Cutaneous Lesions that Mimic Infection in Transplant Patients

23

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Introduction

Many cutaneous conditions may mimic infectious processes. The ability to diagnose non-infectious skin eruptions, especially in cancer patients, is oftentimes challenging. Using the morphology of the primary skin lesion as a starting point, this section will review the clinical presentation, physical examination, and diagnostic work-up of many of these conditions. This should help the clinician generate a differential diagnosis when evaluating cutaneous lesions in immunosuppressed patients.

Section 1: Pustular Lesions

Pustules are purulent collections which can be solitary or widespread. Not all the pustular processes in the skin are due to infection; pustular psoriasis is one of the non-infectious examples. They may be mistaken for bacterial, fungal, or superinfected herpetic infections.

Reactive Neutrophilic Dermatoses

Reactive neutrophilic dermatoses are a spectrum of diseases mediated by neutrophils manifested by systemic complaints in association with an underlying disease such as inflammatory bowel disorders or internal malignancies.

Differential Diagnosis: Bacterial, Fungal, and Viral Infections

Pyoderma gangrenosum is an uncommon idiopathic ulcerative skin disorder that often is associated with systemic diseases. The ulcerations are distinctive: an irregular, boggy, undermined border surrounding a purulent necrotic base (Fig. 23.1). Culture-negative pulmonary infiltrates are the most common extracutaneous site of disease [1]. PG is associated with a dysregulation of the immune system, in particular altered neutrophil chemotaxis in reaction to various precipitating causes such as inflammatory bowel diseases [2, 3]. Many conditions can be confused with the early pustular stage: folliculitis, furunculosis, carbuncles, and streptococcal gangrene. The ulcerative stage must be differentiated from cutaneous amebiasis, cryptococcosis, blastomycosis, sporotrichosis, and atypical mycobacterial infections [4–6]. PG has a tendency to recur and it usually heals with scarring.

Behcet's syndrome is a chronic relapsing, idiopathic, multisystem disease of recurrent aphthous ulcers, genital ulcers, and uveitis (Fig. 23.2). The cause is unknown; however, current research points toward an autoimmune etiology following exposure to an infectious agent which includes herpes simplex virus, *Streptococcus* and *Staphylococcus* species, and *Escherichia coli*. It has been suggested that the heat shock proteins (HSPs) found in higher concentrations in

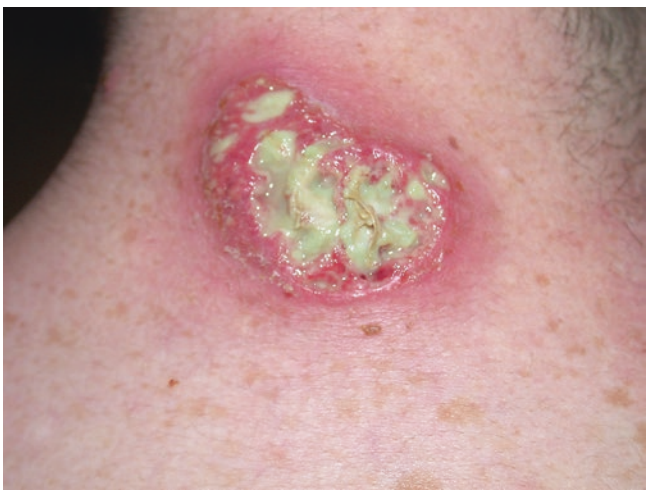

Fig. 23.1 Pyoderma gangrenosum. Painful neck ulceration with an elevated dusky undermined border and fibrinous base

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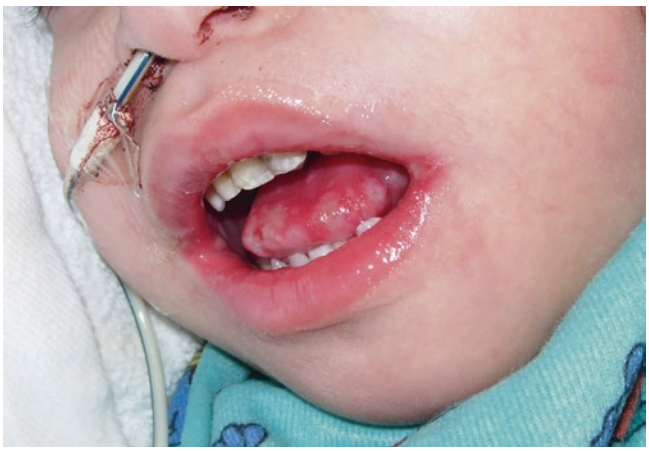

Fig. 23.2 Behcet's disease. Oral ulcerations

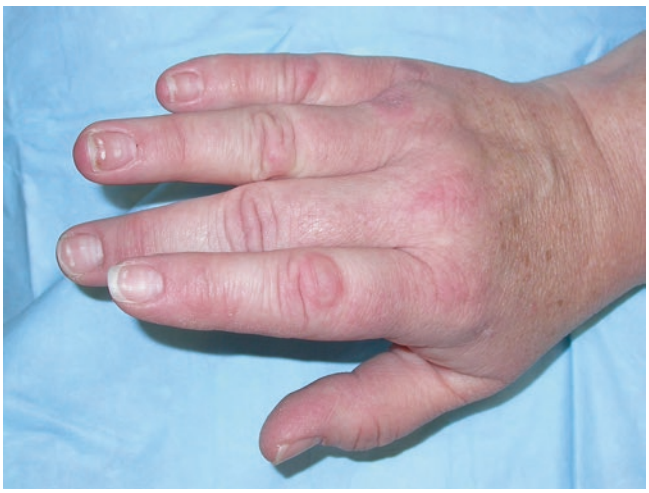

Fig. 23.3 Sweet's syndrome. Erythematous, edematous plaques on the dorsal hand and fingers in a patient with acute myelogenous leukemia

skin lesions and oral aphthae can induce antibody production that cross-react with streptococcal species that are usually found in the mouth [7].

An acneiform papulopustular eruption may be seen on the face, neck, and trunk. The aphthous lesions begin as vesicles and/or pustules and tend to heal with scar formation. Tender, erythematous, recurrent nodules that resemble erythema nodosum are common on the extremities in women. Extragenital ulcerations, if present, are very specific for Behcet's disease [8]. Various treatment regimens have demonstrated benefit including systemic corticosteroids, colchicine, azathioprine, dapsone, interferon-alfa, and infliximab. The disease can be confused with herpetic gingivostomatitis and syphilis.

Acute neutrophilic febrile dermatosis (Sweet's syndrome) is a distinct entity characterized by one or more edematous red, tender, spontaneously painful plaques predominantly on the upper body, accompanied by fever, peripheral leukocytosis, and a variety of constitutional symptoms (Fig. 23.3). It is thought to be a hypersensitivity reaction of unknown cause characterized by infiltration of neutrophils in the skin. It has been associated with various carcinomas and hematopoietic malignancies especially acute myelogenous leukemia (AML) [9]. It responds dramatically to systemic corticosteroids and may resolve with treatment of the underlying disease [9, 10]. Ulcers and bullae are more common in malignancy-associated disease than in other forms. These lesions may be extensive and are generally hard to treat [11]. Sweet's syndrome must be differentiated from erysipelas, cellulitis, arthropod bites, herpetic infections, and drug eruptions.

Bowel bypass syndrome is a constellation of medical complications secondary to intestinal bypass surgery for the treatment of morbid obesity, consisting of fever, asymmetrical polyarthritis, tenosynovitis, sterile skin pustules, mucous membrane ulcerations, retinal vasculitis, and thrombophlebitis [12]. The syndrome is presumed to result from the deposition of circulating immune complexes containing bacterial antigens derived from overgrowth in the bypassed loop of the bowel [13]. Surgical excision of the blind loop or revision of the bowel bypass cures bowel bypass syndrome. The disease may resemble gonococcal sepsis, infectious panniculitis, pyoderma gangrenosum, Behcet's syndrome, and Sweet's syndrome.

Acute Generalized Exanthematous Pustulosis (AGEP)

Differential Diagnosis: Bacterial, Viral, or Fungal Infections

AGEP is a neutrophilic dermatosis characterized by acute-onset monoform, sterile, nonfollicular 1–2-mm pustules on a background of erythema secondary to drug administration, most commonly antibiotics. The lesions have a predilection for the face and intertriginous areas (Fig. 23.4). The eruption is accompanied by fever which can occur several days prior or the same day as the eruption. Widespread desquamation occurs after a few days. Neutrophilia and eosinophilia are commonly seen [14]. The precise mechanism of the disease is unknown. It is suggested that neutrophil-activating cytokines released by drug-specific T lymphocytes (IL-3, IL-8, and G-CSF) are potent triggers for blood neutrophilia and accumulation of neutrophils within the lesions [14]. It is characterized by fever which can occur several days prior to the eruption followed by the onset of classic lesions on the face or intertriginous areas. The withdrawal of the responsible drug is the mainstay of treatment in conjunction with topical corticosteroids [15].

Acneiform Hypersensitivity Drug Eruptions

Differential Diagnosis: Bacterial and Fungal Folliculitis

Acneiform eruptions are characterized by pruritic inflammatory papules or pustules localized primarily on areas with a

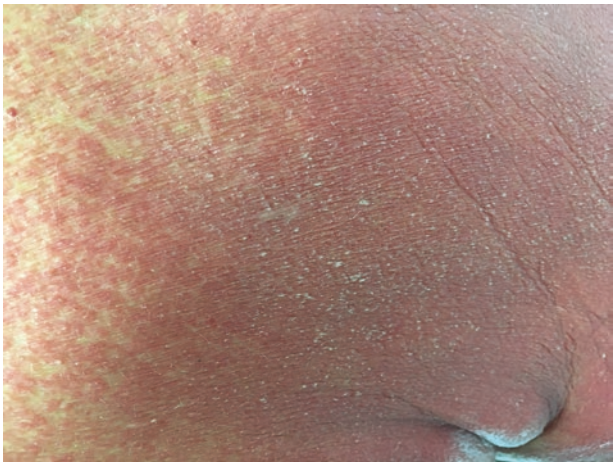

Fig. 23.4 Acute generalized exanthematous pustulosis. Affected individuals show large areas of erythroderma topped with small nonfollicular sterile pustules

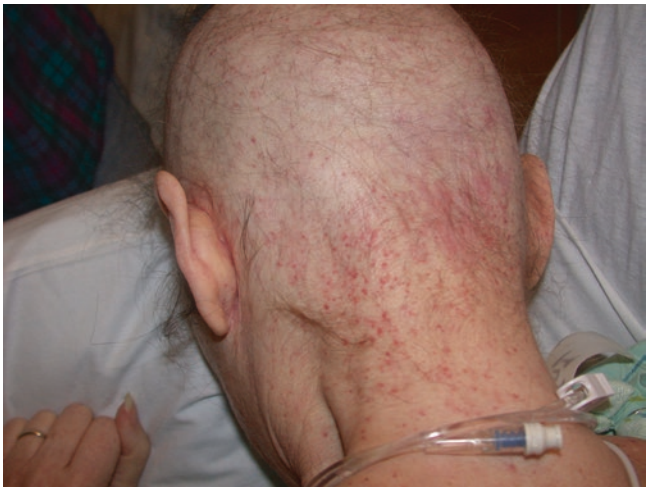

Fig. 23.6 EGFR inhibitor-associated alopecia. Scalp inflammatory papules and scarring alopecia

