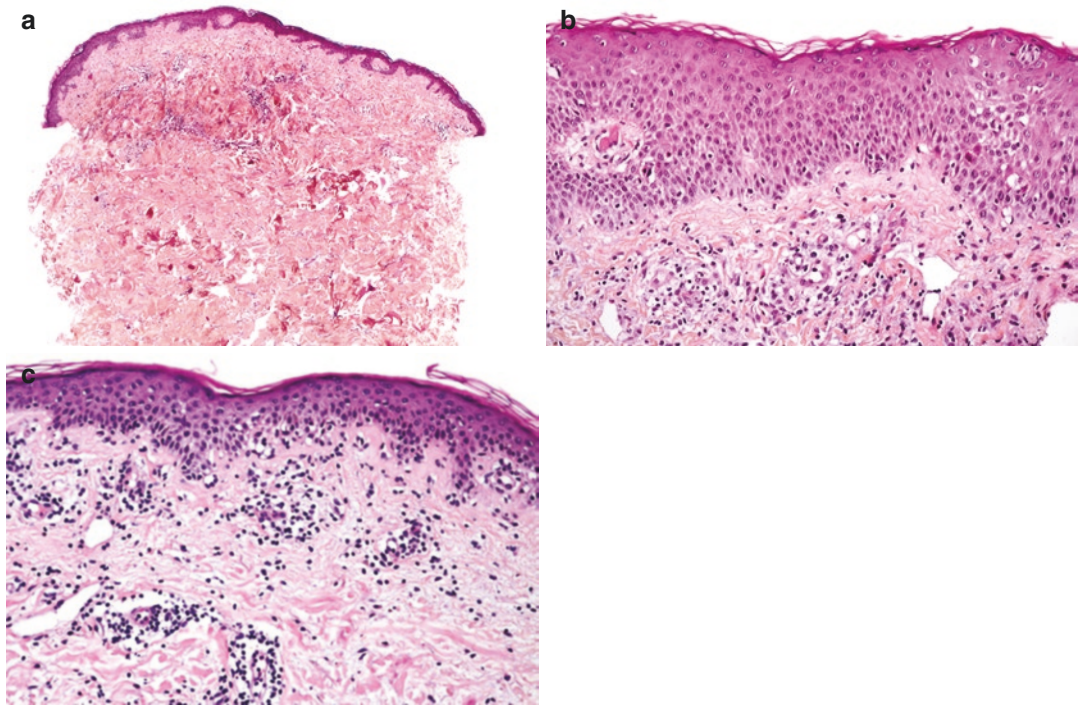

Fig. 3 Histological aspects of the drug-induced exanthem. (**a**) Drug-induced exanthem characterised by a slight perivascular infiltrate in the superficial dermis. Haematoxylin and eosin ×25. (**b**) Drug-induced exanthem with spongiotic reaction pattern: confluent spongiosis and lymphocyte exocytosis. Haematoxylin and eosin ×200. (**c**) Drug-induced exanthem with an interface dermatitis, lymphocytes infiltrating the basal layers of the vacuolized epidermis and a few apoptotic keratinocytes. There is an abundant perivascular lymphocytic infiltrate in the superficial dermis. Haematoxylin and eosin ×200

dermatitis pattern (Fig. 3b, c) (Deschamps et al. 2020; Gerson et al. 2008). From a histological point of view, this supports the existence of a spectrum linking drug-induced exanthem with DRESS, the latter being regarded by some authors as a more severe expression of the former (Pinto Gouveia et al. 2016; Ortonne 2016).

5 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

The histological picture of DRESS is highly variable and reflects the wide range of skin manifestations macroscopically. However, a lymphocytic infiltrate is constant and, as with drug-induced exanthems, may be the sole feature (Fig. 4a). A spongiotic (Fig. 4b) or interface dermatitis reaction pattern (Fig. 4c) can occur, while pustular forms and keratinocyte apoptosis may also be present (Fig. 4d). Dermal oedema and red blood cell extravasation are often observed, reflecting an increased microvascular permeability. Vasculitis is not a feature. The presence of several different inflammatory reaction patterns in a single biopsy may be a clue to the diagnosis of DRESS (Ortonne et al. 2015).

The inflammatory cell infiltrate in DRESS varies. Lymphocytes are usually the predominant cell type, but eosinophils may be prominent, although this is not a predictive feature (Fig. 5a).

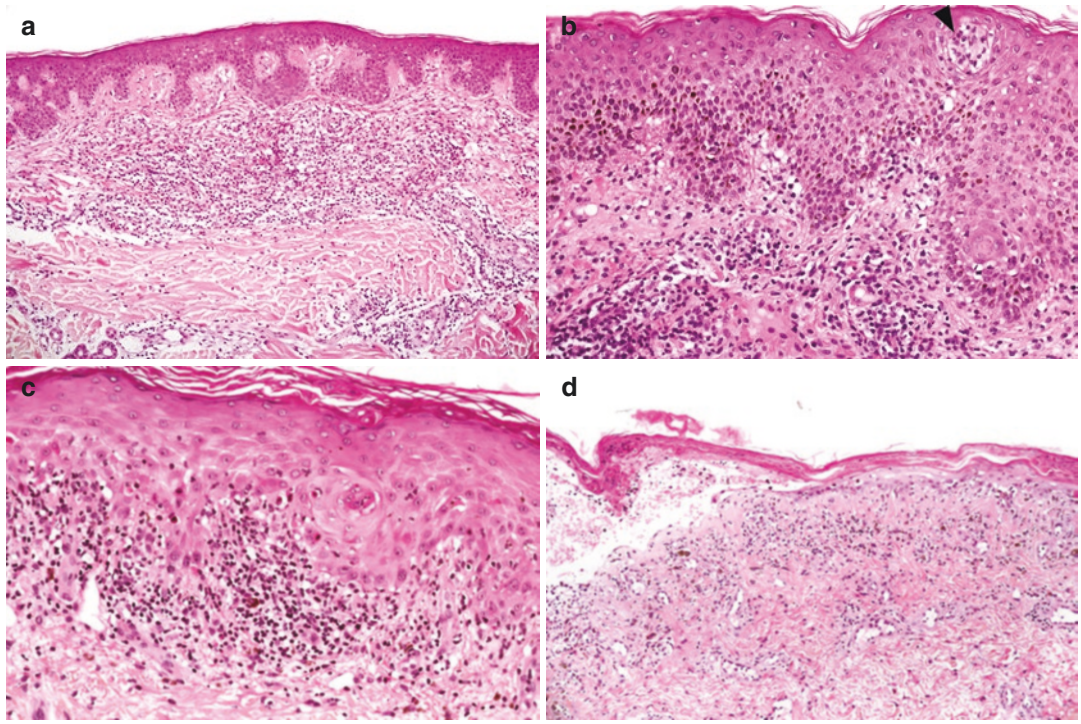

Fig. 4 Various histopathological features of drug reaction with eosinophils and systemic symptoms (DRESS). (**a**) DRESS syndrome with a dense infiltrate composed mainly of lymphocytes in the superficial and mid dermis. Epidermal changes are minimal. Haematoxylin and eosin ×100. (**b**) DRESS syndrome with a spongiotic reaction pattern, showing intra-epidermal vesicles containing lymphocytes and Langerhans' cells (arrow). Haematoxylin and eosin ×200. (**c**) DRESS with interface dermatitis showing a sub-epidermal band-like infiltrate mainly composed of lymphocytes covering the dermal–epidermal junction. Scattered apoptotic keratinocytes are present in the epidermis. Haematoxylin and eosin ×200. (**d**) DRESS syndrome overlapping with toxic epidermal necrolysis. A cluster of apoptotic keratinocytes has resulted in complete detachment of the epidermis. A dense infiltrate is present in the superficial dermis containing a few neutrophils and nuclear debris. Haematoxylin and eosin ×100

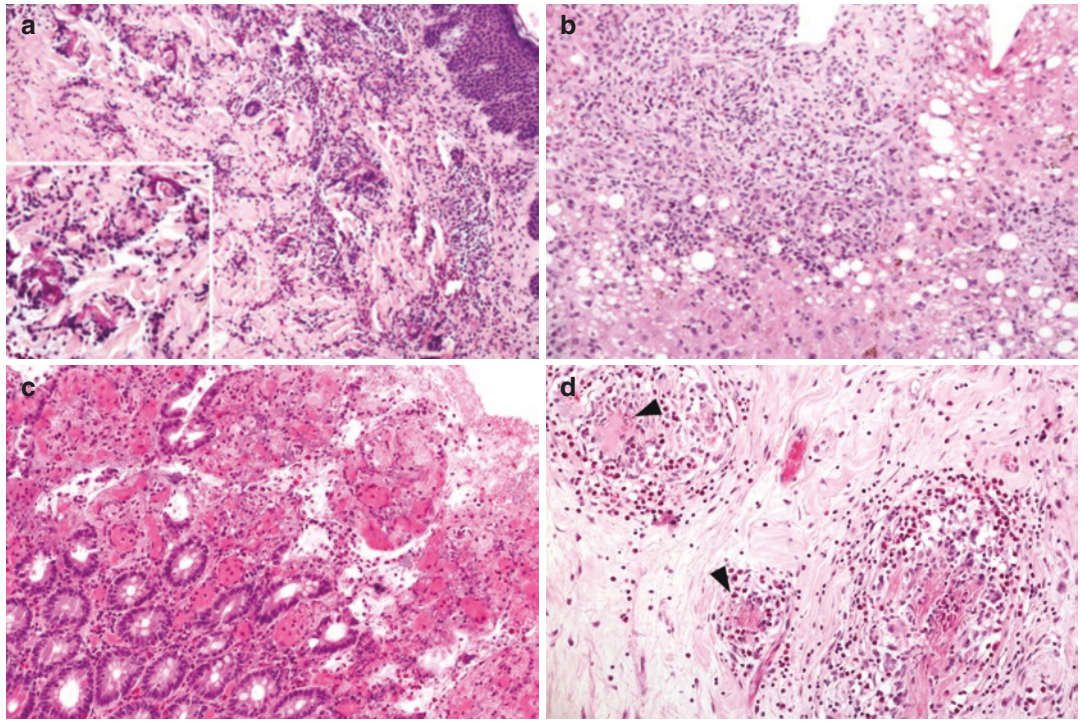

Fig. 5 Eosinophils and visceral injury in DRESS. (**a**) Dense dermal inflammatory infiltrate, mostly made of lymphocytes with numerous widespread eosinophils, with hyperplastic overlying epidermis. Eosinophils are associated with foci of collagen necrosis to yield "flame figures" (inset). Haematoxylin and eosin ×100. (**b**) Severe hepatitis in a patient with DRESS showing dense inflammatory infiltrate of the portal spaces, expanding into the liver lobules with areas of necrosis. The infiltrate is made of lymphocytes, some of which are slightly enlarged or show elongated nuclei, admixed with scattered eosinophils. Haematoxylin and eosin ×200. (**c**) Necrotizing colitis in a patient with DRESS. Areas of necrosis and ulceration of the mucosa. Haematoxylin and eosin ×200. (**d**) Necrotizing colitis in a patient with DRESS. A dense lymphocytic infiltrate in the sub-mucosa with numerous eosinophils and flame figures (arrows). Haematoxylin and eosin ×200

Neutrophils can be seen, and, rarely, plasma cells. The lymphocytic infiltrate in DRESS may be intense and show epidermotropism. Highly activated T lymphocytes with an atypical appearance can also be seen making a differential diagnosis from T-cell lymphoma difficult. Discriminating DRESS from cutaneous lymphomas (Sézary syndrome, angioimmunoblastic T-cell lymphoma, aggressive CD8+ epidermotropic T-cell lymphoma) relies on phenotyping and molecular studies.

The hallmark of DRESS is the systemic involvement which includes acute hepatitis (Fig. 5b), myocarditis, nephritis, pneumonitis and colitis (Fig. 5c, d). Another significant characteristic is its association with reactivation of the herpes viruses, including EBV (Seishima et al. 2006). T-cells which are specific to EBV peptides have been identified in many target tissues of DRESS, raising questions about disease triggers (Picard et al. 2010).

6 Acute Generalized Exanthematous Pustulosis (AGEP)

In contrast to DRESS, acute generalized exanthematous pustulosis (AGEP) usually produces a simple and characteristic histopathology (Halevy et al. 2010). Sub-corneal, multilocular pustules are typical, which are difficult to distinguish from

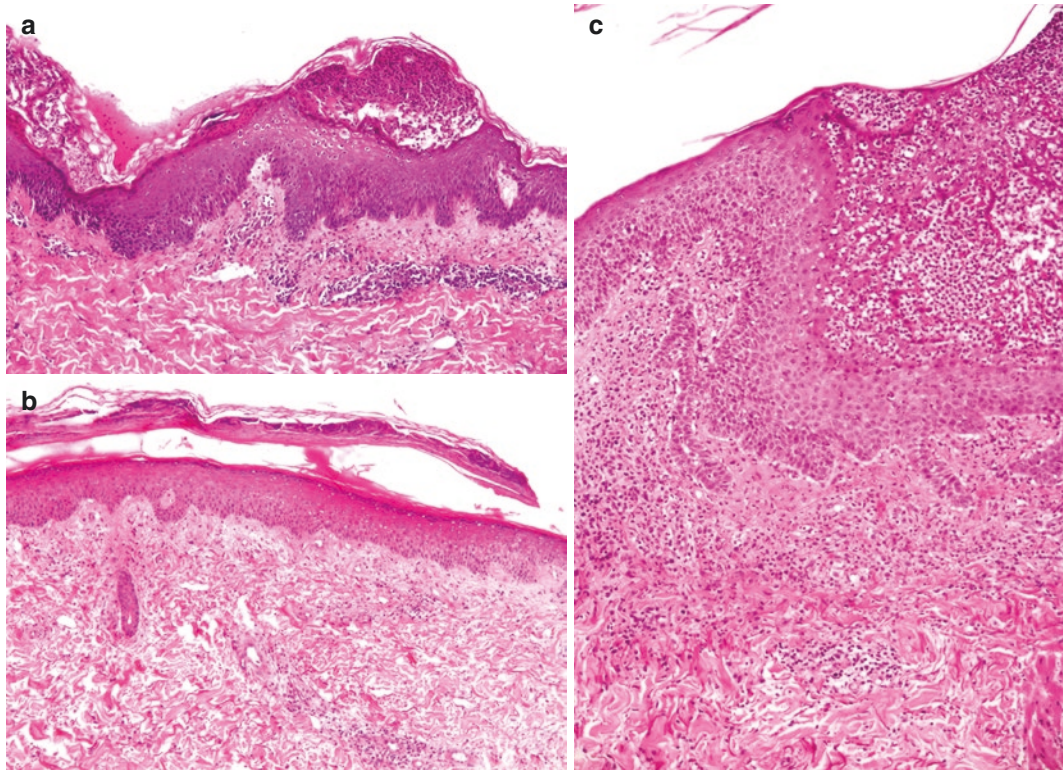

Fig. 6 Acute generalized exanthematous pustulosis (AGEP). (**a**) Early phase showing sub-corneal multilocular neutrophil pustule. Haematoxylin and eosin ×100. (**b**) Late phase showing loss of pustule and elimination of the nuclear debris within a parakeratotic scale. Haematoxylin and eosin ×100. (**c**) Active AGEP with sub-corneal pustule and a dense dermal infiltrate. Haematoxylin and eosin ×200

pustular psoriasis (Fig. 6a, c). Subtle findings which point away from pustular psoriasis and towards AGEP include the presence of eosinophils, necrotic keratinocytes, a mixed mid-dermal interstitial and perivascular infiltrate, and the absence of tortuous or dilated blood vessels (Kardaun et al. 2010). Histopathological diagnosis is aided by the biopsy of a fresh lesion; old pustules are rapidly eliminated from the stratum corneum (Fig. 6b). The small size of AGEP pustules may enforce the need for multiple levels to be cut to reveal the characteristic pathology.

7 Stevens–Johnson Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN)

SJS/TEN has a characteristic histological appearance. The disease is characterized by a massive and confluent apoptosis of epidermal keratinocytes, sometimes including those of the hair or sweat appendages. Keratinocyte death is so extensive that the epidermis detaches from the dermis (epidermal necrolysis) (Fig. 7). A dermal lymphocytic infiltrate is always present but of varying

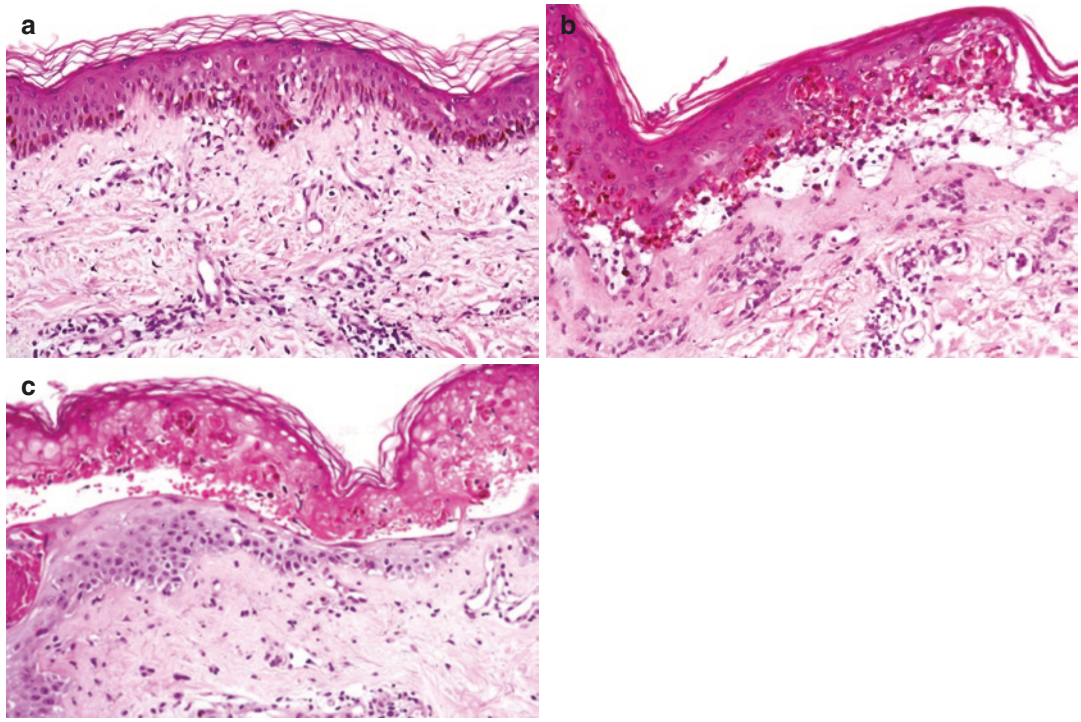

Fig. 7 Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). (**a**) Early lesion showing scattered apoptotic keratinocytes and a minimal dermal lymphocytic infiltrate. Haematoxylin and eosin ×200. (**b**) Established SJS/TEN showing confluent epidermal apoptosis and epidermal detachment. Haematoxylin and eosin ×200. (**c**) Late lesion of SJS/TEN with regenerated epidermis underlying the detached, necrotic epidermis. In the detached epidermis, there is evidence of secondary ischemic necrosis with keratinocyte pallor and vacuolization. Haematoxylin and eosin ×200

density: often, it is scanty and with a paucity which contrasts with the severity of epidermal pathology. The density of the infiltrate has no prognostic significance (Valeyrie-Allanore et al. 2013).

8 Fixed Drug Eruption (FDE)

A histopathological study of FDE demonstrated necrotic keratinocytes, spongiosis, vacuolar degeneration, eosinophils in 73% of cases, and dermal melanophages in 55% (Weinborn et al. 2016). In a further study of generalized bullous FDE (GBFDE) an interface dermatitis was always present, eosinophils were seen in 87.5% and dermal melanophages in all cases (Cho et al. 2014) (Fig. 8). Our studies have demonstrated that GBFDE can present with massive keratinocytes apoptosis, as is commonly seen in SJS/TEN, or with spongiotic and/or interface dermatitis inflammatory patterns. Cho et al. showed that GBFDE and TEN are slightly different, with more eosinophils and melanophages in GBFDE than TEN, and more granulysin + effector cells in the epidermis in TEN than GBFDE (Cho et al. 2014). Misukawa et al. and Shiohara et al. demonstrated that memory $CD8^+$ T cells were rapidly activated after drug intake and were thereafter maintained in the basal layer of lesional epidermis (Mizukawa and Shiohara 2010; Shiohara and Mizukawa 2007; Mizukawa et al. 2002, 2008). CD8+ T cells within the basal layer can be demonstrated in late and "quiescent" skin lesions of FDE (Fig. 8c, d).

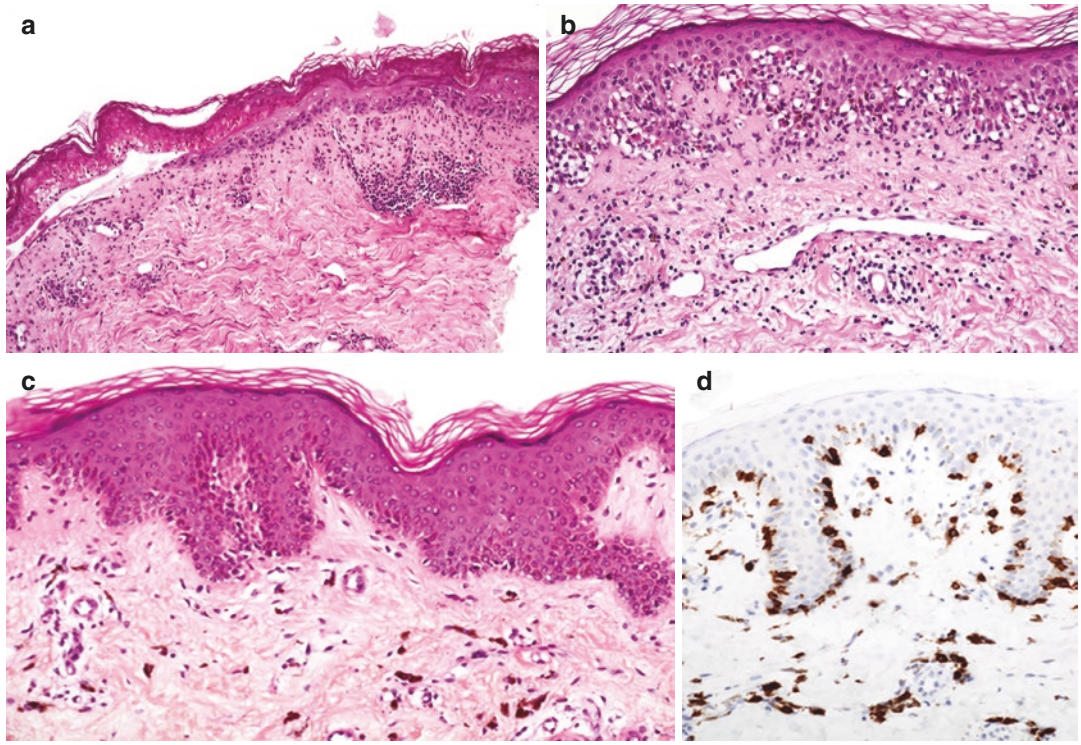

Fig. 8 Fixed drug eruption (FDE). (**a**) Bullous FDE with detached epidermis showing apoptotic keratinocytes, ischaemic necrosis and regenerated epidermis. Haematoxylin and eosin ×100. (**b**) FDE showing an interface dermatitis with numerous lymphocytes infiltrating the vacuolized basal layers of the epidermis and scattered apoptotic keratinocytes. Haematoxylin and eosin ×200. (**c**) Quiescent FDE with numerous melanophages in the superficial dermis with apparently normal overlying epidermis. Haematoxylin and eosin ×200. (**d**) The same sample as (**c**) showing a mild T-cell infiltrate of CD8+ effector cells aligned along the basement membrane zone. Anti-CD8 immunohistochemistry (DAB) ×200

9 Symmetrical Drug-Related Intertriginous and Flexural Exanthem (SDRIFE)

The histopathological features of SDRIFE have not been studies in detail. In our experience, SDRIFE shows a wide range of pathological patterns, including eczematous changes, sub-corneal pustules, superficial dermal oedema and an inflammatory infiltrate which may contain lymphocytes, neutrophils and eosinophils. The diagnosis of SDRIFE is not made from the dermatopathology; however, assessment of a skin biopsy can support the diagnosis in the correct clinical setting.

10 Problems of Differential Diagnosis in Drug Eruption Dermatopathology

Histopathological discrimination of SJS/TEN from other conditions presenting with extensive epidermal necrolysis is challenging. Severe cases of erythema multiforme, lupus erythematosus, dermatomyositis and GVHD can all share physical and dermatopathological manifestations with SJS/TEN. In this acute scenario confirmation of drug-induced SJS/TEN can only be achieved following a careful and informed synthesis of clinical and dermatopathological features.

Similarly, dermatopathological differentiation between a drug-induced exanthem, DRESS syndrome and a viral exanthem is difficult. This diagnostic obstacle may reflect the proposed role of herpesvirus reactivation in DRESS, an hypothesis supported by the identification of EBV-specific clonal T-cells in DRESS-affected organs (Picard et al. 2010). Some authors even suggest that DRESS is a viral disease triggered by medication, a herpesvirus-drug synergy which is well-documented by the eruption occurring in infectious mononucleosis treated with penicillin.

Of greater concern is the differentiation of DRESS from cutaneous T-cell lymphoma (CTCL). Features shared by DRESS and T-cell lymphomas include rash (especially erythroderma), lymphadenopathy, eosinophilia, and the presence of circulating atypical lymphocytes. Histologically, the infiltrate in DRESS may be composed of atypical lymphocytes, strongly resembling those seen in Sezary syndrome (Ortonne et al. 2015). The key features which discriminate DRESS from lymphoma include the presence of inflammatory alterations of the epidermis, the absence of pan-T-cell antigens loss, the negative search for neoplastic T-cell markers, such as CD158k/KIR3DL2 in Sezary syndrome (SS) (Ortonne et al. 2006, 2008) and TFH differentiation markers in angioimmunoblastic T-cell lymphoma (AITL) (Leclaire Alirkilicarslan et al. 2017). DRESS patients will not possess a dominant T-cell clone in the skin and blood. The lymphocyte infiltrates in DRESS are usually enriched in cytotoxic CD8+ effectors T-cells, some of which correspond to the morphologically atypical cells. By contrast, the neoplastic T-cells in SS and AITL are constantly CD4+. The mutational landscape of AITL is well described and recurrent mutations affecting epigenetic regulators (*IDH2* p.R172K/S) or the small RhoA GTPase (*RHOA* p.G17V) are recognized (Sakata-Yanagimoto et al. 2014; Lemonnier et al. 2016).

Despite the problems in differential diagnosis, dermatopathology plays a key role in the assessment of drug-induced skin disease. An understanding of common histopathological features and disease patterns helps the physician both to implicate medication as a trigger and to assign a specific drug eruption diagnosis. A skin biopsy and application of the dermatopathological principles outlined above have primacy in the management of all patients with a suspected cutaneous adverse drug reaction.

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Skin Tests in Evaluating Drug Eruptions

Margarida Gonçalo

Abbreviations

ACE	Angiotensin-converting enzyme
AGEP	Acute generalized exanthematous pustulosis
CADR	Cutaneous adverse drug reactions
DRESS	Drug reaction with eosinophilia and systemic symptoms
EGF	Epidermal growth factor
FDE	Fixed drug eruption
IDT	Intradermal tests
MED	Minimal erythema dose
MPE	Maculopapular exanthema
NSAIDs	Nonsteroidal anti-inflammatory drugs NSAIDs
PaT	Patch tests
SDRIFE	Symmetrical drug-related intertriginous and flexural dermatitis
SJS/TEN	Stevens–Johnson syndrome/toxic epidermal necrolysis
SPT	Skin prick tests

1 Introduction

Skin tests are used to study immune mediated hypersensitivity reactions to exogenous allergens, such as drugs. They are a useful component in the allergological evaluation of cutaneous adverse drug reactions (cADR) in which either an IgE mediated (immediate type hypersensitivity) or T-cell mediated (delayed-type hypersensitivity) is suspected. Collectively, these reactions have been traditionally classified as type B or unexpected and idiosyncratic drug reactions. The role of skin tests in other drug-induced reactions such as in drug-induced lupus erythematosus, drug-induced immunobullous diseases, drug-induced vasculitis, or lichenoid drug reactions has not been demonstrated. Similarly, skin tests are not useful in adverse reactions arising from the pharmacologic mechanisms of the drug (type A or augmented reactions). These would include bradykinin-mediated angioedema related to use of angiotensin-converting enzyme (ACE) inhibitors, mucocutaneous erosions due to methotrexate toxicity, or papulopustular eruptions induced by EGFR (epidermal growth factor receptors) inhibitors in cancer therapy (Gonçalo and Bruynzeel 2020).

Skin tests are intended to reproduce locally, in a controlled manner, the drug eruption that had originally involved a greater extent of the body (Gonçalo 2019). There are a variety of skin tests available for the evaluation of drug reactions and

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the choice is based on the underlying cADR phenotype and mechanism. Skin prick tests (SPT) and intradermal tests (IDT) with immediate readings are indicated for the evaluation of IgE mediated or type I hypersensitivity reactions such as urticaria and anaphylaxis, whereas IDT with delayed readings and epicutaneous patch tests (PaT) are indicated for the evaluation of nonimmediate T-cell-mediated drug eruptions. These include maculopapular exanthema (MPE); drug reaction with eosinophilia and systemic symptoms (DRESS); Stevens–Johnson syndrome/toxic epidermal necrolysis; and acute generalized exanthematous pustulosis (AGEP). Lesional skin testing (open tests or patch testing on lesional skin) are useful for the evaluation of fixed drug eruptions and photopatch tests are utilized for drug-induced photosensitivity.

Nonetheless, there are limitations with skin tests. False-negative readings can occur as a result of several factors: (1) only a small amount of the drug is applied on a localized area; (2) potential cofactors (such as viral infection and lupus flare) that may have been present during the original drug eruption are usually absent; (3) in skin testing, the body is exposed to the drug via a different route, that is, percutaneously instead of orally or intravenously; (4) percutaneous penetration of the drug may not be high enough to trigger an immune response; (5) cutaneous metabolism may be unable to convert the prodrug into the allergenic metabolites that triggered the reaction; (6) finally, timing of the tests is essential as false-negative results can be seen during the acute phase of the reaction.

Despite these limitations, there are several advantages with skin testing: (1) multiple drugs can be evaluated simultaneously, increasing the likelihood of a conclusive result; (2) the procedure is generally well tolerated with minimum discomfort; (3) most skin tests are generally safe and they can be used in severe reactions, like DRESS, and SJS/TEN where oral provocation is contraindicated (Gonçalo et al. 2010; Santiago et al. 2010; Barbaud et al. 2013; Trubiano et al. 2019); (4) in addition, concurrent skin testing with related chemicals, allows for the evaluation of cross-reactivity and provide valuable information on safe alternatives and drugs to avoid (Morgado et al. 2020).

2 Skin Tests for Immediate Drug Eruptions

SPT and IDT are indicated for immediate cutaneous reactions such as drug-induced urticaria, angioedema, or anaphylaxis. Although these have been utilized primarily in the setting of beta-lactam induced reactions, skin tests can be useful in other drug classes such as non-beta-lactam antibiotics, heparins, and radiocontrast media among others (Barbaud 2014; Brockow et al. 2005, 2013). These tests have little role in the study of pseudo-allergic anaphylactoid reactions, such as those induced by nonsteroidal anti-inflammatory drugs (NSAIDs) as well as those reactions which occur due to direct stimulation of the Mas-related G-protein-coupled receptor X2 (MRGPRX2). These reactions are typically induced by fluoroquinolones, opioids, vancomycin, neuromuscular blocking agents, and iodinated radiocontrast media (Navinés-Ferrer et al. 2018; Porebski et al. 2018). Nevertheless, many of these drugs may also induce IgE-mediated reactions that cannot be clearly distinguished based on clinical symptoms.

SPT is performed on the volar forearm with drug test solutions as well as negative and positive controls comprising of 0.9% serum saline and histamine, respectively. Skin reactions are read at 20 min, and a reaction is considered positive when the wheal is 3 mm larger than the negative control or has surrounding erythema or pseudopods (Barbaud 2014; Phillips et al. 2019). If the initial 1/10 dilution is negative, it should be followed within 20 min, by the highest nonirritating dilution (Romano et al. 2020).

Although IDT methodology is not fully standardized, a recent consensus proposes that IDT should be performed by injecting intradermally 0.02 mL of freshly prepared sterile drug solutions, on the volar forearm, upper arm or on the back. IDT can only be performed with drugs that

have soluble forms (Brockow et al. 2013; Barbaud et al. 2020). These tests should start with lower concentration (1/100 or 1/1000 in severe reactions), followed by increasing concentrations until the maximum nonirritating dilution is reached (Romano et al. 2020). Reactions are read at 20 min and considered positive if there is an increase of 3 mm occurs beyond the initial papule produced by the injection of the allergen (Romano et al. 2020; Barbaud et al. 2020). The ENDA (European Network for Drug Allergy) and EAACI (European Academy of Allergy and Clinical Immunology) have recently issued a guidance on maximum nonirritating dilutions for performing prick and intradermal drug testing as well as criteria for assessing positivity (Brockow et al. 2013; Barbaud et al. 2020).

Although generally safe, SPT and IDT should be performed in a setting where resuscitating measures are available, in the rare occurrence of a systemic immediate reaction.

3 Skin Tests for Nonimmediate Drug Eruptions

Intradermal tests with delayed readings and patch testing are indicated for the evaluation of nonimmediate T-cell mediated drug eruptions, such as MPE, DRESS, SJS/TEN, AGEP, SDRIFE, and FDE.

It is generally recommended for patch testing to be performed following 6 weeks after the complete resolution of the cADR till 6–12 months later. Nonetheless, positive PaT have been reported after 10 years in antibiotics and carbamazepine related nonimmediate cADRs (Barbaud et al. 2001; Johansen et al. 2015; Pinho et al. 2017a; Braun et al. 2018; Gilissen et al. 2020). This observation contrasts with immediate reactions where both specific IgE in the serum and SPT reactivity tend to fade with time.

Drug PaT are performed in the same way as for allergic contact dermatitis, with application of the allergens in patch test chambers on the back for 48 h and reading at day 2 or 3 and day 4–7, according to the European Society of Contact Dermatitis (ESCD) guidelines (Gonçalo and Bruynzeel 2020; Johansen et al. 2015).

Some drugs have already been commercialized as allergens for patch testing, mainly antimicrobials, anticonvulsants and nonsteroidal anti-inflammatory drugs (NSAIDs). Although these commercial panels have been shown to be safe and specific for diagnostics, they represent only a limited number of allergens within the extensive list of drugs that can be responsible for nonimmediate cADR.

For patch testing to other culprits, the drug has to be newly prepared from either the commercial preparation used by the patient or preferably, from the powder for parenteral use or the capsule content. The active drug in the final preparation should be at 10% in petrolatum (Johansen et al. 2015). When capsules or IV powder are unavailable, the whole powder of the tablet can be prepared at 30% pet, but there is a risk of having very little active drug in the final preparation (Brajon et al. 2014). Alternatively, the tablet can be smashed into a fine powder and placed directly into the test chamber with a drop of water and/or petrolatum (Assier et al. 2017). Whenever a patch test is positive with such a "homemade" preparation it is recommended to test serial dilutions as well as to have at least 10–20 controls to exclude false-positive irritant reactions. False-positive irritant reactions have been described particularly with the pills of spironolactone (Aldactone®), colchicine, captopril (Lopril®), chloroquine (Nivaquine®), celecoxib (Celebrex®) tested at 30% pet and with omeprazole (Mopral®) tested at 30% aq. (Brajon et al. 2014).

Drug PaT are considered positive when there is at least erythema and infiltration of the tested area. Occasionally, vesicles, bullae, or pustules can also be observed. These positive readings are a local reproduction of the clinical and histopathological features of the acute drug eruption (Gonçalo 2019; Gonçalo et al. 2010; Serra et al. 2011). Patch tests are highly specific and this has been supported by the following observations: (1) isolation of drug specific T cells from positive PaT with similar phenotypes as those exhibited during the acute eruption (Yawalkar et al. 2000),

(2) clinical and pathologic resemblance between the PaT and the acute eruption (Gonçalo 2019; Gonçalo et al. 2010; Serra et al. 2011), (3) their reproducibility even after long periods (Pinho et al. 2017a; Gilissen et al. 2020). As such, whenever a patient presents with positive PaT to a drug that may not be apparently relevant, a careful review of the exposure and drug history is mandatory, looking for hidden uses of the drug, a related chemical within the possible latency period which has resulted in cross-reactivity or to ask for previous episodes of cADR where the current positive PaT drug may have been involved (past/retrospective relevance).

It is recommended to test all possible culprits whenever a drug reaction is suspected. Widely used analgesics and antipyretics such as metamizole has been found to be responsible for recurrent exanthems in the inpatient or postoperative setting (Pinho et al. 2017b). Similarly, in DRESS, some individuals become sensitized to new medications, especially antibiotics that are initiated during the acute phase of the disease, resulting in flare-up reactions. If indicated, these new drugs should also be tested in addition to the main culprit (Santiago et al. 2020; Descamps et al. 2010). Also, as positive patch tests can be observed with cross-reactive drugs it is recommended that whole series of related chemicals (a whole series of antibiotics, of proton-pump inhibitors, etc.) should be tested to provide advice on safe alternatives (Romano et al. 2006, 2016a).

Sensitivity of drug PaT is highly variable and depends on both the phenotype of the cADR and the culprit drug. Some drugs never induce positive patch tests (e.g., allopurinol or its metabolite oxypurinol, salazopyrin) (Santiago et al. 2010; Barbaud 2014; Vieira et al. 2004), whereas others, like carbamazepine, induce more than 80% of positive PaT reactions in different types of cADR (Santiago et al. 2010). It is difficult to ascertain the real sensitivity of PaT in cADR. Drug challenge which is the comparative gold standard may not have been performed or is contraindicated, for example, in severe cutaneous adverse drug reactions. In addition, patient selection in many published studies is not well characterized (certain or possible drug imputability, diverse clinical phenotypes and methodologies). This has resulted in a wide range of PaT sensitivity (from below 10 to >75%) (Lammintausta and KorteKangas-Savolainen 2005; Osawa et al. 1990; Barbaud et al. 1998). In general most studies have shown that, PaT are very frequently positive in drug eruptions from carbamazepine, abacavir (Phillips et al. 2002), tetrazepam (Pirker et al. 2002), diltiazem (Assier et al. 2020), and pristinamycin (Barbaud et al. 2013), whereas positive patch tests occur in 20–30% of nonimmediate CADR from aminopenicillins (Romano et al. 2013; Pinho et al. 2017c), clindamycin (Gilissen et al. 2020; Pereira et al. 2011) or fluoroquinolones (Serra et al. 2011), and still less often with other drugs. The addition of IDT with late readings may increase drug PaT sensitivity, particularly in the case of penicillins (Romano et al. 2013), making this the most sensitive approach for studying nonimmediate drug reactions (Barbaud 2014).

Patch test positivity is also dependent on the phenotype of the drug eruption; positive PaT occur in 1/3 to 1/2 of the patients with MPE (Fig. 1a, b) and DRESS (Fig. 2a, b) (Santiago et al. 2010; Barbaud et al. 2013). It has been reported to be even more frequent in AGEP (Fig. 3), SDRIFE or drug-induced systemic contact dermatitis. Positive PTs are rarely seen in SJS/TEN (<10%) (Wolkenstein et al. 1996).

There are very rare reports of systemic drug reactions induced by patch testing. For example, immediate reactions occurring when patch testing is incorrectly used to study anaphylaxis or reactivation of the CADR when the suggested patch test concentrations are not followed in severe CADR (e.g., pristinamycin or rifampicin in DRESS or in rare cases of AGEP) (Barbaud 2014; Shebe et al. 2014). The safety of PaT is superior to both IDT and oral provocation, even in cases of severe drug eruptions like SJS/TEN and DRESS (Gonçalo et al. 2010; Santiago et al. 2010; Barbaud et al. 2013). A stepwise approach is advocated in the evaluation of delayed reactions. Testing should start with a PaT, followed by an IDT with a delayed reading. In nonsevere

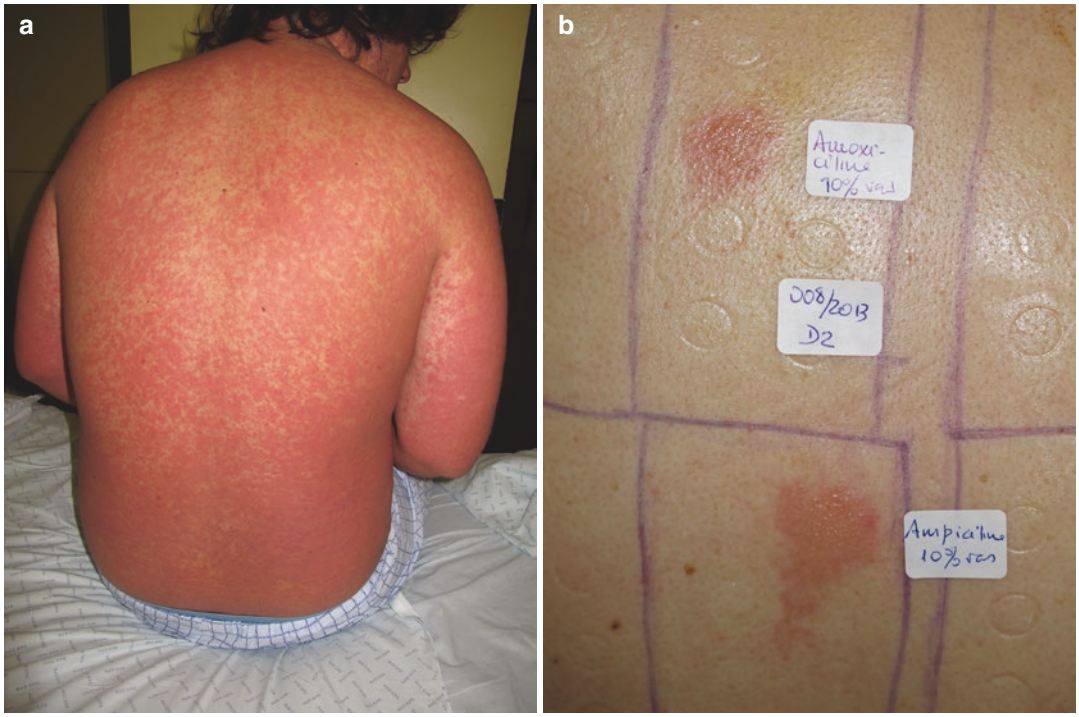

Fig. 1 (**a**, **b**) Maculopapular exanthema from amoxicillin (**a**) with positive patch tests with amoxicillin and ampicillin tested at 10% pet (**b**)

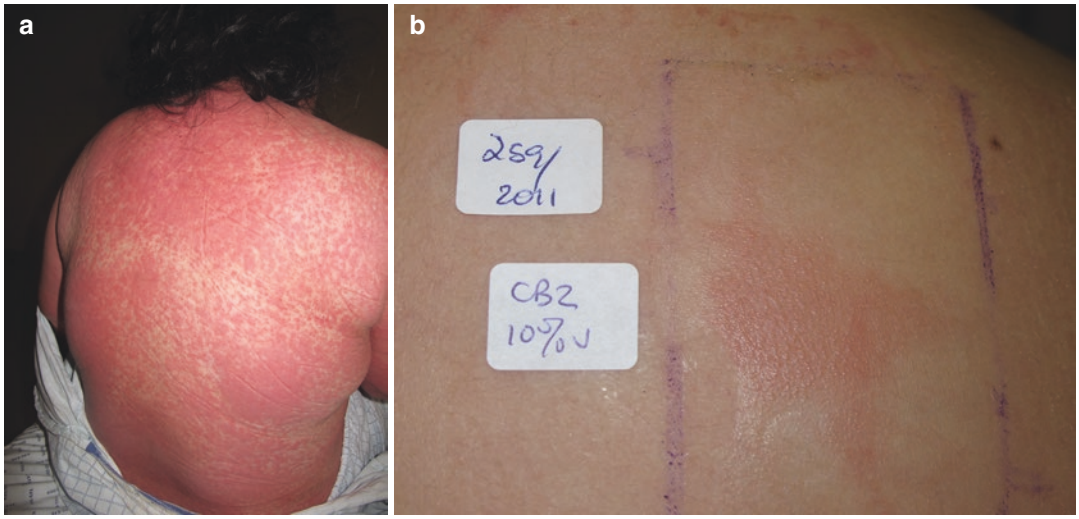

Fig. 2 (**a**, **b**) Exanthema in DRESS from carbamazepine (**a**) with positive patch tests to carbamazepine at 10% pet (**b**)

cases, an oral provocation can be considered if both skin tests are negative (Barbaud et al. 2001).

Intradermal tests for the evaluation of nonimmediate drug eruptions are performed in a similar manner, as in immediate reactions, with 0.02 mL of sterile drug solutions prepared according to the recommended concentrations (Brockow et al. 2013). Any papule at 24 h or later is considered

positive (Barbaud 2014). For some drugs, like heparins and corticosteroids, later readings (after D3) are usually needed (Fig. 4a, b). Largest studies with IDT deal mostly with antibiotics (ampicillin, amoxicillin, amoxicillin–clavulanic acid) (Romano et al. 2016b; Romano and Caubet 2014) and have shown that IDT is more sensitive than PaT, but false-positive reactions are more frequent with IDT than with PaT (Romano et al. 2004). Nonetheless, the IDT is still not the ideal skin test as 10% of negative patients may develop a cutaneous reaction on drug rechallenge (Hjortlund et al. 2013).

IDT is recommended in non-immediate drug eruptions where PaT are negative as well as exanthematous or eczematous reactions induced by heparins, local injection reactions from, biologics (infliximab, adalimumab, interferons) and non-immediate iodinated radiocontrast reactions (Barbaud 2014). Although initially believed to be associated with higher risk of recurrence in severe cutaneous adverse reactions and hence contraindicated (Barbaud 2014), recent data have suggested that IDT may be safe and a possible modality in such cases (Trubiano et al. 2019).

Apart from confirming a possible culprit, both IDT and PaT can be used to study cross-reactivity among drugs with results being confirmed by oral challenge in most instances. In delayed reactions, amoxicillin and ampicillin are cross-reactive based on PaT and IDT but this cross-reactivity rarely extends to benzylpenicillin, cephalosporins, or carbapenems (Romano et al. 2013; Pinho et al. 2017c). Similarly, frequent cross-reactivity in skin tests occurs within certain subgroups of cephalosporins, fluoroqui-

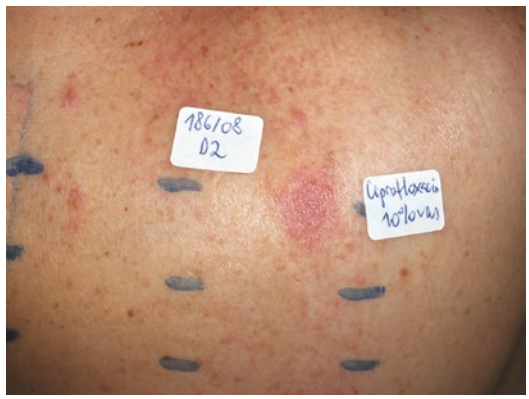

Fig. 3 Pustular patch test reaction to ciprofloxacin observed in a patient with AGEP

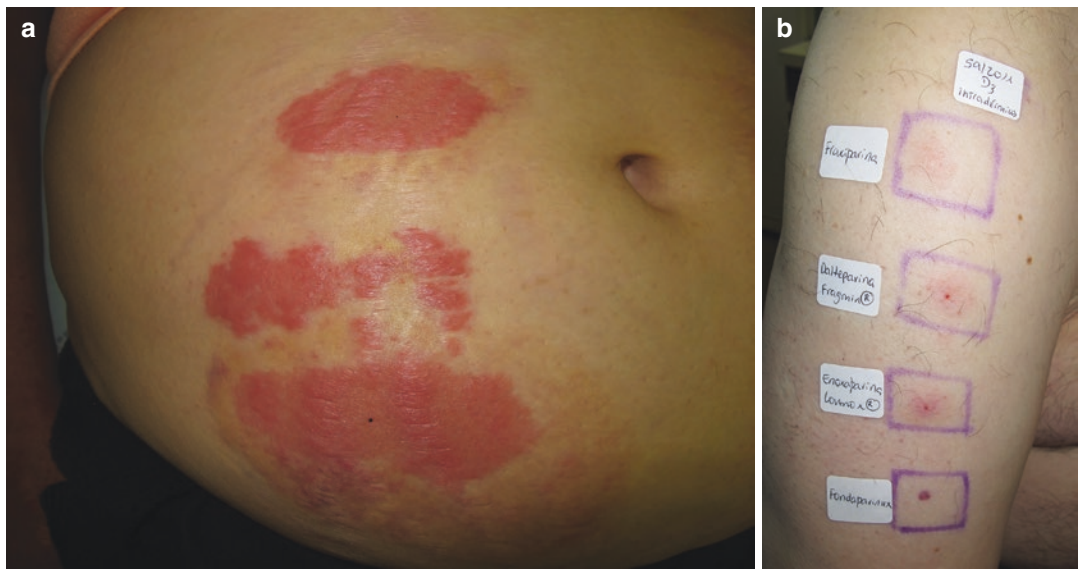

Fig. 4 (**a**, **b**) Eczematous plaques at the injection site of enoxaparin (**a**) with positive intradermal tests observed at day 3 to several LMW heparins tested as is (enoxaparin, dalteparin, and fraxiparin) and negative reaction to fondaparinux, where there is only purpura with no infiltration (**b**)

nolones, pristinamycin, and virginiamycin (Barbaud et al. 2004), as well as among heparins, radiocontrast media and corticosteroids (Romano et al. 2005). However, skin tests seldom express cross-reactivity among anticonvulsant drugs despite it being observed in clinical practice (Romano et al. 2005). In drug eruptions secondary to tetrazepam, PaT and oral provocation confirm the absence of cross-reactivity among other benzodiazepines, in contrast to the cross-reactivity of benzodiazepines seen in occupational allergic contact dermatitis (Barbaud et al. 2009; Vander Hulst et al. 2010).

4 Other Skin Tests

Lesional skin tests are indicated in fixed drug eruptions. PaTs with the possible culprit and related chemicals are applied for 24 h on inactive, residual lesions and, as a control, a duplicate patch is applied on normal back skin. Delaying patch testing to 6 weeks after acute flare of FDE is recommended to avoid false negatives. Due to the rapid reactivation of drug-specific tissue resident memory T cells in residual FDE lesions (Shiohara and Mizukawa 2012; Hoetzenecker et al. 2016), test readings can be performed at D1, or at D2/D3 if previously negative (Andrade et al. 2011). Positive reactions present with erythema and infiltration, occasionally with vesicles and/or bullae. In most instances, the normal skin shows no reaction (Andrade et al. 2011; Andrade and Gonçalo 2011; Calvão et al. 2020). As an alternative, especially in areas where occlusion or application of a patch test chamber is difficult (lips/genitalia), an open test with the culprit drug may also induce positive reactions (Alanko 1994). Oral provocation can be performed safely in patients with a limited number of lesions. NSAIDs are a group of drugs that are frequently positive on lesional testing (Fig. 5, Gonçalo et al. 2002). Similar to other settings, lesional PaT has been used to evaluate cross-reactions, suggesting safety of celecoxib in etoricoxib FDE (De Sousa et al. 2016) and advising against tenoxicam and hydroxyzine or levocetirizine in cases of piroxicam and cetirizine induced FDE respectively (Gonçalo et al. 2002; Cravo et al. 2007).

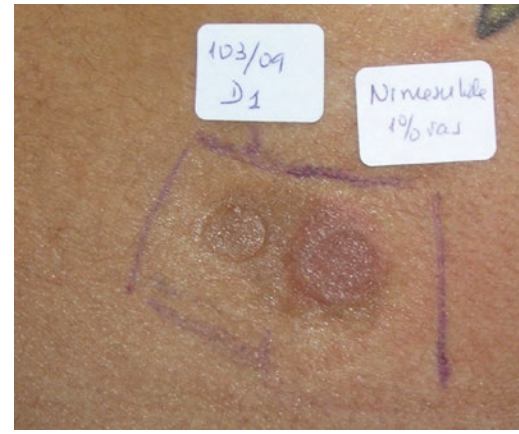

Fig. 5 Positive reaction from the NSAID nimesulide 10% pet. Observed at day 1 at a residual lesion of fixed drug eruption, and a negative reaction to ibuprofen tested on the left side of the same residual lesion

Photopatch tests are recommended to study systemic drug photosensitivity. As in photoallergic contact dermatitis, two equal sets of patches are applied in the back and at D1 or D2 one is irradiated with 5 J/cm^2 UVA, while the other is shielded from light. A third set of patches to be irradiated with UVB may be useful in a few cases. Readings are performed immediately after irradiation and 2–5 days thereafter, comparing irradiated and nonirradiated sites (Gonçalo et al. 2013). Photopatch tests have been shown to be frequently positive in photoallergy from piroxicam (Gonçalo et al. 1992) or ketoprofen (EMCPPTS Taskforce et al. 2012), and also in cases of photosensitivity from fluoroquinolones, hydrochlorothiazide, phenothiazines, pirfenidone, and vandetanib, among others (Gonçalo 2020). A positive photoprovocation test (induction of skin lesions by irradiation a small area of the nonexposed skin with UV-light while the patient is taking the drug) or a significant reduction of the MED (minimal erythema dose) with UVB or UVA while the patient is taking the drug followed by MED normalizing after drug withdrawal, can also be used to confirm the drug as the culprit for a photosensitive reaction (Gonçalo and Giménez-Arnau 2015).

5 Conclusions

The appropriate choice of investigations in the study of drug eruptions is dependent on the pattern of the drug eruption, a knowledge of the underlying pathomechanism as well as a as well as a detailed history of drugs and their associated latency. This data is of utmost importance to make the initial judgment on the possible culprits based on pharmacovigilance algorithms, like the Naranjo's adverse drug reaction probability scale (National Institute of Diabetes and Digestive and Kidney Diseases 2016) or the French pharmacovigilance criteria (Miremont-Salamé et al. 2016). As there are no standardized in vitro diagnostic tests, skin tests are extremely important to confirm the real culprit(s) in order to avoid unnecessary drug avoidance, the use of more costly and less effective alternatives as well as to avoid the recurrence of the drug reaction and inadvertent challenge.

When correctly performed and interpreted, positive skin tests can be of high value in the confirmation of the suspected culprit(s) drug(s). On the other hand, a negative skin test cannot exclude a highly suspicious drug, as sensitivity of skin tests for both immediate and delayed eruptions is far from 100%. In addition, skin tests can provide useful information on cross-reactivity which is of utmost importance for the clinician and the patient.

A stepwise and cost-effective approach in diagnostic skin testing is recommended. In immediate reactions it is recommended to begin with SPT followed by IDT and oral challenge in a unit with resuscitation facilities. In nonimmediate drug reactions, evaluation should begin with PaT followed by IDT and, eventually, oral challenge in nonsevere drug eruptions. In severe reactions, oral challenge is contraindicated and caution needs to be exercised in the use of IDT. Nonetheless, many aspects of drug skin testing will need further standardization. In addition, well-designed multicenter studies are needed to define the real sensitivity and specificity of skin tests with different drugs and phenotypes (Romano et al. 2020).

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In Vitro Drug Allergy Testing

Ying Xin Teo and Michael R. Ardern-Jones

1 Introduction

Identification of the culprit medication causing a drug hypersensitivity reaction (DHR) is essential to prevent recurrence of an allergic reaction in the future. Prevention is the preferred approach to this clinical problem since cutaneous adverse drug reactions can be life-threatening or be complicated by significant lifelong sequelae. However, identification of causal drug and recognition of possible drug cross-reactions can be challenging. In vitro assays are advantageous when compared to skin tests and provocation tests since there is no re-exposure to the suspect drug, making this form of allergy testing risk-free. Accurate diagnostic testing is necessary to avoid exclusion of tolerated medications and to identify medication that can be taken safely. The varied pathomechanisms underlying different DHR syndromes obliges the physician to select the most appropriate laboratory assay in order to minimise false negative results.

Cutaneous adverse drug reactions can present in a variety of ways including urticaria, maculopapular exanthems, eczematous or lichenoid eruptions, fixed drug eruptions and bullous dermatoses [notably Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)] (Brockow et al. 2019). Immunology-driven reactions can be classified into the immediate reactions, being mainly mast cell and IgE-mediated, and the delayed reactions, mediated by T cells (Hari et al. 2001; Beeler et al. 2006). In vitro tests detect specific markers or released mediators following stimulation of cell populations by the suspected culprit drug. Several approaches can be undertaken for the different DHR phenotypes (Table 1). Although many *in vitro* assays have been shown to be highly specific, their variable sensitivity limits clinical utility. These tests are therefore performed as part of a diagnostic algorithm alongside clinical history and skin tests. This is particularly the case in severe DHRs, for example SJS/TEN and drug reaction with eosinophilia and systemic symptoms (DRESS), where testing by drug provocation is contraindicated. In combination with detailed history of the patient's reaction a positive *in vitro* result can support the diagnosis of allergy.

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Table 1 Suitability of in vitro test based on clinical reaction phenotype

	Timing	In vitro test			
Phenotype	Onset after exposure	sIgE/RAST	BAT	LPA/LTT	ELISpot
Urticaria, angioedema, anaphylaxis[a]	Immediate (typically <1 h)	Yes	Yes[b]	No[c]	No
Maculo-papular exanthem	Delayed	No	No	Yes	Yes
DRESS	Delayed	No	No	Yes	Yes
SJS/TEN	Delayed	No	No	Yes	Yes
AGEP	Delayed	No	No	Yes	Yes
FDE	Delayed	No	No	Possible[d]	Yes

AGEP acute generalised exanthematous pustulosis, *BAT* basophil activation test, *DRESS* drug reaction with eosinophilia and systemic symptoms, *ELISpot* enzyme-linked immunospot, *FDE* fixed drug eruption, *LPA* lymphocyte proliferation assay, *LTT* lymphocyte transformation test, *RAST* radioallergosorbent test, *sIgE* specific immunoglobulin E, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

[a] Urticaria (mast cell mediated) needs to be distinguished from fixed urticaria, or urticated exanthems which are mediated by T cell hypersensitivity reactions and arise as part of delayed rashes

[b] Not routinely performed

[c] Lymphocyte proliferation is not routinely utilised for mast cell driven reactions, but lymphocyte (B cell) proliferation is induced by IgE ligation to antigen on the cell surface and can give rise to a positive LPA

[d] Enhanced sensitivity achieved by isolation of lymphocytes from skin biopsy of affected skin

2 Immediate Drug Hypersensitivity Reactions

Type I DHRs typically occur within 1 hour of exposure to drug: most are mediated by drug-specific immunoglobulin E (IgE) antibodies (Brockow et al. 2019, Demoly et al. 2014). Non-IgE-mediated immediate reactions ("pseudoallergic") can present with similar features and are usually due to direct stimulation of mast cell degranulation by drugs (e.g. opiates, non-steroidal anti-inflammatory drugs (NSAIDs), radiocontrast media). Quantification of released vasoactive mediators or phenotypic changes of activated cells can be harnessed to aid diagnosis. In various assays, β-lactam antibiotics and neuromuscular blocking agents (NMBA) have been the most widely studied.

2.1 Acute Phase Mediators

In the acute phase of a clinical reaction, measurement of peak serum tryptase levels and to a lesser extent histamine levels (with quantification of baseline levels) can be used to assess whether mast cell degranulation was implicated in mediating the reaction. Quantification of blood analyte concentrations can also act as an approximate marker of reaction severity. Tryptase, histamine, platelet-activating factor, prostaglandin D2 and leukotriene E4 have all been considered as potential biomarkers (Takazawa et al. 2019; Sanz et al. 2010). In both tryptase and histamine measurements, a degree of variability in sensitivity has been observed (31–67%; 61–92% respectively), as well as inter-individual variability (Mertes et al. 2003; Berroa et al. 2014). Measurement of serum tryptase 30–120 min after the acute event is the most widely used assay (Montañez et al. 2017). While positive predictive value (PPV) has been reported to be high (93%) when serum tryptase is elevated, the negative predictive value (NPV) is low (17%) (Buka et al. 2017). Innate variation of blood levels necessitates careful exploration of optimal measurement timing. Modification of currently used tryptase threshold to a calculated ratio (1.2 × [basal tryptase level] + 2 μg/L) has been suggested (Baretto et al. 2017) as being more specific, but compromises on sensitivity in perioperative anaphylaxis (sensitivity: 78%, specificity: 91%, PPV: 98%, NPV: 44%). Histamine, as the initial mediator released, could in theory confirm anaphylaxis; however, rapid metabolism by histamine transferase (half-life of 20 min) and non-specific elevation due to other causes (drug or food intake, presence of bacteria) limits its reliability as a diagnostic test (Montañez et al. 2017). In specific situations, other mediators have been shown to be discrimi-

natory, but these require further validation. Urinary leukotriene E4, for example, has high NPV (96%) for aspirin-exacerbated respiratory disease (Bochenek et al. 2018). The need for baseline level sampling, the problem of short half-lives and the possibility of falsely low levels in mild reactions all affect the utility of these acute phase markers.

2.2 Immunoassays

In the past serum drug-specific IgE (sIgE) was detected using the radioallergosorbent test (RAST), but this has now been superseded by enzyme linked immunosorbent assay (ELISA) or fluoroenzyme immunoassay (FEIA) (Takazawa et al. 2019). Allergens bound to a carrier protein are embedded in a solid phase polymer. Serum from an affected patient is flowed over the polymer chip. Allergen-specific IgE in the serum binds to the allergen on the chip and is quantified by addition of fluorescent anti-human IgE antibodies (Fig. 1). Due to technical limitations, detection cut-off was traditionally 0.35 kUA/L (arbitrary units of allergen per volume); however, with progressive technical improvement, lower levels have become measurable (Ebo et al. 2007). Commercially available testing kits are available for certain drugs, including β-lactam antibiotics, NMBAs, chlorhexidine, quinolones and biological agents. In identification of food and airborne allergens, high PPV have been found with application of appropriate cut-off values. The most widely studied antibiotic-specific IgE assays are for β-lactam antibiotics: reported sensitivity with penicillin testing for RAST is 42.9–62.5%, and 12.5–25% for FEIA. Detection rates reduce over time, and therefore it is recommended that testing should be performed within 3 years of the reaction (Takazawa et al. 2019; Fontaine et al. 2007). Findings of drug-specific IgE to penicillins,

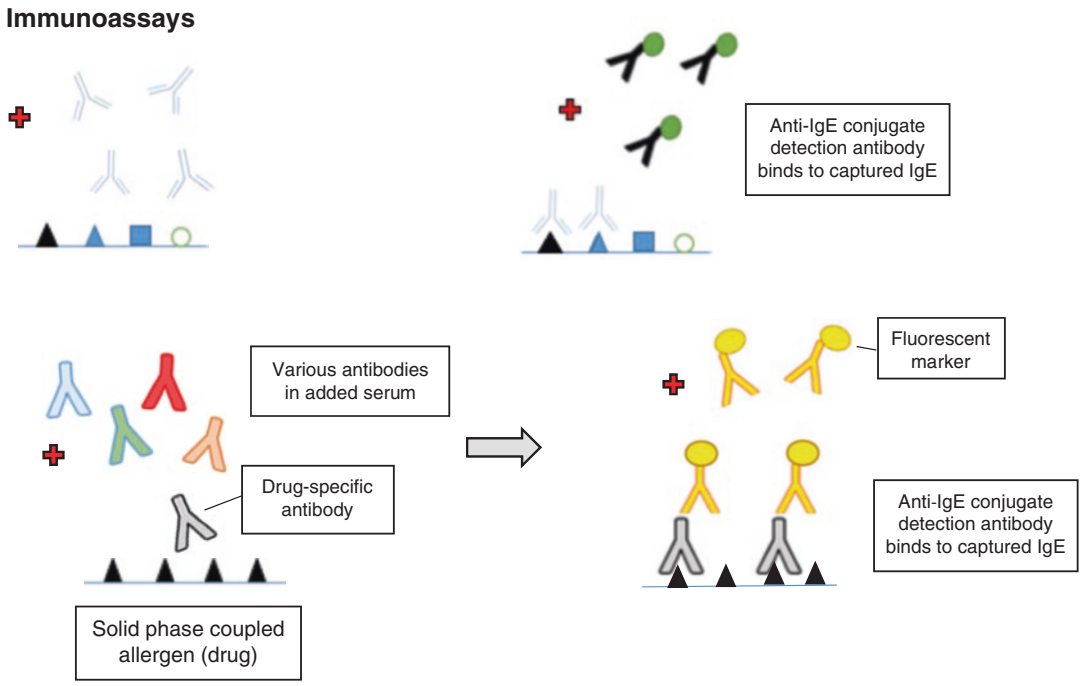

Fig. 1 Specific allergen (drug) bound to solid phase (usually polystyrene or cellulose wells). Anti-drug IgE (grey) present in sample serum binds to form antigen–antibody complex. Binding of detection antibody (yellow) coupled to either colour-emitting enzyme (ELISA) or fluorescence (FEIA). Intensity of signal generated is then measured against calibration curve of known concentrations of analyte

NMBA, chymopapain or tetanus toxoid does not necessarily equate to hypersensitivity and must be assessed in conjunction with the clinical history (Demoly et al. 2014). Sensitivity and specificity to β-lactam antibiotics varies between 0–85% and 52–100%, with reported values of 39–92% and 86–100% for NMDA (Decuyper et al. 2017). Similar to the acute phase reactants, the available time interval for sampling limits utility of testing to drug-specific IgE, as does the restricted spectrum and cost of commercially available assays. National Institute for Health and Care Excellence (NICE) review of diagnostic testing by specific IgE for immediate drug allergy reactions found that the quality of evidence was low and showed a high-false negative rate. This report concluded that blood testing for serum specific immunoglobulin E (IgE) to diagnose drug allergy should not be used in a non-specialist setting (Dworzynski et al. 2014; National Institute for Health and Care Excellence (NICE) 2018).

2.3 Basophil Activation Test (BAT)

Basophils are the effector cells of immediate hypersensitivity reactions in blood, whereas mast cells are tissue resident. In vitro tests for drug-induced degranulation target basophils; however, the principal mediators of IgE-mediated reactions are mast cells. While there are some differences between mast cells and basophils, it is largely accepted that basophils offer suitable model to predict mast cell responses. Following incubation (several minutes to hours) with suspect drug, changes in cell surface activation and degranulation markers are detected by flow cytometry via binding of specific fluorescent-labelled antibodies. Presence of cell surface markers enable detection and quantification of basophils (anti-IgE, CCR3, CRTH2 and CD203c) and stimulated basophils (CD203c and CD63) (Campos et al. 2019). CD63 is also expressed on activated platelets, degranulated neutrophils, monocytes, macrophages and endothelium; therefore, other markers such as CD123 and human leukocyte antigen-DR (HLA-DR) are also labelled on analysed cells. Transition of intra-cellular vesicles containing pre-formed mediators results in a pronounced rise of fluorescence intensity on detection of surface CD63 with concomitant upregulation of CD203c (Fig. 2). BAT has been validated in diagnosis of immediate drug hypersensitivity to NMBAs, beta-lactam antibiotics, iodinated radiocontrast media, NSAIDs, chemotherapeutic agents and several biological agents. Despite this, there remains significant variations in BAT test results (Campos et al. 2019; Mayorga et al. 2016). Direct assessment of basophils provides an advantage in assessment of non-IgE mediated pathways, including triggering of basophil degranulation by direct activation by opioids, iodinated contrast media, vancomycin and quinolones (McNeil et al. 2015). Studies differ on interpretation of positive findings, although a twofold increase in stimulation index (calculated by dividing mean fluorescence intensity of stimulated compared to control cells) is generally accepted (Campos et al. 2019). In general, the BAT has sensitivity between 40–90% and specificity of 80%, although this can be lower in testing to quinolones and NSAIDs. 6–17% of patients may not respond to stimulation (Hoffmann et al. 2015). In β-lactam antibiotics, BAT performs better compared to drug-specific IgE although findings may not corroborate with skin tests (De Week et al. 2009). Compared to serum IgE measurements, BAT better simulates the physiological presentation and overcomes the problem of unexposed epitopes in a solid-phase assay (Mayorga et al. 2016). Many factors affect the usefulness of BAT: variable sensitivity, differing protocols, capacity of isolated basophils to conjugate with serum proteins, and drug-carrier or drug-metabolite dependent stimulation. The BAT is recommended where skin tests are unavailable or have not elucidated clear results; it is also recommended in severe life-threatening reactions where drug provocation is contraindicated.

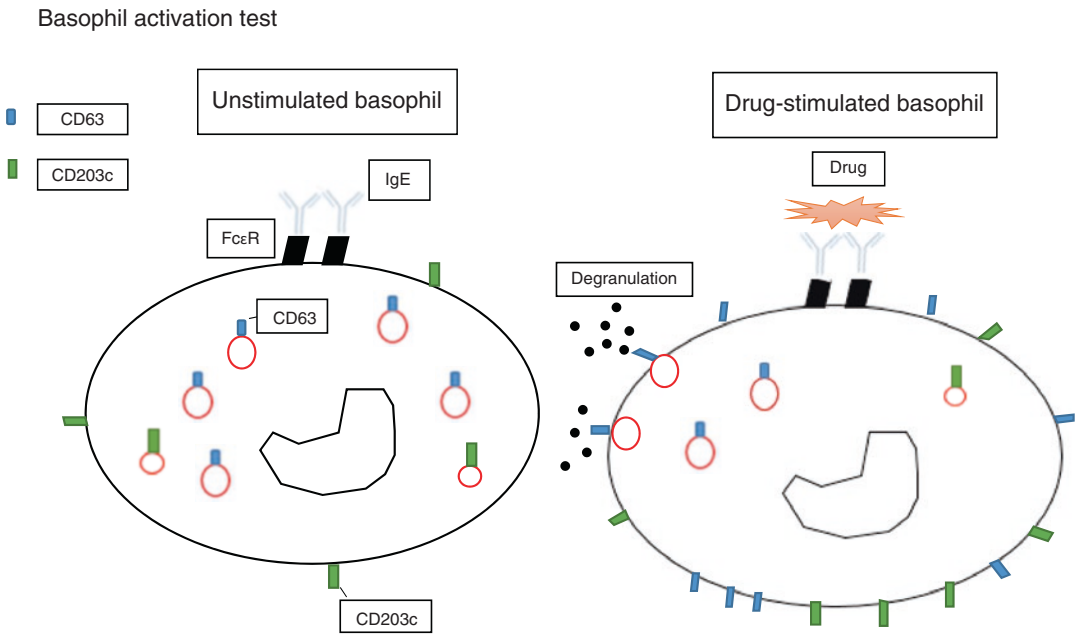

Fig. 2 Sensitised basophils become activated on re-exposure to drug, resulting in trafficking of intra-cellular vesicles to cell surface and upregulation of CD63 and CD203c, detectable by fluorescence-conjugated antibodies

3 Delayed Drug Hypersensitivity Reactions

The range of distinct clinical manifestations under the umbrella term of "delayed type IV DHRs" is thought to be mediated by differing T-cell subset responses unique to each phenotype (Table 2). Therefore, it is important to align the phenotype to the correct in vitro diagnostic method to achieve high sensitivity and specificity.

Exposure of lymphocytes to causal drug in an affected patient induces an immunological change which can be detected by an immunological assay. Tests utilised include lymphocyte proliferation assays (LPA; *syn.* lymphocyte transformation tests, LTT), enzyme-linked immunosorbent spot assay (ELISpot), enzyme-linked immunosorbent assay (ELISA) and flow cytometry (Table 3). Each assay uses different equipment and techniques and therefore availability of all methods may be limited to certain specialist centres.

3.1 Lymphocyte Proliferation Assay (LPA), Lymphocyte Transformation Test (LTT)

The lymphocyte proliferation assay has been the most widely studied in vitro test to determine drug culpability (Pichler and Tilch 2004). Peripheral blood lymphocytes are extracted from blood samples and cultured with non-toxic concentrations of suspected drug or control. Drug-specific T cells become activated by engagement of the T cell receptor with its cognate drug-related ligand, and this induces proliferation. Cell activation and proliferation does not occur in control experiments which omit the active drug. One approach to measurement of proliferation uses a radioactive isotope of thymidine (3H-thymidine). The radioactive nucleotide becomes incorporated in replicating DNA and proliferating cells are quantified by detection of the α-emitting radioisotope tritium. Following culture for 5–7 days with drug or control substance, 3H-thymidine is added to the T cells for

Table 2 Effector mechanisms and cytokine mediators in delayed drug hypersensitivity

Type of reaction	Immune response	Effector mechanism	Clinical features
IVa	Th1 Monocytes/macrophages Via IFN-γ, TNF-α	Monocytic inflammation	Bullous exanthem
IVb	Th2 Via IL-4, IL-5, IL-13	Eosinophilic inflammation	Maculopapular exanthem, DRESS
IVc	CD4+/CD8+ cytotoxic T cells Via perforin, granzyme B, FasL	Keratinocyte death	Maculopapular exanthem, FDE, SJS/TEN
IVd	T cells Via IL-8/CXCL8, GM-CSF	Neutrophilic inflammation	AGEP

AGEP acute generalised exanthematous pustulosis, *DRESS* drug reaction with eosinophilia and systemic symptoms, *FDE* fixed drug exanthem, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis
*Adapted from Posadas and Pichler (2007)

Table 3 In vitro tests in delayed drug hypersensitivity

In vitro test	T cell change	Assay
^{3}H-thymidine incorporation, CSFE label, bromodeoxyuridine (BrdU) incorporation	Proliferation	Clonal expansion (LPA) Transformation to blast cells (LTT)
Flow cytometry	Phenotype	CD69, CD38, CD25, CD40L cleavage
ELISA, ELISpot, flow cytometry	Function	Cytokine synthesis and secretion (IL-2, IL-5, IL-13, IFN-γ)
ELISA, ELISpot, flow cytometry	Function	Cytotoxicity (perforin, granzyme B, granulysin, CD107a)

CFSE carboxyfluorescein succinimidyl ester, *ELISA* enzyme-linked immunosorbent assay, *ELISpot* enzyme-linked immunosorbent spot, *IFN-γ* interferon gamma, *IL* interleukin, *LPA* lymphocyte proliferation assay, *LTT* lymphocyte transformation test

4–5 h. The cells are the washed to remove excess 3H-thymidine, before lysing and filtering to allow DNA binding to a multiwell plate. The amount of proliferation (count per minute = cpm) is then assessed in a plate reader which measures the radioactivity of each well. Stimulation index (SI) [cpm culture with drug/cpm culture without drug] above 2.0 is typically considered the threshold for positivity, although higher SIs such as >3 has been suggested for beta-lactam antibiotics (Pichler and Tilch 2004). Published sensitivity and specificity has been wide-ranging (14.9–75% and 63–100% respectively) (Mayorga et al. 2016) and are likely to be drug and phenotype dependent. Certain drugs (vancomycin, NSAIDs, radiocontrast media) may intrinsically result in proliferation even in patients without hypersensitivity to these medications (Pichler and Tilch 2004). In SJS/TEN, sensitivity and specificity of LPA are lower when compared to other reaction phenotypes (MPE, DRESS, FDE and AGEP) (Porebski 2017). LPA for β-lactams has been the most widely tested (sensitivity 58–88%, specificity 83–100%) (Mayorga et al. 2019) but the assay has been used with other known delayed hypersensitivity drug culprits, such as anti-convulsants, NSAIDs, sulfanamides and quinolones.

3.2 Flow Cytometry

Flow cytometric analysis is an alternative approach to measurement of T cell proliferation using a non-radioactive approach (Fig. 3). Carboxyfluorescein succinimidyl ester (CFSE) covalently binds to cytoplasmic molecules in cells. Cell proliferation results in reduction in CFSE staining in daughter cells in comparison with non-proliferating populations, which remain CFSE bright (Fig. 2). Flow

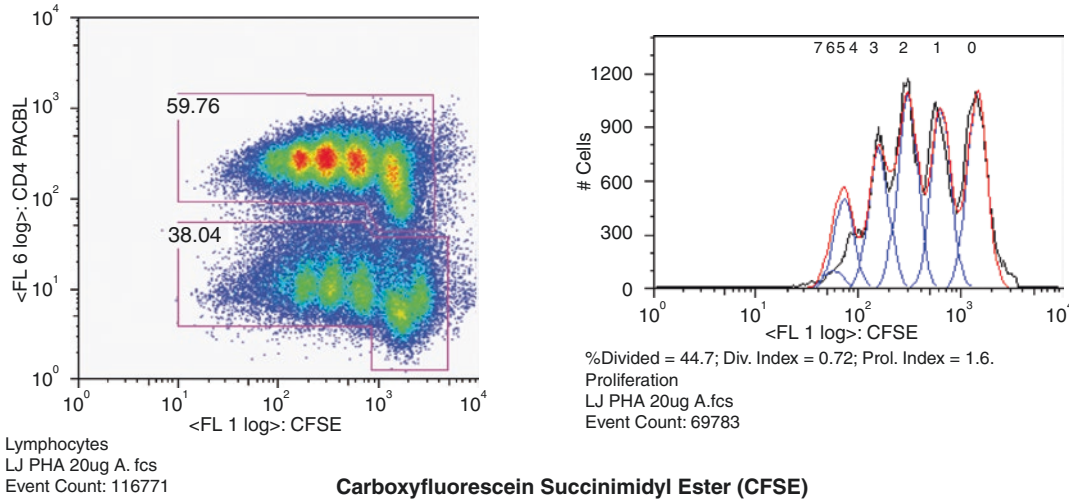

Fig. 3 Fluorescent CFSE-labelled T cells measured with flow cytometry. Non-proliferating cells produce the brightest peak, with sequential decrease as intra-cellular CFSE is incorporated into dividing cells

cytometry is used to analyse activation and, similar in principle to the BAT, phenotypic changes of T lymphocytes activated by drug exposure show changes in expression of key surface markers [e.g. CD25, CD38, CD69, CD71, CD154 (CD40L) and HLA-DR] (Porebski 2017; Beeler et al. 2008). The proportion of cells expressing a particular activation marker varies with the drug tested and reaction phenotype.

3.3 Enzyme-Linked Immunospot (ELISpot) and Enzyme-Linked Immunosorbent Assay (ELISA)

Both ELISpot and ELISA assays are functional tests, designed to detect cytokine production following drug-induced T cell activation (Fig. 4). The ELISA methodology relies on plate-bound anti-cytokine monoclonal antibodies. By incubating culture supernatants of activated T cells, the cytokine of interest is captured by the plate. A secondary anti-cytokine (targeting a different cytokine epitope) is then applied, followed by strategies to amplify a colorimetric signal to detect the concentration of bound anti-cytokine antibodies. Therefore, the ELISA measures the concentration of soluble molecules released by T cells.

ELISpot uses a similar approach, but the cells are exposed to drug directly on the anti-cytokine coated plate surface. Drug-specific T cells activated on exposure to drug release cytokine into the area on the plate where the cells are adherent. Cytokine detection is undertaken in the same way with detection antibody and colorimetric amplification. The localised cytokine release results in "spots". Therefore the ELISpot test quantifies the number of cells releasing a specific cytokine or other protein (e.g. IFN-γ, IL-4, IL-5, IL-17, granulysin, sFasL or granzyme B) following activation by the drug in question. The IFN-γ ELISpot has been the most widely used in drug hypersensitivity reactions, but other cytotoxic markers (granulysin and granzyme B) have also been assayed in severe cutaneous reactions (Porebski et al. 2011). Compared to the proliferation assays, these functional assays are advantageous as they are less reliant on cell proliferation, do not require use of radioisotopes, and can yield a result quickly.

Taking into consideration limitations of individual assays, combinations of T cell assays have been shown to increase sensitivity above that of single assay interpretation (Table 4).

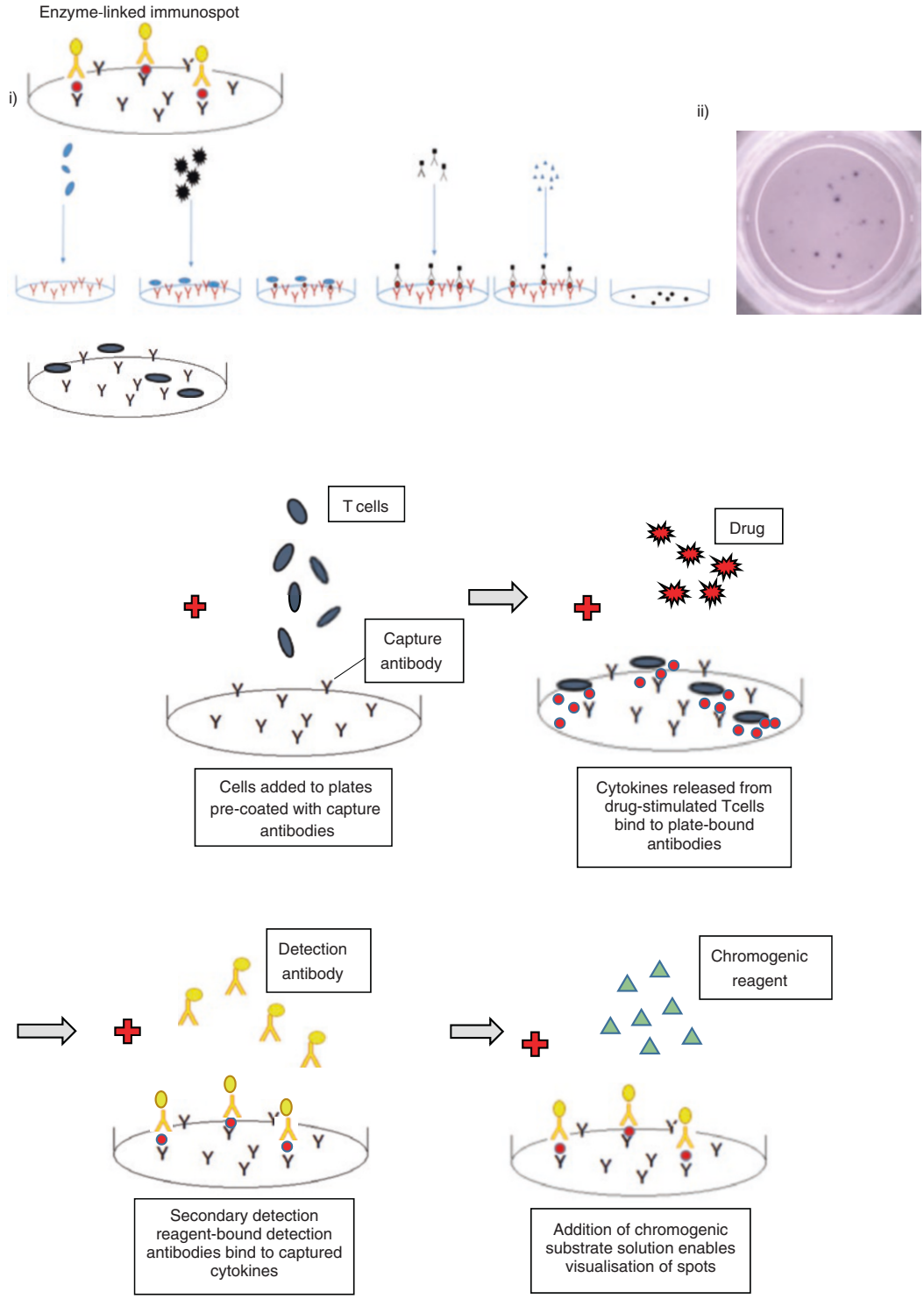

Fig. 4 ELISpot test. (**i**) Plates are initially pre-coated with antibody specific to the cytokine/chemical mediator of interest. Release of mediator from added drug-stimulated T cells are captured. Antibody conjugated to an enzyme enables visualisation of spot-forming units (SFU). (**ii**) Positive ELISpot assay on testing to ranitidine (Teo and Ardern-Jones 2020). T cells stimulated with (**a**) ranitidine (**b**) media (negative control) (**c**) phytohaemagglutinin (PHA) (positive control) respectively

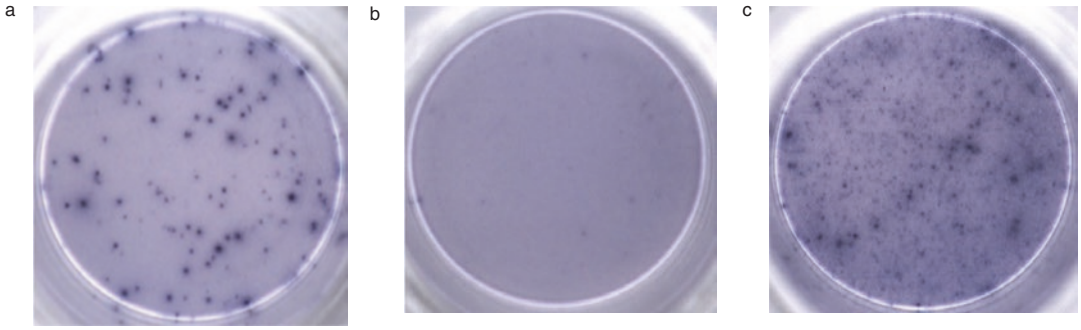

Fig. 4 (continued)

Table 4 Sensitivities of combination T cell tests in delayed drug hypersensitivity

Publication	*n*	DHR type	Drug analysed	Combined sensitivity
Martin et al. (2010)	19	Various	Various	Flow cytometry and ELISA: 100%
Porebski et al. (2013)	15	SJS/TEN	Various	Granulysin expression + granzyme B ELISpot + IFN-γ: 80%
Polak et al. (2013)	43	Various	Various	LTT + ELISpot IFN-γ + IL-4: 83%
Tanvarasethee et al. (2013)	25	MPE	Cephalosporins	ELISpot IFN-γ + IL-5: 40%
Kumkamthornkul et al. (2018)	20	DRESS, SJS/TEN	Anti-epileptic	DRESS: LTT + cytokines: 56.3–75% Cytokines combined: 75–81.3%
				SJS/TEN: LTT + cytokines: 30–55% Cytokines combined: 45–50%

n number of patients, *DRESS* drug eruption with eosinophilia and systemic symptoms, *ELISA* enzyme-linked immunosorbent assay, *ELISpot* enzyme-linked immunosorbent spot, *IFN-γ* interferon gamma, *IL* interleukin, *LTT* lymphocyte transformation test, *GzB* granzyme B, *MPE* maculopapular exanthem, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis

3.4 Practical Utility of In Vitro Tests

In vitro tests represent an attractive method to: (a) confirm diagnosis of drug hypersensitivity, (b) identify the culprit drug, and (c) explore potential cross-reactivity. These three objectives are reached without the risk of exposing an affected individual to culprit drug. However, the very nature of this *ex vivo* advantage is its primary limitation: the human immune system can never be perfectly replicated in a culture well. For example, certain drugs require prior liver metabolism in order to become antigenic, a process not mirrored in cell cultures systems.

