10 Reactive Erythemas and Panniculitides in Connective Tissue Disease

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Key Points

- Reactive erythemas are cutaneous eruptions that generally develop in response to a systemic trigger
- Associated conditions include autoimmune diseases, inflammatory bowel disease (IBD), malignancy, and infection
- Reactive erythemas often require systemic immunomodulatory therapy that may influence the underlying disease state, and they may also respond to therapy directed towards the underlying disease association
- An interdisciplinary approach to management and surveillance in patients with reactive erythemas is imperative

Interdisciplinary Introduction

Reactive erythemas are inflammatory dermatoses that often have extracutaneous manifestations. These conditions include several types of panniculitis, as well as pyoderma gangrenosum (PG), Sweet syndrome, palisaded neutrophilic granulomatous dermatitis (PNGD), interstitial granulomatous dermatitis (IGD), and interstitial granulomatous drug reaction (IGDR). Although their pathogenesis is largely uncertain, reactive erythemas generally occur as a response to a systemic trigger or underlying disorder, such as connective tissue diseases, inflammatory bowel disease (IBD), malignancy, infections, systemic vasculitides, medication use, and pregnancy.

The cutaneous manifestations of the various reactive erythemas differ according to the specific disease, but lesions are typically pink to violaceous during the active phase of inflammation. Musculoskeletal symptoms are common in patients with reactive erythemas. These symptoms may be related either to the underlying condition or to the reactive process itself, may parallel or be independent of the cutaneous manifestations, and vary according to the cutaneous association. For example, seronegative, non-erosive, monoarticular arthritis is the most common arthritis in PG, whereas in PNGD and IGD, rheumatoid arthritis (RA) is the most common association. Musculoskeletal manifestations of Sweet syndrome may include arthritis as well as myositis, fasciitis, tendinitis, and/or tenosynovitis. Arthralgias in the absence of arthritis are also common in patients with reactive erythemas, occurring in up to half of patients with EN, as well as in patients with PG. The arthralgias of IGD tend to be symmetric, polyarticular, and favor peripheral

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joints, while 10% of patients with IGDR have an underlying arthropathy.

While some reactive erythemas may occur in the absence of a systemic association, reactive erythemas often serve as a clue to an underlying internal disease. For example, PNGD and IGD are often associated with autoimmune disease or malignancy. PG is frequently associated with IBD, and both PG and Sweet syndrome are commonly associated with hematologic malignancies. Furthermore, both PG and an IGD-like eruption [1] have been reported as coinciding with the transformation of myelodysplastic syndrome (MDS) into acute myeloid leukemia, and the development of panniculitis in patients with systemic sclerosis (SSc) may be a portent of pulmonary hypertension. Given the frequency of internal disease associations with the reactive erythemas, interdisciplinary management, including long-term monitoring and surveillance for internal disease in patients with reactive erythemas, is imperative.

Erythema Nodosum, Erythema Induratum, and Connective Tissue Panniculitides

The subcutaneous fat, or panniculus, is composed of fat lobules (collections of adipocytes) and septae (interlobular connective tissue). Inflammation occurring within the subcutaneous fat is known as panniculitis. Clinical distinction between the panniculitides can be difficult, as all forms typically present with tender, erythematous subcutaneous nodules; however, the location on the body can often serve as a clinical clue, as we review in detail below.

Due to the large degree of clinical overlap between the panniculitides, classification is primarily based on histology. The most important distinction is whether the panniculitis predominantly affects the septae or the fat lobules (although a degree of overlap is present in almost all cases), or whether the infiltrate is mixed (see Table 10.1). For example, EN is, as a rule, a septal panniculitis, whereas lupus erythematosus panniculitis (LEP) affects the fat lobules; this classification has implications for disease course and sequelae. Once the distinction between a septal or lobular panniculitis has been made, the histologic presence of vasculitis may also help further subclassify the panniculitides.

Erythema nodosum is the prototypical septal panniculitis. In septal panniculitides, the fat lobules are relatively spared, and thus healing occurs without atrophy. In contrast, lobular or mixed panniculitides, such as erythema induratum/nodular vasculitis (EI/NV) and those associated with connective tissue diseases, can obliterate the fat lobules. The resulting sequelae include disfiguring and irreversible contour change (see Fig. 10.1), and, in severe or long-standing lesions, ulcerations and calcinosis, which are painful and cause functional impairment.

Of note, the term Weber-Christian disease, or nodular panniculitis, was used in older literature to describe an idiopathic, relapsing syndrome of fever, lobular panniculitis, and variable internal organ involvement. Many such cases have since been reclassified as other diseases, and therefore in the authors' experience and the literature at large, the terminology has mostly been abandoned in favor of more specific diagnoses [2, 3].

Erythema Nodosum

Key Summary Capsule Bullets

- Prototypical septal panniculitis; thus, heals without permanent sequelae
- Presents with acute onset of erythematous, tender subcutaneous nodules and/or plaques in crops on bilateral pretibial surfaces, often with associated arthralgias
- Etiologies vary regionally, but idiopathic and post-streptococcal are most common
- Diagnosed clinically, with skin biopsies generally reserved for atypical cases
- Treatment is directed towards underlying cause and is otherwise supportive and aimed at alleviating symptoms
- Spontaneous resolution is expected within several weeks in the majority of patients

Table 10.1 Classification of the panniculitides

–	Clinical features	Main site(s) of involvement	Type of panniculitis	Vasculitis	Other characteristic histologic features
Erythema nodosum	Acute-onset, tender, erythematous subcutaneous nodules	Bilateral shins	Septal	No	Miescher granulomas
Erythema induratum/ nodular vasculitis (EI/NV)	Erythematous subcutaneous nodules that ulcerate	Bilateral calves	Lobular or mixed, granulomatous	Yes	–
Lupus erythematosus panniculitis (LEP)	Tender, erythematous subcutaneous nodules and/or plaques, some with overlying discoid lupus erythematosus (DLE)	Fatty areas of face (especially cheeks), proximal limbs, trunk (including breasts)	Lobular	Usually no	Mucin, hyaline fact necrosis, lymphoid follicles with germinal centers, overlying DLE
Dermatomyositis-associated panniculitis (DAP)	Tender, erythematous subcutaneous nodules and/or plaques	Buttocks, thighs, arms	Lobular	Usually yes	Vacuolar interface dermatitis, dermal mucin, calcification
Panniculitis of sclerosing disorders (morphea, systemic sclerosis/SSc)	Morphea: indurated, sclerotic plaques SSc: well-circumscribed, indurated, painful, hyperpigmented plaques	Morphea: extremities, trunk Systemic sclerosis: shin	Morphea: septal SSc: mixed	No	Morphea: thickened, hyalinized collagen SSc: lipophagic fat necrosis, lipomembranous change
Pancreatic panniculitis (PP)	Erythematous, edematous subcutaneous nodules that ulcerate and drain oily material; associated with various pancreatic disorders	Legs > trunk, upper extremities, buttocks, scalp	Lobular or mixed (septal only early in course)	No	"Ghost cells" (anucleate adipocytes)
Lipodermatosclerosis (LDS)	Tender, erythematous plaques (acute); sclerotic plaques with "inverted champagne bottle" appearance (chronic); associated with chronic venous insufficiency	One or both lower extremities, often above medial malleoli	Mixed	No	Lobular necrosis, hemosiderin deposition (acute); lipomembranous change, septal sclerosis (chronic)
Infectious panniculitis	Subcutaneous nodules and abscesses that may be inflamed and fluctuant	Legs, feet	Mixed, neutrophilic	No	Positive cultures and special stains
Alpha-1 antitrypsin deficiency panniculitis	Erythematous, subcutaneous nodules and/or plaques that ulcerate and drain oily material; associated with alpha-1 antitrypsin, deficiency	Trunk, proximal extremities	Mixed	Yes	"Splaying" of neutrophils between dermal collagen bundles, liquefactive necrosis with "skip areas" of normal fat

(continued)

Table 10.1 (continued)