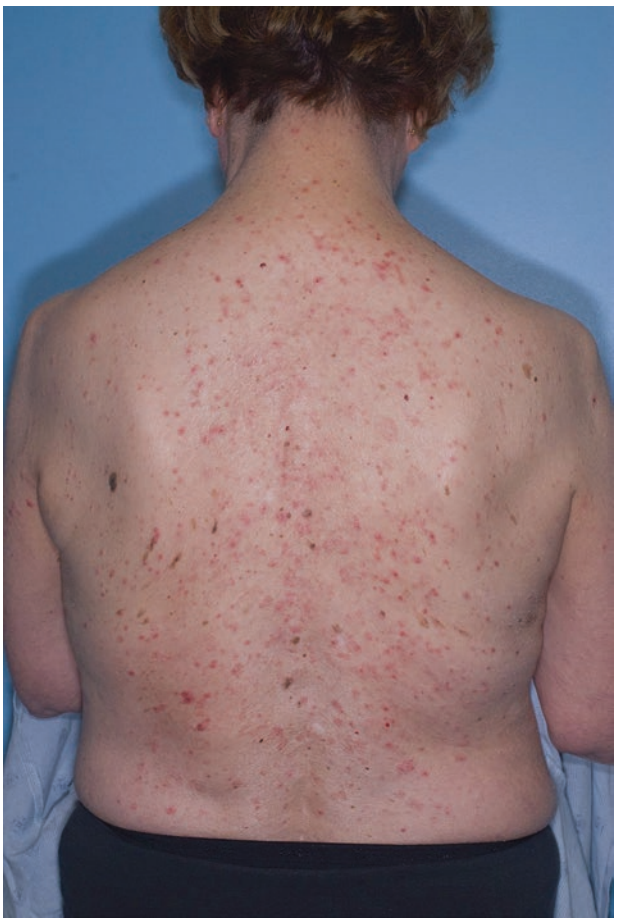

Fig. 23.5 Acneiform drug eruption due to EGFR inhibitor erlotinib. Follicular pustules, located on the skin of the face and trunk in patient with metastatic lung cancer

large number of pilosebaceous units: face, neck, chest, and upper back, sparing the palmar or plantar surfaces (Fig. 23.5). In contrast to acne vulgaris, comedones are absent in acneiform eruptions. The eruption is common in cancer patients treated with systemic corticosteroids. Isoniazid, as well as chemotherapeutic agents including cyclosporine, azathioprine, and sirolimus, may induce acneiform drug eruptions [16, 17]. Cutaneous adverse events associated with epidermal growth factor inhibitors (EGFR) include pustular skin eruptions usually on the scalp, neck, chest, and back along with paronychia, xerosis, and alopecia (Fig. 23.6). Although the exact mechanism of the development of the rash is not completely understood, the inhibitor therapy disrupts the EGFR function by inducing terminal differentiation and apoptosis in the stratum corneum and hair follicles. Patients are often managed symptomatically or by adjusting the dose of the targeted therapy [18]. It is important to promptly identify and treat the adverse events during therapy with EGFR inhibitors to avoid drug suspension. The infectious diseases that enter the differential diagnosis of acneiform drug eruptions are folliculitis, measles, rubeola, rubella, and syphilis.

Eosinophilic Folliculitis

Differential Diagnosis: Bacterial and Fungal Folliculitis

Eosinophilic folliculitis is an uncommon recurrent eosinophilic infiltration of hair follicles manifested by pruritic papules and pustules associated with soft tissue edema seen most commonly on the head, neck, and trunk mostly in immunosuppressed patients [19, 20] (Fig. 23.7). Eosinophilic folliculitis has been classified as an AIDS-defining illness [19]. Although the exact etiology is unknown, an autoimmune reaction against sebocytes or sebum component and an abnormal T-cell immune response to a follicular antigen, such as caused by Demodex species, may be responsible for the eruption [19]. Topical corticosteroids are the mainstay of treatment for eosinophilic folliculitis. Highly active antiretroviral therapy along with isotretinoin therapy is

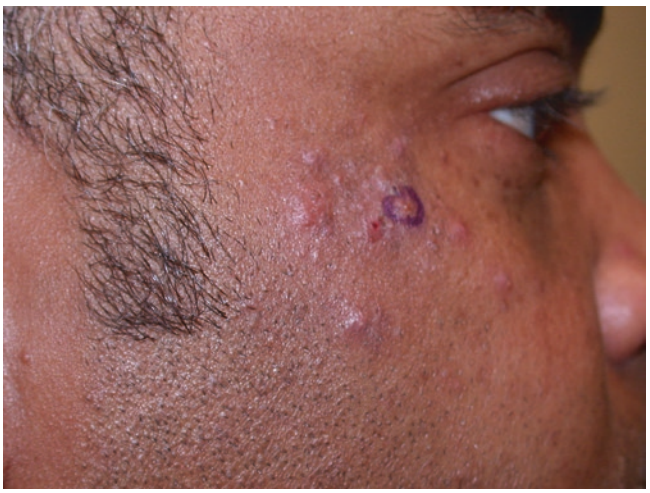

Fig. 23.7 Eosinophilic folliculitis. Crops of sterile papules and pustules on the face

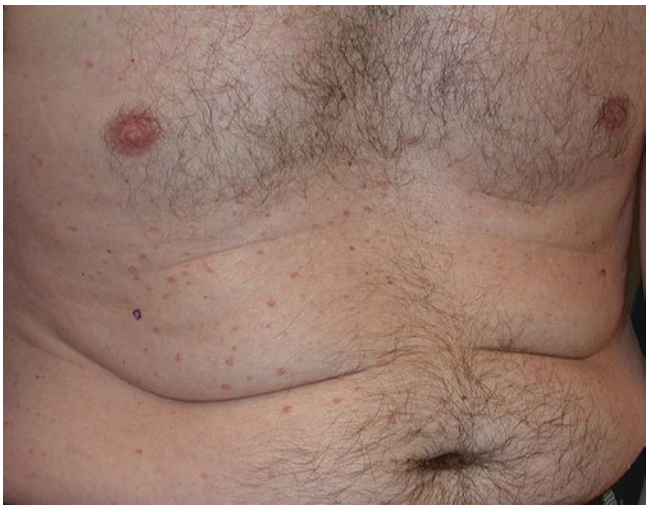

Fig. 23.8 Transient acantholytic dermatosis or Grover's disease. This is an acquired condition that presents with pruritic vesicles and erosions on the upper trunk, most often in men

beneficial for eosinophilic folliculitis in the setting of HIV disease [21]. Clinically, it resembles bacterial folliculitis and candidiasis.

Grover's Disease

Differential Diagnosis: Bacterial and Fungal Folliculitis and Allergic Drug Eruptions

Also known as transient acantholytic dermatosis, this condition is benign, self-limited, exacerbated by heat and sweating, characterized by a sparse eruption of inflammatory papules, and fragile vesicles that erode. It is limited to the chest and upper abdomen, and it can be confused with bacterial folliculitis, herpes simplex and zoster infections, scabies, and syphilis (Fig. 23.8). Viral and bacterial pathogens have been proposed, but no causative role has been established. Potent topical corticosteroids are effective in diminishing inflammation and in controlling pruritus associated with transient acantholytic dermatosis.

Miliaria Rubra

Differential Diagnosis: Bacterial and Fungal Folliculitis

Miliaria rubra is a common anhidrotic disorder in which an obstruction of the sweat duct occurs in the deeper level of the epidermis characterized by minute erythematous macules with a punctate vesicle usually centrally located. The lesions can be seen to be extrafollicular, in contrast to the pustules of folliculitis (Fig. 23.9). It is the only type of miliaria in which the symptom of pruritus is experienced [22]. It occurs primarily at sites of occlusion such as the back of febrile,

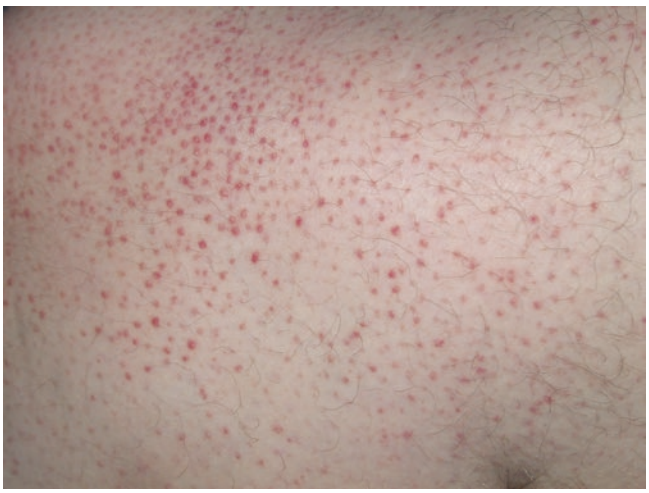

Fig. 23.9 Miliaria rubra. Multiple erythematous pinpoint macules and papules, especially prominent on the occluded surface of the back

ill patients. Resident bacteria, such as *Staphylococcus epidermidis and Staphylococcus aureus*, may play a role in the pathogenesis of miliaria [23].

Neutrophilic Eccrine Hidradenitis

Differential Diagnosis: Cellulitis

Also known as toxic erythema of chemotherapy, neutrophilic eccrine hidradenitis is a skin condition observed in the setting of AML treated with cytarabine and has been reported in persons with various neoplastic and non-neoplastic conditions and otherwise healthy individuals [24]. It is characterized by solitary or multiple, red and purpuric, macules,

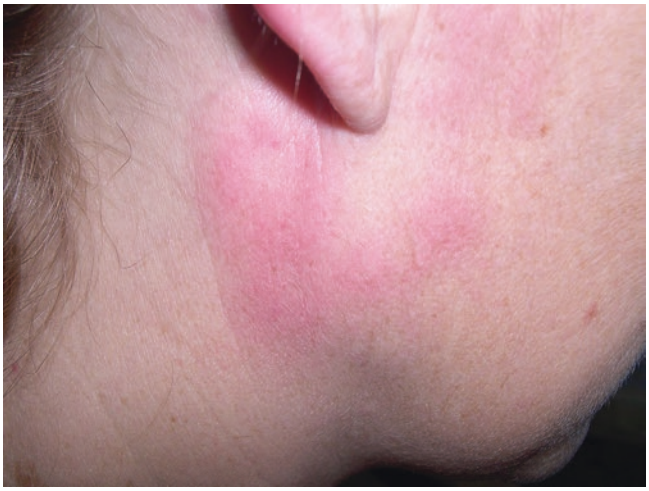

Fig. 23.10 Neutrophilic eccrine hidradenitis. Facial erythematous, indurated plaques

papules, nodules, or plaques most frequently located on the trunk or extremities (Fig. 23.10). The plaques are often tender. Neutrophilic eccrine hidradenitis can simulate orbital and facial cellulitis [24, 25]. Anthracyclines, antimetabolites, taxanes, vinca alkaloids, mitotic inhibitors, and granulocyte colony-stimulating factors may induce this disorder [26].

Section 2: Papulosquamous Lesions

Dermatitis

Dermatitis also known as eczema reflects an inflammatory skin reaction due to exposure to irritants, drugs, and other unknown triggers. It often presents as scaly erythematous plaques and patches, not uncommonly secondarily infected. 90% will be culture positive for *Staphylococcus aureus* [27].

Differential Diagnosis: Superficial Fungal Infection and Cellulitis

Stasis dermatitis presents as erythema and light-brown pigmentation on the lower extremities, especially above malleolus, associated with eczematous dermatitis (Fig. 23.11). It is a cutaneous marker for venous insufficiency and often mistaken for cellulitis. When chronic venous insufficiency is present, patients may present with marked woody induration in a stocking distribution associated with dyspigmentation, termed "lipodermatosclerosis."

Pityriasis alba is a form of dermatitis frequently atopic in origin, characterized by slightly scaly hypopigmented patches on the cheeks, upper arms, and trunk in children (Fig. 23.12). Potassium hydroxide examination of the fine white scale can rule out superficial cutaneous dermatophyte infection.