A further problem relates to the tested compound. At first glance, use of the medicine dissolved in aqueous form is the obvious choice; however, most medications are compounds of drug, excipients and binding agents. Testing a pure substance is preferable to avoid confounding results from excipients but obtaining pure drug can be complicated if it is not commercially available in this form. Solubility of the tested drug has to be taken into consideration to ensure that the appropriate buffer is used. In some situations the hypersensitivity reaction is caused by an unspecified drug metabolite; in other cases the threshold concentration for toxicity is unknown.

Protocols are lengthy, time-consuming and vary from laboratory to laboratory, all of which contributes to differences in reported sensitivity. Testing is performed at a range of concentrations,

using a variety of drug preparations (or pure drug if available) and, when possible, known drug metabolites. Specialist equipment, technically complex protocols and the need for radioactive reagents result in these assays being restricted to specialist laboratories.

Proliferation assays are reliant on induction of proliferation by drug compared to that measured in control experiments (background). High background proliferation in the collected blood samples, for example in settings of concurrent infection, can result in difficulty in interpretation of assay read-outs. Similarly, immunosuppressant drugs such as azathioprine, ciclosporin and systemic corticosteroids impair proliferation and reduce the sensitivity of the assay (Pichler and Tilch 2004). Therefore, both a negative (no stimulation) and a positive (mitogen stimulation) control should be included in all diagnostic assays. Assays less reliant on proliferation, such as the ELISpot or ELISA, are better options for drugs which can inhibit proliferation. All assays are inhibited by drugs which exert their mode of action by direct toxicity, for example, chemotherapeutic agents.

Drug provocation remains the "gold standard" for diagnostic accuracy. However, for ethical reasons, this is not a practical option in severe cutaneous adverse reactions because of a significant risk of disease induction. As a consequence, correlating the results of novel diagnostic assays with the "true" cause is challenging and not usually reported in publications. Instead, most approaches examine the proportion of positive cases identified by the novel assay, in a cohort of patients with a "known" drug allergy. While this approach facilitates a reasonable analysis of specificity, it makes true measures of sensitivity limited.

In both immediate and delayed DHRs the combination of multiple tests yields a sensitivity range of 65–76% in immediate DHR, and 50–79% in delayed DHR (Mayorga et al. 2017). Several technical difficulties can interfere with the interpretation of results. The timing of the test is crucial, for example the short half-lives of tryptase and histamine can give rise to falsely low levels if sampled at a late timepoint. The duration of drug-specific T cells persistence following a delayed DHR remains unclear, an uncertainty which can potentially compromise assays. Persistence of drug-specific T cells has been documented years following index reaction (Beeler et al. 2006), but it is likely that immunity against a drug will wane over time. Conversely, biological samples taken for analysis during the active phase of the reaction can cause high background signals in assays. Nonetheless, proliferation tests during the acute period of SJS/TEN are often positive (Kano et al. 2007).

Consideration is therefore required of test suitability in the context of suspected drug, phenotype of the reaction, and acuteness of the illness at the time of sampling. Test results require careful interpretation as these act as surrogate markers of *in vivo* processes; a negative assay does not definitely exclude drug imputability, while a positive finding demonstrates sensitivity but not necessarily causality (Table 5).

Table 5 Benefits and limitations of *in vitro* tests

Pros	Cons
• Safe: avoids patient re-exposure to culprit drug, particularly relevant in the severe cutaneous adverse reactions • Can be performed to wide range of medications • Simultaneous assessment of multiple drugs • Facilitates examination of cross-reactivity • Can be undertaken remotely (by a distant site) • Demonstrates pathomechanisms of drug hypersensitivity • Potentially may provide the opportunity for pre-emptive testing with high risk drugs • Usable for widespread drug allergy testing, compared to skin testing	• Extent of sensitivity and specificity dependent on phenotype of reaction and drug • Not suitable for immunosuppressive drugs • Unclear pathomechanism of some delayed drug reactions limits usage of appropriate biomarker • Specialist skills and equipment needed • Time-dependent following onset of reaction • Relevance of *in vitro* response in tolerant individual unclear • False negatives likely with intake of concurrent immunosuppressant medications • Requires testing to correct drug metabolite

4 Conclusions

In vitro testing offers a valuable tool in the investigation of drug hypersensitivity, but is currently underused as an approach to identify culprit (and safe) drugs. Principally this is due to the complexity of test methodology and the problems in determining sensitivity and specificity—the results cannot be compared against challenge data. Despite uncertainties over sensitivity, *in vitro* assays show good specificity, meaning that they can reliably confirm immunological hypersensitivity and provide useful information to recommend avoidance of a culprit drug and related medications. In challenging cases, where definitive confirmation with drug provocation is required, these assays can be used to de-risk the process by providing an analytical step before human exposure (Ardern-Jones and Mockenhaupt 2019). Furthermore, testing multiple drugs and exploration of cross-reactivity can guide future therapeutic options. Increased availability of *in vitro* assays by their incorporation into diagnostic algorithms should be seen as an important goal in the future management of drug hypersensitivity reactions.

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Part II

Reaction Patterns

Drug-Induced Urticaria

Karen J. L. Choo, Alison V. Sears, and Clive Grattan

1 Introduction

Urticaria is characterised by the sudden appearance of weals, angioedema or both (Zuberbier et al. 2018). A weal consists of a fleeting, itchy or burning, variably sized swelling which is usually surrounded by reflex erythema. Classically the skin returns to its normal appearance within 1–24 h. Angioedema is characterised by a sudden pronounced swelling of the lower dermis and subcutis, often painful rather than itchy, which frequently occurs at sites deep to mucous membranes. Resolution of angioedema takes longer than weals, typically up to 72 h. Weals and angioedema often co-exist in the same patient but may appear sequentially or independently. The clinical features of drug-induced urticaria are indistinguishable from those of spontaneous urticaria (Fig. 1).

After drug-induced exanthems, urticaria is the second most common type of drug eruption pattern. A drug-induced exanthem classically presents as a morbilliform or maculopapular eruption but there may be a degree of clinical overlap with urticaria if the exanthem is urticated (i.e. urticaria-like). An exanthem typically involves the trunk and proximal limbs and is more persistent than urticaria, lasting up to a week. Unlike urticaria, exanthems are fixed and tend to resolve with desquamation and, on occasions, post-inflammatory dyspigmentation. Anaphylaxis and serum sickness are other disorders which can be caused by drug hypersensitivity and may be characterised by urticaria or an urticated dermatosis.

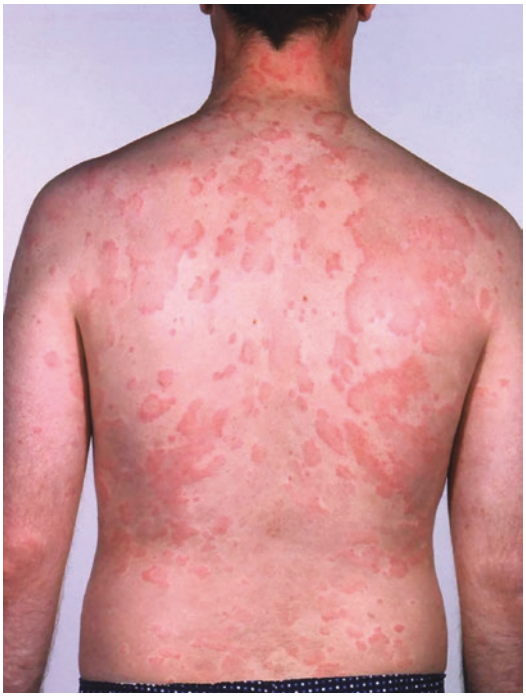

Fig. 1 Drug-induced urticaria. An extensive eruption of widespread weals induced by ibuprofen

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Drug-induced urticaria (DIU) is a term used to encompass urticaria caused by, or aggravated by, medication. DIU may present with weals alone, angioedema alone or both. Acute DIU usually occurs within 24 h of ingesting a drug, and less than 1 h if the individual is pre-sensitised with specific IgE against the culprit (allergic urticaria). The drug in question is usually easy to identify given the short latency period between drug exposure and development of urticaria. DIU may occur the first time a culprit drug is ingested (in the context of a histamine liberator, such as codeine) or after many exposures to a drug which was previously tolerated, indicating the development of a new IgE response. Resolution is expected within days of stopping the culprit drug, although sometimes it may take longer.

In urticaria lasting more than 6 weeks (chronic urticaria), a culprit medication may be harder to identify, making differentiation between DIU and idiopathic chronic spontaneous urticaria (CSU) more challenging. An episodic eruption of urticaria over at least 6 weeks should raise the possibility of a drug cause if there is a history of co-incidental drug exposure. However, continuous chronic urticaria is unlikely to be drug related. Analgesia, antipyretics and non-steroidal anti-inflammatory drugs (NSAIDs) have been widely implicated, however, unlike in acute DIU, they usually aggravate rather than cause urticaria. Risk factors that may predispose an individual to NSAID-aggravated urticaria include personal history of atopy (Asero 1999), being female (Sánchez-Borges et al. 2002) and a previous episode of NSAID-induced urticaria.

2 Pathophysiology

DIU may be immunological (allergic) or non-immunological (due to intolerance) (Fig. 2). IgE-mediated urticaria accounts for fewer than 10% of all DIUs (Tan and Grattan 2004).

Regardless of the pathomechanism, both immunological and non-immunological urticaria share similar allergy symptoms caused by mast cell mediators such as histamine, platelet activating factor (PAF) and cysteinyl leukotrienes (Montañez et al. 2017; Castells 2017).

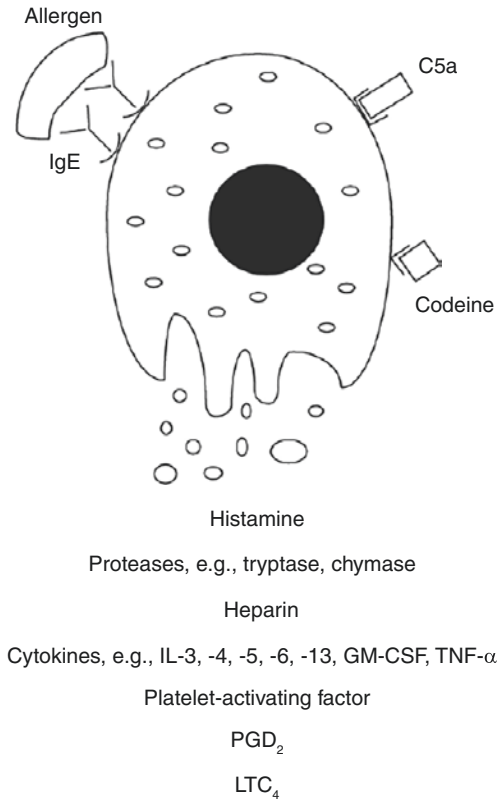

Fig. 2 Mechanism of mast cell degranulation: immunological (IgE mediated) and non-immunological methods. (Taken from Tan and Grattan (2004))

2.1 Immunologically Mediated Reactions

IgE Antibody-Dependent Reactions

A type I hypersensitivity reaction (Gell and Coombs classification) is invoked by cross linking of the drug (hapten) with specific drug IgE bound to IgE receptors on mast cells and basophils. It can only occur if the individual has been previously exposed to the drug, this process is otherwise known as sensitisation. On re-exposure to the drug, the hypersensitivity reaction occurs immediately. Antibiotics, and anticonvulsants are examples of drugs which may cause DIU via these pathways.

Formation of Immune Complexes

In this type of reaction, soluble drug-specific IgG, IgM and IgA immune complexes activate the complement pathway, resulting in release of

C3a and C5a anaphylatoxin. These anaphylatoxins trigger degranulation (activation) of mast cells and basophils with release of pro-inflammatory mediators, such as histamine, and induction of an acute inflammatory response. It is this pathway which accounts for the biological responses in urticarial vasculitis and serum sickness. Symptoms of serum sickness may appear 6–14 days after initial exposure to the culprit drug, the time needed to produce antibodies. Fever and constitutional symptoms are followed by a widespread exanthem which may be urticated. Visceral involvement with arthralgia and arthritis are hallmarks of serum sickness. Penicillins, anti-sera and thiouracils have been reported to cause serum sickness.

2.2 Non-Immunological Reactions

Unlike the IgE mediated reaction, there is no sensitisation phase and reactions may occur on first exposure to the drug. Reactions may occur up to 24 h after ingestion, although up to 50% occur within the first 6 h. They appear to be dose-dependent with a "threshold dose" which, once crossed, will induce a reaction.

Direct Mast Cell Degranulation

Opioids pain killers, such as codeine and morphine, best demonstrate this pathomechanism. Historically, codeine was used as a positive control for skin prick testing due to its ability to degranulate cutaneous mast cells, thereby producing a weal and flare response. Other medications that may cause this include antibiotics, such as polymyxin B, ciprofloxacin, vancomycin, as well as anaesthetic muscle relaxants (e.g. atracurium) and iodinated radiocontrast media. These drugs are referred to as "histamine liberators".

Kinin-Mediated Angioedema

Angiotensin converting enzyme (ACE) inhibitor-induced angioedema is associated with decreased degradation and catabolism of bradykinin. ACE converts angiotensin I to angiotensin II in the renin–angiotensin–aldosterone system. ACE also functions as a kininase. Inhibition of ACE results in a build-up of bradykinin, which is demonstrable during episodes of ACEi-induced angioedema (Stone and Brown 2017). Bradykinin causes vasodilatation and increases vascular permeability leading to tissue oedema.

Interference with the Arachidonic Metabolism

NSAID-induced angioedema (and urticaria) can be explained partly by shunting of arachidonic metabolites from the cyclo-oxygenase to the lipoxygenase pathway, resulting in an overproduction of pro-inflammatory leukotrienes (LTC_4, LTD_4 and LTE_4) (Doña et al. 2020), and reduced production of the inhibitory prostaglandin E2 (PGE_2) (Fig. 3).

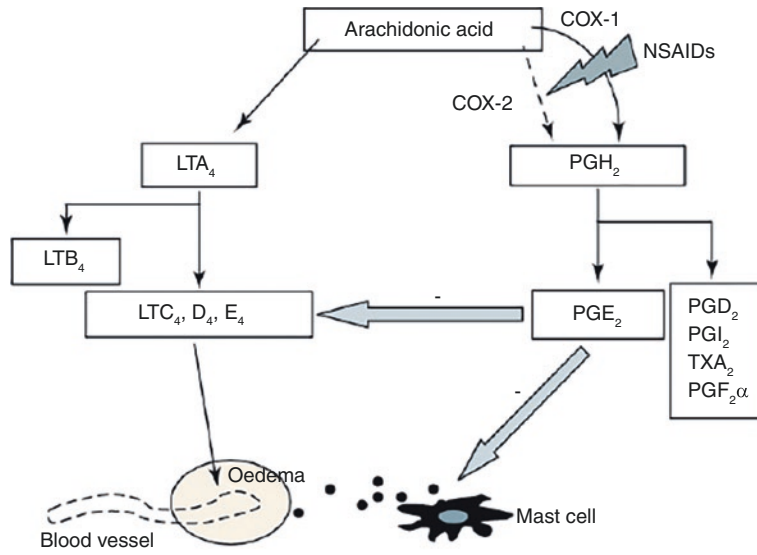

Fig. 3 Mechanism of mast cell degranulation: Shunting of arachidonic metabolites from the cyclo-oxygenase (COX) to the lipoxygenase by NSAIDS leading to an increase in pro-inflammatory leukotrienes and reduction of inhibitory prostaglandin resulting in weals and angioedema (Taken from Tan and Grattan (2004))

3 Evaluation of a Patient with Suspected DIU

A clinical history is essential when evaluating a patient with DIU. The following may serve as a guide during patient interviews (Shipley and Ormerod 2001; Demoly et al. 1999; Centre NCG 2014).

(a) Morphology and severity: Is the morphology consistent with urticaria or angioedema? Is there systemic involvement? (e.g. anaphylaxis, serum sickness)
(b) Alternative diagnosis: Is there an alternative aetiology which needs to be excluded? (e.g. infection, chronic spontaneous urticaria)
(c) Medication latency: What is the interval between the introduction of the potential culprit drug and the onset of reaction? The typical interval for IgE-mediated drug-induced urticaria in a pre-sensitised individual is within an hour (minutes if administered intravenously). NSAID-induced angioedema occurs 1–24 h after ingestion. Angioedema associated with ACE inhibitors typically occurs in the first 3 weeks following initiation but can be later.
(d) Drug notoriety: Have similar reactions been reported with the same drug? Beta lactam antibiotics, NSAIDs, opioids, iodinated radiocontrast media are well recognised offenders in DIU.
(e) Resolution after withdrawal: Was there an improvement or complete resolution after withdrawal of the offending drug? If so, how long did it take to resolve after cessation of medication? DIU classically has a shorter time to resolution than delayed-type adverse reactions, such as a drug-induced exanthem.
(f) Metabolism and clearance: Are there any existing medical conditions or concurrent medications which may affect the metabolism and clearance of the medication, and hence alter the time to resolution?
(g) Re-challenge: Was there any reaction on re-administration of the drug? Or was there previous history of similar reactions with the same drug or those with similar chemical structure?

Diagnostic challenges arise in the setting of polypharmacy. Problems may also arise when the patient is receiving treatment for a disorder, such as an infection, which itself can be the cause of acute urticaria. Confusion may also arise in a patient with pre-existing chronic spontaneous urticaria who takes a drug which can exacerbate the underlying urticaria.

Skin tests, histamine release assays, and drug-specific IgE may provide helpful information when teasing out the culprit drug. After the acute episode, oral challenge test remains the gold standard in attributing causality in DIU.

4 Investigating DIU

4.1 In Vitro Testing

In vitro testing may aid diagnosis by analysis of involved cells and mediators. It is also used to identify the culprit drug after resolution of a drug hypersensitivity reaction (Mayorga et al. 2016). In clinical practice, it is rarely available to assist bedside diagnosis.

Tests to Aid Diagnosis

Tryptase and histamine are the most studied markers for immediate reactions in the context of anaphylaxis, but these mediators are not usually assayed in DIU unless the patient presents with systemic features. Tryptase is a protease enzyme which is stored in its matured isoform in mast cells as a pre-formed mediator. It is released rapidly during the acute phase of an anaphylactic reaction. UK guidelines recommend measuring serum tryptase after a suspected anaphylaxis reaction (Centre NCG 2014). The levels of tryptase reach a peak at 60–90 mins after the onset of symptoms and then decline thereafter with a half-life of 2 h (see Fig. 4) (Egner et al. 2016). Thus, the timing of blood collection from onset of symptoms affects the interpretation of tryptase levels (Beck et al. 2019). An international (European) consensus in 2012 agreed that a significant acute rise should be 20% + 2 μg/mL over the baseline tryptase level (Valent et al. 2012). Persistently elevated tryptase may be due to an underlying

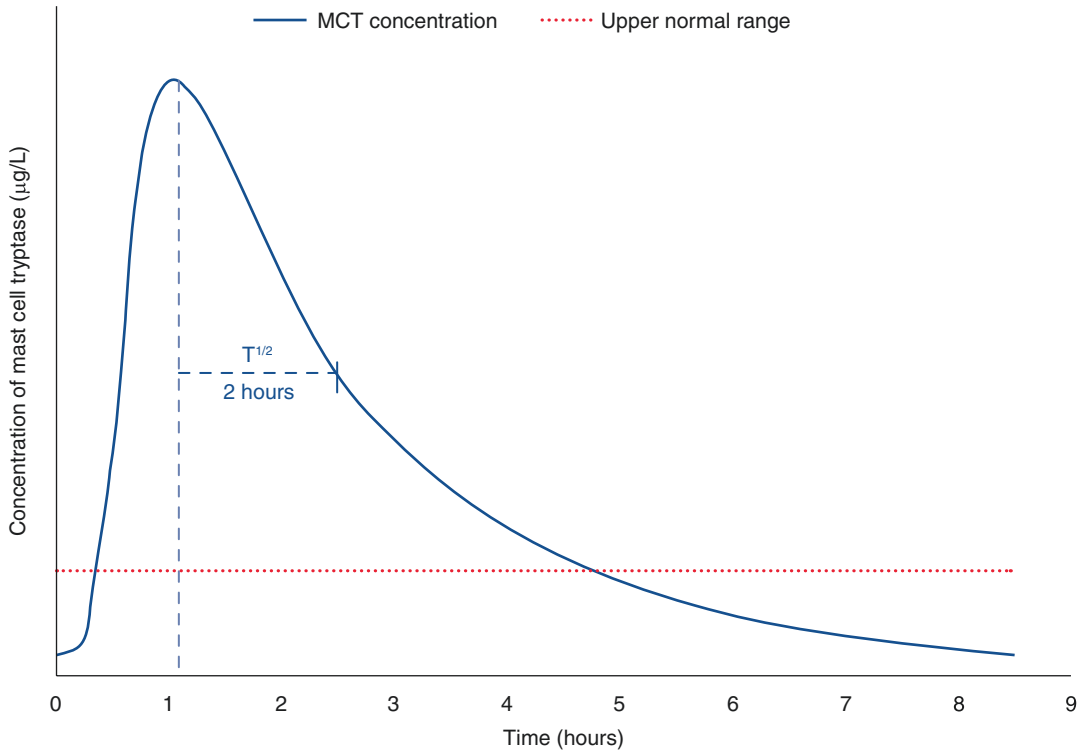

Fig. 4 Serum tryptase levels post anaphylaxis. (Taken from Beck et al. (2019)]

clonal mast cell disorder (Bonadonna et al. 2015; Akin 2015). False-positive results may also occur in trauma victims and in patients with critical illness of any cause (Francis et al. 2018).

Histamine, a mediator of allergic inflammation, is found in large quantities in mast cells and basophils. In an immediate hypersensitivity drug reaction, measurement of serum histamine is more sensitive than serum tryptase. However, serum histamine is rapidly metabolised with a half-life of only 15–30 min (Kabashima et al. 2018). Furthermore, there is great inter-individual and intra-individual variability in serum histamine levels (Mayorga et al. 2016). For optimum diagnostic utility collection of serum histamine must be completed within 1 h of onset of symptoms. In practice this type of specimen is challenging to obtain and therefore investigators have opted to collect urinary metabolites of histamines instead. Urinary N-methylhistamine and N-methylimidazoleacetic acid can be assayed in a 24-h collection and will act as an indirect measurement of serum histamine. The levels may be affected by bacteria in the gastrointestinal and genitourinary tracts as well as consumption of histamine-rich foods (Mayorga et al. 2016).

Tests to Help Identify Culprit Drug

Detection of serum-specific IgEs are available commercially using either the fluoroimmunoassay (ImmunoCAP, ThermoFisher, Sweden) or enzyme-linked immunosorbent assay (ELISA) method. The advantage of these methods is that serum may be stored and tested for multiple drugs. However, the reported sensitivity of the tests is low (0–50% for beta-lactams; 83–92% for rocuronium; 44% for suxmethonium; 78–84% for morphine) (Mayorga et al. 2016). Moreover, the levels of drug-specific IgEs drop over years and, for this reason, it is recommended that fluoroimmunoassays or ELISAs are performed within 3 years of the index reaction.

CD63 and CD203c can be used to identify basophil activation in the basophil activation test

(BAT) after stimulation of the patient's blood with the culprit drug or its metabolites. BAT for penicillin has a sensitivity of 48.6–50% and a specificity of 91–93% (Sanz et al. 2009). BAT for neuromuscular blocking agents has a sensitivity of 64–85.7% and a specificity range of 93–100% (Ebo et al. 2018). BAT protocols vary between different centres undertaking these assays: lack of methodological consistency complicates interpretation of test results (Mayorga et al. 2016).

4.2 In Vivo Testing

Skin prick tests (SPT) or intradermal tests (IDT) may be used in drug allergy evaluation (Blanca et al. 2009). They are generally safe, although systemic reactions have been reported after 0.1–2% of all tested patients (Co Minh et al. 2006), a history of previous anaphylaxis being a risk factor. Technical expertise is needed to conduct and interpret in vivo skin tests; therefore, these investigations are usually carried out at a specialist drug allergy centre. Histamine is used as the positive control and saline (or the diluent) as the negative control (Mirakian et al. 2015). SPTs and IDTs are read at 15–20 mins and are most useful for IgE-mediated drug allergy (Mirakian et al. 2009). There are standardised commercially available reagents, including the penicillin major and minor determinants. Some drugs, however, require in-house dilution for SPT and IDT. Guidance on non-irritative concentrations are available for beta lactam antibiotics, macrolides, perioperative drugs, local anaesthetics, iodinated contrast media and chemotherapy agents (platinum salts) (Brockow et al. 2009, 2013; Ünal et al. 2018).

Drug provocation tests (DPT) remain the gold standard in drug allergy evaluation; however, this investigation can provoke a life-threatening reaction in patients with an immediate hypersensitivity disorder. The general consensus among allergists is that DPT should usually be performed after skin testing, and possibly omitted if skin tests are positive in patients with poorly controlled asthma, on beta blockers, or in those at risk of developing a severe reaction during DPT. DPT protocols vary between centres. If performed, this test has a high negative predictive value: 94–98% in beta lactam allergy (Ponvert et al. 2007; Demoly et al. 2010).

5 Management of DIU

The goal of treatment is to

(a) Treat the symptoms:

Mild to moderate DIU should be treated with non-sedating H1 antihistamines. Patients with severe DIU and systemic manifestations may benefit from a short course of corticosteroids. Acute anaphylaxis with cardio-respiratory compromise should be treated with adrenaline and resuscitation as per local guidelines (Simons et al. 2014; Soar et al. 2010; Tse and Rylance 2009).

(b) Identify, stop and avoid the culprit medication:

Attempts should be made to identify the drug responsible and to stop it. Identification of the culprit drug (as described above) should be considered on a case-by-case basis. Education on similar and/or cross-reacting drugs should be provided alongside rescue medication such as antihistamine or adrenaline autoinjector.

(c) Document the drug allergy:

Documentation of the allergy in the medical records and spoken/written advice about avoidance are strongly recommended (Brockow et al. 2016). Patients may be advised to carry some form of documentation, either a drug allergy alert card, Medic Alert bracelet, or discharge letter, especially when travelling. They should show this document to healthcare providers when seeking medical attention to prevent accidental exposure. The documentation should contain the name of the culprit drug, severity of reaction, clinical manifestations, allergy work-up, potential cross reactivity and alternative drugs that the patient has tolerated.

(d) Desensitise (if benefits outweigh risks):

Desensitisation is the induction of a temporary state of immune tolerance to the culprit drug by introducing it in a slow, incremental fashion. It is a potentially high-risk procedure, usually undertaken only after careful risk–benefit analysis and performed when there is no suitable alternative medication. Desensitisation protocols are available for IgE allergy to aspirin, penicillin, chemotherapy agents, and biologics (Cernadas et al. 2010).

6 Medications Associated with DIU

DIU has been reported in association with a wide range of drugs and vaccines. Indeed, Meyler's "Side Effects of Drugs" lists 175 drug causes of urticaria (Aronson 2015). Searching for "urticaria" as an undesired effect of medication on the "Electronic Medicines Compendium" (EMC) generates almost 6000 hits of relevant drugs (albeit including different formulations with the same active constituents) (EMC 2020). Condensing the breadth of reported causes is therefore challenging, particularly as reliable data from prospective studies is lacking.

Spontaneous reports of drug-induced urticaria (reported via the Yellow Card Scheme) extracted from the Committee of Safety of Medicines, UK, over a 40-year period (July 1963–March 2003) found NSAIDs, analgesics, antibiotics and vaccines to be the most frequently reported causes (Tan and Grattan 2004). In diminishing order of frequency, bupropion, antidepressants (most commonly selective serotonin reuptake inhibitors [SSRIs]), antihypertensives (most commonly ACE inhibitors, followed by calcium channel blockers), H2 antihistamines, systemic antifungals and H1 antihistamines were also implicated. However, it is important to remember that these suspected adverse drug reactions are not clinically confirmed cases and many factors influence the frequency and quality of reporting via this mechanism. These data should be interpreted with caution and used to highlight potential important areas in post-marketing drug safety surveillance rather than being accepted as accurate population-based incidence data.

6.1 Aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

A proportion of patients with asthma and chronic spontaneous urticaria (CSU) are sensitive to aspirin and other NSAIDs. These drugs block cyclooxygenase (see Fig. 3) and can induce asthma exacerbation in patients with aspirin-exacerbated respiratory disease and urticaria in patients with CSU. The two conditions seem to affect different populations; therefore, while combined cutaneous and respiratory reactions may occur, they are rare (Stevenson 2004). NSAID-induced urticaria and angioedema are among the most frequently encountered drug hypersensitivity reactions in clinical practice. Three major clinical phenotypes are recognised; for each, urticaria is defined as weals, angioedema or both (Kowalski et al. 2015).

(a) NSAID-induced urticaria (NIU)

The most common manifestation of hypersensitivity reactions to NSAIDs. Acute urticaria/angioedema occurs within minutes to 24 h of NSAID ingestion in an otherwise healthy individual. Most cases resolve within 1–2 days but may last up to 2 weeks. The reaction is generally reproduced by different NSAIDs, but may be selective.

(b) NSAID-exacerbated cutaneous disease (NECD): (syn. NSAID-exacerbated chronic urticaria):

Up to 30% of patients with CSU experience an urticaria exacerbation caused by nonselective COX-Inhibiting NSAIDs (Blanca-Lopez et al. 2019). This effect is more severe with higher doses of aspirin and when the NSAID is administered during a period of disease activity (Warin 1960).

(c) Single NSAID-induced urticaria (SNIU)

Where the reaction is specific for a single, specific NSAID medication.

Diagnostic evaluation is based on clinical history and, where appropriate, oral drug provocation challenge testing. The specific clinical phenotype (above) must be established since this has implications for future management. For example, in patients with single NSAID-induced reactions, chemically unrelated COX inhibitors may be safely used to replace the culprit drug (Kowalski et al. 2015). In contrast, in patients with NECD and NIU there is cross-reactivity between NSAIDs, and therefore, unless aspirin desensitisation therapy is undertaken, all NSAIDs except for selective COX-2 inhibitors must be avoided (Grattan 2003). It must be noted that while selective COX-2 inhibitors do not cross-react, all NSAIDs (including selective COX-2 inhibitors) may sensitise patients and induce urticaria or anaphylaxis on repeat exposure to the drug (Stevenson 2004). Aspirin may also act as a co-factor with food or exercise or both to precipitate anaphylaxis (Grattan 2003). Cavkayatar et al. tested children with CSU for aspirin hypersensitivity (n = 58) (Cavkaytar et al. 2015), reporting that 24% of the study group were positive on single-blind placebo-controlled provocation test with aspirin, the majority experiencing unequivocal lip angioedema as the positive reaction.

6.2 Opiates

Opiates induce release of histamine from mast cells through direct mast cell degranulation (see Fig. 2), which accounts for many undesirable side effects, including urticaria, hypotension, pruritus, and tachycardia (Barke and Hough 1993). Some of this action may be inhibited by opiate antagonists. Kozel et al. (Kozel et al. 2001) reported codeine as a cause of chronic spontaneous urticaria in 0.4% of a series of 220 patients. In the majority of patients this reaction is non-immunological, that is, not IgE-mediated. Consequently, skin prick testing with opiates is not usually of diagnostic value, except perhaps in the investigation of anaphylaxis if morphine allergy is suspected (Tan and Grattan 2004; Prieto-Lastra et al. 2006). Generally, controlled oral challenge test with the suspect drug can be undertaken, or the patient can be treated with a non-histamine releasing alternative. Codeine, morphine and pethidine are reported to exhibit the greatest histamine-releasing capacity, while tramadol, fentanyl and remifentanil do not release histamine and have therefore been recommended as alternative agents (Prieto-Lastra et al. 2006). In a retrospective uncontrolled study of 1071 patients with NSAID-hypersensitivity who underwent oral drug provocation testing in an allergy clinic, 301 were challenged with codeine, of which 7.3% had a positive reaction (Celebioglu et al. 2013). This reaction rate to codeine was significantly lower than to meloxicam and nimesulide, but similar to the reaction rates to benzydamine, rofecoxib and paracetamol. Interestingly, symptomatic dermographism was associated with test positivity to any drug (p = 0.009) (Celebioglu et al. 2013).

6.3 Angiotensin-Converting Enzyme Inhibitors (ACEi)

ACEi are widely used in the management of hypertension, chronic kidney disease, heart failure, and are commonly prescribed following myocardial infarction. While DIU is a relatively infrequent adverse effect of ACEi [reported as 0.3% for enalapril (Inman et al. 1988)], ACEi associated angioedema (without weals) is a more common and potentially serious problem.

The underlying pathophysiology is not yet fully understood but involves inhibition of bradykinin degradation by ACE (kininase II) leading to vasodilation, microvascular hyperpermeability and plasma extravasation (Kostis et al. 2018). The reported incidence ranges from 0.1 to 0.7% (Montinaro and Cicardi 2020), with variable frequencies reported across different racial groups. There is four to fivefold greater risk reported in African and Caribbean patients than in Caucasian patients (Burkhart et al. 1996; Brown et al. 1996). This suggests a genetic association, but there are currently no recognised genetic variants with sufficiently strong association to be useful clinically (Liau et al. 2019). Other risk factors for ACEi-

associated angioedema include smoking, female sex, increasing age, and prior history of drug rash or angioedema, seasonal allergies and co-administration of certain medications, including mammalian target of rapamycin (mTOR) inhibitors (Kostis et al. 2018). Recently, ACEi-associated angioedema has been reported in the setting of concurrent SARS-CoV-2, the virus responsible for COVID-19 infection (Grewal et al. 2020). ACEi are contraindicated in patients with angioedema without weals of any cause, including C_1 esterase inhibitor deficiency.

The onset of symptoms may be days, weeks or even years after initiation of treatment with ACEi, and episodes may be recurrent. Commonly affected body sites include the face, neck and oropharynx, and attacks generally last 48–72 h. Although most cases are mild, acute airway obstruction may, rarely, lead to life-threatening respiratory compromise. Intestinal involvement with sub-occlusive symptoms has also been reported (Montinaro and Cicardi 2020).

Diagnosis is from clinical history and examination; there is no diagnostic test. The most important action in a patient with suspected drug-induced angioedema is to discontinue the culprit drug immediately (Agostoni and Cicardi 2001). Best treatment remains a matter of debate: systemic corticosteroids, antihistamines and adrenaline are used, though in contrast to histamine-mediated angioedema, ACEi-associated angioedema is often unresponsive to glucocorticoids and antihistamines. Fresh frozen plasma (FFP) has intrinsic ACE and C1-esterase inhibitor activity, which can catabolise bradykinin. Although readily available, risks of FFP use include initial worsening of angioedema (FFP contains kininogen and high molecular weight kallikrein, precursors of bradykinin), volume overload and transfusion-related reactions/infections (Kostis et al. 2018). In a systematic review of pharmacotherapy for ACEi-induced angioedema, Lawlor et al. (2018) identified 3 randomised controlled trials and 2 prospective case series with historical controls: no studies compared efficacy of corticosteroids with antihistamines, or fresh frozen plasma, or combination therapy. Two studies of ecallantide (plasma kallikrein inhibitor) and one study of C1 inhibitor replacement found no significant benefit over control. One of two studies of icatibant (bradykinin B2 receptor antagonist) found more rapid symptom improvement than that with a control group of corticosteroids and antihistamines. Conflicting results from interventional studies with icatibant warrant further study: predisposition to icatibant efficacy may vary according to ethnicity factors (Brown et al. 1996). In the setting of life-threatening respiratory compromise early endotracheal intubation or emergency tracheotomy/cricothyroidotomy must be performed (Agostoni and Cicardi 2001). Patients with a history of ACEi-associated angioedema should not be re-challenged with any of the ACE inhibitors (Lawlor et al. 2018; Brown at al. 1997).

Angiotensin II receptor antagonists (ARBs) have many similar properties to ACEi but act downstream in the renin–angiotensin–aldosterone pathway by blocking angiotensin II receptor type I and thus do not inhibit the breakdown of bradykinin. While theoretically they should be safe in patients with ACEi-associated reactions, ARB-induced angioedema has been reported in patients with ACEi-induced angioedema. However, epidemiological studies on large cohorts have shown that ARBs do not increase the likelihood of angioedema compared to other antihypertensives (Montinaro and Cicardi 2020). Other reported causes of drug associated angioedema include fibrinolytic agents [such as intravenous alteplase (Censori et al. 2018)], oestrogens, antihypertensive drugs other than ACE inhibitors, psychotropic drugs and NSAIDs (Agostoni and Cicardi 2001).

6.4 Others

Recent literature identifies case reports of DIU and drug-associated angioedema triggered by newer therapies, including targeted treatments and immunomodulatory agents. While it is likely that some reports of urticaria have been confused with urticarial reactions (which differ in presentation and pathogenesis) recent pharmacovigilance notifications highlight novel agents as potential culprits.

Infliximab, an intravenously infused chimeric human-mouse TNF-α antibody, has been associated with many immunogenic reactions including infusion reactions and serum-sickness-like syndrome. Drug-induced urticaria has also been reported in 3 of 16 patients treated with infliximab and methotrexate (Feletar et al. 2004), and in 4 of 340 patients (1%) in another study, one of whom required discontinuation of therapy (Maini et al. 1998). Etanercept (a human dimeric fusion protein which inhibits TNF-α by blocking its interaction with cell surface TNF receptors) and adalimumab (fully human monoclonal antibody to TNF-α) cause fewer immunogenic reactions, but both have been reported to cause urticaria (George et al. 2006; Fellner and Yohe 2013). In clinical trials of adalimumab, allergic reactions (including allergic rash, anaphylactoid reaction, fixed drug reaction, nonspecific drug reaction, and urticaria) were observed in 1% of patients (US Food and Drug Administration 2004).

Sorafenib, a multi-targeted tyrosine kinase inhibitor used to treat renal, thyroid and hepatocellular cancer, was reported to induce urticaria after 8 weeks of treatment in a patient with hepatocellular carcinoma which settled 1 week after discontinuation of therapy (Musri et al. 2016). Everolimus, a derivative of sirolimus, which inhibits mammalian target of rapamycin (mTOR) is a recognised cause of drug-induced angioedema when used as an immunosuppressant for organ transplant and in cancer treatment (Roe et al. 2017; Fuchs et al. 2005). In a heart transplant centre 6 out of 114 patients on everolimus developed lingual angioedema (5.3%) 2–41 days after initiation of therapy, one of which was severe and recurrent, leading the authors to recommend that everolimus-associated lingual angioedema must be considered a severe drug reaction (Fuchs et al. 2005). Angioedema has also been reported in association with lenalidomide (an immunomodulatory agent given in combination with dexamethasone for multiple myeloma), a reaction which preceded the development of hypersensitivity pneumonitis (Hatsuse et al. 2016). Urticaria has also been reported in the context of interleukin (IL)-2 therapy, used to treat renal cell cancer: 6 of 8 patients developing urticaria in one report had a prior history of urticaria unrelated to IL-2 therapy, so this phenomenon may represent aggravation (Logan et al. 2007).

These examples are given as a flavour rather than a comprehensive overview of all possible causes of DIU. However, it is important to remember that in complicated cancer regimens drug-induced urticaria may be caused not by the anti-cancer agent(s) but by co-administered medication, such as an anti-emetic. It is also worth being aware of a rare paradoxical reaction whereby H1-antihistamines may, in exceptional circumstances, induce or exacerbate urticaria despite being its mainstay of management. Positive SPTs and positive oral challenge tests have been documented (González De Olano et al. 2006) and thus hypersensitivity to H1-antihistamines should be considered when urticaria worsens following H1-antihistamine administration (Inomata et al. 2009).

7 Summary

Patterns of DIU case reporting generally reflect shifting trends in prescribing practice. Certain medications are relatively common causes of DIU, such as antibiotics, analgesics and vaccines; therefore, a strong suspicion of culpability can be held in many clinical situations. A basic understanding of the pathophysiologic mechanisms of DIU will direct the clinician to the most appropriate investigation and management options for individual patients. Drug-associated angioedema tends to respond poorly to conventional treatment and may be life threatening: in these cases it is important to recognise the culprit medication and to discontinue it as soon as the diagnosis is made.

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Exanthematous Drug Eruptions

Colleen Gabel and Daniela Kroshinsky

Abbreviations

AGEP	Acute generalized exanthematous pustulosis
BUN	Blood urea nitrogen
CADR	Cutaneous adverse drug reaction
CBC	Complete blood count
DIHS	Drug-induced hypersensitivity syndrome
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBV	Epstein–Barr virus
FDE	Fixed drug eruption
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IHC	Immunohistochemistry
IL	Interleukin
MHC	Major histocompatibility complex
NSAIDs	Nonsteroidal anti-inflammatory drugs
p–i	Pharmacologic interaction of drugs with immune receptors
SCAR	Severe cutaneous adverse reaction
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthem
SJS	Stevens–Johnson syndrome
SLE	Systemic lupus erythematosus
TEN	Toxic epidermal necrolysis
TMP-SMX	Trimethoprim–sulfamethoxazole

1 Introduction

Exanthematous (also known as "morbilliform") drug reactions are one of the most common cutaneous adverse drug reactions (CADRs), comprising 95% of all CADRs (Bigby 2001). While the exanthematous drug reaction typically has a mild clinical course, it can sometimes be the first sign of a severe cutaneous adverse reaction (SCAR) and warrants a thorough history and physical examination. In this chapter, the pathogenesis, common offending agents, clinical features, diagnosis, and management of this cutaneous drug eruption will be discussed.

2 Pathogenesis

Exanthematous drug reactions are thought to be immunologic in nature, as a form of type IV or delayed T-cell hypersensitivity reaction

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(Warrington et al. 1993; Barbaud et al. 1997). However, details of the underlying pathophysiological mechanism remain to be elucidated. In a study of skin biopsy specimens obtained from patients with an exanthematous rash due to amoxicillin, perivascular infiltrates were found to contain mostly CD4+ cells with 30% CD8+ cells. This is in contrast with other delayed-type hypersensitivity drug reactions, such as fixed drug eruptions (FDE), which have a predominance of CD8+ T cells. However, other studies have found a greater role of CD8+ T-cells in the exanthematous drug eruption (Hertl and Merk 1995). Both infiltrating T cells and resident endothelial cells have been found to be highly activated, with endothelial cells expressing a number of adhesion molecules (Lerch and Pichler 2004). Further study on skin samples of patients with exanthematous drug reactions has found perforin and granzyme B-mediated cytotoxic CD4+ and CD8+ cell destruction. Upregulation of major histocompatibility complex (MHC) II molecules on keratinocytes, which are thought to bind and activate cytotoxic T cells, lead to production of inflammatory cytokines and resulting in the reaction seen. Finally, enhanced interleukin (IL)-12 expression by macrophages and dendritic cells may stimulate cell-mediated cytotoxicity (Yawalkar et al. 2000).

An alternate pathophysiological theory is that of the pharmacologic interaction of drugs with immune receptors (p–i) model, by which small molecules directly activate T-cells by binding to T-cell receptors, rather than by way of antigen-presenting cells processing and presenting haptens composed of the drug or its metabolite to T-cells (Pichler et al. 2011).

On histopathological examination, exanthematous drug eruptions are often characterized by interface dermatitis with lymphocytes along the dermal–epidermal junction. There is a perivascular lymphocytic infiltrate, on occasion with eosinophilia and dermal papillary edema (Crowson and Magro 1999). Scattered dyskeratotic keratinocytes are present along the dermal–epidermal junction (Justiniano et al. 2008). Differential diagnosis on histopathological examination includes viral exanthem, which would be more characterized by hemorrhage and lack of eosinophilia but may be indistinguishable from a drug reaction (Crowson and Magro 1999). It is important to note that drug reactions can cause a number of inflammatory patterns in the skin, none of which are highly specific (Justiniano et al. 2008).

Interestingly, viral infection has been associated with increased frequency of exanthematous drug reactions. Specifically, Epstein–Barr virus (EBV) treated with amoxicillin (Ónodi-Nagy et al. 2015) and human immunodeficiency virus (HIV) treated with trimethoprim–sulfamethoxazole (TMP-SMX) have been described (Roujeau 2006). In fact, infectious mononucleosis has been found to increase the risk of amoxicillin-induced rash by a factor of 58 (van der Linden et al. 1998). Histopathological examination of antibiotic-induced exanthematous eruptions associated with EBV was found to have acute interface epidermal reaction with vacuolar alteration, rare necrotic keratinocytes, perivascular nuclear debris, and lymphocytic infiltrate in superficial, deep, and interstitial layers. Immunohistochemistry (IHC) has found numerous CD68 and CD123+ plasmacytoid monocytes. The findings of perivascular nuclear dust and CD68+/CD123+ cells are similar to Kikuchi–Fujimoto disease, which has pathological findings that overlap between infectious mononucleosis and systemic lupus erythematosus (SLE). These plasmacytoid monocytes are thought to activate an antiviral immune response, possibly connecting viral infection with exanthematous drug reactions (Carlson et al. 2006). Other infections found to be associated with exanthematous drug reactions include respiratory tract infections and urinary tract infections, indicating that bacterial infection may also play a role; however, further study is needed to confirm this association (Cohen et al. 2001). The association between viral illness and exanthematous drug eruptions makes diagnosis particularly challenging in children, who are at a high likelihood of developing a viral exanthem (Waldman et al. 2017), and who may receive empiric antibiotics for viral illness (Shin and Chang 2001).

3 Epidemiology

Cutaneous drug reactions occur in up to 2–3% of patients taking medications, with 95% of these cutaneous reactions being exanthematous drug eruptions. CADRs may affect patients of any demographic background. In general, women and the elderly have been found to have higher rates of reactions, thought to be due to higher rates of drug consumption by women and a greater proportion of women in the elderly population (Bigby 2001). Exanthematous drug eruptions are more common in adults, only comprising 30% of CADRs in children (Dilek et al. 2014).

A genetic component has been connected to the development of exanthematous drug eruptions. An association has been found with human leukocyte antigen (HLA)-A*31:01 and exanthematous drug reactions triggered by carbamazepine (Amstutz et al. 2014). While HLA studies have typically focused on the many associations found with SCARs (Fan et al. 2017), finding a specific HLA haplotype associated with an exanthematous drug reaction provides a specific example of its genetic link.

In addition to genetics, underlying comorbidities may increase the risk of developing an exanthematous drug reaction, possibly due to underlying immune dysregulation. Infection with HIV increases risk of adverse drug reactions (Stokes and Tankersley 2011), with morbilliform reactions found to be the most common etiology (Coopman et al. 1993). It appears that the risk of cutaneous drug eruption was highest with the use of TMP-SMX, sulfadiazine, trimethoprim–dapsone, and aminopenicillins (Coopman et al. 1993). Additional study is needed to further understand this relationship.

4 Clinical Features

The exanthematous drug reaction is sometimes referred to as a "morbilliform" reaction for its resemblance to the measles viral exanthem. Most cases have a benign, mild course. Skin findings are characterized by erythematous macules and papules, sometimes extending to patches and plaques, often symmetrically distributed (Fig. 1). There may rarely be nonulcerative erythematous

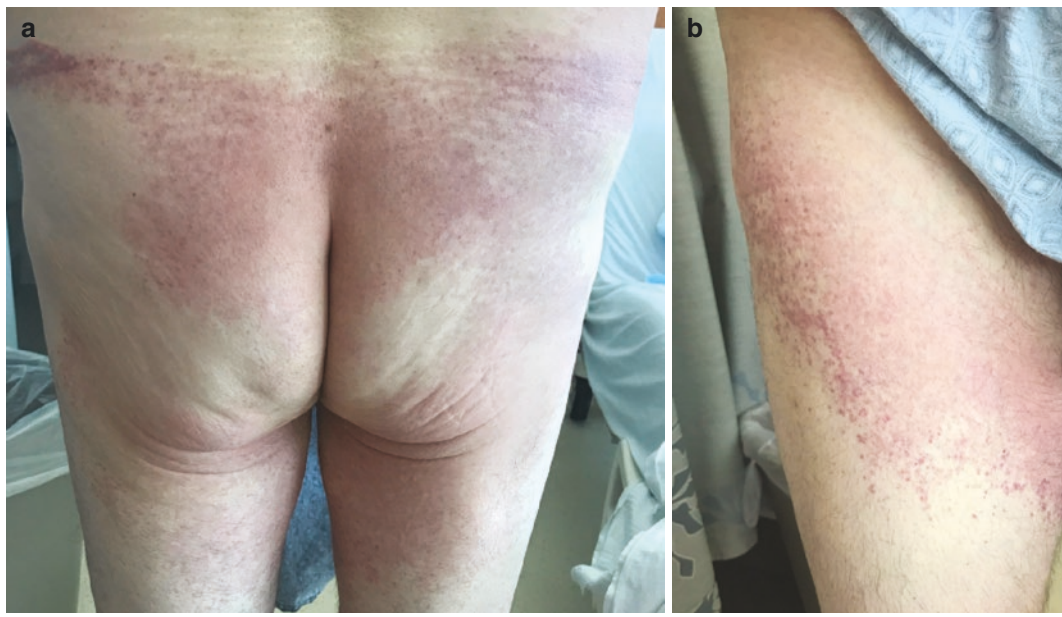

Fig. 1 A male patient who presented with mildly pruritic light pink thinly raised coalescing papules on the (**a**) buttocks and (**b**) upper thigh consistent with an exanthematous drug eruption, likely due to furosemide. (Photography courtesy of Lauren Ko, MD, MEd)

involvement of the mucous membranes (Stern 2012). While the macular and papular presentation is the most common, there may also be eczematoid-, psoriasiform-, or lichenoid-like patterns, and while it is typically not associated with skin detachment, bullae may develop from some lesions. Typically, lesions begin on the trunk and spread to the extremities; however, exanthematous reactions with a predominantly papular morphology may begin on the extremities (Hoetzenecker et al. 2016). Associated symptoms are typically mild and may include pruritus and low grade fever (Stern 2012).

The exanthematous eruption typically evolves after a sensitization period of 5–7 days after initial exposure (Hoetzenecker et al. 2016), but may occur more quickly, within 1–3 days (Lerch and Pichler 2004), or even 6–12 h (Hoetzenecker et al. 2016), in previously sensitized individuals. Antibiotics and allopurinol may notably induce rashes over 2 weeks after initial exposure. Most exanthematous eruptions reach their peak extent within 2 days after stopping the inciting agent, fading within a week after the medication is stopped. On occasion, the eruption may begin to resolve even as the medication is still being administered (Stern 2012).

One rare variant of the exanthematous drug eruption is known as symmetrical drug-related intertriginous and flexural exanthem (SDRIFE). This syndrome has previously been called "baboon syndrome," although this term has fallen out of favor due to its offensive nature. There have been approximately 100 cases reported since 1984. SDRIFE may occur either due to systemic or cutaneous drug administration. Causative agents include antibiotics (particularly beta-lactam antibiotics) (Hausermann et al. 2004). SDRIFE presents with V-shaped erythema in the inguinal, genital, gluteal, and perianal area, with an exanthematous appearance in the flexural areas. There may sometimes be development of papules, pustules, and vesicles, and this syndrome must be distinguished from potentially serious reactions such as acute generalized exanthematous pustulosis (AGEP) (Fig. 2) and drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS) (Fig. 3) (Hausermann et al. 2004).

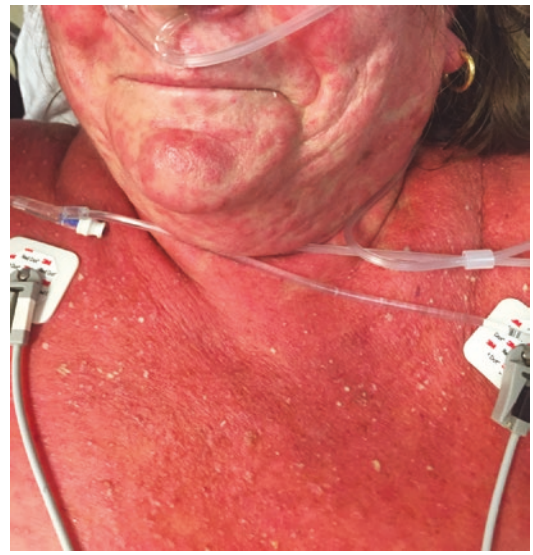

Fig. 2 A female patient with erythematous patches and plaques on the face and chest with overlying small superficial pustules consistent with acute generalized exanthematous pustulosis (AGEP), likely due to dicloxacillin. Additional findings not pictured are involvement of the abdomen, upper extremities, and lower extremities. (Photography courtesy of Daniel Yanes, MD)

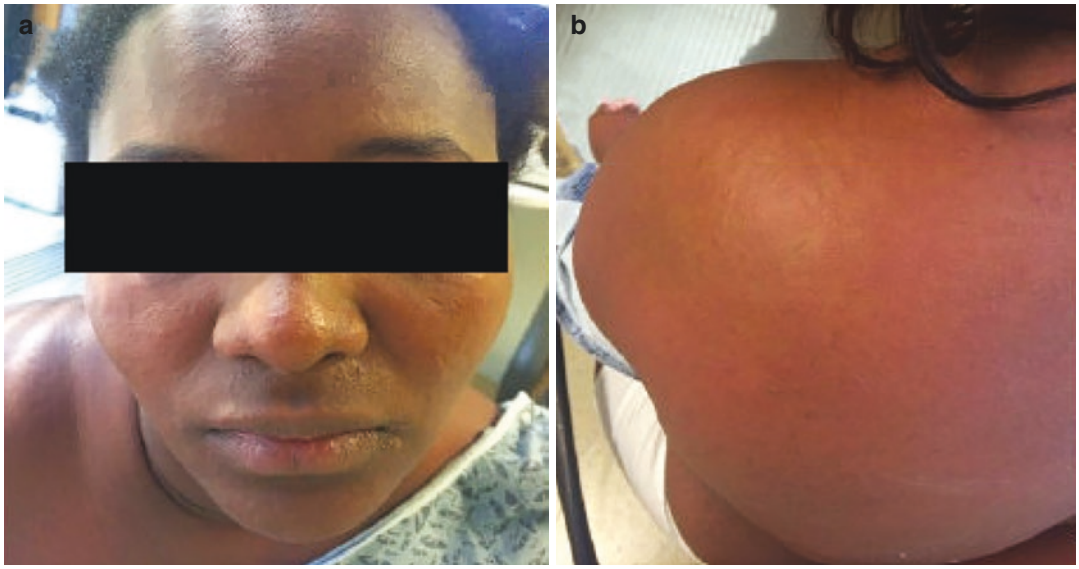

Fig. 3 A female patient diagnosed with drug-induced hypersensitivity syndrome (DIHS) (also known as drug reaction with eosinophilia and systemic symptoms) who presented with (**a**) facial edema and (**b**) erythematous diffuse patches and plaques on the back. Additional findings not pictured are edema of the hands as well as supraclavicular and cervical lymphadenopathy. (Photography courtesy of Rebecca Hartman, MD, MPH)

5 Offending Agents

The list of agents that may cause an exanthematous drug reaction is large and ever-growing. Although almost any agent could cause an exanthematous reaction, penicillin antibiotics are the most common culprit (Shin and Chang 2001). An extensive list of causative agents has been developed, including but not limited to nonnucleoside reverse transcriptase inhibitors (Lackmann et al. 2003), X-ray contrast (Christiansen et al. 2002), aminopenicillins (amoxicillin, epicillin, ampicillin), TMP-SMX, cephalosporins, allopurinol (Sonntag et al. 1986), and nonsteroidal anti-inflammatory drugs (NSAIDs) (Oberholzer et al. 1993; deShazo and Kemp 1997). This list is certainly not exhaustive, and drug-related rash has been reported for almost all prescription medications (Stern 2012).

6 Diagnosis

Diagnosis of an exanthematous drug eruption (as with other forms of drug eruptions) begins with a thorough history and physical examination.

Table 1 Sample of a drug timeline chart

Drugs	Time course					
Drug W	X	X	X	X	X	X
Drug X			X	X	X	
Drug Y				X	X	X
Drug Z	X	X				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
					(Rash appeared)	

The *y*-axis represents different medications started relative to the drug eruption, and the *x*-axis represents time course
Adapted from Fitzpatrick et al. (2018)

Particular attention should be placed to the patient's medication list with timeframes each drug was used for. It is important to gather risk factors for the development of CADRs, such as family history, as genetics may play a role. Creation of a log or "drug chart" may be helpful in narrowing the differential diagnosis if other etiologies (such as viral exanthem) are being considered, labeling each medication the patient has taken and start dates. This may help determine temporal relationship and knowledge of typical offenders, as demonstrated in Table 1. If the reac-

tion resolves with drug discontinuation, suspicion for a drug-induced exanthem climbs.

Differential diagnosis includes a viral exanthem (particularly in pediatric cases). In nonimmunized individuals, measles in particular should be kept on the differential diagnosis. Exanthems that occur fewer than 72 h after initiating a new medication are more likely to be viral in etiology, because the nature of exanthematous drug eruptions as a delayed-type hypersensitivity reaction results in a later presentation unless there has been previous sensitization (Stern 2012). If the reaction occurs within a few hours and presents with wheals predominantly, an urticarial reaction must be considered and caution should be taken for signs of an anaphylactic reaction (Hoetzenecker et al. 2016). Importantly, an exanthematous drug eruption may be the first sign of a SCAR such as DIHS/DRESS or Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Shin and Chang 2001).

In general, laboratory testing is not required for the diagnosis of an exanthematous drug eruption. However, laboratory testing may be indicated when considering the differential diagnosis, which may include SCARs. Laboratory testing when evaluating these more severe reactions include complete blood count (CBC) with differential, liver tests including transaminase levels, blood urea nitrogen (BUN), creatinine, urinalysis, and thyroid function tests. Similarly, skin biopsy typically is not necessary to diagnose an exanthematous drug eruption but may help in evaluating potential other causes such as DIHS/DRESS, AGEP, or SJS/TEN.

Additional drug-specific testing such as patch testing or a lymphocyte transformation test, which quantifies drug-induced in vitro T-cell activation, are not typically employed in clinical practice today due to poor standardization or risk of false results (Stern 2012).

In diagnosing an exanthematous drug eruption, it is important to consider the long-term implications of assigning a patient with a drug allergy, and to carefully consider the differential diagnosis. Especially in pediatric cases, the drug allergy label can follow a patient for life, and the list of allergies can amass. A strategy that can be employed is to use descriptive terms in describing a drug allergy, such as "probable" or "possible" drug allergy, as well as documenting the actual reaction to a medication, such as "exanthematous rash," versus "urticaria" (Shin and Chang 2001). Furthermore, the Naranjo criteria may be employed to estimate the probability of a CADR. This scale, which was developed in 1981, estimates the probability of a CADR and categorizes likelihood into "definite," "probably," "possible," and "doubtful" (Naranjo et al. 1981).

7 Management

Exanthematous drug reactions typically do not require intensive management on their own. However, it is critical in the initial stages of diagnosis to properly identify morphology and recognize warning signs that may suggest a SCAR. These warning signs include mucous membrane involvement (exanthematous reactions, if involving the mucosa, typically are nonblistering and nonulcerative), facial edema, lymphadenopathy, pustules, blistering and denuded skin, systemic symptoms, or fever, or symptoms that might suggest evolution to these features such as skin pain, dysuria, dysphagia, or photophobia (Waldman et al. 2017). Development of these warning signs warrants immediate medical evaluation and possibly hospitalization. Exanthematous drug reactions, especially those with evidence of progression to a more severe reaction such as generalized erythroderma (deShazo and Kemp 1997), should result in discontinuation of the offending agent (Stern 2012). If the medication is deemed absolutely necessary and there is no development of a serious reaction, managing through the process with close monitoring can take place or desensitization may be attempted once the current episode resolves (Stern 2012). Once a SCAR has been ruled out from clinical consideration, patients may be provided symptomatic relief with oral antihistamines and topical corticosteroids. Topical lidocaine and diphenhydramine have high rates of allergic contact dermatitis, and should generally be avoided

in pediatric populations (Hanson and Nigro 1998). In severe cases, a short course systemic corticosteroids may be considered (Hoetzenecker et al. 2016). In general, the causative agent should be avoided in the future because it is possible the reaction will amplify in severity upon rechallenge (Stern 2012).

It is important to note that patients who have developed one exanthematous drug eruption may be at risk of developing another due to cross-reactivity between pharmacologically related medications. For example, there is cross-reactivity between the aromatic antiepileptic drugs, especially carbamazepine and phenytoin (Hirsch et al. 2008). There is very limited data on the safety and efficacy of drug desensitization in exanthematous drug eruptions (Scherer et al. 2013).

8 Conclusion and Future Directions

Exanthematous drug reactions, while largely mild in presentation, represent the majority of cutaneous drug reactions, and thus clinicians may see an abundance of these cases. Future study is needed to further elucidate the underlying pathophysiological mechanism of this reaction, the link between exanthematous drug reactions and genetic haplotypes, the role of systemic therapies for symptomatic relief, and the possible role of desensitization to causative medications.

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Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

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1 Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN, or Lyell syndrome) represent the most threatening of the severe cutaneous adverse reactions (SCARs) to drugs. During the acute phase of the reaction, SJS/TEN is associated with multiple morbidities and a high mortality (15–30%). Patients who survive the early phase of SJS/TEN commonly go on to suffer disabling long-term sequelae. The incidence ranges between 1–6 cases/million inhabitants/year (Duong et al. 2017; Sekula et al. 2013; Micheletti et al. 2018; Bettuzzi et al. 2019; Chaby et al. 2019a).

SJS and TEN are variants of the epidermal necrolysis spectrum (Heng et al. 2015) defined by the extent of body surface area (BSA) involvement: in SJS there is less than 10% BSA epidermal detachment; in SJS–TEN overlap syndrome there is 10–29% detachment; in TEN or Lyell syndrome ≥30% detachment. The disease generally occurs 4–28 days after drug exposure following first use of the culprit drug. Although epidermal necrolysis is induced by medication in the majority of cases, a drug trigger is not found in approximately 15% of cases (Roujeau et al. 1995; Auquier et al. 2002; Mockenhaupt et al. 2008; Sassolas et al. 2010; Chaby et al. 2019b). In nondrug cases (so-called nontoxic epidermal necrolysis), two major etiologies have been identified and should be systematically investigated: *Mycoplasma pneumoniae* infection, which is more frequent in children and young people (Tomaino et al. 2012), and autoimmune disorders, especially Ro-SSA-positive subacute cutaneous lupus erythematosus ("TEN-like lupus") and anti-MDA5 dermatomyositis (Ting et al. 2004; Dumas et al. 2018). Some cases induced by *Coxsackievirus* A6 have been described (Horsten et al. 2018); however, several cases remain "idiopathic" despite extensive infectious and immunological investigations.

2 Medication Risk

Drug causality assessment involves the appraisal of several data from the patient, such as the time since drug intake, the half-life of the drug, the

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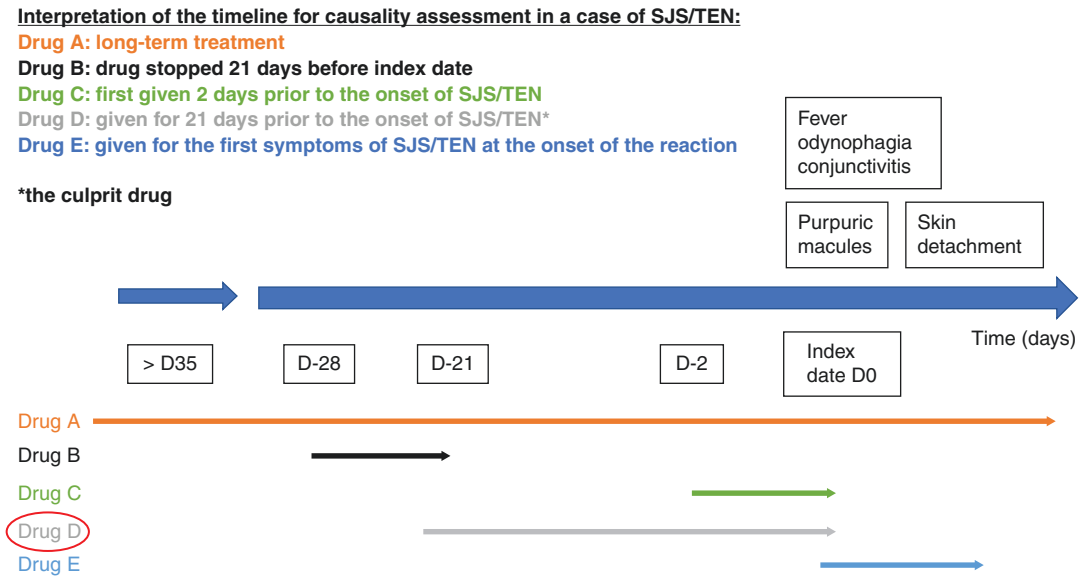

Fig. 1 Interpretation of the timeline for causality assessment in a case of SJS/TEN

index day (first day of symptoms, including general/non dermatological manifestations) and underlying comorbidities such as renal impairment, cancer or immunosuppression. A timeline is useful for thinking about drug accountability (Fig. 1).

ALDEN (ALgorithm of Drug causality for Epidermal Necrolysis) is a tool designed to assess culpability of individual suspected drugs in cases of SJS/TEN. The ALDEN score uses time since drug intake, pharmacokinetics, rechallenge or dechallenge, and drug notoriety to classify drug causality into one of five categories: very unlikely, unlikely, possible, probable or very probable (Sassolas et al. 2010).

European case–control studies have provided a list of high-risk drugs for SJS/TEN (Mockenhaupt et al. 2008). The major culprits from these analyses are: antibacterial sulfonamides (including cotrimoxazole, sulfasalazine and dapsone), allopurinol, antiepileptics of the aromatic amine family (carbamazepine, oxcarbazepine, phenobarbital, and phenytoin), lamotrigine, nonsteroidal anti-inflammatory drugs (NSAIDs) of the oxicam family, and nevirapine. Other drugs at significant risk include proton pump inhibitors (pantoprazole), NSAIDs from arylcarboxylic acid class (e.g., ketoprofen), and other antibiotics (macrolides, quinolones, aminopenicillins, cephalosporins, tetracyclines).

In children, antibacterial sulfonamides and antiepileptics are the most common triggers, without any identified risk for vaccines (Levi et al. 2009; Raucci et al. 2013). Paracetamol has been a suspected culprit, but confounding protopathic bias was demonstrated with the drug being prescribed for the flu-like symptoms in early-stage SJS/TEN (Levi et al. 2009). An hypothesis suggested to explain "idiopathic" SJS/TEN implicated a role for drugs used in veterinary medicine, such as phenylbutazone, entering meat and subsequently being ingested. This source of culprit drug has not, however, been confirmed (Haddad et al. 2017).

3 Pathophysiology

SJS/TEN results from a type IVc nonimmediate hypersensitivity reaction, mediated by cytotoxic CD8+ T cells (Morel et al. 2011; Pichler et al. 2011; Takahashi et al. 2009).

Several models have been proposed to explain the activation of cytotoxic T cells in SJS/TEN:

- In the "hapten–prohapten model," covalent bonds are established at the surface of antigen-presenting cells (APCs) between drugs (native or after metabolism) and autologous proteins/peptides. This interaction then induces drug-specific humoral or cellular immune responses (Padovan et al. 1996).
- In the "pharmacological interaction model" (also called the "p–i concept") the drug in its native form, or a metabolite, binds directly and noncovalently to the T cell receptor (TCR) or to some specific HLA molecules, without being processed by APCs (Pichler et al. 2011).
- In the "altered peptide repertoire model," mainly described with abacavir, the drug binds noncovalently to the pocket of the major histocompatibility complex (HLA B*57:01 in the case of abacavir) leading to alteration the self-peptide repertoire, which thus allows T cell activation (Illing et al. 2012; Ostrov et al. 2012).

Genetic factor predisposition to SJS/TEN is now clearly demonstrated. This is especially prominent in the Asian population, mainly from Han ancestry (Table 1) (Cheng et al. 2014; Chung et al. 2004; Hung et al. 2005; Lonjou et al. 2008; Mallal et al. 2008; Saag et al. 2008; Kaniwa et al. 2010; Génin et al. 2011; McCormack et al. 2011; Carr et al. 2013). In this population a close link has been demonstrated between SJS/TEN to carbamazepine and HLA-B*15:02, and between SJS/TEN to allopurinol and HLA-B*58:01 (Hung et al. 2005). Although European studies failed to replicate these associations (Génin et al. 2011), HLA-A*31:01 was observed to be a risk factor for drug-induced exanthem, DRESS and SJS/TEN to carbamazepine in subjects with Northern European and Japanese ancestry (McCormack et al. 2011). More recently, a study showed that HLA-B*57:01 was strongly associated with SJS/TEN (but not DRESS) to carbamazepine in Europeans (Mockenhaupt et al. 2019). Other HLA associations have been described in Asia, such as dapsone-induced DRESS and HLA-B*13:01 (Tangamornsuksan and Lohitnavy 2018). These causal relationships have given rise to a policy of systematic HLA screening in many countries prior to the prescription of certain drugs to an at-risk individual (Chung et al. 2007). The worldwide association between HLA-B*57:01 and severe hypersensitivity reactions to abacavir has led to a global prevention policy (Tangamornsuksan et al. 2015).

The T cell receptor (TCR) also seems to be a key factor in triggering SJS/TEN. The specificity and diversity of TCR depend on the CDR3 (complementarity determining region 3) hypervariable regions which are the sites of contact with the antigen presented on the HLA molecule. Those CDR3 sequences are often used to identify clonal T cells, especially the sequences located on the β chain. Several studies have shown the preferential use of a TCR-Vβ on drug-specific CD8+ T cells. TCRs sharing the same Vβ sequence are considered clonotypic (Chung et al. 2015; Pan et al. 2019). Following the induction of cytotoxic T cells, there is an activation of inflammatory cells, including regulatory T cells, and the secretion of various cytokines which leads to epidermal and epithelial necroptosis. Indeed, the disease is characterized by a massive production of death mediators by cytotoxic T cells, NK cells, and keratinocytes themselves by an amplification loop phenomenon (Takahashi et al. 2009; de Araujo et al. 2011). Three main pathways are described: Fas–Fas-ligand interaction, perforin–granzyme B, and granulysin (Chung et al. 2008; Viard-Leveugle et al. 2013). A major inflammatory environment, involving pro-inflammatory cytokines such as TNF-α, IFN-γ, and TRAIL, increases expression of FasL on the surface of keratinocytes thus amplifying keratinocyte death signals. Granulysin appears to be the major cytotoxic molecule responsible for keratinocyte necrosis (Chung et al. 2008). IL-15 may also have a role in SJS/TEN pathogenesis: levels of IL-15 have been correlated with disease severity and mortality (Su et al. 2016). High expression of receptor-interacting protein kinase 3 (RIP3) in SJS/TEN lesions indicates that RIPK3 may also be an essential factor in keratinocyte programmed death (Kim et al. 2015).

Table 1 SJS/TEN drug-HLA associations (Cheng et al. 2014; Chung et al. 2004; Hung et al. 2005; Lonjou et al. 2008; Mallal et al. 2008; Saag et al. 2008; Kaniwa et al. 2010; Génin et al. 2011; McCormack et al. 2011; Carr et al. 2013; Mockenhaupt et al. 2019; Tangamornsuksan and Lohitnavy 2018; Chung et al. 2007; Tangamornsuksan et al. 2015)

Drugs	HLA	Population strongly associated	Screening recommendation
Carbamazepine	*B*15:02* *B*15:11* *B*59:01*	Han Chinese Asian ancestry Thai Indian Japanese, Korean Japanese	Asia: Taiwan, Singapore, Thailand
	*A*31:01*	Northern Europe	
	*A*31:01*	Japanese	
	*B*15:11*	Japanese	
Oxcarbazepine	*B*15:02*	Han Chinese	Asia: Taiwan
Phenytoin	*B*15:02*	Han Chinese, Thai	
	*B*13:01*	Han Chinese	
	*Cw*08:01*	Han Chinese	
	*DRB1*16:02*	Han Chinese	
	*B*15:02*	Thai	
Lamotrigine	*B*15:02*	Han Chinese	
	*B*38*	Han Chinese	
	*B*58:01*	European	
	*A*68:01*	European	
	*Cw*07:18*	European	
	*DQB1*06:09*	European	
	*DRB1*13:01*	European	
Abacavir	*B*57:01*	European, western countries	Europe, USA, Australia
Allopurinol	*B*58:01*	Han Chinese European Japanese Asian	
Antibacterial sulfonamides	*Cw*4* *B*38*	Han Chinese European	
Nevirapine	*C*04:01*	Malawian	
Dapsone	*B*13:01*	Han Chinese	
Methazolamide	*B*59:01*	Korean, Japanese	
	*CW*01:02*	Korean, Japanese	
Oxicam	*B*73*	European	
	*A*2*	European	
	*B*12*	European	

HLA human leukocyte antigen

4 Clinical Presentation

A flu-like syndrome with ocular and nasopharyngeal symptoms frequently precedes the dermatological manifestations of SJS/TEN. Odynophagia (painful swallowing) is often a prominent early symptom. The first day of these manifestations should be considered as the index day of the disease (Duong et al. 2017; Heng et al. 2015; Auquier et al. 2002; Ingen-Housz-Oro et al. 2018a). Cutaneous lesions appear a few days later, often accompanied by skin pain. The eruption usually begins on the face, upper trunk and proximal limbs before extending cephalocaudally.

Initial lesions are dusky-red/purpuric macules and atypical targets (which lack the three concentric rings of typical erythema multiforme) (Ingen-Housz-Oro et al. 2017). Vesicles and bullae then appear on the purpuric macules (Fig. 2a).

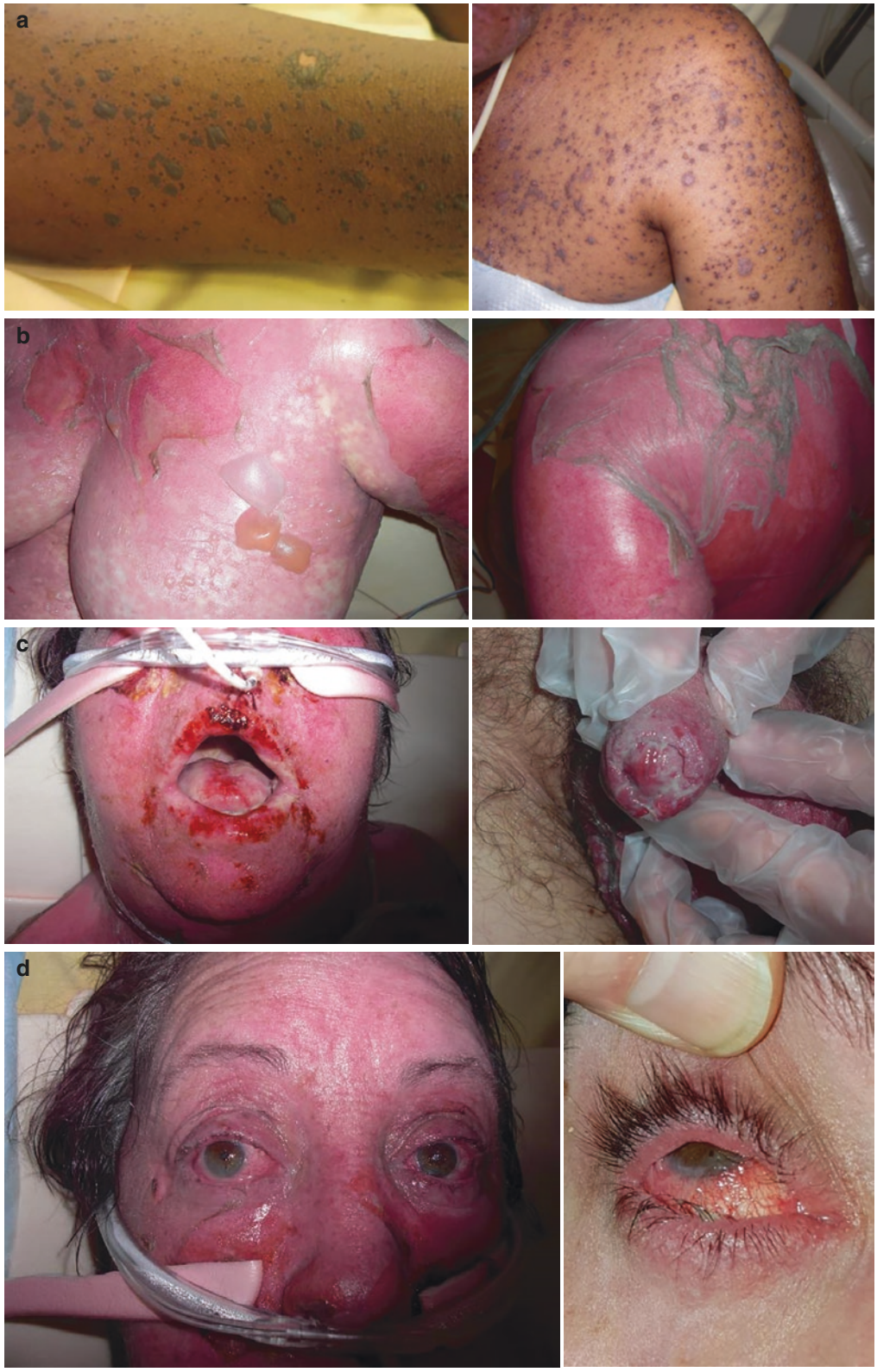

Fig. 2 (**a**) SJS: small blisters with minor epidermal detachment. (**b**) TEN: extensive detachment of epidermal sheets. (**c**) Oral and genital involvement in SJS/TEN. (**d**) Ocular involvement in SJS/TEN

Confluence of necrotic lesions leads to blistering and detachment of epidermal sheets, revealing areas of denuded, red dermis (Fig. 2b). Nikolski's sign is positive on lesional skin (gentle lateral pressure causes detachable epidermis to slide over the dermis).

Two or more mucous membranes are involved in almost all cases. Confluent erosions are observed on the buccal, nasopharyngeal, oropharyngeal, ocular, anal, and genital mucous membranes (Fig. 2c). Lips are usually extensively eroded and coated with hemorrhagic crust. Extensive laryngeal lesions are associated with a higher risk of short-term pulmonary involvement (Bequignon et al. 2015). Ocular involvement is of varying severity (Gueudry et al. 2009) and is graded according the Power or Sotozono systems (Power et al. 1995; Sotozono et al. 2015). Eyelid edema, conjunctival injection, membranous conjunctivitis, and chemosis are the most frequent lesions (Fig. 2d). Severe forms lead to corneal epithelial defects, corneal ulceration and symblepharon formation (Gueudry et al. 2009).

Disease progression is time-limited (7–10 days). The skin then heals (reepithelialization), the rate of which depends on the patient's general medical and nutritional status. Mucous membrane healing tends to follow skin resolution. In general complete mucocutaneous healing is achieved within 1 month.

Visceral involvement includes transient liver enzyme increase, renal dysfunction, neutropenia, lymphopenia, bronchial and digestive tract epithelial necrosis (Lebargy et al. 1997; Gendreau et al. 2019). Table 2 summarizes the mucocutaneous lesions which typify the acute phase of SJS/TEN. Severe renal involvement needing renal replacement therapy and respiratory failure requiring mechanical ventilation are factors which indicate a poor prognosis (Papo et al. 2017; de Prost et al. 2014).

Table 2 Acute stage lesions in SJS/TEN: location, sequelae, and local treatment (Ingen-Housz-Oro et al. 2018a; Bequignon et al. 2015; Gueudry et al. 2009; Power et al. 1995; Sotozono et al. 2015; Hajj et al. 2019; Lebargy et al. 1997; Gendreau et al. 2019; Papo et al. 2017; Creamer et al. 2016)

Site involved	Acute stage lesion	Sequelae	Local treatment
Skin	Purpuric macules, atypical targets, blisters, erosions, denuded dermis	Dystrophic scars, hyperpigmentation, alopecia, nail loss	Antiseptic baths or diluted antiseptic spray, ointment-based emollients, nonadhesive hydrocellular dressings
Eye	Hyperemia, tearing, chemosis, photophobia, adhesions, erosions	Dry eye, synechiae, symblepharon, loss of vision	Ocular emollients, eye drops, topical vitamin A ointment, inflammatory debris removal with daily saline rinses, amniotic membrane transplantation with severe erosions/ulcers, scleral lens for cicatricial complications
Mouth	Erosions, blisters, mucosal hemorrhage, labial hemorrhagic crusts	Dental agenesia, sialadenitis, tooth decay	Topical analgesia, mouthwashes, local administration of adrenaline and tranexamic acid for mucosal bleeding
Ear, nose throat	Erosions, blisters, epiglottitis, nasal obstruction, epistaxis, otorrhea	Cough, chondritis, otalgia, external otitis, scars, dysphonia, dysphagia, conductive deafness	Analgesia, emollients
Genital	Erosions, blisters	Genital synechiae, vaginal stricture, phimosis	Emollients, debridement
Pulmonary	Bronchial epithelial necrosis, respiratory failure	DLCO diffusion impairment, dyspnea, bronchiolitis obliterans	Bronchoscopic clearance of necrotic mucosal debris
Digestive tract	Digestive necrosis	Diarrhea	
Psychiatric	Anxiety, stress	Post-traumatic stress disorder, anxiety, depression	Anxiolytic, analgesia

The main complications result from acute skin failure (Roujeau 1992). Most frequent are life-threatening pulmonary or systemic infections. Denuded skin is the main portal of entry for microorganisms; however, translocation of gut bacteria is also implicated in TEN-related septicemia (Lecadet et al. 2019; Chosidow et al. 1991). In most instances bacteremia involves patients with > 10% BSA detachment, that is SJS-TEN overlap or TEN (de Prost et al. 2010; Koh et al. 2019). Sequential skin cultures are useful to monitor cutaneous bacterial colonization and predict which bacteria are involved in bloodstream infections, thus guiding antibiotic decision-making (see below) (Lecadet et al. 2019; de Prost et al. 2010).