–	Clinical features	Main site(s) of involvement	Type of panniculitis	Vasculitis	Other characteristic histologic features
Sclerema neonatorum	Woody induration of skin in preterm neonates	Diffuse; spares, palms, soles, genitalia	Minimal	No	Needle-shaped clefts within adipocytes and giant cells
Subcutaneous fat necrosis of the newborn	Indurated, subcutaneous nodules and/or plaques in full- and post-term neonates	Bilateral extremities, buttocks, back	Lobular, granulomatous	No	Needle-shaped clefts within adipocytes and giant cells
Post-steroid panniculitis	Erythematous, indurated, subcutaneous nodules and/or plaques after abrupt cessation of systemic corticosteroids	Cheeks	Lobular, granulomatous	No	Needle-shaped clefts within adipocytes and giant cells
Traumatic panniculitis	Tender subcutaneous nodules	Any site of blunt trauma	Mixed	No	–
Cold panniculitis	Acute-onset, erythematous, subcutaneous nodules and/or plaques	Cold-exposed areas (chin, cheeks, thighs)	Lobular or mixed	No	–
Factitial panniculitis	Tender, erythematous nodules; potential presence of geometric ulcers and/or abscesses	Buttocks, thighs (areas accessible for self-injection)	Lobular, neutrophilic	No	Fat necrosis, foreign (sometimes birefringent) material

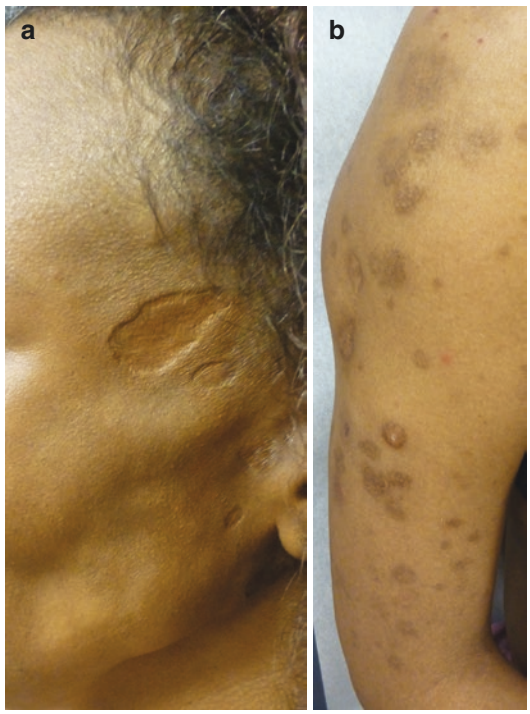

Fig. 10.1 Lupus erythematosus panniculitis (LEP): contour changes on the (**a**) face and (**b**) proximal upper extremity due to atrophy of the pannus with longstanding disease

Classification and Epidemiology

Erythema nodosum is the most common panniculitis and the prototypical septal panniculitis. Its incidence has been estimated as 2–5 per 100,000 people per year [4, 5]. It predominates in women of childbearing age, with the largest case series reporting a female-to-male ratio of 5:1 [6, 7]. Erythema nodosum has been linked to various underlying triggers, and the relative ranking of etiologies varies geographically. For example, the most common association is group A streptococcal tonsillopharyngitis in Israel, France, and Turkey; sarcoidosis in Spain and Greece; and primary tuberculosis in Thailand [8].

Pathogenesis

The pathogenesis of EN is poorly understood, but the disorder is generally regarded as a delayed hypersensitivity reaction to antigens associated with various systemic conditions or medications. Type 1 helper (Th1) cells are believed to play a

role, and the Th1 cytokines interleukin-2 (IL-2) and interferon-γ (IFN-γ) have been found to be overexpressed in the skin and peripheral blood of patients with EN as compared with healthy controls [9]. Further supporting the role of Th1 cells in EN pathogenesis is the finding that lymphocytes from a patient with estradiol-induced EN produced more IFN-γ when re-exposed to estradiol than did lymphocytes from a healthy control [10]. Other potential mediators of EN include neutrophils [11, 12] and tumor necrosis factor-α (TNF-α) [13].

Clinical Features

In the vast majority of patients, EN presents acutely with crops of erythematous, tender subcutaneous nodules and/or plaques on the pretibial regions of the bilateral lower extremities (see Fig. 10.2). Less commonly, EN may also involve the knees, thighs, upper extremities, and trunk. The nodules heal in approximately 3–6 weeks without scarring, ulceration, atrophy, or other permanent sequelae. This lack of scarring is attributed to the fact that the underlying inflammatory process targets the subcutaneous septae, with relative sparing of the fat lobules, which remain intact.

Erythema nodosum may be associated with several underlying conditions; this list is vast and varies according to the geographic region. Group A streptococcal tonsillopharyngitis in the 1–3 weeks prior to onset is the most common identifiable cause (6–44% of patients) [4–7, 14]. Most other etiologies involve either the pulmonary system (4–30% of patients) or gastrointestinal system (2–9%) [4–8, 14].

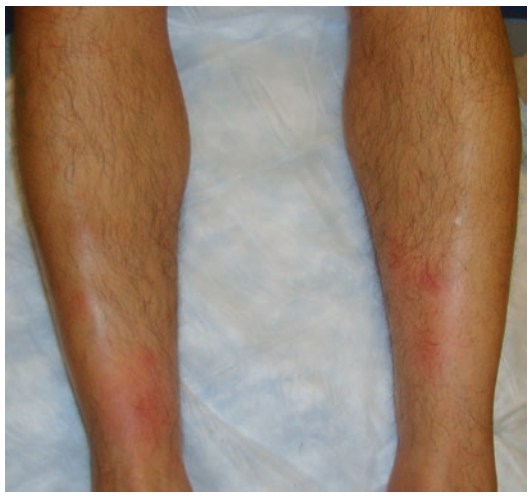

Fig. 10.2 Erythema nodosum: erythematous nodules on the bilateral pretibial surfaces

EN-associated diseases with pulmonary manifestations include granulomatous conditions, such as sarcoidosis, primary tuberculosis, and fungal infections (e.g. coccidioidomycosis, histoplasmosis, blastomycosis). Bacterial infections, namely *Chlamydophila pneumoniae* or *psittaci* may also present with pulmonary symptoms; yersiniosis presenting with pulmonary but not gastrointestinal symptoms has also been described [15]. Hodgkin lymphoma may also involve the lungs, often presenting with lymphadenopathy.

Etiologies associated with gastrointestinal findings include Behçet disease, IBD (Crohn disease more so than ulcerative colitis [16]), and bacterial gastroenteritis (e.g. due to *Yersinia enterocolitica*, Salmonella, Campylobacter). Other triggers of EN include medication use in the 1–2 weeks prior to onset (classically penicillins, sulphonamides, halides, or oral contraceptive pills; 0–10% of patients) and pregnancy (0–6%) [4–8, 14].

Extracutaneous clinical features of EN vary depending on the underlying systemic association. A large prospective study found that the presence of cough, sore throat, diarrhea, arthritis, and pulmonary pathology were predictors of secondary EN [8]. Other clinical features, such as fever, leukocytosis, and elevated inflammatory markers (e.g., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), are significantly more common in patients with secondary EN than idiopathic EN. By contrast, in a large prospective study, recurrence of EN predicted an idiopathic etiology [8]. Up to 50% of patients with EN have arthralgias [6–8].

Histopathology

Histopathologically, EN is typified by a septal panniculitis without vasculitis. The inflammatory cells within the septae characteristically aggregate around a banana- or stellate-shaped cleft,

forming structures known as Miescher granulomas, which are relatively specific for erythema nodosum. The septal infiltrate variably extends into the periphery of adjacent fat lobules and may be accompanied by a lymphocytic perivascular dermal infiltrate.

As lesions age, the predominant cell type in the septal infiltrate and Miescher granulomas changes from neutrophils to histiocytes to multinucleated giant cells. Miescher granulomas also decrease in number as lesions evolve. Early lesions also feature septal edema and hemorrhage, which are replaced by septal fibrosis in late lesions [17]. Although the endothelium of small vessels may be necrotic, true vasculitis is characteristically absent [18]. The exception to this is EN associated with Behçet disease, in which vasculitis is common [19].

Diagnostic Considerations

Histologically, several conditions other than EN may involve the fat septae, but these are not considered primary panniculitides (see Table 10.2). The clinical differential diagnosis of EN includes other conditions that can cause tender, erythematous subcutaneous nodules and/or plaques on the legs, which we review below.

Like EN, EI/NV affects predominantly young to middle-aged women and may be idiopathic or precipitated by infection (classically tuberculosis) or medications. However, unlike EN, EI/NV favors the calves, may ulcerate and drain, and heals with scarring (see Fig. 10.3). Furthermore, EI/NV is readily differentiated from EN histologically by its characteristic lobular or mixed panniculitis and usual presence of vasculitis.