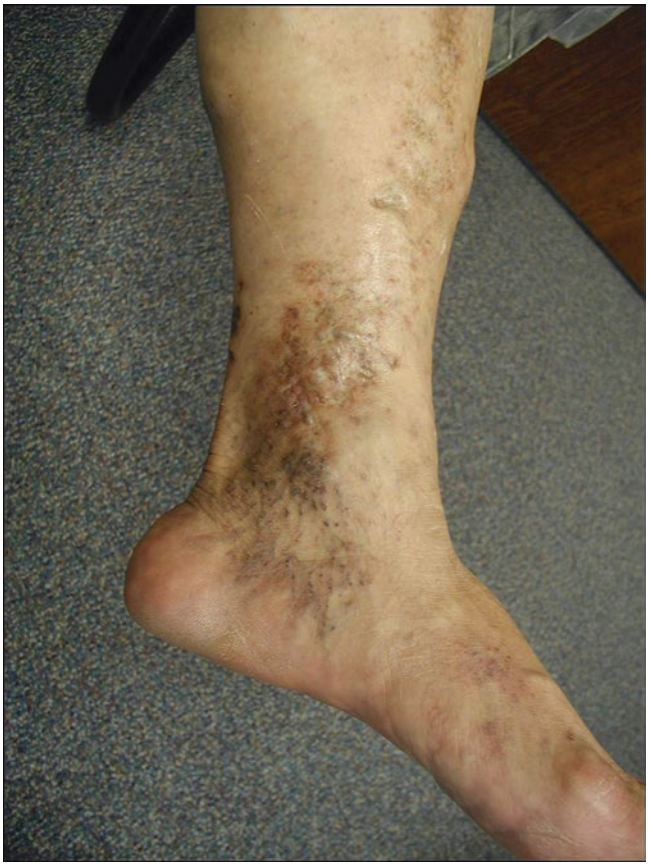

Fig. 23.11 Stasis dermatitis. Post-inflammatory hyperpigmentation over the medial malleolus on the background of varicose veins

Drug eruptions mimic various dermatoses and the morphology includes exanthem (morbilliform), papulosquamous, urticaria, vasculitis, and erythema nodosum. It should be suspected in any patient taking medication who developed a symmetric cutaneous eruption (Fig. 23.13). Chemotherapeutic agents such as busulfan and gentifinib are common causes for intertriginous drug eruption which can be confused with dermatophyte or yeast infection [28, 29].

Acute radiation dermatitis commonly occurs following local radiation therapy for various malignancies, with more than 90% of the patients experiencing erythema and more than 30% experiencing moist desquamation [30] (Fig. 23.14). Intense inflammatory reaction may result in a breakdown of the skin's barrier function and accompanying bacterial colonization, with organisms like *Staphylococcus aureus* [31, 32].

Psoriasis

Differential Diagnosis: Superficial Fungal Infection

Psoriasis is a complex multisystem inflammatory disorder of unknown etiology showing wide variation in severity and

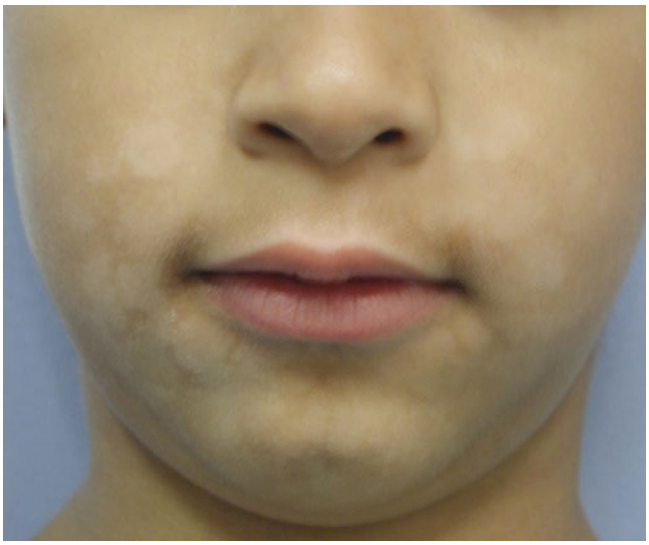

Fig. 23.12 Pityriasis alba. Circumscribed scaly hypopigmented lesions on the face

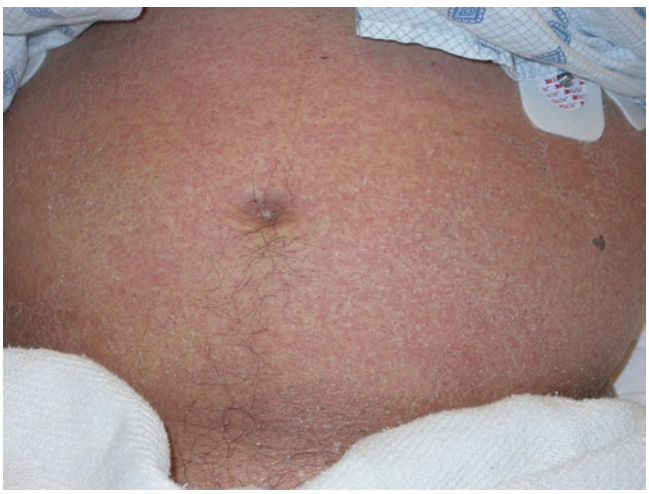

Fig. 23.13 Drug eruption. Morbilliform macules and papules on the abdomen resulting from cefepime

distribution of skin lesions. The most common skin manifestations are erythematous macules, papules, and plaques with thick silvery scale that follow an irregular chronic course marked by remissions and exacerbations of unpredictable onset and duration (Fig. 23.15). Although no region is exempt from involvement, psoriasis has a predilection for the scalp, elbows, and knees [33]. Psoriasis plaques can be mistaken for cutaneous tinea corporis or secondary syphilis.

Pityriasis Rubra Pilaris

Differential Diagnosis: Superficial Fungal Infection

Pityriasis rubra pilaris, a rare scaly, erythematous skin condition of unknown etiology with a preference for the follic-

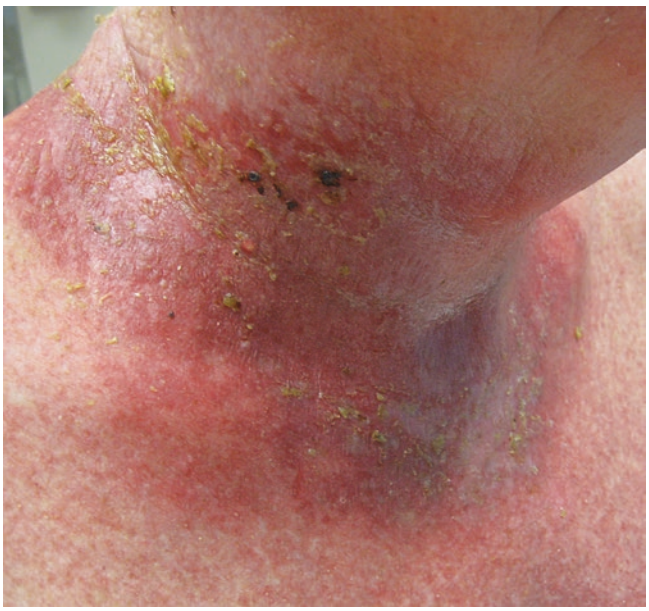

Fig. 23.14 Acute radiation dermatitis. Extensive erythema and crusting with geographic borders defined by the radiation field

ular apparatus, is considered a disturbance of keratinization with predilection for the ears, trunk, neck, and extremities. Clinical features include discrete follicular-based reddish papules on the hands dorsum and diffuse palmar exfoliation (Fig. 23.16). Confluent scaly, salmon-colored plaques may appear on the trunk within islands of normal skin. A skin biopsy is mandatory to distinguish this from psoriasis and fungal infection and a search for occult malignancy should be considered if the presentation is atypical or in older patients.

Pityriasis Rosea

Differential Diagnosis: Superficial Fungal Infection and Syphilis

This is an acute self-limited, clinically distinctive exanthematous eruption of unknown etiology more commonly seen in adolescents and young adults. A mild prodrome manifested by malaise, fatigue, headache, and sore throat precedes the skin eruption with a few days. The earliest change is the "herald patch," a solitary, oval, or annular plaque on the trunk, arms, and thighs, followed by eruptive erythematous, flat plaques measuring 0.5–1.5 cm in diameter (Fig. 23.17). The clinical features and course of pityriasis rosea strongly suggest a viral etiology; however, no single virus has been proven to cause the disease. The widespread lesions of secondary syphilis and tinea versicolor may resemble pityriasis rosea [34]. Tinea corporis can be confused with the herald patch seen earlier during the course of the disease.

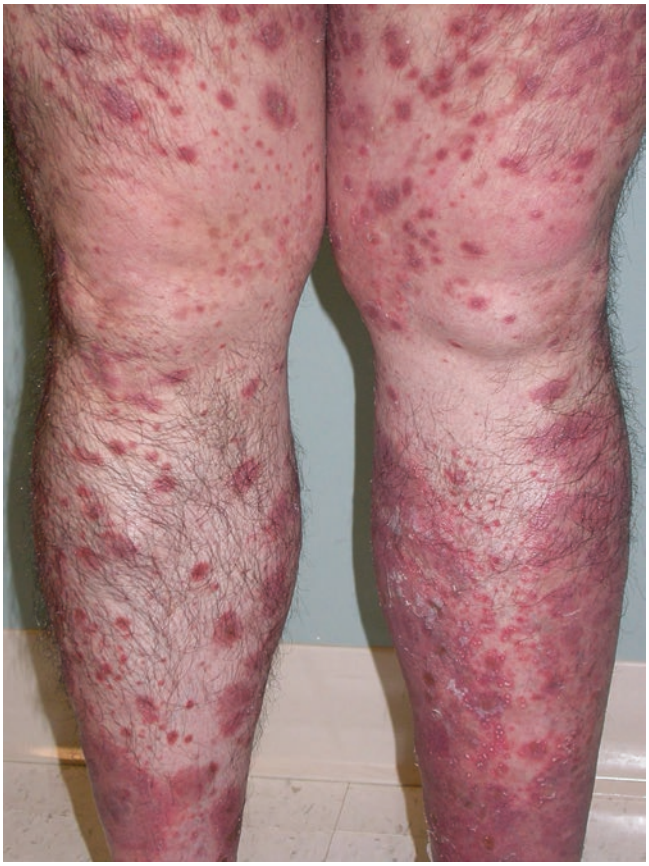

Fig. 23.15 Psoriasis vulgaris. Typical plaques of psoriasis with thick, white scaly overlying erythema

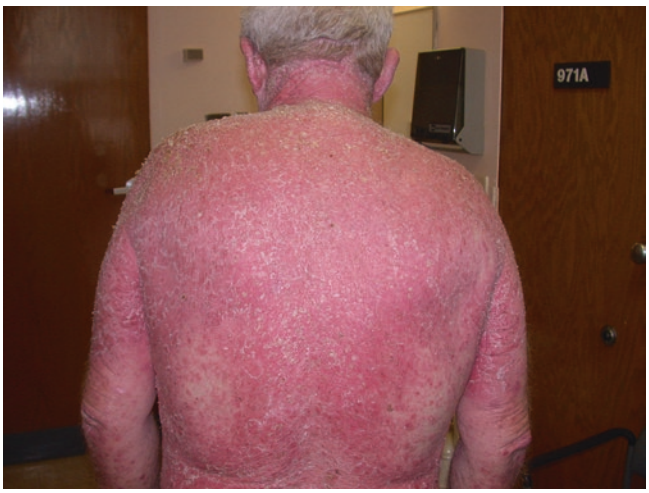

Fig. 23.16 Pityriasis rubra pilaris. Symmetric, diffuse, scaly erythema

Cutaneous T-Cell Lymphoma

Differential Diagnosis: Superficial Fungal Infection

Cutaneous T-cell lymphoma, a class of non-Hodgkin lymphoma, is characterized by infiltration of the skin by clonal malignant T-cells and has many clinical variants, but the classic subtype is characterized by sharply demarcated plaques, uniform in color, ranging from an erythematous to a violaceous hue (Fig. 23.18). The clinical features, histomorphology, and cytomorphology of the lesions are diagnostic clues, and demonstration of a dominant T-cell clone in skin biopsy specimens constitutes an additional diagnostic test to distinguish CTCL from inflammatory dermatoses.