The SCORTEN score, introduced in 2000, is used to predict mortality during the acute phase. Seven parameters are assessed at admission and/or during the 5 first days of hospitalization, each parameter is one point and therefore SCORTENs vary between 0 and 7. Four of SCORTEN's parameters are clinical: age ≥40 years-old; detachment >10% BSA; underlying malignancy; pulse rate ≥120/min. Three SCORTEN parameters are laboratory results: serum urea >10 mmol/L; serum bicarbonate <20 mmol/L; blood glucose >14 mmol/L. Mortality risk varies from 3% for patients with SCORTEN of 0 or 1, to 90% for those with SCORTEN 5–7 (Bastuji-Garin et al. 2000; Guégan et al. 2006).

Skin biopsy for histology and direct immunofluorescence is mandatory at admission. Histology shows keratinocyte necrosis with full-thickness epidermal necrolysis and a minimal dermal infiltrate (Ortonne 2018; Valeyrie-Allanore et al. 2013). The dermatopathology of SJS/TEN is similar to other diseases of the acute syndrome of apoptotic pan-epidermolysis (ASAP), such as TEN-like lupus erythematosus, *Mycoplasma pneumoniae*-induced erythema multiforme major, and acute graft-versus-host disease (Ting et al. 2004; Amode et al. 2018). Direct immunofluorescence yields negative results, excluding autoimmune blistering diseases such as linear IgA bullous disease, which may mimic TEN especially if induced by vancomycin (Chanal et al. 2013; Garel et al. 2019).

5 Management and Treatment

Patients with SJS/TEN should be admitted to a unit with specialist expertise in the management of skin loss syndromes and acute skin failure (specialized intensive care unit or burn unit) (Ingen-Housz-Oro et al. 2018a; Kaffenberger and Rosenbach 2014; Traikia et al. 2019; Creamer et al. 2016). Survival is associated with an early diagnosis (within 7 days of onset) (Palmieri et al. 2002), and supportive care delivered in a specialized unit. A TEN multidisciplinary team should be coordinated by a specialist in skin failure (usually a dermatologist) and must include clinicians from skincare nursing, intensive care, ophthalmology and respiratory medicine.

The identification of the culprit drug and its withdrawal must be undertaken immediately. Early discontinuation of the culprit has been shown to improve prognosis (Garcia-Doval et al. 2000). Following a diagnosis of SJS/TEN the patient should carry an allergy card to prevent inappropriate reintroduction of the causative drug. As well as the standard name of the culprit, the allergy card should list relevant generic and brand names, as well as drugs of same structure and family.

6 Supportive Care

During the acute phase the main complications of SJS/TEN result from skin failure (Roujeau 1992) and its potential to progress to multiorgan failure. Therefore, the goal of supportive care is to reestablish hemodynamic equilibrium and to prevent life-threatening sequelae (mainly hypovolemia, renal insufficiency, thermal dysregulation, sepsis and respiratory complications) (Table 3) (Ingen-Housz-Oro et al. 2018a; Creamer et al. 2016). Resuscitation to offset massive transcutaneous water loss necessitates fluid replacement which should be started urgently and adjusted daily. The supply of intravenous fluids and electrolytes should be adapted to the patient's needs on a case-to-case basis. At admission, a formula such as the Brooke one (Pruitt et al. 1971) can be used (1.5 mL × % detached and detachable BSA × kg

Table 3 Preventative management for the acute complications in SJS/TEN (Ingen-Housz-Oro et al. 2018a; Creamer et al. 2016)

Acute stage complication	Prevention
Dehydration	Limitation of thermal and caloric losses Enteral feeding Fluid replacement using the formula (1.5 mL × % detached and detachable BSA × kg body weight), adapted to the diuresis (objective: 0.5–1 mL/kg/h)
Septicemia	Antiseptic baths or diluted antiseptic spray No prophylactic antibiotics Repeated blood culture and qualitative and quantitative skin cultures Avoid cannula insertion into lesional skin
Respiratory failure	Airway humidification Removal of mouth debris Nasotracheal aspiration Avoid mechanical ventilation, unless absolutely necessary
Pain, anxiety	Opiate analgesia, hydroxyzine

body weight), then followed by an adaptation according the diuresis (aiming for 0.5–1 mL/kg/h). Peripheral cannulas sited on nondetached skin are preferred for vascular access (Ingen-Housz-Oro et al. 2018a; Palmieri et al. 2002).

Environmental temperature should be raised to 28–32 °C to limit caloric and thermal losses. Nutritional hypercaloric and protidic enteral feeding is initiated through a nasogastric tube (aiming for 20–30 kcal/kg/day), except in the case of a severe esophageal involvement (Gendreau et al. 2019; Weinand et al. 2013).

Opioid agonists are generally used (with respiratory surveillance) to alleviate skin and mucosal pain (Ingen-Housz-Oro et al. 2018a; Valeyrie-Allanore et al. 2011).

Tracheal intubation and mechanical ventilation are necessary in about 25% of cases. The need for mechanical ventilation can be anticipated in patients with extensive laryngeal involvement and in situations when uncontrolled pain limits patient handling for skin and mucosal care. Mechanical ventilation in SJS/TEN is associated with a worse outcome (de Prost et al. 2014).

Antibiotic prophylaxis is not recommended; however, antibiotics should be introduced without delay when clinical features and laboratory results suggest sepsis (hemodynamic instability, hypothermia, oliguria, elevation of procalcitonin) (Ingen-Housz-Oro et al. 2018a; Koh et al. 2019; Palmieri et al. 2002). The results of skin cultures can predict bacteria involved in bloodstream infections and guide antibiotic prescribing (Lecadet et al. 2019).

If *Mycoplasma pneumoniae* is suspected (young age, no culprit drug, cough and high fever at disease onset), treatment with a macrolide is recommended until the results from nasopharyngeal PCR and specific serology are obtained (McPherson et al. 2019).

7 Local Management of Skin and Mucous Membranes

Caution is needed in handling the patient: particular care must be taken to minimize shearing forces applied to the skin which might increase epidermal detachment. Skin cleansing should be performed daily with a diluted solution of antiseptic, such as chlorhexidine, delivered in a bath or by aerosolized spray. There is a lack of consensus regarding the best dressing to be used to denuded areas; however, we recommend white petroleum (white soft paraffin) to be applied to all detached areas and nonadhesive dressings (e.g., hydrocellular) to cover pressure points, particularly on the back (Ingen-Housz-Oro et al. 2018a; Firoz et al. 2012; Struck et al. 2010). Topical antimicrobial agents, including sulfadiazine ointment (containing antibacterial sulfonamides), are not recommended (Ingen-Housz-Oro et al. 2018a).

In contrast with burns, we do not recommend skin debridement. Necrotic epidermal sheets act as a natural biological dressing (Castillo et al. 2018).

During the acute phase frequent applications of an appropriate emollient to ocular, oral, nasal, genital and anal mucosae will limit fibrotic scarring. Local care to the eyes is of particular importance: preservative-free lubricant eye drops and/

or a vitamin A ophthalmic ointment should be administered every 2 h. Regular removal of adhesions by the ophthalmologist is mandatory. In severe cases amniotic membrane transplantation should be considered (Liu et al. 2011; Sharma et al. 2016). The use of topical antibiotics, ciclosporine, or corticosteroids has not shown to be beneficial in lessening long-term ocular sequelae (Ingen-Housz-Oro et al. 2018b).

8 Immunomodulatory Approaches

The benefits of targeted therapeutic approaches are still being debated (White et al. 2018; Zimmermann et al. 2017). Most published data are case reports and small-uncontrolled series (Sekula et al. 2013; Schneck et al. 2008). The role of immunosuppressants or immunomodulatory treatments, including corticosteroids (Lee et al. 2012; Morita et al. 2019), cyclophosphamide (Rajaratnam et al. 2010), calcineurin inhibitors (especially ciclosporin) (Valeyrie-Allanore et al. 2010), anti-TNF therapy (Paradisi et al. 2014), and intravenous immunoglobulins (IVIg) (Bachot et al. 2003; Chen et al. 2010), has been reported with controversial results and without evidence for an unbiased, positive effect on healing or mortality.

High-dose systemic corticosteroids are considered to be a treatment option. However, recent large studies have challenged the therapeutic efficacy of systemic glucocorticoids in SJS/TEN (Lee et al. 2012; Morita et al. 2019). It has also been shown that prior exposure to corticosteroids is associated with a longer disease progression with no impact on mortality (Lee et al. 2012). Treatment with IVIg has produced conflicting results (Firoz et al. 2012; Bachot et al. 2003; Chen et al. 2010; Lee et al. 2013; Huang et al. 2012). Pooled analysis of previously published studies failed to show mortality benefit, even if used in conjunction with corticosteroids (Schneck et al. 2008).

Ciclosporin, an anti-apoptotic agent which inhibits CD8+ T cells, was shown to limit disease progression after a short-term administration of 3–10 mg/kg (Valeyrie-Allanore et al. 2010). In our first, open, single-centre trial on 29 patients, 3 mg ciclosporin/kg/day resulted in the absence of observed death, whereas 2.75 deaths were predicted by SCORTEN score, with control of epidermal detachment progression in 62% of patients. Other small retrospective studies have been performed with the same encouraging results. A Spanish study compared 26 patients treated with ciclosporin in a single burns unit with 16 patients not treated with this drug in another burns unit. The authors then pooled their results with those of five previous case series. They found that ciclosporin decreased mortality by 60% (González-Herrada et al. 2017; Lee et al. 2017a). However, in our second, larger, single-center retrospective study (of 174 patients) in which a propensity score method was used to compare patients receiving ciclosporin plus supportive care with those who received supportive care only, the initial encouraging results of ciclosporin were not confirmed, neither for reducing the mortality nor for improving the time to healing (Poizeau et al. 2018).

In an Italian small case series, a single dose of etanercept (anti-TNF agent) was shown to provide quick healing of SJS/TEN within 8.5 days (Paradisi et al. 2014). Another uncontrolled prospective study in Taïwan compared etanercept with corticosteroids in 96 patients (60% of the study population had SJS) and reported a quicker healing time in the etanercept group; however, the mortality rate was similar (Wang et al. 2018). Previously, a randomized controlled trial had shown an unexpected higher rate of mortality with thalidomide, which has anti-TNF properties, than with placebo (Wolkenstein et al. 1998).

GM–CSF may have a therapeutic role in SJS/TEN as preliminary data from two patients suggested that it had a positive effect on promoting epithelialization (de Sica-Chapman et al. 2010).

9 Long-Term Follow-Up

After the acute phase, survivors of SJS/TEN are commonly troubled by chronic sequelae which have a significant impact on quality of life (Yang et al. 2016; Lee et al. 2017b; Ingen-Housz-Oro et al. 2019) (see Table 2).

The most frequent and disabling sequelae are as follows

Cutaneous (Magina et al. 2003)

Hypo/hyperpigmentation, dystrophic scars, hypertrophic scars, photosensitivity, chronic pruritus, dysesthesia, nail dystrophy, telogen effluvium.

Ocular (Gueudry et al. 2009; Hajj et al. 2019; Thorel et al. 2019; Tougeron-Brousseau et al. 2009)

Dry eyes, ocular pain, photophobia, eyelid and conjunctival scarring causing trichiasis and symblepharon, corneal erosions and ulcers, neovascularization, loss of sight

Psychological (Hefez et al. 2018; Dodiuk-Gad et al. 2016)

Fatigue, anxiety, depression, fear of drugs, post-traumatic stress disorder.

Other sequelae include the following

Genital (Kaser et al. 2011)

Scars, synechiae, pain, dyspareunia, impaired normal vaginal delivery

Oral and dental (Sibaud et al. 2005; Gaultier et al. 2009)

Chronic erosions of the tongue, sialadenitis, tooth decay

Respiratory (Duong et al. 2015; Seccombe et al. 2019)

Asymptomatic alteration of diffusion capacity, rarely bronchiolitis obliterans, especially in children

Regular multidisciplinary follow-up with the help of a psychologist and social worker is helpful in reducing the impact of long-term sequelae (Ingen-Housz-Oro et al. 2018a; Ingen-Housz-Oro et al. 2019; Dodiuk-Gad et al. 2016).

10 Tests to Identify the Culprit Drug

No currently available test has sufficient sensitivity and specificity to rule out a potential culprit drug when negative and thus permit rechallenge with zero risk of triggering further SJS/TEN. Intradermal tests and drug provocation tests are contraindicated in SJS/TEN. Patch testing is safe and best performed within 6 months of the acute phase; however, this investigation has a low sensitivity in SJS/TEN (Barbaud et al. 2013; Wolkenstein et al. 1996). Thus, in the situation of negative patch tests all suspected drugs remain contraindicated (Bergmann and Caubet 2019; Phillips et al. 2019).

In vitro tests, which include lymphocyte-transformation test (LTT) or enzyme-linked immunospot assay (ELISPOT), are not available in routine practice in most centers. In SJS/TEN, these tests are of best value in the early stage of the disease (Kano et al. 2007; Srinoulprasert and Pichler 2014). However, LTT has a low sensitivity in SJS/TEN when used alone (Tang et al. 2012). Other tests, such as granulysin expression, granzyme B-ELISPOT, and IFNγ production, when used in combination may have a higher sensitivity and specificity (Kano et al. 2007; Srinoulprasert and Pichler 2014; Porebski et al. 2013).

11 Prevention of SJS/TEN

Prevention of this life-threatening disorder is a major aim in the management of SJS/TEN. Central to preventative strategies is the identification of individuals at high risk of SJS/TEN. In many countries pharmacogenomic screening before the administration of HLA-associated drugs has been established for at-risk populations, a public health initiative which has significantly reduced the incidence of SJS/TEN. There is also a recognition that certain drugs which carry a high notoriety for SJS/TEN may be prescribed inappropriately. A key example is the use of allopurinol to manage asymp-

tomatic hyperuricemia. It has been argued that this indication for allopurinol represents a high jeopardy prescribing practice and should, perhaps, be challenged. Other prescribing anomalies which can potentially cause SJS/TEN include the problem of similarities in drug nomenclature. Several SJS/TEN cases have been reported after erroneous dispensing of Lamictal (lamotrigine) instead of Lamisil (terbinafine) (Cassius et al. 2019). Tackling flaws in both drug prescribing and drug dispensing offers a simple opportunity to lessen the risk of SJS/TEN.

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Acute Generalised Exanthematous Pustulosis

Chantal Cotter and Daniel Creamer

1 Introduction

The recognition of a medication-induced generalised pustulosis, separate from pustular psoriasis, was first reported by Baker and Ryan in 1968 (Baker and Ryan 1968). Their description defined patients without a history of psoriasis who developed a drug-triggered pustular eruption which was both acute in onset and rapid in resolution. Subsequent recurrence of the pustulosis did not occur. A number of terms have been used to label this drug reaction: it is currently referred to as "acute generalised exanthematous pustulosis" or AGEP.

2 Epidemiology

The European case–control study on severe cutaneous adverse reactions, EuroSCAR, was carried out from 1997 to 2001 and included the largest validated cohort of AGEP patients, most of whom were recruited from France (Sidoroff et al. 2007). As this case–control study was not population-based, reliable incidence rates for AGEP were not calculated. However, the reaction occurs rarely in clinical practice and an estimated incidence of 1–5 cases per million population per year seems a reasonable approximation. The average age was 56 years (4–91 years) and 80% of patients were female (Sidoroff et al. 2007). No ethnic variations were described. A death rate of approximately 4% was calculated. AGEP may be more frequent in some European countries than in others due, in part, to the availability of specific drugs with a high AGEP risk (Sidoroff et al. 2007).

3 Pathophysiology

As with all the severe cutaneous adverse reactions, drug-specific T lymphocytes are central to the pathogenesis of AGEP; however, the ultimate end-product of AGEP inflammation is accumulation of neutrophils in the epidermis. Positive patch tests and lymphocyte transformation tests to culprit medication implicate the involvement of a delayed-type hypersensitivity reaction, while drug-specific CD4+ and CD8+ cells showing a high level of CXCL8 production have been isolated both from lesional skin and circulating blood in patients with AGEP (Pichler 2002; Britschgi et al. 2001). A sub-group of T cells producing interleukin-8 (IL-8), which is a neutrophil-attracting chemokine, have also been identified in the peripheral blood of patients with AGEP (Britschgi and Pichler 2002; Schmid et al. 2002). The attraction of neutrophils into lesional epidermis is central to the pathology of AGEP and

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therefore IL-8 may be a key player in the expression of drug-induced pustulosis.

Genetic studies investigating the immunopathogenesis of generalised pustular psoriasis (GPP) have shed further light on the aetiopathogenesis of AGEP. Studies have identified homozygous or composite heterozygous loss-of-function mutations in the *IL36RN* gene in consanguineous family members expressing GPP (Onoufriadis et al. 2011). Mutations of the same gene have been identified in a minority of patients with AGEP, while detection of null mutations (mutations leading to complete absence of the IL-36Ra protein) are associated with the most severe forms of GPP and AGEP (Tauber et al. 2016). IL-36Ra (receptor antagonist) is an inhibitor of pro-inflammatory pathways. Mutations in the *IL36RN* gene impair structure, expression and regulatory function of the IL-36Ra protein leading to an enhanced inflammatory cascade downstream of the interaction between the IL-36a, IL-36b and IL-36c agonistic ligands and their receptors (Onoufriadis et al. 2011). The consequence of defective immune inhibitory control results in an upregulated expression of inflammatory mediators CXCL8/IL-8, TNF-a, IL-1, IL-17 and IL-23. This cytokine abnormality may also cause dysregulated activation of dendritic cells and T cells (Pichler 2002; Britschgi et al. 2001).

4 Pathology

A study of the histopathological features of 102 patients with a validated diagnosis of AGEP was undertaken by Halevy et al. using subjects recruited to the EuroSCAR and RegiSCAR projects (Halevy et al. 2010). Spongiform pustules were noted within the epidermis in 92% of all patients. In 41% of cases the pustules were sub- or intra-corneal, in 20% they were intra-epithelial, and in 38% the pustules were observed in both sites. Follicular pustules were seen in 23% of patients. The other common epidermal changes were necrotic keratinocytes, spongiosis and neutrophil exocytosis. The main dermal features were papillary oedema and a mixed infiltrate in the superficial and mid dermis containing neutrophils and eosinophils. Red cell extravasation was observed in 54% of cases (Halevy et al. 2010).

Although AGEP can resemble generalised pustular psoriasis, many of the histopathological features of plaque psoriasis (parakeratosis, suprapapillary thinning, tortuous blood vessels, absence of granular layer) are absent in biopsies of AGEP.

5 Culprit Drugs

More than 90% of AGEP cases are caused by an identifiable drug (Roujeau et al. 1991). A full drug history is necessary, including over-the-counter agents, paying particular attention to drugs started in the few days prior to the onset of the reaction. Certain drugs are more closely associated with the development of AGEP: in the largest study the most commonly implicated agents were pristinamycin, aminopenicillins, quinolones, chloroquine, hydroxychloroquine, sulphonamides, terbinafine and diltiazem (Sidoroff et al. 2007). Less commonly associated drugs in this study were corticosteroids, macrolide antibiotics, non-steroidal anti-inflammatory drugs of the oxicam class, and anti-epileptic medications (except valproate). Other drugs which have been implicated in AGEP include clopidogrel (Nakamizo et al. 2010), azathioprine (Elston et al. 2007) and targeted therapies such as sorafenib (Liang et al. 2011) and gefitinib (Shih et al. 2006). Cases of AGEP induced by unusual substances have been reported, including reaction to topical contact with 2-chlorobenzylidene malonitrile (CS) gas (Wu et al. 2011). Reports have implicated an infective trigger in a few cases of AGEP: mycoplasma pneumoniae (Lim and Lim 2009), coxsackie virus (Feio et al. 1997), parvovirus B19 (Naides et al. 1988; Calistru et al. 2012) cytomegalovirus (Haro-Gabaldon et al. 1996), mumps (Azib et al. 2014) and Epstein-Barr virus (Ropars et al. 2014). Mercury exposure (Lerch and Bircher 2004) and spider bites (Makris et al. 2009) have also been cited as AGEP triggers.

6 Clinical Features

In AGEP the latency period between commencement of the culprit drug and onset of the reaction is characteristically short, usually being between 2 and 5 days. A sensation of skin burning and itching is typical at the outset and accompanies fever and malaise. Initially the dermatosis starts in the major flexures (neck, axillae, inframammary and inguinal folds) before spreading to involve the torso, limbs and face (Fig. 1). Patients can rapidly become erythrodermic (Fig. 2). However, there is a clinical sub-group of AGEP in which the erythema and pustulation is limited to one body site, most commonly the neck or a limb flexure. This form of the disorder is called "acute localised exanthematous pustulosis" (ALEP) (Corral de la Calle et al. 2005). ALEP is characterised by a similar clinical course of short latency, rapid recovery and lack of recurrence.

Lesional skin in AGEP and ALEP is deep red and oedematous. In AGEP facial oedema is common (as it is in DRESS). Pustulation is usually obvious with myriads of tiny superficial pustules overlying the erythema forming sheets of pinpoint-sized white dots. However, in dark skin the key sign may be less easy to appreciate—pustulation can sometimes be mistaken for fine scaling. Additional skin signs seen in some cases of AGEP include purpuric macules, atypical targets, blisters and cheilitis (Szatkowski and Schwartz 2015). Once the culprit drug has been discontinued the dermatosis resolves within a few days, passing through a phase of post-pustular desquamation (Fig. 3). In some cases there is extensive peeling of lesional stratum corneum during the

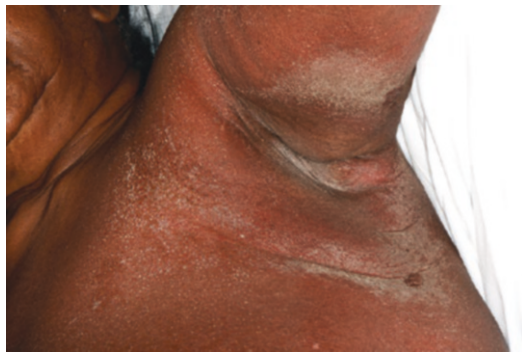

Fig. 1 Sheets of tiny white pustules in the axilla of this woman with AGEP induced by penicillin. AGEP typically commences in the major flexures (neck, axillae, inframammary and inguinal folds) and spreads to involve the torso

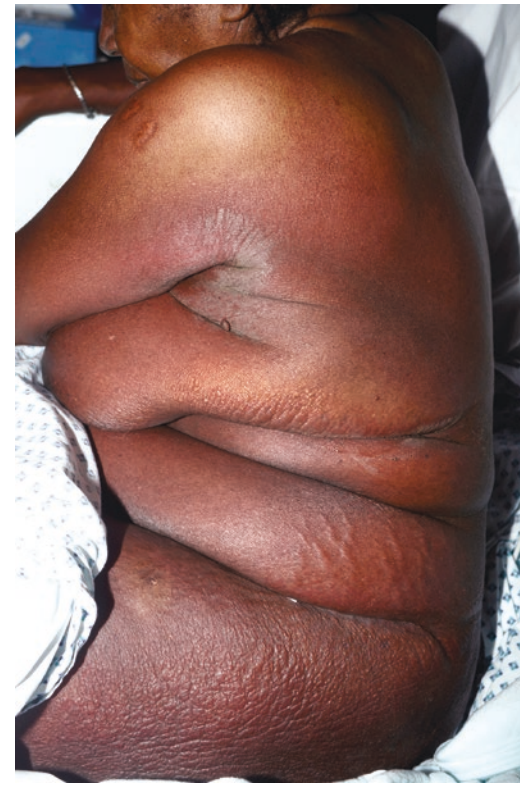

Fig. 2 Generalised erythema and oedema on the flank of this patient with AGEP (same patient as in Fig. 1). The patient developed acute kidney injury secondary to AGEP

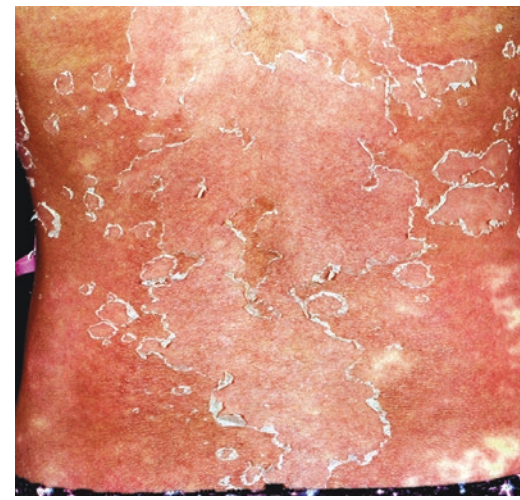

Fig. 3 Resolution of the pustuloderma of AGEP is characterised by post-pustular desquamation

acute illness, a feature which can be confused for epidermal necrolysis and a mistaken diagnosis of TEN (Natkunarajah and Ostlere 2012).

As well as fever (often greater than 38 °C) and malaise, patients complain of asthenia and, often, myalgia. Laboratory investigations reveal a leucocytosis, typically a neutrophilia and sometimes an eosinophilia. A raised ESR and CRP is usual. Hypocalcaemia during the acute phase is often observed (Mohaghegh et al. 2018). Skin swabs are sterile. Erythrodermic AGEP may be complicated by the systemic sequelae of skin failure, most typically acute kidney injury (AKI). A study of 58 patients with AGEP has suggested that involvement of internal organs may be present in up to 18% of patients with AGEP, including hepatic, renal and pulmonary dysfunction (Hotz et al. 2013).

AGEP caused by hydroxychloroquine (HCQ) produces an idiosyncratic version of the disorder. The cases reported are marked by an unusually long latency period, up to 3 weeks, and a prolonged disease course once HCQ has been stopped (Sidoroff et al. 2007; Mohaghegh et al. 2018). The morphology of HCQ-induced AGEP can also be curious with some patients producing an eruption reminiscent of the Lapiere form of pustular psoriasis in which annular pustulation is characteristic. In HCQ-induced AGEP, annular or serpiginous lesions spread outwards to leave a trail of fine scale (Fig. 4). The protracted and extensive skin inflammation in HCQ-induced AGEP requires, in some instances, treatment with a short course of a systemic immunosuppressant agent, such as prednisolone or ciclosporin (Castner et al. 2018).

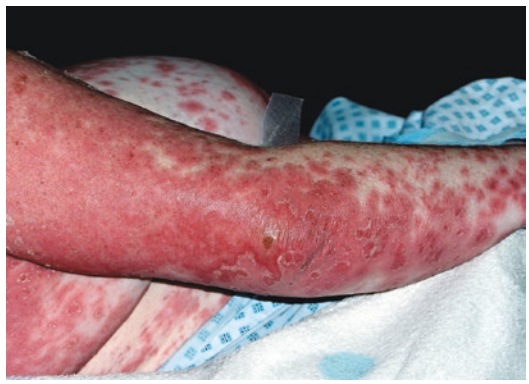

Fig. 4 Hydroxychloroquine-induced AGEP is characterised by lesions with annular pustulation, as seen on the outer aspect of the forearm. Confluence of lesions has produced polycyclic pustulation at the elbow

7 Differential Diagnosis

Generalised pustular psoriasis (the von Zumbusch variant) is the most important differential diagnosis in a patient presenting with AGEP. The two entities are virtually indistinguishable; however, there are clinical features which point towards AGEP and away from pustular psoriasis. A relevant drug history with a potential culprit being started a few days prior to the onset of the reaction is highly suggestive of AGEP, this diagnosis being further supported by lack of a personal history of psoriasis (Sidoroff et al. 2001). An eruption favouring the flexures is more in keeping with AGEP, while a sudden onset and short course is also more in keeping with a drug-induced pustuloderma. Histologically both entities are characterised by sub-corneal pustules; however, in AGEP there may be exocytosis of eosinophils and occasional apoptotic keratinocytes.

Subcorneal pustular dermatosis (Sneddon–Wilkinson disease) can be distinguished from AGEP by its chronic course and the presence of flaccid blisters, some of which contain a hypopyon. Pustules may be a prominent feature in drug reaction with eosinophilia and systemic symptoms (DRESS); however, pustulation is generally less prominent in DRESS than in AGEP (Walsh and Creamer 2011). DRESS is typically associated with significant involvement of an internal organ, usually the liver, whereas systemic upset is generally more modest in AGEP. IgA pemphigus can present with pustules and can be mistaken for AGEP: if there is doubt, a skin biopsy for direct immunofluorescence is needed, along with serum sent for indirect immunofluorescence. Pustulation is an unusual sign in cutaneous small vessel vasculitis and although it may mimic ALEP it is unlikely to be mistaken for the extensive pustuloderma of AGEP. In the right

clinical settings candidiasis, bullous impetigo, varicella and disseminated gonorrhoea are all infective processes which can enter the differential diagnosis of a drug-induced pustuloderma.

8 Investigations

Baseline haematological investigations should be taken at presentation looking for neutrophilia, eosinophilia, renal impairment, liver dysfunction and hypocalcaemia. Acute phase reactants, such as CRP and ESR, are typically elevated in AGEP. A skin biopsy should be taken early in the disease course to confirm sub-corneal pustulosis. If IgA pemphigus is considered a further biopsy for direct immunofluorescence is necessary.

In most cases, a careful drug history is adequate to elucidate the culprit drug. Patch testing to the culprit drug can be undertaken once the acute illness has resolved and the skin has returned to normal. Patch tests can confirm the culprit in approximately 60% of cases: positive results are most frequently seen with beta lactam antibiotics (Barbaud et al. 2013). In vitro drug allergy assays, such as lymphocyte transformation tests and cytokine release analysis, can also be used to help identify the culprit (Pichler and Tilch 2004).

9 Management

As with all drug eruptions, immediate removal of the precipitating agent is the primary and most important therapeutic manoeuvre. Prompt withdrawal of the offending drug usually results in resolution of the inflammatory process over the next few days. Clearance of the dermatosis is characterised by an exfoliation referred to as "post-pustular desquamation".

Intervention in AGEP generally involves glucocorticoid therapy: in cases of erythroderma and systemic involvement, oral corticosteroids may be needed to augment the effects of a potent topical corticosteroid ointment. Emollient therapy must be administered throughout the acute phase. In cases where acute skin failure complicates AGEP (acute kidney injury, fluid imbalance, thermoregulatory dysfunction) full supportive care is necessary, which includes intravenous fluid replacement, cardiovascular monitoring, ambient temperature control and sepsis surveillance.

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Sarah Walsh

1 Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is one of the severe cutaneous adverse reaction, or SCAR, syndromes. It is a drug-induced hypersensitivity phenomenon characterised by rash and the systemic upset of fever, lymphadenopathy, haematological abnormalities and dysfunction of one or more internal organs (Walsh and Creamer 2011; Husain et al. 2013a). Typically, it is the liver which is involved in DRESS, however renal, respiratory, gastrointestinal, cardiac, neurological and endocrine systems can all be affected. DRESS is distinguished from other forms of drug hypersensitivity disorder by a characteristic delay between the commencement of the culprit drug and the onset of the adverse reaction. This may range from 2 to 8 weeks; at the longer end of this spectrum the non-specialist may discount a medication as the cause of the presentation given that most adverse drug reactions occur more rapidly. This prolonged latency, so distinctive of DRESS, not uncommonly results in a delay in diagnosis (Lee et al. 2012).

DRESS was first recognised as a clinical entity in the 1940s when a pattern of idiosyncratic hypersensitivity to certain newly discovered anticonvulsants was described and subsequently named the "anticonvulsant hypersensitivity syndrome" (Merritt and Putnam 1939). It has been referred to by different terms in the literature since that time. Conditions considered synonymous include drug hypersensitivity syndrome (DHS), hypersensitivity syndrome (HSS), and drug-induced delayed multi-organ hypersensitivity syndrome (DIDMOHS). The acronym "DRESS"—drug reaction with eosinophilia and systemic symptoms—was proposed by Bocquet et al. in 1996 and is preferred by this author for its mnemonic quality (Bocquet et al. 1996).

2 Epidemiology

Collection of accurate incidence data for DRESS has been hampered by the frequency with which the condition is mistaken for infection by non-specialists. It is likely that reported rates are considerably lower than actual rates. Estimates range from 1 case per 1000 to 1 case per 10,000 population per year. The largest study of validated cases described a median age of onset of 48 years, and a slight female preponderance (1F,0.8M) (Kardaun et al. 2013).

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Table 1 HLA associations with DRESS

Drug	HLA type	Population
Abacavir	B*5701	Europe
Allopurinol	B*5801	Han Chinese
Carbamazepine	B*1502 B*3103	South-east Asia Europe, Japan
Phenytoin	B*5602	Thailand
Phenytoin/carbamazepine	A*2402	Europe (Spain)
Phenytoin	B*1513	Malaysia

While no specific ethnic preponderance has been described, certain HLA types are associated with a higher risk of developing DRESS in response to particular drugs (Fricke-Galindo et al. 2017). The paradigm for this HLA-associated susceptibility was the discovery that HIV positive patients carrying HLA-B*5701 had a high likelihood of developing a severe drug hypersensitivity syndrome to abacavir (Hetherington et al. 2001). This discovery led to the routine testing of patients for this HLA type prior to the prescribing of abacavir—an early example of personalised medicine.

A number of HLA types have subsequently been described as predisposing patients to DRESS-type reactions to certain drugs. These are summarised in Table 1 (Ardern-Jones and Mockenhaupt 2019).

3 Drug Causality

The concept of notoriety is particularly important when evaluating cases of DRESS. Notoriety describes the propensity of a particular drug to cause a particular reaction pattern. High notoriety drugs for DRESS are listed in Table 2.

Table 2 Drugs carrying a high notoriety for DRESS

Antibiotics	Amoxicillin Minocycline Piperacillin–tazobactam Trimethoprim–sulfamethoxazole (Septrin) Vancomycin Isoniazid Ethambutol
Antiepileptics	Carbamazepine Phenytoin Lamotrigine Sodium valproate
Anti-hypertensives	Amlodipine Captopril
Anti-viral agents	Abacavir Nevirapine
Non-steroidal anti-inflammatory drugs	Ibuprofen Naproxen Celecoxib
Sulpha drugs	Sulfasalazine Dapsone Sulphadiazine
Miscellaneous	Allopurinol Omeprazole

4 Pathophysiology

A number of pathogenetic models have been proposed to explain the multisystem nature of DRESS, however none is fully accepted. Although drug-specific T-cell hypersensitivity appears to be central, some investigators highlight the role of herpes virus reactivation in the pathogenesis of DRESS (Chen et al. 2015). It may be that both mechanisms are in play, acting synergistically, to produce the clinical phenotype. DRESS is more likely to occur in the context of hepatic or renal impairment, both of which may allow accumulation of reactive drug metabolites (Eshki et al. 2009).

An imbalance between the effector T lymphocytes (Teff) and the regulatory T lymphocytes (Treg) is thought to occur at the onset of DRESS. An expansion of the immunosuppressive Treg population during the acute phase of the disease may be permissive to the reactivation of herpes viruses, particularly human herpes virus-6 (HHV-6) (Chen et al. 2015). Following resolution of DRESS syndrome, the Treg population diminishes and returns to normal levels.

Reactivation of herpes viruses HHV-6, HHV-7, cytomegalovirus (CMV), and Epstein Barr virus (EBV) during an acute episode of DRESS has been demonstrated by numerous investigators. PCR studies have shown that viral reactivation occurs in a sequential fashion, with levels rising and falling independently of one another (Ishida et al. 2014). This phenomenon has been invoked to explain the fluctuation of clinical features in DRESS: symptoms and signs come and go and tend to resolve independently of each other. It seems likely that DRESS results from an interplay between drug-specific hypersensitivity, reactivated virus, and the host's immune response to the virus.

5 Clinical Features

DRESS is characterised by a prolonged latency (time lag between initiation of culprit and onset of symptoms), typically ranging from 2 to 8 weeks. Since the causative medication may have been started up to 8 weeks prior to onset a drug reaction is easily overlooked and the early, non-specific signs (fever, malaise, rash) mistaken for infection. Diagnostic delay is thus common in DRESS, particularly if patients present to a non-specialist. Diagnostic accuracy can be enhanced by using the scoring system developed by RegiSCAR, the international drug eruption registry, which quantifies clinical signs and laboratory parameters in DRESS (Table 3) (Kardaun et al. 2007). Scoring each suspected DRESS case helps the clinician attribute a degree of certainty to the diagnosis: "possible", "probable", "definite" (Table 4). However, the existence of a drug hypersensitivity reaction of DRESS-type which fails to breach the scoring threshold (often having been scored in the "possible" range) is recognised. This limited version of DRESS (which can also be referred to as "DRESS minor") lies within

Table 3 Diagnostic criteria for DRESS

Rash suggestive of a drug eruption	
Fever	>38°
Lymphadenopathy	At least 2 sites
Haematological abnormalities	Eosinophilia Lymphopaenia or lymphocytosis Thrombocytopaenia
Involvement of one internal organ	Hepatitis (transaminitis >2 times upper limit of normal) Interstitial nephritis Interstitial pneumonia Myocarditis

Table 4 RegiSCAR scoring system for DRESS (Kardaun et al. 2007)

Clinical feature		Score
Rash of >50% extent of body surface area		1 point
Rash suggestive of DRESS		1 point
Systemic involvement	Lymphadenopathy[a] Eosinophilia[b] Atypical lymphocytosis[b] Organ involvement[c]	Maximum 6 points
Relevant negative serological tests[d]		1 point

<2 points: no case; 2–3 points: possible case; 4–5 points: probable case; > 5 points: definite case

[a] ≥2 sites, ≥1 cm. A maximum 1 point gained from lymphadenopathy

[b] Eosinophilia: 10–19% of total white cell count = 1 point; ≥20% = 2 points (if total leucocytes $<4 \times 10^9$/L, an eosinophil count of $0.7–1.5 \times 10^9$/L will gain 1 point, an eosinophil count $\geq 1.5 \times 10^9$/L will score 2 points). Atypical lymphocytosis will gain 1 point

[c] Liver: transaminases >2 × upper limit of normal (ULN) on two successive dates *or* bilirubin × 2 ULN on 2 successive days *or* aspartate aminotransferase (AST), γ-glutamyltransferase (GGT) and alkaline phosphatase >2 × ULN on one occasion. Renal: creatinine 1.5 × patient's baseline. Cardiac: echocardiographic evidence of pericarditis. Maximum of 2 points gained from internal organ involvement

[d] ≥3 of the following performed and negative: hepatitis A, B and C; *Mycoplasma*/chlamydia; antinuclear antibody; blood culture (performed ≤ 3 days after hospitalisation). A maximum of 1 point gained for relevant negative serological tests

a severity spectrum between an uncomplicated drug-induced exanthem at one end and full-blown DRESS ("DRESS major") at the other end.

A rash is one of the key diagnostic criteria in DRESS. The morphology of the skin rash in DRESS is variable and so a classification system has been suggested with four different phenotypes (Walsh et al. 2013). The most common morphology, seen in 50–60% of cases, is an urticated papular exanthem (Fig. 1), in which erythematous urticated papules are widely distributed, in places coalescing in to plaques. The second commonest phenotype is an erythema multiforme-like reaction characterised by dusky purpuric and/or targetoid lesions, again in a widespread distribution (Fig. 2). The final two categories are the morbilliform erythema in which a less livid, measles-like eruption is seen (Fig. 3), and the erythrodermic phenotype where the patient has > 90% body surface area involvement presenting as an exfoliative erythroderma (Fig. 4). It has been suggested that the erythema multiforme-like pattern in the skin is associated with a more severe form of DRESS with pronounced liver dysfunction and a worse prognosis.

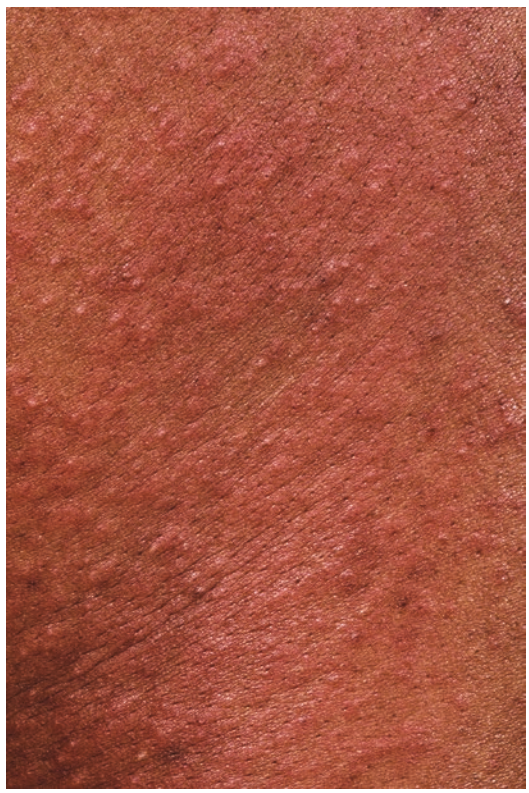

Fig. 1 An eruption of urticated papules is the most typical exanthem occurring in DRESS

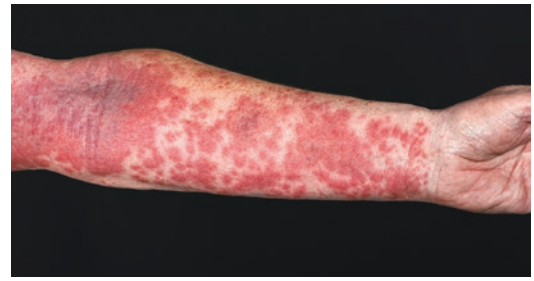

Fig. 2 Multiple, circular, urticated plaques with central duskiness suggestive of erythema multiforme. This type of DRESS eruption may be an indicator of severe liver involvement

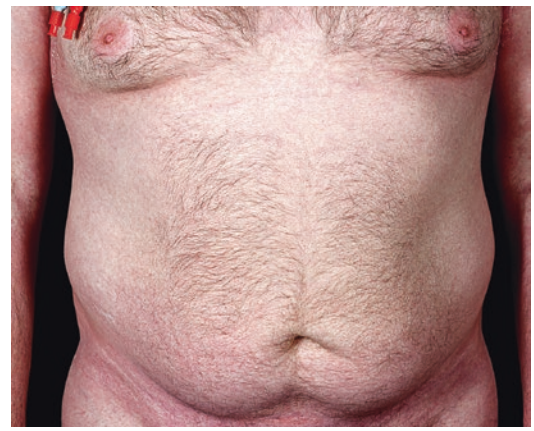

Fig. 3 A morbilliform (measles-like) erythema in DRESS is indistinguishable from a viral exanthem or a drug-induced exanthem

Secondary clinical features are also seen in the skin. Oedema of the head and neck is a frequent observation and its presence in conjunction with a rash should always prompt consideration of DRESS syndrome (Fig. 5). Although oral mucosal involvement is rare, cheilitis may be seen and should not be confused with the more severe mucosal involvement seen in Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Pustules can occur in DRESS, albeit infrequently,

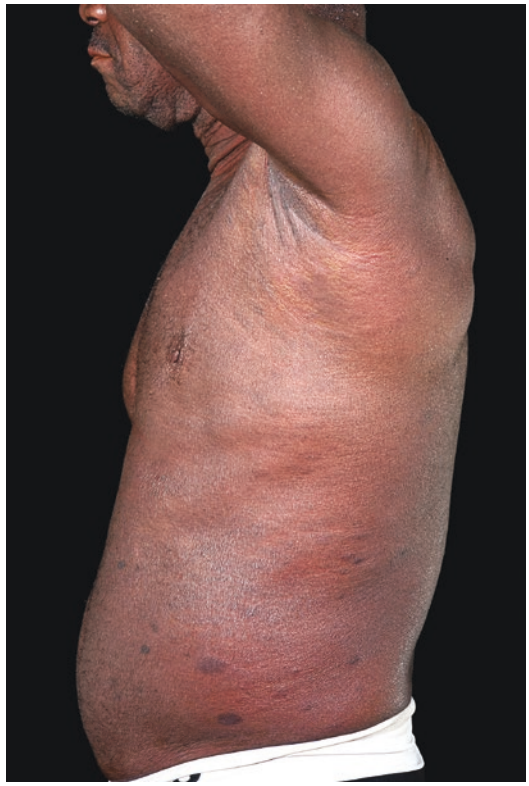

Fig. 4 Erythroderma is confluent erythema involving > 90% of the body surface area and can be the presenting dermatosis of DRESS

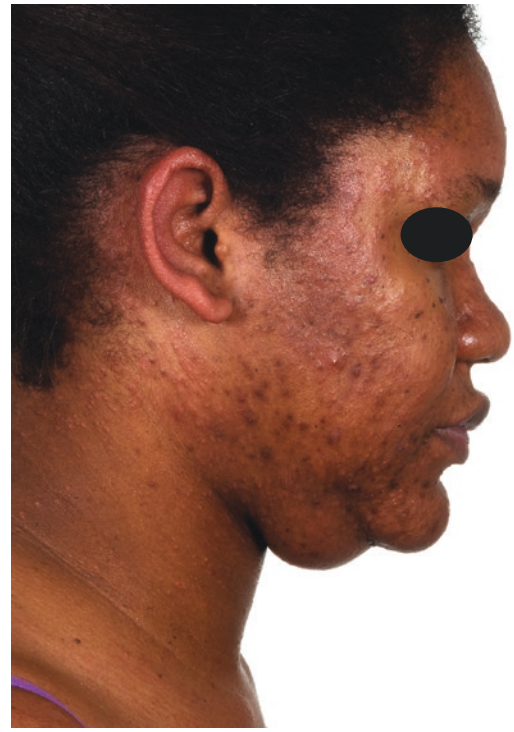

Fig. 5 Facial oedema with swollen ears is a characteristic cutaneous feature of DRESS

and may be either follicular or non-follicular (Husain et al. 2013a; Walsh et al. 2013).

Systemic involvement is indicated by an array of constitutional features, the commonest being a fever (in >95% of cases) which is often >38.5 °C. Haematological abnormalities are usual, with eosinophilia (>0.4 × 10^9/L) being the most frequent. The level of eosinophilia may be subtle or marked and can fluctuate over time in an asynchronous fashion with the other test abnormalities. Elevated levels of interleukin-5, a cytokine which stimulates eosinophil activation, have been demonstrated in DRESS (Mikami et al. 1999). A lymphocytosis may occur and atypical lymphocytes are often found on examination of a blood film, which should form part of the work-up. However, lymphopenia, thrombocytopenia and pancytopenia can also be seen. Haemophagocytic syndrome has been described in the context of DRESS. This rare, life-threatening complication can develop 10–14 days after the reaction's onset and is characterised by jaundice, fever, hepatosplenomegaly, consumption of platelets, and a fall in white blood cells (Mizukawa et al. 2019). Lymph node basins should be examined thoroughly in a patient with suspected DRESS, as lymphadenopathy is present in 70% of cases. A lymph node diameter of >2 cm has been suggested to qualify as significantly enlarged. Solid organ involvement forms an important part of the diagnostic criteria for DRESS.

The liver is the most common internal organ affected (70–95% of cases), however involvement of the gastrointestinal and respiratory tracts, myocardium, renal, endocrine and nervous systems have all been described. Both hepatocellular and cholestatic pictures of liver dysfunction may be seen, but the former predominates (Kano et al. 2010). Extent of involvement can range from mild, asymptomatic disturbance of liver function to fulminant liver

failure accompanied by jaundice and coagulopathy, sometimes requiring liver transplantation (Eshki et al. 2009). Severe liver involvement is the primary cause of mortality from DRESS. Attempts have been made to predict which cases of DRESS will suffer severe liver involvement: an erythema multiforme (EM) pattern clinically with an EM-type dermatopathology on biopsy appears to be associated with a worse hepatic prognosis (Walsh et al. 2013). Although any drug can provoke liver dysfunction in the context of DRESS the usual culprits for drug-induced liver injury are phenytoin, minocycline and dapsone (Ushigome et al. 2013).

Renal involvement is detectable by a rise in urea and creatinine and the presence of haematuria and proteinuria on urinalysis. Although usually mild and self-limiting, in a small number of cases an interstitial nephritis can supervene leading to temporary, or less frequently long-term, renal insufficiency (Marchese et al. 2017; Augusto et al. 2009). Use of renal replacement therapy in the acute phase has been described but fulminant renal failure, analogous to that seen in the liver, is exceptionally rare. Allopurinol is a recognised trigger for renal involvement in DRESS. Kidney involvement in DRESS is also more likely to occur in those with pre-existing renal dysfunction.

Involvement of the respiratory tract is less common, however pleuritis, pleural effusion and interstitial pneumonitis have been described. Presence of cough, dyspnoea, a raised respiratory rate, or reduced oxygen saturations should prompt investigation with a chest X-ray to exclude this complication.

Cardiac involvement in DRESS is a rare but potentially fatal complication (Thongsri et al. 2017). Involvement of the myocardium or pericardium is suggested by chest pain and shortness of breath; however, DRESS myocarditis may be asymptomatic. An electrocardiogram (ECG), echocardiogram, and serum troponin should be undertaken if cardiac involvement is suspected. A more severe form of myocarditis, termed "acute necrotising eosinophilic myocarditis" (ANEM) is described, which carries a mortality of > 50%. In this form of fulminant myocarditis the echocardiogram demonstrates a greatly reduced ejection fraction and pronounced systolic dysfunction.

Diarrhoea is a symptom often reported by patients with DRESS in the acute phase. It may represent gastrointestinal involvement and if severe can cause dehydration. An eosinophilic infiltrate on endoscopic biopsy has been reported, although an absence of specific endoscopic features is not unusual. Faecal calprotectin is not consistently elevated (Kaffenberger et al. 2018; Do-Pham et al. 2011). A case of dysphagia in DRESS was found to have an eosinophilic oesophagitis on endoscopy.

While confirmed neurological involvement in DRESS is rare, headache as a presenting symptom is common. Meningitis and encephalitis have been described along with isolated phenomena such as cranial nerve palsies and seizures. A DRESS patient with symptoms indicative of limbic encephalitis underwent brain magnetic resonance imaging (MRI) which demonstrated enhancement of the amygdala, cingulate gyrus and temporal lobes. Examination of the same patient's cerebrospinal fluid demonstrated the presence of HHV-6.

Endocrine sequelae of DRESS, mainly thyroid, are more commonly seen in the convalescent than the acute phase of disease. Both thyroiditis and sick euthyroid syndrome have been described, leading to long-term thyroid dysfunction. Graves's disease may develop between 2 and 4 months following the onset of DRESS. Hashimoto's thyroiditis can also develop with elevated antithyroid peroxidase and antithyroglobulin antibodies. Acute pancreatitis has been described in the context of DRESS, leading to long-term pancreatic insufficiency (Kano et al. 2015).

6 Histopathology

The histopathological features of DRESS vary widely but typical changes include spongiosis, a superficial perivascular lymphocytic infiltrate and interstitial dermal eosinophils. Interface inflammation is also common with a lichenoid

infiltrate, basal cell vacuolar degeneration and necrotic keratinocytes, changes which resemble erythema multiforme (EM) (Ortonne et al. 2015). A correlation between the presence of histopathological changes of EM and more severe liver dysfunction has been demonstrated. Such features may be predictive of a higher mortality (Schäfer et al. 2001).

7 Long-Term Sequelae of DRESS

Many of the long-term sequelae of DRESS are autoimmune in origin, such as thyroid dysfunction and alopecia areata. It is advisable to check convalescent thyroid function at 6 weeks and 12 weeks after the acute presentation (Cookson et al. 2013). New-onset diabetes, again autoimmune in origin, has also been described in the post-acute phase while the need for corticosteroid treatment, sometimes over many weeks, may unmask latent type 2 diabetes. Psychological side effects from DRESS are under-investigated but can commonly complicate the disorder. In one small study, symptoms of post-traumatic stress disorder (PTSD) were found in a majority of DRESS patients (Lew et al. 2015).

8 Differential Diagnosis

The constellation of clinical symptoms occurring in the presentation of DRESS may also be encountered in an infective disorder. This is the commonest differential diagnosis: a study demonstrated that 50% of DRESS cases are initially misdiagnosed as a bacterial or viral infection (Lee et al. 2012). The other SCAR syndromes, Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and acute generalised exanthematous pustulosis (AGEP) should also be borne in mind as differential diagnoses. Purpura, atypical target lesions, and cheilitis are common to both SJS/TEN and DRESS, while pustules are seen DRESS as well as AGEP, although in the former they tend to be less numerous and do not show a flexural predilection.

"Overlap" syndromes have been reported which describe a SCAR presentation with phenotypic features of DRESS and another disorder. A study drawn from the RegiSCAR database described 3 such cases, two of SJS/TEN + DRESS and one of AGEP + DRESS (Bouvresse et al. 2012). If the morphology of DRESS is an exfoliative dermatitis then the clinical picture may be similar to that of erythrodermic eczema or psoriasis. An erythrodermic variant of cutaneous T-cell lymphoma (erythrodermic mycosis fungoides, Sezary syndrome) also enters the differential diagnosis. Angioimmunoblastic T-cell lymphoma may mimic the presentation of DRESS: patients with this rare form of lymphoma develop an extensive pruritic dermatosis, fever and lymphadenopathy.

9 Prognosis and Management

Withdrawal of the culprit drug and institution of appropriate treatment usually results in a full recovery. A small minority of DRESS cases (<10%) have a fatal outcome, usually due to fulminant liver failure or, more rarely, cardiac involvement. Attempts have been made to determine outcome indicators in DRESS: the presence of atypical targets, and skin biopsy histology that is EM-like has been associated with more severe liver involvement (Walsh et al. 2013).

The cornerstone of clinical management of DRESS is corticosteroid: both oral and topical steroids are used. The latter is associated with a lower side effect profile and infection risk, but topical corticosteroid alone is unlikely to be adequate for the management of significant systemic disease. Cases with marked internal organ involvement or extensive rash require oral or intravenous corticosteroid. Oral prednisolone at 0.5–1.0 mg/kg/day is usually effective in controlling skin involvement, eosinophilia, and mild or moderate liver disturbance. The course of oral corticosteroid can usually be tapered to zero over 3–6 weeks. In cases of severe liver involvement, 3 consecutive days of high-dose intravenous methylprednisolone at a dose of 3–5 mg/kg/day

should be considered (Natkunarajah et al. 2011; Funck-Brentano et al. 2015).

In a small number of cases corticosteroid is inadequate to control the disease, or the symptoms relapse as the corticosteroid is weaned. In this situation alternative immunosuppressive agents may be considered; ciclosporin is the steroid-sparing agent of choice. Ciclosporin may also be useful in cases of DRESS when the rash or liver inflammation enters a chronic phase (Zuliani et al. 2005).

Alternative treatments for DRESS have been tried. Exchange treatments such as plasmapheresis and Extracorporeal Membrane Oxygenation (ECMO) have been employed in isolated cases. The latter has been employed in a case of DRESS-induced myocarditis, resulting in poor organ perfusion which failed to respond to inotropic support (Lo et al. 2013).

Alternative immunosuppressive therapies such as cyclophosphamide and rituximab may have a role (Laban et al. 2010). Anti-viral treatments such as valganciclovir have been used to tackle viral reactivation, but published results have not been consistently positive. N-Acetylcysteine has been administered as concomitant therapy to patients with severe liver involvement (Moling et al. 2012).

10 Conclusion

Awareness of DRESS as a severe drug-induced hypersensitivity reaction is increasing. In particular, recognition of the disorder is becoming widespread amongst physicians who prescribe high-notoriety drugs for DRESS, such as rheumatologists and neurologists. Any patient receiving a drug commonly associated with DRESS should be counselled to stop the medication immediately following the development of a rash accompanied by systemic features. Reporting the occurrence of a case of DRESS to a national pharmacovigilance network is important to ensure that reaction patterns—especially to new and emerging medicines—are detected early, and drugs with the potential to trigger DRESS are identified. DRESS is managed by withdrawal of the culprit drug and, often, with administration of systemic corticosteroid. Prompt initiation of both therapeutic manoeuvres should halt disease progression and reduce the risk for serious systemic disease.

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Fixed Drug Eruptions and Generalized Bullous Fixed Drug Eruptions

Yung-Tsu Cho and Chia-Yu Chu

1 Introduction

Fixed drug eruption (FDE) is a unique drug eruption with characteristic features. It was first reported in 1889 by Bourns, who described a patient having recurrent skin lesions occurring at the same limited sites following the administration of antipyrine (Bourns 1889). Later on, in 1894, Brocq used the term "eruption-erythemato-pigmentee fixe" to describe this kind of eruption (Brocq 1894).

Fixed drug eruption is characterized by well-demarcated, oval or round, dusky red or hyperpigmented patches involving the skin and mucosal sites. The lips, genitals, and hands are the most commonly affected areas (Kauppinen and Stubb 1985). Sometimes, blisters may develop within these patches. These lesions recur stereotypically at the same sites when the patients are reexposed to the causative drugs (Ozkaya 2008).

Generalized bullous fixed drug eruption (GBFDE) is a rare and severe form of FDE and is classified as one of the severe cutaneous adverse reactions (SCARs) (Paulmann and Mockenhaupt 2015). Patients with GBFDE usually present with widespread lesions resembling typical FDE lesions with blister formation. In some cases, differentiation of GBFDE from Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can be challenging (Paulmann and Mockenhaupt 2015). In this chapter, the epidemiology, clinical features, pathological findings, and management of FDE and GBFDE will be elaborated.

2 Epidemiology

The incidence and prevalence rates of FDE is unclear and difficult to determine (Lipowicz et al. 2013). Nonetheless, it is generally accepted that FDE is not uncommon as studies including hundreds of patients have been published (Lee 2000). A challenge in evaluating the incidence and causality of the disease is that the initial lesion may go unnoticed, and individuals may only be made aware following repeated recurrences (Lee 2000).

On the other hand, although the incidence and prevalence rates of GBFDE is largely unknown (Paulmann and Mockenhaupt 2015), it is thought to be a rare disease (Cho et al. 2014). In our previous report, only 23 patients with GBFDE were seen at two referral medical centers in Taiwan over a period of 10 years (Cho et al. 2014). In compari-

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son, there were more than 100 patients with SJS or TEN managed in the same centers during the corresponding period. These findings indicate that GBFDE might be even rarer than SJS/TEN.

3 Pathophysiology

3.1 Histopathology

Typically, the lesions of FDE show a hallmark of interface dermatitis (Lee et al. 2012). Superficial perivascular infiltration can be observed and, in some cases, deep perivascular infiltration may be present (Fig. 1a). In lesions with blisters, the whole epidermis may detach from the underlying dermis (Fig. 1a). In the margin of blisters or in those lesions without blisters, basal vacuolization with scattered apoptotic keratinocytes can be found (Fig. 1b). The perivascular infiltrate usually includes various quantities of eosinophils and neutrophils (Fig. 1c). Dermal melanophages are also a characteristic finding in the lesions of FDE (Fig. 1d). The histopathologic features of GBFDE are generally the same as those of FDE.

Due to the clinical similarity between GBFDE and SJS/TEN, histopathologic evaluation may help to differentiate the diseases. A higher number of patients with GBFDE exhibit deep perivascular infiltration, which is absent in patients with SJS/TEN (Cho et al. 2014; Lee et al. 2012). In addition, the infiltrates seen in GBFDE comprises of more eosinophils, neutrophils, and dermal melanophages as compared to SJS/TEN (Cho et al. 2014; Lee et al. 2012). Meanwhile, it should be noted that in SJS/TEN, the apoptotic keratinocytes are more abundant and more likely

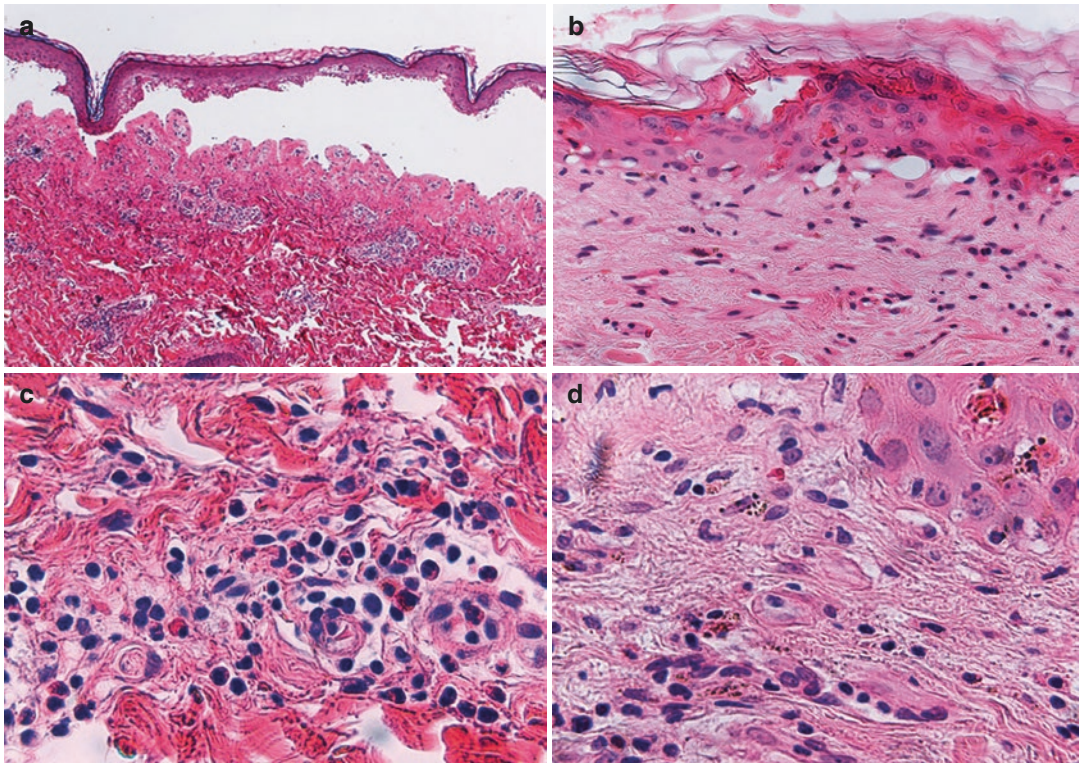

Fig. 1 Histopathology of FDE and GBFDE. (**a**) Epidermal detachment from the underlying dermis can be found in FDE lesions with blisters. Superficial perivascular infiltration is evident in most cases of FDE and GBFDE. (**b**) Interface dermatitis showing basal vacuolarization and discrete apoptotic keratinocytes is the hallmark feature of FDE. (**c**) Perivascular infiltrates include mononuclear cells, neutrophils, and eosinophils. (**d**) Dermal melanophagocytosis is observed in almost all cases of FDE

to form aggregations reminiscent of a red fire flag, that is,"fire-flag sign" which is a distinguishing feature from GBFDE (Lee et al. 2012).

3.2 Pathomechanism

Like SJS/TEN, FDE is a delayed-type hypersensitivity reaction and is mediated by cytotoxic T cells (Type IVc) (Phillips et al. 2019). Shiohara et al. have shown that intraepidermal $CD8^+$ T cells in FDE lesions play an important role in the formation of localized tissue damage (Mizukawa et al. 2002; Shiohara et al. 2002; Shiohara and Mizukawa 2007). These $CD8^+$ T cells can be identified in resting FDE lesions long after clinical remission and are characterized by expressions of T cell receptor (TCR)-αβ, CD3, CD8, CD45RA, and CD11β, but not CD27 and CD56. The constellation of expressed T cell markers resemble those of an effector-memory phenotype (Sallusto et al. 1999; Masopust et al. 2001). These effector-memory phenotype $CD8^+$ T cells preferentially locate at the sites of infection, such as mucosal areas, and at the sites of previous trauma (Shiohara 2009). These locations also correspond to the predilection sites of FDE lesions (that is, the lips, genital areas, and hands). These intraepidermal effector-memory phenotype $CD8^+$ T cells may have immunity-related functions, that are typically protective in nature, for example, anti-herpes simplex virus (HSV) activity (Shiohara 2009). Upon the administration of culprit drugs, these cells are cross-activated, killing surrounding keratinocytes and releasing large amounts of cytokines, such as interferon-γ. The subsequent recruitment of $CD4^+$ cells, $CD8^+$ cells, eosinophils, and neutrophils are responsible for the enhancement of tissue damage and the exacerbation of skin lesions (Shiohara 2009). Once the lesion is fully developed, the influx of $CD4^+$ $FoxP3^+$ regulatory T cells increases, which eventually results in clinical resolution (Teraki et al. 1994).

In GBFDE, both the lesional infiltrates of $CD3^+$ cells and $CD8^+$ cells as well as the expression of cytotoxic granules, Fas/Fas ligand, and perforin/granzyme are similar to SJS/TEN (Cho et al. 2014). Nevertheless, dermal $CD4^+$ cells are more abundant in GBFDE, especially those of $FoxP3^+$ phenotype, whereas epidermal $CD56^+$ cells are more abundant in SJS/TEN (Cho et al. 2014). Furthermore, the number of epidermal granulysin-expressing cells is in SJS/TEN, and these epidermal granulysin-expressing cells collocate with $CD56^+$ cells in the epidermis. The higher numbers of dermal $CD4^+$ $FoxP3^+$ regulatory T cells and the lower number of epidermal granulysin-expressing cells may account for the limited clinical course of GBFDE as compared to SJS/TEN.

4 Clinical Features

4.1 Clinical Presentation

FDE can present either singly (Fig. 2a) or as several discrete lesions (Fig. 2b). Around 20–30% of FDE patients have been reported to have a single lesion (Fadhel et al. 2019; Heng et al. 2015). The lesions of FDE typically present as well-defined, dusky red or hyperpigmented macules or patches. Blisters or erosions may develop within the patches. The lesions of FDE usually develop rapidly after the administration of the culprit drugs, appearing anytime from several hours to several days thereafter (Kauppinen and Stubb 1985). Old lesions will recur at the same sites and new lesions may also develop after repeated exposures to the culprit drugs (Ozkaya 2008). There is no gender preference in the occurrence of FDE (Shiohara 2009). Although FDE may develop on any part of the skin and mucosal membranes, it has been reported that male patients are more likely to have lesions on the genitalia (Heng et al. 2015; Brahimi et al. 2010; Ozkaya-Bayazit 2003). As for drug-specific associations, bullous lesions were reported to be significantly associated with acetaminophen use in one study (Fadhel

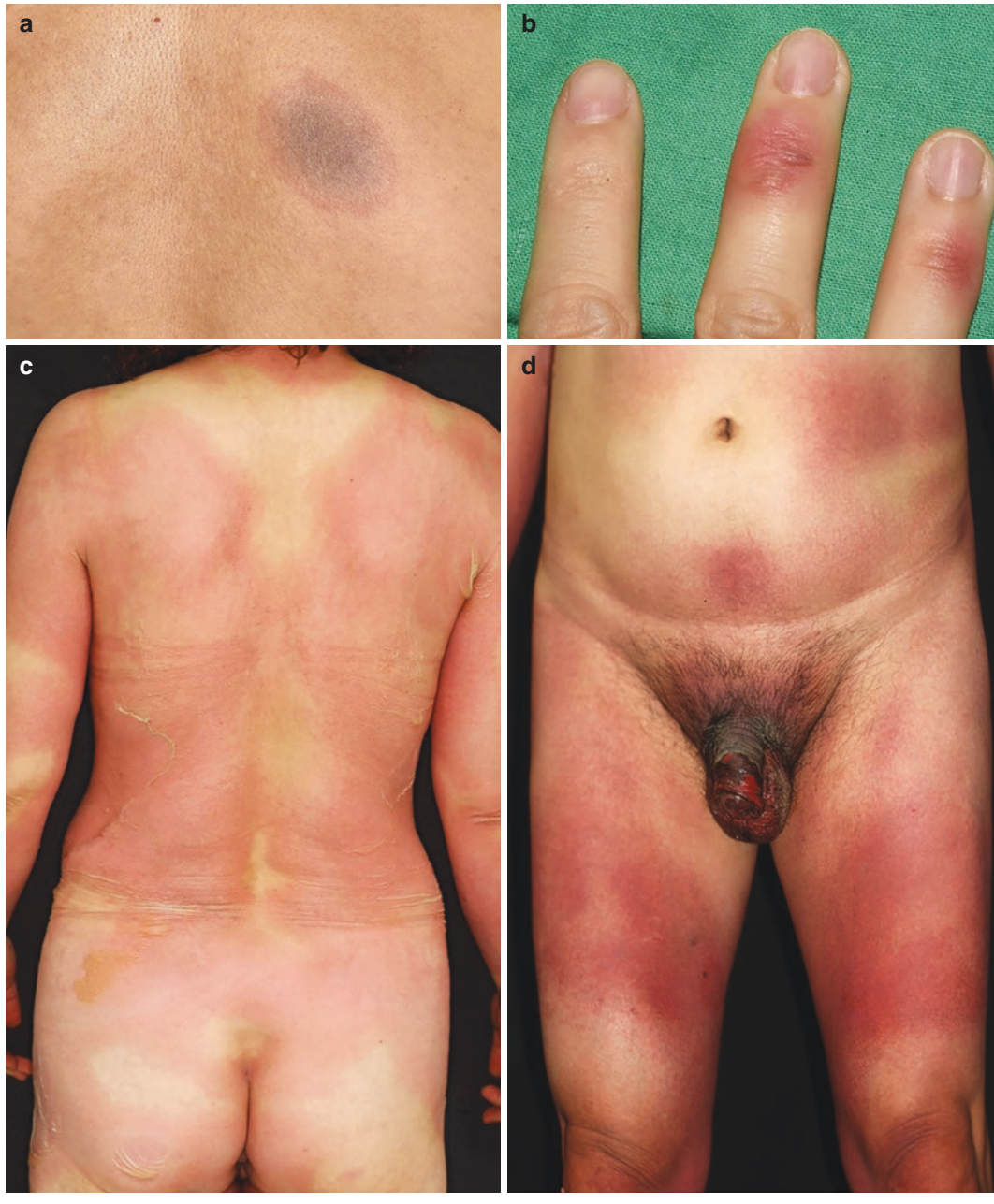

Fig. 2 Clinical features of FDE and GBFDE. Patients with FDE can present with (**a**) a solitary lesion consisting of a well-defined, oval-shaped, red-to-purple patch and can also present with (**b**) several discrete well-demarcated dusky-red patches. Patients with GBFDE usually present with multiple variously sized, well-defined erythematous or hyperpigmented patches with blisters or erosions on the whole body (**c**, **d**)

et al. 2019). In another study, the drug naproxen was demonstrated to be highly and significantly associated with FDE on the lips (Ozkaya-Bayazit 2003). However, it should be noted that such associations might differ in different countries or different clinical settings.

Patients with GBFDE tend to be older than those with FDE and SJS/TEN (Paulmann and Mockenhaupt 2015; Cho et al. 2014). Such patients usually present with large areas of well-demarcated red-to-purple or hyperpigmented patches with various extents of blisters or erosions

on the whole body (Fig. 2c, d). Sometimes, it is difficult to differentiate GBFDE from SJS/TEN based solely on cutaneous presentations. Mucosal lesions can also be found in 40–50% of GBFDE patients (Cho et al. 2014). As in FDE, the time interval between the intake of drugs and the development of lesions in GBFDE is short, with a mean value of 3 days (Cho et al. 2014). There is a lack of consensus regarding the definition of GBFDE. Our group has proposed that GBFDE might be defined as a condition characterized by widespread blisters and erosions with typical FDE lesions involving at least 10% of the body surface area and distributed on at least 3 of 6 different anatomical sites, including the head and neck, front of the trunk, back, upper extremities, lower extremities, and genitalia (Cho et al. 2014). On the other hand, Lipowicz et al. have proposed that, in order to make a diagnosis of GBFDE, 2 or 3 out of the following criteria should be fulfilled (Lipowicz et al. 2013). These criteria include (1) similar reaction in the past; (2) fewer than two mucous membranes involved, with the absence of spots or target lesions; (3) large and well-demarcated blisters and erosions; and (4) lesions and erosions on at least two different sites of the body. Although these two definitions are not exactly the same, such criteria may be useful in distinguishing GBFDE from localized forms of FDE and SJS/TEN.

4.2 Differential Diagnosis

The differential diagnoses of FDE are many and is dependent on the presentation of FDE (Paulmann and Mockenhaupt 2015; Shiohara 2009). For a solitary FDE lesion or a limited number of FDE lesions, differential diagnoses include contact dermatitis, insect bite reaction, trauma, lichen planus pigmentosus, urticaria pigmentosa, autoimmune progesterone dermatitis, and erythema multiforme. For GBFDE, the differential diagnoses include SJS, TEN, burns, graft-versus-host disease, bullous pemphigoid, and staphylococcal scalded skin syndrome.

Among these differential diagnoses, distinguishing GBFDE from SJS/TEN can be challenging (Paulmann and Mockenhaupt 2015). The lesions of FDE or GBFDE usually do not present with target lesions or spots, which are more frequently seen in SJS/TEN and erythema multiforme (Paulmann and Mockenhaupt 2015; Lipowicz et al. 2013). In addition to clinical presentations, a histopathological examination may help to differentiate FDE from other differential diagnoses.

4.3 Culprit Drugs

The causative medications of FDE and GBFDE vary among countries due to different prescription patterns and causality is also likely to evolve with time (Sehgal and Sirvastava 2006; Savin 2001). Although many medications have been implicated (Table 1), nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and antibiotics are the most commonly reported culprit drugs. NSAIDs have been reported as the leading causative drugs in reports from Taiwan (Cho et al. 2014; Lee et al. 2012), Singapore (Heng et al. 2015), Korea (Jung et al. 2014), and Tunisia (Fadhel et al. 2019). Meanwhile, acetaminophen was identified as the most common culprit drug in one report from

Table 1 List of reported triggers of FDE (Kauppinen and Stubb 1985; Ozkaya 2008; Lipowicz et al. 2013; Cho et al. 2014; Lee et al. 2012; Heng et al. 2015; Brahimi et al. 2010; Savin 2001)

Nonsteroidal anti-inflammatory drugs[a]
Paracetamol[a]
Co-trimoxazole[a]
Tetracyclines[a]
Penicillins
Metronidazole
Rifampicin
Erythromycin
Carbocisteine
Pseudoephedrine
Phenolphthalein
Barbiturates
Carbamazepine
Sulfasalazine
Calcium-channel blockers
Angiotensin-converting enzyme inhibitors
Iodinated contrast
Omeprazole
Complementary medicines

[a] Most commonly reported drugs

France (Brahimi et al. 2010), whereas the antibiotic co-trimoxazole (a combination of sulfamethoxazole and trimethoprim) was the top-ranked offender for FDE in reports from India (Sharma et al. 1996), Bangladesh (Rahman 2014), Pakistan (Mahboob and Haroon 1998), Iran (Kavoussi et al. 2015), and Turkey (Ozkaya-Bayazit 2003). There is no difference in culprit drugs between FDE and GBFDE.

4.4 Prognosis

The prognosis of FDE is generally good. Once the causative drug is suspended, the lesions are usually self-limiting and will resolve gradually. Nevertheless, with each repeated exposure, the number of lesions may increase (Paulmann and Mockenhaupt 2015). As shown in Fig. 3, a patient with GBFDE presented with widespread red-to-

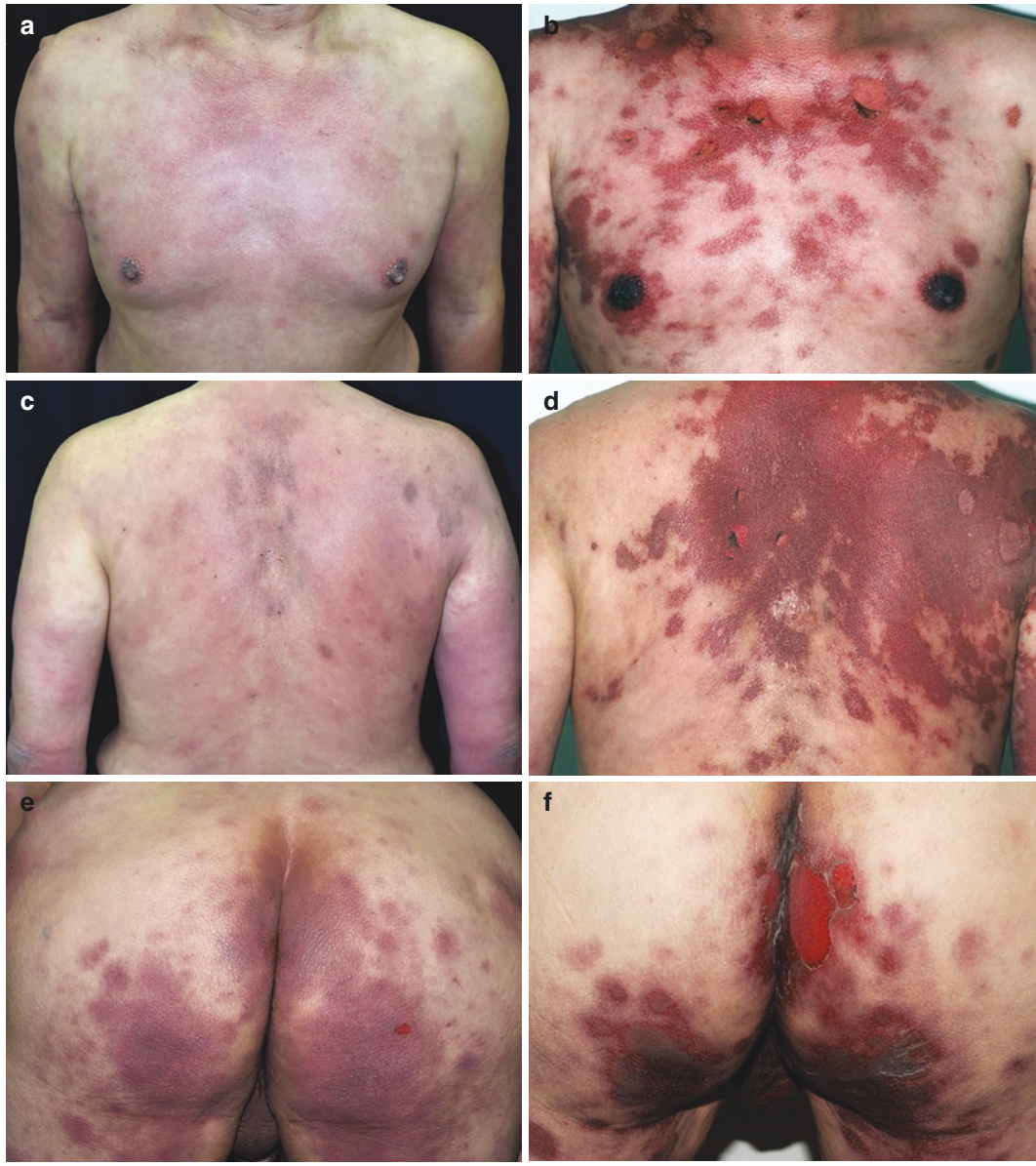

Fig. 3 Progression of GBFDE after repeated exposure to the culprit drug. One patient with GBFDE presented with widespread red-to-purple patches involving the trunk and buttocks (**a**, **c**, **e**). These lesions recurred and progressed to become blisters and erosions after reexposure to the culprit drug (**b**, **d**, **f**)

purple patches with erosions (Fig. 3a, c, e). The area of detachment markedly enlarged the next time the FDE recurred (Fig. 3b, d, f). The prognosis of GBFDE is thought to be better than that of SJS/TEN by most physicians. However, Lipowics et al. found in a case-control study of 58 GBFDE patients matched by age and extent of skin detachment to 170 patients with SJS/TEN that the mortality rate was slightly but not significantly lower for patients with GBFDE (odds ratio 0.6, 95% confidence interval 0.30–1.4) (Lipowicz et al. 2013). Their results put into question the general belief that the prognosis of GBFDE is better than SJS/TEN. It is possible that this was due to the fact that the extent of skin lesions is a severity marker (Pfutze et al. 2007). Another possible explanation is that patients with GBFDE are older than those with SJS/TEN, which may result in greater disease and treatment-related morbidity and mortality.

5 Investigations

Confirming the culprit drug is one of the cornerstones of care, as correct identification can prevent recurrences. Oral challenge or provocation is by far the gold standard to confirm the causative medication (Shiohara 2009). While there is no standardized method for performing the oral challenge in patients with FDE, a sub-therapeutic dose of the suspect drug, such as a dose one-tenth the size of the therapeutic dose (Shiohara 2009), or even a full dose of the drug (Phillips et al. 2019), is usually used and is relatively safe in most of the cases. Besides the dosage, there is also a lack of standardized protocol with respect to the timing of the oral provocation. However, performing the challenge 1–2 months after the remission of the eruptions is suggested by most experts (Phillips et al. 2019; Shiohara 2009).

In addition to systemic provocation tests, patch testing is also a reliable method for determining the possible culprits in patients with FDE, especially in those patients with multiple suspected drugs. A positive patch test result can be obtained in around 40% of the patients (Phillips et al. 2019; Andrade et al. 2011). In brief, suspected drugs are mixed in petrolatum or vehicles with a concentration of 20% (Brockow et al. 2002) or 30% (Barbaud et al. 2001). Drug patch tests should be performed at the sites of previous FDE lesions rather than on the normal skin on the back. The best timing for performing a patch test has yet to be determined, however, a delay of at least 4–6 weeks after the resolution of the lesions is suggested by most experts in order to avoid false positive reactions, false-negative reactions, and the aggravation of the disease (Phillips et al. 2019). Several factors may contribute to a false negative drug patch test result. Firstly, the optimal concentration and penetration ability of the patch-tested drug is unclear. Secondly, patients may react to metabolites of the causative drugs rather than to the drugs per se. As such the use of a drug patch test without its metabolites may yield a negative result (Andrade et al. 2011).

Although lymphocyte transformation test (LTT) is used to determine drug causality in many different drug eruptions, including SJS/TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), maculopapular eruptions (MPE), and acute generalized exanthematous pustulosis (AGEP) (Pichler and Tilch 2004), its role in FDE is not yet established (Phillips et al. 2019; Shiohara 2009).

6 Management

There is no consensus regarding the management of patients with FDE and GBFDE. However, as with other drug eruptions, the removal of the culprit drugs is the most important step (Paulmann and Mockenhaupt 2015). In most cases of FDE, the cutaneous lesions rapidly improve after withdrawal of the causative drug. Although there is still insufficient evidence, some patients may benefit from topical or systemic corticosteroids. One study from a tertiary hospital in Korea reported that around 40% of the patients received no medical treatment, around 43% applied topical corticosteroids, and around 11% received systemic corticosteroids (Jung et al. 2014). All of the patients in the study recovered well from the disease.

Patients with GBFDE usually improve after the discontinuation of the culprits, just like FDE (Paulmann and Mockenhaupt 2015; Lipowicz et al. 2013; Cho et al. 2014). However, for patients with extensive skin detachment, comprehensive supportive care in a reference center is suggested. As with SJS/TEN, patients with GBFDE should be monitored for disease progression, wound infections, electrolyte imbalance, and possible deterioration of internal organ function. Mucosal lesions should also be managed since involvement of the lips and genitalia is common. Pain control, the avoidance of trauma and irritation of the mucosal surfaces are vital in the care of these patients. In severe mucosal lesions, parenteral nutrient supplementation and urine catheterization might be needed. Systemic corticosteroids may be beneficial in the management of patients with GBFDE. According to our own unpublished data regarding 36 patients with GBFDE, all of them received systemic corticosteroid treatment, and there was only 1 mortality during the acute stage of the disease. Nevertheless, the evidence remains anecdotal and further investigations are needed to evaluate the role of systemic corticosteroids in the management of patients with GBFDE.

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Lichenoid Drug Eruptions

Yee Kiat Heng and Yen Loo Lim

1 Introduction

Lichenoid disorders are inflammatory dermatoses characterised clinically by flat-topped, pruritic, papular lesions and histologically by a band-like infiltrate of lymphocytes in the papillary dermis. Lichen planus (LP) is the most typical and well-recognised of the lichenoid dermatoses and presents with firm, shiny, polygonal, 1–3 mm papules with a red to violaceous colour and overlying fine white lines known as Wickham's striae. Grey-brown pigmented macules may result upon resolution of primary lesions. On mucosal surfaces, Wickham's striae are also often seen (Tziotzios et al. 2018; Shiohara and Mizukawa 2018).

LP-like or lichenoid drug eruptions (LDE) may be difficult to distinguish clinically and histologically from classic LP (Tziotzios et al. 2018; Shiohara and Mizukawa 2018; Ardern-Jones and Lee 2016). Identification of a drug cause may be difficult as the latency period between drug administration and onset of rash is variable and may be prolonged, up to several months or even years (Halevy and Shai 1993). Furthermore, resolution of the rash after discontinuation of the causative drug may take weeks to months (Halevy and Shai 1993), adding to the uncertainty of the diagnosis. Causality may be confirmed by re-exposure to the drug, but may not be acceptable to the patient.