Pancreatic panniculitis (PP) is an uncommon manifestation of various pancreatic disorders, including acute and chronic pancreatitis and pancreatic carcinoma. PP may mimic EN, as it frequently arises on the legs and early histology demonstrates a septal panniculitis. Factors that distinguish PP include its predilection for sites other than the legs (i.e., chest, upper extremities, buttocks, scalp), potential for ulceration and drainage of oily material, and association with elevated serum amylase and lipase. In addition, the histology of PP is typically lobular or mixed, with septal involvement seen only early in the course. Characteristic "ghost cells" (anucleate adipocytes) due to fat necrosis also help to distinguish PP histologically.

Lipodermatosclerosis (LDS) is a panniculitis associated with chronic venous insufficiency. Although the tender, erythematous plaques of the acute phase of LDS may be confused for EN, clinical features more suggestive of LDS include a background of venous insufficiency (i.e., varicose veins, chronic lower extremity edema, hemosiderin discoloration) and predilection for the area of the leg above the medial malleolus.

Table 10.2 Conditions that are not primary panniculitides but histologically involve the fat septae

Condition	Vasculitis present histologically?
Rheumatoid nodule	No
Subcutaneous granuloma annulare	No
Necrobiosis lipoidica diabeticorum	No
Superficial thrombophlebitis	Yes
Cutaneous polyarteritis nodosa	Yes
Necrobiotic xanthogranuloma	No

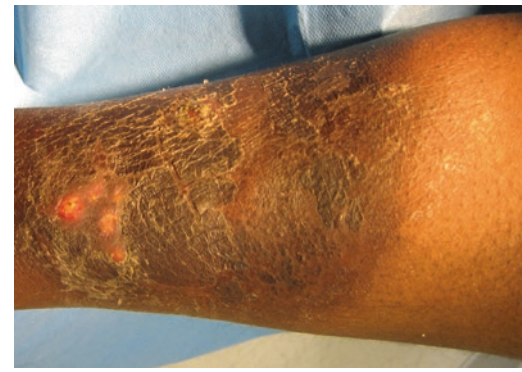

Fig. 10.3 Erythema induratum/nodular vasculitis (EI/NV): hyperpigmented plaques with ulcerations overlying tender subcutaneous nodules on the calf

Moreover, unlike EN, early LDS histologically demonstrates a mixed panniculitis, ischemic fat necrosis, and septal fibrosis. As LDS progresses, the clinical picture is characterized by indurated skin with an "inverted champagne bottle" appearance.

Infectious panniculitis (i.e., bacterial, fungal, or atypical mycobacterial) usually occurs in immunosuppressed patients. The diagnosis is favored when the histology demonstrates a mixed neutrophilic panniculitis, vascular proliferation, cellular necrosis including necrosis of sweat glands, and discrete abscesses. Furthermore, microorganisms can often be identified via special stains and cultures [20], although in some cases, repeated stains and cultures may be necessary prior to identifying an infectious cause.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare cutaneous lymphoma in which neoplastic cytotoxic T-cells infiltrate the subcutaneous fat lobules, resulting in a predominantly lobular panniculitis. The diagnosis of SPTCL should be considered in patients with presumed EN who follow an atypical course or those with systemic B symptoms (e.g., night sweats and weight loss). The diagnosis can be confirmed with immunohistochemical identification of a monoclonal T-cell receptor gene rearrangement.

Unlike EN, subcutaneous Sweet syndrome is a predominantly lobular panniculitis. Cellulitis and erysipelas usually affect the lower extremities unilaterally, in contrast to EN, which is typically bilateral. The tender, erythematous lesions of superficial thrombophlebitis are distinguished by their distribution along a superficial vein and presence of a palpable cord. The cutaneous nodules of polyarteritis nodosa may be differentiated from EN both clinically (as they may ulcerate and co-occur with livedo racemosa) and histologically (as they display a necrotizing vasculitis of medium-sized arteries in the septae). In subcutaneous sarcoidosis, nodules favor the upper extremities, are generally asymptomatic to slightly tender, and demonstrate noncaseating granulomas. Lastly, the nodules of subcutaneous granuloma annulare (GA) tend to be painless, occur in children, and feature histiocytic palisades surrounding degenerated collagen and mucin in the septae.

Disease and Comorbidity Assessment

The evaluation of patients with EN generally begins with an evaluation for potential underlying causes, through history (including a medication review and travel history), review of systems (focusing on articular, respiratory, and gastrointestinal symptoms), and physical examination. Further testing is driven by the patient's associated symptoms and the region's most frequent etiologic factors, but workup generally includes a complete blood count (CBC) with differential, complete metabolic panel, antistreptolysin O titer (at the time of diagnosis and again 2–4 weeks later), throat culture, tuberculin skin test, pregnancy test in women, and chest radiograph. However, the etiology of EN remains unidentifiable in 32–72% of patients [4–7, 14]. Additional studies, such as a colonoscopy, are considered on a case-by-case basis.

Skin biopsies are generally reserved for persistent or refractory cases of EN, or for atypical cases in which mimickers of EN are suspected as reviewed above. In these cases, a deep incisional biopsy is preferred over a punch biopsy, to ensure adequate sampling of the subcutaneous fat. Depending on the clinical suspicion, tissue should be sent for culture, special stains, immunohistochemistry, and/or T-cell receptor gene rearrangement studies. Biopsy is not generally recommended in straightforward cases, particularly because the morbidity associated with a deep incisional biopsy on the lower leg, which may take months to heal and will certainly scar, may exceed the morbidity from EN itself, which typically heals within weeks without atrophy or scarring.

Principles of Management

Therapy in EN is supportive and directed at the underlying cause, as the skin lesions themselves are typically self-limited and resolve without scar-

ring. In patients with idiopathic EN or those desiring treatment for symptomatic relief, several medical therapies may be considered. A prospective study of 100 patients with EN found that bed rest and non-steroidal anti-inflammatory drugs (NSAIDs) resulted in clinical improvement in 95% of patients (93/98), generally within 7 days. Among the five patients who were NSAID-resistant, oral potassium iodide was used with similar efficacy [8]. For resistant or recurrent disease, colchicine as well as oral dapsone have been reported [21].

Management of pregnant patients with EN should be done in conjunction with the patient's obstetrician, particularly because NSAIDs and potassium iodide are relatively contraindicated in pregnancy [22]. In addition, any patient being managed with potassium iodide should have close monitoring of thyroid function, as thyroid abnormalities may develop with this therapy. The use of systemic corticosteroids is generally not necessary, and a risk-benefit analysis prior to considering corticosteroid use should include the possibility of an underlying infectious cause.

In addition to symptom management, if the underlying cause of EN can be identified, it should be treated. For the treatment of EN related to Behçet disease, two double-blinded trials found that colchicine was superior to placebo [23, 24]. Expert clinical opinion and one case report support the use of infliximab for IBD-related EN, with lesions improving soon after the first infusion and nearly resolving after the second to third dose [25, 26]. In cases of drug-induced EN, the offending medication should be discontinued.

An important exception to the need to treat the underlying cause is streptococcal-associated EN: in patients with evidence of an antecedent streptococcal infection, but without streptococcal-related symptoms, treatment with antibiotics may not be necessary. In such cases, EN is indicative of an immune response, not active infection, and many cases have been reported to resolve without antibiotic use [5].

Lastly, patients should be provided with anticipatory guidance regarding the risk of recurrence, which is more likely in idiopathic EN within the first year of onset [5, 8].

Erythema Induratum/Nodular Vasculitis

Key Summary Capsule Bullets

- Lobular or mixed (septal and lobular) panniculitis; thus, may ulcerate, drain, and scar
- Presents with crops of erythematous, tender, subcutaneous nodules and/or plaques on bilateral calves
- Associated with *Mycobacterium tuberculosis* infection (EI) or other systemic conditions, medications, or idiopathic etiology (NV)
- Differentiated from EN by typical location on bilateral calves, rather than pretibial surfaces, and potential for permanent sequelae

Classification

EI, or NV, is a lobular panniculitis that predominantly affects women and most often occurs on the lower extremities, although involvement of other body surfaces areas may be seen. When lesions occur in association with a *Mycobacterium tuberculosis* infection, the term EI is applied. Otherwise, the term NV is used.