The early stage is typically nonspecific and is often misdiagnosed as eczema, psoriasis and superficial fungal infection.

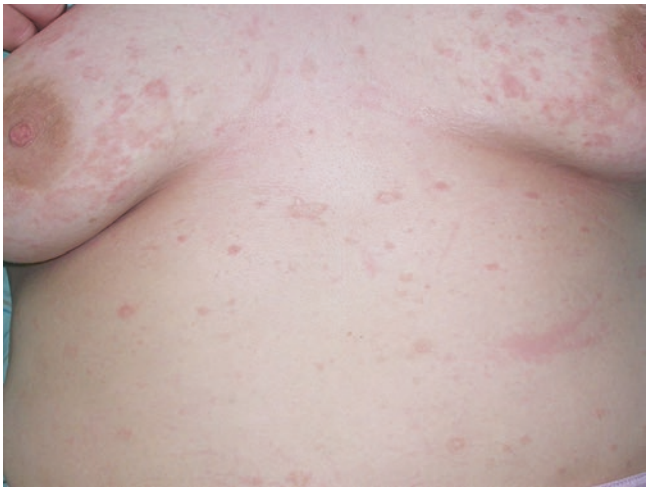

Fig. 23.17 Pityriasis rosea. Truncal involvement with larger plaques and predominantly round patches with peripheral scale

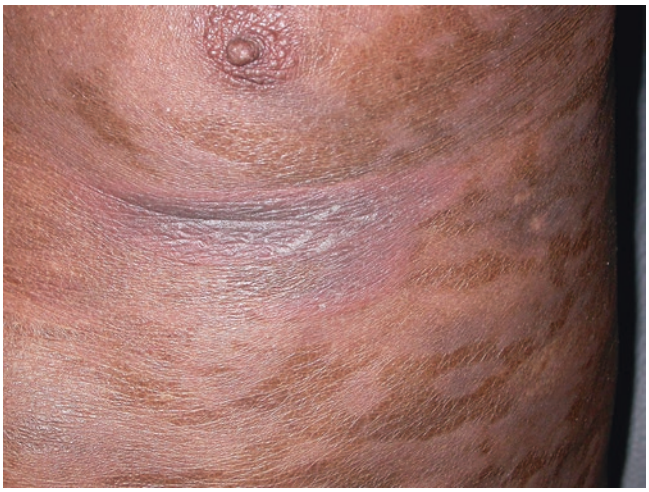

Fig. 23.18 Cutaneous T-cell lymphoma. Hyperpigmented scaly patches with minimal scaling

Section 3: Purpuric and Petechial Lesions

Purpura is the multifocal extravasation of blood into the skin or mucous membranes manifested by distinctive red macules a few millimeters in size. Petechiae are superficial, pin-

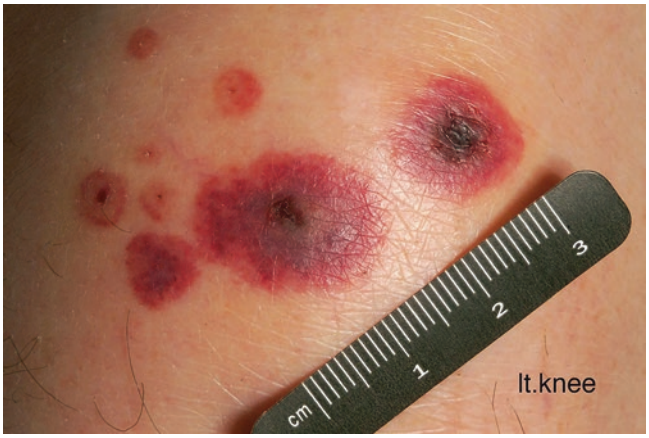

Fig. 23.19 Leukocytoclastic vasculitis. Multiple purpuric papules in a patient with drug-induced hypersensitivity vasculitis

head-sized hemorrhagic macules, bright red at first, seen in the dependent areas. Petechiae most often imply a disorder of platelets.

Leukocytoclastic Vasculitis

Differential Diagnosis: Bacterial and Fungal Infection

Leukocytoclastic vasculitis (LCV) represents a hypersensitivity reaction secondary to immune complex deposition, other autoantibodies, inflammatory mediators, and local factors that involve the endothelial cells. Palpable purpura is the clinical prototype of LCV in which the vascular insult is at the level of arterioles and postcapillary venules. Lesions appear in crops, ranging from 1 to 2 mm in size, and have a predilection for dependent parts. Palpable purpura is generally asymptomatic, but in severe cases (with erosions, bullae, and hemorrhagic vesicles) patients may experience pruritus, edema, and burning [35] (Fig. 23.19). It can be mistaken for systemic bacterial infections including candidiasis and meningococcemia. Skin biopsy reveals the presence of vascular and perivascular infiltration of polymorphonuclear leukocytes with formation of nuclear dust (leukocytoclasis), extravasation of erythrocytes, and fibrinoid necrosis of the vessel walls.

Superficial Thrombophlebitis

Differential Diagnosis: Cellulitis

An inflammatory reaction in which clotting appears on the wall of an inflamed vein in patients with idiopathic venous stasis, prolonged bed rest, local injury to endothelium by trauma, and superficial thrombophlebitis presents with erythema, edema, and tenderness in the affected limb (Fig. 23.20). This needs to be distinguished from cellulitis which is a nonnecrotizing inflammation of the skin and subcutaneous tissues.

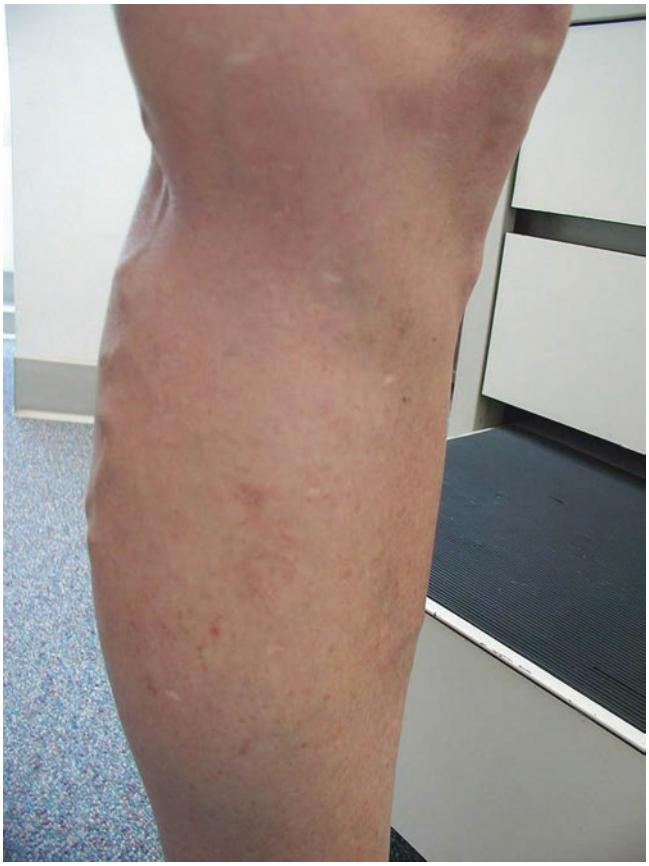

Fig. 23.20 Superficial thrombophlebitis. Erythema and edema along the leg vein

Calciphylaxis

Differential Diagnosis: Cellulitis, Ecthyma Gangrenosum, and Bacterial and Deep Fungal Infections

This is a highly morbid syndrome characterized by painful ischemic tissue necrosis primarily on fingers, legs, and thighs surrounded by livedo reticularis in patients with chronic renal insufficiency and hyperparathyroidism [36]. Lesions of calciphylaxis typically develop suddenly and progress rapidly. The clinical manifestations of calciphylaxis are similar to those of a significant number of other disorders, including among others cellulitis, necrotizing fasciitis, ecthyma gangrenosum, vibrio vulnificus infection, cholesterol embolization, warfarin necrosis, cryoglobulinemia, and vasculitis [37, 38] (Fig. 23.21).

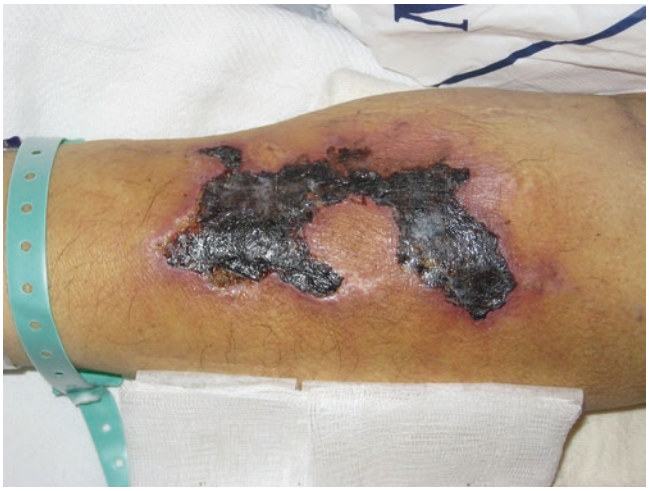

Fig. 23.21 Calciphylaxis. Deep skin necrosis and non-healing ulcer

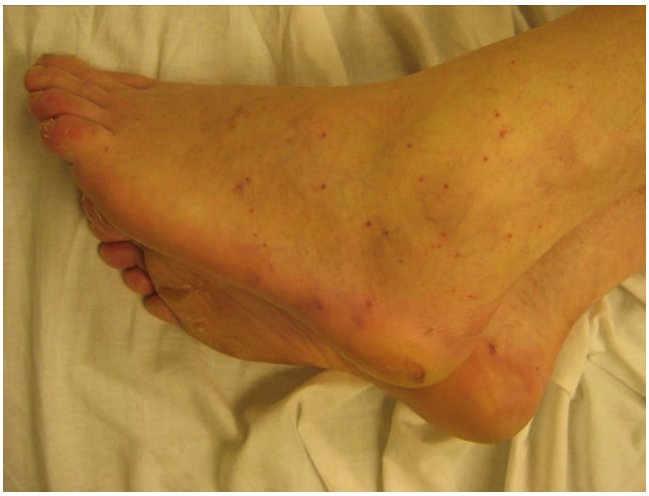

Fig. 23.22 Petechiae. Pinpoint, monoform red macules on the lower legs

Petechiae

Differential Diagnosis: Rickettsial, Bacterial, and Fungal Infection

Petechiae are small purpuric lesions up to 2 mm in size often occurring in crops due to extravasation of red blood cells into the skin. The purpura is not palpable, in contrast to palpable and sometimes tender purpura observed in patients with vasculitis. It tends to form in areas of increased venous pressure, such as the legs (Fig. 23.22). The etiology is multifactorial and includes among others thrombocytopenia, defective platelet function, increased intravascular venous pressure, vitamin C deficiency, and localized trauma or pressure. Purpura is often seen at intravenous injection sites in cancer patients. It must be distinguished from the eruption of Rocky Mountain spotted fever (RMSF), a tick-borne disease caused by the organism *Rickettsia rickettsii.* The hallmark of RMSF is a petechial eruption beginning on the palms of the hands and soles of the feet [39].