2 Epidemiology

LDE is generally uncommon though specific reports on incidence rates are lacking. In fact, most epidemiological studies on cutaneous adverse drug reactions (CADRs) do not mention LDE. One study reported that LDE accounted for only 4% of all CADRs in a tertiary hospital in India (Qayoom et al. 2015). Approximately 10% of all LP cases are drug induced (Ardern-Jones and Lee 2016).

Age of presentation does not differ much between LDE and LP, reportedly ranging from 44 to 66 years for LDE (Halevy and Shai 1993; Lage et al. 2012; Fessa et al. 2012; West et al. 1990) and 47 to 50 years for LP (Lage et al. 2012). Paediatric LDE is rare (Payette et al. 2015) but may result from childhood vaccinations. There is reportedly no gender bias (Tziotzios et al. 2018).

3 Description of Features

Clinical and histological features which distinguish LDE from LP are summarised in Table 1. LDE tends to present with LP-like lesions (Fig. 1) which are more generalised, polymorphous, lack Wickham's striae and have a more eczematous or psoriasiform appearance (Fig. 2).

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Table 1 Clinical and histological differences between lichen planus and lichenoid drug eruption

–	Lichenoid drug eruption	Classical idiopathic lichen planus
Clinical		
Mean age of onset	65 years	50 years
Latency period	Months–years	Not relevant
Distribution	More generalised, including trunk Symmetric	Predilection for wrists, flexor areas of forearms, lower legs, genitalia
Morphology	Similar to LP but with more 'eczematous' or 'psoriasiform' features	Shiny, flat-topped, polygonal violaceous papules
Wickham striae	Less common	Common
Photodistribution	Common	Uncommon
Mucous membranes	Usually spared	Common
Nail involvement	Rare	Common
Histological		
–	Focal parakeratosis and focal interruption of the granular layer	Parakeratosis uncommon
–	Numerous clusters of apoptotic keratinocytes	Few clusters of apoptotic keratinocytes
–	Cytoid bodies in cornified, granular and upper spinous layers	Cytoid bodies in lower spinous layers
–	Varying degree of eosinophilic and/or plasma cell infiltrates	Eosinophils and plasma cells uncommon
–	Deep perivascular infiltrate may be present	Dense band-like infiltrate of lymphocytes in papillary dermis

Adapted from references (Tziotzios et al. 2018; Shiohara and Mizukawa 2018; Lage et al. 2012)

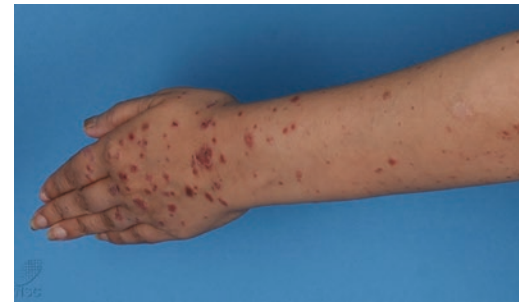

Fig. 1 Lichen planus-like papules and plaques on the dorsal hand and forearm

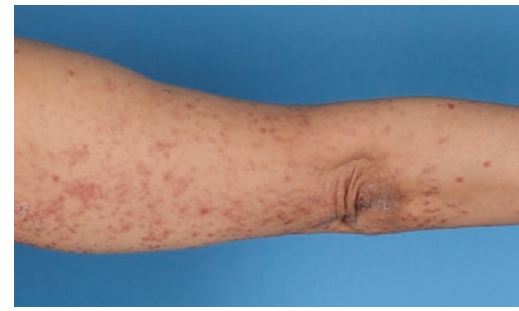

Fig. 2 Lichenoid drug eruption with a more polymorphous appearance with mixture of LP-like and eczematous papules and plaques

Photodistribution is more common in LDE and may be a useful diagnostic clue (Shiohara and Mizukawa 2018). Mucosal involvement (Fig. 3) is less common in LDE than in LP (Shiohara and Mizukawa 2018).

Differential diagnoses to consider include LP-like contact dermatitis [e.g. to methacrylic acid esters (Kawamura et al. 1996) and dimethyl fumarates (Guillet et al. 2009)], lichenoid keratosis (Pitney et al. 2016), paraneoplastic pemphigus (Tey and Tang 2009; Lim et al. 2018) drug-induced subacute cutaneous lupus (Crowson and Magro 1999), dermatomyositis (Al-Najjar et al. 1985), graft-versus-host disease (Hymes et al. 2006) and secondary syphilis (Tang et al. 2004).

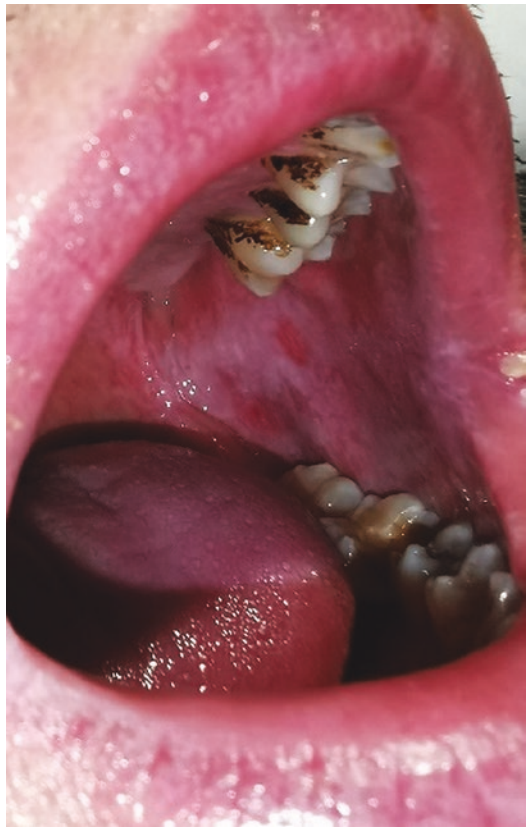

Fig. 3 White plaques with lace-like pattern and erosions on the buccal mucosa

4 Drug Causality

Arsenic was the first drug reported to cause LDE in 1929 (Almeyda and Levantine 1971). Since then, LDE has been reported to a long and growing list of drugs (Table 2). Many commonly used drugs, for example, beta-blockers, thiazide diuretics, angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs), are now recognised to cause LDE. Drugs which have been recognised to be associated with LDE at certain anatomical locations, for example, sun-exposed areas or mucosa, are listed in Table 3.

Older drugs such as gold (Penneys et al. 1974, Glenert 1984, Russell et al. 1997), penicillamine (Seehafer et al. 1981) and anti-malarials [e.g. quinine (Dawson 1986), quinacrine (Bauer 1981), chloroquine (Savage 1958)] were well-recognised to cause LDE but have become less commonly used.

Relatively new drugs which affect the immune system have now been reported to cause LDE. These include vaccines, for example, hepatitis B (Saywell et al. 1997; Rebora et al. 1999; Ferrando et al. 1998; Calista and Morri 2004; Schupp and Vente 1999; Limas and Limas 2002; Al-Khenaizan 2001) and human papillomavirus vaccines (Laschinger et al. 2015), interferon (IFN) therapy (Bush et al. 2017) and anti-HIV therapy [e.g. efavirenz (Baumrin et al. 2018), tenofovir (Gupta et al. 2015)]. In recent years, biological therapies [e.g. tumour necrosis factor [TNF] inhibitors (Inoue et al. 2017; El Habr et al. 2014; De Simone et al. 2008; Darrigade et al. 2016; Andrade et al. 2015; Utsu et al. 2012; Gonzalez et al. 2018)], targeted oncological drugs [e.g. imatinib (Sendagorta et al. 2009; Gómez Fernández et al. 2010; Sudha et al. 2011; Ena et al. 2004; Dalmau et al. 2006; Pascual et al. 2006; Lim and Muir 2002; Kawakami et al. 2009; Kuraishi et al. 2010)] and immune checkpoint inhibitors (Hwang et al. 2016; Cogen et al. 2018; Min Lee et al. 2018; Coleman et al. 2019; Curry et al. 2017; Shi et al. 2016; Obara et al. 2018; Biolo et al. 2019; Siegel et al. 2018; Coscarart et al. 2019) have featured as new and emerging causes of LDE.

4.1 Biologics

While TNF-inhibitors have well-known clinical efficacy in treating inflammatory conditions, it is now recognised that they may cause paradoxical inflammatory skin reactions (e.g. psoriasis). Numerous cases of LDE due to anti-TNFs have been reported (Inoue et al. 2017; El Habr et al. 2014; De Simone et al. 2008; Darrigade et al. 2016; Andrade et al. 2015; Utsu et al. 2012; Gonzalez et al. 2018). Interestingly, LDE has been reported to develop in a patient after switching from infliximab to its biosimilar, suggesting possibly different immunogenicity of the biosimilar drug (Gonzalez et al. 2018). Change in therapeutic class of biologics may still re-elicit the

Table 2 Drugs implicated in lichenoid drug eruptions

Drugs implicated in lichenoid drug eruptions		
Well-recognised causes	Less well-recognised causes	Newer drugs
Anti-malarials [e.g. quinine (Dawson 1986), quinacrine (Bauer 1981), chloroquine (Savage 1958)]	ACE inhibitors [e.g. captopril (West et al. 1990; Firth and Reade 1989), enalapril (Kanwar et al. 1993)]	Immune checkpoint inhibitors (Hwang et al. 2016; Cogen et al. 2018; Min Lee et al. 2018; Coleman et al. 2019; Curry et al. 2017; Shi et al. 2016; Obara et al. 2018; Biolo et al. 2019; Siegel et al. 2018; Coscarart et al. 2019) (e.g. pembrolizumab, nivolumab, ipilimumab)
Gold[a] (Penneys et al. 1974; Glenert 1984; Russell et al. 1997)	Diuretics [e.g. frusemide (West et al. 1990), spironolactone (Downham 1978)]	Targeted oncologic drugs [e.g. imatinib (Sendagorta et al. 2009; Gómez Fernández et al. 2010; Sudha et al. 2011; Ena et al. 2004; Dalmau et al. 2006; Pascual et al. 2006; Lim and Muir 2002; Kawakami et al. 2009; Kuraishi et al. 2010)]
Penicillamine (Seehafer et al. 1981)	Calcium channel blockers [e.g. diltiazem (Kubo et al. 2010), nifedipine (Leibovici et al. 1988)]	Anti-TNFα (Inoue et al. 2017) [e.g. adalimumab (Inoue et al. 2017; El Habr et al. 2014; De Simone et al. 2008; Darrigade et al. 2016; Andrade et al. 2015), etanercept (Utsu et al. 2012), infliximab (Darrigade et al. 2016; Andrade et al. 2015), infliximab biosimilar (Gonzalez et al. 2018)]
Beta-blockers [e.g. labetalol (Fessa et al. 2012; Gange and Jones 1978), propranolol (Massa et al. 1991)]	HMG-CoA reductase inhibitors [e.g. pravastatin (Pua et al. 2006), lovastatin (Sebök et al. 2004), fluvastatin (Sebök et al. 2004)]	Anti- IL17 drugs [e.g. secukinumab (Maglie et al. 2018; Thompson et al. 2016; Komori et al. 2017)]
Thiazide diuretics (Harber et al. 1959)	Anti-diabetic medication [e.g. chlorpropamide (Barnett and Barnett 1984), tolazamide (Barnett and Barnett 1984), glimepiride (Hammami et al. 2015)]	Anti-CD20 drugs (Kuten-Shorrer et al. 2014; Bakkour and Coulson 2012; O'Connor et al. 2017) (e.g. rituximab)
NSAIDs [e.g. naproxen (Güneş et al. 2006), acetylsalicylic acid (Ruiz Villaverde et al. 2003), ibuprofen (Hamburger and Potts 1983), indomethacin (Hamburger and Potts 1983)]	Vaccines [e.g. influenza (Sato et al. 2010), hepatitis B (Saywell et al. 1997; Rebora et al. 1999; Ferrando et al. 1998; Calista and Morri 2004; Schupp and Vente 1999; Limas and Limas 2002; Al-Khenaizan 2001), human papillomavirus (Laschinger et al. 2015)]	
	Immunomodulatory drugs [e.g. anakinra (Vila et al. 2005), immunoglobulin (Yockey and Ahmed 1997), interferon-α (Bush et al. 2017), leflunomide (May et al. 2017), mesalazine (Alstead et al. 1991), sulfasalazine (Ghosh et al. 2013)]	

Table 2 (continued)

Drugs implicated in lichenoid drug eruptions		
Well-recognised causes	Less well-recognised causes	Newer drugs
Miscellaneous drugs Allopurinol (Chau et al. 1984), arsenic (Almeyda and Levantine 1971), bismuth (Roxburgh and Klaber 1940), capecitabine (Shah et al. 2017), carbamazepine (Atkin et al. 1990), colchicine (An et al. 2017; Akin Belli et al. 2016), hydroxyurea (Eming et al. 2001), lithium (Srebrnik et al. 1991; Hogan et al. 1985), methyldopa (Holt and Navaratnam 1974; Fortuna et al. 2017), omeprazole (Bong et al. 2000), para-aminosalicylic acid (Shatin et al. 1953), propylthiouracil (Saito et al. 2007), radiocontrast media (Grunwald et al. 1985), ranitidine (Horiuchi and Katagiri 1996), solifenacin (Shalders and Gach 2008), valsartan (Gencoglan et al. 2009), antibiotics [e.g. cycloserine (Shim et al. 1995), dactinomycin (Ridola et al. 2006), ethambutol (Frentz et al. 1981), isoniazid (Chen et al. 2018; Lee and Jung 1998), streptomycin (Renkin 1958), terbinafine (Zheng et al. 2017)], thiopronin (Hsiao et al. 1986) and anti-viral drugs [e.g. efavirenz (Baumrin et al. 2018), simeprevir (Simpson et al. 2015), sofosbuvir (Simpson et al. 2015), tenofovir (Gupta et al. 2015; Woolley et al. 2004)]		

Adapted from references (Tziotzios et al. 2018; Shiohara and Mizukawa 2018; Ardern-Jones and Lee 2016; Halevy and Shai 1993; Qayoom et al. 2015)

[a] Including reports of LDE to gold-containing alcoholic beverages

Table 3 Drugs implicated in photodistributed and oral mucosal lichenoid drug eruption

Photodistributed lichenoid drug eruption	Oral mucosal lichenoid drug eruption
Anti-malarials [e.g. quinine (Dawson 1986), quinacrine (Bauer 1981)]	ACE inhibitors (Firth and Reade 1989) (e.g. enalapril, captopril)
ACE inhibitors (Kanwar et al. 1993)	Allopurinol (Chau et al. 1984)
Capecitabine (Shah et al. 2017)	Anti-malarials [e.g. quinacrine (Bauer 1981), chloroquine (Savage 1958)]
Diltiazem (Kubo et al. 2010)	Anti-PD-1 drugs (Coleman et al. 2019; Obara et al. 2018)
Frusemide (West et al. 1990)	Anti-TNFα [e.g. infliximab (Asarch et al. 2009; Andrade et al. 2015)]
Hydrochlorothiazide (Harber et al. 1959)	Beta-blockers (Seehafer et al. 1981)
Isoniazid (Lee and Jung 1998)	Glimepiride (Hammami et al. 2015)
Pravastatin (Pua et al. 2006)	Gold (Glenert 1984)
Simeprevir, sofosbuvir (Simpson et al. 2015)	Imatinib (Gómez Fernández et al. 2010; Ena et al. 2004; Pascual et al. 2006; Lim and Muir 2002)
Solifenacin (Shalders and Gach 2008)	Interferon-α (Bush et al. 2017)
–	Lithium (Hogan et al. 1985)
–	Methyldopa (Fortuna et al. 2017)
–	NSAIDs (Hamburger and Potts 1983)
–	Para-amino salicylic acid (Shatin et al. 1953)
–	Secukinumab (Thompson et al. 2016)

reaction, as reported in a psoriasis patient who developed LDE to an anti-TNF biosimilar with resolution after cessation but recurrence after introduction of an anti-IL17A drug (Maglie et al. 2018). LDE affecting oral mucosa due to anti-IL17A drugs have been reported (Thompson et al. 2016; Komori et al. 2017).

There are reports of LDE to anti-CD20 drugs which occurred in patients with follicular lymphoma (Kuten-Shorrer et al. 2014; Bakkour and Coulson 2012) and one of possible photodistributed LDE to rituximab in a patient with systemic lupus erythematosus (O'Connor et al. 2017).

4.2 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors such as anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (e.g. ipilimumab), anti-programmed cell death 1 (PD-1) (e.g. nivolumab or pembrolizumab) and anti-programmed death ligand 1 (PD-L1) inhibitors (e.g. atezolizumab) are new therapies which activate the immune system against cancer cells and have demonstrated remarkable clinical efficacy. However, cutaneous toxicity is a common side effect and may be seen in up to 49% of pembrolizumab-treated (Hwang et al. 2016) and 60% of ipilimumab-treated (Min Lee et al. 2018) patients.

17–25% of all cutaneous toxicities in patients treated with anti-PD-1 drugs are lichenoid reactions (Hwang et al. 2016; Coleman et al. 2019). Interestingly anti-CTLA-4 drugs, and even anti-PD-L-1 drugs do not seem to cause lichenoid reactions as frequently as anti-PD1 drugs despite similar mechanism of action (Min Lee et al. 2018; Curry et al. 2017). Peripheral blood eosinophilia is only seen in 20% of anti-PD-1-induced lichenoid reaction. The mean time to onset is 88 days (range 1–266 days) and rash may even occur after discontinuation of the treatment (Hwang et al. 2016).

5 Variations in Clinical Features of LDE

Erosive LDE afflicting the oral or genital mucosa is not uncommon. Drugs implicated include beta-blockers (Fessa et al. 2012), anti-PD-1 drugs (Shi et al. 2016; Obara et al. 2018), lithium (Srebrnik et al. 1991; Hogan et al. 1985), NSAIDs (Hamburger and Potts 1983) and sulphonylureas [e.g. glimepiride (Hammami et al. 2015)].

Cutaneous blisters are rarely associated with LDE and have been reported in cases of LDE to naproxen (Güneş et al. 2006), labetolol (Gange and Jones 1978), radiocontrast media (Grunwald et al. 1985) and tiopronin (Hsiao et al. 1986). Anti-PD-1 drugs may occasionally cause blisters (Biolo et al. 2019) but clinicians should also consider differential diagnoses of bullous pemphigoid or Stevens–Johnson Syndrome in such cases (Siegel et al. 2018).

Hypertrophic (Coscarart et al. 2019) and linear (Utsu et al. 2012; Gencoglan et al. 2009) forms of LDE have been rarely reported.

Nail changes are rarely reported in LDE but are similar to those in LP and include longitudinal ridging, onychoschizia and dorsal pterygium (May et al. 2017; Zheng et al. 2017). Subungual hyperkeratosis has been reported in LDE to imatinib (Dalmau et al. 2006). Interestingly, one patient developed LDE to propylthiouracil with only nail changes (red nodules on the nail bed) without lesions on skin or mucous membrane (Saito et al. 2007).

Scarring alopecia has been reported in a patient with lichen planopilaris with concurrent oral erosive LDE induced by pembrolizumab (Cogen et al. 2018).

Other rare associations with LDE include decreased sweat production with atrophic sweat glands in quinacrine-induced LDE (Sulzberger et al. 1947) and palmoplantar hyperkeratosis in imatinib-induced LDE (Kuraishi et al. 2010).

6 Histological Findings

The most characteristic histological feature of both LDE and LP is lichenoid interface dermatitis which is a band-like lymphocyte infiltration of the papillary dermis associated with apoptosis of the basal keratinocytes.

The “classical” histopathologic findings that are indicative of LDE are eosinophils and plasma cells in the cellular infiltrate, focal parakeratosis, and an infiltrate around deep vessels (Figs. 4 and 5) (Van den Haute et al. 1989). Lage et al. reported that focal parakeratosis, focal interruption of the granular layer and cytoid bodies (representing apoptotic keratinocytes) in the cornified and granular layers were present in more than 50% of LDE and never in idiopathic LP (Lage et al. 2012).

Histological findings in photodistributed LDE may be indistinguishable from those of idiopathic LP and that a biopsy specimen which shows the

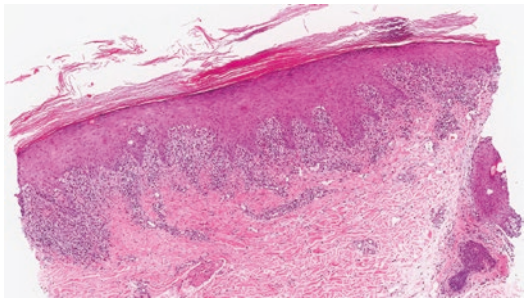

Fig. 4 Histology of lichenoid drug eruption. The epidermis is acanthotic with wedge-shaped hypergranulosis, "saw-toothed" rete ridges and focal parakeratosis. Civatte bodies are present within the epidermis. There is a dense band-like lymphocytic infiltrate in the upper dermis associated with vacuolar alteration of the basal keratinocytes (haematoxylin and eosin, low magnification)

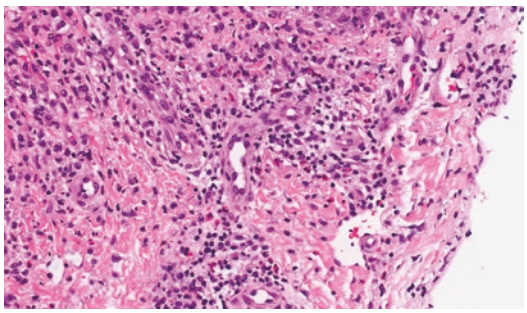

Fig. 5 Inflammatory infiltrate of lichen drug eruption consisting of lymphocytes and numerous eosinophils (haematoxylin and eosin, high magnification)

classic features of LP should not be used as evidence against a drug eruption, especially if the lesions are photodistributed (West et al. 1990).

Histologic features of anti-PD-1-induced lichenoid reaction have been reported to be polymorphous, that is, one lesion may have features of LDE while other lesions may demonstrate other histological patterns (e.g. spongiotic dermatitis) (Tetzlaff et al. 2017).

Immunohistochemistry demonstrates that the inflammatory infiltrate is predominantly of CD8 cytotoxic cells. The number of granzyme B-expressing cells is reported to be positively correlated with degree of keratinocyte apoptosis (Lage et al. 2012).

Giant cell lichenoid dermatitis is an uncommon histologic variant first reported in 1986 by Gonzalez et al. (1986). It is characterised by granulomatous inflammation in the dermis in addition to the usual features of LP. Groups of histiocytes, with or without giant cell formation, are seen in the mid to reticular dermis or admixed with the lichenoid inflammatory cells. This particular histological pattern is not associated with specific drugs. A wide range of drugs have been implicated, for example, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, statins, proton pump inhibitors, non-steroidal anti-inflammatory drugs and sulphonamide antibiotics (Magro and Crowson 2000; Braswell et al. 2019).

There are no significant differences in direct immunofluorescence (DIF) staining between LDE and idiopathic LP (Halevy and Shai 1993). DIF reveals "shaggy" band-like deposits of fibrinogen along the dermoepidermal junction, well as colloid bodies staining with any of the autoantibodies immunoglobulin M (IgM), IgG, IgA and C3 with or without fibrin. DIF remains useful to distinguish LDE from auto-immune conditions.

7 Pathogenesis

Mechanisms leading to the development of LDE have not been well elucidated. It is likely that the condition occurs in a predisposed individual when the causative drug triggers off immune dysregulation in a conducive micro-environment.

While genetic factors such as human leucocyte antigen (HLA) haplotype have been strongly associated with other CADR, these have not been well-investigated in LDE. Studies performed in oral LDE have also failed to show a pathogenic role for polymorphisms in cytochrome P450 enzymes which may influence drug metabolism (Kragelund et al. 2009, 2010).

It has been proposed that peripheral blood lymphocytes recruited during an immune or inflammatory reaction (e.g. virus infections) could remain in the skin as resident memory T cells. These memory T cells could be reactivated, cross-reacting with different agents, resulting in localised damage of the epithelium (Giuliani et al. 2008).

Ultraviolet radiation (UVR) may play a contributory role as seen by the photo-distribution commonly seen in LDE and involvement of drugs such as anti-malarials, thiazides and statins, which are well-recognised photosensitisers. UVR may induce free radical production by drugs, resulting in cellular damage leading to an inflammatory cascade involving various cytokines and inflammatory cells (Khandpur et al. 2017).

The role of type 1 interferon in pathogenesis of LDE has been suggested by the occurrence of LDE in patients treated with interferon-α and TNF-α inhibitors. It has been proposed that TNF-α inhibition allows for upregulation of IFN-α and in turn, IFN-α induces activation of resident T cells and plasmacytoid dendritic cells, mediates recruitment of cytotoxic T cells and upregulates the expression of cytotoxic agents (e.g. perforin) by cytotoxic T cells and NK cells (Asarch et al. 2009).

LDEs induced by beta-blockers may offer another clue to pathogenesis. Beta-adrenoreceptors are found in keratinocytes, Langerhans and dendritic cells and have a role in controlling the Th1 response to pathogens. Beta-adrenergic dysfunction has been reported in keratinocytes in psoriasis and vitiligo lesions (Sivamani et al. 2007). Likewise, beta-blockers may theoretically result in sustained inflammatory reaction.

The PD-1/PD-L1 pathway plays a vital role in inhibitory control of T lymphocytes. PD-1 inhibitors may cause lichenoid reactions by unleashing the immune response to an antigen in the skin or alternatively, by unmasking an immune response to another drug which was previously tolerated (Shi et al. 2016).

7.1 Treatment

Identification of causative agent may be difficult in patients taking multiple chronic medications. Dietary exposure must not be neglected as quinine in tonic water (Russell et al. 1997) and gold in certain alcoholic beverages (Russell et al. 1997) have been reported to cause LDE. Stopping the causative drug typically results in resolution of the lesions over a period of weeks to months. Patch tests are of low sensitivity in LDE (Osawa et al. 1990) but may be considered if there is uncertainty about which drug to stop. There have been reports of LDE which improved or resolved completely despite continuation of the causative drug (Asarch et al. 2009).

Treatment with topical steroids is usually beneficial with occasional cases requiring systemic steroids. Acitretin has been reported to be useful in treating LDE due to imatinib, allowing continuation of treatment in a cancer patient (Asarch et al. 2009).

For lichenoid reactions induced by anti-PD-1 and anti-PD-L-1 drugs, the condition is usually not severe and with appropriate management, only a small percentage (< 10%) require interruption of treatment (Coleman et al. 2019; Shi et al. 2016). Continuation of treatment is generally favoured as the occurrence of immune-related adverse events and dermatologic reactions appears to be associated with more favourable oncologic outcomes (Min Lee et al. 2018; Sanlorenzo et al. 2015; Chan et al. 2019). Nevertheless, clinicians should remain aware of potential complications of oral mucosal LDE. Just as classic oral lichen planus has potential for malignant transformation, squamous cell carcinoma has been reported in a case of mucosal LDE to pembrolizumab (Owosho et al. 2016).

In conclusion, diagnosis and management of lichenoid drug eruptions is a challenging task for the clinician. Keeping up to date with developments in new drugs remains crucial.

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Drug-Induced Connective Tissue Disorders

Stephen J. Mounsey and Emma Benton

1 Drug-Induced Lupus Erythematosus

Since the identification of drug-induced lupus erythematosus (LE) by hydralazine in 1952 more than 100 agents from over ten pharmacological classes have been implicated in the induction of lupus-like syndromes (Morrow et al. 1953; Rubin 2015). Although similar to idiopathic LE, there are differences between the two entities with drug-induced LE typically causing less frequent and less severe involvement of internal organs. Development of clinical symptoms is unpredictable with a larger proportion of patients developing antibodies than those developing symptoms. The pathogenetic mechanisms behind drug-induced LE remain poorly understood, however it is likely that the disease process is mediated by a complex interplay between genetic and environmental factors (Chang and Gershwin 2011; Vaglio et al. 2018).

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1.1 Epidemiology

The frequency of drug-induced LE varies greatly between patient groups, across geographical regions and with local prescription practices. Incidence estimation is often confounded by the under-recognition of drug-induced LE with an estimated 10% of all systemic lupus erythematosus (SLE) diagnoses being made incorrectly.

Unlike idiopathic LE, the typical patient with drug-induced LE is Caucasian and over the age of 50. There is no predominance in younger females, as is seen with idiopathic LE. Increased prescribing of potential culprit drugs to the >50 patient group, without intersex or ethnic variance, explains the major demographic differences between idiopathic and drug-induced LE. An exception to this finding occurs with procainamide and hydralazine which are less likely to cause drug-induced LE in females and individuals of Afro-Caribbean descent (Rubin 2015). Another demographic peculiarity is minocycline which is typically prescribed in younger patients for acne vulgaris (Chang and Gershwin 2011; Borchers et al. 2007; Vasoo 2006).

1.2 Drug Causality in Drug-Induced Lupus Erythematosus

Drug-induced LE has been associated with multiple causative agents (Tables 1 and 2). Although

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Table 1 Drugs identified as causative of drug-induced lupus erythematosus. Adapted with permission from Vaglio et al. (2018)

High risk (>5% of patients)	Procainamide (Borchers et al. 2007)
	Hydralazine (Alarcon-Segovia et al. 1967)
Moderate risk (1–5%)	Quinidine (Alloway and Salata 1995)
Low risk (0.1–1%)	Isoniazid
	Minocycline
	Carbamazepine
	Sulfasalazine
	Methyldopa, captopril, acebutolol, chlorpromazine, propylthiouracil, D-penicillamine
Very low risk (0.1%)	Atorvastatin, Fluvastatin, lovastatin, pravastatin, simvastatin
	Infliximab
	Etanercept
	Adalimumab
	Golimumab
	Certolizumab
	Phenytoin, mephenytoin
Risk not identified	Disopyramide, propafenone, atenolol, clonidine, enalapril, labetalol, minoxidil, pindolol, prazosin, chlorprothixene, lithium carbonate, phenelzine, nitrofurantoin, trimethadione, phenylbutazone, chlorthalidone, aminoglutethimide, levodopa, timolol eye drops, interferon-α, interleukin-2

there are often similarities of chemical structure, such as the presence of an aromatic amine (e.g. procainamide) or aromatic hydrazine (e.g. hydralazine), no specific and unifying chemical structure has been identified in all culprit agents.

The risk of developing drug-induced LE varies greatly among culprit agents. It can develop in up to 20% of all patients exposed to a culprit drug, as occurs with procainamide, or as infrequently as 0.05%, which is the risk for minocycline-induced LE (Borchers et al. 2007). Culprit drugs are thus classified according to their risk: high (>5%), moderate (1–5%), low (<1%) and undetermined (Table 1). However, the exact risk of an agent is difficult to calculate due to the lack of prospective studies and incomplete or inadequate reporting of symptoms.

Table 2 Drugs identified as causative of drug-induced subacute cutaneous lupus erythematosus. Adapted from Vaglio et al. (2018), Lowe et al. (2011)

Calcium channel antagonists	Diltiazem, verapamil, nifedipine, nitrendipine
ACE inhibitors	Enalapril, lisinopril, captopril, cilazapril
Diuretics	Hydrochlorothiazide, chlorothiazide
B blockers	Acebutolol, oxprenolol
HMG CoA reductase inhibitors	Simvastatin, pravastatin
Antifungals	Griseofulvin, terbinafine
Antiepileptics	Carbamazepine, phenytoin
Antiplatelets:	Ticlopidine
NSAIDS	Piroxicam, naproxen
Antidepressants:	Bupropion
Antihistamines	Ranitidine, brompheniramine,
Proton pump inhibitors	Lansoprazole
Chemotherapeutics	Docetaxel, paclitaxel, tamoxifen, capecitabine
Hormone altering drugs	Leuprorelin, anastrozole
Immunomodulators	Leflunomide, interferon α and β
Biologics:	Etanercept, efalizumab

Currently only two agents have been identified as high risk for the provocation of drug-induced LE: procainamide triggers LE in 15–20% of individuals, hydralazine in 7–13% (Table 1) (Borchers et al. 2007; Finks et al. 2006). Since the introduction of these drugs, both have experienced a significant reduction in therapeutic administration due to their LE-inducing propensity. The only agent identified as possessing a moderate risk is quinidine, however since the literature on this drug consists mainly of case reports, an exact risk cannot be defined accurately (Alloway and Salata 1995). Drugs associated with a low risk of drug-induced lupus include penicillamine, carbamazepine, methyldopa, sulfasalazine, minocycline, chlorpromazine, propylthiouracil and isoniazid (Borchers et al. 2007). Case reports exist for other agents but occur with such infrequency as to suggest that their LE-triggering tendency is extremely low or questionable.

A specific group of medications has been identified as causing a form of drug-induced LE which clinically resembles subacute cutaneous lupus erythematosus (SCLE). The patients with

this form of drug-triggered LE develop an inflammatory dermatosis, often with photosensitivity but rarely with systemic involvement (Lowe et al. 2011).

1.3 Pathophysiology

The pathophysiology of drug-induced LE is complex and incompletely understood but is likely to involve the interplay between genetic factors, drug metabolism and immunogenicity. Ultimately there is enhanced auto-immunity causing immune-mediated effects on target organs and thus clinical manifestations (Rubin 2005). Studies into the pathophysiology of drug-induced LE have focused on the archetype causative agents: procainamide and hydralazine. Potential mechanisms have been suggested, including a direct action of drugs or metabolites on the innate or adaptive immune system. Downstream there appears to be an immunostimulatory effect or disruption to central immune tolerance.

Genetic Susceptibility

Procainamide and hydralazine contain aromatic amines or aromatic hydrazines and undergo acetylation during drug metabolism. Drug-induced lupus by these agents has been shown to occur more frequently and more rapidly in patients who have a genetically determined reduction of hepatic n-acetyltransferase synthesis and are consequently slow at acetylating drugs (Hess 1988). Conversely, the development of autoantibodies in patients who are slow acetylators can be avoided by the administration of N-acetylprocainamide, the acetylated metabolite of procainamide (Stec et al. 1979). Similarly, patients who have developed procainamide-induced lupus can experience remission if administered N-acetylprocainamide, rather than procainamide (Stec et al. 1979). Variations in acetylator state are unlikely to be implicated in the development of all drug-induced LE, for example isoniazid-induced lupus occurs with equal frequency in both fast and slow acetylators (Reidenberg et al. 1993). Other implicated genetic variations in drug metabolism include alterations in cytochrome P450 enzymes resulting in the production of toxic metabolites which, in turn, can induce auto-immunity (McKinnon and Nebert 1994).

It has also been suggested that there is an association between certain HLA alleles and the development of drug-induced LE (Batchelor et al. 1980). This relationship varies between agents. HLA-DR4 is aligned to an increased risk of hydralazine- (Batchelor et al. 1980) and minocycline-induced LE (Dunphy et al. 2000), whereas the presence of HLA-DR6Y increases the risk of procainamide-induced LE (Adams and Mongey 1994). HLA-DQB1 and HLA-DR2 have also been associated with minocycline-induced lupus (Batchelor et al. 1980). The presence of the C4 null allele, which would prevent the activation of C3 and clearance of immune complexes, has also been shown to increase susceptibility to hydralazine-induced LE (Speirs et al. 1989).

Effects on Adaptive Immunity

Certain drugs, including procainamide, hydralazine, quinidine and phenytoin, have been shown to act as substrates for myeloperoxidase in activated neutrophils with the subsequent production of a drug metabolite which directly affects lymphocyte function and induces auto-immunity (Jiang et al. 1994). Small molecule drugs can undergo haptenization with proteins and can directly stimulate immune responses (Chang and Gershwin 2011).

Procainamide and hydralazine can also inhibit T cell methylation, similar to the effect seen with ultraviolet radiation (Cornacchia et al. 1988). T cell DNA hypomethylation causes increased lymphocyte function associated antigen-1 (LFA-1) with subsequent induction of autoreactivity (Deng et al. 2003). Other studies have shown that certain drug metabolites can interfere with T cell tolerance, resulting in the development of autoreactive T cells (Rubin 2015).

Effects on Innate Immunity

Recent discovery of neutrophil extracellular traps (NETs) has afforded additional insights into other potential mechanisms of drug-induced LE. Neutrophils can undergo a specific form of cell death, termed NETosis, in which there is a

removal of intracellular granular proteins which are bound to chromatin as a defence mechanism against pathogens. Studies have shown that some drugs, such as procainamide and hydralazine, can trigger NET formation via the stimulation of neutrophil muscarinic receptors and intracellular calcium influx, although this is not seen with all medications (Vaglio et al. 2018; Irizarry-Caro et al. 2018). Increased NET formation and decreased clearance have been associated with auto-immunity (Vaglio et al. 2018).

Clinical Features

Due to the large variety of symptoms and signs, many of which overlap with idiopathic LE, the diagnosis drug-induced lupus can be challenging. There are no clinical features which are pathognomic of drug-induced lupus, however some occur more commonly in the medication-triggered group (Table 3). Unlike idiopathic lupus, there are no universal criteria for the diagnosis of drug-induced LE. The disorder is divided into drug-induced systemic lupus erythematosus (SLE) and drug-induced subacute cutaneous lupus erythematosus (SCLE).

Drug-Induced Systemic Lupus Erythematosus

Drug-induced SLE is the most frequently reported form of drug-induced lupus. Patients with drug-induced SLE typically have fewer and less severe symptoms than those with idiopathic SLE (Antonov et al. 2004). After the initiation of the causative agent symptom onset is usually delayed for 1–3 months; sometimes there is a latency of 1–3 years. Symptoms vary greatly between individuals and causative agents, and can develop gradually or abruptly (Rubin 2015; Vaglio et al. 2018). Arthralgia is one of the more common presenting features, indeed often the only symptom, and occurs in up to 90% of patients (Borchers et al. 2007; Antonov et al. 2004). Myalgia is present in approximately 50% of patients (Antonov et al. 2004); other symptoms include fever, pleurisy and pericarditis (Rubin 2015; Vaglio et al. 2018; Borchers et al. 2007).

Drug-induced lupus SLE rarely causes major internal organ involvement (Borchers et al. 2007; Hess 1988). Exceptions to this include glomerulonephritis caused by hydralazine, quinidine-related central nervous system toxicity, pleuritis in up to 40% of cases of procainamide-induced LE, and auto-immune hepatitis which occurs in approximately 50% of patients with minocycline-induced LE (Borchers et al. 2007; Cemil et al. 2013).

Skin rashes are less common in drug-induced LE than in idiopathic SLE and often present with different characteristics with a low incidence of malar rash, discoid lesions, alopecia and photosensitivity (Chang and Gershwin 2011; Vaglio et al. 2018; Cemil et al. 2013).

Table 3 Demographics and features associated with drug-induced lupus and idiopathic lupus. Adapted from Rubin (2015), Vaglio et al. (2018), Batchelor et al. (1980)

	Drug-induced lupus	Idiopathic lupus
Age of onset	>50	20–40
M:F	1:1	1:9
Fever	40–50%	40–85%
Arthralgia/ myalgia	80–95%	75–95%
Rash	10–30%	50–70%
Malar rash	<5%	40%
Renal involvement	<5%	30–50%
CNS involvement	<5%	20–70%

Drug-Induced Subacute Cutaneous Lupus Erythematosus

Drug-induced SCLE is a distinct form of iatrogenic lupus which occurs following exposure to a specific group of drugs, including the calcium-channel antagonists and proton pump inhibitors (Table 2). Drug-induced SCLE has similarities with the idiopathic form of SCLE including the female predominance and the clinical presentation. Patients typically present with an annular or polycyclic eruption on the torso and proximal arms, although it can become generalized (Fig. 1). The dermatosis can be psoriasiform in morphology and may occur in a photo-exposed distribution. Erythema multiforme-like lesions and bullous lesions have been reported (Laurinaviciene et al. 2017). The majority of

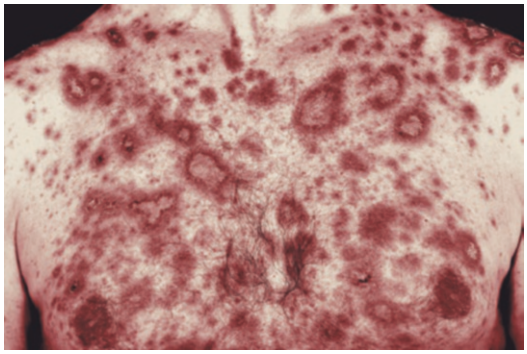

Fig. 1 This patient developed an extensive, inflammatory eruption of annular and polycyclic lesions, consistent with sub-acute cutaneous lupus erythematosus (SCLE), whilst taking omeprazole

patients with drug-induced SCLE carry anti-Ro/La antibodies in conjunction with antinuclear antibodies (ANA), specifically anti-histone antibodies. The lack of factors which discriminate drug-induced SCLE from other entities often leads to a misdiagnosis or a delay in diagnosis (Gronhagen et al. 2012).

1.4 Diagnosis

Patients in whom there is a suspicion of drug-induced lupus should have a complete medical history and examination undertaken to exclude other possible diagnoses. Biochemical, haematological and immunological laboratory testing should include a full blood count, renal and liver profiling, urinalysis, antinuclear antibody (ANA) anti-double stranded DNA, anti-Sm and anti-RNP, anti-Ro/SSA and anti-La/SSB and anti-histone antibodies. ANCA should be assayed in patients who have been treated with minocycline, hydralazine, propylthiouracil or methimazole.

The diagnosis of drug-induced LE should be considered in all patients who have developed at least one characteristic symptom of LE after taking a novel agent for at least a month. Suspicions can be strengthened by a strongly positive ANA, particularly anti-histone, and in patients in whom symptoms and antibodies improve on withdrawal of the causative agent, although recovery can often take months (Hess 1988; Vedove et al. 2009). The differential diagnosis of drug-induced LE following clinical examination includes dermatoses with annular, psoriasiform and photo-distributed morphologies. Skin biopsy in drug-induced LE provides little discriminating benefit since the histopathology in drug-induced LE is similar to that in idiopathic LE (Antonov et al. 2004).

Serological Profile

As with all auto-immune related conditions, drug-induced lupus is associated with autoantibodies. The presence of these antibodies varies between patients and causative agents. There are also variations between drug-induced LE and idiopathic LE which can help identify the underlying diagnosis (Table 4).

Antinuclear antibodies are present in over 90% of patients with drug-induced LE, typically in a homogenous pattern. 75–95% of patients with drug-induced LE have anti-histone antibodies, which is strongly discriminatory since these antibodies occur in only 20% of patients with idiopathic SLE (Antonov et al. 2004; Yung et al. 1995). Drug-related anti-histone antibodies are typically formed against the histone dimer H2A-H2B and DNA, which is in contrast to the H1-H2B dimer complex which is seen in idiopathic lupus (Yung et al. 1995). Other ANA, including those targeted towards Sm, RNP and SS-B/La, are rarely seen in drug induced lupus, whereas they are more common in idiopathic lupus. The exception to this is anti-SS-A/Ro, which is observed in 70–90% of patients with drug-induced SCLE (Rubin 2015). Anti-dsDNA is the antibody associated with active SLE but is much less common in drug-induced lupus. Conversely, anti-ssDNA is more frequently seen in drug-induced LE than idiopathic LE. The exception to this occurs with patients receiving biologic agents, such as tumour necrosis factor-α (TNF-α) antagonists and interferon-α, who commonly develop anti-dsDNA antibodies although their presence correlates poorly with clinical symptoms (De Bandt 2006).

Other immunological tests which can be helpful include the hypocomplementemia induced by quinidine; the circulating immune complexes

Table 4 Autoantibodies associated with drug induced lupus and idiopathic lupus. Adapted from Rubin (2015), Vaglio et al. (2018), Batchelor et al. (1980)

	Drug-induced lupus	Idiopathic lupus
ANA	>90%	>90%
ANA pattern	Homogenous	Heterogenous
Anti dsDNA	0–1%[a]	50–80%
Anti Sm	<5%	20–30%
Anti-Ro (SSA)	In drug-induced SCLE	30–40%
Anti-histone	90–95%	60–70%
Hypocomplementaemia	<5%	40–65%

SCLE subacute cutaneous lupus erythematosus
[a]Much more common in TNFa inhibitors

induced by hydralazine, propothiouracil, minocycline and sulfasalazine; and the positive Coombs test which can occur with methyldopa, chlorpromazine and procainamide (Rubin 2015).

1.5 Management

The cardinal feature of drug-induced LE is the improvement of symptoms on withdrawal of the causative agent. Many patients improve within a month, however in some patients symptoms can persist for several months. Positive autoantibodies are slower to improve and may be present for years.

There are no randomised controlled trials examining the optimal treatment for drug-induced lupus. Management is traditionally orientated around the use of anti-inflammatory agents, such as non-steroidal anti-inflammatory agents, and for the associated dermatosis to be treated with an appropriate topical corticosteroid preparation (Rubin 2015; Borchers et al. 2007). In cases which are resistant to symptomatic treatment antimalarials, such as hydroxychloroquine, may be considered. Occasionally patients require a course of systemic corticosteroids.

2 Drug-Induced Dermatomyositis

Dermatomyositis (DM) is classified alongside polymyositis (PM) in the idiopathic inflammatory myopathies. The clinical manifestations of DM are heterogenous with varying degrees of myositis and skin involvement. Some patients with DM suffer the additional pathological complexity of interstitial lung disease and/or internal malignancy. Across the spectrum of clinical presentations skin involvement is a prominent part of the syndrome; in a subset of patients cutaneous disease occurs in isolation, the so-called clinically amyopathic DM (CADM). Although predominantly a disorder of auto-immunity characterized by myositis specific antibodies (MSAs), a DM-like syndrome can be induced by drugs. Patients affected by drug-induced DM are typically over 50 years of age; there is no sex predilection (Seidler and Gottlieb 2008). Drugs which have been documented as a cause of DM include hydroxycarbamide (hydroxyurea), statins, penicillamine, quinidine and phenylbutazone. Reports have also suggested that the following may be involved in drug-induced DM: caritcaine, niflumic acid, etoposide, imatinib, interferon alpha, omeprazole, phenytoin, alfuzosin, gemfibrozil and etanercept, and the BCG vaccine (Dourmishev and Dourmishev 1999; Seidler and Gottlieb 2008).

Unlike idiopathic dermatomyositis, patients with drug-induced DM dermatomyositis do not carry one of the MSAs, ANA, anti-Ro or anti-Jo-1 (Seidler and Gottlieb 2008). Clinically there may be the typical features of heliotrope eyelid erythema, Gottron's papules and an upper torso dermatosis, along with a proximal myopathy. Hydroxycarbamide-induced DM is associated with a lichenoid dermatosis on the fingers. Patients with drug-induced DM may also have a pre-existing malignancy or auto-immune condition and tend to report a higher incidence of previous adverse drug events (Seidler and Gottlieb 2008).

3 Drug-Induced Scleroderma

In scleroderma, or systemic sclerosis, patients present with thickening and tightening of the skin, typically in acral areas, along with involvement of the renal, pulmonary, cardiac, gastro-intestinal, nervous and hepatic systems (Sahoo et al. 2020; Brogan and Olsen 2003). The idiopathic form is characterized by the presence of autoantibodies, including anti-Scl70 or anti-centromere, which are involved in a multifactorial combination of genetic and environmental pathogenetic events. The resulting disruption of blood vessels, fibroblast dysregulation and aberrant deposition of matrix proteins results in sclerosis (Haustein and Haupt 1998). Drugs have been suggested to contribute towards the development of scleroderma in a few case series. The implicated drugs include bleomycin and docetaxel, morphine, tryptophan, ethosuximide, amphetamines, penicillamine, fosinopril, triamcinolone and cocaine (Haustein and Haupt 1998). Unlike idiopathic scleroderma, drug-induced scleroderma usually does not have positive autoantibodies (Haustein and Haupt 1998). Upon withdrawal of the causative agent a large proportion of patients have either resolution of cessation of disease progression. For the remaining patients with symptomology treatment is orientated towards specific systems, with the use of topical and oral corticosteroids, PUVA or UVA1 therapy.

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Drug-Induced Vasculitis

John Stack

Abbreviations

AAV	ANCA associated vasculitis
ANA	Anti-nuclear antibody
ANCA	Anti neutrophil cytoplasmic antibody
BAFF	B-cell activating factor
bDMARD	Biologic disease modifying anti rheumatic drug
BVAS	Birmingham vasculitis activity score
CPI	Checkpoint inhibitor
CTCAE	Common Terminology Criteria for Adverse Events
DIV	Drug induced vasculitis
DMARD	Disease-modifying anti-rheumatic drug
EULAR	European league against rheumatism
IBD	Inflammatory bowel disease
irAE	Immune-related adverse event
MPO	Myeloperoxidase
NE	Neutrophil elastase
NETs	Neutrophil extracellular traps
PR3	Proteinase 3
PTU	Propylthiouracil
RA	Rheumatoid arthritis
TNF	Tumour necrosis factor

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1 Introduction

Drug-induced vasculitis (DIV) is recognized as a distinct entity within the revised 2012 Chapel Hill vasculitis consensus criteria, under the category "vasculitis with known aetiology" (Sunderkötter et al. 2018). An increasing number of drugs can provoke necrotizing inflammation of the small, medium and sometimes large vessels resulting in tissue ischaemia and inflammation. In the skin this can give rise to petechiae, purpura and skin necrosis. When DIV arises in internal organs life-threatening complications can occur. The exact prevalence of DIV remains unknown as no large population-based studies have been performed. Much of our knowledge derives from case reports and case series and is therefore likely to be prone to reporting bias.

While most cases will be mild, presenting with arthralgia, malaise and cutaneous leucocytoclastic vasculitis, some cases of DIV can be severe and cause major organ involvement, critical illness and rarely death (Sunderkötter et al. 2018; Ortiz-Sanjuán et al. 2014). Clinicians therefore need to be vigilant for systemic disease involvement, stop the offending agent promptly and initiate immunomodulatory therapy when necessary.

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2 Clinical Approach

Although DIV commonly presents with skin signs it is important for dermatologists to be aware of the potential for systemic disease involvement. A full vasculitis work-up is required, including a screen for lung, renal, gastric and CNS involvement. The Birmingham Vasculitis Activity Score (BVAS) is a freely available tool used for scoring disease activity in clinical trials but can also be used as a screening device to identify clinical features of systemic vasculitis (Luqmani et al. 1994).

It is important to remember that DIV is a diagnosis of exclusion. Since there are no established DIV diagnostic criteria, the following questions should help the clinician reach a diagnosis of DIV.

1. Is there a temporal association between drug initiation and vasculitis?
2. Is serum ANCA positive with multi-antigenicity?
3. Have other diseases, including other forms of vasculitis, been excluded?
4. Do symptoms resolve following cessation of culprit drug?

Similarly, there are no established treatment guidelines to help guide management of DIV. As with all adverse drug reactions the critical intervention is stopping the offending drug. Re-challenge with the culprit is not recommended since a disease relapse is likely. Consideration should also be given to the avoidance of medications in the same pharmacological class as the offending drug (Radić et al. 2012). In mild cases of DIV with low-grade arthralgia and a vasculitic rash, simply stopping the causative agent may be all that is required. Some patients will require a short course of oral prednisolone (e.g. 0.5–1.0 mg/kg/day reducing over 6–12 weeks). Cases with internal organ involvement or more severe cutaneous disease may require longer and higher doses of steroid with additional immune suppression using drugs such as mycophenolate mofetil, methotrexate or azathioprine. In situations when DIV is causing life-threatening manifestations (e.g. proliferative glomerulonephritis or alveolar haemorrhage) the treatment approach should be the same as severe ANCA-associated vasculitis: high dose pulsed methylprednisolone and rituximab or cyclophosphamide. In some instances, plasma exchange can be used as induction therapy, followed by long-term maintenance immune suppression and gradual steroid withdrawal. Such cases will require specialist input from clinicians with expertise in treating vasculitis. The EULAR guidelines on the management of ANCA- associated vasculitis provide a helpful resource (Yates et al. 2016). Ultimately management of DIV should be tailored to the individual patient. A proposed algorithm outlining the diagnosis and management of DIV is outlined in Fig. 1.

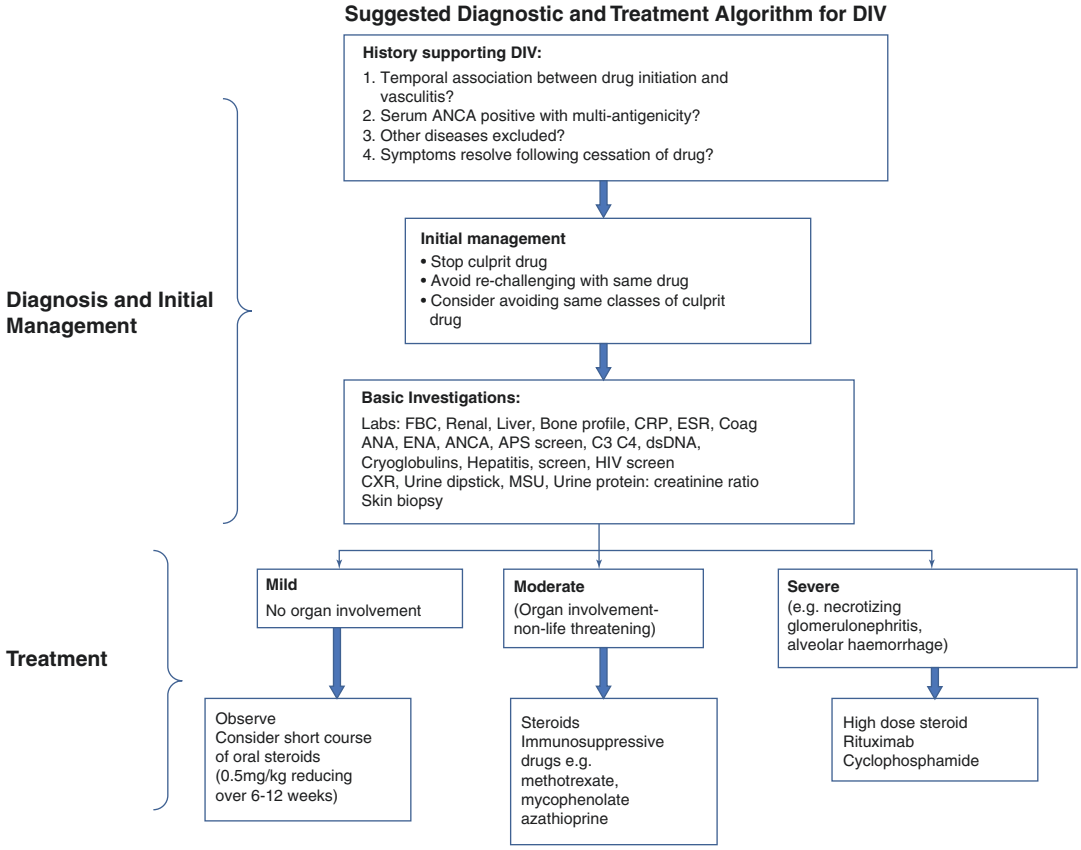

Fig. 1 Outline of the proposed algorithm for the diagnosis and management of DIV

3 Drugs Commonly Associated with Cutaneous Vasculitis

Numerous classes of drugs have been reported to be associated with DIV. The drugs commonly reported to cause cutaneous vasculitis are listed in Table 1. The major drug classes are discussed below.

3.1 Antibiotics

In one large single-centre case series of 773 patients, antibiotics were reported to be the most common trigger of DIV representing 62.3% of all cases (Ortiz-Sanjuán et al. 2014). Among antibiotic class, ß-lactam antibiotics were the most commonly reported. Causality is however often difficult to prove in these cases, as patients will typically have concurrent infections which are also known to trigger cutaneous vasculitis.

3.2 Anti-TNF-α Agents

Since the mid-1990s numerous targeted biologic therapies have been developed to treat a variety of autoimmune diseases and many of these have been associated with DIV. The most commonly reported class of biologic drugs associated with DIV are the anti-TNF-α monoclonal antibodies (Sokumbi et al. 2012). Reported cutaneous manifestations of anti-TNF-α DIV include erythematous macules and bullous lesions as well as palpable purpura. Skin biopsies of anti-TNF-α DIV demonstrate leucocytoclastic vasculitis. Withdrawal of the anti-TNF-α agent usually leads to resolution of symptoms. In a small, retro-

Table 1 Prescribed drugs associated with cutaneous vasculitis

Speciality	Drug class	Drug	References
Oncology-immunotherapy	Checkpoint inhibitors	Dabrafenib	Niro et al. (2018)
		Trametinib	Niro et al. (2018)
		Nivolumab	Tomelleri et al. (2018)
		Pembrolizumab	Tomelleri et al. (2018)
	EGFR inhibitors	Panitumumab	Kamo et al. (2019)
		Lapitinib	Peuvrel et al. (2013)
		Erlotinib	Fekete and Fekete (2019)
	Proteosome inhibitors	Ixazomib	Alloo et al. (2018)
Oncology-Hormonal therapy	Aromatase inhibitors	Anastrazole	Bock et al. (2014)
		Letrozole	Digklia et al. (2014), Woodford et al. (2019)
Rheumatology/Gastroenterology/ Dermatology/	Biologics	Anti-TNF	Sokumbi et al. (2012), Sehgal et al. (2018)
		Rituximab	Abe et al. (2019)
		Denosumab	Sanchez et al. (2019)
		Tocilizumab	Sehgal et al. (2018), Sakaue et al. (2014)
		Abatacept	Shibata et al. (2013)
Microbiology	Antibiotics	Antibiotics	Ortiz-Sanjuán et al. (2014)
		Minocycline	Kermani et al. (2012), Lenert et al. (2013)
Haematology	Anti-coagulant	Warfarin	Hamada et al. (2017), Hsu et al. (2012)
	Direct oral anti-coagulant	Rivaroxaban	Sainz-Gaspar et al. (2018), Dean et al. (2017), Chaaya et al. (2016)
		Dabigatran	An et al. (2017)
Endocrinology	Anti-thyroid medication	Propylthiouracil	Wall et al. (2017)

spective, single-centre case series of 8 patients with histologically proven DIV caused by anti-TNF-α, 7/8 had evidence of systemic vasculitis with confirmed mononeuritis in 6/8 patients and IgA nephropathy in 1/8 patients. A majority of the patients were treated with an immunosuppressant in addition to prednisolone; the mean time to resolution was 6.9 months. In another study of anti-TNF-α DIV, 6/9 of patients who were rechallenged with the same anti-TNF agent relapsed (Mohan et al. 2004).

Despite the studies cited above, determining whether anti-TNF is responsible for causing vasculitis can be difficult. Anti-TNF-α agents are used to treat diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) which can in themselves be associated with vasculitis. A temporal association with commencement of anti-TNF, improvement upon cessation of anti-TNF, and an otherwise quiescent underlying disease can help to support a diagnosis of DIV. Although anti-TNF can induce anti-nuclear antibodies, the association between drug-induced antibodies and subsequent vasculitis has not been well defined. It is hypothesized that development of antibodies can lead to an immune complex-mediated vasculitis (Moustou et al. 2009).

3.3 Propylthiouracil

Propylthiouracil (PTU) causing DIV is well described. A review of 128 cases found that the most common manifestations were rash, fever and arthralgia (Wall et al. 2017). Rash was present in 51% of cases. The vast majority were found to have positive ANCA on immunofluorescence (typically perinuclear, p-ANCA). Up to 84% of

patients with PTU-associated DIV had a positive MPO-ANCA on serological testing. Renal manifestations were common with proteinuria and/or microscopic haematuria in 57% of cases. Renal involvement was an important cause of morbidity and end-stage renal disease was reported in eight patients, four of whom underwent kidney transplant. Extreme cases of PTU-associated cutaneous vasculitis have been reported causing extensive skin involvement with progression to widespread, full-thickness skin necrosis, septic shock and death (Wall et al. 2017).

3.4 Cocaine/Levamisole

One of the more commonly reported and studied forms of DIV relates to cocaine misuse. Cocaine purchased for illicit use is frequently contaminated with the anti-helminth drug levamisole. Powdered levamisole, which is normally used in veterinary practice, resembles cocaine and has been used as an additive (a "cutting agent") in cocaine and crack cocaine, bulking up the drug to increase profit for the dealer. In addition, a metabolite of levamisole potentiates the stimulatory effects of cocaine. However, levamisole is highly immunogenic and is the source of cocaine-induced DIV. Patients present with clinical features resembling an ANCA-associated vasculitis, which include fever, neutropenia, arthralgia, purpura and other signs of cutaneous vasculitis. Some users will develop midline destructive lesions characterized by localized granulomatous inflammation around the nasopharynx, destruction of the nasal septum and, in severe cases, saddle nose deformity (Marquez et al. 2017). A distinguishing feature is that these patients are often positive for multiple autoantibodies including ANCA, ANA, anti-phospholipid and anti-dsDNA antibodies. ANCA antibodies tend to be non-specific; patients can be MPO-ANCA and PR3-ANCA positive (Marquez et al. 2017; Carmona-Rivera et al. 2017).

Addiction counselling is of key importance for these patients as cessation of cocaine misuse will result in resolution of the vasculitis in most cases (Marquez et al. 2017). Occasionally, the vasculitis will perpetuate or will be severe enough to warrant immune suppression with steroids and immunomodulatory therapy (Marquez et al. 2017).

3.5 Cancer Immunotherapy

The development of immunotherapy in the treatment of cancer has dramatically improved the life expectancy of patients with solid organ tumours, haematological malignancies and melanoma. The most commonly prescribed immunotherapeutic drugs are checkpoint inhibitors (CPIs) which enhance the anti-tumour activity of T-cells resulting in tumour suppression and regression, even in patients with unresectable metastatic disease (Kostine et al. 2019). The use of CPIs is associated with a wide variety of manifestations resembling autoimmune disease, collectively termed immune related adverse events irAEs (Calabrese et al. 2018). The frequency of irAEs has been reported to be high, up to 90% in some studies (Calabrese et al. 2018). The majority of irAEs are rheumatic in nature resembling rheumatoid arthritis or polymyalgia rheumatica; however, polymyositis, scleroderma, sicca syndrome and vasculitis syndromes can also occur (Kostine et al. 2019). In one systematic review of vasculitis associated with CPIs, the authors found 20 case reports that met their definition for inclusion (Daxini et al. 2018). The majority of cases were associated with melanoma and the most common manifestations of vasculitis were giant cell arteritis and primary CNS vasculitis. Cases of digital vasculitis, granulomatosis with polyangiitis and cryoglobulinaemic vasculitis were also reported.

The Common Terminology Criteria for Adverse Events (CTCAE) grades irAEs from 1-to-5 based on the severity (grades 1 and 2 are mild, grade 5 is fatal) (Puzanov et al. 2017). Grade 1 events do not typically require intervention while grade 3 or higher usually warrants intervention with corticosteroids, immunomodulation and cessation of the CPI. An important observation is that many irAEs can persist despite

cessation of CPI (Calabrese et al. 2018). In these cases, a close liaison between patient and oncologist is required to formulate a decision about the continuation of CPI therapy.

4 Pathogenesis

Perhaps the most studied form of DIV is cocaine–levamisole vasculitis. Our understanding of this entity has helped to uncover pathogenetic principles which may underlie other DIV syndromes.

The release of neutrophil extracellular traps (NETs) has been shown to be an important mechanism through which cocaine–levamisole can initiate autoimmunity leading to vasculitis (Carmona-Rivera et al. 2017; Lood and Hughes 2017; Pieterse and van der Vlag 2017). The process of NET release is known as NETosis, a type of neutrophil programmed cell death in which chromatin fibres (the breakdown product of DNA, histones and granule-derived antimicrobial proteins) are expelled from cells (Brinkmann and Zychlinsky 2012). It is a powerful defence mechanism used by the body to fight pathogens that are too large to be phagocytosed. Aberrant NETosis has been identified as a feature of autoimmune disease, thrombosis and malignancy (Kaplan and Radic 2012). Lemavisole has been shown to generate NETs enriched in neutrophil elastase (NE), a neutrophil-derived protein which is highly immunogenic and capable of stimulating expression of ANCA (Lood and Hughes 2017). Continuous generation of NETs is hypothesized to lead to a breakdown in immune tolerance. NETs become pathogenic and lead to a perpetuation of the immune response with resulting inflammation and vasculitis (Pieterse and van der Vlag 2017). In addition, cocaine and/or levamisole are both capable of upregulating expression of B cell activating factor (BAFF), a key stimulant of B cell replication and differentiation, which may increase ANCA production and explain why ANCA titres can persist long after cocaine cessation (Lood and Hughes 2017).

These above mechanisms may shed light on other forms of drug-induced vasculitis. For example, DIV associated with PTU has also been associated with NETosis and MPO-ANCA generation in rats, which has been shown to cause pauci-immune glomerulonephritis and pulmonary capillaritis (Nakazawa et al. 2012).

Vasculitis and other irAEs associated with CPIs are not associated with auto-antibody formation and tend not to regress once the CPI has been discontinued (Calabrese et al. 2018). The mechanism by which irAEs occur remains unknown however a number of mechanisms are proposed. One hypothesis suggests that CPIs, acting on the host immune system, impair immune tolerance leading to autoimmunity. Another proposes that CPIs result in the unmasking of pre-existing autoimmunity. T-cell epitope spreading has also been suggested, whereby T-cells start to recognize and react to healthy host tissue antigen in addition to tumour antigen (Calabrese et al. 2018).

5 Conclusion

There are a wide variety of drugs associated with DIV, and a drug aetiology needs to be considered in all patients presenting with vasculitis. Clinicians should be aware of the potential for systemic disease involvement in patients with DIV and to examine the patient and investigate appropriately. Ultimately, however, DIV is a diagnosis of exclusion.

As the use of new cancer immunotherapeutic drugs increases there will be a growing burden of irAEs, which include vasculitis. In this emerging field of oncological therapeutics it is the check point inhibitors which are especially liable to induce vasculitis. Powerful efficacy is coupled to the potential for serious side effects and therefore the ability to recognize autoimmune adverse reactions is an important principle in the use of these drugs.

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Drug-Induced Autoimmune Bullous Diseases

Michael Benzaquen, Michael Hertl, and Luca Borradori

Abbreviations

BP	Bullous pemphigoid
DIBP	Drug-induced BP
DPP4i	Dipeptidyl peptidase-IV inhibitors
EBA	Epidermolysis bullosa acquisita
IF	Immunofluorescence
LABD	Linear IgA bullous dermatosis
NSAIDs	Nonsteroidal anti-inflammatory drugs
PD1i	Programmed cell death protein-1 inhibitors
TNFα	Tumor necrosis factor alpha

Autoimmune bullous diseases comprise two major types: intraepidermal blistering diseases such as the pemphigus group of diseases and the subepidermal blistering diseases comprising pemphigoid group of diseases [bullous pemphigoid (BP), linear IgA bullous dermatosis (LABD), gestational pemphigoid], the group of mucous membrane pemphigoids and epidermolysis bullosa acquisita (EBA) (Amber et al. 2018; Di Zenzo et al. 2016; Kim et al. 2016). Besides the immunological process, a variety of medications have been reported as potential triggers in the pathogenesis. The diagnosis of drug-induced autoimmune bullous diseases is challenging; patients are often exposed to several drugs with prolonged latency periods between exposure and onset of the disease. In addition, the epidemiological risk of many drugs remains unclear. Nevertheless, recognition and cessation of any suspected drug trigger is essential for the management disease.

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1 Drug-Induced Pemphigus

Pemphigus is an autoimmune acquired bullous disease affecting the skin and/or mucous membranes, characterised by intraepidermal blistering. This condition is associated with Nikolsky's sign; the direct Nikolsky is when the application of slight pressure on a blister results in extension of the blistering to adjacent skin and the indirect Nikolsky is when rubbing on clinically normal skin causes shearing. This group of diseases is associated with autoantibodies predominantly

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directed against two desmosomal components: desmoglein 1 and/or desmoglein 3 (Amber et al. 2018).

Despite the identification of genetic and environmental predisposing factors, various drugs have been repeatedly implicated as potential triggers of pemphigus (Kim et al. 2016). The clinical presentation of drug-induced pemphigus is similar to the idiopathic disease. An increasing number of drugs (Brenner and Goldberg 2011) have been reported to induce pemphigus, highlighting the importance of a detailed clinical history and evaluation in order to identify the potential culprit medication.

1.1 Clinical Features

Drug-induced pemphigus presents with mucocutaneous erosions and flaccid vesicles and blisters. It is clinically, histologically and immunologically indistinguishable from the classical disease (Korman et al. 1991; Landau 1997).

1.2 Drug Causality and Pathophysiology

It is postulated that the binding of drugs to cellular proteins induces a structural change or uncovers hidden epitopes, thereby stimulating an autoimmune response (Ruocco et al. 1993). Other postulated mechanisms include direct disruption of cell–cell adhesions, cytokine activation and derangements in intracellular calcium (Brenner et al. 1998; Marsden et al. 1976; Newby et al. 2000; Feliciani et al. 2000).

The four main groups of chemical structures in drugs that have been involved in triggering pemphigus are (1) sulfhydryl radical (thiol drugs or SH drugs), (2) phenolic drugs, (3) drugs with an active amide group and (4) others (Korman et al. 1991).

- Thiol drugs (e.g. penicillamine, captopril or gold sodium thiomalate). Penicillamine was the first drug reported in 1976 to induce pemphigus foliaceus. Up to 7% of patients taking penicillamine for at least 6 months would develop pemphigus (Marsden et al. 1976).

  Thiol drugs are postulated to induce acantholytic changes in skin through the inhibition of enzymes involved in the aggregation of keratinocytes as well as activating enzymes such as plasminogen activator involved in cell adhesion homeostasis. The activation of plasminogen activator may contribute to the loss of cell–cell adhesion, as well as to the formation of thiol-cysteine bonds instead of cysteine–cysteine bonds, resulting in the formation of neo-antigens with its downstream immunological effects (Ruocco et al. 1993).
- Phenolic drugs, including aspirin, levodopa, rifampicin or heroin, have also been linked to anecdotal cases of drug-triggered pemphigus by the release of cytokines such as tumor necrosis factor alpha (TNFα) and interleukin-1α from keratinocytes (Newby et al. 2000). These cytokines are involved in the regulation and synthesis of complement and proteases like plasminogen activator, which are mediators of acantholysis (Feliciani et al. 2000).
- Amide drugs such as acetazolamide was first identified in 2009, as potential trigger of drug-induced pemphigus (Lo Schiavo et al. 2009).
- Others: Calcium channel blockers, angiotensin-converting enzyme inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), or pyrazolone derivatives are some examples of non-thiol non-amide non-phenol drugs that have also been related to some cases of pemphigus. Intracellular calcium is essential for keratinocyte homeostasis, cell differentiation, cell–cell adhesion and the proper conformation of the pemphigus antigens. It is therefore plausible that calcium channel blockers may under certain circumstances act as a trigger or aggravating factor (Brenner et al. 1998).

A list of common drug associations with pemphigus is summarised in Table 1 (Kaplan et al. 1992; Palleria et al. 2019).

The latency period from drug initiation to the onset of pemphigus is variable. In cases associ-

Table 1 Drugs commonly reported to induce pemphigus

Chemical structure	Drug class	Drug name
Thiol drugs		Captopril Fosinopril Gold sodium thiomalate Penicillamine Thiopronine Pyritinol 5-Thiopyridoxine Mercaptopropionylglycine
Phenolic drugs		Levodopa Phenobarbital Phenytoin Heroin Rifampicin Lysine acetylsalicylate Progesterone
Drug with an active amide group		Acetazolamide Glibenclamide Indapamide
Non-thiol non-amide non-phenolic drugs	Angiotensin-converting-enzyme inhibitors	Cilazapril Enalapril Fosinopril Lisinopril Benazepril Quinapril Ramipril
	Pyrazalone derivatives	Aminophenazone Noramidopyrine Azapropazone Oxyphenylbutazone Phenylbutazone
	Antibiotics	Ampicillin Amoxicillin/clavulanic acid Penicillin Isoniazid and ethambutol Cephalexin Norfloxacin Ciprofloxacin
	Nonsteroidal anti-inflammatory drugs	Piroxicam Diclofenac
	Others	Interleukin-2, interferon-α2a and β Propranolol Bisoprolol/hydrochlorothiazide Nifedipine Carbamazepine Hydroxychloroquine Tetanus, diphtheria, typhoid, anthrax, and influenza vaccinations

ated with antibiotics, it typically varies between 2 weeks and 2 months, whereas in ACE inhibitor/ARB related and Penicillamine-related cases, the latency is prolonged; occurring between 4 to 24 months and 2 to 48 months respectively (Saito et al. 2018; Yung and Hambrick 1982).

2 Drug-Induced Bullous Pemphigoid (DIBP)

BP is an acquired autoimmune disease that affects mainly the elderly and is characterised by subepidermal blistering (Amber et al. 2018).

More than 50 different drugs have been associated with the onset of BP (Vassileva 1998) and this number will increase with the emergence of new therapies. Two forms of DIBP have been described. The first one, regarded as a true DIBP, is an acute and self-limited condition with a prompt response after withdrawal of the incriminated drug. The second form, considered as a drug-triggered BP, is characterised by a more chronic and severe course similar to classic BP, in which the medication seems to have a role in the initiation of the disease, which then follows its spontaneous normal course (Lee and Downham 2006).

2.1 Clinical Presentation/ Investigations

Drug-induced BP (DIBP) is characterised by a younger age of onset. The trunk, the limbs (most commonly the lower legs) and the face can be involved and the rash is intensely pruritic. In contrast to classic BP, it has been observed that the bullae in DIBP tends to occur on normal-appearing skin rather than appearing on erythematous or urticarial base (Kawaguchi et al. 2019; Stavropoulos et al. 2014). Erythema multiforme-like target lesions on palms and soles as well as mucosal lesions may be present (Alcalay et al. 1988). Post-bullous erosions heal spontaneously without scarring. Nevertheless, in the absence of prospective series specifically addressing the clinical features of drug-induced cases compared with an adequate control population, there is little evidence supporting the idea that drug-triggered cases can be differentiated entirely on clinical grounds.

Besides subepidermal blisters, histological features often linked to DIBP include intraepidermal vesicles and necrotic keratinocytes. A dense dermal inflammatory infiltrate containing many eosinophils, neutrophils with lymphocytes and histiocytes may be present, as well as thrombus formation. Similarly to classic BP, IgG antibodies and C3 along the linear basement membrane zone are detected in 90% of cases by direct immunofluorescence (IF) microscopy, whereas circulating IgG antibodies are detected in 75% of cases with indirect IF (Stavropoulos et al. 2014).

2.2 Pathophysiology

Several pathomechanisms have been proposed. These include (a) change in T-regulatory cells (CD4+, CD25+, Foxp) resulting in the stimulation of B-cell clones and the release of autoantibodies against the basement membrane zone (Bowman and Delrieu 2009), (b) molecular mimicry arising from structural similarity between drugs and autoantigens leading to the activation of CD4+ T cells and the initiation of the autoimmune cascade in susceptible individuals (Bowman and Delrieu 2009), (c) drugs acting as antigenic haptens, binding and modifying protein molecules in the basement membrane, resulting in the exposure of hidden antigenic sites (Lee and Downham 2006).

In a retrospective study comprising 34 patients, Patsatsi et al. (2009) described an increased detection rate with a significant higher level of anti-BP180 autoantibodies in a group of patients with BP receiving systemic medications prior to the disease, compared with a group of patients who did not receive any medications.

2.3 Drug Causality

Since the first report of salicylazosulphapyridine-induced BP in 1970 (Bean et al. 1970), many other drugs have been reported to induce or trigger BP (detailed in Table 2).

In a case–control study assessing the drugs used on a long-term basis prior to onset of BP, it was found that two classes of drugs, diuretics and neuroleptics, were used more frequently by BP patients than by control subjects. Among diuretics, the risk was linked to aldosterone antagonists (Bastuji-Garin et al. 2011). In a UK case–control study, loop diuretics were used significantly more frequently by the BP patients (Lloyd-Lavery et al. 2013). Antibiotics, antiarrhythmics, antihypertensives, NSAIDs, and TNFα inhibitors have also been incriminated (Vassileva 1998).

Table 2 Drugs commonly reported to induce bullous pemphigoid

Drug class	Drug name
Antibiotics	Actinomycin Amoxicillin Ampicillin Cephalexin Ciprofloxacin Chloroquine Dactinomycin Levofloxacin Penicillin Rifampicin
Antiarrythmics-antihypertensives	*Calcium channel-blockers*: Amlodipine; Nifedipine *Angiotensin-converting-enzyme inhibitors*: Captopril; Enalapril; Lisinopril *Beta-blockers*: Nadolol; Practolol *Angiotensin II antagonists*: Losartan
Diuretics	Furosemide Spironolactone
Neuroleptics	Risperidone Flupentixol Gabapentin Levetiracetam
Salicylates	Aspirin Sulfasalazine Salicylazosulphapyridine
Nonsteroidal anti-inflammatory drugs	Azapropazone Diclofenac (topical) Ibuprofen Mefenamic acid Phenacetin
DPP4 inhibitors	Vildagliptin Sitagliptin Linagliptin
Antirheumatics	D-penicillamine Tiobutarit Tiopronin
TNFα inhibitors	Adalimumab Efalizumab Etanercept
PD1 inhibitors	Nivolumab Pembrolizumab
Vaccines	Influenza Swine flu Tetanus toxoid HZV Hexavalent combined Vaccines
Others	Arsenic Clonidine Erlotinib Galantamine hydrobromide Fluoxetine Gold thiosulphate Interleukin-2 Methyldopa Terbinafine Tolbutamide Omeprazole Psoralens with UVA Placental extracts Potassium iodide Sulphonamide

DPP4 dipeptidyl peptidase-IV, *TNFα* tumour necrosis factor alpha, *PD1* programmed cell death protein-1

Recently, two classes of drugs have been shown to have increased epidemiological risk: Dipeptidyl peptidase-IV inhibitors (DPP4i), and programmed cell death protein-1 inhibitors (PD1i).

DPP4i are oral anti-hyperglycaemic drugs administered to patients with type 2 diabetes. An increasing number of reports have suggested that DPP4i could trigger BP. García et al. (2016) identified 170 cases of BP in patients under DPP4i in the EudraVigilance database, suggesting that the intake of DPP4i was more frequently associated with the development of BP when compared to that of other drugs. In this latter report, a high disproportionality for vildagliptin was found. A French case–non-case study recording all spontaneous reports of DPP4i-related BP in the National Pharmacovigilance Database also provided evidence for a strong signal for an increased risk of BP associated to DPP4i exposure, especially vildagliptin (Béné et al. 2016). Finally, Benzaquen et al. (2018) confirmed for the first time in a retrospective study that DPP4i were associated with an increased risk of developing BP. Association with vildagliptin was significantly higher compared to that with other DPP4i with an adjusted odds-ratio of 3.57.

Immune check point inhibitors which are increasingly used in the treatment of metastatic melanoma and other metastatic cancers, represent another class of drugs increasingly incriminated as a trigger of immune-mediated dermatoses such as vitiligo, lichenoid eruptions and autoimmune blistering diseases. Twenty-two cases of BP associated with PD1i (nivolumab or pembrolizumab) have been reported so far in the literature (Lopez and Geskin 2018). Dysregulation of PD1 pathway can impair peripheral tolerance and alter the balance within the immune system, leading to the development of off-target effects and autoimmunity. With the anticipated significant growth in the number of patients eligible to receive checkpoint inhibitors, physicians should be aware of these additional cutaneous autoimmune association with BP.

3 Drug-Induced Linear IgA Bullous Dermatosis (LABD)

LABD comprises a heterogeneous group of autoimmune subepidermal blistering disorder characterised by the detection of linear deposits of IgA (alone or as the predominant immunoreactant in combination with other immunoglobulins) along the basement membrane zone as detected by direct IF microscopy studies. Immunologically, the detected IgA autoantibodies may demonstrate reactivity with various antigens, including specific antigenic regions of the extracellular domain of BP180, as well as BP230 and type VII collagen (Amber et al. 2018). It is estimated that at least 2% of all LABD is attributed to drug administration (Horiguchi et al. 2008).

3.1 Clinical Presentation

The lesions in LABD often exhibit annular and polycyclic patterns with vesicles and bullae arising on the edge with central crusting or healing. These so-called cluster of jewels or string of pearls signs are characteristic for LABD, especially in the childhood form (Horiguchi et al. 2008). In contrast, drug-induced LABD may present with more polymorphic and/or atypical features mimicking other forms of bullous dermatosis, severe drug eruptions, vasculitis or even neutrophilic dermatoses (Dietrich et al. 2012). Chanal et al. (2013) performed a retrospective single-centre cohort study of 28 patients diagnosed with LABD between 1995 and 2010: 16 patients with spontaneous LABD and 12 with drug-induced LABD. Nikolsky sign and large erosions were significantly more frequent in drug-induced than spontaneous LABD, with no between-group differences for erythematous plaques, target or target-like lesions, string of pearls, location, mucosal involvement or histological features. Hence, drug-induced LABD appear to be more severe than the spontaneous form. Physicians should be aware of this diagnosis and perform a direct IF in case of lesions mimicking toxic epidermal necrolysis.

3.2 Pathophysiology

The mechanism of drug-induced autoimmunity in LABD is not clear. However, it has been shown that in patients with vancomycin-induced LABD, IgA reactivity to collagen VII is acquired in the presence of vancomycin (Yamagami et al. 2018).

3.3 Drug Causality

The latency between drug initiation and onset of disease ranges between 2 days to 4 weeks. A variety of medications have been implicated with vancomycin being the most frequently cited (Baden et al. 1988; Whitworth et al. 1996). Vancomycin-associated LABD has also been reported following exposure to vancomycin-impregnated cement spacers used in knee arthroplasty (Riemenschneider et al. 2018). Several other drugs have also been associated with LABD, including NSAIDs (piroxicam, naproxen, diclofenac) (Bouldin et al. 2000; Plunkett et al. 2001), amiodarone (Primka et al. 1994), antibiotics (ceftriaxone, penicillin) (Combemale et al. 1993; Yawalkar et al. 1999) and acetaminophen (Avci et al. 2003). Recently, Garel et al. have collected, in a French retrospective study from 1985 to 2017, 69 cases of drug-induced LABD. 29

Table 3 Drugs commonly reported to induce linear IgA bullous dermatosis

Drug class	Drug name
Antibiotics	Vancomycin Trimethoprim–sulfamethoxazole Ceftriaxone Amoxicillin/ampicillin Penicillin Imipenem Moxifloxacin Minocycline Doxycycline
Antiarrythmics-antihypertensives	Amiodarone Captopril Verapamil
Diuretics	Furosemide
Nonsteroidal anti-inflammatory drugs	Diclofenac Piroxicam Naproxen Ketoprofen
Antiepileptics	Phenytoin Vigabatrin
Biologics	Infliximab Ustekinumab Interferon γ/interleukin-2
Others	Acetaminophen Lithium carbonate Atorvastatin Gemcitabine Enoxaparin

patients (42%) had a mucosal involvement, and 14 patients (20%) had large erosions mimicking toxic epidermal necrolysis. That study confirms vancomycin as the most common drug trigger, accounting for close to 60% of cases. In addition, three other drugs: enoxaparin, minocycline, and doxycycline have been shown to be high risk triggers (Garel et al. 2018). Table 3 gives a non-exhaustive list of drugs inducing LABD found in the literature (Baltazard et al. 2017).

4 Drug-Induced Epidermolysis Bullosa Acquisita (EBA)

EBA is an acquired autoimmune subepidermal blistering disease characterised by the presence of autoantibodies (mainly IgG class) to type VII collagen, a major component of anchoring fibrils at the dermo-epidermal junction (Amber et al. 2018). There are two major forms of EBA: the inflammatory and the non-inflammatory one. Furthermore, some patients may have predominant mucous membrane involvement, with a mucous membrane pemphigoid phenotype. Patients with the non-inflammatory form of EBA (classical EBA type) have increased skin fragility with subsequent formation of blisters or erosions on the trauma-prone areas of the skin, such as extensor surfaces of elbows, knees, ankles, and buttocks. The inflammatory form of EBA can mimic almost all other chronic bullous diseases, including BP and anti-laminin gamma 1 pemphigoid. This form presents with widespread, tense vesicles and bullae, not localised to trauma-prone sites, which generally heal with minimal scarring and milia formation (Mehren and Gniadecki 2011). Nevertheless patients may present features of both forms in the course of the disease.