Clinical Features

Clinically, EI/NV resembles EN in several ways: both conditions predominate in women of childbearing age, manifest as crops of tender, erythematous, subcutaneous nodules and/or plaques, predominantly involving the legs, and may be idiopathic or precipitated by systemic conditions or medications. However, there are several important ways the two conditions can be distinguished. First, in contrast to EN, which typically affects the pretibial surfaces, EI/NV generally affects the calves (see Fig. 10.3). Moreover, EI/NV is characterized by a lobular or mixed panniculitis and vasculitis, whereas EN is a predominantly septal panniculitis without vasculitis. Only EI/NV has a substantial lobular component and, thus, the potential to ulcerate, drain, and scar [27].

Although vasculitis (chiefly of small lobular venules) is found in most cases of EI/NV, its requirement for the histopathologic diagnosis is controversial [28].

Principles of Management

Treatment of EI centers on antimicrobial treatment of the underlying tuberculosis infection. Treatment of NV is similar to that of EN, primarily consisting of bed rest, NSAIDs, or potassium iodide. Systemic corticosteroids or Mycophenolate mofetil (MMF) may be used in severe cases [27].

Lupus Erythematosus Panniculitis

Key Summary Capsule Bullets

- Uncommon subtype of chronic cutaneous lupus erythematosus (LE)
- Presents with tender, erythematous, subcutaneous nodules and/or plaques on fatty areas of face (especially cheeks), proximal limbs, and trunk (including unilateral breast involvement)
- More often associated with DLE (33–67% of patients, "lupus profundus") than SLE (10–41%)
- Lobular panniculitis; thus, may scar, ulcerate, and develop calcinosis
- Antimalarials and photoprotection are considered first-line therapy

Classification and Epidemiology

LEP, or lupus panniculitis, represents 2–3% of all cases of cutaneous lupus [29]. It is classified as a type of chronic cutaneous lupus, a category that also includes discoid lupus erythematosus (DLE) [30]. When LEP has overlying clinical and/or histologic features of DLE, the term lupus profundus is used.

Like lupus erythematosus (LE) in general, LEP is more common in women, with the largest case series reporting a female-to-male ratio of 4:1 to 4.5:1 [31, 32]. The disease may occur at any age, but patients tend to be in their late 30s or early 40s [31, 32].

Pathogenesis

The basis of LEP is poorly understood, but it is believed to mirror that of other forms of cutaneous lupus. One case series suggests a role for plasmacytoid dendritic cells, which produce type 1 interferons that can recruit CXCR3+ cytotoxic T cells to the subcutaneous fat [33]. In addition, the finding of partial C4 deficiency in one patient with LEP suggests that decreased opsonization of immune complexes may be an underlying mechanism [34]. Although the pathogenesis is unclear, trauma has also been reported to trigger the onset of lupus panniculitis [35].

Clinical Features

The tender, erythematous subcutaneous nodules and/or plaques of LEP favor fatty areas of the face (especially the cheeks), proximal limbs, and trunk. When LEP affects the breasts (usually unilaterally), the term lupus mastitis (LM) is applied. Involvement of the distal legs is unusual and should prompt consideration of other panniculitides. Lesions may arise at one or multiple sites. About one-third of patients have clinically evident DLE overlying their LEP; in these cases, the term lupus profundus is applied [32].

Because LEP is a predominantly lobular panniculitis, without treatment, the fat lobules are destroyed, and patients develop permanent atrophic contour change that is often disfiguring (see Fig. 10.1). Ulcerations and calcinosis may also occur in longstanding lesions and can be detected mammographically in patients with LM [31, 32], often mimicking breast malignancy.

Most patients with LEP (59–90%, depending on the series) do not have systemic lupus erythemato-

sus (SLE) [31, 32]. In the remaining minority, the two conditions either develop simultaneously or LEP develops after the onset of SLE, typically when the systemic disease is quiescent. Rarely, LEP precedes the diagnosis of SLE by several years [31]. When patients with LEP have SLE, manifestations of SLE tend to be relatively non-severe, with involvement mainly of the skin (photosensitivity, discoid lupus, malar rash) and joints (arthritis) [36].

There is some evidence that the LM subset of LEP may be more strongly associated with systemic lupus. One review of 31 patients with LM found that the majority had a preceding diagnosis of SLE (59% of patients) or DLE (23%), although reporting bias may be responsible for this association [37].

Lupus panniculitis has also been described in the setting of other autoimmune conditions, including SSc, dermatomyositis, Sjögren syndrome, mixed connective tissue disease, Hashimoto's thyroiditis, *autoimmune hemolytic anemia*, and immune thrombocytopenia [31, 32]. The clinical features of LEP do not appear to differ between patients with and without systemic disease [31].

Histopathologic findings of LEP include a primarily lobular panniculitis, mucin between fat lobules, hyaline fact necrosis, lymphoid follicles with germinal centers (rarely seen in other panniculitides), nuclear dust, and calcification [38]. Approximately 67% of patients have histopathologic features of overlying DLE, including epidermal atrophy, a dermal lymphocytic infiltrate, follicular plugging, a thickened basement membrane, and dermal mucin [31, 39]. Direct immunofluorescence tends to be positive at the dermal-epidermal junction and within dermal blood vessel walls, regardless of whether patients also have systemic lupus [31].

Diagnostic Considerations

The differential diagnosis of LEP includes other lobular panniculitides, most importantly infectious panniculitis, dermatomyositis-associated panniculitis (DAP), and SPTCL. These conditions may be clinically indistinguishable from lupus panniculitis; therefore, clinicopathologic correlation is required for diagnosis. Whereas the subcutaneous infiltrate of LEP is predominantly lobular and lymphocytic, the infiltrate seen in infectious panniculitis is more evenly mixed (both septal and lobular) and mainly neutrophilic [20]. Lupus panniculitis and DAP are histologically identical in many cases, but the former is favored when overlying features of DLE are present. In addition, histology featuring lymphoid follicles with germinal centers and hyaline necrosis of lobules is fairly characteristic of lupus panniculitis [40].

SPTCL is the most challenging entity to distinguish from lupus panniculitis. Clinically speaking, SPTCL is favored in the setting of systemic B symptoms (fever, chills, night sweats, and/or weight loss), as LEP only uncommonly manifests as part of an SLE flare; however, up to 50% of patients with SPTCL lack constitutional symptoms [40]. A history of SLE or even DLE is not necessarily evidence in favor of the diagnosis of LEP over SPTCL: about 19% of patients with SPTCL have an associated autoimmune disease, most commonly SLE [41], and also including DLE [42, 43].

Lupus panniculitis and SPTCL may also overlap histologically, with some cases of LEP featuring atypical lymphocytes rimming adipocytes (once considered typical of SPTCL [38]) and some cases of SPTCL demonstrating a vacuolar interface dermatitis and dermal mucin [44]. Histologically, the findings most specific for LEP are a positive lupus band test, lymphoid follicles with reactive germinal centers (which have never been observed in SPTCL [38]), relative lack of CD8+ T cells, polyclonal T-cell receptor gene rearrangement (in contrast to the monoclonal population in SPTCL), and the presence of plasma cells [38]. In addition to such histologic findings, an elevated ferritin level may favor the diagnosis of SPTCL over lupus panniculitis.

Given this potential for clinical and histologic overlap, SPTCL should be considered in patients who present atypically with LEP or do not respond to traditional LEP therapies [44]. In such cases, repeated, deep incisional biopsies may be

necessary to establish the diagnosis of SPTCL. Biopsies that do not include an adequate sample of the subcutaneous fat may be misrepresentative and prolong time to accurate diagnosis.

For LM specifically, the differential diagnosis includes breast malignancy, chronic granulomatous mastitis (CGM), and diabetic mastopathy. As is the case in breast malignancy, the overlying skin in LM may be erythematous, dimpled, indurated, and/or ulcerated. There can be nipple retraction and discharge [45, 46], as well as significant breast atrophy and disfigurement [47, 48]. LM may also mimic malignancy radiologically, as over half of mammograms in LM show either calcifications alone or an irregular, ill-defined mass with or without calcifications [37]. However, unlike in breast cancer, where surgical excision is a mainstay of therapy, in LM, there is a theoretical risk of disease activation with trauma, and LM should not be excised. Biopsy for accurate diagnosis is therefore essential.

CGM is an idiopathic, chronic inflammatory condition that often presents with tender, erythematous nodules on the breast that may ulcerate and drain; thus, it may mimic both LM and breast malignancy. However, unlike LM or breast malignancy, CGM features noncaseating granulomas histologically. Diabetic mastopathy is a rare condition that may mimic LM but typically occurs in patients with longstanding type 1 diabetes mellitus. Histopathologically, diabetic mastopathy demonstrates a circumscribed, lymphocytic, lobular, periductal, or perivascular infiltrate, whereas the lymphocytic infiltrate of LM is less circumscribed and mainly lobular. An additional differentiating feature is that, unlike LM, diabetic mastopathy features dense fibrosis and epithelioid fibroblasts [37, 49, 50].