Disseminated Intravascular Coagulation

Differential Diagnosis: Bacterial and Fungal Sepsis

Disseminated intravascular coagulation may produce a clinical picture varying from a severe and rapidly fatal disorder (purpura fulminans) to a relatively minor disorder. Varying combinations of bleeding, thromboembolism, and hemolytic anemia are superimposed on the clinical picture caused by primary disorders which include, among others, extensive tissue damage, severe infections, and malignant diseases. The normal inhibitory mechanisms of clotting are overcome so that there is intravenous coagulation, followed by consumption and depletion of platelets and plasma clotting factors. In the most severe cases onset is sudden with fever and a very extensive, symmetrical purpura of the extremities but also on the ears, nose, and lips (Fig. 23.23). Lesser changes include petechiae, purpuric papules, hemorrhagic bullae, and acral cyanosis. Treatment includes that appropriate for the underlying condition, treatment of shock, and replacement therapy as indicated.

Section 4: Lesions of the Adipose Tissue

Differential Diagnosis: Bacterial, Deep Fungal, and Mycobacterial Infections and Cellulitis

Panniculitis is an inflammation occurring within the adipose tissue. It can occur in the septae, lobules, or both. It is often associated with a variety of systemic diseases and clinical syndromes and it often presents as red-to-violaceous nodules and plaques that have a predilection for lower extremities.

Nodular Vasculitis

Nodular vasculitis also called erythema induratum is a vasculitis of the muscular arteries of the deep dermis and fat that result in secondary lobular panniculitis. It occurs in middle-aged women who develop painful, reddish-blue, variably tender nodules and plaques over the lower extremities, especially the calves (Fig. 23.24). A severe small-vessel vasculitis is seen on histologic examination. Nodular panniculitis may be idiopathic but is most commonly due to infections such as tuberculosis and occasionally histoplasmosis,

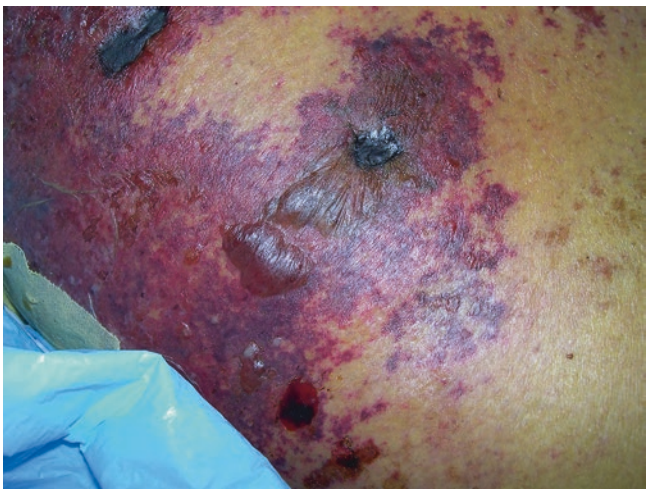

Fig. 23.23 Disseminated intravascular coagulation. Extensive skin necrosis with hemorrhagic bullae

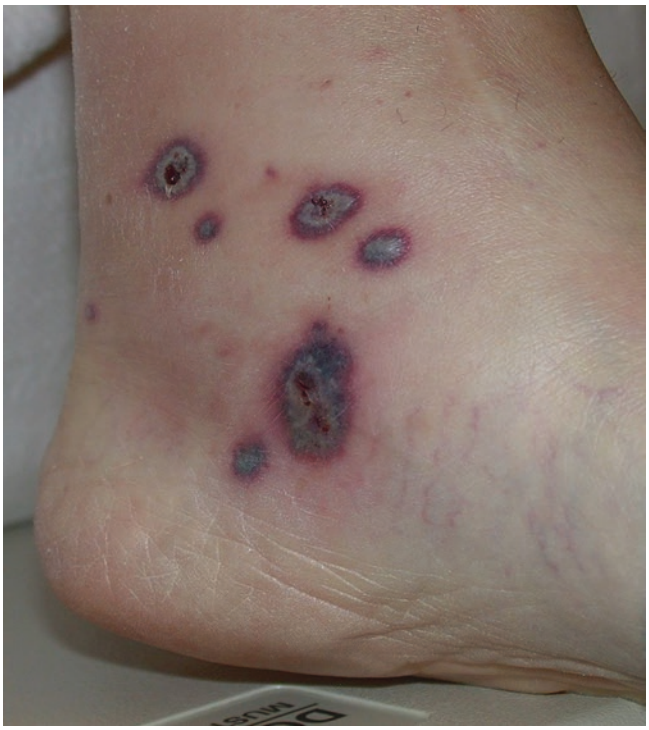

Fig. 23.24 Nodular vasculitis. Tender blue-reddish nodules on the lower legs

HIV, and hepatitis C [40–42]. Painful, indurated red plaques located on the extremities resembling erythema induratum have been reported in patients with chronic myelogenic leukemia undergoing treatment with imatinib [43] and dasatinib [44]. The differential diagnosis of nodular vasculitis includes erythema nodosum, granulomatous vasculitis, and miscellaneous forms of panniculitis.

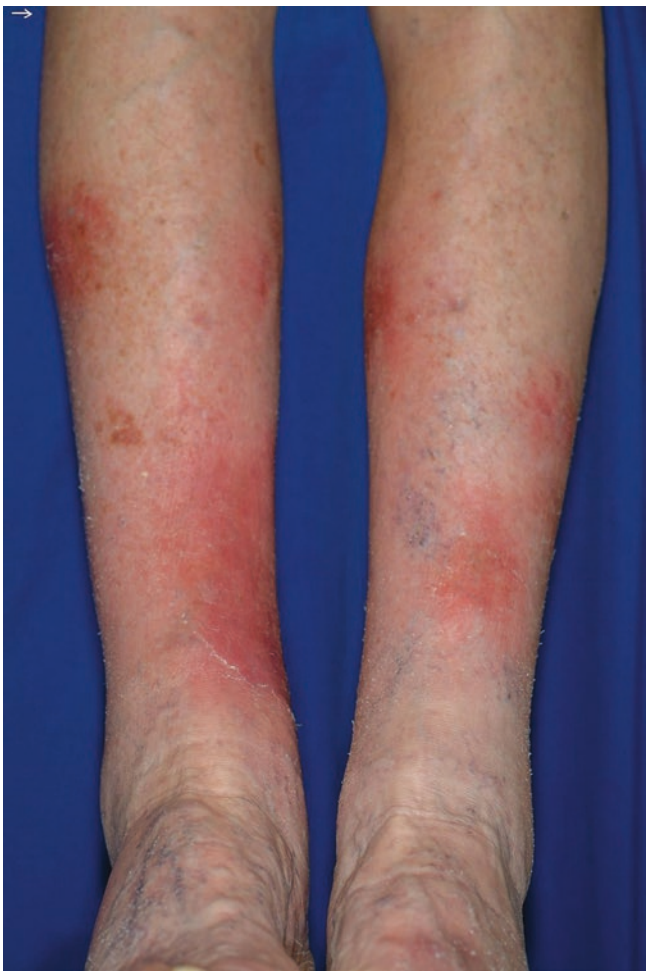

Fig. 23.25 Pancreatic panniculitis. Faint erythematous tender plaques on the lower extremities

Cold Panniculitis

Cold panniculitis is an acute, nodular eruption usually limited to areas exposed to the cold. Cold panniculitis results from a cold injury to the adipose tissue. It is more common in women. The eruptive phase usually begins 48 h (range, 6–72 h) after a cold injury to exposed or poorly protected areas. The lesions should be distinguished from cellulitis and deep fungal or mycobacterial infections.

Pancreatic Panniculitis

Pancreatic panniculitis, acute pancreatitis, and pancreatic tumors may cause fat necrosis of the pancreas and of the subcutaneous tissue. The clinical picture consists of raised, erythematous nodules, 1–3 cm in size, located on the upper and lower extremities (Fig. 23.25). The pathogenic mechanisms underlying the various features of pancreatic panniculitis are unclear.

The histopathology of pancreatic panniculitis is pathognomonic, characterized by ghost adipocytes that are necrotic,

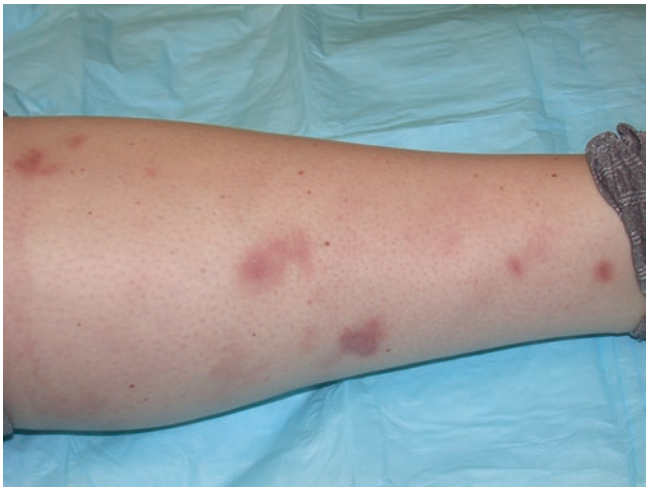

Fig. 23.26 Erythema nodosum. Tender red oval nodules on the extensor aspect of the legs

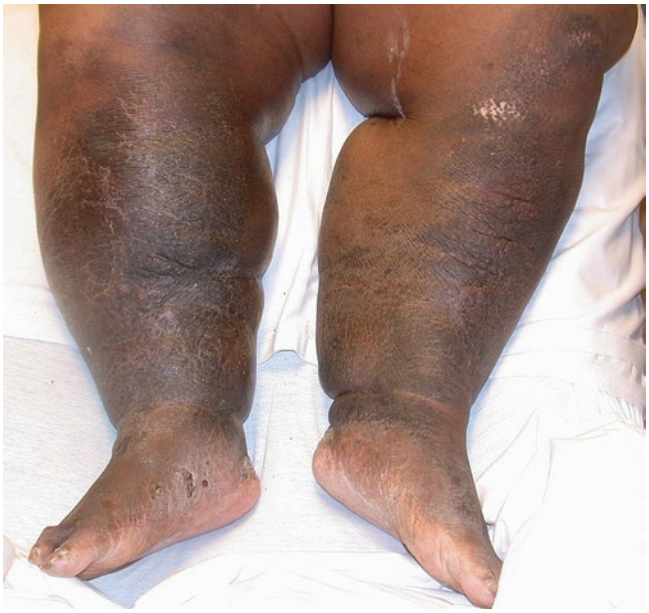

Fig. 23.27 Lipodermatosclerosis. Chronic inflammation and fibrosis of the skin surrounding the entire lower legs

anucleate and contain basophilic material within the cytoplasm indicating dystrophic calcification from the saponification of fat [45]. The exact mechanism is unknown, but it is believed that lipase plays a strong pathogenic role for subcutaneous fat necrosis. The Schmid's triad of panniculitis, polyarthritis, and eosinophilia portends very poor prognosis in a patient with pancreatic carcinoma.

Septal Panniculitis (Erythema Nodosum)

Septal panniculitis (erythema nodosum) is the most common form of inflammatory panniculitis manifested by erythematous, tender nodules on anterior shins, thighs, and lateral aspects of the lower legs and occasionally on the face, accompanied by fever, chills, arthralgias, and leukocytosis (Fig. 23.26). It results from an immunologic reaction triggered by drugs; benign and malignant systemic illness; bacterial, fungal, and viral infections; pregnancy; and medications including oral contraceptives. Circulating immune complexes have not been found in idiopathic and uncomplicated cases but demonstrated in patients with inflammatory bowel disease [46]. It resolves without scarring in 4–6 weeks.