In contrast to the other autoimmune bullous diseases, drug-induced EBA is not a well-defined entity. In their review, Vodegel et al. showed that 11% of EBA with IgA deposits were possibly drug-induced (Vodegel et al. 2002). A case of vancomycin-induced EBA with IgA and IgG deposits has been described in 2002 (Delbaldo et al. 2002). An anecdotal case of EBA developed under systemic estrogen and progesterone treatment with a recurrence during pregnancy can be underlined (Kubo et al. 1997). Finally, D-penicillamine has been reported twice to induce EBA-like eruption: the first case in a patient taking penicillamine for sclerodermatous graft-versus-host disease following bone marrow transplantation. In this case, drug withdrawal and administration of cyclosporine and methylprednisolone controlled the disease (Cetkovská et al. 2003). Two other cases occurred in siblings taking D-penicillamine for a Wilson disease, with a complete healing of lesions in both cases after replacement of D-penicillamine by trientine dihydrochloride (Ingen-Housz-Oro et al. 2014).

4.1 Management of Drug-induced Autoimmune Blistering Diseases

In drug induced autoimmune blistering disease, cessation of the suspected offending agent is an important step towards remission even before ini-

tiating pharmacologic therapy (Mashiah and Brenner 2005). The clinical course is variable; some cases improves or regresses with withdrawal of culprit drug; however, many remain self-perpetuating and requires the use of traditional therapies (Ruoco and Sacerdoti 1991).

5 Conclusion

With the constant emergence of new therapies and increasing polypharmacy, the number of drugs potentially triggering autoimmune bullous diseases is expected to increase in the future. After withdrawal of the suspected medication, patients may show a favourable course, with a rapid response to treatment without further relapse. Therefore, physicians should always raise the possibility of a drug-induced autoimmune bullous disease and lead a careful clinical history and drug investigation. Nevertheless, there is an urgent need to have large prospective epidemiological studies as well as basic investigative studies to identify the most important drug triggers and predisposing genetic factors as well as to gain better insight into their exact disease pathophysiology.

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Other Drug-Induced Inflammatory Skin Reactions

Chai Zi Teng, Shashendra Aponso, and Haur Yueh Lee

The spectrum of drug-induced reactions is broad, including both drug hypersensitivity reactions as well as reactive inflammatory patterns. For the majority of such reactions, the clinical presentation is similar to that of the primary dermatosis and histology is rarely pathognomonic. Unless there is a high index of suspicion, many of these drug-induced dermatoses will be underdiagnosed. In this chapter, we discuss various other inflammatory phenotypes, including granulomatous, neutrophilic, papulosquamous, eczematous and panniculitic reaction patterns.

1 Drug-Induced Granulomatous Reactions

Granulomatous drug eruptions are a rare form of non-infectious granulomatous diseases of the skin. Various subtypes have been described and classification requires clinic-pathologic correlation. The most common subtypes include (a) interstitial granulomatous drug reaction (IGDR), (b) drug-induced sarcoidosis, (c) drug-induced granuloma annulare and (d) drug-induced accelerated rheumatoid nodulosis.

1.1 Interstitial Granulomatous Drug Reaction (IGDR)

The prevalence of IGDR is unknown (Rosenbach and English 2015) but is believed to be rare. The cutaneous presentation of IGDR is similar to the primary interstitial granulomatous dermatitis. Common manifestations include erythematous to violaceous annular plaques, distributed commonly on the flexures including intertriginous areas, medial thighs and inner arms (Regula et al. 2008; Magro et al. 1998). Other presentations include generalized erythematous macules and papules, erythroderma, multiple tender, erythematous-violaceous firm papules and plaques on palms and soles, as well as erythema nodosum-like lesions. Clinical differential diagnoses include erythema annulare centrifugum, subacute cutaneous lupus erythematosus, granuloma annulare and mycosis fungoides. Unlike interstitial granulomatous dermatitis, there is no systemic association in IGDR.

Postulated mechanism in IGDR is believed to occur via antigenic alteration of dermal collagen resulting in a secondary immune response (Regula et al. 2008). Histological features include diffuse interstitial infiltrate of lymphocytes and histiocytes with fragmentation of collagen and elastic fibres. Other features that are usually pres-

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ent includes small numbers of eosinophils, mild interface dermatitis, and variable mucin deposition (scant to absent) (Magro et al. 1998). Rarely, these granulomatous features can be associated with atypical cutaneous T-cell lymphocytic infiltration. The molecule profile resembles mycosis fungoides and this has been termed drug-associated reversible granulomatous T-cell dyscrasia, a subset of IGDR (Magro et al. 2010).

The latency from drug initiation to appearance of lesions can be prolonged, ranging from weeks to years (Regula et al. 2008; Magro et al. 1998). Common culprit drugs are summarized in Table 1 (Rosenbach and English 2015; Regula et al. 2008; Magro et al. 1998, 2010; Perret et al. 2017; Deng et al. 2006; Fujita et al. 2004; Marcollo Pini et al. 2008; Martínez-Morán et al. 2011; Du et al. 2012).

Cutaneous lesions resolve within 1–40 weeks (mean 8 weeks) following discontinuation of the culprit drug (Magro et al. 1998). Oral provocation test with reappearance of lesions confirms the diagnosis. In cases which are slow to respond, a repeat skin biopsy is warranted to exclude granulomatous slack skin, a form of cutaneous T cell lymphoma. Similarly, in suspected cases of IGDR- associated with anti-TNF, an infective etiology would need to be first excluded.

Table 1 Common culprit drugs for IGDR (Rosenbach and English 2015; Regula et al. 2008; Magro et al. 1998, 2010; Perret et al. 2017; Deng et al. 2006; Fujita et al. 2004; Marcollo Pini et al. 2008; Martínez-Morán et al. 2011; Du et al. 2012)

Calcium-channel blockers
Angiotensin-converting enzyme inhibitor
ß-blocker
Diuretics: Furosemide, hydrochlorothiazide
Lipid-lowering agents: Gemfibrozil, lovastatin, pravastatin
Histamine H_2-receptor antagonists: Ranitidine, famotidine
Anticonvulsants: Carbamazepine
Immune checkpoint inhibitors: Ipilimumab, pembrolizumab
Bupropion
Tricyclic antidepressants
Anti–tumor necrosis factor (TNF) agents: Infliximab, adalimumab, etanercept
Sennoside
Ganciclovir (intravenous)
Sorafenib
Strontium ranelate
Febuxostat, allopurinol
Anakinra
Trastuzumab
Darifenacin
Herbal medications

1.2 Drug-Induced Sarcoidosis

Drug-induced sarcoidosis presents as polymorphic cutaneous lesions on face, trunk or extremities, which appear weeks to months after drug intake (Shah et al. 2021). Grouped erythematous papules, indurated violaceous plaques, annular atrophic plaques, erythema nodosum-like lesions and ulceration are among the cutaneous features reported (Friedman and English 2018; Cathcart et al. 2012). Histological features comprise non-caseating, epithelioid histiocytic granulomas with multinucleated giant cells, and lack of extensive inflammatory infiltrate. Treatment involves discontinuing the culprit drug, and in some cases, systemic immunosuppressive therapy may be required (Reule and North 2013; Birnbaum et al. 2017). Common culprit drugs for drug-induced sarcoidosis is shown in Table 2 (Shah et al. 2021; Friedman and English 2018; Cathcart et al. 2012; Reule and North 2013; Birnbaum et al. 2017; Buss et al. 2013; Lheure et al. 2015).

Table 2 Common culprit drugs for sarcoidosis (Shah et al. 2021; Friedman and English 2018; Cathcart et al. 2012; Reule and North 2013; Birnbaum et al. 2017; Buss et al. 2013; Lheure et al. 2015)

Anti-TNFα agents: Etanercept, infliximab, adalimumab
Immune checkpoint inhibitors: Ipilimumab, nivolumab
Interferon-α
Anakinra
Natalizumab
Tocilizumab
Vemurafenib
Injectables: Botulinum toxin, desensitization injections, hyaluronic acid
Hydroquinone
Omalizumab
Ophthalmic drops containing sodium bisulfite
Zinc (component of insulin formulation)

1.3 Drug-Induced Granuloma Annulare (GA)

Clinical presentation of this reaction is similar to classical GA, with erythematous papules with an annular morphology, most commonly over extremities (dorsum of hands and fingers, forearms; legs and knees) (Voulgari et al. 2008; Lim et al. 2002; Guimaraes et al. 2020). While generalized type is the most common form of drug-induced GA, other forms such as localized, subcutaneous, perforating and patch forms can also occur. Histological features are similar to GA, with palisading granulomas, collagen degeneration, mucin and lymphohistiocytic infiltrate. Various drugs are reported to cause this reaction (Voulgari et al. 2008; Lim et al. 2002; Guimaraes et al. 2020; Dodiuk-Gad and Shear 2015; Carlos et al. 2014; Martin et al. 1990; Wu et al. 2018; Wolf et al. 1998) (Table 3). Cutaneous lesions appear as early as 13 days up to 14 months after initiation of the culprit drug, and resolution is seen 2 weeks up to 4 months after discontinuation of drug (Shah et al. 2021; Dodiuk-Gad and Shear 2015). Resolution of lesions with topical corticosteroid without discontinuation of the culprit drug has also been reported (Voulgari et al. 2008; Carlos et al. 2014).

Table 3 Common culprit drugs for granuloma annulare (Voulgari et al. 2008; Lim et al. 2002; Guimaraes et al. 2020; Dodiuk-Gad and Shear 2015; Carlos et al. 2014; Martin et al. 1990; Wu et al. 2018; Wolf et al. 1998)

Anti-TNF agents: Infliximab, adalimumab, etanercept
Amlodipine
Allopurinol
Anticonvulsants: Levetiracetam, Topiramate
Biologics: Secukinumab, tocilizumab
Diclofenac
Desensitization injections
Gold
Immune checkpoint inhibitors
Intranasal calcitonin
Immunizations (hepatitis B and anti-tetanus vaccination)
Paroxetine: Drug-induced photodistributed granuloma annulare
Pegylated interferon-alpha
Thalidomide
Vemurafenib

1.4 Drug-Induced Accelerated Rheumatoid Nodulosis

Connective tissue diseases such as rheumatoid arthritis (RA), psoriatic arthritis and systemic lupus erythematosus are associated with accelerated rheumatoid nodulosis. This reaction presents with multiple flesh-coloured to erythematous indurated papules and nodules, mainly affecting the hands (especially metacarpophalangeal and proximal interphalangeal joints) (Goerttler et al. 1999). Methotrexate (MTX) has been reported as the most common drug inducing this reaction, seen in 8–11% of RA patients (Kerstens et al. 1992). It tends to occur within 3 years of starting MTX, regresses in 6 months if the drug is promptly discontinued, and is not related to cumulative MTX dose (Ahmed et al. 2001). Other possible drugs include anti-TNF agents, aromatase inhibitors, azathioprine, leflunomide and tocilizumab (Dodiuk-Gad and Shear 2015; Talotta et al. 2018). The latency between initiation of drug and onset of reaction can be as short as hours, up to months (Dodiuk-Gad and Shear 2015). Systemic manifestation involving the lung, heart and brain is possible. The culprit drug should be discontinued if pain, ulceration, infection or interference with activities is present.

2 Drug-Induced Neutrophilic Reactions

Drug-induced neutrophilic dermatosis can be classified according to the level of the skin involved. Drug-induced Sweet's syndrome is the prototypic-induced neutrophilic reaction but other subtypes include drug-induced subcorneal pustulosis (due to thiol drugs, adalimumab), neutrophilic panniculitis (refer to drug-induced panniculitis) as well as neutrophilic eccrine hidradenitis which occurs typically after chemotherapy.

2.1 Drug-Induced Sweet's Syndrome

Sweet's syndrome is classified into classical/idiopathic, malignancy-associated and drug-induced subtypes. Drug-induced Sweet's syndrome makes up 1–26% of all Sweet's syndrome (Nelson et al. 2018). Walker and Cohen proposed five major diagnostic criteria for drug-induced Sweet's syndrome: abrupt onset of painful erythematous plaques or nodules; histological evidence of dense neutrophilic infiltrate without leucocytoclastic vasculitis; fever (>38 °C); a temporal relationship between the drug ingestion and clinical presentation, or temporally related recurrence after oral challenge; and a temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids (Walker and Cohen 1996).

The exact pathomechanism is unclear. However, it is suggested that drug-induced Sweet's syndrome could be a simple by-product of neutrophilic activation rather than a true drug-related hypersensitivity reaction. This histology of drug-induced Sweet's syndrome is similar to classical Sweet's syndrome, prominent oedema in the superficial dermis that may lead to subepidermal vesiculation, with dense neutrophilic infiltrate in the dermis.

Cutaneous manifestations includes erythematous tender papule, nodules or plaques, associated with fever. Vesicles, bullae and pustules may develop (Fig. 1). Oral mucosal involvement is present in up to 7% of patients (Martín et al. 2006). Extracutaneous findings such as conjunctivitis, glomerulonephritis, myositis and arthralgia have been reported (Thyssen and Maibach 2008). The interval between drug initiation and the onset of reaction range from days to months, with most cases developing within 2 weeks (Nelson et al. 2018). Common reported medications is shown in Table 4 (Nelson et al. 2018; Walker and Cohen 1996; Khan Durani and Jappe 2002; Draper et al. 2005; Zobniw et al. 2014; Yang et al. 2021; Sáez et al. 2004).

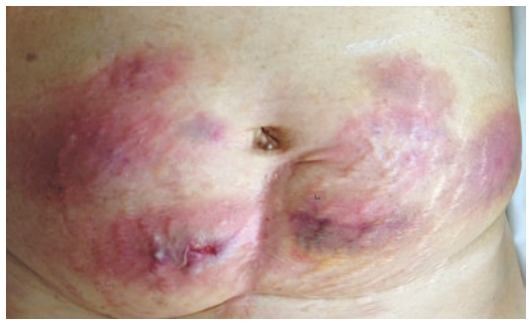

Fig. 1 Drug-induced Sweet's syndrome from azacitidine

Discontinuation of medications leads to resolution of the cutaneous lesions. Resolution typically occurs 1–3 weeks after drug withdrawal (Sáez et al. 2004). In instances when the culprit drug cannot be withdrawn, for example oncologic therapy, concurrent treatment with systemic corticosteroids can be considered (Yang et al. 2021).

3 Drug-Induced Pityriasis Rosea (PR)-like Reactions

Drug-induced PR-like eruption is an uncommon cutaneous adverse reaction, accounting for 2% of all cutaneous adverse reactions presenting at a drug surveillance centre (Atzori et al. 2006). Drug-induced PR-like eruptions present with

Table 4 Common culprit drugs for Sweet's syndrome (Nelson et al. 2018; Walker and Cohen 1996; Khan Durani and Jappe 2002; Draper et al. 2005; Zobniw et al. 2014; Yang et al. 2021; Sáez et al. 2004)

Antibiotics: tetracyclines, trimethoprim–sulfamethoxazole, nitrofurantoin
Anticonvulsants: lamotrigine, carbamazepine, diazepam
Anti-TNF agents: adalimumab
Azacitidine
All-*trans*-retinoic acid
Granulocyte-colony stimulating factor
Hydroxychloroquine
Hydralazine
Immune checkpoint inhibitors: ipilimumab
Mitoxantrone
Oral contraceptive: Ethinyl oestradiol, levonorgestrel
Proteasome inhibitor: bortezomib, ixazomib
Tyrosine kinase inhibitors: Imatinib, dasatinib, nilotinib, ibrutinib, ruxolitinib, vemurafenib, quizartinib, dabrafenib/trametinib, gliteritinib

dusky-erythematous papules or plaques with a collarette of scale and sometimes with desquamation (Fig. 2). As compared to typical PR, drug-induced PR can present with more confluent and diffuse lesions on the trunk, sometimes more extensively on the limbs, with facial involvement and excessive pruritus. The characteristic herald patch might be absent, and mucous membrane might be involved (Atzori et al. 2006; Drago et al. 2014a). In addition, typical PR lesions in the absence of prodromal symptoms should raise suspicion of drug-induced PR-like eruption.

The precise pathomechanism is unknown. There are reports that these reactions are dose dependent, suggesting that they may be due to the pharmacological effect of the medication (e.g. induction of increased levels of kinins by ACE inhibitors; inhibition of cyclo-oxygenase by NSAIDs) rather than a true hypersensitivity reaction (Atzori et al. 2006). Another possible mechanism is that the molecular mimicry with a viral epitope could result in a T-cell-mediated skin reaction (Drago et al. 2016). The histological features of such reactions are similar to classical PR, demonstrating parakeratosis and focal spongiosis with papillary dermal oedema and superficial perivascular infiltrate of lymphocytes. In contrast to classical PR eosinophils may be prominent. Necrotic keratinocytes within the epidermis, and signs of basal vacuolar degeneration may be present (Drago et al. 2014a).

The typical latency from drug initiation to onset of rash ranges from 5 days to 8 weeks (Drago et al. 2016) and the list of common culprit drugs are summarized in Table 5 (Atzori et al. 2006; Drago et al. 2014a, b, 2016).

Drug-induced PR-like eruptions may last more than 2 months or persist if the culprit drug is not withdrawn, and resolves within 1–2 weeks on drug withdrawal. In cases lacking response, topical corticosteroids may be useful.

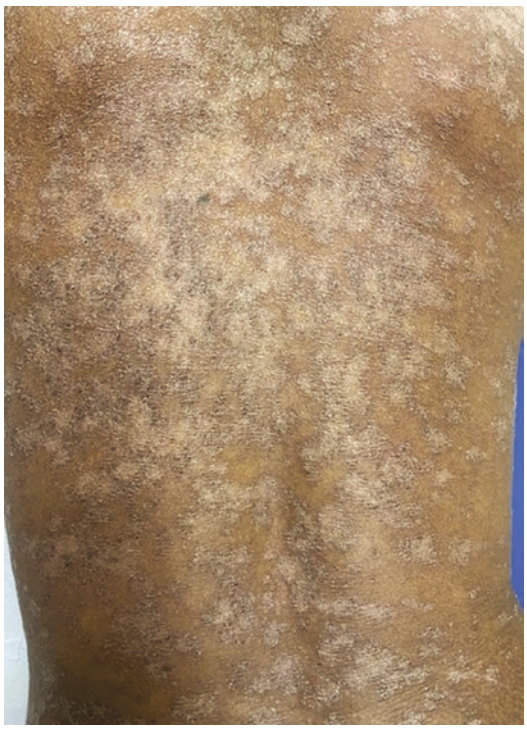

Fig. 2 Pityriasis-rosea like eruption following mRNA vaccination

4 Drug-Induced Panniculitis

4.1 Drug-Induced Erythema Nodosum

Erythema nodosum is the prototype septal panniculitis, and may be due to a range of triggers

Table 5 Common culprit drugs for Pityriasis Rosea-like reactions (Atzori et al. 2006; Drago et al. 2014a, b, 2016)

Angiotensin-converting enzyme inhibitors
Non-steroidal anti-inflammatory drugs
Terbinafine
Isotretinoin
Imatinib
Gold
Omeprazole
Metronidazole
Asenapine
Lamotrigine
Clozapine
Barbiturate
Allopurinol
Ergotamine
Nortriptyline
Rituximab
Interferon 2α
Anti-tumour necrosis factor agents
Vaccinations

including infections and drugs. The most common drug triggers are summarized in Table 6 and include oral contraceptives, hormonal replacement therapy, sulphonamides and penicillins (Requena and Yus 2008; García-Porrúa et al. 2000; Halevy et al. 2004; González-Olivares et al. 2017; De Fonclare et al. 2007; Tan et al. 1997; Bhalla et al. 2007). While the estimated incidence of erythema nodosum is between 1 and 5 cases per 100,000 persons each year, approximately 3–15% of these cases can be attributed to drugs (Requena and Yus 2008).

Drug-induced erythema nodosum is thought to a type IV delayed hypersensitivity reaction to drug antigens (García-Porrúa et al. 2000). Histological examination of erythema nodosum lesions shows oedematous septa with lymphocytic (particularly neutrophilic) infiltrates and Miescher granulomas in early lesions and widened, fibrotic septa, granulomas, multinucleated giant cells and perivascular lymphocytic infiltrates in older lesions.

Clinical Features

Latency from drug initiation to onset of erythema nodosum is usually a few weeks.

Table 6 Common culprit drugs for erythema nodosum (Requena and Yus 2008; García-Porrúa et al. 2000; Halevy et al. 2004; González-Olivares et al. 2017; De Fonclare et al. 2007; Tan et al. 1997; Bhalla et al. 2007)

Oral contraceptive pills
Hormonal replacement therapy
Sulphonamides
Penicillin
Azathioprine
Minocycline
Ciprofloxacin
Non-steroidal anti-inflammatory drugs
Gold
Benzodiazepines
Barbiturates
Isotretinoin
Montelukast
Vaccinations (hepatitis, human papillomavirus, rabies)
Aromatase inhibitors
Granulocyte colony-stimulating factor
Complementary medications

Presents as tender erythematous symmetrically distributed subcutaneous nodules, classically over the shins, but may also involve the forearms. Cases of EN presenting as a hypersensitivity reaction to Azathioprine are associated with systemic signs and symptoms such as fever, malaise, joint pain, and loss of appetite (González-Olivares et al. 2017; De Fonclare et al. 2007). Upon drug withdrawal, the disease course generally resolves within 2–4 weeks (Tan et al. 1997; Bhalla et al. 2007). Management involves the withdrawal of the culprit drug, with symptomatic treatment thereafter. NSAIDs and compression stockings may be used to treat pain and inflammation.

4.2 Drug-Induced (Primarily Lobular) Neutrophilic Panniculitis

Introduction

Neutrophilic panniculitis is a subset of neutrophilic dermatoses featuring an infiltrate of neutrophils predominantly in the subcutaneous tissue. Neutrophilic panniculitis may be due to several causes including alpha-1 antitrypsin deficiency, pancreatic panniculitis, neutrophilic pustular panniculitis associated with connective tissue disease and factitial panniculitis (Chan 2014). In rare cases, it is triggered by medications such as chemotherapy agents and targeted molecular therapies (Vázquez-Osorio et al. 2016).

Common implicated drugs include DNA methyltransferase inhibitors such as azacitadine (Coleman et al. 2019), guadecitabine (Coleman et al. 2019); Tyrosine kinase inhibitors [Ibrutinib (Stewart et al. 2018)] and BRAF inhibitors (Mössner et al. 2015) [Vemurafenib (Wu et al. 2018), Dabrafenib].

Drug-induced neutrophilic panniculitis may be primarily lobular, septal (see section "Drug-Induced Erythema Nodosum") or mixed (Carlos et al. 2014).

Pathophysiology

Since neutrophilic panniculitis has been associated with drugs that promote myeloid differen-

tiation such DNA methyltransferase inhibitors and FMS-like tyrosine kinase 3 (FLT-3) inhibitors, it has been postulated that terminal differentiation may contribute to neutrophilic infiltration of the skin. Histologically, there is an inflammatory infiltrate of predominantly neutrophils, localized to either the fat lobules, septae or both, depending on the type of neutrophilic panniculitis.

Clinical Features

The lesions of drug-induced neutrophilic panniculitis are tender subcutaneous nodules on the limbs (Fig. 3). This may be associated with fever and joint pain (Mössner et al. 2015). Biopsy is required to distinguish neutrophilic panniculitis from other forms of panniculitis.

Upon withdrawal of the culprit drug, resolution typically occurs within 3–4 weeks. The use of systemic corticosteroids may hasten resolution (Coleman et al. 2019). In cases where the continual treatment with the culprit drug is required, the concurrent use of topical and systemic corticosteroids may promote resolution (Mössner et al. 2015).

5 Drug-Induced Eczematous Reactions

Drug-induced eczematous reactions are a heterogenous group of drug reactions. It varies in extent and severity from discrete eczematous scaly papules and plaques to erythroderma (Fig. 4). A long list of drugs have been implicated and summarized in Table 7 (Joly et al. 2007; Summers et al. 2013; Thyssen and Maibach 2008). Among these drugs, calcium channel blockers have been shown to be of higher risk particularly in the elderly as shown in two recent case-control studies (Joly et al. 2007; Summers et al. 2013). In addition, an eczematous reaction pattern can be observed in drug-induced photodermatitis and systemic contact dermatitis to medications (Thyssen and Maibach 2008). In addition, extensive eczematous lesions/erythroderma can be a presentation of drug reaction with eosinophilia and systemic symptoms (DRESS) (Kardaun et al. 2013).

The pathogenesis of drug-induce eczematous reactions is believed to be driven by drug-specific T cells. In cases of systemic contact dermatitis, it is believed that in a patient who is previously sensitized to a contact allergen, systemic exposure of the same drug/structurally similar drug would result in an eczematous reaction (Thyssen and Maibach 2008; Gruen et al. 2001). Such a mechanism would explain a subset of patients, for example patients with contact allergies to P amino compounds such as p-phenylenediamine hair dyes, para-aminobenzoic acid (PABA) sunscreens developing eczem-

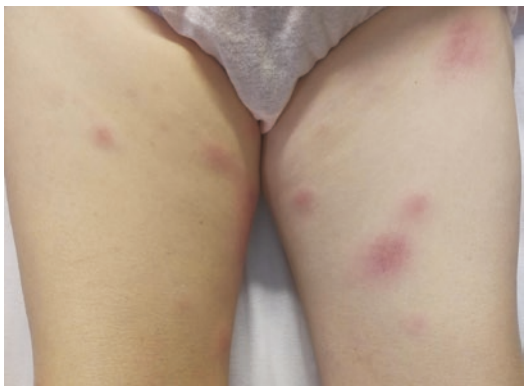

Fig. 3 Neutrophilic lobular panniculitis from azacitidine

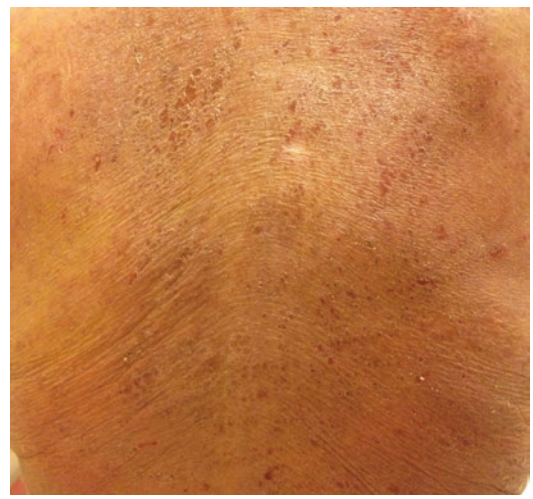

Fig. 4 Imatinib-induced eczematous drug reaction resulting in erythroderma

Table 7 Common culprit drugs for eczematous reactions (Joly et al. 2007; Summers et al. 2013; Thyssen and Maibach 2008)

8-Methoxypsoralen
Alpha-blockers
5-Aminosalicylic acid
Aminophylline
Analgesics: non-steroidal anti-inflammatory drugs, opiates, paracetamol
Antibiotics: amoxicillin, ceftriaxone, chloramphenicol, clindamycin, erythromycin, fusidic acid, gentamicin, isoniazid, miconazole, neomycin, nystatin, quinolones, streptomycin, sulfamethoxazole-trimethoprim, terbinafine
Antihistamines: cetirizine, diphenhydramine, hydroxyzine
Antihypertensives: alprenolol, captopril, telmisartan, hydrochlorothiazide
Anti-inflammatories: acetyl salicylic acid, 5-aminosalicylic acid, corticosteroids, cyclo-oxygenase-2 inhibitors
Antivirals: aciclovir, valaciclovir
Biological agents: cetuximab
Calcium-channel blockers
Chemotherapy agents: 5-fluorouracil, mitomycin C
Clobazam
Clonidine
Doxepin
Ephedrine
Glyceryl trinitrate
Heparin
Hydroxycarbamide
Intravenous human immunoglobulins
Iodinated radiocontrast media
Oestradiol
Phenobarbital
Phenothiazines
Pseudoephedrine
Rivastigmine
Sulphonamides
Suxamethonium

atous reactions on exposure to tolbutamide or chlorpropamide. However, in many cases of suspected drug-induced eczematous reactions, prior sensitization to the index drug or cross-reacting compounds cannot be found. In cases related to calcium channel blockers, nifedipine in its photodegraded form has been shown to stimulate iron uptake and retention in human epidermal keratinocytes (Gruen et al. 2001). This may induce keratinocyte apoptosis and spongiosis, resulting in the histological findings of spongiosis and keratinocyte necrosis seen in such patients, and accounting for the long delay in recovery following drug withdrawal (Trautmann et al. 2001).

The latency from time of drug initiation to onset of eczematous eruption is typically 1–2 weeks. It is usually a symmetrical eruption which may initially/most severely involve the sites of original dermatitis prior to subsequently becoming generalized.

The differential diagnosis of drug-induced eczematous reactions include allergic contact dermatitis, irritant contact dermatitis and idiopathic eczematous reactions. Patch testing may be positive; however, confirmatory diagnosis may require oral challenge, and response to de-challenge. Resolution of clinical symptoms within 1–3 weeks of drug withdrawal.

Withdrawal of the culprit drug, with the use of topical corticosteroids if necessary. Severe reactions may require treatment with systemic corticosteroids.

6 Drug-Induced Acneiform Eruptions (Drug-Induced Acne)

Drug-induced acneiform eruptions refer to inflammatory follicular reactions resembling acne vulgaris, induced by a medication. Acneiform eruptions constitute 1% of all drug-induced skin reactions (Valeyrie-Allanore et al. 2007).

Acneiform reactions are not hypersensitivity reactions. The specific pathological mechanisms vary according to the implicated drug. The pathophysiology of acne vulgaris involves the use of toll-like receptor 2 (TLR-2) by *Propionibacterium acnes* to facilitate inflammation. Keratinocytes treated with glucocorticoids were reported to have up-regulation of TLR-2, a possible mechanism that explains why corticosteroid-associated acne consists of predominantly inflammatory

lesions of papules and pustules (Shibata et al. 2009). Androgenic hormones lead to acneiform eruptions by stimulating keratinocyte production, promoting sebaceous gland hyperplasia and increasing sebum production (Melnik et al. 2007; Scott and Scott 1992). In EGFR-inhibitor related reactions, the EGFR pathway which plays a key role in keratinocyte proliferation, differentiation, migration and survival is directly inhibited. In concert, an inflammatory response ensues resulting in the characteristic acneiform reaction (Lacouture 2006).

The histological features of drug-induced acneiform reactions vary according to the underlying drug. Initial lesions of steroid-induced acne demonstrate features of focal necrosis in the infundibulum of the follicular epithelial, with a localized intrafollicular and perifollicular neutrophilic inflammatory reaction (Fung and Berger 2000). In contrast, acneiform eruptions associated with EGFR show ectatic follicular infundibula with rupture of the epithelial lining associated with superficial neutrophilic folliculitis (Lacouture 2006).

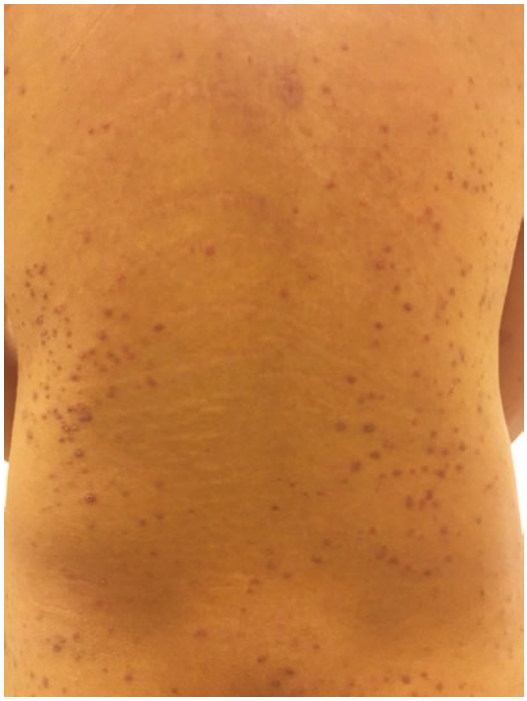

Fig. 5 Steroid-induced acneiform eruption

Features that suggest drug-induced acne include a monomorphic pattern, unusual age of onset, sudden/abrupt new onset acne, distribution beyond seborrheic regions, poor response to conventional acne treatment and the context of recent drug initiation (Fung and Berger 2000) (Fig. 5). The latency period between initiation of the drug and onset of acne depends on the type of drug, with latencies ranging from 1 month or less in systemic corticosteroids, androgens and vitamin B) to greater than 1 month in ciclosporin, lithium, antiepileptics and anti-tuberculosis agents.

Drug-induced acneiform reactions present with monomorphic papules and pustules, typically lacking comedones and cysts. Of note, they may extend beyond seborrheic areas such as the arms, lower back and genitalia. Acneiform eruptions induced by EGFR inhibitors is generally distributed in the seborrheic areas (i.e. neck, chest, shoulders, upper back) (Lacouture 2006).

The list of drug triggers for acneiform eruptions is summarized in Table 8 (Valeyrie-Allanore et al. 2007; Shibata et al. 2009; Melnik et al. 2007; Scott and Scott 1992; Lacouture 2006; Fung and Berger 2000; Brodell et al. 2013; Bencini et al. 1986; Grunwald et al. 1990; Martín et al. 2006).

Acne vulgaris, gram-negative folliculitis, *Pityrosporum* folliculitis.

Drug-induced acneiform eruptions generally improve once the offending drug is withdrawn. Additionally, standard systemic and topical acne medications may be used.

Table 8 Common culprit drugs acneiform eruptions (Valeyrie-Allanore et al. 2007; Shibata et al. 2009; Melnik et al. 2007; Scott and Scott 1992; Lacouture 2006; Fung and Berger 2000; Brodell et al. 2013; Bencini et al. 1986; Grunwald et al. 1990; Martín et al. 2006)

Hormones
Corticosteroids
Androgens and anabolic steroids
Hormonal contraceptives
Danazol
Neuropsychiatric drugs
Tricyclic antidepressants
Lithium
Valproate
Phenytoin
Dantrolene
Aripiprazole
Selective serotonin reuptake inhibitors
Vitamins
Vitamins B1, B6, B12
Immunomodulators
Ciclosporin
Sirolimus
Azathioprine
Chemotherapeutic agents
Dactinomycin
Thiourea, thiouracil
Epidermal growth factor receptors inhibitors
Multikinase inhibitors: imatinib
Histone deacetylase inhibitor: vorinostat
Halogens
Iodine
Bromine
Chlorine
Antituberculosis drugs
Isoniazid
Rifampicin
Ethionamide
Miscellaneous
Granulocyte colony-stimulating factor
Dantrolene
Targeted therapies
EGF inhibitors (cetuximab, panitumumab)
Multitargeted tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, imatinib, sorafenib, sunitinib)
VEGF inhibitor (bevacizumab)
Proteasome inhibitor (bortezomib)
TNF-alpha inhibitors (lenalidomide, infliximab)
Histone deacetylase inhibitor (vorinostat)

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Drug-Induced Photosensitivity

Sally H. Ibbotson

1 Introduction

Abnormal photosensitivity may occur when skin photosensitised by a drug or chemical is exposed to light, generally ultraviolet radiation. Typically, drug-induced photosensitivity presents as an exaggerated sunburn-like reaction, or as a rash on exposed skin. Most prescribed medications absorb ultraviolet and/or visible light and can theoretically cause photosensitivity. However in clinical practice drug-induced photosensitivity is caused by a relatively limited number of medications. The interaction of exogenous chemical and UV radiation can also be used therapeutically, for example in psoralen-UVA photochemotherapy (PUVA) and photodynamic therapy (PDT) (Ling et al. 2016; Wong et al. 2019).

2 Epidemiology

The prevalence of drug photosensitivity in the general population is unknown and is likely to be under-reported as affected subjects are likely to stop a suspected drug without seeking a medical consultation. In one report of cutaneous adverse drug reactions, photosensitivity was the third commonest reaction type in a series of 118 subjects (Chaabane et al. 2013). In specialist photodiagnostic units systemic drug-induced photosensitivity generally accounts for 2–15% of diagnosed photosensitivity diseases (Kerr and Lim 2007; Khoo et al. 1996; Stratigos et al. 2003; Wong and Khoo 2005; Wadhwani et al. 2013) and our own experience in the Scottish Photobiology Service is similar, with drug-induced photosensitivity representing 4% of photodermatoses and photocontact allergic dermatitis to topical drugs or chemicals being an additional 2% (Ibbotson 2018).

Not all individuals exposed to photoactive drug and light will be affected; it is likely that genetic factors influence susceptibility to drug-induced photosensitivity (Ferguson and Johnson 1990). Drug photosensitivity has been reported more commonly in Caucasians than in African-Americans, possibly suggesting a protective effect of constitutive skin pigmentation (Nakamura et al. 2014). There may be susceptibility in specific patient groups, a notion suggested by the relatively high incidence of drug-induced photosensitivity in patients with cystic fibrosis (Tolland et al. 2012).

3 Pathogenesis

The clinical pattern of presentation of drug-induced photosensitivity will depend on whether the drug is delivered systemically or topically,

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Table 1 Characteristics of phototoxicity versus photoallergy

Phototoxicity	Photoallergy
Common	Uncommon
Non-immunological	Immunological (Type IV cell-mediated)
No sensitisation needed	Sensitisation essential
Can occur on first exposure	Not on first exposure
May be immediate onset	Delayed onset
Dose-dependency	Not dose-dependent (can occur with exposure to minute amounts of photoallergen)
Occurs at site of drug/chemical + light	Can extend beyond sites of drug/chemical + light—Can generalise
Often exaggerated sunburn, erythema, oedema	Usually dermatitis
Histopathology: Necrotic keratinocytes, minimal inflammation	Histopathology: Spongiotic dermatitis with eosinophils
Further episodes unlikely	Further episodes likely
Usually systemic route	Usually topical route
Can be used in a controlled way therapeutically, e.g. PUVA + PDT	Not used therapeutically

and on the pathogenetic mechanisms involved in disease expression. Most drug-induced photosensitivity to systemically administered medications occurs through phototoxicity (Ferguson 2002) (Table 1). This is a non-immunological event, which can occur in any individual exposed to enough drug (or photoactive chemical) and irradiated with enough light of the appropriate wavelengths. The process will occur on first exposure to drug + light and demonstrates a dose-dependent relationship (Layton and Cunliffe 1993). The general pathogenetic principles centre on photochemical activation of tissue-localised drug by ultraviolet and/or visible light, resulting in excitation and production of oxidative stress, free radicals and photoproducts. The resulting substrate effects manifest in the skin as phototoxicity. Photoallergy (as opposed to phototoxicity) to systemic drugs is less common and is poorly understood pathogenetically (Ohshima et al. 2000). However, the mechanisms behind *topical* photocontact allergy are clearer. Incident light interacts with the topically applied drug inducing a chemical alteration in that drug which subsequently becomes allergenic. This photoallergen can thereafter elicit a delayed cell-mediated hypersensitivity reaction (Table 1). On subsequent re-exposure to drug + light, a hypersensitivity reaction occurs in involved skin, which manifests as dermatitis. In clinical practice, topical photocontact allergy is encountered most frequently to absorbent sunscreen chemicals and to topical NSAIDs. Following initial sensitisation to both drug and light, a reaction may occur to tiny amounts of photoallergen (Kochevar and Harber 1977). Once a photocontact allergy reaction has been initiated dermatitis can spread beyond the sites of exposure.

Topical phototoxicity may occur following contact with psoralen-containing plants and sunlight exposure, as with phytophotodermatitis, or can be used in a controlled way in PUVA (Ling et al. 2016). Other presentations, such as pseudoporphyria, drug-induced lupus erythematosus, erythema multiforme, lichenoid reactions and pellagra, are less common mechanisms of drug-induced photosensitivity.

4 Systemic Drug Phototoxicity and Common Culprits

Photosensitivity has been reported in association with a diverse range of drugs; however there is a collection of medicines, which feature most frequently (Table 2) (Ibbotson 2018; Glatz and Hofbauer 2012; Drucker and Rosen 2011; Bakkour et al. 2013; Kim et al. 2018; Blakely et al. 2019; Dawe and Ibbotson 2014). In our own experience, in the Scottish Photobiology Service, thiazides are the most commonly documented drug photosensitisers along with doxycycline, demeclocycline, ciprofloxacin, retinoids, furosemide, NSAIDs, quinine, amiodarone, allopurinol, calcium antagonists and chlorpromazine.

Table 2 Examples of phototoxic drugs

Psoralens	
Diuretics and cardiovascular drugs	Thiazides, furosemide, amiodarone, calcium channel antagonists, quinidine, statins
Antibiotics	Doxycycline, demeclocycline, fluoroquinolones, nalidixic acid, sulphonamides
Antifungals	Voriconazole, griseofulvin
Antipsychotics	Phenothiazines, protriptyline
Retinoids	Acitretin, isotretinoin, alitretinoin
Quinine	
Non-steroidal anti-inflammatory drugs	Diclofenac, naproxen
Hypoglycaemics	Sulphonylureas
Porphyrins	
Azathioprine	
BRAF inhibitors	
EGFR inhibitors	
Pirfenidone	

5 Clinical Presentation of Drug Photosensitivity

There is diversity in clinical presentation of drug-induced phototoxicity (Table 3). One of the more usual presentations is of an immediate 'prickling' sensation on light exposure, a symptom which is common with chlorpromazine and amiodarone. Another typical clinical feature is an erythema of exposed skin, often with an 'exaggerated sunburn' phenotype. This reaction occurs with quinine, thiazides, doxycycline and demeclocycline (Fig. 1). Urticaria may also be a presenting sign of drug-induced phototoxicity. Phototoxicity due to the calcium channel antagonists may be evident as photo-exposed site telangiectasiae (Bakkour et al. 2013; Collins and Ferguson 1993; Cooper and Wojnarowska 2003). Pigmentation may also occur as a sequel to phototoxicity, particularly with drugs such as chlorpromazine and amiodarone. Fluoroquinolone phototoxicity may induce melanin pigmentation which can persist for a year or more. Quinine and thiazide phototoxicity may be associated with leucoderma (Masuoka et al. 2011; Lecleach et al. 1995; Beberok et al. 2017). Photo-exposed site skin fragility can be caused by drug photo-

Table 3 Patterns of clinical presentation of drug photosensitivity and examples of culprit drugs

Immediate burning/prickling	Amiodarone, chlorpromazine, porphyrins
Immediate erythema/urticaria	Amiodarone, chlorpromazine, porphyrins
'Exaggerated sunburn' (Fig. 1)	Thiazides, quinine, demeclocycline, doxycycline, voriconazole, fluoroquinolones, chlorpromazine, amiodarone
Delayed erythema	Psoralens
Sun-exposed site telangiectasia	Calcium channel antagonists
Dermatitis	Thiazides
Pseudoporphyria	NSAIDS, fluoroquinolones, doxycycline, retinoids, amiodarone, furosemide, voriconazole, nalidixic acid
Lichenoid	Thiazides, quinine
Altered pigmentation	Chlorpromazine, fluoroquinolones, quinine, thiazides, amiodarone, psoralens
Photo-onycholysis	Doxycycline, psoralens, NSAIDs
Lupus	Thiazides, proton pump inhibitors

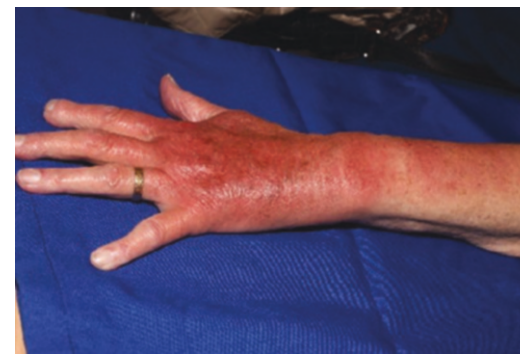

Fig. 1 Drug-induced phototoxicity. 'Exaggerated sunburn' reaction from demeclocycline phototoxicity. Note the sparing of flexed photo-protected distal phalanges and under the watch strap

toxicity and, since it mimics porphyria cutanea tarda, is referred to as pseudoporphyria. The drugs associated with pseudoporphyria include furosemide, NSAIDs (such as diclofenac or naproxen), doxycycline, demeclocycline, fluoroquinolones, oral contraceptives and retinoids. Pseudoporphyria can also be caused by haemodialysis and excess use of sunbeds (Gould et al. 1995; Khandpur et al. 2017; Al-Khenaizan et al. 1999).

Certain drugs, such as psoralens, produce a delayed erythema which peaks at 3 or 4 days after exposure. This temporal relationship contrasts with typical sunburn, which peaks at 12–24 h post-exposure.

The fluoroquinolones are a drug group of particular interest since some are highly phototoxic, particularly in the longer UVA range and visible parts of the spectrum. The fluoroquinolone reaction is usually rapid in onset, with reversibility of phototoxicity occurring within 48 h of stopping the drug (Ferguson and Johnson 1990, 1993; Traynor et al. 2000; Ferguson and Dawe 1997; Oliveira et al. 2000; Kimura et al. 1996; Leone et al. 2003). However, there is wide variation in phototoxicity within this drug class, depending on molecular structure (Ibbotson 2018; Ferguson 2002; Dawe et al. 2018). These drugs are also photogenotoxic, photomutagenic and photocarcinogenic following single dose exposure in animals (Johnson et al. 1997), although there is no convincing evidence of skin cancer risk with fluoroquinolone use in humans.

6 Wavelength Dependency

The absorption spectra of photosensitising drugs, or their photoactive metabolites, indicate that the action spectrum for most drug phototoxicity lies in the UVA part of the electromagnetic spectrum. A history of the clinical reaction occurring with wintertime daylight exposure or with light passing through windows also implicates the role of UVA. Some drugs, such as benoxaprofen, amiodarone, fluoroquinolones, quinine and porphyrins (used in PDT), also photosensitise into the visible part of the spectrum. Although the vast majority of drug-induced photosensitivity reactions are UVA-mediated, a minority of drugs including thiazides, quinine, NSAIDs and retinoids can also photosensitise in the UVB region (Ibbotson 2018).

7 Investigations for Drug-Induced Phototoxicity

If the possibility of drug photosensitivity is considered from the patient's history then clinical examination may yield relevant cutaneous signs. Thereafter the gold standard investigation is monochromator phototesting, undertaken whilst the patient is on the suspected drug (MacKenzie and Frain-Bell 1973). Monochromator light testing will usually show disproportionate UVA photosensitivity, sometimes extending into UVB and/or visible wavelengths (Ibbotson 2018; O'Reilly et al. 1999). Phototesting is also used to distinguish drug-induced photosensitivity from other photodermatoses, in particular chronic actinic dermatitis (CAD) in which UVB sensitivity predominates.

Monochromator phototesting involves the use of a filtered xenon arc lamp, coupled to a monochromator and fibre optic light guide (MacKenzie and Frain-Bell 1973). This enables narrow waveband testing across the solar spectrum to establish, firstly, if there is abnormal photosensitivity and, secondly, which wavebands are involved. The responses are evaluated immediately after irradiation (occasionally phototoxic drugs cause an urticarial reaction on phototesting) and at 24 h after testing. At the phototest readings the minimal erythema dose (MED) at each waveband is determined. It is important that a normal population range for MEDs is available for comparison (Moseley et al. 2009). Solar simulator phototesting may also be of benefit as this allows phototesting to broader wavebands. The solar simulator is not, however, an exact mimic of sunlight since the output has a UVB weighting. Drug-induced UVA sensitivity can be missed if only solar simulator phototesting is undertaken, although the output of the solar simulator can be filtered to deliver light without UVB.

If photosensitivity is confirmed, phototesting should then be repeated once the culprit agent has been discontinued, since drug-induced phototoxicity is reversible. The interval until repeat phototesting will depend on the drug implicated: fluoroquinolone phototoxicity resolves in 24–48 h, whereas thiazide phototoxicity may take 3–6 months and quinine and amiodarone almost a year to settle once the drug is stopped (Ibbotson 2018). Photopatch testing is not a reliable investigation for systemic drug photosensitivity and should be restricted to the investigation of suspected topical photoallergy (Kerr and Ferguson 2010; Kerr et al. 2010, 2012; Gonçalo et al. 2013). Some drugs may cause abnormali-

ties in endogenous porphyrins (Gelot et al. 2013; Woods et al. 2015) or may cause photosensitivity through a lupus erythematosus mechanism. Analysis of plasma porphyrin levels and spectrofluorimetry may be necessary, along with antinuclear antibody, extractable nuclear antigens and anti-histone antibodies.

8 Regulatory Requirements for Photosafety Evaluation

Photosafety investigations are required by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for any drug that absorbs light between 290 and 700 nm (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s10-photosafety-evaluation-pharmaceuticals). Initial in vitro testing using the neutral red phototoxicity assay should be undertaken and, if there is a positive signal for phototoxicity, animal phototoxicity studies should be undertaken. Thereafter, if phototoxicity is confirmed, human photosafety investigations in healthy volunteers should be considered (Dawe et al. 2018, 2003). A negative human study would then supersede pre-clinical data. It is important that knowledge of drug phototoxicity is established prior to drugs going to market to minimise the risk of significant phototoxicity being detected during post-marketing surveillance (Morgado et al. 2019; Yin et al. 2019; Tashkent and Aiyappan 2018). A healthy volunteer study may be undertaken as part of photosafety evaluation using a randomised, controlled, assessor-blinded, clinical trial design with positive and negative controls (Dawe et al. 2018, 2003). Ciprofloxacin may be used as a positive control and phototesting performed with monochromator and solar simulator at baseline and on steady state of drug. If phototoxicity is established, as determined by phototoxic index (the baseline minimal erythema dose pre-drug as a ratio of the MED on steady state of drug) then phototesting should be repeated at intervals in order to establish how long phototoxicity persists. These photosafety evaluations have enabled accurate objective data to be established for many potential drug culprits, such as the fluoroquinolones. Interestingly, whilst the molecular structure of fluoroquinolones influences phototoxic potential, there also seems to be variability within subjects (as seen with ciprofloxacin) indicating that genetic polymorphisms in drug metabolism may be involved in phototoxicity (Ferguson and Johnson 1990; Dawe et al. 2018, 2003). Whilst there does appear to be reasonable correlation between in vitro and in vivo phototoxicity testing with fluoroquinolones, human volunteer testing is still not able to predict or rule out rare idiosyncratic phototoxic reactions.

9 Topical Photoallergy

Photocontact allergy to topically applied drug or chemical is well documented. Initial reports in the 1960s of topical photocontact allergy to halogenated salicylanilides emerged following an outbreak of photoallergic dermatitis caused by use of soaps containing tetrachlorosalicylanilide (Wilkinson 1962). In current times, the absorbent sunscreen chemicals and topical NSAIDs are the most common culprits for topical photoallergy. The investigation of choice in topical photocontact allergy is photopatch testing. At present, a standard European photopatch test methodology is established, although ongoing review is underway (Kerr et al. 2012; Gonçalo et al. 2013). This involves application of duplicate series of allergens to the back, as in patch testing, with one set being irradiated using a sub-erythemal UVA dose (generally 5 J/cm^2) at either 24 or 48 h after application of the patches, and readings undertaken at intervals following irradiation. Forty-eight hours is the key reading point after irradiation, although some centres also read at 24 h and 72 h. A positive reaction on the irradiated site and a negative response on the control site signify a photoallergic reaction. Reactions on both irradiated and control sites generally indicate contact allergy.

10 Other Possible Effects of Drug Photosensitivity

There are other potential consequences of drug photosensitivity, which include the theoretical possibility of retinal toxicity with visible light photosensitising drugs. A cancer risk must be also considered: psoralens, azathioprine, and voriconazole are photocarcinogenic in humans; fluoroquinolones have been shown to be photocarcinogenic in an animal model, although not in humans; vemurafenib is a drug associated with both phototoxicity and increased risk of squamous cell carcinoma (reviewed in 9 and 53). Epidemiological data regarding photocarcinogenic risks of photoactive drugs raise suspicion that drugs such as thiazides and photosensitising antibiotics may be implicated. It is quite likely that there will be individual genetic factors which will influence photocarcinogenic susceptibility, but this needs further investigation (Ibbotson 2018; O'Gorman and Murphy 2014; de Vries et al. 2012).

11 Management

Accurate diagnosis is the key to successful management since identifying the culprit drug and stopping it will reverse drug-induced phototoxicity. Happily, non-phototoxic drug alternatives usually exist and can be used in most clinical settings. Sensible measures of photoprotection are recommended, with reliance on behavioural modification. Seeking the shade, wearing a wide-brimmed hat, using photoprotective clothing, and applying high factor broad-spectrum sunscreen are all advised until resolution of photosensitivity has occurred. If a drug cannot be stopped and there is no alternative, as may be the case for example with amiodarone, narrowband UVB phototherapy may induce 'hardening' and offer some protection (Collins and Ferguson 1995).

12 Practical Advice

Patients referred for phototherapy for indications such as psoriasis or eczema are often taking photoactive drugs. Most of these drugs are not associated with lowering of the MED for narrowband UVB (NB UVB). The exceptions are NSAIDs, calcium channel antagonists and phenothiazines which can lower the NB UVB MED (Cameron and Dawe 2000). With other photoactive drugs there is an increased risk of developing significant erythemal episodes during NB UVB phototherapy, despite normal baseline MEDs. Care is therefore required with dose increments in all patients taking a photoactive drug (Harrop et al. 2018). If PUVA is being delivered, psoralen photosensitisation generally overwhelms the phototoxicity of any other drug, although awareness of increased risk of erythema is needed and lower incremental dose regimens are advised (Stern et al. 1980). Particular caution is required with UVA1 given that this is the maximal waveband for absorption of most photoactive drugs (Beattie et al. 2005).

In the clinical setting, many factors need to be considered: drug, dosage, duration, indication, type of phototherapy and skin phototype. It may be possible to stop phototherapy temporarily, e.g. during a 1-week course of a phototoxic antibiotic, or to use an evening drug dose administration for medications with short half-lives. It would not be advisable to combine phototherapy with drugs such as voriconazole or azathioprine because of the cancer risk. For most drugs, phototherapy is not contraindicated. However, it is important to have an awareness of baseline drugs and to note the addition of any new medication during the course of phototherapy.

13 Conclusions

Drug-induced photosensitivity is relatively common. Careful assessment is essential since there is diversity in clinical presentation. Once the diagnosis has been established the causative drug needs to be identified and stopped. Investigations are key, both diagnostically and for drug photosafety evaluation and regulatory requirements. Controlled phototoxicity is widely used therapeutically, and these photochemical reactions reflect beneficial aspects of drug-light interactions. However, uncertainty remains regarding the potential long-term adverse effects of drug photosensitivity, particularly with respect to skin cancer risk.

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Drug-Induced Pruritus Without Primary Rash

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Abbreviations

5-HT	5-Hydroxytryptophan
ACE	Angiotensin-converting enzyme
EGFR	Epidermal growth factor receptor
EGFRI	Epidermal growth factor receptor inhibitor
GPCR	G-protein-coupled receptor
GRPR	Gastrin-releasing peptide receptor
HES	Hydroxyethyl starch
IL	Interleukin
KOR	Kappa opioid receptor
LPA	Lysophosphatidic acid
MOR	Mu-opioid receptor
Mrgpr	Mas-related G-protein-coupled receptor

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1 Definition

Drugs may induce pruritus as a concomitant symptom of a drug-induced skin reaction, or as a form of pure itch without coexisting skin lesions. Drug-induced pruritus is defined as the latter, in which administration of a drug results in an itchy response unaccompanied by any cutaneous manifestation. In 2007, the International Forum on the Study of Itch classified pruritus into three clinical groups of patients (Ständer et al. 2007). In Group I, pruritus exists on diseased skin, in Group II, pruritus exists on non-diseased skin, and in Group III, pruritus presents with severe secondary scratch lesions. Patients who exhibit drug-induced pruritus may fall into the clinical category of Group II or III, in which itching occurs without preexisting skin lesions. Skin lesions may only result secondarily as a consequence of debilitating itch causing chronic scratching, and thus it may be challenging to differentiate between a drug eruption and secondary cutaneous lesions induced by scratching of the itchy skin.

2 Overall Prevalence

Drug-induced pruritus is likely to be underestimated in the general population, and it would be nearly impossible to list every drug that may induce itching (Cassano et al. 2010). In a report

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from the Boston Collaborative Drug Surveillance which followed over 15,000 patients from the years 1975 to 1982, it was shown that among hospitalized patients, pruritus without concomitant skin lesions accounted for about 5% of adverse reactions after drug intake (Bigby et al. 1986). In 1998, a study on skin reactions secondary to antibacterial agents used in over 13,000 patients showed that general pruritus accounted for 13.3% of adverse events reported (Van der Linden et al. 1998). In an analysis of 200 patients with drug reactions done in 2008, 12.3% of patients exhibited itch without lesions (Raksha and Marfatia 2008). Finally, in 2019, the Johns Hopkins Health electronic medical record system was used to identify patients who developed pruritus within 3 months of drug initiation. Of the patients that were studied, 9802 developed pruritus during this 3-month period, while 1,085,404 did not. Patients with pruritus and no rash accounted for about 50% of cases or more. A higher proportion of patients with pruritus were female (70%) and black (40%) (Huang et al. 2019).

3 Categories

Drug-induced pruritus is categorized as either acute or chronic. In the acute form, itching typically resolves within 6 weeks of drug cessation. Examples of drugs known to induce acute itch include opioids, serotonin reuptake inhibitors, and antimalarials (Reich et al. 2009). Conversely, chronic drug-induced pruritus occurs when itching persists longer than 6 weeks after the drug has been discontinued (Ebata 2016). For example, itching caused by hydroxyethyl starch (HES) infusion does not remit until more than 6 weeks from drug withdrawal, due to slow degradation of this substance from the body (Metze et al. 1997). Additionally, drugs known to induce cholestasis may cause itch that does not remit until months after drug cessation (Kowdley et al. 1992; Larrey et al. 1988).

There are three other important parameters that may be used to differentiate the types of drug-induced pruritus. The first is according to latency, which is the time period between drug initiation to the first symptoms of pruritus. Drugs inducing pruritus may differ in this category. For example, calcium channel blockers have been shown to induce itch within 24 h of drug intake, while reports of beta-blocker-induced itch describe lag periods of up to 6 months (Orme and Da Costa 1997; Hagmeyer and Stein 2001). The second parameter used to differentiate the types of drug-induced itch depends on whether the itch is localized to a specific part of the body, or whether it is generalized. For example, itch associated with cholestasis may be more prominent in the palms and soles, while opioid-induced itch can often be seen in areas of the face (Pusl and Beuers 2007; Szarvas et al. 2003). The third category involves severity of itch, a clinical term used to describe the intensity of a medical event, as in the grading "mild," "moderate," and "severe." Some drugs may cause mild itch, while others may result in intractable itch that decreases quality of life and thus may induce patient noncompliance. Itch severity may also depend upon whether the pruritus is localized or generalized as well.

Furthermore, drug-induced pruritus can further be categorized as direct or indirect. In direct drug-induced pruritus, pruritus results from a direct effect of the drug on the skin. For example, hydroxyethyl starch, a colloid used for volume replacement, is thought to produce itch through its deposition in the skin (Sirtl et al. 1999). Conversely, drugs can cause pruritus indirectly by affecting organs other than the skin. A prototype example of this indirect drug-induced pruritus is the itching that occurs secondary to cholestasis, a consequence of drugs that adversely affect the liver. Note that nephrotoxic drugs causing severe end-stage renal disease may also result in pruritus indirectly; however reports of this adverse event are rare. Many drugs have the potential to both cause direct and indirect drug-induced pruritus. For example, opioids may cause itch due to their direct effect on the skin through mu-opioid receptors, while in other cases opioids can cause itch due to their hepatotoxic effects.

4 Pathogenesis of Drug-Induced Pruritus

4.1 The Itch Pathway

Itch begins at the skin when pruritogens stimulate receptors on itch-selective unmyelinated C neurons (Schmelz et al. 1997). Most of these receptors are G-protein-coupled receptors (GPCRs) which promote the opening of ion channels to generate action potentials (Kittaka and Tominaga 2017). The unmyelinated itch-selective nerve fibers that transmit itch can be categorized as histaminergic or nonhistaminergic depending on the receptors they express (Ikoma et al. 2006). Histaminergic neurons are implicated in acute itch and are activated by histamine. Nonhistaminergic neurons are implicated in chronic itch and express a wide variety of receptors that are activated by pruritogens other than histamine (Yosipovitch et al. 2018). Histaminergic and nonhistaminergic nerve signals travel along distinct spinal tracts and activate different processing areas of the brain (Davidson et al. 2012; Papoiu et al. 2012). Supraspinal processing of itch occurs in multiple sites of the brain, most commonly the primary and secondary somatosensory cortex (Drzezga et al. 2001; Yosipovitch et al. 2004) (see Fig. 1).

The pathogenesis of drug-induced pruritus depends on the culprit drug and is not fully understood for every single causative agent.

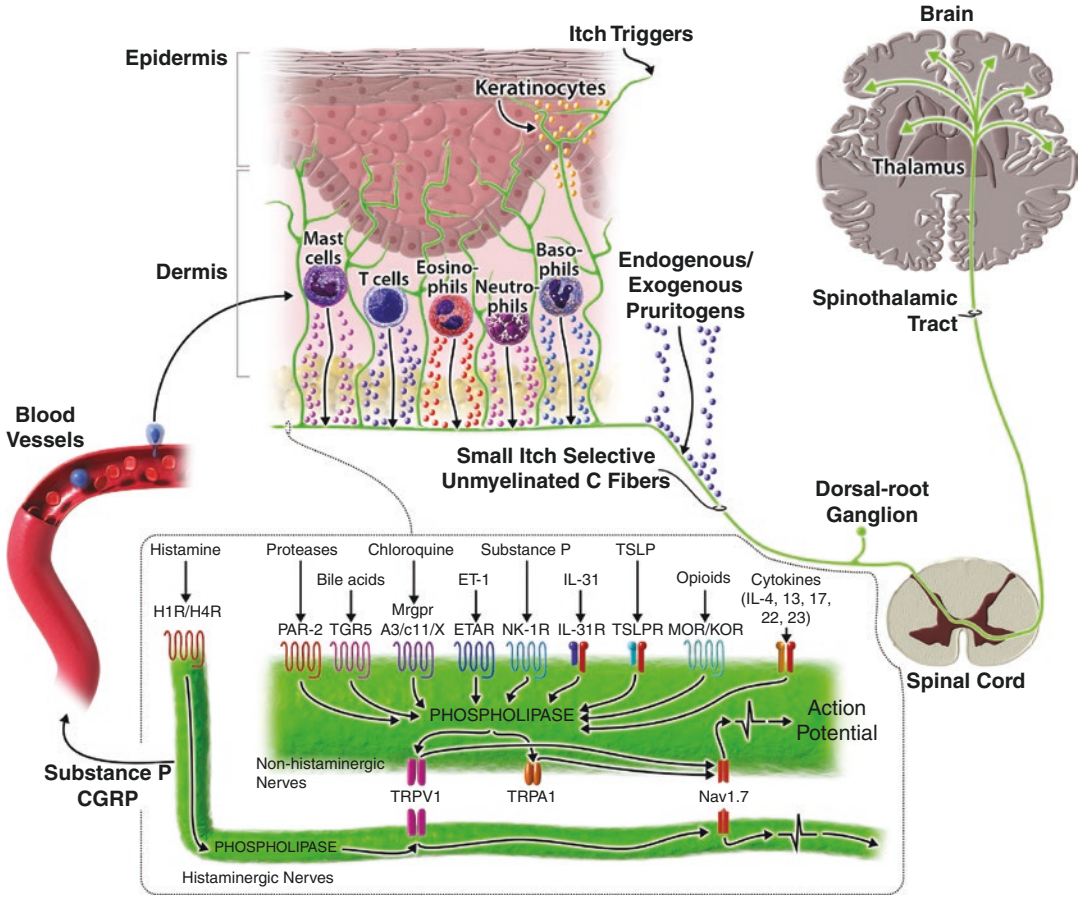

Fig. 1 Itch triggers stimulate receptors on itch-selective unmyelinated C neurons, which can be categorized as histaminergic or nonhistaminergic. These receptors are usually G-protein-coupled receptors which open ion channels to generate action potentials. Itch signals travel along spinal tracts to activate different areas of the brain

4.2 Specific Drugs Inducing Pruritus

(See Table 1).

Opioids

Opioids are medications commonly used to manage acute and chronic pain syndromes associated with a variety of disease states. Unfortunately, their use is limited by several adverse effects, one of the most common being pruritus (Benson et al. 2015). Opioid-induced pruritus is quite prevalent and has been shown to affect 2–20% of patients when administered orally, 10–50% of patients when administered intravenously, and 30–100% after spinal or epidural administration (Szarvas et al. 2003; Swegle and Logemann 2006; Schofferman and Mazanec 2008; Gan et al. 1997;

Table 1 Drugs most commonly inducing pruritus without rash

Group of drugs	Examples	Proposed pathogenesis	Lag period	Frequency of itch
Neurogenic	Mu-opioids[a]	Central nervous system-mediated process via μ-opioid receptors	1.5–12 h (Mohammed 2013; Liao et al. 2011)	Oral: 2–20% (Swegle and Logemann 2006; Schofferman and Mazanec 2008) IV: 10–50% (Gan et al. 1997; Woodhouse et al. 1996) Epidural/spinal: 30–100% (Szarvas et al. 2003)
Antimalarial	Chloroquine[a]	Genetics (Dong et al. 2001; Yang et al. 2005) Histamine release (Osifo 1995) Slower metabolism of the drug (Ademowo et al. 2000) Endogenous opioids (Onigbogi et al. 2000; Ajayi et al. 2004)	Within 24 h (Olayemi et al. 2003)	60–70% in black Africans (Ajayi et al. 1989; Olayemi et al. 2003) Uncommon in Caucasian/Asian (Bussaratid et al. 2000; Spencer et al. 1982)
Plasma volume expander	Hydroxyethyl starch[a]	Deposition in nerves and skin (Metze et al. 1997)	1–6 weeks (Metze et al. 1997; Morgan and Berridge 2000; Waitzinger et al. 2003)	1–64% (Grochenig et al. 1998; Leunig et al. 1995; Murphy et al. 2001)
Antimicrobial	Penicillins[a]	Cholestatic liver injury (Wendel et al. 1985)	24 h (Wendel et al. 1985)	33–61% (Huang et al. 2019; Wendel et al. 1985)
–	Macrolides[a]	Cholestatic liver injury (Diehl et al. 1984)	2–5 days (Diehl et al. 1984; Lockwood et al. 2010; Chandrupatla et al. 2002)	~58% (Huang et al. 2019)
–	Tetracyclines	Cholestatic liver injury (Hunt and Washington 1994) Unknown	2 months (Hunt and Washington 1994)	2.5–50% (Huang et al. 2019; Rafiei and Yaghoobi 2006)
–	Quinolones	Unknown	N/A	7.6–50% (Huang et al. 2019; Lin et al. 2010; Oreagba et al. 2017)

Table 1 (continued)

Group of drugs	Examples	Proposed pathogenesis	Lag period	Frequency of itch
–	Cephalosporin	Unknown	N/A	0.03–48% (Huang et al. 2019; Theopold et al. 1990; Shimokata et al. 1986; Poon et al. 2012)
–	Trimethoprim/ sulphamethoxazole[a]	Cholestatic liver injury (Kowdley et al. 1992; Nair et al. 1980) Unknown	1 month (Nair et al. 1980)	0.01–52% (Huang et al. 2019; Grüneberg and Kolbe 1969)
–	Metronidazole[a]	Unknown	N/A	<5–58% (Huang et al. 2019; Kapoor et al. 1999)
Metabolic	Statins	Cholestatic liver injury (Russo et al. 2009) Xerosis cutis (Huang et al. 2019)	N/A	16–61% (Huang et al. 2019; Kashyap et al. 2002; Russo et al. 2014)
–	Antidiabetics	Cholestatic liver injury (Nammour et al. 2003) Unknown	A few days to 4 weeks (Nammour et al. 2003; Vasapollo et al. 2018; Stewart and Anderson 1965)	Case reports (Nammour et al. 2003; Vasapollo et al. 2018; Anonymous 2018) Not stated (Stewart and Anderson 1965; Kilo et al. 1991)
Antihypertensive	ACE inhibitors[a]	Increased bradykinin level (Steckelings et al. 2001) Cholestatic liver injury (Nunes et al. 2001) Unknown	N/A	0.3–61% (Huang et al. 2019; Thestrup-Pedersen 1987; Gavras 1986; Frank 1989)
–	ARBs	Unknown	N/A	2% (Lacourcière and Asmar 1999)
–	Beta-blockers	Cholestatic liver injury (Hagmeyer and Stein 2001) Unknown	10 days to 6 months (Hagmeyer and Stein 2001; Khunger and Pahwa 2011)	2–61% (Huang et al. 2019; Kunzi-Rapp 2012; Jeck et al. 1992)
–	Calcium channel blockers[a]	Cholestatic liver injury (Odeh and Oliven 1998) Unknown	Within 24 h (Orme and Da Costa 1997; Odeh and Oliven 1998)	2.5–61% (Huang et al. 2019; Bernink et al. 1991)
–	Thiazides	Unknown	N/A	~58% (Huang et al. 2019)
Anticancer	IL-2[a]	Pruritogenic effect (Reich et al. 2009)	N/A	48–64% (Chi et al. 2001; Redman et al. 1990)
–	mTOR inhibitors[a]	Unknown	N/A	23.8% (Ensslin et al. 2013)
–	Bcr-Abl inhibitors[a]	Induction of IL-31 via dermal mast cells	N/A	12.8% (Ensslin et al. 2013)
–	Raf kinase inhibitors[a]	Unknown	N/A	18.3% (Ensslin et al. 2013)
–	VEGFR inhibitors[a]	Unknown	N/A	3.0% (Ensslin et al. 2013)

(continued)

Table 1 (continued)

Group of drugs	Examples	Proposed pathogenesis	Lag period	Frequency of itch
–	EGFR inhibitors[a]	Barrier disruption (xerosis cutis), unknown	N/A	22.7% (Ensslin et al. 2013)
–	EGFR-HER2 inhibitors[a]	Unknown	N/A	14.6% (Ensslin et al. 2013)
–	EGFR-VEGFR inhibitor[a]	Unknown	N/A	9.1% (Ensslin et al. 2013)
–	Monoclonal Ab's to CD20[a]	Unknown	N/A	11.3% (Ensslin et al. 2013)
–	Monoclonal antibodies to CTLA-4[a]	Unknown	N/A	30.7% (Ensslin et al. 2013)
–	PD-1 inhibitors[a]	Modulation of Th2 response (Huber et al. 2010)	N/A	14.1–47% (Yosipovitch 2018)
–	Paclitaxel	Unknown	48–72 h (Dunphy et al. 1997)	14% (Dunphy et al. 1997)
Antiarrhythmic	Amiodarone	Cholestatic liver injury (Salti et al. 1989)	N/A	~61% (Huang et al. 2019)
Anticoagulant	Ticlopidine	Cholestatic liver injury (Skurnik et al. 2003)	10 days to 3 months (Amaro et al. 1999; Skurnik et al. 2003)	Case reports (Amaro et al. 1999; Skurnik et al. 2003)
–	Heparin	Unknown	N/A	~62% (Huang et al. 2019)
Hormones	Oral contraceptives	Cholestatic liver injury (Lieberman et al. 1984; Medline et al. 1976)	Days to 1 month (Lieberman et al. 1984; Medline et al. 1976; Kunzmann et al. 2005)	Case reports (Lieberman et al. 1984; Medline et al. 1976; Kunzmann et al. 2005)
–	Tamoxifen	Unknown (Moredo Anelli et al. 1994; Boström 1999) Xerosis (Love et al. 1999)	N/A	3–5% (Moredo Anelli et al. 1994; Boström 1999; Love et al. 1999)
Psychiatric drugs	Antipsychotics	Cholestatic liver injury (Chlumská et al. 2001)	2 weeks to years (Chlumská et al. 2001; Moradpour et al. 1994; Radzik et al. 2005)	Case reports (Chlumská et al. 2001; Moradpour et al. 1994; Radzik et al. 2005)
–	Tricyclic antidepressants	Cholestatic liver injury (Larrey et al. 1988) Unknown	5 weeks (Larrey et al. 1988)	~52% (Huang et al. 2019)
–	Serotonin reuptake inhibitors[a]	Release of serotonin Unknown	N/A	~54% (Huang et al. 2019)
–	Anticonvulsants	Unknown	Immediately to 2 days (Aggarwal et al. 2011; DeToledo and Ramsay 2000)	48.6% (DeToledo and Ramsay 2000) Not stated (Fischer et al. 2003; Knapp and Kugler 1998)
Other	Granulocyte-macrophage colony-stimulating factor	Unknown	N/A	14–19% (Hamm et al. 1994)

IV intravenous, *UV* ultraviolet, *IM* intramuscular, *TB* tuberculosis, *ACE* angiotensin-converting enzyme, *IL* interleukin, *mTOR* mammalian target of rapamycin, *VEGFR* vascular endothelial growth factor receptor, *EGFR* endothelial growth factor receptor, *Ab* antibody, *CTLA-4* cytotoxic T-lymphocyte–associated antigen-4, *PD-1* programmed cell death protein-1, *NSAID* nonsteroidal anti-inflammatory drug

[a] Major drugs causing drug-induced pruritus

Woodhouse et al. 1996). Patients who experience opioid-induced itch may complain of generalized itching, or they may experience more intense itch in areas with higher concentrations of mu-opioid receptors, such as the face (Benson et al. 2015). Lag time from treatment initiation to onset of pruritus is usually within 12 h (Ganesh and Maxwell 2007; Krajnik and Zylicz 2001; Bounes et al. 2017).

Many mechanisms for opioid-induced pruritus have been postulated. Centrally mediated opioid-induced pruritus occurs secondary to binding of mu-opioid receptors in the spinal cord, where itch signals are modulated by interneurons, and the brain (Benson et al. 2015). Furthermore, an imbalance in the activation of kappa opioid receptors (KORs) vs. mu-opioid receptors (MORs) may result in neuronal sensitization and an enhanced itchy response. Other proposed mechanisms of opioid-induced itch include modulation of serotonin receptors in the trigeminal nerve nucleus and secondary histamine release from mast cells. Peripheral mechanisms may also be involved, as some opioids that cause pruritus are not likely to cause histamine release (Szarvas et al. 2003; Reich and Szepietowski 2010).

Chloroquine

Chloroquine is a drug commonly used for the treatment of chloroquine-sensitive *plasmodium falciparum* malaria and rheumatologic diseases such as systemic lupus erythematosus and rheumatoid arthritis (Freedman and Steinberg 1960; Meinao et al. 1996; Kublin et al. 2003). A major side effect of chloroquine is pruritus without rash, which contributes to decreased compliance and avoidance of the drug (Kaseje et al. 1987). Chloroquine-induced pruritus is experienced by 60–70% of Black Africans, making it the most common drug side effect experienced by this population (Ajayi et al. 1989; Olayemi et al. 2003). Interestingly, this adverse reaction is very uncommon in the Caucasian and Asian population (Bussaratid et al. 2000; Spencer et al. 1982).

Chloroquine-induced pruritus can be quite intense. In a study of 814 patients with chloroquine-induced pruritus, 40% regarded the pruritus as "unbearable" and 21% regarded it as "severe" (Ajayi et al. 1989). In a study in Kenya, 10% of pregnant women refused free malaria prophylaxis with chloroquine due to fear of chloroquine-induced itching (Kaseje et al. 1987). Itching has been reported to occur mainly in the hands, feet, and scalp, but there have also been reports of generalized itching as well (Ekpechi and Okoro 1964; Osifo 1984). Lag time from treatment initiation to onset of pruritus has ranged from 6 to 24 h, and usually subsides within 76 h after onset (Ajayi et al. 1989; Osifo 1984; Adebayo et al. 1997).

Similar to opioids, the pathogenesis of chloroquine-induced itch is thought to be multifactorial. A special type of GPCR called Mas-related G-protein-coupled receptors (Mrgprs), specifically MrgprX1, has recently been discovered to mediate chloroquine-induced itch but not histaminergic itch in humans. The binding of chloroquine to Mrgprs leads to release of gastrin-releasing peptide, an itch-selective neurotransmitter, into the dorsal horn of the spinal cord, where it activates a subset of neurons through gastrin-releasing peptide receptor (GRPR) (Liu et al. 2009). Furthermore, chloroquine has been shown to induce histamine release in healthy volunteers, and antihistaminic drugs have helped to attenuate chloroquine-induced itching in a study population (Ezeamuzie et al. 1990; Mnyika 1991). Additionally, opioidergic mechanisms may be involved in chloroquine-induced itch, as studies have shown that chloroquine-induced itch in rats may be blocked by mu-opioid receptor antagonist naltrexone and potentiated by mu-opioid receptor agonist morphine (Onigbogi et al. 2000).

As stated above, chloroquine-induced pruritus is more commonly seen in African populations, and high genetic polymorphism seen in human Mrgpr genes may provide a molecular explanation for this finding (Dong et al. 2001; Yang et al. 2005). Furthermore, genetics may also impact the way in which chloroquine is metabolized. A study showed that compared with non-itchers, patients with chloroquine-induced itch demonstrated slower metabolism of chloroquine to its main metabolite, desethylchloroquine. Furthermore,

itchy patients also excreted more chloroquine in their urine than non-itchy patients, further suggesting less metabolism of the parent drug by these patients (Ademowo et al. 2000).

Hydroxyethyl Starch

HES is a colloid traditionally used for volume replacement and fluid management. Up to 64% of patients experience pruritus associated with administration of this drug (Grochenig et al. 1998; Leunig et al. 1995; Murphy et al. 2001). Most patients characterize the itching as generalized and severe, with a visual analogue scale median score of 9 out of 10 (Ständer et al. 2014). Lag period is usually delayed and is about 1–6 weeks after initiation of HES infusion, and the itching typically lasts 9–15 weeks or longer (Ebata 2016).

HES-induced pruritus is a form of neuropathic itch, as deposition of this drug has been found in Schwann cells of cutaneous nerves of itchy patients. Drug deposits were also found in epithelia of sweat glands, endothelial cells of blood and lymphatic vessels, dermal macrophages, Langerhans cells, and basal keratinocytes (Ständer et al. 2001). Drug deposition was shown to be proportional to dosage, and more extensive deposits were more likely to be seen in patients who developed pruritus (Sirtl et al. 1999). Furthermore, the disappearance of HES vacuoles in cutaneous nerves paralleled the improvement of pruritus (Metze et al. 1997). It remains unclear how cells that contain HES provoke itching, but it has been suggested that HES deposits may mechanically irritate nerve endings (Roeser and Tronnier 1990). Another possibility is that the cells that contain drug deposits mediate pruritus through the release of specific mediators.

Drugs Inducing Cholestasis

Cholestatic liver injury is one of the most common causes of drug-induced pruritus, as many drugs are known to cause hepatotoxicity. Cholestasis refers to stagnant bile that fails to reach the duodenum (Degott 1997). The list of drugs that may induce cholestatic liver injury is quite extensive, and of note, antimicrobials are the most common culprit (Lucena et al. 2009; Bhamidimarri and Schiff 2013). Although every single drug known to cause cholestatic liver injury has not been shown to induce pruritus, one can extrapolate that any drug which has the potential to trigger this type of liver injury also has the capability of inducing pruritus. Examples of other drugs known to induce pruritus secondary to cholestasis include ACE inhibitors, calcium channel blockers, tricyclic antidepressants, and oral contraceptives.

Patients with drug-induced cholestasis may present with a variety of symptoms, including pruritus with or without jaundice (Bhamidimarri and Schiff 2013). Itching has been shown to be most intense in the palms and soles; however it may also be generalized (Pusl and Beuers 2006; Bergasa et al. 2000). Lag time from treatment initiation to onset of pruritus can range from a few weeks to many months (Orme and Da Costa 1997; Mikhail 2004; Amaro et al. 1999; Quattropani et al. 2001; Hunt and Washington 1994). Furthermore, drugs known to induce cholestasis may cause itch that does not remit until months after drug cessation (Kowdley et al. 1992; Larrey et al. 1988).

The exact mechanism by which cholestasis results in itch is still unclear; however, the pathophysiology is likely multifactorial. Bile salt accumulation is a postulated mechanism of pruritus, and there is recent evidence that MrgprX4 is a bile acid receptor for cholestatic itch (Quist et al. 1991; Yu et al. 2019). A component of neurogenic itch in which pruritus originates centrally but without evidence of neural pathology is likely, as it has been proposed that cholestatic injury results in the accumulation of pruritogens such as endogenous opioids (Swain et al. 1992). It has been hypothesized that the expression of lysophosphatidic acid (LPA) by autotaxin activates unmyelinated nerve endings that transmit itch in cholestasis (Elferink et al. 2011).

Anticancer Therapies

Targeted anticancer therapies are novel drugs that have led to a significant increase in survival rates among various cancer patients. Unfortunately, they are also associated with many unwanted side

effects, including pruritus without rash. When 379 cancer survivors were asked about their perceptions of treatment-related dermatologic toxicities, the third most common dermatologic side effect reported was pruritus (accounting for 36% of patients), and 44% of this patient cohort experienced a negative impact on their quality of life as a result of this side effect (Gandhi et al. 2010). A systematic review and meta-analysis ascertaining the risk of pruritus among patients treated with targeted anticancer therapies found that these patients had a significant risk of developing pruritus, with an overall incidence of 17% (Ensslin et al. 2013).

The mechanism of action of pruritus in targeted anticancer therapies depends on the drug class.

Epidermal growth factor receptor (EGFR) inhibitors such as panitumumab are proposed to produce itch through direct skin barrier disruption. Binding of these drugs to the EGFR (epidermal growth factor inhibitor) in the basal layer of proliferating keratinocytes can result in abnormal proliferation and migration of these cells. Furthermore, these drugs may cause sebaceous and sweat gland dysfunction as well that can contribute to dry skin and itch (Fischer et al. 2013).

PD-1 inhibitors such as pembrolizumab block the interaction of the PD-1 receptor with its ligand (PD-L), an interaction that normally inhibits T cell proliferation and reduces cytokine load (Belum et al. 2016).

Interestingly, a study by Huber et al. showed that blockade of PD-L2, a ligand for the PD-1 receptor, caused an enhanced Th2 response (Huber et al. 2010). As Th2 cells are known to produce IL-31, a pruritic cytokine, it is possible that PD-1 inhibitors induce pruritus through their induction of the Th2 immune response (Kabashima 2013; Raap et al. 2012; Gutzmer et al. 2009).

Tyrosine kinase inhibitors such as imatinib mesylate have been implicated in drug-induced itch, with frequencies of all-grade pruritus of up to 10% (Yosipovitch 2018). This drug selectively targets protooncogenes such as Abl, c-Kit, and the platelet-derived growth factor (PDGF) receptor. Although human mast cells express the c-kit receptor which is susceptible to inhibition by imatinib, a paradoxical increase in the number of dermal mast cells has been identified in patients on a high-dose imatinib regimen (Ugurel et al. 2003; Ma et al. 2002). Furthermore, levels of IL-31 and IL-33 have been identified in the serum of patients undergoing imatinib therapy (Musolino et al. 2015). These findings taken together have led to the postulation that keratinocyte injury secondary to imatinib usage may cause the release of IL-33, which interacts with mast cells to aid in the induction of chemoattractants such as IL-31, a known itchy cytokine (Musolino et al. 2015).

Finally, IL-2 is an anticancer therapy that has been shown to cause pruritus in up to 65% of patients. This is not surprising as IL-2 is among the many known pruritogenic cytokines and has been shown to play a role in eliciting itch in inflammatory skin diseases such as atopic dermatitis (Yosipovitch and Papoiu 2008; Chi et al. 2001; Redman et al. 1990).

Other Drugs

Angiotensin-converting enzyme (ACE) inhibitors are widely used drugs for the treatment of hypertension and, in a large multicenter study, were shown to cause pruritus without rash in up to 61% of patients (Huang et al. 2019). Additional reports of ACE inhibitors causing pruritus have been published (Steckelings et al. 2001; Thestrup-Pedersen 1987; Gibbs et al. 1999). ACE inhibitors degrade bradykinin, an inflammatory mediator that has been shown to activate itch fibers.

Serotonin-reuptake inhibitors have been shown to produce pruritus without rash in up to 54% of patients (Huang et al. 2019). Serotonin has also been shown to cause itch when intradermally injected (Weisshaar et al. 1997). It has been shown that serotonin can act as a pruritogen by acting on the 5-HT2 receptor, and that central 5-hydroxytryptophan (5-HT) signaling facilitates itch transmission (Yosipovitch et al. 2018; Zhao et al. 2014). Interestingly, these drugs have also been used as successful treatment for pruritus, highlighting the complexity regarding itch transmission (Leslie et al. 2015).