Disease and Comorbidity Assessment

Unlike in EN, a skin biopsy is often required to diagnose LEP, especially when certain clinical clues, such as overlying DLE, are absent. A deep incisional biopsy is preferred over a punch biopsy in order to ensure adequate sampling of the subcutaneous fat. Depending on the clinical suspicion, tissue should be sent for culture, special stains, immunohistochemistry, and T-cell receptor gene rearrangement studies to rule out infectious panniculitis and/or SPTCL.

Once LEP or lupus profundus is diagnosed, patients who have never undergone evaluation for SLE should do so, via a thorough review of systems, CBC with differential, urinalysis, and antinuclear antibodies. Additional autoimmune serologies may be sent on a case-by-case basis. Antinuclear antibodies are elevated in 65–95% of patients with LEP; the titer usually ranges from 1:40 to 1:80 in patients without systemic lupus and is greater in those with systemic disease [31, 32]. Patients without evidence of SLE at the time of diagnosis should be monitored clinically for the development of systemic disease.

Principles of Management

Lupus panniculitis is generally a chronic disease characterized by flares and remissions. One retrospective review of 40 patients found disease duration to be an average of 6 years; however, this range is broad (in the same review, 0–38 years), and relapses can continue to occur over decades [32]. Thus, patients often require a prolonged treatment course, especially given the potential for disfiguring scarring as a result of uncontrolled disease activity. The mainstays of treatment during the inflammatory phase are systemic agents, as topical therapies insufficiently penetrate the subcutaneous fat, while intralesional corticosteroid injections may result in atrophy that can be difficult to distinguish from the primary disease process.

Antimalarials are often considered first-line agents in LEP, with one series reporting improvement in 70% of patients [32]. Other therapeutic options include methotrexate (MTX) [51], thalidomide [34, 52, 53], dapsone [54], intravenous immunoglobulin (IVIG) [55], cyclosporine [56–58], and rituximab [59]. Methotrexate is often used as the next agent when antimalarials fail.

MMF, which is traditionally used in the treatment of lupus nephritis, has not been reported in the literature specifically as a treatment for LEP; anecdotally, however, it has been used successfuly. In addition, strict photoprotection should be recommended, especially in patients with coexistent DLE or SLE, although the exact role of ultraviolet radiation in triggering lupus panniculitis is unknown.

Importantly, medical therapies for LEP can halt progression but lack the ability to restore fat that has already been lost. The use of nonpermanent fillers, including hyaluronic acid and poly-L-lactic acid [60] as well as polymethylmethacrylate, a permanent dermal filler [61], has been reported for soft tissue augmentation and volume restoration in patients with quiescent lupus panniculitis. However, prior to considering filler therapy, it is imperative to ensure disease quiescence for a prolonged period, generally 1–2 years, in order to minimize the theoretical risk of reactivation by the filler. In one report, magnetic resonance imaging was used as an adjunctive tool to confirm the absence of subclinical disease activity [60].

Dermatomyositis-Associated Panniculitis

Key Summary Capsule Bullets

- Rare manifestation of DM
- Presents with tender, erythematous subcutaneous nodules and/or plaques often affecting buttocks, thighs, and arms
- Usually parallels classic features of DM; development prior to DM onset (less common) necessitates monitoring for DM
- Lobular panniculitis; thus, may scar, ulcerate, and develop calcinosis

Classification and Epidemiology

Panniculitis is generally regarded as a rare manifestation of classic [62], drug-induced [63], or amyopathic dermatomyositis (DM) [64–66], although some small studies have found clinical and/or histologic evidence of panniculitis in 9–20% of DM patients [67, 68].

Patients with DM who develop panniculitis are demographically similar to the broader cohort of all patients with dermatomyositis, with a male-to-female ratio of 1:2.4 and mean age of 36 years (range 2–80 years) [62].

Pathogenesis

The etiology of panniculitis in DM is unknown. It has been postulated that the cause is "spill-over" of inflammatory cells from muscle into adjacent fat [68]. Supporting this hypothesis is the observation that panniculitis often follows the same course as the muscular features of dermatomyositis [62]. However, the finding, in some patients, of clinical and/or histopathologic panniculitis without myositis suggests that additional or alternative mechanisms are involved [64–66, 68]. Furthermore, panniculitis can occur prior to, concomitant with, or after the onset of typical symptoms of dermatomyositis [62].

Clinical Features

The tender, erythematous subcutaneous nodules and/or plaques of DAP favor the buttocks, thighs, and arms, and compared with LEP, less commonly involve the trunk or face [62, 69]. In exceptional cases, the lesions may migrate [70] or vesiculate [64]. As in LEP and other lobular panniculitides, DAP has the potential to damage the fat lobules and result in ulceration; painful calcinosis causing functional impairment; and irreversible, disfiguring contour changes [71–73]. These sequelae have also been reported to arise insidiously when the preceding panniculitis is not clinically evident [69, 72].

Disease activity in DAP usually tracks in parallel with the classic cutaneous and/or muscular features of DM, manifesting either during a flare of previously diagnosed DM (in 50% of patients) or among the presenting signs of the disease (in 20%). Less frequently (29%), panniculitis occurs

as an isolated manifestation weeks to years before the diagnosis of dermatomyositis [62].

Histopathologically, DAP is characterized by a lymphoplasmacytic lobular infiltrate. Vacuolar interface dermatitis, dermal mucin, calcification, and vasculitis may be seen [62, 74, 75]. Calcinosis and membranocystic changes in an arabesque pattern [76] (believed to represent degenerated adipocyte or macrophage membranes) have been reported in association with treatment resistance [62].

Diagnostic Considerations

The differential diagnosis of DAP includes other lobular panniculitides including LEP, infection (including infectious panniculitis, cellulitis, and erysipelas), and SPTCL. Clinicopathologic correlation helps to distinguish DAP from LEP [77]. Infectious panniculitis and SPTCL, by contrast, may be clinically indistinguishable from DAP [78–80]. However, infectious panniculitis may be distinguished from DAP by positive cultures and special stains, as well as histologic features including neutrophilic panniculitis, vascular proliferation, and coagulation necrosis of vessels and sweat glands (as opposed to fibrinoid necrosis in dermatomyositis) [20, 62]. Unlike cellulitis or erysipelas, DAP is usually bilateral and multifocal.

In one reported case, a patient with subcutaneous fat loss on the face due to DAP developed paradoxical fat hypertrophy of her right arm. Although rare, this phenomenon may be worth considering in patients with DM who develop limb asymmetry, as, in the reported case, fat hypertrophy of one limb could be mistaken for muscle wasting of the contralateral extremity [69].

Disease and Comorbidity Assessment

The treatment of DAP often involves the initiation or escalation of immunosuppressive therapy; therefore, skin biopsies with tissue culture and special stains for microorganisms should be considered in the diagnostic workup. As with the other panniculitides, a deep incisional biopsy is preferred to ensure adequate sampling of the subcutaneous fat. T-cell receptor gene rearrangement studies may be performed on the initial biopsy if SPTCL is suspected, or future biopsies in patients who do not respond to standard therapies for DAP. Although a skin biopsy is the gold standard in the diagnosis of DAP, magnetic resonance imaging has been reported in one case to be an effective adjunct for both diagnosis and assessment of treatment response [81].

Although patients with DM who develop panniculitis were initially believed to be at lower risk for malignancy [82], there have been three reported cases of new or recurrent malignancy (rhabdomyosarcoma, rectal carcinoma, and ovarian adenocarcinoma) in patients with DM and panniculitis [75, 79, 83]. Thus, the same malignancy screening guidelines apply to all patients with DM regardless of whether panniculitis is present.

In patients with a lobular panniculitis in whom the underlying etiology is not identifiable, long-term monitoring for the development of a connective tissue disease such as DM is warranted, as panniculitis has been reported to precede the diagnosis of DM by 2 years [62].

Principles of Management

DAP does not resolve spontaneously [62] and typically results in lipoatrophy, which can be severely disfiguring. Ulceration and calcinosis, which may be painful, can also occur [71–73]. Thus, early and aggressive treatment during the inflammatory stage of the disease is essential. Fortunately, the largest review of 24 patients with DAP found that the disease is generally responsive to the initiation or escalation of immunosuppressive treatment for the underlying DM, most often with systemic corticosteroids (prednisone or pulse methylprednisolone) [62].