Sclerosing Panniculitis (Lipodermatosclerosis)

Sclerosing panniculitis (lipodermatosclerosis) is a disease process that clinically appears as painful indurated erythematous hyperpigmented plaques and nodules on the lower extremities in middle-aged women. The underlying fibrosis and lobular atrophy give the impression of an inverted champagne bottle with a hard, wood-like appearance which becomes circumferential in well-developed lesions (Fig. 23.27). Occasionally there is overlying ulceration or crusting. Lipodermatosclerosis (LDS) is believed to be associated with chronic venous insufficiency. Abnormal fibrinolysis, an excessive proteolytic activity by matrix metalloproteinase, and the upregulation of an inflammatory response by interleukin-8 are thought to be the causes for this condition [47, 48].

Traumatic Panniculitis

Traumatic panniculitis represents a localized reaction of the subcutaneous tissue following minor trauma. It is most frequently seen in obese women. The lesions consist of indurated, inflamed nodules that undergo necrosis. When localized to the breast, they may clinically simulate a carcinoma or infectious mastitis. Traumatic panniculitis is usually a self-limiting disorder and requires only symptomatic treatment.

Section 5: Vesiculobullous Lesions

A vesicle is a fluid-filled blister less than 0.5 cm in its greatest dimension, while bullae is greater than 0.5 cm. Vesiculobullous lesions may be solitary, grouped, or annular and either localized or widespread in distribution. The etiology of these lesions varies, and valuable clues may be found in the patient's history, clinical presentation, and skin biopsy. From an infectious disease specialist's viewpoint, blistering lesions are often caused by herpetic eruptions or infectious pathogens which produce skin necrosis. However, a variety of non-infectious vesiculobullous lesions may occur in the transplant setting and are reviewed in this section.

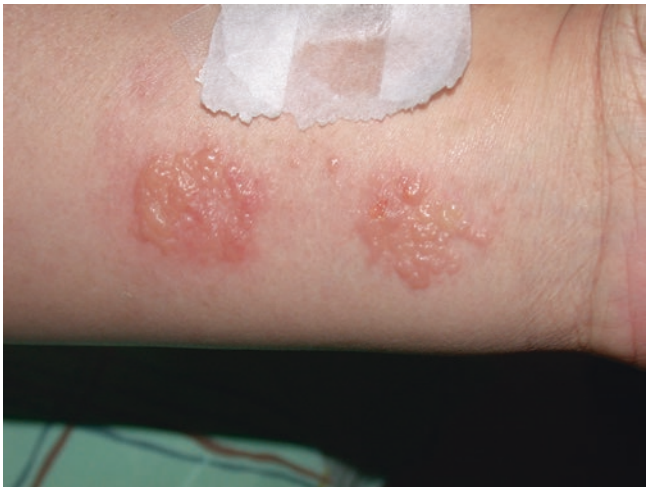

Fig. 23.28 Allergic contact dermatitis. Characterized by well-defined plaques of vesiculopapules overlying erythema and edema. Oozing and secondary infection are common

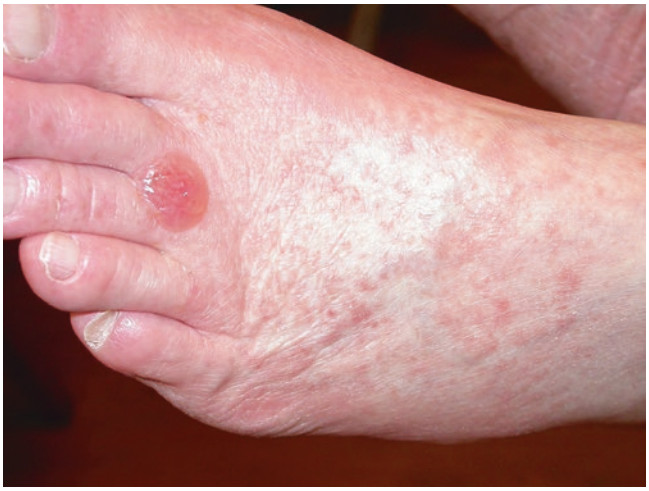

Fig. 23.29 Mechanical blister. Flat bullae on the toe dorsum secondary to trauma

Acute Dermatitis

Differential Diagnosis: Viral Infections and Impetigo

The vesiculobullous eruption associated with acute dermatitis is caused by inter- and intracellular edema in the epidermis, also called spongiosis. The patient may be aware of a preceding irritant or allergen applied to the skin, including surgical preparations, topical antibiotics, or tape. Allergic contact dermatitis may be linear or geometric, corresponding to the application of the precipitating agent (Fig. 23.28). As the blisters rupture, a superficial crust forms, which may be mistaken for impetigo. It is not unusual for the dermatitis to become secondarily infected, especially in the immunosuppressed transplant patient. On occasion, non-infectious vesicular lesions may appear distant to the site of the original dermatitis, a phenomenon known as autosensitization dermatitis. This should be distinguished from a disseminated herpetic process.

Diabetic Blisters

Differential Diagnosis: Viral Infection and Cellulitis

Also known as bullosis diabeticorum [49], this condition is characterized by the spontaneous appearance of intraepidermal or subepidermal, clear, tense bullae on the non-erythematous skin of diabetic patients. These blisters are most often found on the lower extremities and are minimally symptomatic. The pathogenesis may be related to diabetic angiopathy or trauma, and this condition should be distinguished from infectious cellulitis.

Mechanical Blisters

Differential Diagnosis: Cellulitis and Ecthyma

These painful blisters occur in areas of high friction or pressure, which causes epidermal necrosis. The surrounding erythematous rim may mimic cellulitis. Mechanical blisters are also precipitated by burns, extravasations of toxic substances, or vesicants. Hemorrhagic bullae may occur at sites of injections in patients with thrombocytopenia or capillary fragility (Fig. 23.29).

Coma Blister

Differential Diagnosis: Cellulitis and Ecthyma

Skin blisters at sites of pressure and associated with underlying sweat gland necrosis were reported in comatose patients with carbon monoxide intoxication as early as 1812 [50]. Also called barbiturate or neurologic blisters, these lesions are at times associated with surrounding erythema that may look like cellulitis. While barbiturates are the most frequently reported causative agent [51, 52], similar findings have been reported with other medications including tricyclic antidepressants [53] and benzodiazepines [54]. Coma blisters have been associated with central nervous system disorders [55], hypoglycemia [56], and diabetic ketoacidosis [57]. The etiology is multifactorial, but in some cases, a direct toxic drug effect has been implicated, perhaps via drug excretion through the eccrine glands. The bullae may appear as early as 1 h after acute intoxication and usually resolve in 2–4 weeks. They may be clear or hemorrhagic and should be distinguished from ecthyma or cellulitis.

Miliaria Crystallina

Differential Diagnosis: Herpes Infection

Miliaria crystallina, also known as sudamina, occurs in the setting of profuse sweating and epidermal occlusion. It is characterized by 1–2-mm asymptomatic vesicles on a non-inflammatory base, which are easily "wiped away" with pressure. As opposed to grouped herpetic vesicles on a more erythematous base, miliaria crystallina appears on occluded skin, with no underlying erythema (Fig. 23.30).

Edema and Lymphedema Blisters

Differential Diagnosis: Cellulitis

Large dependent bullae may develop in the setting of peripheral edema, anasarca, and lymphedema, especially if the onset of swelling is acute. Although these bullae are usually found on normal-appearing skin, underlying stasis changes may make it difficult to distinguish from bullous cellulitis. Initially, the blisters are tense and clear but may become hemorrhagic or superinfected. Treatment is directed at minimizing the underlying edema.

Bullous Drug Eruptions

Differential Diagnosis: Viral Infections, Ecthyma, and Cellulitis

Bullous drug reactions may be localized or widespread. When localized and recurrent at the same site after drug re-challenge, they are referred to as fixed drug eruptions. Fixed drug eruptions initially appear within 2 weeks of the inciting drug exposure but within 30 min–24 h after re-challenge. The eruption is characterized by erythema, sometimes the formation of bullae, and often characteristic residual "slate-grey" pigmentation as the lesion resolves. Findings suggest that fixed drug eruptions are a form of classic delayed-type hypersensitivity mediated by CD8+ cells [58], although mast cells may play a role [59]. When located on the genitalia the blisters may look like acute herpes simplex infection and, on other sites, cellulitis. Widespread bullous drug reactions have varying etiologies and pathologic features. Certain medications may produce immune-mediated blistering, characterized by the deposition of IgA at the dermal-epidermal junction. This is of special interest to infectious disease specialists as it has been reported with antibiotics like trimethoprim-sulfamethoxazole, penicillin, metronidazole, and rifampicin [60].

Bullous Graft Versus Host Disease

Differential Diagnosis: Viral Infection and Cellulitis

Allogeneic hematopoietic stem cell transplantation is widely used for the treatment of hematologic malignancies, bone marrow failure syndromes, and immunodeficiency. The skin is commonly affected in patients who develop graft-versus-host disease (GVHD). Grade 4 acute GVHD of the skin is characterized by a generalized exfoliative dermatitis, ulcerative dermatitis, and bullae [61] that may be mistaken for disseminated viral infection (Fig. 23.31). In these cases, the damage at the epidermal-dermal junction is severe enough to allow the dermis to separate from the epidermis. Bullae may also appear in the setting of scleroderma-like GVHD changes [62, 63].

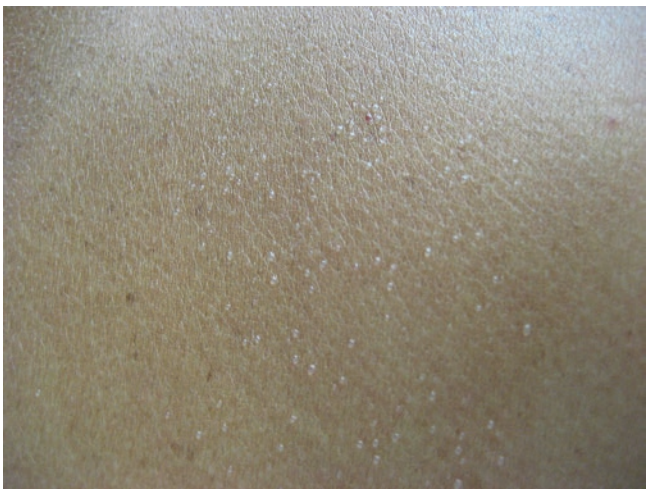

Fig. 23.30 Miliaria crystallina. Clear, thin-walled vesicles occurring in crops on otherwise normal-appearing skin

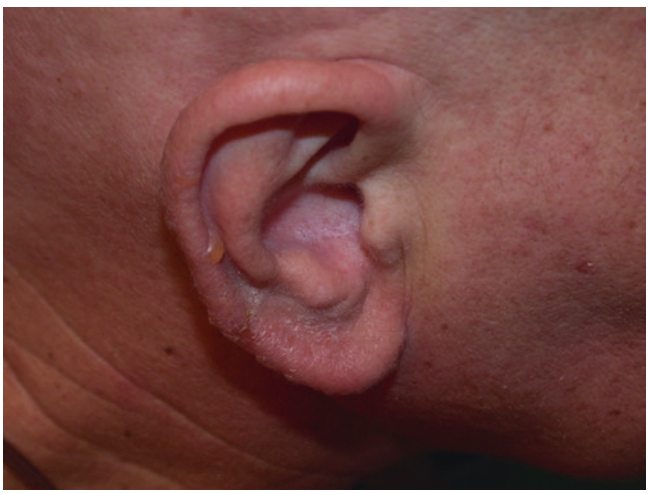

Fig. 23.31 Bullous graft-versus-host disease. Tense bulla and vesicles on the ear in patient with diffuse erythema of the head and neck

Although the pathogenesis is unknown, these cases show significant fibrosis and dermal edema [64, 65].