Statins are drugs that have revolutionized lipid management and work through their modulation of lipid metabolism and inhibition of cholesterol biosynthesis (Stancu and Sima 2001). Statins may cause drug-induced pruritus directly secondary to xerosis cutis; however this side effect is quite rare, as these drugs also have an anti-inflammatory component that may reduce itch (Huang et al. 2019; Garibyan et al. 2013). Note that statin-induced pruritus is likely to be multifactorial, as these drugs have been reported to induce pruritus indirectly through their cholestatic effects as well (Kashyap et al. 2002; Sharma et al. 2006; Russo et al. 2009, 2014).

5 Diagnosis

Drug-induced pruritus may be difficult to diagnose due to the abundance of triggers that may induce itching, such as the primary disease for which the medication has been prescribed (i.e., cancer), the medical background of the patient (i.e., atopic predisposition, liver disease, and chronic renal disease), and other factors (i.e., allergies). Proof of diagnosis is challenging and may be supported through clinical improvement of symptoms upon drug cessation. However, pruritus may continue in some cases even though the offending drug has been discontinued, as elaborated above.

When a patient complains of pruritus and drug-induced itch is highly suspected, a thorough history and physical exam should be performed. All components of the patient history are important, including past medical history, family history, and allergies, including personal and family atopic background. Also, a list of all drugs the patient has been prescribed, including dietary supplements and vitamins, should be recorded. Features of the pruritus should be assessed, including onset timing following drug initiation, intensity, location, quality, and time of day during which the itching occurs. Alleviating or aggravating factors should be elucidated as well, such as exposure to hot water, sweating, temperature changes, and response to various treatments.

Physical exam should include inspection of the entire skin, hair, and nails. Lymph node enlargement and organomegaly should also be assessed. It is crucial to differentiate between primary and secondary lesions of the skin, as drug-induced pruritus does not include primary skin lesions. However, intense rubbing and scratching of the skin induces various secondary skin lesions, such as excoriations (linear or punctate) and thickened and leathery skin with exacerbated markings (lichenification). A diagnosis of drug-induced pruritus is also to be differentiated from the various pruritic rashes that may also be induced by drugs, such as psoriasiform rashes, induction of eczema, drug-induced bullous pemphigoid, etc. Diagnostic testing should include complete blood count and full chemistries, including renal and liver function tests.

6 Treatment

Once an offending drug is suspected, discontinuing the drug should be a consideration. However, a risk-benefit analysis for each case needs to be considered where the benefit of medical treatment with the drug outweighs the decrease in patient quality of life arising from the pruritus. Most causes of drug-induced pruritus typically resolve after cessation of the culprit drug (Nammour et al. 2003; Aggarwal et al. 2011; O'Beirne and Cairns 2001). In cases where the offending drug is not discontinued, treatment should instead focus on symptomatic relief. Mild pruritus that is localized can be treated topically with local anesthetics such as pramoxine, cooling agents such as menthol and calamine, ion channel inhibitors such as strontium, or combined application of ketamine-amitriptyline-lidocaine. Application of cool temperature may also be helpful in attenuating itch. For more severe, generalized itch, systemic therapy such as gabapentin or pregabalin, antidepressants such as mirtazapine and paroxetine, butorphanol, and phototherapy should be considered (Yosipovitch et al. 2018; Ensslin et al. 2013; Santini et al. 2012). Aprepitant may be helpful specifically for

the management of severe pruritus related to anticancer treatments (Santini et al. 2012).

If drug cessation does not result in relief of symptoms, treatment options may depend on the culprit drug. For example, opioid-induced itch has successfully been treated with naloxone, nalbuphine, butorphanol, and ondansetron (Gan et al. 1997; Korhonen et al. 2003; Alhashemi et al. 1997). First-line treatment of chloroquine-induced itch is antihistamines; however prednisolone, niacin, and naltrexone have been used as well (Bussaratid et al. 2000; Adebayo et al. 1997; Ajayi et al. 2004). Chronic itch induced by HES can be treated with topical capsaicin, UV therapy, or naltrexone (Szeimies et al. 1994; Metze et al. 1999). Drugs that induce itch indirectly through cholestatic liver injury should be treated with ursodeoxycholic acid, rifampin, or cholestyramine (Ebata 2016).

7 Conclusion

Drug-induced pruritus accounts for a great proportion of adverse drug reactions. Although common, this adverse reaction can be quite elusive, as pruritus manifests without coexisting skin lesions, and many drugs of different classes have the potential to cause this medical problem. Nevertheless, clinicians must be able to identify this adverse reaction and importantly, to distinguish it from pruritus secondary to a skin eruption. While several putative mechanisms of drug-induced pruritus have been elucidated, in most cases, the role of the drug in the itch pathway remains unclear. Further studies clarifying such mechanisms may help guide future treatment.

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Drug-Induced Nail Changes

Chia-Chun Ang and Eckart Haneke

1 Introduction

Adverse drug reactions can affect multiple organs in the body. The effects of drug reactions on skin, hair, and nails are most accessible to clinical examination and may thus provide the earliest clinical clues. Nail changes in particular can persist for months, giving a clue to a drug-induced reaction from the recent past. Some drug-induced nail toxicity can lead to significant morbidity. In this short review, we aim to provide a framework to assess and manage drug reactions of the nail unit. The strength of evidence for many drug-induced nail changes is limited to case reports and in some cases the causality is difficult to determine, with the possibility of the nail changes being due to the underlying medical condition. While we strive to highlight known associations for drug-induced nail changes, our review is not exhaustive, and readers are encouraged to review the literature as part of their diagnostic consideration when they encounter patients with suspected drug-induced nail changes.

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2 Human Nail Unit Anatomy with Pathophysiological Correlation

A drug can affect the nail unit through its usual mechanism of action (e.g., cytotoxicity of chemotherapeutic agents on the dividing cells of the nail matrix), from direct involvement of the matrix, nail bed, and/or periungual skin in a great number of inflammatory cutaneous drug reactions, or from deposition of the drug or its metabolites in the nail unit, although in some cases the exact causative mechanism is unknown. The clinical picture depends on which part of the nail unit is affected. Usually more than one nail is affected by a systemically administered drug, and the nail changes appear earlier in the faster growing fingernails compared to the toenails (Piraccini et al. 2004).

The nail unit consists of the nail plate, which is surrounded proximally by the proximal nail fold and cuticle, laterally by the lateral nail folds, and distally by the hyponychium. Periungual granulation tissue (incorrectly referred to as drug-induced periungual pyogenic granuloma by some authors) and acute paronychia (Fig. 1a, b) occur along the proximal and lateral nail folds from a combination of drug-induced nail plate brittleness (leading to ingrowing nail), fragility of the epidermis due to decreased epidermal proliferation, and drug-induced predisposition to granulation tissue formation. Synthetic retinoids, reverse transcriptase inhibitors, and, in particular, epidermal growth

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Fig. 1 (**a**). Periungual granulation tissue on the left big toe from Afatinib (courtesy of Adj. Assoc. Prof. Derrick Aw Chen Wee, Sengkang General Hospital, Singapore). (**b**) Periungual granulation tissue on the left big toe from Cetuximab, treated with a cotton wedge to separate the nail plate from the affected nail folds (courtesy of Prof. Eckart Haneke)

factor receptor inhibitors are the drugs most commonly causing painful paronychia with periungual granulation tissue. The thumbs and great toes are more commonly affected as they are more prone to trauma. These changes can be complicated by secondary colonization and infection by Gram positive bacteria, Gram negative bacteria, and candida organisms (Eames et al. 2010).

The nail plate is produced by the nail matrix and grows at a rate of 3 mm per month for fingernails (about 6–9 months for an entire fingernail to be replaced) and 1 mm per month for toenails (about 12–18 months for an entire big toenail to be replaced). Drugs which act on the cell cycle will therefore affect nail plate production by the nail matrix, giving rise to different clinical signs. True transverse leukonychia (Mees lines) occurs when the drug affects the distal nail matrix, leading to parakeratosis of the nail plate and an opaque appearance to the nail. They appear as regular thin white bands in the nail plate, which are parallel to the lunula. Thin brittle nails occur when the insult to the nail matrix is mild but persistent. Beau's lines (transverse depression of the nail plate, Fig. 2) occur when the nail matrix is acutely affected by the drug or drug-induced hypersensitivity reaction, leading to a temporary disruption of nail plate production. The width of the Beau's lines gives a clue to the duration of exposure to the drug. The depth of the Beau's lines gives a clue to how severe the nail matrix function was affected, with onychomadesis (full thickness transverse sulcus of the nail plate, Fig. 3) being the most extreme presentation. The distance from the proximal nail fold to the Beau's lines gives a clue to the time when the culprit drug was introduced. Some medications can increase the growth rate of the nails. Psoriatic and lichenoid drug reactions can affect the nail matrix and nail bed, giving rise to typical nail findings.

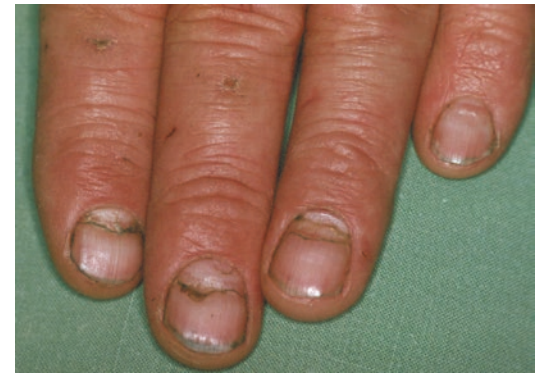

Fig. 2 Beau's lines of the fingernails (courtesy of Prof. Eckart Haneke)

The nail matrix contains melanocytes which are usually quiescent. They can be activated by drugs to produce melanin which is incorporated into the growing nail plate, leading to longitudinal (Fig. 4) to diffuse melanonychia. It may take

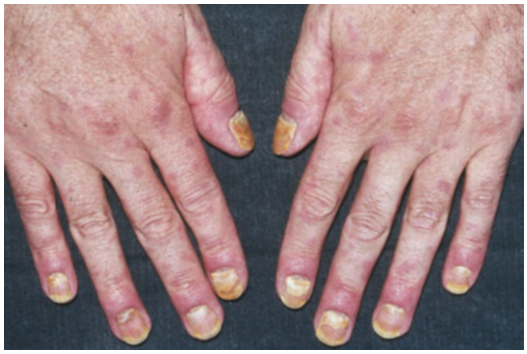

Fig. 3 Onychomadesis of the fingernails post Stevens-Johnson Syndrome (courtesy of Prof. Eckart Haneke)

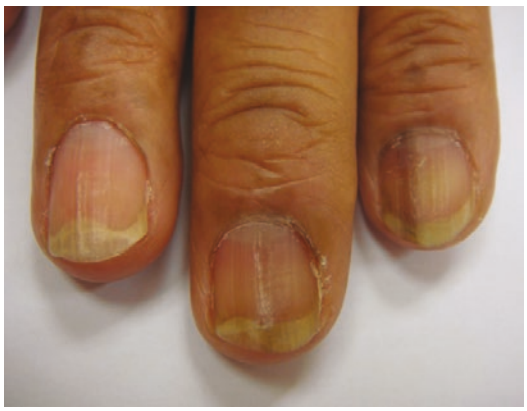

Fig. 4 Longitudinal melanonychia on multiple fingernails from long-term hydroxyurea treatment for chronic plaque psoriasis (courtesy of Dr. Ang Chia Chun)

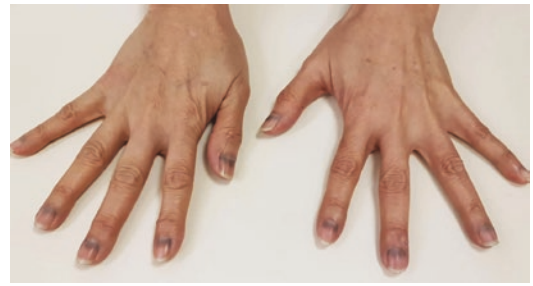

Fig. 5 Transverse melanonychia of the fingernails from combination chemotherapy for breast cancer (courtesy of Dr. Lee Shan Xian, Changi General Hospital, Singapore)

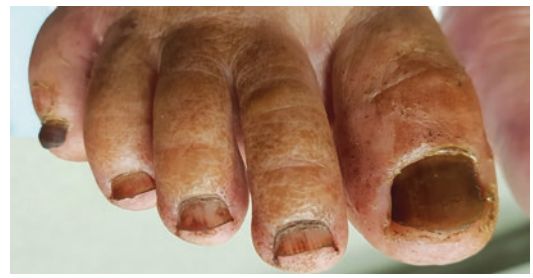

Fig. 6 Exogenous pigmentation of the nail plate and periungual skin from potassium permanganate soaks of the right foot (courtesy of Dr. Ang Chia Chun)

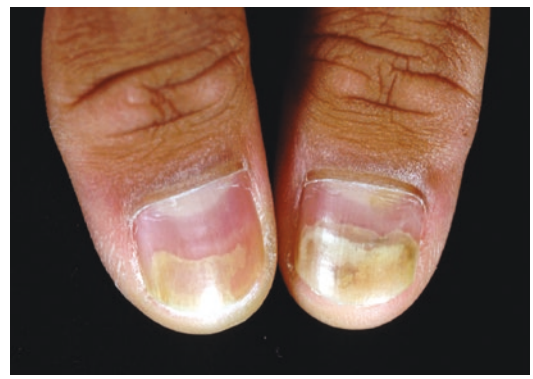

Fig. 7 Photo-onycholysis of both thumbs from doxycycline use (courtesy of Dr. Colin Kwok, Changi General Hospital, Singapore)

many weeks after stopping the culprit drug for the melanin production to subside, and many months for the pigmented nail plate to grow out. Patients can have associated drug-induced skin and mucosal pigmentary changes. In rare cases, the pigmentation appears as transverse bands (Fig. 5). The nail plate can also become pigmented from exogenous pigment deposition (Fig. 6). Drug-induced lunula pigmentation can rarely occur. This is postulated to be due to either pigment deposition in the nail matrix, stimulation of the matrix melanocytes, or injury to the distal nail matrix (Jeevankumar and Thappa 2003).

Onycholysis occurs when there is drug-induced damage to the nail bed epithelium. In severe cases, the onycholysis is associated with painful subungual hemorrhage and rarely subungual abscess; this is particularly characteristic for taxanes (Vanhooteghem et al. 2000). Photo-onycholysis (Fig. 7) usually occurs as a triad of cutaneous photosensitivity, nail discoloration, and photo-onycholysis (Segal's triad) (Segal 1963) in response to photosensitizing drugs, although it can also occur in the absence of other

clinical signs of photosensitivity (Kestel 1972). Four morphologic subtypes have been described, regardless of the causative photosensitizing medication. Photo-onycholysis is usually painful when associated with tetracyclines and psoralen and ultraviolet A therapy (Baran et al. 2019). Drug-induced pigmented nail bed with sparing of the lunula can occur although the exact mechanism is unknown. Drug deposition in the nail plate is useful for therapy (e.g., use of antifungal agents in onychomycosis) and for forensic toxicology examination (e.g., arsenic poisoning and illicit drug use) (Palmeri et al. 2000).

The nail bed is well vascularized and drug-induced changes to the nail bed vasculature are readily visible through the translucent nail plate. Microvascular damage from drugs can present as splinter hemorrhages or subungual hematoma, while changes in blood flow can lead to Raynaud's phenomenon or apparent leukonychia (Muehrcke's lines). Muehrcke's lines appear as paired transverse white bands on the nail bed which do not migrate with nail growth and become inapparent with digital compression.

The nail can be hypoplastic when the growing fetus is exposed to teratogens. This usually presents in the setting of a known teratogenic syndrome, together with other malformations.

3 Approach to Nail Unit Drug Reaction

When evaluating a patient presenting with nail changes, one should consider if the clinical signs are due to patient factors, disease factors, and/or concurrent medications. The probability of a drug being the main cause can be assessed using causality assessment criteria such as the Naranjo's algorithm (Naranjo et al. 1981). However, the assessment of drug causality for nail changes is made difficult because re-introducing the culprit drug may not produce the same signs (Piraccini et al. 2004), resolution of the nail changes may be delayed for many months or irreversible or they may resolve without withdrawing the culprit drug. The same drug can affect different aspects of the nail unit and produce various clinical signs. The most important clue for causality is that the nail unit reaction should follow (usually several weeks) the introduction of the suspected drug, and the reaction should be stereotypic to the class of medication prescribed. The skin, hair, and mucosa can be concurrently involved in the drug reaction and provide further clues to determining causality. It is important to exclude causes other than a drug reaction when there is only one nail affected. For example, a subungual melanoma or other subungual tumors should be ruled out if there is only a single digit affected by longitudinal melanonychia or pyogenic granuloma-like growths (Piraccini et al. 2010).

4 Common Examples of Drugs Causing Specific Clinical Findings in the Nail Unit

4.1 Nail Fold

1. Acute paronychia and ingrown nail with granulation tissue (some authors refer to this as periungual pyogenic granuloma): systemic retinoids (Benedetto et al. 2019), antiretroviral therapy [indinavir (García-Silva et al. 2002)], epidermal growth factor receptor inhibitors (Fox 2007; Garden et al. 2012), chemotherapy agents (taxanes, mitoxantrone, methotrexate, capecitabine, doxorubicin, 5-fluorouracil) (Piraccini et al. 2004; Robert et al. 2015; Paul and Cohen 2012), mTOR (mammalian target of rapamycin) inhibitors (Campistol et al. 2010), imatinib (Dika et al. 2013), vemurafenib (Dika et al. 2016).

4.2 Nail Bed

1. Onycholysis: Cancer chemotherapeutic agents (Vanhooteghem et al. 2000; Robert et al. 2015; Gilbar et al. 2009) (e.g., methotrexate, taxanes, 5-fluorouracil, capecitabine, etoposide, mitoxantrone, doxorubicin, pemetrexed, ixabepilone), systemic retinoids, epidermal growth factor receptor inhibitor therapy (Fox 2007), mTOR inhibitors

(Campistol et al. 2010), dabrafenib (Dika et al. 2016), pan-fibroblast growth factor receptor 1–4 inhibitors (Betrian et al. 2017).
2. Photo-onycholysis: Tetracyclines (especially demeclocycline and doxycycline), psoralens, thiazide diuretics, oral contraceptives, fluoroquinolones, captopril, enalapril, practolol, indomethacin, voriconazole, griseofulvin (Baran et al. 2019).
3. Apparent leukonychia (Muehrcke's lines): Cancer chemotherapeutic agents (5-fluorouracil, adriamycin, cyclophosphamide, transretinoic acid therapy) (Piraccini et al. 2004; Gül and Kiliç 2004; Dasanu et al. 2013).
4. Splinter hemorrhages: mTOR inhibitors (Campistol et al. 2010), kinase inhibitors (sunitinib, sorafenib, cabozantinib), tetracycline, terbinafine, ganciclovir, nitrofurantoin (Sanders et al. 1976; Lorenzi et al. 2003; Tan and Zhu 2006; Nakamura and Miyachi 2008; Cho and Chan 2013).
5. Raynaud's phenomenon: Cancer chemotherapy agents (cisplatin, bleomycin, vincristine), β-adrenoceptor blockers (Khouri et al. 2016).
6. Pigmented nail bed: Minocycline (Tavares and Leung 2011), quinacrine (Kleinegger et al. 2000).

4.3 Nail Plate/Matrix

1. True transverse leukonychia: Cancer chemotherapeutic agents (Robert et al. 2015; Gilbar et al. 2009; Hogan et al. 1991, Shelley and Humhrey 1997) (e.g., cyclophosphamide, doxorubicin, vincristine, cisplatin, daunorubicin, docetaxel), sulfonamide, tetracycline: itraconazole (Chapman and Cohen 1997), retinoids, antimalarials, and pilocarpine (Yoruk and Yukselgungor 2003).
2. Thin brittle nails: Epidermal growth factor receptor inhibitor therapy (Fox 2007), cancer chemotherapeutic drugs (Robert et al. 2015), systemic retinoids (Robert et al. 2015), vemurafenib (Dika et al. 2016), ibrutinib (Bitar et al. 2016).
3. Beau's lines: Cancer chemotherapeutic agents (Gilbar et al. 2009; Susser et al. 1999), etretinate, moxifloxacin (Burkhardt et al. 2003), itraconazole (Chen and Liao 2002).
4. Onychomadesis: Cancer chemotherapeutic agents (Gilbar et al. 2009; Susser et al. 1999), pan-fibroblast growth factor receptor one to four inhibitors (Betrian et al. 2017), antiepileptics, penicillin (Shah et al. 2012), azithromycin (Aksoy et al. 2008), retinoids, lead, lithium (Hardin and Haber 2015).
5. Reduced growth rate: methotrexate, azathioprine, cyclosporine, retinoids, gold, lithium, zidovudine, sulfonamides, heparin (Geyer et al. 2004).
6. Increased growth rate: calcium/vitamin D, benoxaprofen, levodopa, biotin, cysteine, retinoids, oral contraceptives, fluconazole, terbinafine (Geyer et al. 2004), itraconazole (Doncker and Pierard 1994).
7. Yellow discolored nails: quinacrine, 5-fluorouracil, temsirolimus, bucillamine, retinoids, cetuximab (Chiriac et al. 2017), tobacco stain.
8. Yellow fluorescence of the lunula under wood's lamp: Tetracycline (Hendricks 1980).
9. Blue lunula: Hydroxyurea, zidovudine, silver, phenolphthalein, chemotherapy agents (Jeevankumar and Thappa 2003).
10. Psoriatic nail changes: Antimalarials, beta-blockers, lithium (Basavaraj et al. 2010).
11. Lichenoid nail changes: Hydrochlorothiazide, terbinafine, propylthiouracil, leflunomide, imatinib (Sin et al. 2017; Zheng et al. 2017; May et al. 2017; Saito et al. 2007; Wahiduzzaman and Pubalan 2008).

4.4 Nail Matrix Melanocytes

1. Longitudinal melanonychia: Cancer chemotherapeutic agents (Gilbar et al. 2009) (most commonly cyclophosphamide, doxorubicin, fluorouracil, bleomycin, and hydroxyurea), zidovudine, psoralens, interferon-α for hepatitis C (Tsilika et al. 2013), minocycline (Eisen and Hakim 1998), hydroxychloroquine (Zhang et al. 2019).
2. Transverse melanonychia: Minocycline, zidovudine, idarubicin (Borecky et al. 1997),

hydroxyurea (Teo and Tan 2006), chemotherapy agents (Lang et al. 2002; Stephens et al. 2019), electron beam therapy (Quinlan et al. 2005), afamelanotide (Paurobally et al. 2013), radiotherapy (Baumert et al. 2015), imatinib (Di Tullio et al. 2018).

Entire Nail Unit

1. Hypoplastic nails at birth secondary to the teratogenic effect of warfarin (Ruthnum and Tolmie 1987), antiepileptic drugs (phenobarbitone, phenytoin, primidone, carbamazepine, valproate) (Lindhout and Omtzigt 1994; McMahon and Braddock 2001; Bravo et al. 2011), and alcohol (Crain et al. 1983).

5 Management Principles for Nail Unit Drug Reactions

Nail unit changes can lead to pain, disfigurement, and loss of function of the nail. Quantification of the type and extent of nail involvement in cancer therapy has helped to influence management and allows comparative studies of nail toxicities and their management (Chen et al. 2012; Lacouture et al. 2010).

Regardless of the type of nail change, a few common management principles apply.

1. The clinician should anticipate the possibility of drug-induced nail changes and counsel the patient appropriately.
2. The need to stop the culprit medication should be weighed against the need to continue the medication to treat the underlying condition. The decision should also take into consideration the severity of the underlying medical condition, the availability of an alternative medication, the severity of the nail change, and patient's wishes. Although most nail changes are reversible when the culprit medication is stopped, treating through is an option to consider when the underlying condition is severe (e.g., cancer) and requires continuation of the culprit medication and the nail changes are asymptomatic.
3. In patients at higher risk of developing nail toxicity (e.g., when receiving chemotherapy or targeted therapy), and in those who already have nail changes, it is prudent to avoid further trauma to the injured nail unit. This involves keeping the nails trimmed, avoiding excessive contacts with irritants (water or detergents) or using gloves in this situation, avoiding nail unit trauma (biting, manicure, nail cosmetics, ill-fitting shoes), and encouraging the application of moisturizers on the periungual skin.
4. Prevention and treatment of secondary colonization and infection by fungi or bacteria (Eames et al. 2010) by using antiseptic soaks [e.g., chlorhexidine solution or topical povidone iodine (Capriotti et al. 2019)] or specific topical antimicrobial creams.
5. Some nail changes do not need active intervention as they are asymptomatic and do not affect function. Cessation of the culprit drug may not be necessary in these cases. These include true leukonychia, Muehrcke's lines, splinter hemorrhages, small subungual hematoma, and melanonychia.
6. Specific measures:
   (a) "Frozen gloves and socks" to prevent docetaxel-induced onycholysis (Scotté et al. 2005, 2008)
   (b) Partial nail plate avulsion with phenol matricectomy for ingrown nails (Piraccini et al. 2010).
   (c) Destructive physical therapy (liquid nitrogen, topical silver nitrate cautery, topical 8% phenol (Panariello et al. 2015)), topical or systemic antibiotics, topical corticosteroid therapy, or topical timolol (Kiyohara et al. 2013; Cubiro et al. 2018) for periungual granulation tissue and pyogenic granulomas.
   (d) Surgical drainage of periungual abscesses or subungual hematoma.
   (e) Oral biotin supplement may be useful to promote the growth of a healthy nail plate (Lipner and Scher 2018).
   (f) Photo-onycholysis can be prevented by using opaque nail varnish, avoiding excessive direct sun exposure or administering the photosensitizing medication at night.

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Drug-Induced Hair Changes

Leila Asfour, David Rutkowski,
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Abbreviations

AA	Alopecia areata
AGA	Androgenetic alopecia
ANA	Anti-nuclear antibody
AR	Androgen receptor
COCP	Combined oral contraceptive pill
EGFR(I)	Epidermal growth factor receptor (inhibitor)
ER	Oestrogen receptor
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
FPHL	Female pattern hair loss
HF	Hair follicle
ICI	Immune checkpoint inhibitors
IP	Immune privilege
IUD	Intra-uterine device
(p)CIA	(Persistent) Chemotherapy-induced alopecia
POP	Progesterone-only pill
SHBG	Sex hormone binding globulin
TE	Telogen effluvium
TNFα	Tumour necrosis factor alpha

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1 Introduction

Hair growth problems are a relatively common side effect of therapeutic drugs. In the majority of cases hair loss results from changes in the hair growth cycle leading to increased hair fall and diffuse hair thinning. In this situation prompt identification and cessation of the triggering medication will usually result in complete recovery. However, the growing use of new and targeted therapies has led to the recognition of other mechanisms of drug-induced hair loss, including those that exacerbate existing hair loss conditions (e.g. androgenic drugs in androgenetic alopecia), drugs that can trigger autoimmune responses (e.g. immune checkpoint inhibitors), or therapies that result in permanent hair loss (e.g. persistent chemotherapy-induced alopecia). Thus, the modern clinician needs to be aware of a wide range of drug-induced hair changes.

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2 The Hair Cycle and Hair Immune System

An appreciation of the cycle of growth and renewal (the 'hair cycle') is needed to understand how drugs may impact hair growth (Paus and Cotsarelis 1999). The duration of the growth period, anagen, determines the hair fibre length. After anagen there is a short period where the hair follicle regresses, called catagen, which in turn leads to telogen, the refractory stage (lasting 3 months) during which the hair sits in the scalp before being shed. Release of a hair at the conclusion of telogen permits the commencement of a new cycle.

The hair follicle has a complex immune system with immunocytes concentrated around the distal hair follicle ostium to prevent microbes entering the skin. In contrast, the proximal hair follicle actively suppresses immune reactions ('immune privilege') by down-regulating antigen presentation and expressing locally generated immunosuppressants. Hair immune privilege is thought to protect the follicle from an unrestricted immune reaction and resultant hair loss which, from an evolutionary perspective, may have survival and reproductive implications (e.g. the lack of hair loss in polar bears) (Ito et al. 2008; Paus et al. 2005).

3 Clinical Assessment

When drug-induced hair loss is suspected it is important to take a careful history to determine the timing and exposure of various agents relevant to the presenting problem. It should be noted whether the hair loss is diffuse (all over the scalp), patterned (just the vertex or crown), or patchy. A hair pull can be performed to assess ongoing activity: any removed hairs should be examined to determine whether they are telogen, anagen, or broken hairs. Finally, a scalp biopsy (using horizontal sectioning and hair counts) may be required to identify the underlying process and exclude other causes.

4 Telogen Effluvium

Telogen effluvium is probably the commonest cause of drug-induced hair loss. The typical presentation is of increased hair shedding throughout the scalp roughly 3 months after exposure to the triggering medication (Table 1). The increased hair fall is usually associated with a variable degree of decreased hair density, although in most people this is not marked and may only manifest as slight temporal recession. The patient may describe increased hair in the brush or in the plug hole and may bring a collection of hair to demonstrate the problem (the so-called 'bag sign'). The hair pull test will identify active or ongoing hair loss, with telogen hairs being readily removed from the scalp.

When assessing telogen effluvium it is important to appreciate other potential non-drug trig-

Table 1 Drugs associated with telogen effluvium

Anti-coagulants	Heparin Warfarin
Anti-depressants	Lithium Tricyclics SSRIs (may have delayed presentation)
Anti-hypertensives/ anti-arrhythmics	ACE inhibitors Beta-blockers Amiodarone
Anti-thyroid	Propylthiouracil
Anti-epileptics	Valproic acid
Anti-microbials	Anti-TB (isoniazid) Antiretroviral therapy Cidofovir Terbinafine
Others	Fibrates Retinoids (acitretin, isotretinoin) Aromatase inhibitors NSAIDs Methotrexate Gold Allopurinol Levodopa Androgenic hormones Bromocriptine Danazol Interferon alpha Leflunomide

gers for the hair shedding. Acute or chronic illness, nutritional deficiency, and emotional stress have all been implicated (Cunningham et al. 2012). Therefore, caution is required not to falsely assign telogen effluvium to medication taken to relieve symptoms of the true trigger (e.g. paracetamol treatment for a febrile illness). Usually, identification and removal of the cause is all that is required, and the process generally settles within 3–6 months.

Excess hair fall reflects an increased proportion of follicles entering the telogen phase of the hair cycle prematurely. This results in a larger number of hairs being shed 3 months later at the end of telogen. Five types of telogen effluvium have been described depending on where in the hair cycle the changes occur (Headington 1993). Most forms of telogen effluvium, including drug-induced, result from 'immediate anagen release', which describes hairs transitioning immediately from anagen into catagen/telogen. However, the hair shedding which occurs when starting topical minoxidil is due to 'immediate-release telogen hairs', where hairs already in telogen are prematurely released from the scalp as a new hair cycle is stimulated.

5 Chemotherapy-Induced Alopecia/Anagen Effluvium

Alopecia is a common side effect of chemotherapy with around 65% regimens resulting in significant hair loss. This side effect is one of the most feared by patients with 47% citing hair loss as the most traumatic aspect of treatment (McGarvey et al. 2001). Patients view chemotherapy-induced alopecia (CIA) as a constant reminder of their illness; it is associated with a loss of control, distorted self-perception, and social isolation. Worryingly, 8% of patients actually reject chemotherapy for fear of the resulting alopecia (McGarvey et al. 2001).

Cytotoxic chemotherapy predominantly affects rapidly dividing cells. Therefore, the highly metabolically active hair matrix cells in the hair bulb which produce the hair shaft are particularly vulnerable to these agents. Hair shaft production stops abruptly resulting in hair breakage and shedding (Paus et al. 2013; Freites-Martinez et al. 2019a). This so-called anagen effluvium is often rapid (within 2 weeks of starting chemotherapy) and extensive, resulting in almost complete baldness. Patients may also experience loss of eyebrows, eyelashes, and body hair, although the extent of this is variable. Recovery of facial and body hair is generally more rapid than regrowth of scalp hair. Hair generally regrows fully within 3–6 months of treatment completion, although some patients describe a permanent change in their usual colour or hair curl after treatment.

The risk of CIA varies between the different chemotherapy agents. Chemotherapy agents that are most frequently associated with alopecia include alkylating agents (e.g. cyclophosphamide), anti-tumour antibiotics (e.g. doxorubicin), anti-microtubule agents (e.g. paclitaxel, docetaxel), and topoisomerase inhibitors (e.g. etoposide). Hair loss is less common with bleomycin, epirubicin, fluorouracil, gemcitabine, melphalan, and platinum-based agents (Freites-Martinez et al. 2019a). The degree of alopecia also depends on the dose, route, and frequency of drug administration. High dose, intermittent and intravenous regimens tend to have a higher incidence of complete alopecia. Other factors such as poor nutrition, scalp irradiation, older age, and pre-existing hair conditions may all influence the degree of hair loss experienced (Palamaras et al. 2011).

6 Chemotherapy-Induced Alopecia: Prevention and Treatments

Scalp hypothermia is used with variable success to reduce the risk of alopecia in patients undergoing cytotoxic chemotherapy for solid tumours. It is thought to reduce the drug delivery to the hair follicle by reduction of blood flow (through vasoconstriction) and by suppression of metabolic activity. Unfortunately, access to this treatment is often limited. It is also not appropriate in patients

with leukaemia or lymphoma since cold-induced reduction in scalp blood flow might risk circulating tumour cells evading treatment (van den Hurk et al. 2012).

The main strategy for managing CIA focuses on psychological support and wig provision until the hair regrows. It is the authors' experience that topical agents which can hasten hair regrowth (minoxidil for scalp hair and bimatoprost for eyelashes) are rarely recommended to patients after chemotherapy (Duvic et al. 1996; Yeager and Olsen 2011; Glaser et al. 2015).

7 Persistent Chemotherapy-Induced Alopecia

Persistent (permanent) CIA (pCIA) is defined as 'absent or incomplete hair regrowth 6 months beyond the completion of chemotherapy'. Although initially described with more aggressive conditioning regimens prior to bone marrow transplant, there is a growing recognition that newer regimens, such as taxane-based chemotherapy now routinely used for breast cancer, may also induce pCIA. Reportedly up to 30% of breast cancer patients treated with these regimens have some degree of persistent hair loss (Marks et al. 2018; Kanti et al. 2014). Usually, the pattern of hair regrowth is incomplete in either a non-scarring diffuse alopecia (53%) or a female pattern hair loss/androgenetic alopecia-type presentation (46%) (Fig. 1) (Freites-Martinez et al. 2019b). Close inspection and trichoscopy examination reveal variability of hair shaft diameter and increased numbers of vellus hairs but without inflammation or scarring. Histological features of pCIA are not well described, but prominent hair follicle miniaturisation (evidenced by an increased vellus: terminal ratio) and increased proportion of catagen/telogen hairs are reported, whereas significant inflammation and scarring is uncommon. Samples of pCIA are almost indistinguishable from those of androgenetic alopecia/pattern hair loss, although the total hair density may be lower in pCIA (Fonia et al. 2017; Miteva et al. 2011). The pathophysiology of pCIA remains unclear but is likely to result from hair follicle stem cell damage inhibiting regeneration and ongoing hair cycling.

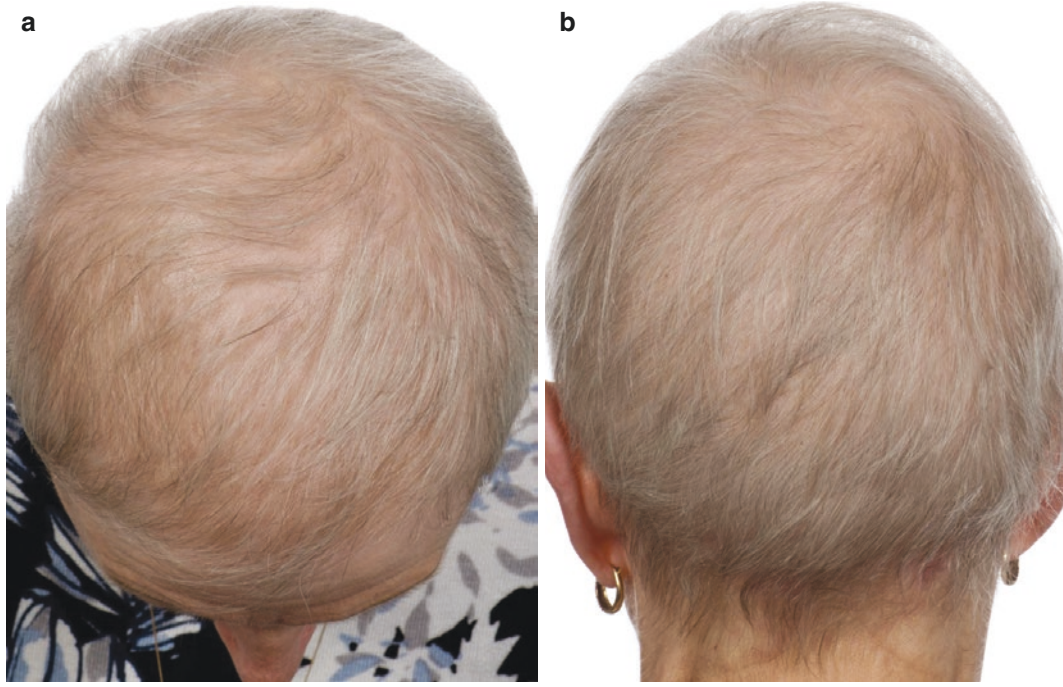

Fig. 1 Persistent chemotherapy-induced alopecia (pCIA). (**a**) and (**b**) show non-inflamed diffuse hair loss with vertex accentuation

8 Targeted Therapies: Anti-tumour Necrosis Factor (Anti-TNF) Therapy

In recent years anti-TNFα therapies have revolutionised the management of psoriasis, inflammatory arthritis, and inflammatory bowel disease. However, paradoxical hair loss side effects have been reported, including alopecia areata and psoriasiform alopecia (Toussirot and Aubin 2016). As TNFα regulates interferon production from plasmacytoid dendritic cells, blockage of TNFα leads to a pro-inflammatory cytokine imbalance, collapse of the hair follicle immune privilege (a key process in alopecia areata [AA] pathogenesis), and T cell trafficking into the tissue (Simakou et al. 2019). Discontinuation of anti-TNF therapy after AA has developed appears to make little difference to the longer-term chance of hair regrowth. Thus, assessment of the risks and benefits of ongoing treatment versus alternative therapeutic options needs to be considered on a case-by-case basis (Tauber et al. 2014).

9 Targeted Oncology Therapies

The development of targeted small molecule and monoclonal antibody therapies has revolutionised medicine. However, many of these targets are also fundamental to epithelial and hair follicle homeostasis, generating a new spectrum of cutaneous side effects. Perhaps the biggest impact on the skin and hair is seen in the growing use of targeted oncology treatments. Experience suggests that some of these features may have prognostic implications, with treatment discontinuation actually being detrimental to long-term survival rates. This is exemplified by EGFR inhibitors in which the presence of severe skin toxicity can serve as a clinical biomarker for treatment efficacy rendering treatment discontinuation an unsatisfactory option.

10 EGFR Inhibitors

Pharmacological inhibition of EGFR via tyrosine kinase inhibitors (e.g. gefitinib, afatinib, erlotinib) or monoclonal antibodies (e.g. cetuximab, panitumumab) is associated with cutaneous reactions in 75–90% of patients (Campbell et al. 2014). A pustular reaction in a sebaceous distribution usually develops within the first few weeks of treatment. Previously labelled as an acneiform eruption, the absence of comedones and distal follicular inflammation identifies this reaction as a folliculitis (Fig. 2). In 10–12% of cases these features are associated with non-scarring alopecia, more rarely a scarring 'folliculitis decalvans-like' presentation can occur (Keith and Stewart 2013). Trichomegaly (increased length and density of the eyelashes) is observed in 6–10% cases (Lacouture et al. 2011; Monjazeb and Wilson 2017). The folliculitis is generally low grade and does not usually necessitate treatment interruption or discontinuation. However, in a small proportion of patients grade 3–4 reactions can occur which are symptomatic and impact on quality of life. Preventative strategies focus on emollient therapy and sun protection since sunlight potentiates this reaction. Active treatment includes potent topical corticosteroid, oral tetracycline antibiotics, and, in resistant cases, low-dose isotretinoin or dapsone (Lacouture et al. 2011; Monjazeb and Wilson 2017). Hair loss is usually reversible on treatment discontinuation and topical minoxidil may be used to improve regrowth. Treatment for the 'folliculitis decalvans-like' presentation involves reduction or discontinuation of the therapy along with a prolonged course of oral tetracyclines, topical steroids, or isotretinoin. Patients who develop trichomegaly should be encouraged to regularly trim their eyelashes to prevent blepharitis or keratitis. Interestingly, patients commenced on MEK inhibitors (e.g. trametinib, cobimetinib, and dabrafenib) commonly develop skin toxicities similar to those encountered with the EGFR inhibitors (Anforth et al. 2014).

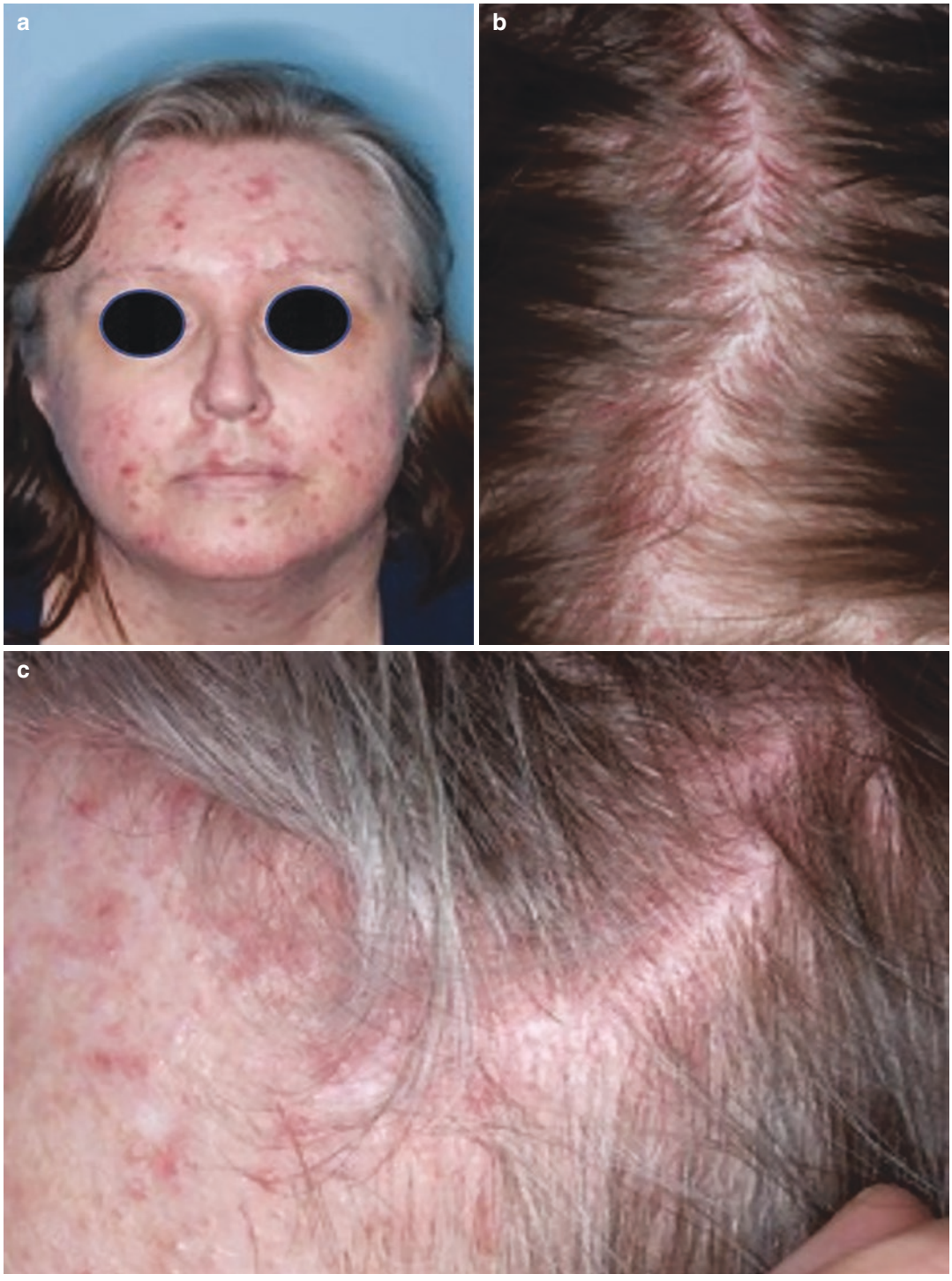

Fig. 2 (**a**–**c**): EGFR inhibitor (Erlotinib)-induced folliculitis and hair thinning

11 Tyrosine Kinase Inhibitors and Hair Pigmentation

Gain-of-function mutations in the tyrosine kinase, c-kit, expressed on haematopoietic stem cells, are associated with several cancers. C-kit also modulates genes involved in tyrosinase enzyme activity and melanin synthesis, with loss of function mutations in this gene resulting in piebaldism. As such, tyrosine kinase inhibitors, such as sunitinib, can induce skin depigmentation and hair depigmentation (poliosis) in up to 60% of patients. An interruption in the treatment regimen can result in renewed hair repigmentation within the same hair fibre, giving the striking appearance of alternating bands of pigmentation and depigmentation along the hair length (Rosenbaum et al. 2008).

12 Immune Checkpoint Inhibitors and Autoimmune Reactions

Immune checkpoint inhibitors are increasingly being used in oncology to mobilise the immune system and promote a cytotoxic T cell response against immunogenic cancers. However, a significant proportion of patients exhibit autoimmune toxicities, manifesting as colitis, endocrinopathies, pneumonitis, or dermatitis. Follicular reactions, although rare, have been reported, including AA (Zarbo et al. 2016). Hair pigmentation changes may be seen and appear cancer-specific; for example, depigmentation/poliosis is seen in melanoma patients, while hair repigmentation has been observed in lung cancer patients. This curious differential response between cancer types treated with an immune checkpoint inhibitor is not currently understood. Importantly, immune checkpoint inhibitor-induced toxicity may manifest at different time points during or after the treatment course. As such, clinicians should consider immune checkpoint inhibitor toxicity in any unusual skin manifestations in patients currently or previously treated with an agent from this class (Brahmer et al. 2018).

13 Hormone Effects on Hair Growth

Hormonal contraceptives suppress gonadotrophins to inhibit ovulation (combined oral contraceptive pill [COCP]) or increase uterine mucus (progesterone only pill [POP]) to prevent pregnancy. Oestrogens prolong anagen (Paus and Cotsarelis 1999), antagonise androgens, and induce sex hormone binding globulin (SHBG), thereby reducing free testosterone in the blood. Some progestins (synthetic progestogens) are less androgenic than others, either by not inhibiting oestrogen-induced SHBG induction, or are directly anti-androgenic by blocking the androgen receptor on cells. In individuals genetically predisposed to androgen-induced scalp hair loss or hirsutism certain progestins may exacerbate the problem (Table 2). The net effect of most COCP is anti-androgenic (Azarchi et al. 2019). Avoidance of high androgenic progestins and substitution of low androgenic COCP may be a useful therapeutic option in some people, although the risk/benefit of each agent must be assessed for each individual, particularly as stopping or starting hormonal therapy may trigger telogen effluvium (Cunningham et al. 2012).

Table 2 Hormonal contraception and androgenic progestins

Androgen index	Progestins	Advice in FPHL/ hirsutism
Anti-androgen	Dienogest Cyproterone acetate Nomegestrol	Good
Least androgenic	Drospirenone Desogestrel Gestodene Norgestimate	Good–neutral
Moderate–high androgenic	Norethisterone/norethindrone Norgestrel Levonorgestrel	Avoid
Other (non-COCP) high androgenic progestin-containing products	Medroxyprogesterone acetate (depot contraceptive injection) Norethisterone (depot contraceptive injection) Etonogestrel (contraceptive implant; vaginal ring) Levonorgestrel (hormone-IUD) Norelgestromin (skin patch)	Avoid

14 Anti-oestrogen Therapy

Approximately 70% breast cancers are hormone receptor positive, allowing anti-oestrogen therapy to be used as a targeted therapy. Various agents are used including anti-oestrogen receptor (ER) modulators which directly block the ER (e.g. tamoxifen), aromatase inhibitors that block conversion of testosterone to oestrogen (e.g. anastrozole, letrozole, exemestane), and cyclin inhibitors (e.g. palbociclib). These therapies are associated with hair loss through a number of mechanisms, such as loss of direct anagen-prolonging effects of oestrogens as well as pro-androgenic action due to relative increased levels of testosterone. Reported mean time to hair loss is 16.8 months (range 1–91 months) with these agents, and typically presents with diffuse hair loss in a distribution suggesting female pattern hair loss (Freites-Martinez et al. 2019a, b).

15 Hirsutism, Hypertrichosis, and Trichomegaly

Hirsutism is defined as terminal hair growth occurring in androgen-dependent areas due to excessive androgen stimulation. Important additional signs of virilisation should be sought, including acne, seborrhoea, alopecia, and clitoromegaly. Certain drugs may exacerbate hirsutism, such as testosterone, danazol (androgen-receptor agonist), ACTH, metyrapone (an inhibitor of cortisol synthesis), anabolic steroids, and glucocorticoids.

Hypertrichosis is excessive hair growth throughout the body in both men and women occurring in a non-androgen-dependent pattern. Drug-induced hypertrichosis tends to be dose dependent and reverses after drug withdrawal. It is suggested that in utero exposure to medications such as minoxidil can lead to congenital generalised hypertrichosis (Kaler et al. 1987). There is an extensive list of medications associated with acquired hypertrichosis (Table 3).

Table 3 Drug-induced hypertrichosis

Antibiotics	Streptomycin
Anti-inflammatory	Benoxaprofen Corticosteroids
Vasodilators	Minoxidil Diazoxide Prostaglandin analogues Diltiazem Nifedipine Verapamil
Diuretics	Acetazolamide
Anticonvulsants	Phenytoin Valproic acid
Immunosuppressants	Ciclosporin Mycophenolate mofetil
Psoralens	Methoxypsoralen Trimethylpsoralen
Antiseptic agent	Hexachlorobenzene
Chelators	Penicillamine
Beta-adrenergic agonist	Fenoterol
Cytokine	Interferon alpha
Colony-stimulating factors	Erythropoietin
Antiretroviral	Zidovudine
EGFR inhibitors	Cetuximab Panitumumab Erlotinib Gefitinib

Trichomegaly is the increased length, thickness, and pigmentation of eyelashes due to dysregulation of the eyelash hair cycle. Medications associated with trichomegaly include ciclosporin, tacrolimus, EGFR inhibitors, interferon alpha, prostaglandin analogues, zidovudine, and topiramate (Paus et al. 2016).

16 Drug-Induced Hair Colour and Texture Changes

Certain drugs are reported to induced colour or textural changes to the hair shaft (Ricci et al. 2016). Hair darkening may be observed with acitretin, valproate, and EGFR inhibitors. Hair depigmentation/poliosis is seen with antimalarials, imiquimod, multi-kinase inhibitors, and immune checkpoint inhibitors (Freites-Martinez et al. 2019a). Increased hair curling is reported with retinoids, cetuximab, sorafenib, and antiretroviral therapy. Excessive hair 'weathering' and fragility may complicate retinoid and BRAF-inhibitor therapy.

17 Conclusions

A better understanding of the different types and causes of drug-induced hair changes will allow a patient-focused approach to management and providing insights into the mechanisms and prognostic implications of the different side effects seen. As EGFRi therapy has shown, a nuanced individualised approach is increasingly required when dealing with the growing spectrum of side effects encountered in the modern health setting.

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Drug-Induced Pigmentary Disorders

Tan WeiXuan Colin, Yiping Emily Gan, and Alain Taieb

1 Introduction

Drug-induced pigmentary changes can affect the skin, nails, hair, and mucous membranes. The incidence of drug-induced pigmentation is variable, but there have been estimates that up to 20% of all cases of acquired hyperpigmentation may be due to drugs (Dereure 2001). It is important to consider this in elderly patients on multiple medications, who present with otherwise unexplained patterns of pigmentary changes.

2 Pathogenesis

2.1 Drug-Induced Hyperpigmentation

The pathogenesis of hyperpigmentation largely depends on the drug itself. There are four established mechanisms. The first mechanism involves the accumulation of melanin, which can be due to a nonspecific drug-induced cutaneous inflammatory response resulting in the stimulation of melanocytes with an increase in melanin production or the formation of stable drug-melanin complexes that prevent melanin clearance within dermal melanophages. The second mechanism involves drug-induced synthesis of special pigments such as lipofuscin. The third mechanism involves drug accumulation either in dermal melanophages, which are unable to eliminate the drug, or in the dermis as freely scattered granules. The last mechanism is iron or hemosiderin deposition, which occurs as a result of drug-induced vessel damage leading to leakage of red blood cells into the dermis and subsequent lysis (Dereure 2001; Nahhas et al. 2019).

Sun exposure often worsens this process, leading to more significant pigmentation in exposed sites. Exposure to ultraviolet (UV) rays and visible light aggravates and prolongs pre-existing drug-induced inflammation. This results in worsening and persistence of the pigmentation.

2.2 Drug-Induced Hypopigmentation

The exact mechanisms of drug-induced hypopigmentation are uncertain. One of the more classic drugs, monobenzyl ether of hydroquinone or monobenzone, is converted by tyrosinase in pigmented cells, thereby triggering a cascade of immunological events that result in depigmentation. These include the formation of quinone-

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hapten complexes and the generation of reactive oxygen species (van den Boorn et al. 2011).

Anti-programmed cell death-1 (PD1) inhibitors used in the treatment of melanoma are thought to trigger an immune response that reacts with common melanocyte antigens, which can lead to melanocyte destruction (Larsabal et al. 2017). Tyrosine kinase inhibitors act on the c-kit pathway, which in combination with ligand stem cell factor is involved in melanogenesis and melanocyte homeostasis. This commonly results in depigmentation but may rarely have hyperpigmentation as well (McPartlin and Leach 2005).

3 Approach to Diagnosis of Drug Induced Pigmentary Disorders

3.1 Clinical Presentation

The evaluation of drug-induced pigmentary disorders begins with a thorough medical history to determine the drugs taken. All previous and current medications should be reviewed and particular attention paid to drugs known to cause dyschromia. Determining the chronology with respect to the onset, worsening, and fading of pigmentation can help to identify the offending agent. However, this may be challenging, as drug-induced pigmentation is often progressive and insidious in onset, extending over months to years. Fading of pigmentation after withdrawal of the suspected drug can be helpful in confirming the diagnosis of drug-induced pigmentation. However, resolution is often slow, taking months to years and may be incomplete.

A careful examination of the skin and mucous membranes is important to distinguish drug-induced pigmentation from other forms of acquired pigmentation. The topographic distribution commonly includes sun-exposed areas and the mucous membranes, especially mouth and conjunctivae. Presence of unusual coloration is often due to drug-induced pigmentation and may vary from purple, red, yellow, slate or blue-gray shades. Some aspects of discoloration are very suggestive, like the mauve color caused by chlorpromazine. Nonspecific inflammatory lesions, blistering, or lichenoid lesions with or without photosensitivity are often found in drug-induced hyperpigmentation.

Certain drugs are known to produce characteristic patterns of pigmentation. It is important to be familiar with the more commonly used drugs and their typical patterns (see below for details). A skin biopsy for histology may be helpful in making the diagnosis. This can demonstrate characteristic melanin or hemosiderin accumulation and distribution patterns, inflammatory features or specific pigments either found free or in dermal melanophages.

3.2 Differential Diagnosis

Metabolic, hormonal, and nutritional disorders may present with pigmentation resembling drug-induced pigmentation. For example, Addison's disease presents with diffuse pigmentation of the skin and mucosa with accentuation over skin folds and scars. This is associated with electrolyte abnormalities such as hyponatremia, hyperkalemia, low serum cortisol levels, and an inappropriate response to a corticotrophin stimulation test. Wilson's disease and hemochromatosis present with a generalized blue-gray pigmentation with a metallic sheen. This is accompanied by abnormal copper or iron studies, respectively, and may have a significant family history. Dyschromia can be seen in states of malnutrition or vitamin deficiencies, particularly vitamin B_{12} and nicotinic acid. When pigmentation involves the face, melasma and lichen planus pigmentosus are common differentials to consider. Melasma typically presents with brown to gray macules or patches over the sun-exposed areas on the face such as the cheeks, forehead, temples, and nasal bridge. Lichen planus pigmentosus (LPP) describes macular pigmentation with or without typical lichen planus elsewhere. This most commonly occurs on the head and neck region and the flexures. Histological examination shows the presence of dermal melanophages with or without interface dermatitis or a lichenoid reaction.

4 Common and New Drugs Inducing Hyperpigmentation

4.1 Antimalarials, e.g., Hydroxychloroquine (HCQ), Chloroquine, Mefloquine, Quinacrine

The incidence of drug-induced pigmentation in patients receiving the above antimalarials is estimated to be 25%. Patients typically present with bluish-gray pigmented macules, which may coalesce into large patches in sun-exposed areas such as the anterior aspect of legs (Fig. 1) and head, including the oral mucosa. Some studies have reported the appearance of pigmented lesions in areas of previous ecchymoses (Jallouli et al. 2013). Transverse bands or diffuse pigmentation of the nails may be observed. Rarely, chloroquine may induce pigmentation of the hard palate (de Andrade et al. 2017). Histological stains may demonstrate hemosiderin deposition surrounding capillaries, increased melanin, or both. In one study, onset of pigmentation occurred after a median HCQ treatment duration of 6.1 years (range 3 months to 22 years) (Jallouli et al. 2013). Lesions typically resolve within 2–6 months of drug discontinuation (Skare et al. 2011).

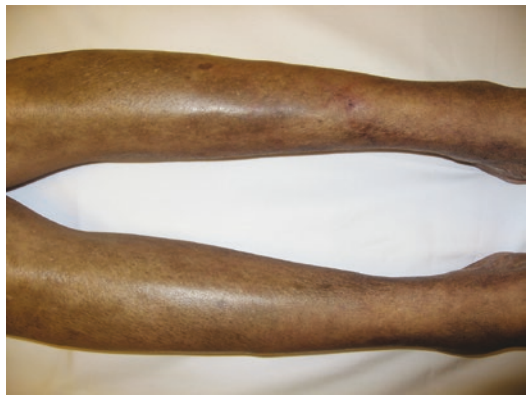

Fig. 1 Hyperpigmentation on the shins induced by hydroxychloroquine

4.2 Analgesics, e.g., Non-steroidal Anti-inflammatory Drugs (NSAIDS), Paracetamol

Analgesics can cause fixed drug eruptions with resultant post-inflammatory hyperpigmentation. This is thought to be due to the suspect drug acting as a hapten, which binds to a melanocyte-linked protein leading to the melanocyte being the target of a cytotoxic reaction to the drug. Patch testing to the suspected drug can be performed on initial sites of reaction, and oral challenges are diagnostic in case of failure of patch testing.

5 Cardiac Drugs, e.g., Amiodarone, Diltiazem, Amlodipine

Amiodarone characteristically causes a blue-gray or violaceous discoloration over sun-exposed areas, most often involving the face and ears. The cornea may be the first site of pigmentation and presents as a yellowish-brown pigmentation. Hyperpigmentation typically occurs after 6 months of therapy with those receiving a higher dose (≥400–800 mg/day) at higher risk of developing dyspigmentation. The exact pathogenesis is unknown but is postulated to involve deposits of lipofuscin in dermal histiocytes. Lesions tend to be quite persistent but may improve after cessation of the drug, albeit slowly (Delage et al. 1975).

Diltiazem-induced hyperpigmentation is rare with limited reports to date, mainly in darker skinned individuals. The extended-release form of diltiazem is frequently implicated in pigmentary changes. This presents as reticulated or macular blue, gray, or brown pigmentation over sun-exposed areas, occasionally with perifollicular accentuation. Pigmentation begins after at least 6 months of continued therapy although the onset may be significantly prolonged, numbering in years. Diltiazem demonstrates absorption mainly in the UV-B spectrum which supports the

photosensitizing effect of diltiazem, although the exact mechanism is unknown (Scherschun et al. 2001; Saladi et al. 2006; Desai et al. 2010).

Amlodipine has rarely been associated with pigmentary disturbances. A case report describes gradual, generalized hyperpigmentation in sun-exposed areas with pigmentation of the lips, tongue, and hard palate after taking amlodipine for three years. Another case report describes longitudinal pigmented bands and periungual pigmentation after amlodipine ingestion for 2 years. In both cases, there was improvement of the pigmentation after amlodipine was stopped (Erbagci 2004; Sladden et al. 2005).

6 Chemotherapeutic Agents, e.g., 5-Fluorouracil, Bleomycin, Hydroxyurea, Anthracyclines

Chemotherapeutic agents are responsible for a wide variety of pigmentary alterations in the skin, mucous membranes, hair, and nails. The list of chemotherapeutic agents is extensive with newer, targeted treatments being developed rapidly. As such, it is important to have a high index of suspicion when confronted with the possibility of pigmentary alterations with chemotherapeutic agents, particularly the newer drugs. The incidence of targeted cancer therapy-induced pigmentary changes has been estimated to be up to 17.7% in the skin and 21.5% in the hair (Dai et al. 2017). The onset of pigmentation may range from weeks to months and can be localized or diffuse. Distinctive patterns of discoloration have been described with specific drugs, and pigmentary alterations tend to improve with cessation of the offending agent although permanent dyspigmentation may occur in some cases.

5-fluorouracil causes diffuse pigmentation involving the palms, soles, nails, oral mucosa, and also transverse bands on the interphalangeal joints that resolve after drug cessation (Hrushesky 1980). Less commonly, it may present as a serpentine supravenous pigmentation after infusions (Rao and Balachandran 2010). Tegafur is structurally similar to 5-fluorouracil and can cause pigmented macules on the palms, soles, nails, and unusually, the glans penis (Llistosella et al. 1991).

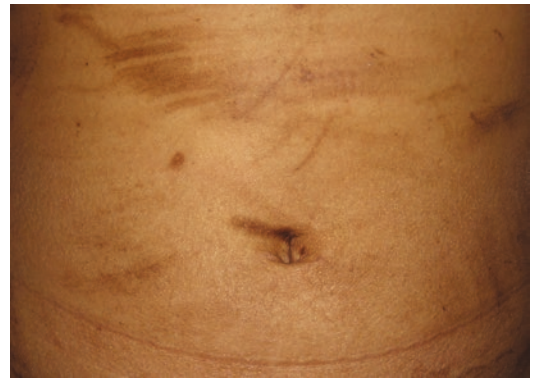

Fig. 2 Flagellate pigmentation caused by bleomycin

Bleomycin is well characterized by flagellate pigmentation (Fig. 2) after use with a varied distribution, resolving within weeks to months after the drug is discontinued (Werner and Thornberg 1976; Pinto et al. 2018). Cyclophosphamide can discolor the skin, mucous membranes, palms, fingers, toes, and teeth (Harrison and Wood 1972). A wide variety of nail changes have been reported with cyclophosphamide, ranging from longitudinal streaks, transverse bands to diffuse pigmentation (Kumar et al. 2010). Hydroxyurea can cause skin and mucosal pigmentary alterations and nail changes such as pigmented bands or diffuse nail pigmentation (Gropper et al. 1993). Rarely, a bluish discoloration of the lunula has been reported (Uskudar Teke and Erden 2013). Anthracyclines such as daunorubicin and doxorubicin can cause a photo-distributed pattern of pigmentation with mucosal and nail involvement, forming pigmented bands and/or a pigmented nail bed (Pratt and Shanks 1974).

7 Antimicrobial Agents, e.g., Antibiotics, Anti-mycobacterial Agents, Anti-retrovirals

Minocycline is one of the best characterized examples of drug-induced dyspigmentation (Fig. 3). The overall incidence of minocycline-induced hyperpigmentation is estimated at 3–5% of patients (McGrae and Zelickson 1980; Simons and Morales 1980; Patel et al. 1998; Eisen and Hakim 1998; Fraunfelder and Randall 1997; Pepine et al. 1993) and is most common after several months of treatment. The latency between drug consumption and the onset of hyperpigmentation may be a few years after initiation of minocycline therapy. Other risk factors include a higher cumulative dose (above 50 g), prior history of skin inflammation or excessive sun exposure, and the consumption of other drugs associated with dyspigmentation. Other tetracyclines such as doxycycline are much less frequently associated with pigmentary alterations.

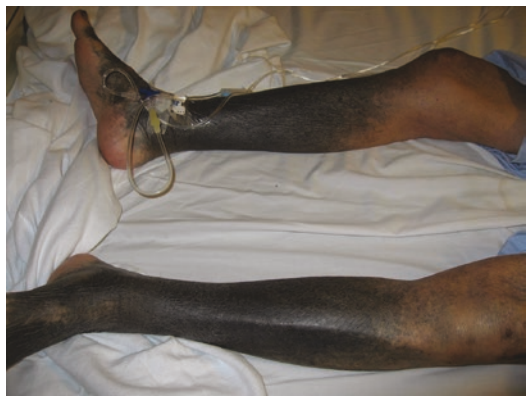

Fig. 3 Minocycline-induced blue-gray hyperpigmentation on the anterior shins

The mechanisms by which minocycline causes hyperpigmentation are not fully understood but are thought to be due to: (1) Direct effect of minocycline on melanocytes in susceptible skin (usually with prior inflammation or sun damage) resulting in excessive melanin production, (2) Deposition of minocycline crystals or of its by-products in the skin. Table 1 describes the clinical characteristics of minocycline-induced hyperpigmentation as well as that of other antimicrobial agents.

Table 1 Antimicrobial agents known to cause hyperpigmentation

Drug implicated	Characteristics of dyspigmentation
Antibiotics	
Minocycline (McGrae and Zelickson 1980; Simons and Morales 1980; Patel et al. 1998; Eisen and Hakim 1998; Fraunfelder and Randall 1997; Pepine et al. 1993)	• Blue-gray macules over areas of acne scarring or other sites of inflammation. • Hyperpigmented macules on areas distant from original site of inflammation or infection; on areas with sun exposure or on anterior aspects of lower limbs. • Diffuse brown, blue, or gray hyperpigmentation with photoaggravation. • Hyperpigmentation of vermillion border of lower lip. • May affect hair, nails, oral cavity, ophthalmic structures.
Polymyxin (Mattos et al. 2016; Mattos et al. 2017)	• Diffuse pigmentation. • Face and neck distribution.
Anti-mycobacterial agents	
Isoniazid (Holdiness 1985; Bilgili et al. 2011)	• Violaceous discoloration. • Brownish pellagra-like eruption. • Yellowish discoloration of jaundice with higher doses.
Rifampicin (Holdiness 1985)	• Reddish pigmentation.
Levofloxacin (Holdiness 1985; Lorente et al. 2013)	• Blue-gray discoloration. • Neck, shins, dorsal aspect of hands, and extensor aspect of forearms.
Clofazimine (Karat et al. 1971; Murashov et al. 2018)	• Reddish-brown pigmentation on lesional skin. • May affect conjunctiva with prolonged use.
Dapsone (Burke et al. 2013)	• Hyperpigmentation at sun-exposed sites. • Blue-gray pigmentation on skin and nails.

(continued)

Table 1 (continued)

Drug implicated	Characteristics of dyspigmentation
Anti-retrovirals	
Zidovudine (Rahav and Maayan 1992; Chawre et al. 2012)	• Dose-dependent and reversible. • Diffuse brownish discoloration on palms and soles. • Bluish dyschromia of lunula. • Longitudinal pigmented bands on nails.
Emtricitabine (Shirasaka et al. 2011; Mondou et al. 2004)	• Pigmentation of the palms, soles, and dorsal hand surfaces. • May resolve before drug is discontinued.

Table 2 Heavy metals known to cause hyperpigmentation

Drug implicated	Characteristics of dyspigmentation
Silver salts (Rodriguez et al. 2017; White et al. 2003; White 1997; Legat et al. 1998)	• Argyria—diffuse slate-gray pigmentation. • Sun-exposed areas, mucous membranes, sclera, and nails. • Relative sparing of skin folds. • Localized pigmentation due to prolonged direct contact.
Gold salts (Smith et al. 1995; Trotter et al. 1995)	• Chrysiasis—blue-gray pigmentation. • Sun-exposed areas. • Spares mucous membranes. • More obvious discoloration around eyes.
Iron salts (Drakensjo et al. 2014)	• Blue, gray, or brown discoloration. • Tends to be permanent.
Bismuth subsalicylate (Cohen 2009; Bradley et al. 1989)	• Black discoloration of tongue. • Appears and disappears within 24 h of ingestion.

8 Metals, e.g., Bismuth, Gold, Silver, Iron

Heavy metals are historically well known to cause pigmentary changes but are now abandoned as drug medication, except for iron salts (Table 2). Direct deposition of the metals into the skin triggers inflammation and melanogenesis which is further worsened after sun exposure. Pigmentation usually fades after discontinuation of the drug but does not resolve completely, often with residual discoloration.

9 Psychotropic Agents, e.g., Chlorpromazine, Desipramine, Imipramine, Amitriptyline

Phenothiazines may cause pigmentation, particularly with a longer duration of intake and consequent higher cumulative dose. The incidence is uncertain but case reports and series indicate that among the phenothiazines, chlorpromazine is the most common offending member. Other phenothiazines seem to be less likely to induce pigmentation with the exception of trifluoperazine which can cause a similar pigmentary change.

A violaceous to gray dyspigmentation "mauve" with metallic sheen over sun-exposed areas on the face, exposed areas of the eyes, limbs, and nail beds is most commonly described. Interestingly, this may spare facial wrinkles and the mucous membranes and the deposited pigment granules may migrate to the bloodstream from the skin and move to the liver, kidney, or heart (Wolf et al. 1993; Molina-Ruiz et al. 2016). This pigmentation is thought to be due to: (1) melanogenesis from chlorpromazine-melanocyte complexes, (2) melanin accumulating in macrophages, (3) chlorpromazine polymers that form as a result of sun exposure, and (4) chlorpromazine-induced inhibition of pigment-diluting factors in the autonomic nervous system (Dereure 2001).

Tricyclic antidepressants are structurally related to phenothiazines but are less commonly associated with pigmentary alterations.

Drug-induced pigmentation has been reported with amitriptyline, desipramine, and imipramine (Sicari et al. 1999; Narurkar et al. 1993; Steele and Ashby 1993; D'Agostino et al. 2009). The incidence has not been fully characterized and pigmentation tends to occur after prolonged drug use with slow resolution after discontinuation. A blue to slate-gray hyperpigmentation over sun-exposed areas has been described, particularly with desipramine and imipramine (Narurkar et al. 1993; Steele and Ashby 1993; D'Agostino et al. 2009). Amitriptyline-induced pigmentation may appear years after ingestion of the drug (Eichenfield and Cohen 2016). The mechanism by which tricyclic antidepressants induce pigmentation is uncertain but likely involves sun-induced activation of the drug with subsequent drug-melanosome complexes and increased melanogenesis (Sicari et al. 1999).

9.1 Others

A wide variety of medications have been reported to cause hyperpigmentation. Much of the literature exists as case reports or limited case series; hence these are poorly characterized. Table 3 highlights the more common drugs involved in hyperpigmentation.

Table 3 Other drugs commonly implicated in hyperpigmentation

Drug implicated	Characteristics of dyspigmentation
Anticoagulants	
Tinzaparin (Takci and Ozoguz 2012)	• Diffuse, brown to black nail pigmentation. • Increased pigmentation over axillae, perineum, and nipple-areola complex.
Eltrombopag (Braunstein et al. 2013; Bowen et al. 2010)	• Graying of the face and limbs. • Sparing of the hands, nails, eyes, and mucous membranes.
Antiepileptics	
Barbiturates (Dereure 2001)	• Brownish discoloration over face. • May be mistaken for melasma.
Phenytoin (Scheinfeld 2003)	
Bleaching agents	
Hydroquinone (Tan et al. 2008; Penneys 1985)	• Exogenous ochronosis with prolonged use. • Dark blue to black discoloration over face.
Vitamins and supplements	
Beta-carotene/Vitamin A (Lascari 1981)	• Yellow to orange diffuse discoloration. • Accentuation on palms, soles, and nasolabial folds. • More common with prolonged and excessive intake. • Fades within a few months after cessation.
Hormonal agents	
Oral contraceptives (Resnik 1967)	• Trigger or worsen melasma. • Brown to gray macules on the cheeks, nose bridge, temples, and upper lips.
Adrenocorticotropic hormone (Dereure 2001)	• Bronze discoloration similar to Addison's disease. • Occurs within a few weeks of use. • Resolves after discontinuation.
Afamelanotide (Biolcati et al. 2015)	• Mild pigmentation over sun-exposed and sun-covered areas. • Darken existing melanocytic nevi.
Proton pump inhibitors	
Omeprazole (Baker and Pandya 2014)	• Ashy dermatosis-like pigmentation (Fig. 4). • Diffuse blue-gray macules and patches on the trunk. • May extend to limbs. • Fades months after cessation.

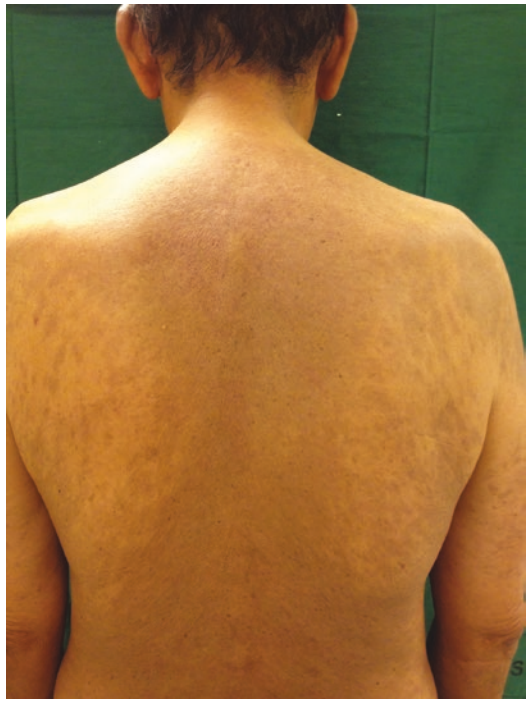

Fig. 4 Brown-gray hyperpigmented patches on the back caused by omeprazole use

10 Common and New Drugs Inducing Hypopigmentation

Topical steroids are known to induce hypopigmentation; these are commonly used in dermatology and other fields. The exact mechanism is unknown but is thought to be due to either a reduction in function or number of melanocytes (Firooz et al. 1995). The degree of hypopigmentation depends on the concentration and type of corticosteroid injected. This usually occurs a few weeks after injection, is more prominent in those of a darker skin color, and tends to fade in a few months (Baker and Pandya 2014; Firooz et al. 1995; Gupta et al. 2019; Jang et al. 2011).

Immunotherapy for recalcitrant warts, such as application of contact sensitizers, topical imiquimod and injection of candida antigen, has been known to cause hypopigmentation at the site of injection or application (Pan et al. 2009; Pires et al. 2010; Mashiah and Brenner 2008; Brown et al. 2005; Wilmer et al. 2013). The mechanism of hypopigmentation is unknown but is hypothesized to be either a (1) Direct cytotoxic effect on melanocytes, (2) Koebnerization which unmasks occult vitiligo, or (3) Induction of a local inflammatory response (Baker and Pandya 2014).

Anti-programmed cell death-1 (PD-1) inhibitors are new drugs used in the treatment of melanoma. They are frequently associated with the development of vitiligo-like lesions which is thought to confer a better prognosis during melanoma therapy (Nahhas et al. 2019). The incidence of vitiligo-like lesions with pembrolizumab and nivolumab was estimated to be 8.3% and 7.5% respectively (Dai et al. 2017; Belum et al. 2016). The depigmented lesions appear progressively after months of treatment which may be preceded by an inflammatory phase (Fig. 5). There may be regression of pre-existing melanocytic nevi. Unlike classic vitiligo, the depigmented lesions induced by PD-1 inhibitors occur mainly over sun-exposed sites without Koebner's phenome-

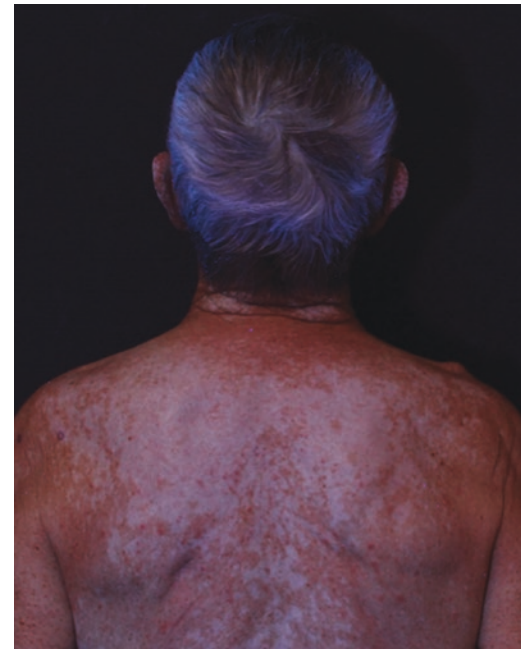

Fig. 5 Depigmentation of the trunk and neck with scalp poliosis in a patient who had been treated with Nivolumab for 6 months. (Source: Professor Julien Seneschal, National Reference Centre for Rare Skin Disorders, Hôpital Saint Andre, CHU de Bordeaux, Bordeaux, France, with permission)

non, without a personal or family history of vitiligo, thyroid disorders, or other autoimmune disease, and may have more rapid involvement of hair follicles. The vitiligo-like lesions tend to persist, even after treatment is discontinued. The pathogenesis is thought to be related to a PD-1 inhibitor-driven immune response that reacts with common melanocyte antigens leading to melanocyte destruction (Dai et al. 2017).

Chemical-induced leukoderma is a well-recognized entity which presents as acquired vitiligo-like lesions after repeated exposure to the offending agent. This may be induced by a wide variety of chemical agents which are often phenol or catechol derivatives, sulfhydryls, or other compounds used in various industrial processes, household products, and cultural practices. The pathogenesis is not completely understood but is thought to be due to melanocyte toxicity in genetically predisposed individuals. Clinical and histological features are similar to that of vitiligo and a careful history must be elicited to differentiate the two. Depigmentation often occurs with prior inflammation and may develop distant from the site of contact with the offending agent. The face is the most commonly affected area, especially around the eyes, followed by the hands and feet. Confetti-like macules may be seen more commonly in chemical-induced leukoderma although this is not diagnostic (Ghosh 2010; Harris 2017).

Monobenzyl ether of hydroquinone or monobenzone is a phenol derivative which is a potent depigmenting agent used to induce complete depigmentation in patients with extensive vitiligo and has been used as immunotherapy for melanoma. Hydroquinone, which is primarily used for the treatment of melasma, may rarely result in depigmentation. This may occur with repeated use and can have a protracted onset within weeks to months of application (van den Boorn et al. 2011; Jow and Hantash 2014).

Rhododendrol is a phenolic compound developed in Japan that was used for bleaching and whitening cosmetic products and which has since been removed from the market. Rhododendrol-induced leukoderma (RIL) has been widely reported and characterized, especially in Japanese literature, with an estimated incidence of 2% in patients using rhododendrol-containing cosmetics (Yoshikawa et al. 2017). Rhododendrol is metabolized by tyrosinase in melanocytes to toxic metabolites, which bind to intracellular proteins and produce reactive oxygen species that ultimately result in melanocyte death (Ito and Wakamatsu 2018).

The development of RIL is dependent on innate tyrosinase activity, which is influenced by genetic and hormonal factors and external triggers such as UV radiation. Morphologically, the lesions of RIL are similar to vitiligo and can be difficult to tell apart (Fig. 6). These similarities persist to a light-microscopic level with differences only seen on examination with electron microscopy. Unlike vitiligo, melanocytes are not completely absent but may still be found in reduced numbers in the depigmented lesions accompanied by a reduction in the number of melanosomes in keratinocytes (Tsutsumi et al. 2019). Vitiligo is thought to be an autoimmune process and is frequently associated with other autoimmune diseases, especially thyroid disease. Thyroid-specific antibodies such as anti-thyroid

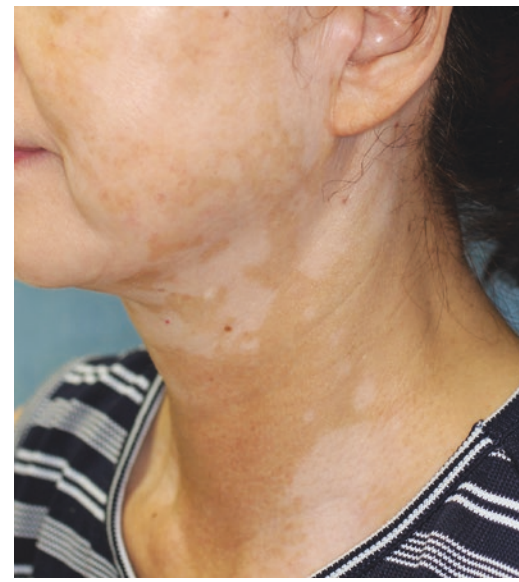

Fig. 6 Depigmented patches on the cheek and neck after use of skin-whitening cosmetics containing rhododendrol. (Source: Professor Tamio Suzuki, Department of Dermatology, Faculty of Medicine, Yamagata University, Japan, with permission)

peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies are frequently elevated in vitiligo but not in RIL (Arase et al. 2019). These differences point to a different pathological process and predisposing factors which portend a better prognosis for cases of RIL compared to vitiligo (Tsutsumi et al. 2019). Bimatoprost has shown promising results for treating refractory RIL although larger studies are needed to assess efficacy (Fukaya et al. 2018).

11 Special Mention: Tyrosine Kinase Inhibitors

Of special mention are tyrosine kinase inhibitors (TKI) which are capable of inducing both hypopigmentation and hyperpigmentation. TKIs are common chemotherapeutic agents used to treat a wide variety of hematologic and solid organ malignancies. Pigmentary alterations of the skin, hair, and nails have been frequently reported and incidence ranges from 16.1% to 25.5% depending on the specific drug (Nahhas et al. 2019). Tyrosine kinase inhibitors act on the c-kit pathway, which in combination with ligand stem cell factor is involved in melanogenesis and melanocyte homeostasis (McPartlin and Leach 2005). This is thought to be either due to a genetic susceptibility, direct melanocyte activation, drug-melanin complexes, or an immune dysregulation secondary to drug use (Bombeccari et al. 2017; Di Tullio et al. 2018).

TKIs are frequently reported to cause hypopigmentation. Imatinib and dasatinib may induce patchy and generalized depigmentation with prominence over the periorbital areas (Llamas-Velasco et al. 2014; McPartlin and Leach 2005; Tsao et al. 2003; Valeyrie et al. 2003; Chang et al. 2004). This can start immediately after initiating therapy or occur months to years later (Tsao et al. 2003). The incidence has been estimated to be 12.9–65% based on limited case series (Llamas-Velasco et al. 2014; McPartlin and Leach 2005; Tsao et al. 2003; Valeyrie et al. 2003; Chang et al. 2004). Depigmentation tends to improve after cessation of therapy and may be dose-related (Valeyrie et al. 2003).

Less commonly, TKIs may cause hyperpigmentation. Gefitinib has been described to cause pigmentation over the face, trunk, and legs after prolonged therapy (Chang et al. 2004). Sorafenib and sunitinib may cause a yellowish discoloration of the skin and nails, sparing the sclera and mucous membranes. This is thought to be related to drug excretion via the skin due to the yellowish color of the medication and resolves after the drug is discontinued (Dasanu et al. 2007; Espinosa Lara et al. 2016).

TKIs are well known to trigger hair depigmentation through the c-kit signaling pathway, which can affect normal pigment development in newly growing hair. Similar to its cutaneous depigmenting effects, hair depigmentation is often reversible after stopping the drug. Imatinib and dasatinib are able to induce hair depigmentation alongside the depigmented patches on the skin (Alharbi et al. 2018; Ricci et al. 2016). Sunitinib induces a dose-dependent depigmentation of the scalp, eyebrows, eyelashes, and body hair with an incidence of 64% in those given >50 mg daily. Depigmentation can occur within 1 week to 3 months of treatment (Ricci et al. 2016; Mariani et al. 2010; Yun et al. 2014; Hartmann and Kanz 2008; Vignand-Courtin et al. 2012; Brzezniak and Szabo 2014; Lee et al. 2009; Rosenbaum et al. 2008; Hurwitz et al. 2009). Pazopanib is used for the treatment of metastatic renal cell carcinoma and can induce reversible hair depigmentation that occurs within 2 months of treatment. The incidence is estimated at 32–44% of patients on treatment with Pazopanib (Hutson et al. 2010; Sternberg et al. 2010; Sideras et al. 2010). Apatinib is used to treat sarcomas and commonly causes hair depigmentation, with an estimated incidence of 42.9–47.4% (Tian et al. 2020).