Although antimalarials are often considered first-line for cutaneous dermatomyositis, these medications are insufficient to control cutaneous

disease in the majority of patients, and the limited reports evaluating their efficacy in DAP showed mixed results. In addition to antimalarials, MTX, azathioprine (AZA), and/or thalidomide have been used successfully in conjunction with systemic corticosteroids in DAP [67, 74, 82, 84], and although not reported specifically for DAP, MMF may be effective for cutaneous dermatomyositis. MTX [75] and cyclosporine [74, 82] have also been reported as effective corticosteroid-sparing treatments for this condition.

IVIG has been found to be effective for both the cutaneous [85] and muscular manifestations [86] of recalcitrant DM; similarly, patients with DAP refractory to systemic therapies, including systemic corticosteroids, MTX, and AZA, have improved dramatically with IVIG [87, 88]. MTX, MMF, and IVIG are often considered preferred therapies for cutaneous DM, and they may be used with or without systemic corticosteroids for DM-associated panniculitis.

In addition to the above therapies, photoprotection is recommended for patients with DAP, as DM is a photo-exacerbated condition, and DAP usually flares in parallel with the disease's classic manifestations. Treatment of panniculitis in drug-induced dermatomyositis involves withdrawal of the causative agent [63]. In patients with associated malignancy, therapeutic decisions should be made in collaboration with the patient's oncologist.

Volume restoration with inert dermal fillers has not been reported specifically in DAP but has been performed successfully in LEP [60] and may be considered after a period of clinical remission (at least 1 year) to minimize the risk of filler-induced disease reactivation.

Panniculitis of Sclerosing Disorders

Key Summary Capsule Bullets

- Rare manifestation of morphea and SSc
- In morphea, presents with indurated sclerotic plaques due to principal subcutaneous involvement or subcutaneous extension
- First-line treatment in morphea subtype includes MTX and ultraviolet A1 phototherapy
- In SSc, panniculitis is rare; typically presents as well-circumscribed, indurated, painful, hyperpigmented plaques on pretibial area
- May be related to venous hypertension and signify impending pulmonary hypertension in SSc

Classification

Morphea and systemic sclerosis (SSc, or scleroderma) are two fibrosing connective tissue disorders in which inflammation of the subcutaneous fat can occur. Although the term localized scleroderma has been applied to describe morphea, it is important to differentiate this condition from SSc, because in morphea the fibrosis is generally limited to the dermis and subcutaneous tissue, but in SSc it can involve both the skin and the connective tissue of internal organs. Thus, systemic involvement is typical in SSc, whereas in morphea, internal organ manifestations are generally absent. In both disorders, panniculitis can occur but is a rare manifestation.

Clinical Features

While classification schemes in morphea are controversial, a deep variant, known as morphea profunda, is widely recognized, involving at least the subcutaneous fat and potentially extending to muscle and bone. Patients present with bound-down, sclerotic plaques that are better felt than seen, and may be localized or generalized (see Fig. 10.4).

Histopathologically, morphea profunda is characterized by thickened, hyalinized collagen in the deep dermis and subcutaneous septae, as well as a perivascular and interstitial lymphocyte-predominant infiltrate. The presence of mucin has also been reported [89]. In addition to morphea profunda, subcutaneous extension may occur in other types of morphea, such as deep circumscribed morphea, pansclerotic morphea, generalized morphea, and linear morphea.

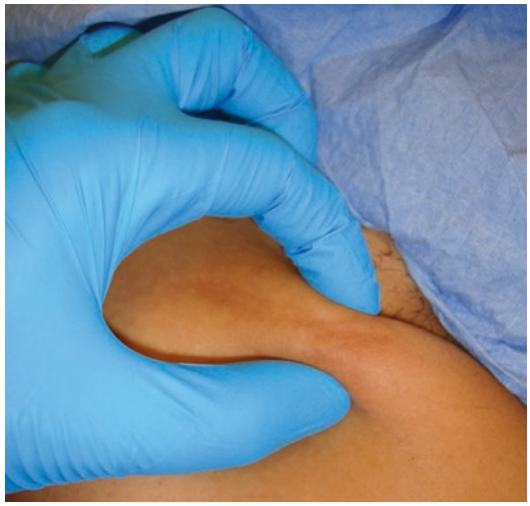

Fig. 10.4 Morphea profunda: indurated, sclerotic, hyperpigmented plauqe on the anterior thigh

Panniculitis rarely occurs in patients with SSc, but in patients who develop this complication, the typical presentation is well-circumscribed, indurated, painful, hyperpigmented plaques on the pretibial area [90]. Involvement of the arm, lateral thighs, gluteal region, and abdomen has also been described [91, 92]. The histopathology of these lesions is significant for a mixed septal-lobular panniculitis. The lobular features range from mild lipophagic fat necrosis to extensive lipomembranous change, characterized by membranous fat necrosis and resultant fat microcysts with luminal projections [91, 92].

Importantly, unlike LEP and DAP, panniculitis related to SSc has not been reported to develop in the absence of other manifestations of the disease. One retrospective study of 128 patients with diffuse or limited cutaneous SSc found that 10 (8%) had panniculitis. Significantly, the patients with panniculitis were more likely to have pulmonary hypertension as well as ventilation/perfusion lung scan defects, suggesting that pulmonary infarction was the major cause of pulmonary hypertension. Given the clinicopathologic overlap between these patients' SSc-associated panniculitis and LDS, a type of panniculitis associated with chronic venous insufficiency, the authors hypothesized that venous hypertension of the legs was responsible for both the panniculitis and (as a result of venous thrombosis and pulmonary infarction) the pulmonary hypertension [90]. Whether panniculitis truly presages pulmonary hypertension in SSc remains to be elucidated.

Principles of Management

Aggressive therapy is often necessary for morphea extending to the fat, as morphea is a fibrosing condition with the potential for permanent, irreversible sequelae, including joint contractures and limb-length discrepancies. First-line therapies for deep morphea include ultraviolet A1 phototherapy and MTX, in combination with systemic corticosteroids if progression is rapid or if the skin overlying a joint is involved [93, 94]. MMF [95], cyclosporine [96–99], extracorporeal photopheresis [1, 100, 101], abatacept [102], bosentan [103], and anti-thymocyte globulin [104] have also been reported with success. Although volume restoration with inert dermal fillers has not been reported in morphea profunda, it has been used successfully to re-contour the sequelae of linear morphea [105]. As with other autoimmune diseases, filler therapy should only be considered once disease is quiescent.

Treatment of panniculitis in SSc is likely to mirror that of the disorder's classic cutaneous manifestations, as the former has never been reported to occur in the absence of the latter.

Pyoderma Gangrenosum

Key Summary Capsule Bullets

- Four clinical variants: ulcerative/classic, bullous/atypical, pustular, vegetative
- Morphology, location, and disease associations differ with each variant
- Diagnosis of exclusion with no pathognomonic features and several disease mimickers
- Benefits of skin biopsy outweigh risk of biopsy-induced pathergy
- Ideal biopsy is elliptical incision that includes both lesion edge and ulcer base

- Treatment includes wound care measures, pain control, and topical and/or systemic therapy

Classification and Epidemiology

PG is an inflammatory skin condition that is associated with systemic disease—most often IBD, arthritis (usually seronegative monoarticular arthritis), or a hematologic disorder—in a reported 52–67% of cases [106, 107]. Alternatively, PG may occur as part of the rare genetic condition PAPA (pyogenic arthritis, PG, and acne) syndrome. In addition, rare familial cases not associated with PAPA syndrome have been reported [108]. Despite its name, PG is neither infectious nor gangrenous. Rather, PG is considered a neutrophilic dermatosis, due to the dense neutrophilic infiltrate that is characteristically seen on histology.

PG is rare. According to the only population-based PG study, the estimated incidence is six cases per million people per year [109]. Although PG is frequently associated with IBD, the prevalence of PG in IBD patients is low, ranging in the literature from 0.5% to 5% [110]. PG is slightly more common in women and peaks between the second and sixth decades of life, although any age group, including children, may be affected [106, 107, 109, 111].

Pathogenesis

The pathogenic basis of PG is uncertain, but an aberrant immune response mediated by neutrophils and T-cells directed against an unknown self-antigen is thought to be responsible [112].