Porphyria Cutanea Tarda (PCT) and Pseudoporphyria Cutanea Tarda

Differential Diagnosis: Viral and Bacterial Infections

Porphyria cutanea tarda (PCT) is a group of familial and acquired disorders characterized by deficiency in the activity of uroporphyrinogen decarboxylase, an enzyme key in heme synthesis. In the transplant setting, this may be precipitated by exposure to environmental agent such as excess iron [66], coexisting conditions that affect the liver, and infection agents including hepatitis C [67] and HIV [68]. Patients exhibit skin fragility and blistering, especially in sun-exposed areas, as well as hypertrichosis, scleroderma-like changes, milia (small white cysts), and dystrophic calcification (Fig. 23.32). Pseudoporphyria mimics the findings of PCT without demonstrable porphyrin abnormalities. It has been reported in the setting of chronic renal failure and dialysis [69], as well with medications like beta-lactam antibiotics [70], ciprofloxacin [71], voriconazole [72], and tetracycline [73].

Autoimmune Bullous Diseases

Differential Diagnosis: Viral Infection, Cellulitis, and Scabies

This broad category of diseases is characterized as immune-mediated blistering of the skin. Bullous pemphigoid presents with tense skin blisters, urticarial (hive-like) lesions, and variable mucosal involvement. It is characterized by autoantibodies located in the hemidesmosomal complex of the basement membrane zone. It may occur de novo, with other autoimmune diseases, or occasionally with malignancies. Some antibiotics implicated in pathogenesis include amoxicillin [74], cephalexin [75], and ciprofloxacin [76]. The clinical presentation of tense blisters associated with urticaria may be mistaken for cellulitis.

Pemphigus presents on the skin and mucous membranes with intraepidermal flaccid bullae. It is divided into three forms: vulgaris; foliaceus; and paraneoplastic. Patients with pemphigus vulgaris develop painful mucosal erosions and skin lesions, which may resemble a herpetic process. Patients with pemphigus foliaceus develop extensive crusted erosions, easily confused with cutaneous infection (Fig. 23.33). Paraneoplastic pemphigus is associated with underlying neoplasms, and characterized by severe stomatitis, often mistaken for herpetic stomatitis. The lesions on the skin are polymorphous and may resemble lichen planus or erythema multiforme. (These patients may also develop lung involvement characterized by bronchiolitis obliterans [77]). Antibiotics are implicated in the pathogenesis of pemphigus vulgaris, including ampicillin, penicillin, cefadroxil, and rifampicin [60, 78]. In these cases, the eruption usually starts a few weeks after starting the medication. The diagnosis of pemphigus is made by performing a skin biopsy, which demonstrates an intraepidermal vesicle with acantholysis (separation between epidermal cells). Direct immunofluorescence of peri-lesional skin demonstrates IgG and/or C3 binding to the intercellular cement or keratinocyte cell surface [79]. Dermatitis herpetiformis, a cutaneous manifestation of

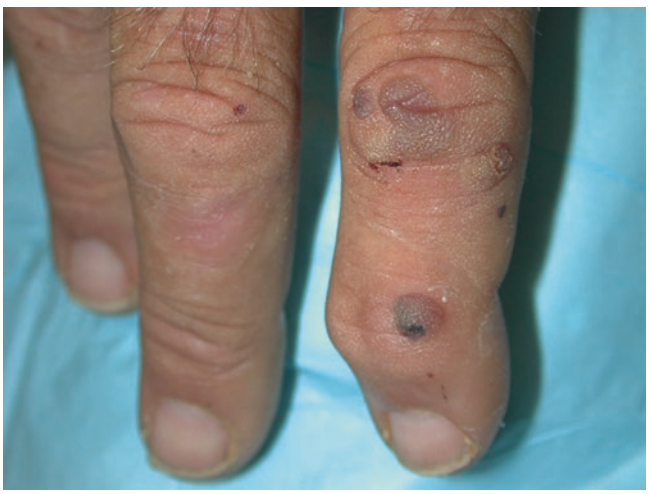

Fig. 23.32 Porphyria cutanea tarda. Vesicles and bullae on light-exposed cutaneous surfaces, especially the dorsal aspects of the hands

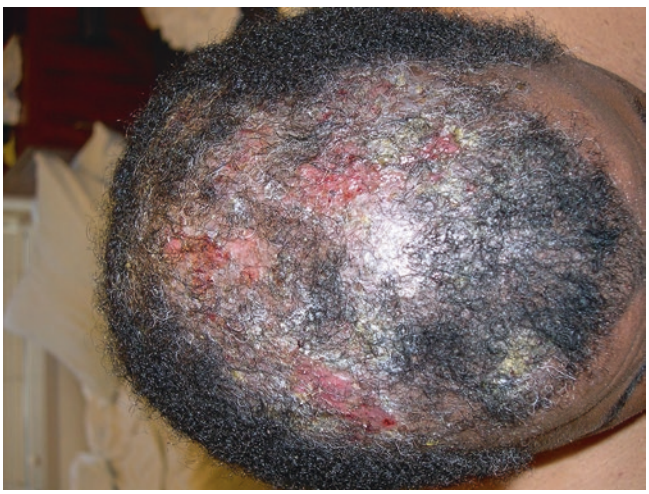

Fig. 23.33 Pemphigus vulgaris. Painful scalp erosions with underlying erythema

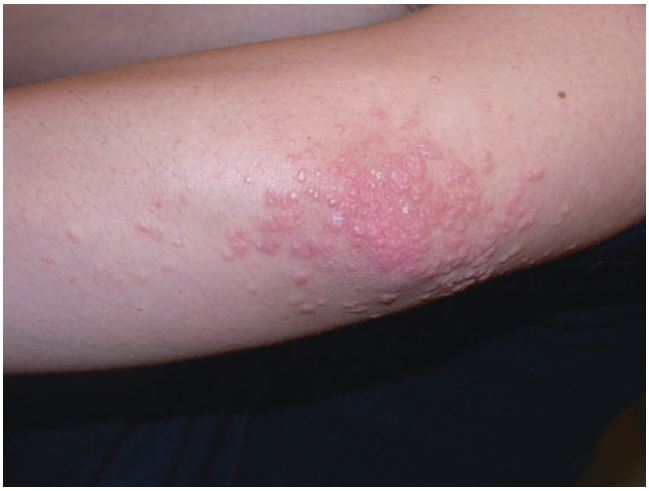

Fig. 23.34 Dermatitis herpetiformis. Grouped, symmetric, and pruritic papules on the elbow

gluten-sensitive enteropathy, is characterized by pruritic, tiny vesicles easily reminiscent of scabies or herpes infections. These are most commonly found on the elbows, back buttocks, and knees (Fig. 23.34). The biopsy shows neutrophils in the dermal papillae and granular deposits of IgA. The eruption may be worsened by ingestion or application of iodide [80].

Bullous Insect Bite Reaction

Differential Diagnosis: Ecthyma, Viral Infection, and Cellulitis

Insect bite reactions may produce varying degrees of erythema and are less commonly vesicles, bullae, and necrosis. Exaggerated bite reactions have been reported in the setting of chronic lymphocytic leukemia as well as other hematoproliferative disorders and human immunodeficiency virus infections [81, 82]. Many patients have no recollection of the bite.

Section 6: Erythematous Lesions

Injury, infection, vascular reactivity, and inflammation may cause erythema of the skin. Most of the conditions discussed in this section produce blanchable erythema, that is, resolution of the erythema with pressure. So-called reactive erythema is a cutaneous response to an underlying systemic process, which may be infectious, malignant, or drug related. The primary lesions are red plaques that may be annular, transient, or fixed.

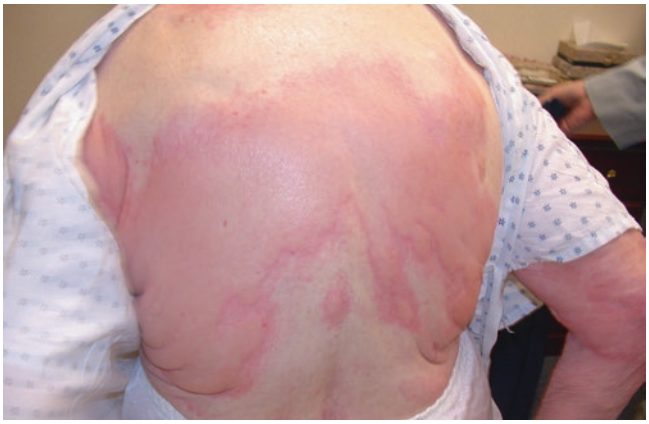

Fig. 23.35 Urticaria. Transient, well-circumscribed erythematous dermal plaques on the trunk

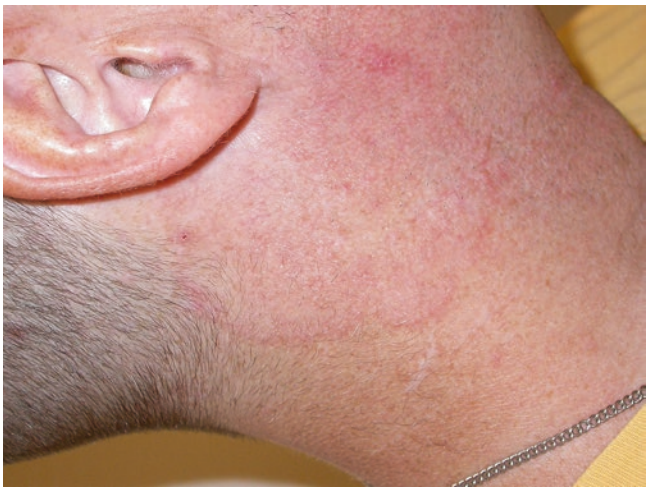

Fig. 23.36 Tinea corporis. An expanding, erythematous annular plaque

Urticaria

Differential Diagnosis: Cellulitis and Superficial Fungal Infections

Urticaria, commonly referred to as hives or wheals, are well-demarcated, smooth, dermal plaques that may become confluent and demonstrate a variable degree of pruritus. When associated with significant edema and warmth, they are mistaken for cellulitis (Fig. 23.35) and when annular in configuration, for tinea corporis (Fig. 23.36). Because they result from transient dermal edema, they tend to change in size and shape and are rarely present in the same spot for more than 48 h. When persistent, a biopsy may demonstrate urticarial vasculitis, characterized by small vessel destruction.

Angioedema presents with deep and painful swelling, without urticaria. Transplant patients may be at increased risk

of angiotensin-converting enzyme (ACE)-associated angioedema because of the effects of immunosuppressants on the activity of circulating dipeptidyl peptidase IV (DPPIV) [83].

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

Differential Diagnosis: Disseminated Viral, Bacterial, or Fungal Infections

At the onset, erythema multiforme presents as erythematous macules and plaques on the extensor surfaces of the limbs and on the palms and soles. Other infectious etiologies for palm and sole lesions including rickettsia, spirochetes, or viruses should be considered. The classic target or iris lesion is characterized by a dusky center, red border, and surrounding pallor (Fig. 23.37). If enough epidermal apoptosis is present, the center may appear bullous, hemorrhagic, or necrotic, suggestive of ecthyma or embolic infection. SJS may be complicated by significant mucous membrane involvement of the lips, buccal mucosa palate, conjunctivae, urethra, and vagina. TEN is a life-threatening condition characterized by detachment of the epidermis from the dermis (Fig. 23.38). The differential diagnosis includes staphylococcal scalded skin syndrome (SSSS). However, SSSS causes a more superficial subcorneal skin split that can readily be distinguished by skin biopsy.