12 Conclusion

Establishing the diagnosis of drug-induced dyspigmentation is challenging and requires a high index of suspicion. Polypharmacy is common and patients may not be fully aware of the medications they are taking and when they were pre-

scribed. In addition, the onset of drug-induced dyspigmentation is often insidious and may go unnoticed by the patient or may have a long latency, resulting in an unreliable clinical history.

Discussions with the patient and their prescribing physician on the importance of any suspect medications and the impact of the dyspigmentation are necessary to manage any drug-induced dyspigmentation. For essential medications with a clear impact on patient survival such as chemotherapeutic agents, it may not be possible to stop or reduce the dose. This would differ greatly in a drug that is nonessential and has limited impact on patient survival. Patients should be aware that the course of the pigmentary alteration varies significantly depending on the drug involved. Sun protection and avoidance should be emphasized in the case of drug-induced hyperpigmentation. Patients should be counseled that the pigmentation may fade only after cessation of the drug and this may take months to years, if at all.

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Part III

Special Drug Categories

Immediate and Delayed Reactions to Beta-Lactams

María José Torres Jaén and Adriana Ariza Veguillas

1 Introduction

Beta-lactams (BLs) are the most widely used antibiotics in the treatment of bacterial infections and are also the drugs most frequently involved in drug reactions. Such reactions are induced by specific immunological mechanisms (Dona et al. 2014), occur in both adults and children (Rubio et al. 2012; Gomes et al. 2016) and present as either immediate (IRs) or nonimmediate reactions (NIRs) (Torres and Blanca 2010).

All BL compounds can potentially induce a specific immunological response due to the widespread prescription of these antibiotics. BL allergy and its associated implications is now a worldwide health problem. Almost half of all hospitalized patients would require antibiotic treatment, and around 10–15% of these patients are considered allergic to BLs and have to receive an alternative treatment that is not the first therapeutic choice (Thong et al. 2003; Gomes and Demoly 2005). These second-line drugs are usually less effective, more toxic, more expensive, and contributes to the increase in bacterial resistance (Dona et al. 2012; Jeffres et al. 2016; Macy et al. 2009; Picard et al. 2013). It is estimated that 70–90% of patients "labelled" as allergic to BL may not have true allergies (Sastre et al. 2012; Lee et al. 2000). Hospital admission and treatment of patients "labelled" as allergic to BL are more expensive compared to "unlabelled patients" ($14,193 and $609 respectively) (Antunez et al. 2006). Therefore, an accurate evaluation and diagnosis of BL allergy (Rubio et al. 2012; Gomes and Demoly 2005; Demoly et al. 2010; Torres and Blanca 2006) have a relevant impact on health systems and should be included as a strategy in antibiotic stewardship programmes, as bacterial resistance is an important global problem, with the majority of pharmaceutical companies no longer interested in the development of new antibiotics (Fernandez et al. 2017).

2 BL Consumption and Sensitization Patterns over Time

In general, BL antibiotics include different chemical compounds with a common structure (Table 1), and the patterns of prescription and

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consumption have evolved over time and differ among countries (Versporten et al. 2011a, b; Torres et al. 2019, 2016; Lazaro Bengoa et al. 2002). Following the discovery of benzylpenicillin (BP) in 1929, new semisynthetic penicillins were developed and introduced, such as penicillin V (PV), ampicillin (AMP), and amoxicillin (AX) (Versporten et al. 2011b). Cephalosporins constitute the second most consumed BL antibiotic after penicillins and consist of different generations of cephalosporins with different chemical structures and antibacterial properties (Versporten et al. 2011a) developed over time. In addition to penicillins and

Table 1 Chemical structure of β-lactam antibiotics

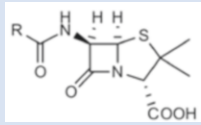
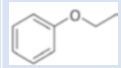
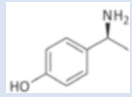
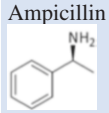
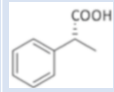
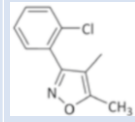
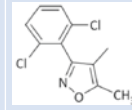
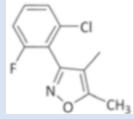
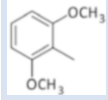
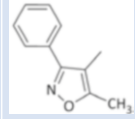
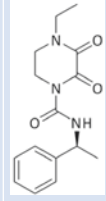
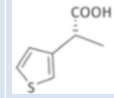
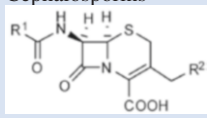
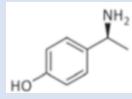
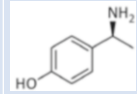
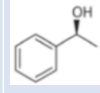
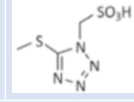
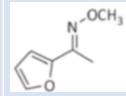
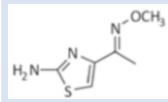
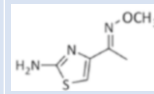
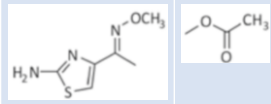
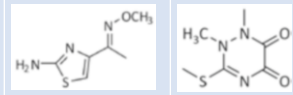
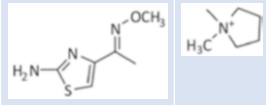
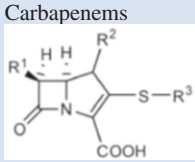
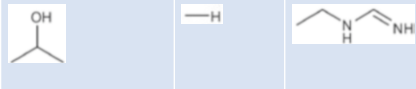
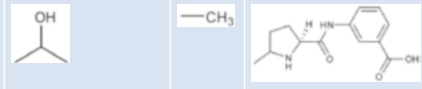
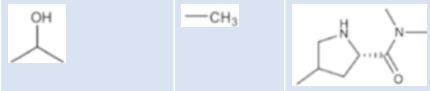
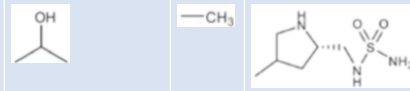
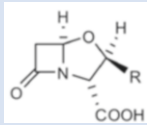
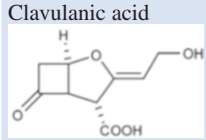
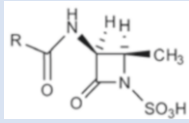
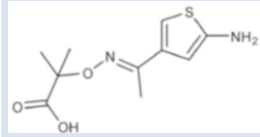
Beta-lactam groups	Chemical structures				
Penicillins 	Natural penicillins (R)				
	Benzylpenicillin (penicillin G) 		Penicillin V 		
	Semisynthetic penicillins (R)				
	Amoxicillin 	Ampicillin 	Carbenicillin 	Cloxacillin 	Dicloxacillin 
	Flucloxacillin 	Methicillin 	Oxacillin 	Piperacillin 	Ticarcillin 
Cephalosporins 	*1st generation*				
	R^1	R^2	R^1	R^2	
	Cefadroxil		Cefalotine		
		—H			
	Cefalexin		Cefprozil		
		—H			
	2nd generation				
	R^1	R^2	R^1	R^2	
	Cefaclor		Cefonicid		
		—Cl			
	Cefamandole		Cefuroxime		
					

Table 1 (continued)

Beta-lactam groups	Chemical structures					
	3rd generation					
	R^1	R^2		R^1	R^2	
	Cefodizime			Ceftizoxime		
					—H	
	Cefotaxime			Ceftriaxone		
						
	4th generation					
	R^1	R^2		R^1	R^2	
	Cefepime					
						
Carbapenems	R^1	R^2	R^3	R^1	R^2	R^3
	Imipenem			Ertapenem		
						
	Meropenem			Doripenem		
						
Clavams	Clavulanic acid					
						
Monobactams	Aztreonam					
						

cephalosporins, other BL compounds with β-lactamase inhibitory activity are frequently prescribed in combination with penicillins to maintain their antimicrobial activity due to the increase in bacterial resistance (Dona et al. 2012). Clavulanic acid (CLV) is a potent and the most relevant β-lactamase inhibitor administered in combination with AX (Torres et al. 2016), but there are other inhibitors applied in clinical practice, such as sulbactam and tazobactam which are prescribed along with other BL antibiotics.

All these changes not only resulted in the evolution of sensitization patterns but also affected the sensitivity of available diagnostic tests. Since the 1970s, BP has been gradually replaced by new BLs (Torres and Blanca 2010; Levine and Ovary 1961) and the progressive decreased consumption of BP has resulted in

reactions falling steadily from 20% to 5% of reported clinical cases. Consequently, the determinant benzylpenicilloyl (BPO) has become a less relevant sensitizer (Macy et al. 2009). The progressive use of semisynthetic penicillins has caused a progressive increase in the appearance of selective reactions to these compounds (Silviu-Dan et al. 1993). Data published in 2001 showed that the most common antibiotics used in Europe were broad-spectrum penicillins, ranging from 56% in Spain to 20% in Germany (Cars et al. 2001). In 2003, similar values were reported for Austria, Belgium, Hungary, Luxemburg, Portugal, and Spain, with AX alone or in combination with CLV as the main elicitor for allergic reactions to BL in Europe (Torres and Blanca 2010; Bousquet et al. 2005; Ferech et al. 2006) and the most frequent cause of anaphylaxis to BL (Blanca 1995). On the other hand, narrow-spectrum penicillins, mainly PV, still represented more than 60% of the total penicillin use in Norway, Sweden, and Denmark, whereas in Belgium, France, Italy, Luxemburg, Portugal, and Spain, they represented less than 2% (Ferech et al. 2006). As mentioned, cephalosporins have been the second most highly prescribed BL antibiotic (Van Boeckel et al. 2014) and between 1997 and 2009, their consumption was higher in Southern and Eastern European countries compared to Northern Europe. In general, their administration has increased over time in Europe, mainly due to the increased use of second-, third-, and fourth-generation cephalosporins (Versporten et al. 2011a). Regarding the β-lactamase inhibitor CLV, the combination AX-CLV is nowadays the most frequently prescribed antimicrobial treatment (Lazaro Bengoa et al. 2002) and its consumption is still increasing (Mayorga et al. 2016), especially in Southern Europe (Fernandez et al. 2017).

3 Clinical Manifestations

Drug hypersensitivity reactions are usually classified as immediate or nonimmediate/delayed based on the time interval between the drug exposure and the onset of the symptoms (Levine 1966). The cut-off point between immediate and nonimmediate reactions remains controversial. A new cut-off point that classified these reactions into immediate (<1–6 h after drug exposure) and nonimmediate (>1 h after drug exposure) has been proposed (Demoly et al. 2014), with an overlapping group of IRs and NIRs that occurred between 1 h and 6 h (Levine 1966; Montanez et al. 2017). These overlapping reactions were originally defined by Levine (1966) as "accelerated reactions." Clinical manifestations of immediate and nonimmediate reactions are heterogeneous and are described below.

3.1 Cutaneous Immediate Adverse Reactions

Two main clinical entities are associated with immediate adverse reactions: urticaria, with or without angioedema, and anaphylaxis. Urticaria is characterized by rapidly evolving transient pruritic wheals occurring at different sites of the body. Urticaria may represent the first stage of an anaphylactic reaction (Blanca et al. 2009). On the other hand, anaphylaxis is defined as "a serious allergic reaction with a rapid onset that may cause death" (Sampson et al. 2006).

3.2 Cutaneous Nonimmediate Adverse Reactions

NIRs to BLs are characterized by the heterogeneity of the clinical manifestations. These reactions may be precipitated by a concomitant viral infection (Shiohara and Kano 2007). A high proportion of such subjects with exanthematous reactions may have good tolerance to the culprit BL a few weeks after resolution of the viral infection (Romano et al. 1995); This is in contrast to others who develop a new reaction after BL re-exposure in the absence of the viral disease (Padial et al. 2008). Such individuals are defined as true allergic patients.

The most common nonimmediate cutaneous adverse reactions are maculopapular exanthema

(MPE) and delayed urticaria/angioedema, which have been reported to be induced by the administration of penicillins and cephalosporins (Hunziker et al. 1997; Bigby 2001; Stern 2012; Roujeau et al. 2014; Romano et al. 2002, 2010, 2012, 2013, 2016; Lammintausta and Kortekangas-Savolainen 2005; Macy and Ngor 2013; Pinho et al. 2017; Ponvert et al. 2011; Atanaskovic-Markovic et al. 2016). Moreover, BLs are also involved less commonly in other nonsevere reactions such as fixed drug eruption (FDE), palmar exfoliative exanthema, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), as well as severe reactions such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (Lammintausta and Kortekangas-Savolainen 2005; Romano et al. 2010, 2013; Pinho et al. 2017; Ponvert et al. 2011; Atanaskovic-Markovic et al. 2016; Gastaminza et al. 2000; Hausermann et al. 2004; Andrade et al. 2011; Sidoroff 2012; Papay et al. 2012; Kardaun et al. 2013; Lin et al. 2014).

4 Diagnostic Procedure

The diagnostic approach in suspected hypersensitivity reactions to BLs is based on a complex allergological workup that includes: (1) detailed clinical history, (2) skin tests (STs), and (3) drug provocation tests (DPTs). These tests are long, expensive, and not risk-free procedures. For this reason, complementary in vitro tests are usually recommended in high-risk patients before ST in order to reduce the risk of systemic reactions (Demoly et al. 2010; Romano et al. 2020; Torres et al. 2002).

4.1 Clinical History

The clinical history is the starting point for the diagnosis of patients with allergic reactions to BLs, allowing both differentiation of IRs from NIRs as well as risk assessment. Risk stratification involves classifaction of patients into high and low risk based on the morphology and chronology of the index reaction, the reaction severity, and the underlying characteristics of the patient (beta-blocker treatments, cardiac disease, and so on) (Romano et al. 2020). However the clinical history alone is not diagnostic even when mathematical models are used (Hierro Santurino et al. 2016; Soria et al. 2017; Chiriac et al. 2018). In addition, the sensitivity of ST is not optimal; therefore DPT may be required to establish diagnosis in many cases (Demoly et al. 2010; Romano et al. 2020; Torres et al. 2002).

4.2 Skin Tests

Skin testing is used for the diagnosis of both IR and NIR and is considered the best validated in vivo method for diagnosing IR to BLs (Blanca et al. 2009). In IRs, STs are usually performed using skin prick test, consisting of pricking the skin with a needle through an allergen solution. If the skin prick test is negative, an intradermal test (IDT) is performed, by the injection of 0.02–0.05 ml of the drug solution, raising a small bleb that is marked initially (Torres et al. 2003). STs should include a panel of reagents composed of the traditional major and minor BP determinants (described below), as well as semisynthetic compounds with different side chains such as AX, AMP, cephalosporins, CLV, or any other suspected BL since selective reactions to these compounds have been reported over time (Blanca et al. 2009; Gadde et al. 1993; Green et al. 1977). Currently, benzylpenicilloyl-octa-L-lysine (0.04 mg/ml, DAP®) is the commercially available BP major determinant, whereas sodium benzylpenilloate (0.5 mg/ml, DAP®) and BP are the commercially available minor determinants in Europe (Torres et al. 2019). However, a recent study showed that the inclusion of BP in STs is not clearly useful for the diagnostic algorithm as the determinants penicilloyl-polylysine (PPL) and minor determinant (MD) are already included and the population is mainly sensitized to AX/AX-CLV (Lacombe-Barrios et al. 2016; Dona et al. 2019) (Table 2).

Table 2 Beta-lactam determinants and highest concentrations recommended for skin tests

Haptens	Concentration
Benzylpenicillin-octa-L-lysine (BP-OL)	0.04 mg/ml
Minor determinant (MD)	0.5 mg/ml
Amoxicillin (AX)	20 mg/ml
Clavulanic acid (CLV)	20 mg/ml
Cephalosporins	20 mg/ml

In the evaluation of NIR, both patch tests (PT) and delayed-reading IDTs can be used, although the latter are not as standardized as for IR and the usefulness of BP determinants is limited (Torres et al. 2019; Dona et al. 2019). However, ST sensitivity in NIR is low especially in children and therefore it is not mandatory to perform STs in children with mild exanthema before DPT (Caubet et al. 2011).

Remarkably, for evaluating patients who suffered severe anaphylactic reactions (Co Minh et al. 2006) and severe cutaneous NIR (Barbaud et al. 2001), starting concentrations of reagents should be lower, at least 1/10 dilution of the highest nonirritating concentration (Torres et al. 2019; Sacco et al. 2017).

4.3 Drug Provocation Test

DPT is recommended by the European Network of Drug Allergy (ENDA) to confirm the allergy diagnosis (Aberer et al. 2003) when (1) STs are negative and (2) to assess the tolerance of potentially cross-reactive BLs (Torres et al. 2019; Sacco et al. 2017; Chiriac et al. 2017), due to the excellent negative predictive value reported in both adults and children (Mirakian et al. 2009; Misirlioglu et al. 2014; Kuruvilla and Khan 2015). DPT consists in the single blind controlled administration of escalating doses of the drug, which are administered at intervals of 30–90 min up to reach the full therapeutic dose. Starting doses are lower in the evaluation of IR compared with NIR (Chiriac et al. 2017) and a lower starting dose should be administered in patients with a history of prior severe reactions. Similarly, the cumulative dose has to be adapted for children or subjects with kidney or liver diseases (Dona et al. 2019). DPTs are time-consuming and costly tests and they are not risk-free. Therefore, DPTs should only be performed by trained personnel after a risk/benefit evaluation. If symptoms manifest during the test, the procedure must be stopped. DPT is contraindicated in cases with severe life-threatening reactions (Aberer et al. 2003; Chiriac et al. 2017). On the contrary, it may be recommended in children with a clinical history of mild cutaneous reactions since most of them are not allergic reactions but viral exanthemas (Gomes et al. 2016). Most of the prescribed BL antibiotics can be used in DPT. In the case of AX-CLV allergy, DPT can be used to assess AX allergy/tolerance directly. However, CLV allergy must be confirmed indirectly by determining AX tolerance in patients with positive DPT to the combination AX-CLV, as CLV not combined with AX is not available (Roujeau et al. 2014).

4.4 In Vitro Tests

In vitro tests can be used as complementary diagnostic tests, especially to avoid in vivo assays in the diagnosis of severe and life-threatening reactions. However, limitations of in vitro tests include suboptimal sensitivity, certain BL structures are not readily tested by commercial assays, or the short time interval from blood extraction to perform the test in the case of cellular methods. It is therefore crucial to improve our existing in vitro tests for the diagnosis of drug allergy, and specifically for BL allergy, through the search and inclusion of new antigenic determinants, the use of nano-engineered solid phases, or the modification and optimization of currently methods (Fernandez et al. 2017).

Immediate Reactions

Two main in vitro methods are used for the diagnosis of IR to BLs: specific IgE determination and basophil activation test (BAT), although other tests can be applied.

Detection and Quantification of Specific IgE

Specific IgE is quantified by different immunochemical methods, although FEIA-ImmunoCAP® (ThermoFisher, Uppsala, Sweden) system is nowadays the commercially available method more suitable for routine analysis (Torres et al. 2003). The specific IgE ranges from 0.01–100 kUA/l, with a cut-off value of 0.35 kUA/l for positive results, and levels higher than 0.10 kUA/l indicating sensitization. Unfortunately, the ImmunoCAP® is only available for some BL antibiotics, including BP, PV, AX, AMP, and cefaclor, and the sensitivity is low and variable depending on the drug involved (Fontaine et al. 2007; Blanca et al. 2001; Torres et al. 2001). Other detection methods can be performed, such as enzymoimmunoassay and in-house radioimmunoassay, which can be customized to use the more adequate solid phase and carrier molecule to detect specific IgE against the interest drug; however these methods are not always available for routine diagnosis (Fernandez et al. 2017).

Basophil Activation Test

The basophil activation test (BAT) is based on the detection by flow cytometry of basophil activation in the presence of specific stimulus, being CD63 and CD203c the most common molecules to determine basophil activation (Mayorga et al. 2019a). BAT is recommended for the diagnostic evaluation of IgE-mediated reactions to BLs, with the advantage of including drugs with no other in vitro test available, such as CLV (Mayorga et al. 2019b; Sanz et al. 2002; Torres et al. 2004). The potential use of BAT as a complementary tool has been reported in different studies, with reported values of 55% sensitivity, 89% specificity, and 96% positive predictive value (PPV) (Torres et al. 2011, 2010; De Week et al. 2009; Eberlein et al. 2010; Garcia-Ortega and Marin 2010). A strategy to improve the sensitivity of in vitro tests could be the inclusion of drug metabolites besides the native drug (Ariza et al. 2016). Indeed, a recent study has shown that the use of one CLV synthetic determinant, together with CLV itself, improves significantly the sensitivity from 41% to 69% in patients with hypersensitivity reaction to AX-CLV (Barbero et al. 2019). It has to be noted that BAT should be performed in a short interval time since the allergic episode to reduce false-negative results due to the negativization rates of BAT over time (Salas et al. 2018; Fernandez et al. 2009). In a study published by Fernandez et al. (2009) it was shown that BAT results for AX allergic patients became negative for more than 50% of cases in tests performed over 18 months after the allergic reactions (Mayorga et al. 2019a).

Histamine Release Test

Regarding the determination of basophil activation, histamine release test (HRT) is based on the detection of histamine release by basophils after stimulation with the drug. The method uses glass-microfiber plates where released histamine is adsorbed and detected by fluorometric methods (Stahl Skov et al. 1984; Wenande et al. 2013). Although this assay is not widely used, it has shown promising preliminary results for the diagnosis of allergic reactions to CLV (Pineda et al. 2015), with the possibility of using patients' basophils (direct HRT) as well as IgE-stripped donors' basophils combined with patients' sera (passive HRT). Sensitivity and specificity values reported in this study were 55% and 85%, respectively, for both direct and passive HRT. Interestingly, passive HRT is useful to confirm by indirect methods the presence of specific IgE when no direct methods are available, as is the case of CLV.

Nonimmediate Reactions

Lymphocyte Transformation Test

Lymphocyte transformation test (LTT) is the most widely used in vitro test to confirm drug-specific cellular sensitization (Fernandez et al. 2017; Mayorga et al. 2019a; Kano et al. 2007; Pichler and Tilch 2004; Beeler et al. 2008). Different studies have shown differences in the values of sensitivity and specificity related with the clinical manifestations and the selection criteria, and there is no consensus regarding the best time to perform the test (Mayorga et al. 2016; Kano et al. 2007; Polak et al. 2013). LTT with the

inclusion of professional antigen-presenting cells, such as monocyte-derived dendritic cells (Chaves et al. 2010; Rodriguez-Pena et al. 2006) can improve the sensitivity as shown in the evaluation of NIR elicited by AX whereby sensitivity is increased from 22% to 88% (Rodriguez-Pena et al. 2006). Another study has proved that the use of TLR agonists in the LTT can also improve the sensitivity from 40.5% to 80.7% for the evaluation of NIR induced by AX (Sanchez-Quintero et al. 2013).

Immunospot Assay (ELISpot)

Other approaches in the evaluation of NIR induced by BLs include the determination of inflammatory mediators by ELISpot. This method is based on the detection of inflammatory cytokine producing cells (e.g., IFN-γ) (Mayorga et al. 2019a) and has shown a sensitivity ranging from 13% to 91% in different studies (Fernandez et al. 2017; Mayorga et al. 2016; Hjortlund et al. 2013; Lochmatter et al. 2009; Martin et al. 2010; Zawodniak et al. 2010; Haw et al. 2016). This assay has been demonstrated to be a good alternative in the evaluation of severe cutaneous reactions (Porebski et al. 2013). Recently the use of preactivated T cells has been reported to increase the sensitivity of IFN-γ ELISpot (Kato et al. 2017).

5 Conclusions

BL therapeutic options have changed and increased over time, inducing a wide sensitization pattern involved in the development of hypersensitivity reactions against all these compounds. The confirmed diagnosis of hypersensitivity reactions to BL entails the use of alternative treatments that usually are more expensive, with greater adverse effects and potentially involved in bacterial resistance, with relevant implications for the public health system. Since bacterial resistance is becoming a worldwide major problem and the majority of pharmaceutical companies are no longer interested in the development of new antibiotics, the World Health Organization (WHO) initiated a strategic antimicrobial resistance. An accurate diagnosis of BL allergy should be included as a strategy in the optimization programs for the use of antimicrobials in order to reduce the percentage of patients "labeled" as allergic to BL that are not real allergic subjects. For that, the development of in vitro methods and the improvement in terms of sensitivity are crucial aspects to advance in the accurate diagnostics and to avoid in vivo assays in many situations, especially for severe and life-threatening reactions.

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Hypersensitivity Reactions to Iodinated Radiocontrast Media

Knut Brockow

1 Introduction

Radio contrast media (RCM) for X-ray and CT scans are increasingly used for both the diagnosis and monitoring of diseases. It is estimated that more than 70 million doses of iodinated contrast media are administered worldwide per year (Christiansen 2005).

Adverse reactions have been frequently observed after the use of RCM. Three different categories of adverse reactions have been described: (1) allergic and nonallergic hypersensitivity reactions, (2) toxic reactions, and (3) events unrelated to exposure to contrast agent (Brockow et al. 2005). Not all reported adverse reactions after RCM exposure can be attributed to them. These may include, e.g., acute urticaria, exanthems elicited by infections or other drugs given at the same time or unspecific subjective symptoms which may be associated with the anxious patient. In addition, discrimination of vasovagal or toxic ("physiological") reactions from anaphylaxis may be difficult. Toxic reactions often present with transient warmth/flushing, metallic taste, pallor, weakness, nausea and vomiting as well as bradycardia. In contrast, cutaneous reactions (urticaria, pruritus, angioedema), tachycardia, bronchospasm, and wheezing are indicators of anaphylaxis, particularly, if three or four different organ systems are affected (Clement et al. 2018). This chapter will address hypersensitivity reactions to RCM.

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2 Classification of Hypersensitivity Reactions to RCM

RCM hypersensitivity reactions may be divided according to chronology as either immediate hypersensitivity reactions (IHR) or nonimmediate hypersensitivity reactions (NIHR) (Brockow et al. 2005). In IHRs, symptoms start within 1 (to 6) h after RCM administration and present with immediate-type symptoms of anaphylaxis. NIHRs present with exanthems, which develop >6 h, mostly 1–3 days and up to 10 days after RCM application.

3 Epidemiology and Risk Factors

There are no accurate data on the incidences of hypersensitivity reactions to RCM. Different definitions of anaphylaxis, IHR, NIHR, RCM attributed to toxicity, use of premedication, and low incidences impede standardized reporting and published data varies widely. It is estimated that

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mild IHR to nonionic (low-osmolar) RCM occur in 0.5–2.0% administrations and severe reactions in 0.02–0.04% (Katayama et al. 1990). Estimates of the incidence of NIHR to RCM are around 0.5–3%; a higher incidence for dimeric isoosmolar RCM has been suggested (Webb et al. 2003; Sutton et al. 2001). The major risk factor for IHR as well as for NIHR on re-exposure is a previous reaction to RCM. Of note, a previous IHR does not increase the risk for an NIHR and vice versa.

4 Clinical Manifestations

Manifestations of IHR to RCM may range from mild skin symptoms, such as urticaria to anaphylaxis, which may be fatal (Brockow et al. 1999a, 2009). The majority of IHRs to RCM start within the first 5 min after RCM administration and present with cutaneous symptoms, such as urticaria/angioedema and pruritus. Almost all severe reactions (96%) occur within 20 min (Brockow et al. 2009; Brockow and Sanchez-Borges 2014). For NIHR, maculopapular exanthem (MPE) of mild or moderate severity is the by far most common manifestation, whereas severe cutaneous adverse reactions, such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or acute generalized exanthematous pustulosis (AGEP) are very rare (Brockow and Sanchez-Borges 2014). Erythema multiforme major, bullous fixed drug eruption, and pompholyx have also been reported in individual cases (Brockow and Sanchez-Borges 2014).

5 Mechanisms of RCM Hypersensitivity

Traditionally, the mechanism of RCM hypersensitivity was initially considered nonallergic. However, over the years, evidence is accumulating that some RCM reactions may have an immunological basis (Brockow 2009). An immunoglobulin E (IgE)-mediated allergic mechanism for IHR to RCM has particularly been proposed in patients with severe anaphylaxis (Yoon et al. 2015). In a prospective study, positive skin test was demonstrated in one in tenth, a quarter, half, and all patients with cutaneous, moderate-systemic, life-threatening anaphylaxis, and cardiac arrest, respectively (Clement et al. 2018). Evidence for such an IgE- or mast cell-mediated mechanism includes positive skin tests, tryptase and histamine release during the reaction, and basophil activation tests (Brockow 2009). However, it should be highlighted that the majority of patients with IHR show no sensitization by skin testing or basophil activation tests to RCM. In such cases, a nonallergic mechanism is still assumed. No plausible mechanism for nonallergic RCM reactions, which is present in vivo selectively in reactors, but not in tolerant controls, has been demonstrated to date (Brockow 2009).

The mechanism of NIHRs to RCM is T cell-mediated as evidenced by the time of onset, clinical presentation, and duration of the exanthem which is similar to other drug exanthems, positive patch tests, activated T cells in positive skin test sites, and positive lymphocyte transformation tests (LTT) (Brockow et al. 2005). In the majority of clearly defined and early tested patients, an underlying type IV allergic mechanism can be demonstrated by positive delayed skin tests (Brockow et al. 2005, 1999b; Trautmann et al. 2019). The responsible allergic structure appears to be within the RCM molecule with its benzene ring and not the iodine ion, since patients rarely have positive skin tests to iodine or provocation tests with Lugol's solution (Scherer et al. 2010; Trautmann et al. 2019).

6 Diagnosis

6.1 Indication for Testing

Not all patients with reported adverse reactions after receiving RCM should get an allergological workup (Table 1) (Torres et al. 2021). Patients who only experienced subjective symptoms, particularly if only one symptom, e.g., feeling of warmth or erythema on injection side, nausea,

Table 1 Indications for allergy testing after reported adverse reactions to RCM

Reported reaction	Indication for testing
Food, respiratory, cutaneous, drug allergies, but no previous reaction to RCM, suspected "iodine" allergy (i.e., crustaceans, molluscs, povidone iodine)	No
Unspecific symptoms (generalized pruritus, heat sensation, flushing, dizziness, nausea, sneezing, rhinorrhea, chest tightness)	No
Localized cutaneous reaction at the injection site (isolated wheals, erythema)	No
Generalized cutaneous reaction (urticaria, angioedema, erythema) Isolated bronchospasm	Yes
Anaphylaxis	Yes
Unspecific symptoms (generalized pruritus, transient erythema, dizziness, nausea)	No
Delayed-appearing urticaria and angioedema	Yes
Maculopapular exanthema	Yes
Morphological variants of exanthema (e.g., fixed drug eruption, SDRIFE, AGEP)	Yes
Severe bullous skin reactions (SJS, TEN), severe systemic reaction (DRESS)	Yes (only skin test)

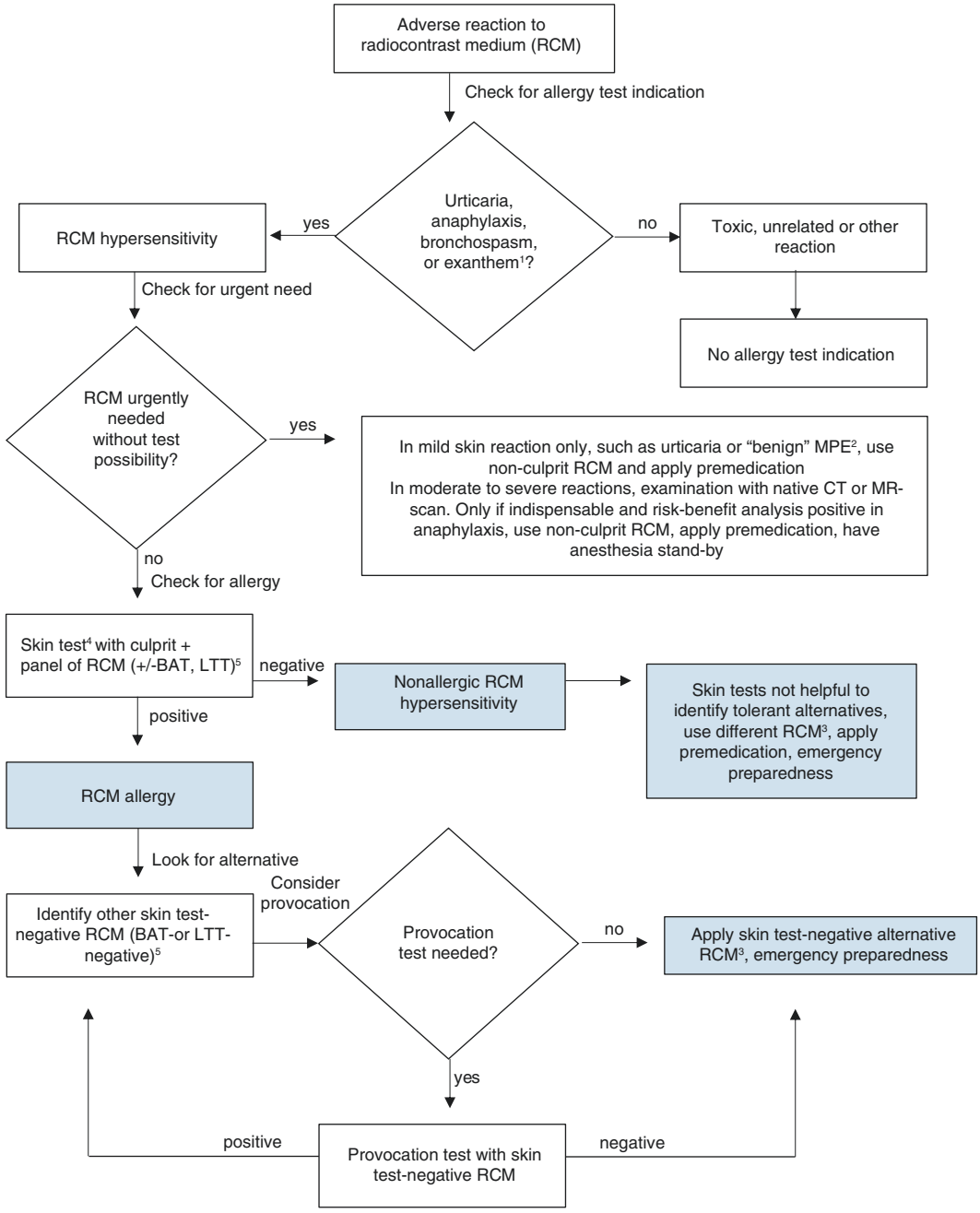
SJS Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *FDE* fixed drug eruption, *DRESS* drug reaction with eosinophilia and systemic symptoms, *SDRIFE* symmetric drug-related intertriginous and flexural exanthema, *AGEP* acute generalized exanthematous pustulosis

paresthesia, headache, or dizziness and/or delayed symptom onset most likely did not suffer from a hypersensitivity reaction. Only patients with reporting immediately occurring urticaria/angioedema/bronchospasm or suspicion of anaphylaxis and patients with exanthems after 6 hours to 7 days consistent with NIHR should be allergologically tested (Torres et al. 2021).

6.2 Skin Tests

Patients should be allergologically tested 2–6 month after IHR and NIHR for best sensitivity, although positive skin tests several years after the incident have been described in individual patients (Brockow et al. 2009). Although the utility of skin testing has been reported to be helpful for diagnosing RCM hypersensitivity for more than two decades, this approach has only recently been agreed and supported by experts (Brockow et al. 1999b; Sánchez-Borges et al. 2019). Skin testing is able to differentiate allergy from nonallergic reactions, and thus identifies a safe alternative as proven by intravenous provocation (Trautmann et al. 2019). Figure 1 shows an algorithm on skin testing in the management of patients (Brockow 2020). For IHR, skin prick tests (SPT) and intradermal tests (IDT) with immediate readings are done, whereas for NIHR, patch test and late readings for SPT and IDT are added. Skin tests should be performed with the culprit contrast agent and, if possible, with a panel of alternative contrast agents for selecting a skin test-negative RCM for subsequent procedures (Torres et al. 2021). The panel should consider contrast agents that are used routinely in the institution for imaging. Dilutions of RCM used for skin tests and recommended reading times are shown in Table 2. However, the validity of different reading times for skin tests is to be determined and additional readings, e.g., after 1 day or 7 days may be considered.

Sensitivity of skin tests depends on the time interval between reaction and skin test and on reaction severity (Brockow et al. 2009). In a meta-analysis, 52% of skin tests were positive in severe IHRs to RCM, whereas the rate dropped to 17%, if mild and moderate reactions were also included (Yoon et al. 2015). In this analysis, 26% of patients with NIHR had positive skin tests. In my personal experience, the rate is much higher, if patients have been diagnosed in our department and tested within a few months afterwards. The specificity of skin tests is 95% for undiluted SPT, 91–96% for 1/10 diluted IDT in IHR, and is considered to be close to 100% for SPT, IDT, and patch test in NIHR (Brockow et al. 2009; Yoon et al. 2015). Cross-sensitivity between RCM does occur and is higher in NIHR as compared to IHR (Brockow et al. 2009). There is no final conclusion on the pattern of structure relationship for cross-reactivity of different RCMs, although cross-reactivity to iobitridol has been reported to be low in NIHR (Lerondeau et al. 2016).



[1]including exanthem variants, however, after severe bullous exanthems or after reactions with systemic symptoms skin test can be done, but future total RCM avoidance is normally recommended; [2]MPE= maculopapular exanthema; [3]not after severe bullous exanthems orafter drug reaction with systemic symptoms: here RCM avoidance; [4]see Table1; [5]BAT= basophil activation test, and LTT= lymphocyte transformation test may be helpful in some cases

Fig. 1 Management of patients with previous radiocontrast medium reaction (adapted from Brockow 2020, with permission)

Table 2 Skin test concentrations recommended for iodinated radiocontrast media

		Readings	
Test method	RCM concentration	Immediate reactions	Nonimmediate reactions
Skin prick test	Undiluted	20 min	20 min, 48 h, 72 h
Intradermal test	1:10	20 min	20 min, 48 h, 72 h
Patch test	Undiluted		20 min, 48 h, 72 h

For nonimmediate reactions readings at 96 h and 7 days may also be applied. Brockow K et al. Allergy 2009; 64: 234–241, with permission

6.3 Laboratory Tests

Measuring increased tryptase levels in serum 1–4 h after anaphylaxis onset can be helpful to confirm this diagnosis, if levels are sufficiently elevated from baseline (Valent et al. 2019). Measurements of increased histamine levels a few minutes after reaction onset are theoretically also possible, but less practicable.

Whereas the basophil activation test (BAT) has been reported to be useful for confirmation of IHR to RCM, it has so far only been applied in few patients. Specificity has been estimated to be 88.4–100% (Pinnobphun et al. 2011). In NIHR, lymphocyte transformation tests (LTT) may be positive and RCM-reactive T cell lines and clones have been isolated (Lerch et al. 2007). However, LTT has a lower sensitivity as compared to skin tests and is primarily used for experimental studies and not in the clinical routine.

6.4 Drug Provocation Test (DPT)

Intravenous DPT with RCM has been increasingly done either with the skin test-negative culprit to exclude RCM allergy or with an alternative skin test-negative RCM to find a substitute, which can be used in the next contrasted imaging procedure (Torres et al. 2021). It is potentially harmful, thus, only trained allergists using adequate safety precautions should perform DPTs with RCM. It should not be performed in patients at high risk, including those with renal insufficiency, hyperthyroidism, radioactive iodine therapy, pregnant and breastfeeding women (Torres et al. 2021). The decision needs to be taken based on a risk-benefit analysis of each patient. Performing DPT may be particularly considered in patients with severe anaphylaxis using a skin test-negative alternative substance. Available protocols are still diverse and would require further standardization.

7 Management of Patients with RCM Hypersensitivity

7.1 Patients with Urgent Need of RCM Without Possibility of Immediate Testing

There are different principal options for patients with previous RCM hypersensitivity reactions (Table 3). For patients with a history of RCM hypersensitivity with immediate and urgent need of another RCM-based imaging and no suitable alternative (e.g., magnetic resonance tomography or avoidance), the severity of initial reaction has to be evaluated. In patients with mild IHR (urticaria ± angioedema) or mild NIHR (maculopapular exanthem), a nonculprit RCM may be given under emergency preparedness and after premedication, because the risk of an allergic reaction is low and premedication suppresses the majority of nonallergic reactions (Fig. 1) (Trautmann et al. 2019; Brockow 2020). It has been reported that in a patient with previous RCM reaction, changing the RCM from the culprit to a different RCM may be more effective than premedication with an antihistamine or with a corticosteroid given single dose (Park et al. 2017, 2018). Different premedication protocols have been published. A protocol

Table 3 Options for management of patients with previous hypersensitivity reaction to RCM (adapted from Torres et al. 2021, with permission)

Management	Advantages	Disadvantages	Comment
Avoidance	Safety	Diagnosis unresolved	For patients with other diagnostic options (e.g., magnet resonance tomography)
Premedication	Easy	Breakthrough reactions False sense of security No evidence for strong benefit No standard regime Risk of side effects	Probably not helpful for preventing severe allergic HR Considered increasingly controversial Generally not recommended for allergic reactions, as there is not enough evidence of its effectiveness
Use of a nonculprit alternative only by history	Easy Reduction of reaction rates	Weak evidence Cross-sensitivity not excluded	Use of different RCM more effective compared with single-dose premedication
Alternative by ST negativity	High negative predictive value in patients with positive ST to culprit Exclusion of RCM highly suspected not to be tolerated Severe anaphylaxis unlikely	Time consuming Expertise needed Only few patients with IHR have positive ST Useful in NIHR No benefit for nonallergic reactions	Increasing evidence Increasingly recommended by experts
Alternative by DPT negativity	RCM application is better controlled by experts in DPT than by radiologists RCM dose can be titrated	Time consuming Hospitalization necessary Expertise needed also for emergency treatment	Risk stratification needed Increasing evidence that DPT is not less safe than DPT to other drugs

using a combination of H1-antihistamine (e.g., 50 mg diphenhydramine 1 h before application) and corticosteroids (e.g., 50 mg prednisone 13, 7, and 1 h before application) is often cited (Sánchez-Borges et al. 2019). The efficiency of premedication is likely to be low and one should not rely on their efficacy. For high-risk patients, the setting should be as safe as possible, e.g., taking place in hospitals with code teams and under close observation (possibly using pulse oxImetry).

In patients with severe anaphylaxis and urgent need, RCM should be avoided before allergological workup. Sometimes a noncontrasted CT scan or MR scan can be performed. If RCM is considered indispensable, after a risk-benefit analysis one may administer the nonculprit RCM after premedication and with emergency preparedness including anesthesia standby.

7.2 Management of Patients After Allergy Workup

For patients without the need for immediate contrasted imaging, an allergy workup is recommended (Fig. 1). In those patients with IHR being skin test-positive to the culprit RCM, a skin test-negative alternative can be administered without premedication under emergency preparedness. Applying premedication might be considered in very severe IHRs. The positive culprit and other skin test-positive RCMs should be avoided. If available, BAT or LTT may supplement skin testing to select a RCM for future use. Whether DPT is advisable is decided on an individual basis, e.g., depending on the severity of the reaction. In patients with negative skin tests to the culprit and alternatives, a nonculprit agent with premedication and under emergency preparedness can be applied.

Contraindications for the further use of RCM may be those with very severe IHRs after risk-benefit analysis and after severe bullous or systemic NIHR. However, in the vast majority of patients, allergy testing in addition to changing the RCM substantially helps to increase safety of subsequent RCM exposures in patients with previous RCM hypersensitivity.

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Cutaneous Adverse Reactions to Biologic Agents

Karen J. L. Choo and Yi Wei Yeo

1 Introduction

The usage of targeted biologic agents in the form of monoclonal antibodies (mAbs) is rapidly expanding in the treatment of neoplastic, autoimmune, and inflammatory conditions. In contrast to most other drugs, which are small molecules, mAbs are proteins. Many of the mAbs contain variable amounts of mouse (murine) origin, considered as chimeric, rendering them more immunogenic. Fully human mAbs are considered less immunogenic than chimeric mAbs (Isabwe et al. 2018). However, even fully human proteins can cause adverse reactions. The World Health Organization established guidelines for the nomenclature of these biologic agents in 2017 based on the antibody target (molecule, cell, and organ) (WHO 2017). It no longer required that the source of different parts of the antibodies be determined by its name (see Table 1).

Familiarity with the adverse cutaneous reactions of these medications will enable clinicians to better balance the potential risks and benefits of these biologic medications in the clinical management of patients. In this chapter, we aim to summarise the hypersensitivity mechanism, presentations, and management considerations of mAb-related drug eruptions. Cutaneous infections and malignancies due to the specific immune blockade of biologic agents, another important aspect of biologic use, are beyond the scope of this chapter and are not specifically covered.

Table 1 Nomenclature of monoclonal antibody (mAb) biologic agents

Prefix	Substem	Target class	Stem
Random	*-ba-*	Bacterial	-mab
	-ami-	Serum amyloid protein (SAP)/amyloidosis	
	-ci-	(Pre-Sub-Stem)	
	-fung-	Cardiovascular	
	-gros-	Fungal	
	-ki-	Skeletal muscle mass-related growth factors and receptors	
	-li-	Interleukin	
	-ne-	Immunomodulating	
	-os-	Neural	
	-toxa-	Bone	
	-ta-	Toxin	
	-vet-	Tumour	
	-vi-	Veterinary use (Pre-Stem)	
		Viral	

2 General Principles/ Classification

Consensus definitions and classification of mAbs hypersensitivity reactions are lacking. A practical approach that classifies these reactions based on

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their clinical presentation, underlying mechanism, and temporal presentation is suggested (Jackson and Bahna 2020; Hong and Sloane 2019; Santos and Galvão 2017; Picard and Galvão 2017).

2.1 Localised Injection Site Reactions

Injection site reactions (ISRs) are common with the use of subcutaneous biological agents with an incidence of 0.5–40% (Thomaidou and Ramot 2019). ISRs present as swelling, erythema, pruritis, and pain around the site of injection and can be divided into two groups based on their mechanism of action—namely irritative reactions (immediate) and allergic reactions (immediate or delayed) to the excipient or the drug itself (Thomaidou and Ramot 2019).

The reported incidence of ISRs with common biologics was highest with Etanercept (2.97–37%), Adalimumab (5–20%), and Omalizumab (2.7–45%), while Ustekinumab, Secukinumab, Brodalumab, and Guselkumab had the lowest reported incidence of less than 5% (Thomaidou and Ramot 2019).

2.2 Systemic Hypersensitivity Reactions

Although overlapping mechanisms and clinical presentation exist, generally, these reactions can be divided into the following categories based on the primary disease mechanism and tempo of onset:

Immediate Hypersensitivity Reactions

Cytokine Release Syndrome

Cytokine release syndrome is a result of rapid destruction of cells targeted by the mAbs through complement-mediated or antibody-mediated cell death, which leads to the release of IL6 and TNFα pro-inflammatory cytokines (Santos and Galvão 2017). These reactions usually occur on first administration of mAbs and may wane with subsequent administrations. Distinctive features of cytokine release syndrome (or sometimes referred to as infusion reactions) are headache, fever, chills, rigors, or chest/back pain. Often, patients may also have non-specific symptoms such as flushing, breathlessness, giddiness, nausea, and/or vomiting. Most of these symptoms can be prevented or attenuated with premedication with paracetamol, glucocorticosteroids, and a slower infusion rate. The majority of cytokine release syndrome are mild. Yet, there is one infamous example (Suntharalingam et al. 2006) of a severe cytokine release syndrome: TGN1412, an anti-CD28 mAb. In its phase 1 clinical trial, six healthy men were given a single iv bolus of TGN1412 and after an hour, all of them developed severe headaches, low back pain, nausea, vomiting, diarrhoea, fever, hypotension, and bilateral pulmonary infiltrates. Most went on to develop multiorgan failure with two requiring intubation and mechanical ventilation.

Type I Reactions: IgE Mediated

IgE-mediated reactions require a sensitisation phase before a reaction can develop. Reactions typically occur after at least one uneventful administration (with one notable exception: cetuximab). Clinical presentation of IgE-mediated reactions ranges from cutaneous only reactions (urticaria or angioedema) to systemic anaphylactic shock and often, overlaps with clinical features of cytokine release syndrome. An elevated serum tryptase (indicative of mast cell degranulation) at the time of the reaction suggests the possibility of IgE-mediated reaction. Skin tests (skin prick and intradermal test) to culprit mAb could be performed 4–6 weeks after the reaction. A positive test on immediate reading suggests IgE-mediated reactions.

IgG Mediated

The mechanism of IgG-mediated reactions against mAbs is less well defined. In the case of infliximab, IgG antibodies can be associated with reduced efficacy (due to increased clearance or by blocking the antibody binding site) and/or hypersensitivity reactions. In mouse models, IgG-dependent anaphylaxis occurred due to the

binding of anti-mAbs IgG to Fc-gamma-receptors on macrophages, basophils, and neutrophils (Jönsson et al. 2019). Another postulated mechanism of IgG-dependent reaction is the formation of large immune complexes that activates the complement system, which in turn generates anaphylatoxins (C3a and C5a) (Finkelman et al. 2016). Based on these mechanisms, it is not surprising that the clinical symptoms of IgG-mediated reaction may mimic those of IgE-mediated type I reactions. The difference between the two may be apparent during skin prick tests reading as these tend to be negative for IgG-mediated reactions.

Non-immediate Hypersensitivity Reactions

Type III Reactions: Serum Sickness like Reactions (SSLR)

This is the commonest non-immediate hypersensitivity reaction to mAbs and can occur at first exposure although they most frequently develop after at least one uneventful infusion. These reactions are thought to be due to the deposition of immune complexes of mAb and anti-mAb IgGs in capillaries of the skin, kidney, and other organs. Onset is typically 5–7 days post infusion. Clinical manifestations include fever, malaise, arthralgia/arthritis, jaw pain/tightness, erythematous/urticarial rash, purpura, or conjunctival haemorrhage. In some cases, immediate-type hypersensitivity reactions may precede or follow SSLR.

Delayed Type IV Reactions

A wide range of reactions have been reported ranging from maculopapular exanthema and symmetrical drug-related intertriginous and flexural exanthem (SDRIFE) (Yang et al. 2017) to more severe phenotypes such as SJS/TEN (Urosevic-Maiwald et al. 2012) (the latter are rare and there are only a few case reports in the literature).

Data on the frequency of hypersensitivity reactions is limited due to differences in definition and classification of these reactions. The prevalence of mAbs hypersensitivity reactions has been reported to be 63%, 13%, 21%, and 3% for type I, cytokine release, mixed type, and delayed type IV reactions in her cohort (Isabwe et al. 2018).

2.3 Off-Target Inflammatory Cutaneous Eruptions

A wide range of inflammatory dermatoses have been reported in association with biological agents (Murphy et al. 2022). Most well recognised are those of psoriasiform eruptions or psoriasis with the use of anti-tumour necrosis factor-α (anti-TNF) agents. Commonly referred to as "paradoxical eruptions" in the literature, this term is best limited to the appearance or exacerbation of a condition that usually responds to the same class of drug (Toussirot and Aubin 2016). Various mechanisms have been proposed for these off-target inflammatory cutaneous eruptions. This includes:

1. Polarisation of T cell responses where inhibition of a cytokine associated with a particular Th subset may skew responses towards another Th polarisation. For example, Th17 pathway blockade for the treatment of psoriasis may result in polarisation towards a Th2 phenotype resulting in an eczematous eruption (Mufti et al. 2021; Eyerich et al. 2011).
2. Disruption of negative feedback loops leading to the overproduction of other cytokines. Paradoxical psoriasis due to anti-TNF agents is proposed to be due to increased production of type I interferons by plasmacytoid dendritic cells which are normally downregulated by TNFα (Murphy et al. 2022; Collamer and Battafarano 2010).
3. Secondary effects related to the antidrug immune responses (Murphy et al. 2022).
4. Non-specific interactions with Fc receptors that may activate innate immunity (Murphy et al. 2022).
5. Host factors and genetic predisposition may play a role (Murphy et al. 2022; Bucalo et al. 2020).

3 Classes of Biologic Agents and Their Reactions

3.1 Anti-tumour Necrosis Factor-α Agents (Anti-TNFs)

Five agents that are currently available include Infliximab, Adalimumab, Etanercept, Certolizumab Pegol, and Golimumab and are approved for use in the treatment of chronic plaque psoriasis, hidradenitis suppurativa, rheumatoid arthritis, spondylarthritis, and inflammatory bowel disease, among other indications.

Hypersensitivity Reactions

Local Injection Site Reactions (ISRs)

ISRs are frequent with anti-TNFs with a reported incidence of 3–37% with Etanercept and 5–20% with Adalimumab (Thomaidou and Ramot 2019). ISRs to anti-TNFs are usually self-limiting (Zeltser et al. 2001; Murdaca et al. 2013) although there have been occasional reports of severe reactions. Bavbek et al. described an immediate ISR with Etanercept in a 28-year-old man who presented with localised erythema, swelling, and pruritis after the 22nd injection followed by generalised urticaria and pruritis (Bavbek 2011). Skin prick testing with Etanercept 25 mg/1 ml, 13 days post reaction, was negative but intradermal testing was positive at 1/100 dilution. Patient was challenged with 2.5 mg of Etanercept and reacted with generalised urticaria. He was eventually managed with a desensitisation protocol with concurrent antihistamines and was able to tolerate the medication with small local ISR reactions of less than 3 cm (Bavbek 2011). Recall phenomenon has been reported with Etanercept (Zeltser et al. 2001).

Acute Infusion Reactions and Anaphylaxis

Intravenous Infliximab administration has been associated with a 20% risk of infusion reactions (O'Meara et al. 2014; FDA 2018). A systematic review on infliximab-related infusion reactions in patients with inflammatory bowel disease found that 5–23% of IBD patients on Infliximab developed immediate infusion reactions while 1–3% of patients developed late reactions, usually of the serum sickness type (Lichtenstein et al. 2015). Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash, and hypotension (FDA 2018).

The presence of antidrug antibodies to Infliximab has been correlated with the development of infusion reactions. A meta-analysis on patients with IBD treated with Infliximab showed that the presence of antidrug antibodies conferred a 2.4-fold risk increase of acute infusion reactions and a 5.8-fold risk increase of serious infusion reactions (O'Meara et al. 2014). Conversely, the concomitant use of immunosuppressive agents such as methotrexate or low-dose glucocorticoids has been shown to reduce the formation of anti-Infliximab antibodies and the risk of infusion reactions (Galvão and Castells 2015). While acute infusion reactions to Infliximab often show symptoms resembling anaphylaxis, detection of IgE antibodies has only been rarely demonstrated, suggesting that many may represent cytokine release syndrome. Further support for this comes from the diminishing of some of these reactions by reducing the infusion rate, reports of normal tryptase levels in some cases, and the development of anaphylactic type reactions during the first infusion (Lecluse et al. 2008).

Apart from infliximab, there are few reports of true anaphylactic reactions to other anti-TNFs (Sala-Cunill et al. 2019). A single centre Italian study of 671 patients on anti-TNF agents observed the highest frequency and severity of hypersensitivity reactions to Infliximab (68%) compared with 6% to Etanercept and 12% to Adalimumab. 91% of anaphylactic events were attributed to Infliximab. In contrast, anaphylaxis was only seen in 2% of patients treated with Etanercept and none on Adalimumab (Puxeddu et al. 2012). Nonetheless, rare cases of anaphylaxis have been reported with adalimumab in postmarking surveillance (Murdaca et al. 2013). Several reports of successful desensitisation to anti-TNF agents have been reported (Makowska and Lewandowska-Polak 2020).

Off-Target Inflammatory Cutaneous Eruptions

Off-target inflammatory cutaneous eruptions have been most commonly reported with anti-TNF agents (Murphy et al. 2022). A recent systematic review showed that the most commonly reported inflammatory cutaneous reaction with anti-TNFs was psoriasis or psoriasiform eruptions (n = 1051), followed by eczematous eruptions (n = 267), lupus-like eruptions (n = 216), sarcoidosis-like eruptions (n = 91), and alopecia areata (n = 66) (Murphy et al. 2022). Other recognised but less common reactions include hidradenitis suppurativa, lichenoid eruptions, granuloma annulare, bullous pemphigoid, dermatomyositis, pyoderma gangrenosum, and cutaneous vasculitis (Murphy et al. 2022).

Psoriasis/Psoriasiform Eruptions

Paradoxical psoriasis in the form of palmoplantar pustulosis was first reported in a systematic safety follow-up in a cohort of 107 patients with spondyloarthropathy who received Infliximab in 2003 (Baeten et al. 2003). This was followed by increasing reports of psoriasiform eruptions and new onset psoriasis. Anti-TNFs have been reported to induce and/or exacerbate psoriasis in about 3.8–10.7% of patients (Murphy et al. 2022). Thought to be a class effect, paradoxical psoriasis has been most reported with Infliximab (56.6%), followed by Adalimumab (30%), Etanercept (11%), Certolizumab pegol, and Golimumab (Murphy et al. 2022). Latency is variable, ranging from less than 1 month to more than 10 years after drug initiation, with an average of 16.4 months (Murphy et al. 2022). Infections have not been observed to be a triggering factor (Toussirot and Aubin 2016). However, a recent case-control study found that a family history of psoriasis, psychological stressors, and tobacco use was significantly associated with the development of TNF-inhibitor-induced psoriasis (Ya et al. 2020).

A systematic review by Collamer et al. showed that the most common morphologies were pustular psoriasis (56%), plaque psoriasis (50%), and guttate psoriasis (12%) (Collamer and Battafarano 2010). Of these, 15% of patients experienced more than one type of reaction. In patients with pre-existing psoriasis, paradoxical reactions may exhibit different morphology to the original presentation such as guttate or pustular lesions in a patient with pre-existing plaque psoriasis. The most frequently affected areas include palmoplantar areas, the scalp and flexures seen in more than 50% of cases (Toussirot and Aubin 2016). Indeed, palmoplantar pustulosis seems to be over-represented in anti-TNF-induced psoriasis with a report from the French Pharmacovigilance Database showing that such eruptions were mostly pustular lesions and occurred mainly on the palms and/or soles (33.3% in the French Pharmacovigilance Database and 42.9% in the literature), while palmoplantar pustular psoriasis represents only 1.7% of the psoriatic patients (Joyau et al. 2012).

Histology may be indistinguishable from psoriasis or palmoplantar pustulosis unrelated to anti-TNF therapy with features including epidermal hyperplasia, parakeratosis, epidermal lymphocytic infiltrate, dilated capillaries, and intraepidermal pustulosis. However, other reports have suggested some subtle differences including the presence of spongiosis, lichenoid infiltrate, and eosinophils (Navarro and Daudén 2014).

Various mechanisms have been proposed:

1. Increased production of type I interferons by plasmacytoid dendritic cells which are normally downregulated by TNF-alpha (Collamer and Battafarano 2010).
2. Blocking TNF-α may increase T helper 17 (Th17) cell production of pro-inflammatory cytokine IL-22 (Ma et al. 2010). Blocking IL-23, a driver of Th17 differentiation, has been reported to be effective in the treatment of paradoxical psoriasiform lesions (Tillack et al. 2014).
3. Anti-TNF inhibitors may predispose to infection (Li et al. 2019), which is a known trigger of psoriasis, although in most cases of paradoxical reactions, no infectious triggers were noted.
4. Patients with inflammatory bowel disease and chronic rheumatological conditions may have a higher incidence of psoriasis (Li et al. 2019)

with genetic polymorphisms possibly playing a role in the predisposition to the development of paradoxical reactions (Collamer and Battafarano 2010).

Eczematous Reactions

Eczema as an adverse effect of anti-TNF therapy has been reported to occur in approximately 5–20% of patients (Nakamura et al. 2017). Personal history of atopy appears to increase this risk. In a review by Nakamura et al., Infliximab was most strongly associated with development or exacerbation of pre-existing eczema (Nakamura et al. 2017). The anti-TNF agent has to be discontinued in 7 of 12 cases due to the severity of the eczema with resolution following cessation of therapy. In the other five cases, eczema was treated with topical or oral corticosteroids with continuation of the biologic agent. Proposed mechanisms for the development of eczematous eruptions with anti-TNFs include tipping the balance in favour of Th2 pathway inflammatory conditions such as eczema due to Th1 pathway blockade (Nakamura et al. 2017).

Granulomatous Reactions

Sarcoidosis or sarcoid-like granulomas occurring in the setting of anti-TNF use are rare but have been increasingly recognised, following a report of 10 cases by Daïen et al. (2009). The estimated incidence is about 0.04% with the most often implicated biologic that of Etanercept (Murphy et al. 2022) and other reports after use of Infliximab and Adalimumab (Toussirot and Aubin 2016). Clinical features reported did not differ from de novo sarcoidosis with cutaneous involvement estimated to occur in 24–50% of patients and systemic involvement reported (Murphy et al. 2022). Reported time to diagnosis ranges from 1 to 84 months with an average of about 2 years (Murphy et al. 2022). The anti-TNF was discontinued in most cases with at least partial improvement, with some requiring systemic steroids. Rechallenge was not performed and a limited number of patients switched therapy without relapse (Toussirot and Aubin 2016).

Other granulomatous diseases such as granuloma annulare and interstitial granulomatous dermatitis have also been described (Murphy et al. 2022). In a series of nine patient with granuloma annulare, the mean onset was 6 months from drug initiation and adalimumab was the most frequently implicated anti-TNF agent. Rash resolved with topical corticosteroids in seven out of nine cases despite continuation of the anti-TNF (Voulgari et al. 2008). Interstitial granulomatous drug reactions have been reported with Adalimumab with at least two cases in the literature (Martorell-Calatayud 2010).

Lupus-like Reactions

While uncommon, lupus-like reactions are recognised with the most common inciting biologic being Infliximab (56%), followed by adalimumab (25%) and Etanercept (15.5%) (Murphy et al. 2022). Presentations include isolated cutaneous lupus (45–56%) and lupus-like syndromes with systemic lupus erythematosus occurring in 17–30% of lupus cases (Murphy et al. 2022). Cases of cutaneous lupus were predominantly of the discoid lupus or subacute cutaneous lupus subtype (Murphy et al. 2022; Jani et al. 2017). While earlier reports suggest a significant association between anti-TNF use and lupus (Moulis et al. 2014), this association has been questioned in a prospective observational cohort study by Jani et al. which failed to show a significant increase in lupus-like events with anti-TNF use after adjusting for differences in baseline characteristics (adjHR 1.86; 95% CI 0.52 to 6.58) compared to rheumatological patients on non-biologic DMARD (Jani et al. 2017).

Most cases exhibited positive anti-nuclear antibody (ANA) titres. However, the induction of ANAs and anti-double stranded DNA (anti-dsDNA) antibodies has been recognised in clinical trials and post-marketing surveillance, even in the absence of clinical lupus-like features (Sehgal et al. 2015). Anti-histone, Anti-Ro, and Anti-La antibodies are also not consistently positive (Murphy et al. 2022). Most reported patients achieved complete or partial resolution with withdrawal of anti-TNF treatment (Jani et al. 2017; Moulis et al. 2014).

Cutaneous Vasculitis

There have been numerous reports on anti-TNF induced cutaneous vasculitis (Toussirot and Aubin 2016). Reported latency ranges from 9.6 to 34.5 months (Saint Marcoux and de Bandt 2006; Sokumbi et al. 2012). Most cases were limited to cutaneous small vessel vasculitis although some cases involved medium to large vessels or had systemic extra-cutaneous involvement (Sokumbi et al. 2012). Clinical presentations included purpura, ulceration, blisters, and erythematous macules. A case series of 39 patients from a nationwide study in France found Etanercept to be the most implicated biologic (54%) (Saint Marcoux and de Bandt 2006). However, similar to lupus-like reactions, the study by Jani et al. failed to show a significant increase in vasculitis-like events after adjusting for differences in baseline characteristics (adjHR 1.27; 95% CI 0.40 to 4.04) compared to rheumatological patients on non-biologic DMARDs (Jani et al. 2017). In the French series, cessation of medication resulted in resolution in most cases without further treatment although some required high-dose glucocorticoids with or without immunosuppressant therapy (Saint Marcoux and de Bandt 2006).

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic relapsing skin disease characterised by abscesses, nodules, and draining fistulae often in the axilla and groin of young adults. Adalimumab was FDA approved for the management of moderate to severe HS in 2015. Interestingly, HS has also been reported as a paradoxical event with anti-TNF treatment. Faivre et al. reported a series of 25 patients of paradoxical HS. Biologics implicated were TNF inhibitors in 22/25 cases including adalimumab (12/25), infliximab (6/25), and etanercept (4/25) with the remaining three attributed to rituximab and tocilizumab (Faivre et al. 2016). Median duration of drug exposure to HS onset was 12 (range 1–120) months. Patients were mostly Hurley stage I ($n = 13$) or II ($n = 11$). Complete improvement of HS was seen in 60% of patients who were discontinued on the medication compared to only 7% in those that were continued. Reintroduction of the same biologic agent resulted in HS relapse in all three patients (Faivre et al. 2016).

Other reported reactions include alopecia areata, vitiligo, lichenoid eruptions, bullous pemphigoid, dermatomyositis, and pyoderma gangrenosum (Murphy et al. 2022).

3.2 Anti-CD-20 (Rituximab)

Rituximab is a chimeric mAb that binds to CD20 antigen present on all peripheral B Cells, rapidly depleting their numbers. It is licensed for the treatment of B Cell Lymphoma and many autoimmune diseases. Rituximab treatment results in two main categories of adverse reactions: immunodeficiency and hypersensitivity reactions.

Hypersensitivity Reactions

Among all mAbs reported here, Rituximab has the highest rate of immediate hypersensitivity reactions (Fouda and Bavbek 2020). These tend to occur early in the infusions and the symptoms are often an overlap of cytokine release syndrome caused by B cell lysis and that of IgE-mediated hypersensitivity. TNFα and IL-6 levels correlate with symptom severity (Santos and Galvão 2017). The frequency and severity of these infusion reactions may differ according to the B Cell counts, the underlying disease for which Rituximab is used for and whether premedication with glucocorticosteroids were included as pretreatment (Fouda and Bavbek 2020). For example, the rate of infusion tends to be higher for lymphoma patients with a high tumour burden (77%) (Régnier Galvão et al. 2015) compared to patients with autoimmune diseases (between 11 and 30%) (Picard and Galvão 2017). Most of these reactions tend to be mild, with the frequency decreasing with each subsequent infusion. Severe reactions and late reactions that occur after at least one uneventful administration would benefit from skin tests and if positive, desensitisation.

Serum sickness-like reactions have been reported, with patients receiving Rituximab for the treatment of autoimmune conditions (Bayer

et al. 2019). Re-exposure has been attempted with at least one in seven patients suffering a recurrence in this French cohort (Bayer et al. 2019).

Other notable non-cutaneous adverse reactions associated with Rituximab are increased risk of infection including the reactivation of hepatitis B virus, progressive multifocal leukoencephalopathy associated with JC virus, tumour lysis syndrome, cardiac arrhythmias, acute renal impairment, bowel obstruction and perforation (Bayer et al. 2019; Iaccarino et al. 2015).

Off-Target Inflammatory Cutaneous Eruptions

Cutaneous, pulmonary, neurological, gastrointestinal, and joint autoimmune and/or inflammatory reactions to Rituximab are uncommon but have been reported (Thomas et al. 2012). Psoriasiform dermatoses have been reported in patients receiving rituximab for Rheumatoid Arthritis and Lupus Erythematosus (Thomas et al. 2012). It can affect patients of any age and occur as early as 6 weeks to as late as 2 years into the treatment of Rituximab. Interestingly, the underlying disease responds well to Rituximab.

3.3 Anti-IL 1 (Anakinra, Canakinumab)

Anakinra is a recombinant human IL-1 receptor antagonist with indications in rheumatoid arthritis, cryopyrin-associated periodic syndrome, and Still's disease. The most common and consistently reported treatment-related adverse event associated is injection site reactions, reported in up to 71% of patients and typically within the first month of therapy (Mertens and Singh 2009). The majority were mild to moderate, typically lasting 2–4 weeks, and were characterised by erythema, ecchymosis, inflammation, and/or pain (Kaiser et al. 2012). Rare cases of anaphylaxis exist, with reports of successful desensitisation protocols for anakinra hypersensitivity (Emmi et al. 2017; Yilmaz et al. 2018). A paediatric patient with anakinra-induced anaphylaxis was also successfully treated with canakinumab, an alternative IL-1 blocking agent (Aguiar et al. 2015).

Canakinumab is a human mAb against IL-1 beta and is indicated in periodic fever syndromes, cryopyrin-associated periodic syndrome, familial Mediterranean fever, and Still's disease among other indications.

No cases of anaphylactoid or anaphylactic reactions were reported during clinical development (Gülsen et al. 2020) and patients with anakinra anaphylaxis may tolerate canakinumab (Aguiar et al. 2015). However, Sanan et al. reported a patient with anakinra anaphylaxis who developed anaphylactic symptoms during intradermal testing to canakinumab. The patient subsequently underwent successful desensitisation to canakinumab (Sanan et al. 2020).

3.4 Anti-IL 4/13 (Dupilumab)

Dupilumab targets IL4α receptors which inhibits both IL4 and IL13 signalling pathways. It has been approved for patients with severe atopic dermatitis, eosinophilic asthma, and nasal polyposis (Halling et al. 2021; Fargnoli et al. 2019). Hypersensitivity reactions, mainly generalised urticaria, occurred in <1% of trial patients (Jackson and Bahna 2020).

The most common adverse reactions were ocular in nature, conjunctivitis being the most common, affecting up to a third of patients on dupilumab, especially if there are pre-existing allergic conjunctivitis. Apart from conjunctivitis, blepharitis and keratitis have also been reported (Fargnoli et al. 2019; Halling et al. 2021; Ou et al. 2018).

Off-Target Inflammatory Cutaneous Eruptions

Psoriasiform dermatitis has been one of the more commonly reported inflammatory cutaneous reactions with an incidence of 3.3%; the onset is usually within 1 year of starting dupilumab (Murphy et al. 2022). Most of these patients who developed psoriasiform paradoxical reactions were given dupilumab for their atopic dermatitis but at least 1 was treated for asthma. The

morphology resembles plaque psoriasis although erythrodermic, guttate, scalp, and palmoplantar reactions have been described (Fowler et al. 2019). Skin histology revealed an overlap of psoriasis and spongiosis features. Most cases resolved with either topical steroids or discontinuation of dupilumab.

Eczematous dermatitis has also been reported as a paradoxical reaction with Dupilumab, although these tend to be localised/regional affecting the periocular region, the face and neck (de Wijs et al. 2020). The majority of patients suffering from eczematous dermatitis were being treated for pre-existing atopic dermatitis, although Zhu et al. argued that the onset of facial dermatitis was new and only came on after starting dupilumab (Zhu et al. 2019). Some are of the opinion that this facial dermatitis may be a manifestation of undiagnosed allergic contact dermatitis although larger studies with biopsy and patch test may be required to further define this subset of patients (de Wijs et al. 2020; Jaros et al. 2020).

Facial erythema (without dermatitis) affects 5–10% of patients, some of them diagnosed as rosacea (Jaros et al. 2020). Alopecia has been reported in 3.8% of the Dutch cohort (Ariëns et al. 2020) and arthralgia in 1.8% of 108 patients in Italy (Fargnoli et al. 2019; FDA 2019a).

3.5 Anti-IL-5 (Mepolizumab, Reslizumab, and Benralizumab)

IL5 is essential for the maturation, differentiation, and activation of eosinophils. Hence, anti-IL5 mAbs are used to treat eosinophilic disorders, namely eosinophilic asthma, eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome (HES). Currently, there are three licensed anti-IL5 mAbs: mepolizumab, reslizumab, and benralizumab (Agache et al. 2020).

In their phase 3 clinical trials for patients with eosinophilic asthma, there was no increase in significant hypersensitivity reactions that were reported compared to placebo, although more injection site reactions were reported, 8% (mepolizumab 100 mg) vs 3% (placebo) (Agache et al. 2020). Injection site reactions were also a problem for patients receiving 300 mg mepolizumab for the treatment for HES. Six per cent of patients receiving 300 mg of mepolizumab experienced hypersensitivity reactions manifested by itch, rashes, flushing, fatigue, hypertension, a warm sensation in the trunk and neck, cold extremities, dyspnoea, and stridor; half of which were on the same day of dosing (Agache et al. 2020; Albers et al. 2019).

Reslizumab and Benralizumab, however, have had cases of anaphylaxis during their phase 3 clinical trials (FitzGerald et al. 2016; Castro et al. 2015). Although the incidence is low, 0.3% and 3% respectively, it has prompted a black box warning advising in-office administration and close monitoring thereafter (Agache et al. 2020).

3.6 Anti-IL-6 (Tocilizumab)

Tocilizumab is an IL-6 blocking agent approved for use in rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis (JIA), and treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Hypersensitivity Reactions

ISRs have been reported in up to 10% of patients with subcutaneous Tocilizumab, while infusion reactions have been reported in about 7–8% when given intravenously with symptoms including hypertension, headache, rash, urticaria, and pruritis (Burmester et al. 2014). These events were not treatment limiting (FDA 2019a).

Hypersensitivity reactions resulting in treatment discontinuation have been reported in 0.1–0.7% in clinical trials on rheumatoid arthritis. In post-marketing surveillance, these hypersensitivity reactions, including anaphylaxis and death, have occurred in patients treated with a range of doses, with or without concomitant therapies and in patients who received premedication. They have also been reported as early as the first infusion, although most commonly after the third or fourth infusion. As such, it is recommended that

intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis (FDA 2019a).

In addition, few isolated reports of suspected Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) or eosinophilia have emerged (Zuelgaray et al. 2017; Massolino et al. 2018) with one unconfirmed case of Stevens-Johnson syndrome (Villiger et al. 2016) and one case of acute generalised exanthematous pustulosis (Izquierdo et al. 2012).

Off-Target Inflammatory Cutaneous Eruptions

At least eight cases of psoriasiform eruptions have been reported with tocilizumab. Latency was 10 days to 84 weeks and was independent of underlying disease activity (Hayakawa et al. 2019). In some cases, psoriasiform eruption was triggered upon withdrawal of tocilizumab, leading authors to suggest that a rebound in IL-6 may result in downstream differentiation of Th17 cells resulting in psoriasis (Saito et al. 2020). However, reports also exist of developing psoriasiform eruptions while on treatment for which the exact mechanisms are unknown (Hayakawa et al. 2019). Of these cases, four required discontinuation while four were successfully continued on treatment with improvement of rash with topical treatment. One patient had dose intensification together with topical steroid therapy with resolution of rash (Hayakawa et al. 2019). Other reports include palmoplantar pustulosis (Sparsa et al. 2014) and interstitial granulomatous dermatitis (Altemir et al. 2020).

3.7 Interleukin 17 Inhibitors

Approved for use in psoriasis, psoriatic arthritis, and ankylosing spondylitis, the three IL-17 inhibitors available are secukinumab, ixekizumab, and brodalumab.

Hypersensitivity Reactions

Injection site reactions with anti-IL17 agents are most seen with Ixekizumab (13–17%) compared to Secukinumab (0.8–1.3%) and brodalumab (0.5–1.4%) (Thomaidou and Ramot 2019; Gülsen et al. 2020). Reports of anaphylaxis are rare but have been reported with Secukinumab (FDA 2015). No definite cases of anaphylaxis were reported in the landmark Ixekizumab trials but were noted in post-marketing surveillance (FDA 2019b). Urticaria was reported in up to 8.8% of patients in the Japanese Ixekizumab UNCOVER-J substudy (Saeki et al. 2017).

Off-Target Inflammatory Cutaneous Eruptions

Eczematous eruptions are the most reported paradoxical reaction with the IL-17 inhibitors with a reported incidence of up to 12% in the Phase 3 UNCOVER-J study on ixekizumab and several reports with secukinumab (Murphy et al. 2022). There have yet to be reports of eczematous eruptions due to brodalumab which is the latest to be approved (Murphy et al. 2022). These eczematous eruptions usually occur within 4 months of treatment with morphologies such as atopic dermatitis, eyelid dermatitis, and pompholyx reported. About half of reported cases required treatment discontinuation (Murphy et al. 2022).

As eczema is regarded as a Th2-mediated disease, proposed mechanisms include the compensatory increase in the Th2 pathway due to downregulation of the Th1/Th17 pathway from IL-17 inhibition (Eyerich et al. 2011).

At least 15 reports of paradoxical psoriasiform eruptions due to IL-17 inhibitors have been reported (Murphy et al. 2022) with reported morphologies including pustular psoriasis and flares of pre-existing psoriasis (Dogra et al. 2019). Psoriasiform paradoxical reactions in the form of palmoplantar pustulosis have also been reported in three patients on brodalumab, all of them after switching from secukinumab due to loss of therapeutic efficacy. It was hypothesised that patients losing responsiveness to the therapeutic neutralisation of IL17A may become prone to paradoxical activation of neutrophils under IL-17RA inhibition by brodalumab (Iznardo and Puig 2020).

Other less frequently reported cutaneous reactions with IL-17 inhibitors include sarcoidosis-like granulomatous reactions, alopecia areata,

pyoderma gangrenosum, lichenoid eruptions, Bechet's syndrome, hidradenitis suppurativa, granuloma annulare, lupus-like, vitiligo, erythema multiforme, bullous pemphigoid, and pemphigus (Murphy et al. 2022).

3.8 Anti IL12/23 Inhibitor (Ustekinumab)

Ustekinumab inhibits the p40 subunit of IL-12 and IL-23 and is approved for use for psoriasis, psoriatic arthritis, and inflammatory bowel disease.

Hypersensitivity Reactions

Injection site reactions are reported in about 1–3% of patients on ustekinumab (Thomaidou and Ramot 2019; Gülsen et al. 2020). Hypersensitivity reactions including anaphylaxis and angioedema are rare but have been reported (Ghosh et al. 2019). In a review on ustekinumab safety in psoriasis, psoriatic arthritis, and Crohn's disease, no serious anaphylactic reactions or serum sickness-like reactions to ustekinumab were observed. However, two patients with Crohn's disease displayed signs and symptoms of hypersensitivity including throat tightness, shortness of breath, and flushing after the first and only subcutaneous dose, while the second patient developed chest discomfort, flushing, urticaria, and fever after initial intravenous administration. These cases prompted a caution in the FDA label regarding the possibility of anaphylaxis. In those cases, symptoms resolved within 1 h following oral corticosteroid and antihistamine treatment (Ghosh et al. 2019).

Off-Target Inflammatory Cutaneous Eruptions

Compared to the anti-TNFs and IL-17 inhibitors, inflammatory cutaneous eruptions have been less frequently reported despite over a decade of clinical use. These include few of reports of vitiligo, psoriasis, alopecia areata, eczematous eruptions, granulomatous eruptions, bullous pemphigoid, lupus-like reactions and morphoea, with single reports of hidradenitis suppurativa, frontal fibrosing alopecia, Well's syndrome, erythema annulare centrifugum, and linear IgA bullous dermatosis (Murphy et al. 2022).

Interestingly, ustekinumab has been reported to be an effective treatment for anti-TNF-related psoriasiform reactions with a response rate of 75–100% (Tillack et al. 2014; Mazloom et al. 2020).

3.9 Anti-IL23 Inhibitor (Guselkumab)

As a relatively new biologic, reports on cutaneous adverse reactions to Guselkumab are currently lacking with two reports of an eczematous eruptions (Truong et al. 2019; Reyn et al. 2019). It has been postulated that inhibition of TNFα can lead to an unopposed increase in IFN-a by plasmacytoid dendritic cells, resulting in psoriasiform-eczematous skin lesions. As IL-23 induces upregulation of TNF-a through TH17 cells, it has been suggested that guselkumab may partially act as a TNFα inhibitor, resulting in increased IFN-a production and an eczematous skin reaction in predisposed individuals (Reyn et al. 2019).

3.10 Anti-IgE (Omalizumab)

Omalizumab, a recombinant mAb with 95% human protein fused with 5% mouse protein, targets free serum IgE, preventing its binding to basophils and mast cells and with it, downstream release of pro-inflammatory mediators. The main mechanism of omalizumab (Agache et al. 2021) is a downregulation of IgE receptors on these cells and rapid reduction of free levels of IgE, thus blunting the allergic response. Omalizumab has been approved for moderate to severe allergic asthma and refractory chronic spontaneous urticaria (Agache et al. 2020, 2021).

Injection site reactions appear to be the most common adverse reactions, accounting for 45% of reports. Anaphylaxis has been reported in 0.1–0.2% of patients on omalizumab, occurring early in the treatment, usually within the first

3 injections (Shankar and Petrov 2013; Cox et al. 2007). The onset of symptoms is typically within 2 h of injection. As a result, the FDA has a black box warning (Cox et al. 2007) recommending in-office monitoring for 2 h for the first 3 doses and 30 min for subsequent ones. Delayed onset anaphylaxis cases have also been reported among asthmatic patients receiving omalizumab with symptoms starting 1-day post-injection (Agache et al. 2021). Patients are recommended to be provided with and taught how to use adrenaline autoinjector. A case-control study (Lieberman et al. 2016) identified prior history of anaphylaxis to drug, food, or idiopathic increased subsequent risk of anaphylaxis association with omalizumab use (OR 8.1; 95% CI, 2.7 to 24.3).

In some cases, skin tests (skin prick and intradermal tests) are positive suggestive of an IgE-mediated hypersensitivity reaction. Desensitisation with omalizumab has been reported (Owens and Petrov 2012). Some authors have proposed that the hypersensitivity reactions may not be due to active drug itself but due to additives such as polysorbate used to enhance drug solubility (Bergmann et al. 2020; Perino et al. 2018). Others have suggested that these reactions could be a result of IgG antibodies against omalizumab (Balbino et al. 2020). However, a post-marketing surveillance study did not show any correlation between anaphylaxis or skin test reactivity to the presence of IgE antibody to Omalizumab (Shankar and Petrov 2013).

4 Management of Hypersensitivity Reactions to Monoclonal Antibodies Biologic Agents

4.1 Acute Management

Once a hypersensitivity reaction has occurred, the priority is to stabilise the patient by immediately stopping the infusion, followed swiftly by an assessment of vital signs.

In the event of an anaphylactic shock, intramuscular doses of adrenaline should be administered and advanced cardiac life support initiated (Resuscitation Council 2008). Corticosteroids (Choo et al. 2013) and antihistamines (H1 and H2) (Sheikh et al. 2007), although helpful as adjuncts, should not substitute the prompt administration of adrenaline (Shaker et al. 2020). The patient should be positioned supine with their lower limbs elevated. Large bore intravenous access should be obtained, and isotonic crystalloid administered if hypotension or shock occurs. Supplemental oxygen should be given to patients with respiratory distress. Serum tryptase levels measured within 30–120 min of the anaphylactic reactions, if elevated, carry a high positive predictive value (Buka et al. 2017).

Symptomatic relief can be provided for milder hypersensitivity reactions with the following medications (Picard and Galvão 2017):

1. Acetylsalicylic acid can be used for flushing.
2. Meperidine for chills and/or rigors.
3. Acetaminophen for fever.
4. Salbutamol or montelukast for bronchospasm.

4.2 Local/Injection Site Reactions

Most injection site reactions are mild and do not necessitate treatment discontinuation. Reports also suggest that at least in some patients, the severity of ISRs may improve with continuation of injections and only in severe cases does treatment need to be discontinued (Murdaca et al. 2013).

Measures that may reduce injection site reactions include the following (Thomaidou and Ramot 2019):

1. Patient education and training on the correct injection technique.
2. Ensuring the medication is at room temperature prior to injection.
3. Appropriate choice of injection sites, rotating the sites.
4. Applying cold compresses to the injection site afterwards.
5. Symptomatic treatment with oral antihistamines, topical steroids, and oral analgesic agents as required.