Evidence for the role of neutrophils is derived from case reports that describe abnormal neutrophil chemotaxis in PG [113]; overexpression [114–116] and induction [115] of the neutrophil chemokine interleukin-8 (IL-8) in PG lesions; and correlation of improvement of PG with a reduction in serum IL-8 [114, 116, 117]. In addition, TNF-α and IL-1 have been implicated in PG pathogenesis, and both induce IL-8 expression [118, 119]. Notably, TNF-α inhibitors such as infliximab and the IL-1 inhibitors anakinra and gevokizumab (currently in phase III clinical trials for PG) have been successfully reported in the treatment of PG [120, 121] and PAPA syndrome [122].

The role of aberrant T-cells in PG pathogenesis is supported by the presence of expanded T-cell clones in PG lesions and in the peripheral blood of patients with PG [123]. In addition, the well-documented response of PG to cyclosporine, a suppressor of Th cells, supports the role of T-cells in PG pathogenesis [124]. Recent reports of PG responsive to the IL-23 inhibitor ustekinumab also implicate T-cells in PG pathogenesis, as IL-23 is essential for the differentiation of Th17 cells [125–128].

In PAPA syndrome, the *PSTPIP1*/*CD2BP1* gene on chromosome 15q, which encodes proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1, also known as CD2 antigen-binding protein 1), is mutated, and this mutation is thought to promote inflammation. No genetic mutation has been identified in the rare cases of familial PG distinct from PAPA syndrome [108].

Clinical Features

PG has four clinically distinct variants with different prevalence, morphology, location, and systemic disease associations. Ulcerative (classic) PG is the most common variant, while the bullous (atypical), pustular, and vegetative variants are less frequently encountered. In all variants other than vegetative PG, rapid progression is typical, and pain is often out of proportion to what may be expected based upon physical examination. Disease in any one individual is typically limited to only one variant. PG may follow an acute, relapsing, or chronic course, with relapsing or chronic being more likely when PG is associated with systemic disease.

Ulcerative PG generally begins as one or multiple severely painful pustules or nodules on the lower extremities, especially the pretibial region.

Over the course of days, the lesions ulcerate centrally and expand peripherally (see Fig. 10.5). The resulting ulcer features a typically violaceous, undermined border, which is a characteristic feature and a sign of disease activity (see Fig. 10.6). Clinically, the undermined border appears as PG expands centrifugally, presenting as erosion underneath a border of necrotic skin. The ulcer base often appears purulent and/or necrotic. When ulceration extends through the subcutaneous fat and muscular fascia, underlying structures, such as tendons and ligaments, may be exposed. Lesions typically express an exudate, which may be purulent, hemorrhagic, and/or malodorous. Healing results in a typical pattern of cribriform scarring (see Fig. 10.7), which may serve as a diagnostic clue in patients with undiagnosed recurrent PG or with multiple lesions in various stages of development.

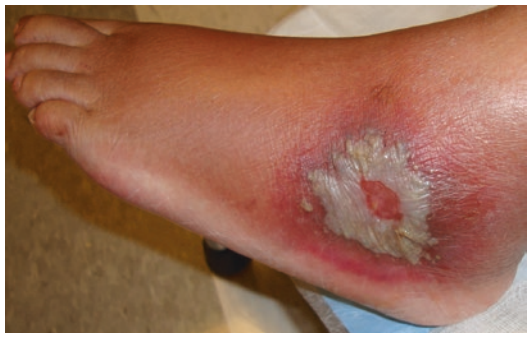

Fig. 10.5 Ulcerative pyoderma gangrenosum (PG): hemorrhagic pustule that ulcerated centrally and developed a violaceous, undermined border over the course of days

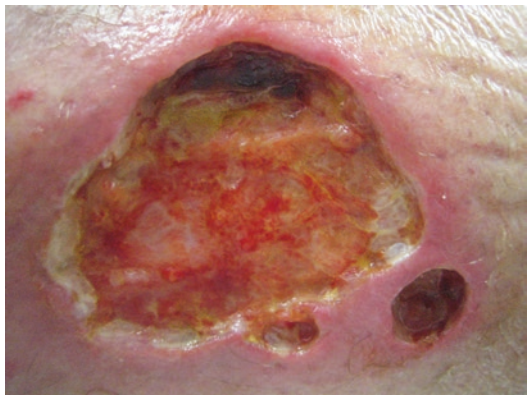

Fig. 10.6 Ulcerative PG: central ulcer surrounded by an undermined border with a violaceous to erythematous rim

Although the pretibial region is the most commonly involved site in ulcerative PG, any skin surface may be affected. For example, peristomal PG is often seen in patients with an underlying IBD. In rare cases, PG of the genitals may occur; this presentation may be more common in newborns [129].

Ulcerative PG is associated with systemic disease in the majority of patients: IBD (ulcerative colitis or Crohn disease, 27–36% of patients), arthritis (usually seronegative, non-erosive arthritis of a large joint, 19–37%), or a hematologic disorder (most often IgA monoclonal gammopathy, 11%) [106, 107]. Rarely, PG has been associated with solid organ malignancies, and this possibility should be considered in patients with a history of malignancy or with PG of unknown etiology [130]. In cases in which no underlying disorder is identified, the presence of leukocyte adhesion deficiency-1, an autosomal recessive disorder characterized by recurrent bacterial infections, persistent neutrophilia, and poor wound healing, should be considered, as this disorder has been associated with PG-like lesions in several cases [131].

Bullous PG typically manifests as painful, blue-grey, hemorrhagic vesicles on the face and upper extremities, especially the dorsal hands.

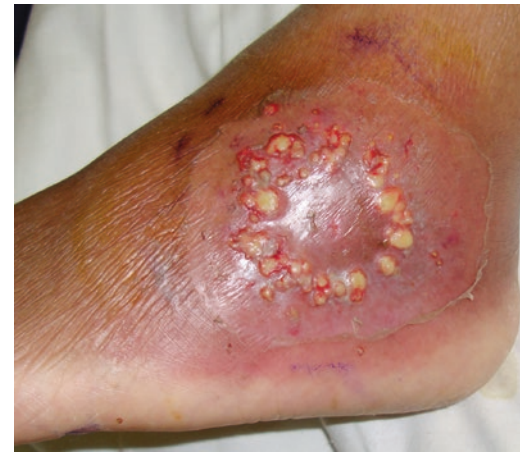

Fig. 10.7 Uulcerative PG: healing of an ulcer in a cribriform pattern with loss of the undermined border

The vesicles expand rapidly and centrifugally into bullae and then rupture, leaving behind deep erosions or superficial ulcers that may lack the undermined border of ulcerative PG. Bullous PG is more likely to be associated with a hematologic disorder (66% of patients) than with IBD (11%) or arthritis (3–18%) [106, 132]. The most common hematologic disorder associated with bullous PG is acute myelogenous leukemia (AML), followed by chronic myelogenous leukemia, and less frequently, MDS, multiple myeloma, and myeloid metaplasia [132]. The development of bullous PG may coincide with transformation of the underlying hematologic disorder (e.g., MDS into AML) [132]. Furthermore, the development of bullous PG in patients with AML portends a poor prognosis; therefore, swift recognition of a potential underlying hematologic disorder in patients with bullous PG is imperative.

Vegetative PG (also referred to as superficial granulomatous pyoderma) is characterized by a superficial and sometimes verrucous ulcer, plaque, or nodule. Unlike ulcerative PG, vegetative PG develops slowly and is typically painless. According to the largest review of vegetative PG, including 46 patients, the lesion favors the trunk in 52% of cases, the extremities in 31%, and the head or groin in the minority. Compared with other variants, vegetative PG is less aggressive and lacks a clear association with systemic disease [133].

In pustular PG, painful pustules surrounded by erythema are symmetrically distributed on the extensor surfaces of the lower extremities and upper trunk. Pustular PG occurs almost exclusively in association with IBD, often during flares; thus, concomitant fever, arthralgias, and myalgias are common. Pyostomatitis vegetans, which presents with oropharyngeal pustules and snail track-like erosions, is generally considered a mucosal variant of pustular PG.

Rarely, patients with PG develop sterile neutrophilic infiltrates in the lungs (the most common extramucocutaneous site), heart, muscles, bones, central nervous system, spleen, liver, lymph nodes, gastrointestinal tract, or cornea [134].