EM, SJS, and TEN are associated with many different etiologies. Infectious agents are important precipitating factors in children and young adults [84], whereas drug reactions and malignancy are more important in adults [85, 86]. Herpes simplex, mycoplasma pneumonia, Coxasackie B-5, influenza type A, and echo viruses have all been implicated in pathogenesis [87].

Gyrate Erythema

Differential Diagnosis: Superficial Fungal, Bacterial, or Rickettsial Infections

A gyrate erythema is characterized by polycyclic erythematous plaques. In the case of erythema annulare centrifugum, the lesions slowly expand, disappear over weeks, and are replaced by new annular lesions (Fig. 23.39). Some cases are associated with dermatophyte infections, but the lesions themselves do not contain fungus. This condition is rarely associated with internal malignancy, and the clinical presentation may mimic secondary syphilis, dermatophytosis, Hansen's disease or erythema migrans, and the gyrate erythema associated with Lyme disease.

Necrolytic migratory erythema, associated with glucagon-secreting tumors of the pancreas, is a gyrate erythema that

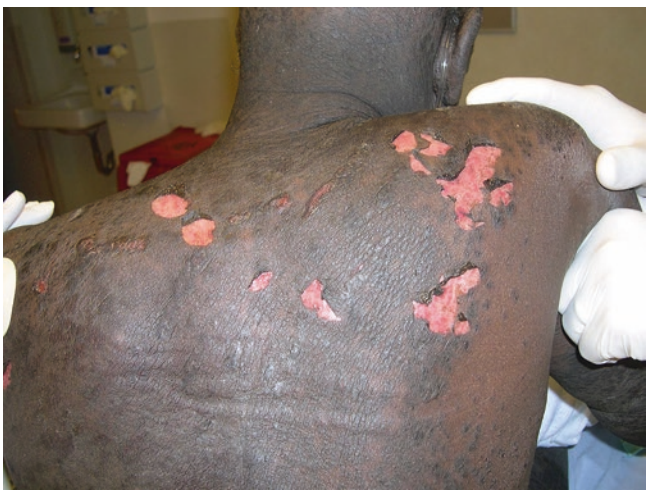

Fig. 23.38 Toxic epidermal necrolysis. Extensive erosions and sloughing of skin resembling wrinkled, wet tissue paper

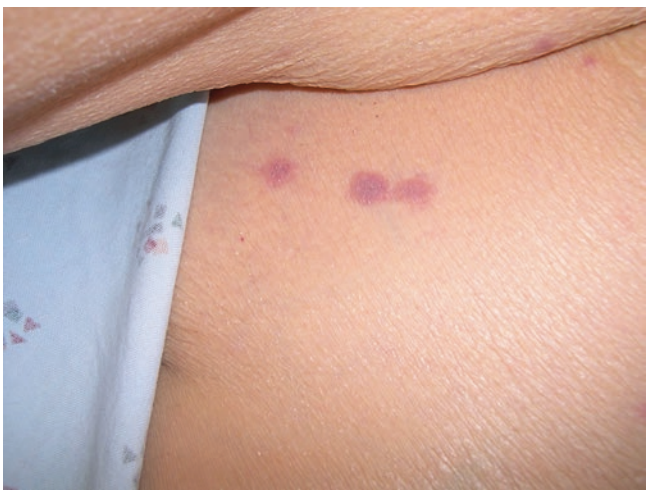

Fig. 23.37 Erythema multiforme. Round lesions in which concentric rings with color variation are present

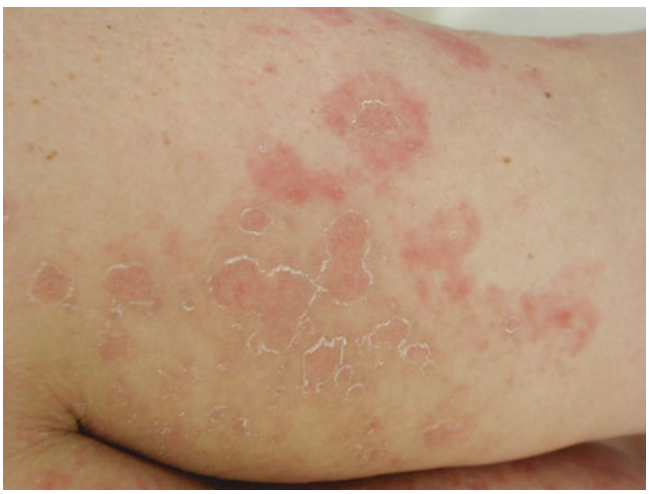

Fig. 23.39 Gyrate erythema. Slowly expanding annular lesions and palpable scaly erythematous borders

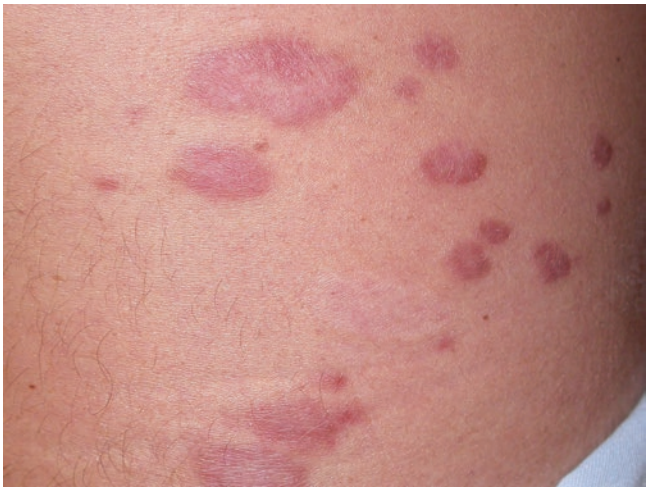

Fig. 23.40 Granuloma annulare. Annular, dusky-red, nonscaly plaques on the trunk

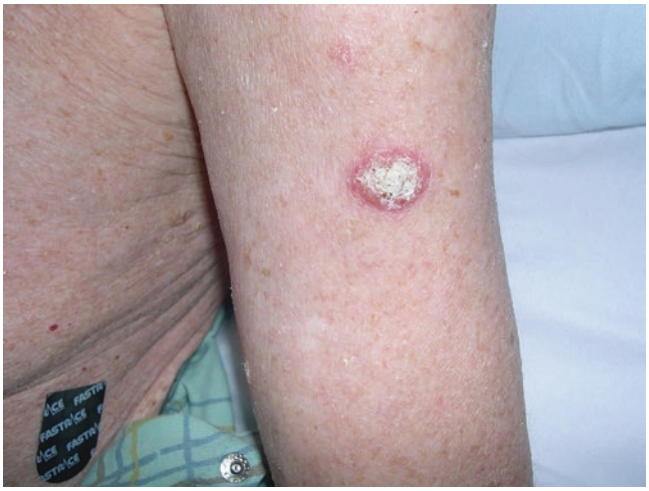

Fig. 23.41 Squamous cell carcinoma. Large, sun-induced, keratotic, non-ulcerated nodule on the arm

occurs in periorificial, flexural, and acral areas. The eruption may resemble chronic mucocutaneous candidiasis, severe seborrheic dermatitis, or acrodermatitis enteropathica associated with zinc deficiency. It has also been associated with hepatitis C [88].

Granuloma Annulare

Differential Diagnosis: Superficial Fungal Infection

This granulomatous process presents with annular and serpiginous plaques with no significant scale (Fig. 23.40). In some studies, GA has been associated with diabetes mellitus [89], but many cases are idiopathic. The lesions may be confused with a superficial fungal infection.

Section 7: Ulcerative Lesions and Skin Tumors

Differential Diagnosis: Bacterial, Fungal, Mycobacterial, or Parasitic Infections

Organ transplantation markedly increases the risk of developing non-melanoma skin cancers, the most common of which are squamous cell carcinoma followed by basal cell carcinoma [90] (Fig. 23.41). Compared to the biologic behavior in non-immunosuppressed individuals, the squamous cell carcinomas tend to be more aggressive, with a higher risk of invasion of surrounding structures as well as metastasis [91, 92]. Kaposi's sarcoma and Merkel cell carcinomas occur with increased frequency [90]. In organ transplant patients with chronic ulcerations, it may be prudent to biopsy for bacterial, fungal, and acid-fast culture as well as for histopathology.

Section 8: Hair and Scalp Lesions

Transplant patients may present with inflammatory lesions of the scalp and alopecia as a result of bacterial and fungal infections. This section will review some of the non-infectious etiologies of hair and scalp lesions.

Tumors

Differential Diagnosis: Bacterial and Deep Fungal Infections

The incidence of squamous cell and basal cell carcinomas of the skin increase with the duration of immunosuppressive therapy in transplant recipients and affect at least 50% of Caucasian transplant patients [93]. Approximately 80% of tumors develop on the head [94] with associated ulceration, crusting, and erosions. Early on, these crusted lesions may be mistaken for bacterial or fungal infections, delaying the diagnosis. Some of these tumors resemble warts and, in fact, human papillomaviruses may be cocarcinogenic [95]. Patients post-organ transplantation may also be at a higher risk for melanoma [96], Kaposi's sarcoma [97], and Merkel cell carcinoma [98].

Plaques and Pustules

Differential Diagnosis: Bacterial and Fungal Infections

While erythematous plaques and pustules on the scalp may be caused by dermatophyte and bacterial infections, this is also a common presentation of scalp psoriasis. The characteristic well-demarcated, scaly plaques may be studded with

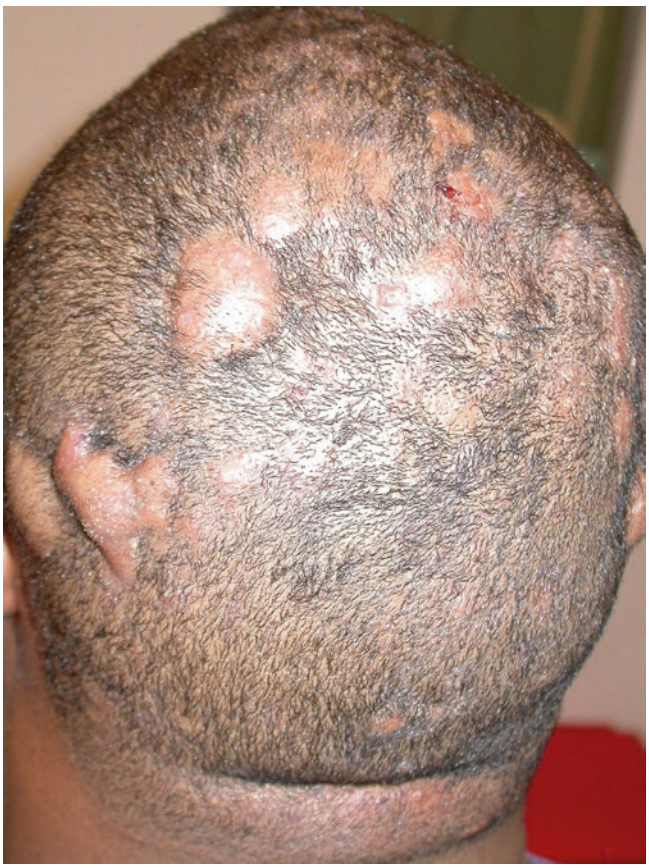

Fig. 23.42 Dissecting cellulitis of the scalp. Painful cutaneous nodules and patchy alopecia

sterile pustules; the latter may be precipitated by systemic corticosteroid withdrawal or taper. Dissecting cellulitis of the scalp, also called perifolliculitis capitis abscedens et suffodiens, produces boggy and fluctuant scalp nodules with interconnecting sinus tracts and sterile, purulent discharge (Fig. 23.42). This disorder often responds better to retinoids than antibiotics [99]. Other common causes of sterile pustules and inflammation on the scalp include acne keloidalis or inflamed cysts.

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