4.3 Off-Target Inflammatory Cutaneous Eruptions

Management of off-target inflammatory cutaneous eruptions and paradoxical reactions remains challenging and requires close collaboration with the primary prescribing physician and the dermatologist. Several treatment algorithms have been proposed, particularly for anti-TNF-induced psoriasis/psoriasiform eruption (Navarro and Daudén 2014; Li et al. 2019; Mazloom et al. 2020). Factors that need to be considered include, firstly, the severity of the reaction as assessed by body surface area, disease-specific severity scores such as Psoriasis Activity and Severity Index (PASI), dermatological life quality index (DLQI), or involvement of special sites such as palmoplantar pustulosis. Secondly, the control of the underlying condition for which the biologic is indicated and thirdly, if there are alternative biologic classes that have been shown to be effective for the underlying condition.

For example, if the psoriasiform reaction is mild and the underlying condition is well controlled on the anti-TNF agent then consideration may be given to either continue on ("treat through") or switch to an alternative anti-TNF agent, bearing in mind that these paradoxical reactions are a class effect. In moderate to severe cases, consideration may be made to switch to a biologic of a different class except in cases where the primary condition is well controlled in conditions where anti-TNF therapy is currently preferred, such as in uveitis, and the anti-TNF agent is deemed critical in disease control (Li et al. 2019).

In patients whom a "treat through" strategy is employed, the efficacy of topical therapy alone has been reported to be between 28% and 63.5% in various cohorts (Mazloom et al. 2020). In moderate to severe cases, the addition of traditional systemic agents such as methotrexate, cyclosporine, acitretin, or phototherapy has been reported to be effective in a subset of patients (Li et al. 2019; Mazloom et al. 2020).

Despite this, reports on paradoxical psoriasiform lesions have suggested that 41–50% of patients required treatment discontinuation. Discontinuation resulted in psoriasis resolution (47.7%) more often than switching to another anti-TNF agent (36.7%), or continuing (32.9%) TNF-alpha therapy (Brown et al. 2017), supporting the consideration of switching biologic class in moderate to severe paradoxical reactions where alternatives are available. Furthermore, rechallenge with an anti-TNF agent has been associated with a 50% recurrence rate of paradoxical psoriasis (Mazloom et al. 2020). Several studies have shown benefit in switching to other non-TNF biologics. Reports have shown promising results with the use of ustekinumab in the management of paradoxical psoriasis due to anti-TNFs with response rates up to 75–100% (Tillack et al. 2014; Mazloom et al. 2020).

While most patients experience resolution of paradoxical psoriasiform eruptions, up to 46% of patients may experience improvement but incomplete resolution of psoriasis despite discontinuation. Those with more severe reactions such as generalised pustular psoriasis may also be more likely to have persistent disease despite discontinuation with only 27.3% experiencing resolution in the systematic review by Brown et al. (2017). Thus, it is important to counsel patients regarding the possibility of persistent skin disease.

4.4 Diagnostic Evaluation of Hypersensitivity Reactions

The first question to address in the diagnostic evaluation of mAbs hypersensitivity reaction, like any drug hypersensitivity reaction, is whether the benefit of continuing the mAbs outweighs the risk of harm of testing. If a safe and equally efficacious alternative treatment is available, the best solution would be to switch out of the culprit mAb. To date, there is a lack of data on the extent of cross reactivity between mAbs of the same class. Extrapolating from other drugs, one could logically speculate some degree of cross reactivity in mAbs that share similar chemical structures or similar target specificity.

However, if both patient and clinician are keen to pursue diagnostic evaluation of a mAbs hyper-

Table 2 Brown grading system of the severity of hypersensitivity reactions

Brown classification Severity grading	Description
1	Mild reactions: symptoms and signs limited to the skin, e.g. urticaria, angioedema, flushing, pruritus
2	Moderate reactions: symptoms and signs that involve the respiratory, gastrointestinal, and cardiovascular system without hypotension, e.g. dyspnoea, wheezing, cough, chest tightness, presyncope, abdominal pain, nausea, vomiting, diarrhoea
3	Severe impairment of cardiovascular or neurologic system, e.g. hypotension, collapse, hypoxia, cyanosis, seizure, confusion, syncope

sensitivity reaction, then the goal of such evaluations is threefold: to determine its main mechanism of action, the severity of the index reaction, and the culprit drug.

The Brown classification system (Brown 2004) has been utilised in grading the severity of hypersensitivity reactions (see Table 2).

Drug causality may be deduced from a detailed clinical history from the patient and/or observers as well as scrutiny of his/her drug chart. In some cases, it is straightforward with only one mAbs administered. In cases where multiple mAbs are given in succession, skin tests may be helpful to identify the culprit agent. However, there are several limitations to skin tests (Brown et al. 2017) namely:

1. Immediate reading of skin prick and intradermal tests are useful only in type I IgE-mediated reactions.
2. To date, mAbs skin tests are not fully validated and their sensitivity, specificity, negative and positive predictive values are extrapolated from small cohort studies.
3. Data on non-irritating concentration for skin tests have not been determined for all mAbs.
4. As small aliquots of mAbs are not available, the entire dose/vial may need to be used, making testing prohibitively expensive.

Table 3 Published non-irritating concentration for skin tests

Monoclonal antibodies	SPT	IDT
Adalimumab	40 mg/ml (neat)	0.4 mg/ml (1/100 dilution)
Etanercept	50 mg/ml (neat) or 25 mg/ml (1:2)[a]	0.5 mg/ml (1/100 dilution)
Infliximab	10 mg/ml (neat)	1 mg/ml (1/10 dilution) or 10 mg/ml (neat)[a]
Omalizumab	125 mg/ml (neat) or 0.00125 mg/ml (1/100,000 dilution)[a]	0.00125 mg/ml (1/100,000 dilution)
Rituximab	10 mg/ml (neat)	1 mg/ml (1/10 dilution), 10 mg/ml (neat)
Tocilizumab	20 mg/ml (neat)	20 mg/ml (neat)

[a]Based on ENDA/EAACI Drug Allergy Interest Group position paper (Brockow et al. 2013), with permission

A positive skin test at non-irritating concentrations of mAbs (see Table 3) strongly suggests type I IgE-mediated hypersensitivity reactions (Picard and Galvão 2017). As re-exposure carries the risk of anaphylaxis, it should only be carried out via the process of desensitisation.

For non-IgE-mediated reactions, the method of re-exposure should be based on the severity of the index hypersensitivity reactions (Fouda and Bavbek 2020). Patients with mild (Brown's class I) reactions may attempt a challenge test with the culprit mAbs. Re-exposure for severe (Brown's class III) non-IgE-mediated reactions should only be performed via the desensitisation protocol. In patients with moderate severity reactions, the decision to challenge vs desensitise could be made on a case-by-case basis, considering the risk of provoking a recurrent reaction and its impact on the patient.

4.5 Desensitisation

The best reported desensitisation protocol for mAbs is the 12 steps protocol developed at Brigham and Women's Hospital (see Table 4) (Brennan et al. 2009; Castells et al. 2008; Isabwe et al. 2017). It should only be performed by

Table 4 Example of an infliximab desensitisation protocol (12 step/3 bag) protocol (taken from Picard and Galvao et al.) (Picard and Galvão 2017), with permission

Drug: infliximab						
Target dose: 400 mg						
Bag	Volume (ml) per bag	Concentration (mg/ml) per bag	Amount (ml) of bag infused	Dose infused (mg) per bag		
Solution 1	250	0.016	9.25	0.148		
Solution 2	250	0.16	18.75	3		
Solution 3	250	1.587	250	396.75		
Step	*Solution*	*Rate (ml/h)*	*Time (min)*	*Volume infused (ml)*	*Dose infused (mg) per step*	*Cumulative dose (mg)*
1	1	2	15	0.5	0.008	0.008
2	1	5	15	1.25	0.02	0.028
3	1	10	15	2.5	0.02	0068
4	1	20	15	5	0.08	0.148
5	2	5	15	1.25	0.20	0.348
6	2	10	15	2.5	0.40	0.748
7	2	20	15	5	0.80	1.548
8	2	40	15	10	1.6	3.148
9	3	10	15	2.5	3.969	7.117
10	3	20	15	5	7.937	15.054
11	3	40	15	10	15.874	30.928
12	3	80	174.4	232.5	369.072	400
Total time (h) = 5.7 h						

trained clinicians and a facility equipped to treat anaphylactic patients. About 30% of patients suffer breakthrough reactions, usually during the last step, and these are generally mild (Makowska and Lewandowska-Polak 2020). When a breakthrough reaction occurs, the infusion should be halted, and the patient's symptoms treated. Depending on the symptoms, H1 and H2 antihistamines, inhaled beta agonists, intravenous fluids, montelukast, and corticosteroids could be used. Intramuscular adrenaline should be available on site and used if indicated, although this happens rarely (Brennan et al. 2009). Once the symptoms resolve, the infusion is resumed where it is stopped and most patient are able to complete the protocol. Premedications can be considered in patients requiring subsequent desensitisation if they experience breakthrough reaction with it before. Other interventions that could prevent breakthrough reactions include co-administration of normal saline at rates between 100 and 250 ml/h in parallel to the desensitisation protocol, adding an intermediate step just before the step when breakthrough reactions occur and limiting the final infusion rates to 40–60 ml/h and using a 4 bag/16 step desensitisation protocol in patients with very low threshold.

4.6 Challenge

There is no standardised protocol for mAbs challenge test. One review suggests starting the mAb infusion at one-tenth of the target infusion rate for 15 min and if tolerated, to increase the rate to its target according to the manufacturer's instructions or regular infusion protocol (Picard and Galvão 2017).

4.7 Premedication

Premedication, typically administered 30–60 min prior, can be used as an adjunct to desensitisation and should be tailored to the patient's index or breakthrough reactions (Chung 2008). H1 and

H2 antihistamines are given for cutaneous symptoms, montelukast for respiratory bronchospasm, paracetamol, corticosteroid, and nonsteroidal anti-inflammatory drugs to prevent fever, and aspirin to prevent flushing (Chung 2008). A short-acting benzodiazepam such as lorazepam can be prescribed to alleviate anxiety associated with desensitisation.

5 Conclusion

The use of mAbs has increased exponentially, covering a myriad of indications. This is likely to continue to grow in the future. While these drugs have given hope to many patients with previously intractable diseases, like all medications, they come with potential adverse reactions which is important for medical practitioners to be aware of and familiar with. While more varied types of mAbs are being discovered with a variety of modes of action, they share certain common characteristics and knowledge of first principles can help to predict and prepare for potential adverse reactions for improved patient outcomes.

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Cutaneous Reactions to Oncologic Targeted Therapy

Chia-Yu Chu

1 Introduction

The identification of molecular drivers of carcinogenesis has led to the development of newer targeted agents aimed at specific molecular and genetic targets. Targeted therapy is a type of cancer treatment that targets the pathways in cancer cells that help them grow, divide, and spread. With the advent of these therapies, novel types of skin toxicities have also developed (Ransohoff and Kwong 2017; Lacouture and Sibaud 2018).

These targeted therapies may be either small-molecular drugs or monoclonal antibodies, and are usually categorized according to their specific targets such as epidermal growth factor receptor inhibitors (EGFRi), multikinase inhibitors (MKi), BRAF inhibitors (BRAFi), MEK inhibitors (MEKi), mammalian target of rapamycin inhibitors (mTORi), hedgehog signaling pathway (HhSP) inhibitors (HhSPi), and KIT inhibitors (KITi). These agents frequently give rise to cutaneous reactions (Table 1) (Kaul et al. 2019; Macdonald et al. 2015a, b; Shia et al. 2016; Dai et al. 2017; Lee et al. 2017).

Although designed to be more "precise" in targeting cancer cells than traditional chemotherapies, these targeted therapies continue to induce various cutaneous adverse effects (Macdonald et al. 2015a, b). Cutaneous reactions are among the most frequently observed adverse effects and may result in significant morbidity and dose modification or discontinuation (Macdonald et al. 2015a; Agha et al. 2007; Dy and Adjei 2013). The patient's quality of life, including the physical (Eilers et al. 2010), emotional (Joshi et al. 2010), and psychological domain (Balagula et al. 2011) may all be affected. In addition, these reactions can affect medication compliance and adherence to cancer therapy, resulting in substantial healthcare utilization and economic burden (Balagula et al. 2011; Borovicka et al. 2011).

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Table 1 Common cutaneous reactions associated with various types of cancer targeted therapies

Agents	Cutaneous reactions	Clinical features
Epidermal growth factor receptor inhibitors (EGFRi)	1. Acneiform eruption 2. Pruritus 3. Dry skin (xerosis) 4. Nail changes 5. Hair changes	1. Papular or pustular eruption without comedones 2. A symptom of subclinical dry skin 3. Pruritus, fine scaling, and fissures and may progress into xerotic dermatitis 4. Paronychia with or without granulation tissues. In some occasion, it may progress into pyogenic granuloma-like changes 5. Curly, fine, and brittle hair; trichomegaly
Multikinase inhibitors (MKi)	1. Morbilliform eruptions 2. Hand-foot skin reaction (HFSR)	1. Beginning on the face with centripetal spread 2. Well-demarcated, bean- to coin-sized, hyperkeratotic, painful plaques with underlying erythema localized to the pressure areas of the soles and palms
BRAF inhibitors (BRAFi)	1. Morbilliform eruptions 2. Benign keratotic squamoproliferative lesions 3. Keratoacanthomas and squamous cell carcinoma 4. Photosensitivity	1. Folliculocentric smooth papules that coalesce into broad maculopapular lesions 2. Verrucous keratosis is the most common manifestation 3. Hyperkeratotic papules with central craters 4. Well-demarcated blistering and painful erythema on the sun-exposed sites
MEK inhibitors (MEKi)	1. Morbilliform eruption 2. Acneiform eruption 3. Xerosis 4. Paronychia	1. Generalized maculopapular eruptions 2. Primarily involves the head, neck, and upper torso
Mammalian target of rapamycin inhibitors (mTORi)	1. Mucositis 2. Rash	1. Aphthous-like lesions with well-circumscribed, round, superficial, painful ulcers are solely localized in the nonkeratinized mucosa and occasionally surrounded by an erythematous halo
Hedgehog signaling pathway (HhSP) inhibitors (HhSPi)	1. Alopecia 2. Dysgeusia	1. Grade 2 hair loss. Nonscarring universal alopecia similar to alopecia universalis may also be seen 2. Taste disturbances
KIT inhibitors (KITi)	1. Facial edema 2. Morbilliform eruption 3. Pigmentary changes	1. May occur in about two-thirds of patients at around 8 weeks after receiving imatinib 2. Morbilliform eruption may have either localized, patchy, or diffuse distribution 3. Depigmentation or vitiligo changes

2 Epidemiology

Cutaneous reactions develop in a considerable number of patients treated with EGFRi that target EGFR. Acneiform (papulopustular) eruption is the most frequent side effect; xerosis, eczema, telangiectasia, hyperpigmentation, hair changes, and paronychia may also occur (Albanell et al. 2002; Segaert and Van Cutsem 2005; Lacouture 2006; Lacouture et al. 2013). Skin adverse events that result from treatment with EGFRi may affect 45–100% of patients (Lacouture 2006; Lacouture et al. 2013; Chen et al. 2016). Four major skin toxic effects with different incidences have been reported from clinical studies, including acneiform eruption (60–94%), pruritus (16–60%), xerosis (4–38%), and paronychia (6–12%) (Chen et al. 2016).

A retrospective study comparing the incidences and severity of skin toxicity for three different epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) showed that the incidence of acneiform eruption was the highest (67.2–76.3%), followed by pruritus and xerosis (47.5–63.4%). The incidence of paronychia was the lowest but differed significantly among the 3 EGFR-TKIs (9.8% for gefitinib, 12.8% for erlotinib, and 39.8% for afatinib) (Chen et al. 2016). Afatinib is an irreversible EGFR family blocker and its side effect is similar to other EGFRi, with

skin toxicity and diarrhea being the most frequently reported adverse events (Lacouture et al. 2013). Novel molecularly targeted therapies developed to overcome *EGFR* T790M resistance (such as osimertinib) have been shown to have lower frequency and severity of cutaneous reactions than first- and second-generation EGFR-TKIs (Chu et al. 2018). Dacomitinib is another irreversible inhibitor of EGFR. The monoclonal antibodies cetuximab and panitumumab also may produce similar skin toxicities because of their EGFR inhibition effect on EGFR (Agero et al. 2006).

Morbilliform eruptions have been described in the early weeks after initiation of imatinib (66%) (Ransohoff and Kwong 2017; Shia et al. 2016), sorafenib (all grade, 10–60%), sunitinib (all grade, 13–24%), pazopanib (all grade, 6–8%), and MEKi (46–74%) (Macdonald et al. 2015a, b).

Hand-foot skin reaction (HFSR) is a painful complication seen most frequently during the early weeks of use with MKi such as sorafenib (10–63%) (Abou-Alfa et al. 2006; Blumenschein et al. 2009; Cheng et al. 2009; Escudier et al. 2009; Llovet et al. 2008; Ratain et al. 2006; Ryan et al. 2007), sunitinib (10–28%) (Demetri et al. 2006; Gore et al. 2009; Motzer et al. 2007, 2006), and pazopanib (11%) (Hurwitz et al. 2009), as well as BRAFi (vemurafenib, 6%) (Macdonald et al. 2015b).

Hair changes in texture, density, and color can be seen with MKi. Alopecia occurs in up to 44% of sorafenib patients (Autier et al. 2008; Kong and Turner 2009), but less frequently with sunitinib (5–21%) (Robert et al. 2012) and pazopanib (8–10%) (Hurwitz et al. 2009; Hutson et al. 2010; Sternberg et al. 2010). Reversible hair depigmentation is seen during therapy with sunitinib (7–14%) (Hartmann and Kanz 2008; Robert et al. 2003; Lee et al. 2009) and pazopanib (27–44%) (Hurwitz et al. 2009; Sternberg et al. 2010).

Keratinocyte proliferation is characteristic of BRAFi-induced skin reactions and may present as various forms of cutaneous toxicities from verrucous keratoses to invasive squamous cell carcinoma (SCC) (Macdonald et al. 2015b; Chu et al. 2012). Verrucous keratoses are characterized by verruciform keratotic papules occurring in a widespread distribution (in both sun-exposed and non-sun-exposed skin) in up to 50–86% of studied patients (Macdonald et al. 2015b; Chu et al. 2012; Anforth et al. 2012; Lacouture et al. 2012), and are the most commonly encountered squamoproliferative lesions induced by BRAFi (Macdonald et al. 2015b). Well-differentiated SCCs and keratoacanthomas occur in 20–30% of patients receiving BRAFi (Anforth et al. 2012; Chapman et al. 2011; Flaherty et al. 2010).

Stomatitis related to mTOR inhibitors has been reported in 44% of patients and grade 3 or more toxicity in 3% (Macdonald et al. 2015b; Gomez-Fernandez et al. 2012). Inflammatory eruptions have been described with high frequency in treatment with both everolimus (25%) and temsirolimus (46%) (Gomez-Fernandez et al. 2012; Motzer et al. 2008). Several clinical patterns of cutaneous eruptions have been described, including morbilliform, eczematoid, and acneiform (Sankhala et al. 2009).

Mucocutaneous toxicities of HhSPi (vismodegib) are common in tow main forms, alopecia (58–63%) and dysgeusia (51–85%) (Sekulic et al. 2012; Tang et al. 2012; Chang et al. 2014).

The overall incidence of pigmentary changes in the skin and hair in patients exposed to targeted anticancer therapies is 17.7% and 21.5% respectively. The targeted agents imatinib, cabozantinib, nivolumab, pazopanib, pembrolizumab, sorafenib, and sunitinib appeared to be the most common culprits (Lee et al. 2017).

3 Pathophysiology

The mechanisms underlying the skin toxicities associated with cancer targeted therapies vary among different categories of the therapies. Targeted drug-induced exanthem or maculopapular eruption, which is also referred to as exanthematous or morbilliform (measles-like) eruption, is the most common type of reactions. This common drug eruption is usually caused by hypersensitivity reactions or referred to as drug allergy.

The skin reactions of EGFRi are thought to be related to the disruption of physiologic EGFR-mediated signaling processes in the epidermis, especially the basal keratinocytes (Lacouture 2006; Lacouture et al. 2013). Inhibition of EGFR-mediated signaling pathways affects keratinocytes in several ways, such as inducing growth arrest and apoptosis, decreasing cell migration, increasing cell attachment and differentiation, and stimulating inflammation, which result in distinct cutaneous conditions (Lacouture 2006; Lacouture et al. 2013). An EGFR-independent pathway, known as c-Jun NH2-terminal kinase (JNK) activation, may also be related to keratinocyte damage induced by EGFR-TKIs (Lu et al. 2011). The histopathologic results reveal aseptic suppurative folliculitis; however, the epidermal disruption associated with evolving papules and pustules often leads to bacterial superinfection.

Several factors have been associated with an increased tendency for the development of EGFRi-related skin reactions. Among patients treated with erlotinib, rash is most likely to develop in non-smokers, patients with fair skin, and individuals older than 70 years (Lacouture et al. 2013). In contrast, men younger than 70 years old are at increased risk for the development of cetuximab-related skin toxicities (Lacouture et al. 2011). When investigating pharmacogenomic and clinical correlations, researchers found that variability in germline polymorphisms in *EGFR* was a determinant of cutaneous toxicities in erlotinib-treated patients (Rudin et al. 2008).

Although, histology of MKi-related HFSR shows progressive accumulation of hyperkeratosis with focal parakeratosis (Macdonald et al. 2015a; Yang et al. 2008), the disease mechanism remains unclear. It is likely related to VEGF inhibition/vessel regression and negative effects on trauma-induced vascular repair capacities (Macdonald et al. 2015a; Jain et al. 2010; Blanchet et al. 2010).

The mechanism for the development of SCC in patients receiving BRAFi has been elucidated. BRAF blockade in wild-type BRAF cells, particularly in the presence of oncogenic *RAS* mutations, can lead to paradoxical MAPK pathway activation through dimerization of RAF isomers (Hatzivassiliou et al. 2010; Heidorn et al. 2010; Poulikakos et al. 2010, 2011; Sanchez-Laorden et al. 2014; Su et al. 2012). Studies have also shown a high prevalence of *RAS* mutations in cutaneous SCCs developing in patients treated with BRAFi, preferentially in lesions arising in sun-damaged skin (Su et al. 2012; Oberholzer et al. 2012). BRAFi-driven activation of MAPK likely unmasks the oncogenic events in keratinocytes harboring preexisting sun-induced *RAS* mutations (Su et al. 2012). Importantly, downstream inhibition of the MAPK pathway by concurrent inhibition of MEK in combination with BRAF blockade has been shown to reduce the incidence of squamoproliferative lesions (Macdonald et al. 2015b; Flaherty et al. 2012). Verrucous keratoses are the most commonly encountered squamoproliferative lesions induced by BRAFi. Pathologically, minimal to mild atypia and lack of viral cytopathologic changes are noted (Macdonald et al. 2015b).

4 Clinical Features

The most common cutaneous reactions of cancer targeted therapies are drug-induced exanthem or maculopapular eruptions, which are also referred to as exanthematous or morbilliform (measles-like) eruptions (Fig. 1).

4.1 EGFRi

EGFRi such as gefitinib, erlotinib, afatinib, erlotinib, and cetuximab generate a unique constellation of skin toxicities, including acneiform eruptions, dry skin (xerosis), hair and nail changes, mucositis, and pruritus. Acneiform eruption in a seborrheic distribution is the most common and earliest cutaneous side effect of EGFRi.

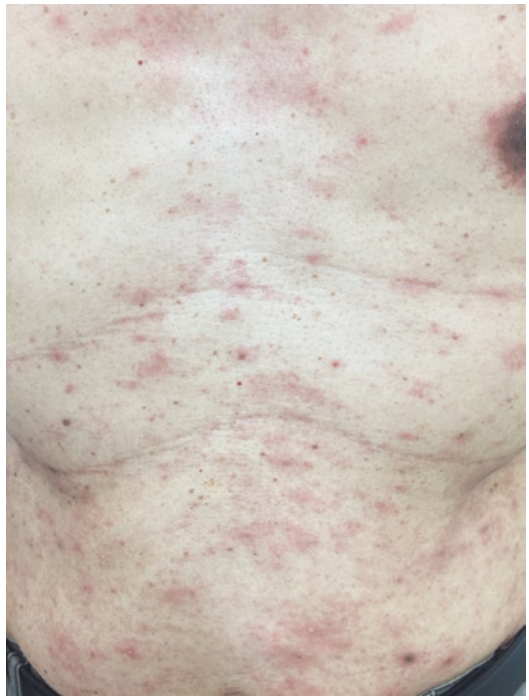

Fig. 1 Exanthematous or morbilliform (measles-like) eruptions. Drug-induced exanthem or maculopapular eruptions, which are also referred to as exanthematous or morbilliform (measles-like) eruptions, are the most common cutaneous reactions of cancer targeted therapies

Acneiform Eruption

Such eruption consists of folliculo-centric pruritic papules or pustules that may coalesce into lakes of pus. Rupture of these pustules may lead to crusting and hyperkeratosis. The rash resembles acne vulgaris, but it is characterized by papular or pustular eruption without comedones (Fig. 2a). This is pathologically and etiologically distinct from acne vulgaris. Commonly affected areas are the face (nose, cheeks, nasolabial folds, chin, and forehead), V-areas of the upper chest and back, and less frequently, the scalp, arms, legs, abdomen, and buttocks (Fig. 2b–d). The palms, soles, and mucosa are usually spared. The acneiform eruption appears within 1 to 3 weeks of starting EGFRi (Agero et al. 2006). The reaction is reversible, usually with complete resolution within 4 weeks of withdrawal from treatment, but the rash may reappear or worsen once treatment is resumed. Spontaneous improvement with resolution or stabilization of the rash occurs with continued treatment (Fig. 2e, f). Acneiform rash associated with osimertinib is less severe and less commonly associated with pruritus (Chu et al. 2018).

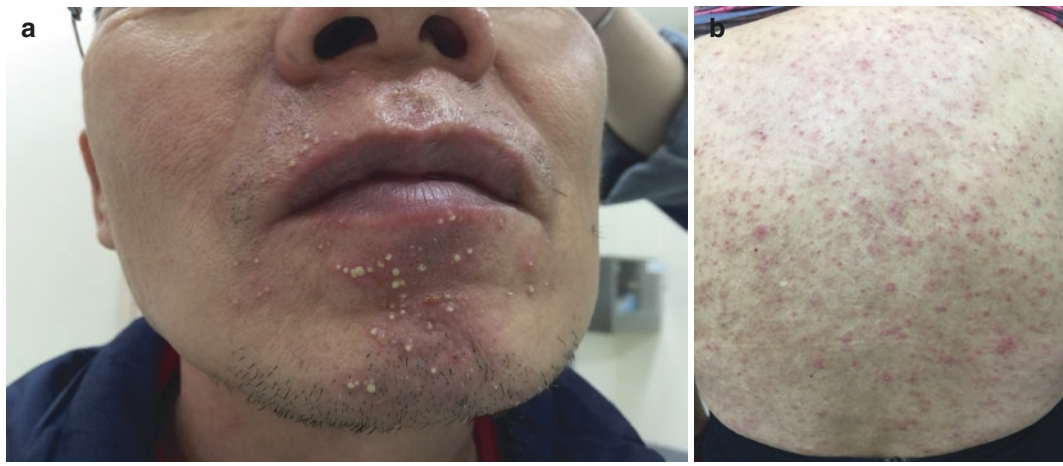

Fig. 2 Acneiform rash related to EGFRi treatment. Acneiform rash is characterized by papular or pustular eruption without comedones (**a**). Commonly affected areas are the face (**b**), upper chest and back (**c**), and less frequently, the scalp, arms (**d**), legs, abdomen, and buttocks. Spontaneous improvement occurs with continued treatment (**e**, **f**)

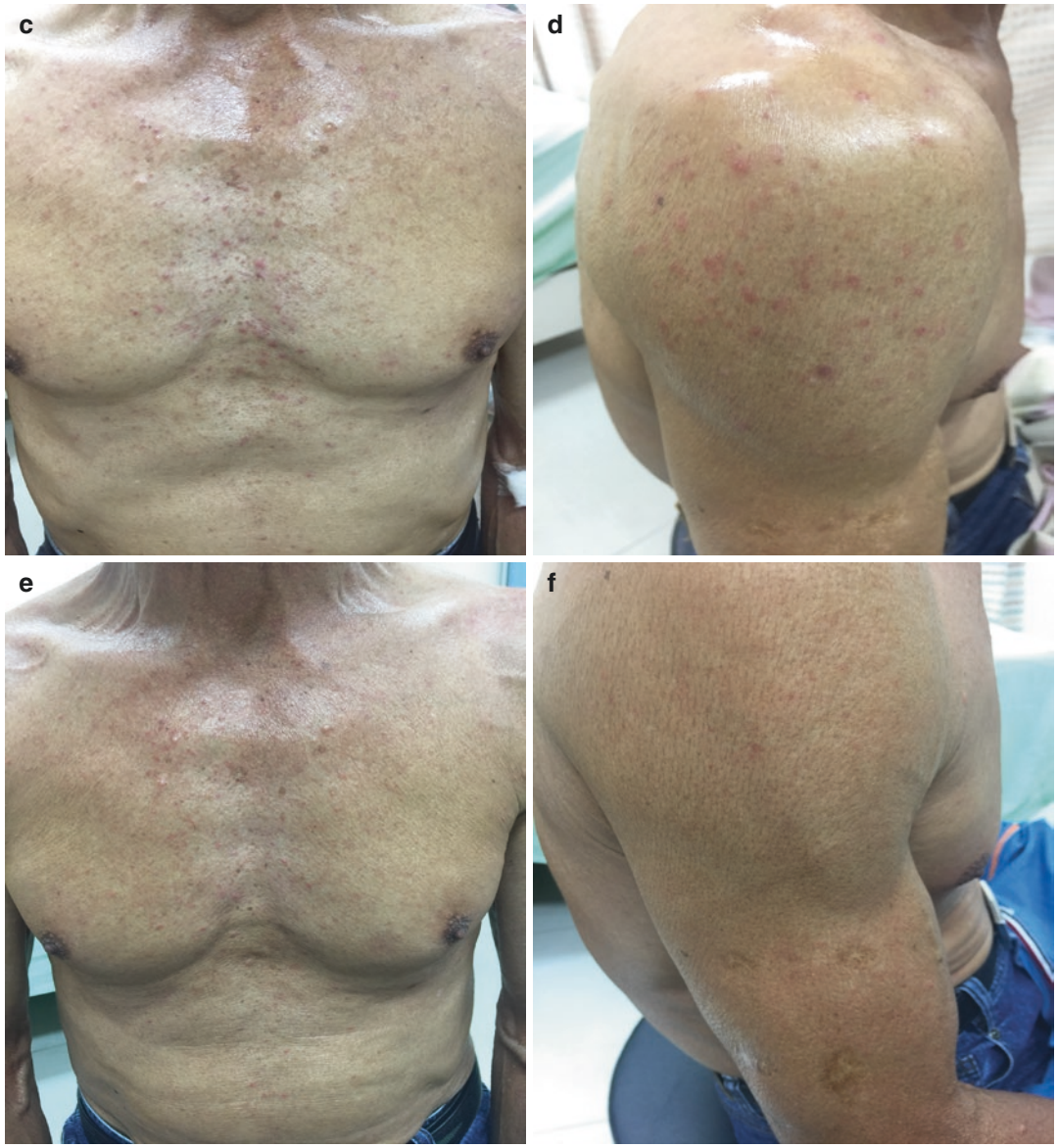

Fig. 2 (continued)

Pruritus and Dry Skin (Xerosis)

Pruritus associated with first- and second-generation EGFR-TKIs is often reported in conjunction with acneiform rash and dry skin. It may be a symptom of subclinical dry skin and often occurs after 1–2 months of EGFRi therapy. Pruritus associated with osimertinib is distinct, as it often presents in the absence of rash and is generally diffuse and of moderate or severe intensity (Chu et al. 2018). Similarly, dry skin (xerosis) manifests after 1–2 months of therapy and often accompanies or succeeds the acneiform rash. Xerosis may manifest as pruritus, fine scaling, and fissures. It may also progress into xerotic dermatitis (Chu et al. 2018). A rare, peculiar form of severe purpuric xerotic dermatitis or purpuric drug eruption has also been reported in patients receiving EGFRi therapy and might represent an exaggerated xerotic dermatitis with vascular damage and superimposed bacterial infection

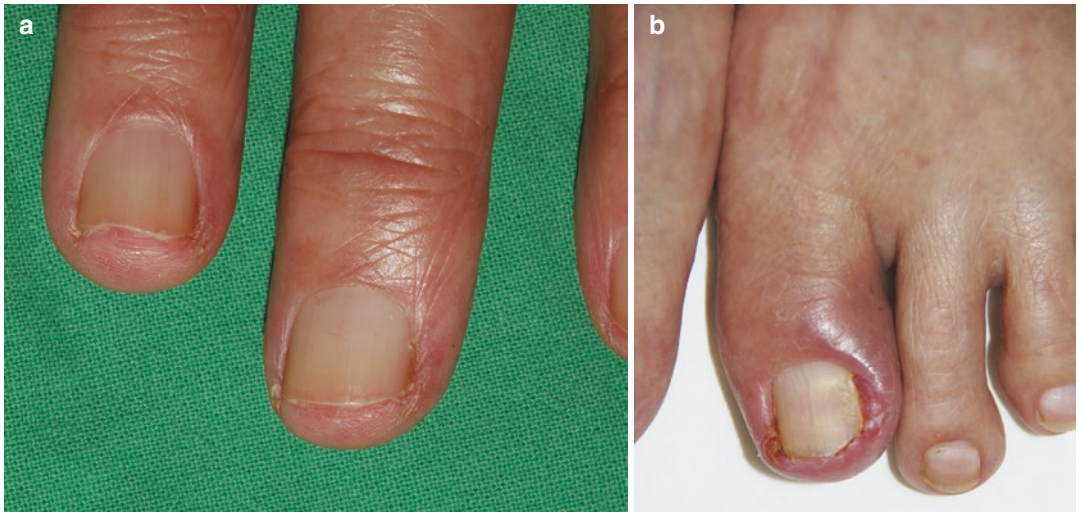

Fig. 3 Paronychia associated with EGFRi treatment. Paronychia without granulation tissues in a patient receiving EGFRi treatment (**a**). Pyogenic granuloma-like changes of lateral nailfolds or distal finger tufts may impair patients' quality of life (**b**)

(Chu et al. 2018; Sheen et al. 2008; Cho et al. 2017).

Nail Changes

EGFRi may induce paronychia with or without granulation tissues (Fig. 3a). In some occasion, it may progress into pyogenic granuloma-like changes, presenting as erythema, tenderness, swelling, and fissuring of lateral nailfolds or distal finger tufts (Fig. 3b), which may lead to disability and impairment of patients' quality of life (Ho et al. 2019).

Hair Changes

In patients on chronic EGFRi therapy, hair abnormalities may develop. The hair shaft may become more curly, coarse and brittle. Partial hair loss with a androgenetic alopecia-like pattern has also been noted. Extensive growth of eyelashes and eyebrows resulting in trichomegaly, curling and ingrowth have been reported with long term treatment (Fig. 4). Patients who report symptoms of eye irritation should be seen by an ophthalmologist because of the risk of trichiasis

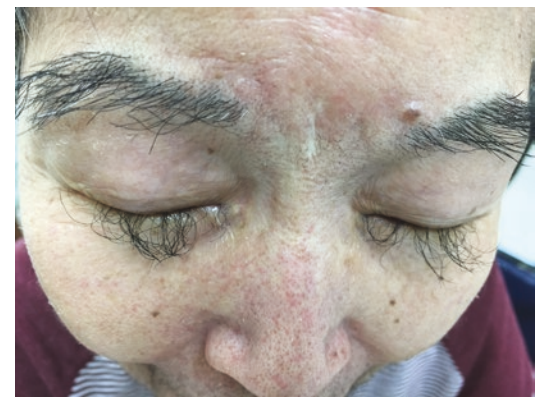

Fig. 4 Trichomegaly with curly hair. Extensive growth of the eyelashes and eyebrows has also been seen in some patients after many months of EGFRi therapy

(Lacouture and Sibaud 2018; Kaul et al. 2019; Macdonald et al. 2015a; Lacouture et al. 2013).

Mucositis

The oral mucosa may develop aphthae, diffuse mucositis, xerostomia, or geographic tongue. Conjunctivitis and keratitis may also occur (Macdonald et al. 2015a).

4.2 Multikinase Inhibitors (MKi)

Morbilliform eruptions beginning on the face with centripetal spread are the most common skin reaction in the initial weeks after initiation of MKi (Macdonald et al. 2015a).

Hand-Foot Skin Reaction (HFSR)

The small molecule tyrosine kinase inhibitors: sunitinib, sorafenib, regorafenib, pazopanib target angiogenesis are associated with a high incidence of HFSR. The clinical and histologic patterns of HFSR differ from the classic acral erythema or hand-foot syndrome (HFS) caused by conventional cytotoxic agents (Table 2). HFSR is characterized by well-demarcated, bean- to coin-sized, hyperkeratotic, painful plaques with underlying erythema localized to the pressure areas of the soles (Fig. 5a). In contrast, acral erythema or HFS is most often characterized by a symmetric edema and diffuse erythema of the palms and soles (Fig. 5b) which may progress to blistering and necrosis.

Table 2 Comparison between hand-foot skin reaction (HFSR) and hand-foot syndrome (HFS)

	HFSR	HSF
Incidence	1. 4.5–79% 2. Sorafenib plus bevacizumab has a highest reported incidence of 79%	1. 6–89% 2. Doxorubicin plus continuous 5-FU has a highest reported incidence of 89%
Clinical presentation	1. Localized, tender lesions on the areas subjected to friction or trauma 2. Well-demarcated, bean- to coin-sized, hyperkeratotic, painful plaques with underlying erythema localized to the pressure areas of the soles and palms 3. May appear as well-demarcated blisters or ulcers	1. Symmetric erythema and edema in palms and soles, accompanied by preceding numbness, itching, or tingling pain (dysesthesia) 2. Can progress to blistering with desquamation, erosion, ulceration, or necrosis
Histopathology	1. Hyperkeratosis 2. Well-defined band of discohesive dyskeratotic keratinocytes	1. Hyperkeratosis, parakeratosis; epidermal dysmaturation with some dyskeratotic keratinocytes in the epidermis 2. Basal layer vacuolar degeneration or full-thickness necrosis; spongiosis
Causative agents	1. Mainly targeted anticancer therapies 2. Multikinase inhibitors (sorafenib, sunitinib, axitinib, pazopanib, regorafenib, bevacizumab, and vemurafenib)	1. Mainly chemotherapeutic agents 2. Pegylated liposomal doxorubicin, capecitabine, 5-fluorouracil, cytarabine, docetaxel and doxorubicin, other cytotoxic agents

HFS hand-foot syndrome, *HFSR* hand-foot skin reaction

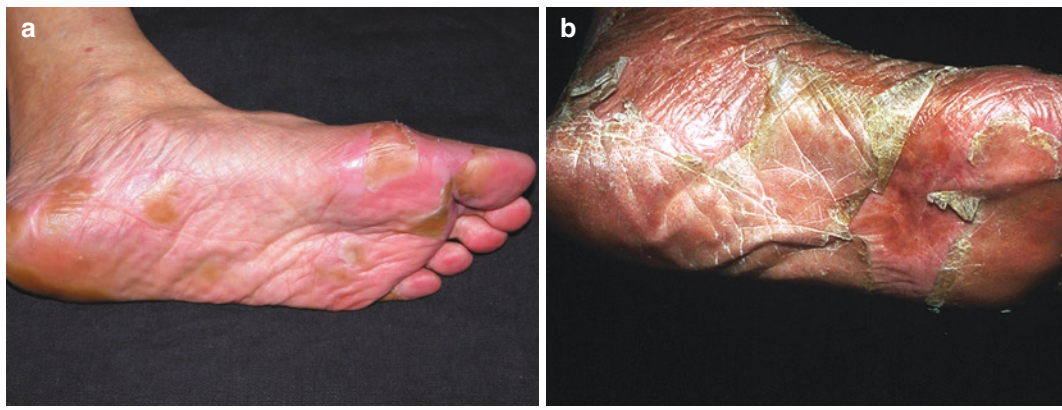

Fig. 5 HFSR associated with MKi. It is characterized by well-demarcated, bean- to coin-sized, hyperkeratotic, painful plaques with underlying erythema localized to the pressure areas of the soles (**a**). Acral erythema or HFS is characterized by a symmetric edema and diffuse erythema of the palms and soles (**b**)

4.3 BRAF Inhibitors (BRAFi)

Cutaneous eruptions, keratotic squamoproliferative lesions, and photosensitivity are among the most debilitating skin-related adverse effects of BRAFi. Morbilliform eruptions may occur in up to 68% of patients taking vemurafenib (Macdonald et al. 2015b).

Keratotic Lesions

Keratinocyte proliferation related to BRAFi may present as a spectrum of cutaneous toxicities from verrucous keratoses to invasive SCC (Macdonald et al. 2015b). In patients treated with vemurafenib and dabrafenib, 20–30% have been reported to develop cutaneous SCC and keratoacanthoma (Fig. 6), respectively (Lacouture and Sibaud 2018; Macdonald et al. 2015b; Chu et al. 2012; Anforth et al. 2012; Lacouture et al. 2012; Chapman et al. 2011; Flaherty et al. 2010). Benign keratotic lesions can also be found, and several studies have shown that verrucous keratosis is the most common manifestation. Most of them growths appear 6–12 weeks after treatment (Macdonald et al. 2015b). Treatment consists of cryotherapy, curettage and electrodessication, CO_2 laser, photodynamic therapy, and excision (Macdonald et al. 2015b).

Photosensitivity

UVA photosensitivity is noted in up to 50% of patients administered vemurafenib and presents with erythema and edema on sun-exposed sites (Kaul et al. 2019; Peuvrel and Dréno 2014; de Golian et al. 2016). Photosensitive eruptions are characterized by blistering and painful erythema that can adversely affect daily activities.

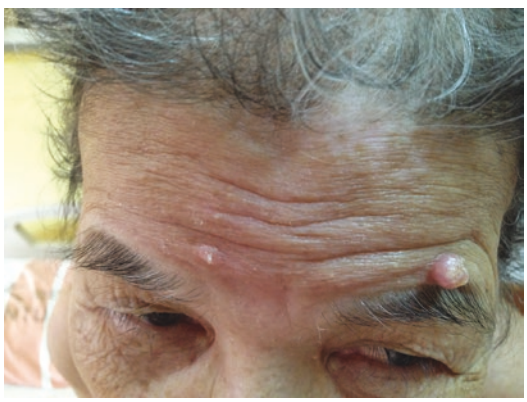

Fig. 6 Keratoacanthoma developed in a patient treated with dabrafenib

4.4 MEK Inhibitors (MEKi)

MEKi include selumetinib and trametinib. The side effect profile of MEKi is similar to that of EGFRi (Macdonald et al. 2015b; Anforth et al. 2014). The most common cutaneous reaction of MEKi is morbilliform eruption (Macdonald et al. 2015b). Another common skin reaction of MEKi is an acneiform eruption that primarily involves the head, neck, and upper torso (Macdonald et al. 2015b; Flaherty et al. 2012; Anforth et al. 2014). The onset, course, and treatment strategies are very similar to those seen with EGFRi. The concomitant use of MEKi and BRAFi has resulted in the reduction of verrucous keratosis and squamous cell cancers associated with BRAF inhibition (Macdonald et al. 2015b; Flaherty et al. 2010, 2012).

4.5 Mammalian Target of Rapamycin Inhibitors (mTORi)

Oral mucositis is the most frequent dose-limiting toxicity observed mTORi (everolimus, temsirolimus, and sirolimus). It is characterized by aphthous-like lesions different from those induced by chemotherapy or radiotherapy. These single or multiple well-circumscribed, round, superficial, painful ulcers are localized in the nonkeratinized mucosa and occasionally surrounded by an erythematous halo (Lacouture and Sibaud 2018; Macdonald et al. 2015b; Gomez-Fernandez et al. 2012; Motzer et al. 2008; Sankhala et al. 2009). Other common cutaneous reactions include morbilliform, eczematoid, and acneiform eruptions and nailfold paronychia (Lacouture and Sibaud 2018; Macdonald et al. 2015b).

4.6 Hedgehog Signaling Pathway Inhibitors (HhSPi)

Alopecia may occur with HhSPI, Grade 2 hair loss was seen in 10–14% of patients and rarely alopecia universalis has been reported (Macdonald et al. 2015b; Sekulic et al. 2012; Tang et al. 2012; Chang et al. 2014). The HhSP pathway is known to have activity in the taste papillae, so HhSP inhibition may cause taste disturbances (Macdonald et al. 2015b).

4.7 KIT Inhibitors (KITi)

Common cutaneous reactions to KITi include facial edema, a nonspecific maculopapular rash and pigmentary changes. Maculopapular (morbilliform) eruptions may occur in up to two-thirds of patients at around 8 weeks following imatinib therapy (Macdonald et al. 2015b).

Pigmentary Changes

Dyspigmentation associated with imatinib use has been described as having a localized, patchy, or diffuse distribution. This is consistent with the documented role of c-kit in the physiology of melanocytes, including the regulation of melanogenesis and the proliferation, migration, and survival of melanocytes (Macdonald et al. 2015b).

5 Prognosis

The prognosis of skin reactions to oncologic targeted therapies is good in most cases, with most being generally mild or moderate in severity.

Nonetheless, such eruption may affect visible areas of the body, which can cause distress, anxiety, negative self-image, and low self-esteem. If untreated, these skin reactions may lead to morbidity, poor treatment compliance, inappropriate dose interruption all of which may have an impact on the overall survival of the patient. As such, patient education, early recognition and proactive management of these reactions is key (Lacouture et al. 2013; Agero et al. 2006).

The relationship between treatment outcomes and cutaneous reactions induced by cancer targeted therapies has been clarified in the past decade (Rzepecki et al. 2018). The association between the onset or severity of rash and improved survival following treatment with an EGFRi (especially gefitinib, erlotinib, and cetuximab) has been increasingly documented (Rzepecki et al. 2018; Pérez-Soler 2003; Tiseo et al. 2010, 2014; Mohamed et al. 2005; Pérez-Soler et al. 2004; Johnson et al. 2005; Gatzemeier et al. 2007; Herbst et al. 2005; Fiala et al. 2013; Faehling et al. 2010; Wacker et al. 2007). Similarly, HFSR has also been shown to be associated with survival (Vincenzi et al. 2010; Poprach et al. 2012; Nakano et al. 2013; Wang et al. 2018). A recent systematic review and meta-analysis of 12 cohort studies of patients with hepatocellular carcinoma treated with sorafenib reported that development of HFSR was significantly associated with reduced risk of death (Wang et al. 2018).

Although preliminary studies are promising with regard to the potential role of cutaneous toxicities as a surrogate biomarker of efficacy of treatment, larger prospective studies are needed to confirm this relationship (Rzepecki et al. 2018).

6 Management

Symptomatic and preventive treatments are usually helpful for patients with cutaneous reactions to cancer targeted therapies. Strategies include use of topical moisturizers or corticosteroids, administration of systemic steroidal medications or antihistamine drugs to reduce pruritus and inflammation, and dose delay or reduction in some cases with severe reactions (Ransohoff and Kwong 2017; Lacouture and Sibaud 2018; Kaul et al. 2019; Macdonald et al. 2015a, b; Shia et al. 2016; Dai et al. 2017; Lee et al. 2017; Agha et al. 2007; Dy and Adjei 2013; Lacouture et al. 2013).

Patients who are undergoing EGFRi therapy should take precautions to protect their skin, such as using alcohol-free skin products and minimiz-

ing sun exposure by wearing protective clothing, a hat, and sunscreen with both ultraviolet A and B protection. Various expert opinion guidelines have been proposed for the management of EGFRi reactions (Lacouture et al. 2013; Chu et al. 2018). Topical and oral corticosteroids or antibiotics are recommended for acneiform rash; topical or systemic antipruritic agents may be used for pruritus. Topical corticosteroids, ammonium lactate, and moisturizing creams are recommended for xerosis. For paronychia, topical antibiotics or antiseptics and silver nitrate applications can be beneficial. Patients with an intolerable grade 2 skin reaction and patients with a severe skin reaction (grade 3 or higher) should be referred to a dermatologist with experience in managing patients taking targeted therapies. These patients may also benefit from dose modification. Temporary interruption of EGFRi may relieve severe skin symptoms but should not last for more than 28 days. EGFRi treatment should be permanently discontinued if skin reactions remain at or above grade 3 despite dermatologic interventions and treatment interruption for 28 days. EGFRi may be reintroduced at a lower dose for patients with a severe skin reaction (grade 3 or higher) that improves within 28 days of treatment interruption (Lacouture et al. 2013).

Antibacterial soaks (diluted bleach or vinegar in water) are recommended to prevent superinfection of the nail folds. Warm compresses, silver nitrate, topical corticosteroids, and systemic tetracyclines may also be used to reduce periungual inflammation in paronychia. For HFSR, high potency topical corticosteroids combined with topical keratolytics such as urea or salicylic acid are useful interventions.

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Cutaneous Reactions to Oncologic Immunotherapy

Rachel Choi and Jonathan Leventhal

Abbreviations

ADLs	Activities of daily living
AGEP	Acute generalized exanthematous pustulosis
APC	Antigen-presenting cell
ASCO	American Society of Clinical Oncology
BSA	Body surface area
CBC	Complete blood count
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DIHS	Drug-induced hypersensitivity syndrome
DMARD	Disease-modifying antirheumatic drug
DRESS	Drug rash with eosinophilia and systemic symptoms
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GVHD	Graft vs. host disease
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
IVIG	Intravenous immunoglobulin G
JAK	Janus kinase
MHCII	Major histocompatibility complex II
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
RA	Rheumatoid arthritis
SCAR	Severe cutaneous adverse reaction
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
TCR	T cell receptor
TEN	Toxic epidermal necrolysis
UVB NB	Ultraviolet B-narrow band

1 Introduction

The introduction of T cell-targeted immunomodulator anticancer therapy in the past decade has revolutionized the treatment of previously incurable cancers. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1). Their efficacy was first demonstrated in metastatic melanoma (Robert et al. 2015), and they are presently used as monotherapy or in combination with chemotherapy as first- or second-line treatments for about 50 solid organ as well as hematologic cancers (Robert 2020).

In brief, ICIs target T cell activation, as this is the rate-limiting step of the adaptive immune

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response. Antigen-presenting cells (APCs) activate T cells through the association of the major histocompatibility complex II (MHCII) receptor with a T cell receptor (TCR) in response to an antigenic stimulus. This interaction occurs concurrently with several other receptor-ligand associations. One of the interactions relevant to modern immunotherapy drugs is that between the CD28 protein on T cells and the B7 protein on B cells, which can be competitively inhibited by the CTLA-4 protein expressed on T cells. Another relevant interaction is that between the PD-1 receptor of T cells and the PD-L1 and PD-L2 ligands found on monocytes and dendritic cells, and leukocytes and peripheral somatic cells, respectively. Upregulation of this interaction may allow cancer cells to evade detection by the immune system. By inhibiting CTLA-4 or PD-L1/PD-1 interactions, ICIs promote immune system upregulation and antitumoral immune response.

However, the immune upregulation caused by ICIs has broad-ranging effects in addition to the intended antitumoral activity, resulting in a variety of immune-related adverse events (irAEs). Among the most frequent irAEs from ICIs is skin toxicity, including rash and pruritus (Bertrand et al. 2015; Sibaud et al. 2016). Cutaneous irAEs affect 30–50% of patients treated with ICIs, and range widely in form and severity (Villadolid and Amin 2015; Donaldson et al. 2018; Hwang et al. 2016; Ishihara et al. 2019). Skin toxicity (along with pneumonitis and arthritis) was also found to be one of the top three reasons for referral to a multidisciplinary irAE toxicity team at a major medical center (Naidoo et al. 2019). In this chapter, we discuss the major classes of immunotherapy and review the epidemiology, clinical features, histopathology, and recommended treatment guidelines for the most frequently encountered cutaneous irAEs. We also provide a synopsis of less commonly encountered cutaneous irAEs, including severe cutaneous adverse reactions (SCARs).

2 Epidemiology

The incidence and severity of irAEs varies by patient population and by agent used (Martins et al. 2019). It is important to categorize the degree of severity in a standardized approach, as higher-grade rashes generally require a more aggressive therapeutic approach and are more likely to impact immunotherapy interruption. The Common Terminology Criteria for Adverse Events (CTCAE), which is maintained by the American Society of Clinical Oncology (ASCO), is popularly used and classifies cutaneous irAEs primarily by body surface area (BSA) involvement and impact on quality of life, as well as evidence of superinfection and potential for life-threatening complications (Brahmer et al. 2018). The ASCO and European Society for Medical Oncology (ESMO) have also put forth recommendations for management of cutaneous irAEs based on disease severity (Brahmer et al. 2018). In this section we characterize the cutaneous irAEs associated with each ICI.

2.1 Anti-CTLA-4 Therapy: Ipilimumab

Ipilimumab, a recombinant human monoclonal antibody, is an anti-CTLA-4 ICI that first demonstrated a survival benefit in metastatic melanoma patients (Hodi et al. 2010). irAEs generally occur in a dose-dependent pattern for patients treated with ipilimumab. Pooled analysis of patients treated with 10 mg/kg ipilimumab for 3 weeks showed Grade 3 or 4 irAEs (across all categories) in 25.2% of patients, vs 7% of patients treated with 3 mg/kg dose of ipilimumab (Weber et al. 2012). Specifically in the skin, a study of ipilimumab given at a 10 mg/kg dose showed an incidence of 34.2% for rash of any grade vs. another study of ipilimumab given at a 3 mg/kg dose that showed an incidence of 19.1% for rash of any grade (Hodi et al. 2010; Eggermont et al. 2016). In patients treated with ipilimumab, cutaneous irAEs have the earliest latency of onset (usually within 3–6 weeks after initiation of cancer therapy) (Eggermont et al. 2016). Thus, cutaneous irAEs have the potential to interrupt cancer therapy most prematurely.

The most common cutaneous irAE associated with ipilimumab, affecting 14–26% of patients, is a morbilliform eruption similar to that seen from antibiotic use, which typically manifests on

the trunk and extremities (sparing the head, palms, and soles) (Sibaud et al. 2016; Minkis et al. 2013; Jaber et al. 2006; Zimmer et al. 2012). The morbilliform rash is commonly associated with pruritus, and occasionally with peripheral eosinophilia (Minkis et al. 2013; Jaber et al. 2006; Zimmer et al. 2012). Of note, vitiligo-like depigmentation, which has been linked to improved prognosis during treatment of melanoma patients with interferon, has also been observed in patients treated with ipilimumab (Babai et al. 2020; Gogas et al. 2006; Collins et al. 2017). Other less common cutaneous irAEs linked to ipilimumab include pruritus, toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and prurigo nodularis (Collins et al. 2017; Voskens et al. 2013).

2.2 Anti-PD-1 Therapy: Nivolumab, Pembrolizumab, and Cemiplimab

Nivolumab, pembrolizumab, and cemiplimab are currently the three United States Food and Drug Administration (FDA)-approved anti-PD-1 ICIs. They are generally thought to induce less severe toxicities compared to ipilimumab (Hwang et al. 2016; Collins et al. 2017). The most common cutaneous irAEs associated with single-agent anti-PD-1 therapy are pruritus (11–18% of patients on anti-PD-1 therapy), morbilliform exanthem (15% of patients treated with single-agent anti-PD-1 therapy), vitiligo-like depigmentation, and lichenoid reaction (20% of patients on anti-PD-1 therapy) (Tattersall and Leventhal 2020). Interestingly, a recent study of 82 patients receiving single-agent anti-PD-1 therapy found that of the 40 patients who developed cutaneous irAE, 11 developed a combination of lichenoid reaction, eczema, and vitiligo (Hwang et al. 2016). They concluded that there was a statistically significant association among the presence of these three conditions (Hwang et al. 2016). Unlike with anti-CTLA-4 therapy, studies of the safety profile of anti-PD-1 therapy have not suggested a dose-dependent effect on cutaneous AE thus far (Shulgin et al. 2020; Sanlorenzo et al. 2015). Also in contrast with anti-CTLA-4 therapy, the cutaneous irAEs linked to anti-PD-1 therapy have a more variable time of onset, but generally occur within 10 months of starting therapy (Hwang et al. 2016).

2.3 Anti-PD-L1 Therapy: Atezolizumab, Avelumab, Durvalumab

Anti-PD-L1 agents approved by the FDA include atezolizumab, avelumab, and durvalumab. Their overall safety profile (including cutaneous reactions) is generally thought to be similar to that of anti-PD-1 agents, but it has been suggested that anti-PD-L1 agents may theoretically be more safe considering that PD-L2 signaling is preserved (Collins et al. 2017; Shi et al. 2016; Khoja et al. 2017). In fact, atezolizumab had the best overall safety profile in a systematic review and meta-analysis of phase II and III trials of ICIs (Xu et al. 2018). Overall safety profile was characterized by incidence of grade 1–5 adverse events and grade 3 or 4 adverse events, for which atezolizumab showed a pooled incidence of 66.4% and 15.1% respectively, in an analysis of 1210 patients who received the drug (Xu et al. 2018).

In terms of skin toxicity, atezolizumab showed an odds ratio of 1.21 for pruritus and 1.13 for rash when compared to nivolumab as a control (Xu et al. 2018). Only 1.3% of the 310 patients enrolled in a phase II trial of atezolizumab for locally advanced or metastatic urothelial carcinoma were observed to have grade III rash (Ning et al. 2017; Balar et al. 2017). Another study of 70 patients receiving atezolizumab for renal cell cancer showed the most common irAE to be a grade I rash affecting 20% of patients (McDermott et al. 2016). Durvalumab and avelumab, which were more recently approved by the FDA in 2018 and 2020 respectively, have also shown promising cutaneous AE profiles similar to that of atezolizumab (Kelly et al. 2018; Powles et al. 2017; Patel et al. 2018).

2.4 Combination CTLA-4-PD-1 Inhibition Therapy

The first FDA-approved combination immunotherapy regimen was ipilimumab and nivolumab for treatment of advanced melanoma in 2015; since then, this combination has been approved for several other cancers such as metastatic colorectal cancer, unresectable mesothelioma, and metastatic NSCLC (The ASCO post n.d.). Combination CTLA-4/PD-l inhibition has been shown to improve overall survival in patients with advanced melanoma, with a phase III trial reporting a 58% 3-year survival rate for patients in the combined immunotherapy group compared to 52% in the nivolumab and 34% in the ipilimumab group (Wolchok et al. 2017). However, the rate of grade III-IV adverse events was increased overall in the combination therapy group, with 59% of patients experiencing such effects (Wolchok et al. 2017). Similar to single-agent ICI therapy, the most common toxicities associated with combination therapy were cutaneous (affecting 62% of patients), including pruritus (35%), vitiligo (9%), and maculopapular rash (12%) (Wolchok et al. 2017).

3 Clinical Features and Histopathology of Cutaneous irAE

ICIs are associated with a diverse range of cutaneous irAE, but most commonly with pruritus, morbilliform rash, vitiligo-like depigmentation, and lichenoid reactions. With the increasing use of ICIs in the past decade, less common cutaneous adverse events such as immunobullous eruptions and SCARs have also been observed. Finally, rare instances of Sweet's syndrome, granulomatous reactions, and other autoimmune disorders (e.g., lupus, dermatomyositis) have been demonstrated in association with ICIs. In this section, we provide a discussion of the clinical presentation, histopathology, grading criteria, and recommended management of the predominant cutaneous irAE.

3.1 Common Cutaneous AE

Pruritus

Pruritus with or without associated rash is one of the most common findings in patients treated with ICIs. Generally, pruritus independent of rash may appear at varying times after initiation of therapy. For example, one study of cutaneous irAE in patients on pembrolizumab found a median time of three treatment cycles prior to onset, with a range of 1–17 cycles prior to onset (Sanlorenzo et al. 2015). The most common clinical presentations of independent pruritus in patients treated with ICIs are prurigo nodularis and prurigo simplex with discrete excoriations.

Recommendations for management of pruritus depend on the grade. For mild independent pruritus, gentle skin care and moisturizer are recommended, with topical camphor/menthol for symptomatic relief (Malviya et al. 2020). Antihistamines taken when pruritus is most severe (often at night) may also provide symptomatic relief (Wu and Lacouture 2018). Potent/Ultrapotent topical corticosteroids such as clobetasol or betamethasone are advised for grade I or II pruritus (Puzanov et al. 2017). Alternative agents for rash of this severity include gabapentin or pregabalin and ultraviolet B-narrow band (UVB NB) therapy (Wu and Lacouture 2018). Grade III pruritus is rare and may necessitate interrupting or discontinuing ICI therapy. Patients should be referred to dermatology if possible when making this decision, as many patients may be able to continue with ICI therapy on a combination of antipruritic medications (Malviya et al. 2020). Patients with severe pruritus are usually treated with systemic corticosteroids; naloxone or naltrexone and the neurokinin-1 receptor antagonist aprepitant may also provide benefit (Tattersall and Leventhal 2020; Malviya et al. 2020; Puzanov et al. 2017). Finally, cases of recalcitrant pruritus should be worked up for potentially more severe causes (e.g., bullous pemphigoid), with basic laboratory evaluation (complete blood count (CBC), electrolytes, liver and kidney function) as well as consideration for

skin biopsy and direct immunofluorescence (to rule out prebullous stages of bullous pemphigoid) (Malviya et al. 2020).

3.2 Morbilliform Rash

Morbilliform eruption is a common cutaneous adverse event that may occur from numerous types of ICIs, but is most common with anti-CTLA-4 therapy or combination anti-CTLA-4/PD-1 therapy (Sibaud et al. 2016; Minkis et al. 2013; Jaber et al. 2006; Zimmer et al. 2012). Interestingly, the development of morbilliform rash has been demonstrated to have a statistically significant association with improved overall survival in patients treated with nivolumab and combination ipilimumab-nivolumab (Freeman-Keller et al. 2016; Quach et al. 2019). Patients classically present within weeks of starting immunotherapy with blanching, coalescent erythematous macules and papules on the trunk and extremities, often accompanied by pruritus (Fig. 1). The face and palmoplantar surfaces are usually spared. Of note, morbilliform rash associated with ipilimumab may involve peripheral eosinophilia (Malviya et al. 2020).

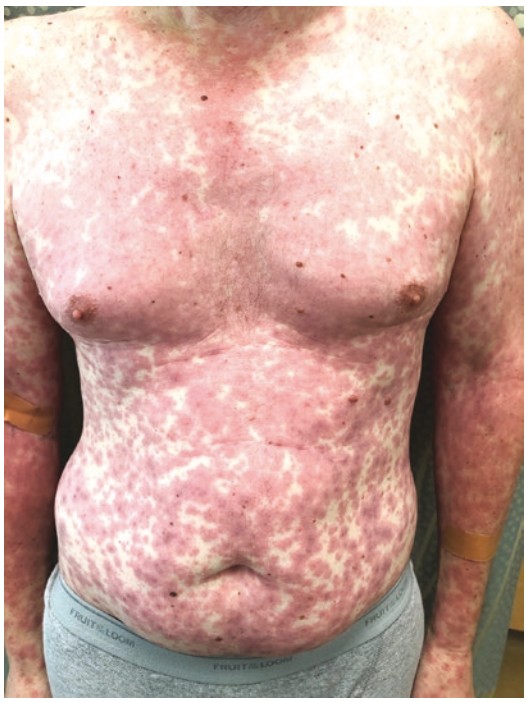

Fig. 1 Morbilliform exanthem to combination ipilimumab and nivolumab in a patient with metastatic melanoma

The differential diagnosis should include morbilliform eruption to other medications, viral exanthem (though typically less pruritic and often associated with other symptoms like cough or conjunctivitis), or acute graft vs. host disease (GVHD) in the correct clinical setting (Malviya et al. 2020). Additionally, patients should be monitored for signs of progression to more severe reactions like DRESS.

Grading of the ICI-associated morbilliform rash depends on % BSA affected and the impact on quality of life. Grade 1 rashes (<10% BSA) and grade 2 rashes (10–30% BSA, with or without impact on instrumental activities of daily living) can be managed with topical corticosteroids, liberal moisturizer use, and oral antihistamines (Common Terminology Criteria for Adverse Events (CTCAE) 2017). Grade 3 reactions involve >30% BSA involvement and limitations of self-care activities of daily living (ADLs), and are generally treated with systemic corticosteroids and treatment interruption (Common Terminology Criteria for Adverse Events (CTCAE) 2017). Most patients will be able to resume ICI therapy once the rash returns to grade 1 (Puzanov et al. 2017).

3.3 Lichenoid Reaction and Other Papulosquamous Disorders

Lichenoid eruptions are well-characterized and common mucocutaneous reactions in patients on PD-1 or PD-L1 agents, occurring in up to 15–25% of patients on these therapies (Hwang et al. 2016; Shi et al. 2016; Coleman et al. 2019; Geisler et al. 2020; Curry et al. 2017; Phillips et al. 2019; Kaunitz et al. 2017). The clinical presentation includes multiple erythematous, violaceous papules and plaques favoring the torso and extremities (Fig. 2), but hypertrophic variants, palmoplantar involvement, and mucosal lesions may also occur. In addition, uncommon presentations like inverse lichen planus or lichen planus

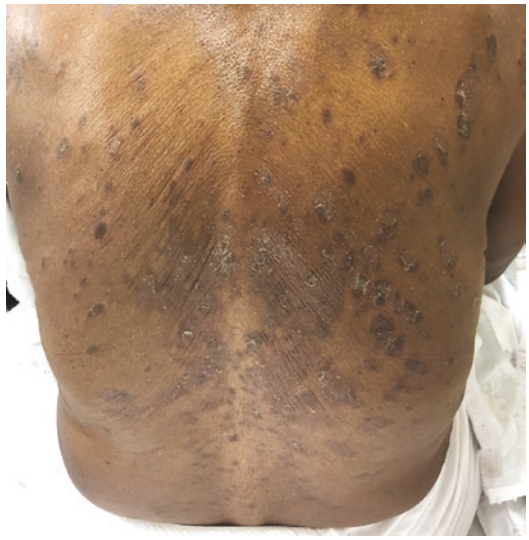

Fig. 2 Lichenoid dermatitis in a woman with lung cancer on pembrolizumab

pemphigoides may be seen (Malviya et al. 2020; Geisler et al. 2020). The mean time of onset for a lichenoid reaction is 6–12 weeks after initiation of therapy, but time of onset can vary widely from days after initiation to a year into therapy (Malviya et al. 2020; Geisler et al. 2020; Tetzlaff et al. 2017). Some cases of lichenoid reactions may even persist after discontinuation of immunotherapy (Tetzlaff et al. 2017).

Histopathological examination has special implications for a supposed lichenoid drug reaction in response to immunotherapy. Similar to idiopathic lichen planus, lichenoid drug reaction shows superficial band-like lymphocytic infiltrate with vacuolar degeneration and keratinocyte necrosis at the basal layer of the epidermis. Variable degrees of epidermal spongiosis with eosinophils may be seen. Immunotherapy-induced lichenoid reaction has also been associated with increased CD163+ histiocytic infiltrates and increased epidermal necrosis, with no changes in expression of CD3, CD4, CD8, CD20, PD-1, CD25, and PD-L1 (Shi et al. 2016; Schaberg et al. 2016). This difference is particularly interesting in the context of evidence suggesting that lichenoid reaction during or after immunotherapy may have positive prognostic implications (Min Lee et al. 2018). A study of 114 patients who had received pembrolizumab, nivolumab, or atezolizumab showed that the 20 patients who developed lichenoid dermatitis had better progression-free survival and overall survival time compared with the 94 patients who did not develop lichenoid dermatitis (Min Lee et al. 2018). More research is necessary to determine the molecular mechanism for this phenomenon.

Treatment of lichenoid reaction most commonly involves high-potency topical corticosteroids twice a day, without interruption of immunotherapy, for grade 1 or 2 reaction (Brahmer et al. 2018; Coleman et al. 2019). Patients with recalcitrant lichenoid reaction after a trial of topical corticosteroids may be treated with systemic corticosteroids, narrowband ultraviolet phototherapy, or acitretin (Malviya et al. 2020; Geisler et al. 2020). Interruption of immunotherapy is only advised if the reaction is grade 3 or higher (Malviya et al. 2020; Geisler et al. 2020).

Other papulosquamous disorders may present similarly to lichenoid dermatitis, including psoriasiform and eczematous reactions. Regarding psoriasiform rashes, existing disease which flares is more common than new-onset psoriasis. For example, a case series of five patients who developed psoriasis during treatment with PD-1 or PD-L1 agents showed that four of the patients had either personal or family history of psoriasis (Voudouri et al. 2017). The clinical presentation of psoriasis in these patients was variable, ranging from guttate and/or plaque psoriasis to psoriatic arthritis (Voudouri et al. 2017). Furthermore, a multicenter study of adverse effects from ICIs showed that of 31 patients with pre-existing history of psoriasis, 21 experienced a flare while being treated with an ICI (Tison et al. 2019). ICI-induced psoriasis may be treated similarly to idiopathic psoriasis, starting with topical corticosteroids and considering UVB NB therapy, acitretin, apremilast, and other systemic biologic agents in recalcitrant cases after discussion with oncology.

Eczematous reactions, which may have overlapping features with lichenoid reactions, may also occur from immunotherapy. Clinically, these patients present with pruritus and pink, scaly

papules, patches, or plaques, resembling atopic or nummular dermatitis (Kaunitz et al. 2017). Histopathologically, spongiotic dermatitis with eosinophils is seen (Sibaud 2018).

In addition to these dermatoses, atypical squamous proliferations may develop uncommonly and can be associated with concurrent lichenoid inflammation (Antonov et al. 2019). Eruptive keratoacanthomas and squamous cell carcinomas may occur and can be challenging to distinguish from hypertrophic lichen planus. Conservative management of these atypical squamous proliferations and treatment of concurrent lichenoid dermatitis is recommended.

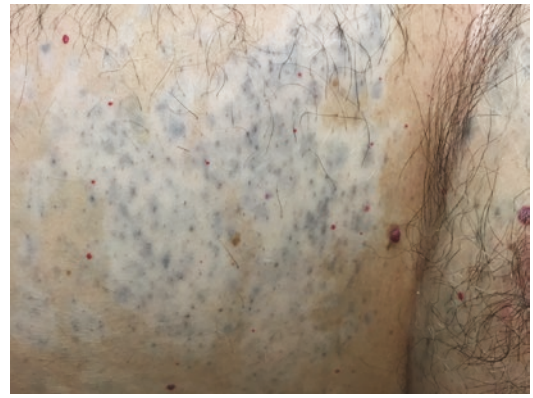

Fig. 3 Vitiligo-like depigmentation surrounding in-transit melanoma metastases during ipilimumab/nivolumab therapy

3.4 Vitiligo-like Depigmentation

Vitiligo-like depigmentation is a common cutaneous irAE that has been associated with improved overall survival in patients with melanoma, but may also occur less often in patients with other malignancies (e.g., acute myeloid leukemia, lung cancer, and renal cell cancer) (Teulings et al. 2015; Lolli et al. 2018; Yin et al. 2017; Yun et al. 2020; Nishino et al. 2018). Unlike the timeline of pruritus or morbilliform rash associated with ICIs, vitiligo-like depigmentation onset is more gradual with lesions forming progressively over months of treatment (Teulings et al. 2015; Hua et al. 2016). Several clinical features help differentiate ICI-associated vitiligo-like depigmentation from primary vitiligo (Larsabal et al. 2017). The lesions for ICI-associated vitiligo are often distributed in a sun-exposed pattern (Fig. 3), unlike primary vitiligo which often appears on acral and periorificial areas (Larsabal et al. 2017). ICI-associated depigmentation has been reported to occur together with poliosis (Wolner et al. 2018).

ICI-associated vitiligo-like depigmentation is thought to be a separate biological disease process from primary vitiligo. Murine experiments have shown that blockade of the PD-1 pathway induces expression of the chemokine CXCL10 by IFN-y, thereby causing CXCR3+ CD8 T cell migration to tumor sites (Peng et al. 2012). Interestingly, a study of blood samples and biopsies from eight patients with vitiligo-like depigmentation from nivolumab or pembrolizumab found prominent CXCR3+ CD8 T cell skin infiltration (Larsabal et al. 2017).

As is the case with primary vitiligo, treatment of vitiligo-like depigmentation can be difficult. Depigmentation may progress after completion of immunotherapy, as demonstrated in a study of patients treated with nivolumab (Freeman-Keller et al. 2016). Vitiligo-like depigmentation in patients treated with ICIs, which is largely asymptomatic without medical complications, can be Grade 1 (<10% BSA affected) or Grade 2 (>10% BSA affected and/or has a psychosocial impact on patient) (Brahmer et al. 2018). Most cases require no treatment; however, patients with grade 1 disease may be managed with topical steroids or topical calcineurin inhibitors. For grade 2, patients may try narrowband UVB phototherapy as well as topical corticosteroids (Miyagawa et al. 2017). Janus kinase (JAK) inhibitors, which have demonstrated efficacy in primary vitiligo, should be avoided until further studies evaluate its impact on immune response in this population (Malviya et al. 2020).

Bullous Eruptions

Bullous eruptions, typically in the form of bullous pemphigoid, may uncommonly occur with ICIs. Between 2015 and 2020, a total of 58 cases of bullous pemphigoid eruptions linked to anti-PD-1 or anti-PD-L1 agents was reported, and one

study noted an incidence rate of ~1% in patients on these therapies (Siegel et al. 2018; Tsiogka et al. 2021). A unique feature of bullous pemphigoid associated with immunotherapy, compared to other cutaneous irAE, is that the time of onset is delayed, with a mean time of 6 months after treatment initiation (Coleman et al. 2019; Siegel et al. 2018). Furthermore, clinical suspicion for bullous pemphigoid must be sustained after initiation of immunotherapy, as the condition typically presents with a nonspecific, nonbullous pruritic prodromal phase prior to the development of classical urticarial papules, plaques, and tense vesicles and bullae (Fig. 4). Mucosal involvement may occur in some cases. Recent research suggests that lesions of idiopathic BP as well as of pemphigus vulgaris show increased expression of PD-1, and thus further investigation may help elucidate the molecular mechanism of immunotherapy-associated BP (Ernst et al. 2021). Hemidesmosomal antigens may also be present in various malignancies.

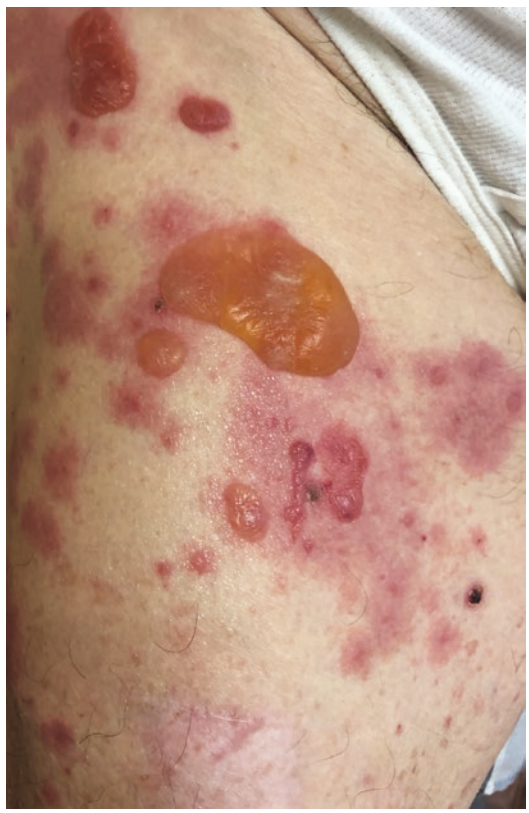

Fig. 4 Bullous pemphigoid in a patient on pembrolizumab for metastatic melanoma

Treatment of immunotherapy-associated BP is similar to that of idiopathic BP. Grade 1 eruptions can be treated with topical corticosteroids without interruption of immunotherapy. Doxycycline with or without niacinamide may be helpful for lower grade cases. Grade 2 reactions may require systemic corticosteroids, as well as holding immunotherapy until rash returns to Grade 1 (Brahmer et al. 2018). Grade 3 or 4 immunotherapy-associated BP should be treated with discontinuation of immunotherapy, intravenous corticosteroids, and close following by dermatology (Brahmer et al. 2018). Rituximab may be used in recalcitrant cases (Geisler et al. 2020). It is important to note that immunotherapy-associated BP may persist even after immunotherapy discontinuation (Heymann 2018; Naidoo et al. 2016). Other potential treatment agents include methotrexate, dapsone, omalizumab, dupilumab, and intravenous immunoglobulin G (IVIG) (Damsky et al. 2016; Czernik 2014).

SCARs

SCARs that have been reported with immunotherapy include DRESS syndrome, acute generalized exanthematous pustulosis (AGEP), and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (Malviya et al. 2020). Because of the severity of these potentially life-threatening conditions, a diagnosis of a SCAR of any grade mandates interruption, or more likely, discontinuation of immunotherapy (Brahmer et al. 2018). Of note, the use of targeted therapy with BRAF inhibitors after the use of immunotherapy is associated with a particularly high risk for the development of SCARs (Harding et al. 2012). Furthermore, atypical presentations of SCARs including delayed reactions of SJS/TEN-like eruptions may occur, necessitating a high index of suspicion when any "red-flag" signs or symptoms occur (e.g., skin pain, blisters, mucosal involvement, fevers). The time of onset of SCAR after initiation of immunotherapy may vary between 1 and 20 weeks (Chen et al. 2018). The Society for Immunotherapy of Cancer Toxicity Management Working Group recom-

mends: hospitalization and immediate dermatology consult for suspected SJS/TEN or severe mucocutaneous reaction; same-day dermatology consult for blisters covering >1% BSA, mucosal rash, painful rash, any rash >30% BSA, and any grade III cutaneous toxicity; and nonacute dermatology referral for rashes of unclear diagnosis, grade 2 rash, and erythema multiforme (Puzanov et al. 2017).

SJS/TEN has been reported with most ICIs, including ipilimumab, nivolumab, pembrolizumab, atezolizumab, and combination immunotherapy (Coleman et al. 2019; Haratake et al. 2018; Chirasuthat and Chayavichitsilp 2018; Dika et al. 2017; Logan et al. 2020). Patients usually present with painful pink dusky-centered papules and plaques that quickly develop into vesicles and bullae, often with mucosal involvement. Histopathology demonstrates epidermal necrolysis. The grade of SJS/TEN depends on BSA involved, although any SJS/TEN is at least a grade 3 reaction, and grade 4 reactions involve >10% of BSA (Brahmer et al. 2018). Treatment is with discontinuation of immunotherapy, hospitalization, and intravenous systemic corticosteroids. Cyclosporine, IVIG, and TNF-alpha inhibitors have also been used to treat SJS/TEN-like reactions associated with immunotherapy (Woolridge et al. 2018; Zhang et al. 2020).

AGEP has also been reported in patients undergoing immunotherapy, including combination ipilimumab and nivolumab, and pembrolizumab with chemotherapy (Matsubara et al. 2020; Page et al. 2018). Like classic AGEP, these cases presented with an initial erythematous eruption with small nonfollicular pustules concentrated in the axillary and inguinal folds (Matsubara et al. 2020; Page et al. 2018). Histopathology demonstrated subepidermal mixed cellular infiltrate with eosinophils, diffuse spongiosis, and subcorneal pustules (Matsubara et al. 2020; Page et al. 2018). Management of AGEP generally involves discontinuation of the offending agent and systemic corticosteroids (ranging from 0.5 to 2.0 mg/kg/daily of prednisone based on % BSA involvement) (Brahmer et al. 2018).

Finally, DRESS, also known as drug-induced hypersensitivity syndrome (DIHS), has been reported in patients on nivolumab, ipilimumab, and pembrolizumab (Lu et al. 2019; Di Palma-Grisi et al. 2019; Naqash et al. 2019). Patients with DRESS present with systemic symptoms including fever and lymphadenopathy, laboratory abnormalities including eosinophilia, atypical leukocytosis, and abnormal liver function testing, and skin findings of diffuse maculopapular eruption and marked facial edema. Histopathology of DRESS can vary and may show overlap with several different conditions, but typically demonstrates an interface dermatitis with eosinophilia. Management of DRESS requires close monitoring of abnormal laboratory findings (particularly CBC with differential and peripheral smear, basic metabolic panel, liver function tests, thyroid function tests, and baseline echocardiogram), withdrawal of the offending agent, and systemic corticosteroids (again ranging from 0.5 to 2.0 mg/kg/daily of oral prednisone based on severity) with taper over 6–8 weeks (Brahmer et al. 2018). All cases of immunotherapy-associated DRESS were managed successfully with systemic corticosteroids (Lu et al. 2019; Naqash et al. 2019).

3.5 Miscellaneous Reactions

In addition to the above categories of cutaneous irAEs, a variety of other cutaneous reactions have been reported in association with immunotherapy agents. For example, connective tissue disorders including subacute cutaneous lupus erythematosus, eosinophilic fasciitis, and dermatomyositis have all been reported (Kosche et al. 2019, 2020; Blakeway et al. 2019; Chan et al. 2020). In severe presentations impacting quality of life or those resulting in joint immobility (e.g., eosinophilic fasciitis), immunotherapy interruption and treatment with oral prednisone (with or without other steroid-sparing immunosuppressive agents) may be required.

Another group of dermatological adverse effects to ICIs includes granulomatous reactions (Cornejo et al. 2019). A 2019 review of granulo-

matous reactions to ICIs identified 59 reported cases of sarcoidosis-like reactions (Cornejo et al. 2019). Interestingly, most of these patients did not have a history of sarcoidosis or other granulomatous pulmonary disease (93.2%) (Cornejo et al. 2019). Clinical presentation usually involves pulmonary lesions (84.7% of patients), with cutaneous lesions presenting as papules, plaques, and nodules on any area of the body but sometimes within past tattoos or scars (Cornejo et al. 2019). In addition to sarcoidosis-like reactions, granuloma annulare may occur, and presents as pink papules or annular plaques on the extremities or torso. Contrary to sarcoidosis-like reactions, granuloma annulare does not have systemic involvement (Cornejo et al. 2019). Other less common granulomatous reactions such as erythema nodosum-like panniculitis or interstitial granulomatous dermatitis may occur. In general, sarcoidosis responds well to treatment with systemic corticosteroids (Cornejo et al. 2019). Hydroxychloroquine may be used as steroid-sparing therapy (Korsten et al. 2013).

Finally, patients with a pre-existing autoimmune disease may experience flares while on ICIs, as was discussed previously in the psoriasis section. One multicenter study found that of patients with pre-existing rheumatoid arthritis (RA) treated with ICIs, 60% had a flare of RA (Tison et al. 2019). Rates of flare were lower for the other autoimmune diseases examined in this study, including inflammatory bowel disease, lupus, and polymyalgia rheumatica (Tison et al. 2019). One important note is that some flares of pre-existing autoimmune disease may be severe enough to require additional immunomodulating therapy; 54% of patients with pre-existing autoimmune disease who developed an ICI-induced flare in this study required treatment with a form of immunosuppressive agent (including systemic corticosteroids, disease-modifying antirheumatic drug (DMARD), or acitretin) (Tison et al. 2019).

4 Conclusion

The development of ICIs has changed the landscape of cancer therapy for years to come. As these agents modulate the function of the immune system, they induce irAEs in most organ systems, ranging from mild pruritus to severe multisystem organ dysfunction. Although some of these adverse events require new therapeutic solutions, they also allow for a detailed examination of the molecular mechanisms of skin diseases in ways that were not possible before. The association of positive antitumor response with various cutaneous irAEs underscores the importance of promptly diagnosing and managing these untoward reactions, to allow patients to remain on these potentially life-sustaining therapies.

In conclusion, this chapter presented an overview of the clinical presentations, diagnosis, grading, and therapeutic strategies for cutaneous adverse events associated with currently available immunotherapy agents. In particular, we presented the treatment regimens with a focus on whether immunotherapy must be discontinued or withdrawn in each of these scenarios, as this is the question that is often most important for the primary oncologic team. The diversity of effects and severities as outlined here demonstrates the critical role of the oncodermatologist and of integrated oncodermatology clinics (Kwong 2020). There is evidence to suggest that an embedded oncodermatology clinic in cancer hospitals is associated with reduction of unnecessary discontinuation of cancer therapy, as well as of rehospitalizations (Naidoo et al. 2016; Chen et al. 2020). As some studies have suggested, one potential model for the future may be a multidisciplinary team dedicated to irAE at cancer hospitals (Naidoo et al. 2019).

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