The potential for pathergy, or the development or worsening of lesions in areas of skin trauma, should be considered in all patients with PG. However, while pathergy has long been considered a key trigger of PG, one of the largest retrospective cohort studies on PG, including 103 patients, found a pathergic response was present in only 31% of patients [111]. These findings have important implications in the management of patients with PG. For example, while gentle wound care and avoidance of aggressive debridement is essential to prevent a pathergic response, the potential for pathergy should not hinder the use of biopsy in establishing proper diagnosis.

The presence of a leukemoid reaction may be seen in patients with PG, as has been reported in two cases [135]. In such cases, patients may be febrile, and the white blood cell count is highly elevated (>50,000/μL), sometimes with neutrophil precursors present in the serum. Exclusion of infectious etiologies in such cases is imperative.

There are no pathognomonic features of PG seen histologically. Typically, a heavy neutrophilic infiltrate is expected; however, one retrospective review of 103 patients with PG found that only 8 of 67 histopathology reports documented "typical neutrophilic infiltrate and early abscess formation" [111], and therefore the lack of this finding on histopathology could not be used to exclude the diagnosis of PG.

Histopathologic findings in PG also differ depending upon the area of the lesion sampled. For example, the base of the ulcer will typically demonstrate an intradermal abscess (collections of neutrophils), while the undermined border classically features early abscess formation and a mixed neutrophilic and lymphocytic infiltrate, and the erythematous rim may demonstrate lymphocytic vasculitis [136].

Additional features can differ depending upon PG subtype. For example, subcorneal neutrophils are often seen in ulcerative and pustular PG, and subepidermal bullae in bullous PG, whereas in vegetative PG, pseudoepitheliomatous hyperplasia, sinus tracts, and "three-layered granulomas" (made of an inner layer of neutrophilic abscesses,

middle layer of histiocytes and giant cells, and outer layer of plasma cells and eosinophils) can be seen [133].

Histopathology may also differ based on the underlying systemic association; for example, in the setting of hematologic malignancy, atypical lymphocytes may be present. Despite the highly variable findings on histopathology of PG, skin biopsy is essential for excluding mimicking conditions, and for this reason should be considered in all patients.

Diagnostic Considerations

Pathognomonic clinical, laboratory, or histologic features of PG are lacking. As such, PG is considered a diagnosis of exclusion, requiring the presence of consistent clinical features as well as the elimination of several disease mimickers as possibilities (see Table 10.3). Consideration of skin biopsy evaluated with infectious stains, as well as tissue culture for bacteria, mycobacteria, and fungus, is important in establishing the diagnosis of PG, especially given that treatment for PG is often immunosuppressive in nature, and, thus, likely to exacerbate any infectious etiology.

One retrospective cohort study and literature review from a tertiary referral center emphasized the need to exclude alternative diagnoses in patients with potential PG [137]. In this study, 64 of 95 patients (67%) with ulcerations resembling PG received PG-directed therapy prior to the establishment of a correct, alternative diagnosis. Of these patients, 23% were refractory to PG-directed therapy, 12% experienced an exacerbation of the underlying condition, and 23% had a further delay in proper diagnosis. Ultimate diagnoses were delayed on average by 10 months, and misdiagnoses included malignancies, vasculopathies, vasculitis, infectious etiologies, and drug-induced or exogenous tissue injury [137]. These findings underscore the importance of careful exclusion of alternative etiologies to prevent unnecessary morbidity and mortality in patients with suspected PG. For example, correct diagnosis of PG in a patient with a suspected infectious etiology may prevent unnecessary wound debridement that has the potential to exacerbate PG. Alternatively, correct diagnosis of an infectious etiology mimicking PG may protect a patient from undergoing immunosuppressive therapy that may worsen the underlying infection.

Given the importance of considering all etiologies, exclusion of alternative diagnoses is considered one of the two major diagnostic criteria for PG that have been proposed [138] and adapted [134], though not validated. According to these guidelines, two major and two minor criteria are required for a diagnosis of PG (see Table 10.4).

Table 10.3 Differential diagnosis of pyoderma gangrenosum (PG)

Vasculopathy (e.g. antiphospholipid antibody syndrome, venous stasis ulcer, livedoid vasculopathy)
Vasculitis (e.g. granulomatosis with polyangiitis, polyarteritis nodosa, cryoglobulinemic vasculitis)
Neuropathic etiologies (e.g. diabetic ulcer, Charcot-Marie-Tooth disease)
Malignancy (e.g. basal cell carcinoma, squamous cell carcinoma, cutaneous T-cell lymphoma, leukemia cutis)
Infection (e.g. bacterial, myocobacterial, fungal)
Other neutrophilic dermatoses (e.g. Sweet syndrome)
Metastatic Crohn disease
Exogenous tissue injury (e.g. arthropod/spider bites, factitious dermatitis)

Disease and Comorbidity Assessment

In the assessment of suspected PG, two primary objectives are most relevant: (1) the exclusion of disease mimickers, and (2) the determination of whether an underlying systemic disease is present. To this end, a complete history and physical examination should be performed with an emphasis on symptoms and signs suggestive of gastrointestinal, rheumatologic, hematologic, and vascular disorders.

In addition, as reviewed, a skin biopsy is essential for ruling out mimickers of PG. Given the relative infrequency of pathergy among PG patients [111], as well as the morbidity and mortality associated with misdiagnosis and mistreatment [137], most experts concur that the benefits

Table 10.4 Diagnostic criteria for PG [135]

Major criteria
1. Rapid[a] progression of a painful[b] necrolytic cutaneous ulcer[c] with an irregular, violaceous, and undermined border
2. Exclusion of other causes of cutaneous ulceration
Minor criteria
1. History suggestive of pathergy[d] or clinical finding of cribriform scarring
2. Systemic diseases associated with PG[e]
3. Histopathologic findings (sterile dermal neutrophilia ± mixed inflammation ± lymphocytic vasculitis)
4. Treatment response (rapid response to systemic glucocorticoid treatment)[f]

[a]Characteristic margin expansion of 1–2 cm/d, or a 50% increase in ulcer size within 1 month
[b]Pain is usually out of proportion to the size of the ulceration
[c]Typically preceded by a papule, pustule, or bulla
[d]Ulcer development at sites of minor cutaneous injury
[e]Inflammatory bowel disease, polyarthritis, myelocytic leukemia, or preleukemia
[f]Generally responds to a dosage of 1–2 mg/kg/d, with a 50% decrease in size within 1 month

of a skin biopsy outweigh the risk of biopsy-induced pathergy.

An elliptical incision with adequate subcutaneous fat sampling is ideal for histopathologic analysis in PG. However, in some cases, particularly in superficial lesions, a punch biopsy may provide adequate depth for analysis, and this technique further minimizes the relatively low risk of pathergy. In cases in which an elliptical incision cannot be performed but sampling of a deeper lesion is required, the "double-punch" technique may be utilized. In this technique, a second punch biopsy is performed within the ulcer created by the first punch biopsy in order to obtain a deeper sample. All biopsies should aim to include sampling of both the edge of the lesion as well as of the ulcer base, if an ulcer is present. In general, in addition to the sample sent for routine hematoxylin and eosin (H&E) analysis, a second biopsy should also be performed and sent for bacterial, mycobacterial, and fungal cultures. In addition, stains infectious etiologies should be requested on the sample sent for H&E. It is ideal for biopsies to be interpreted by a dermatopathologist, as histopathologic analysis can be challenging given the lack of pathognomonic features for PG and the need to exclude the many disease mimickers, as reviewed above.

Although no guidelines for a formal workup in PG exist, experts concur that a search for an underlying condition and testing to exclude alternative diagnoses are warranted. A thorough history, review of systems, and physical examination are essential and help to guide further workup. Among other entities, eliciting signs or symptoms of an underlying IBD or hematologic disorder is important, given that these conditions occur commonly in patients with PG.

Particular attention should also be given to the musculoskeletal system, as up to 37% of patients with PG have arthritis. Most commonly, as reviewed, arthritis in PG manifests as a seronegative, non-erosive arthritis of a large joint (knee, ankle, or elbow). However, RA, ankylosing spondylitis, and osteoarthritis have been reported as well [106, 107, 132]. Of note, the severity of the arthritis does not usually correlate with the severity of PG [138].

Workup generally includes, at minimum, a CBC with differential, complete metabolic panel, and urinalysis. Fecal occult blood test, sigmoidoscopy, or colonoscopy is often useful, particularly in patients with gastrointestinal symptoms or with ulcerative or pustular PG. A peripheral blood smear, serum and urine immunofixation and electrophoresis, and/or bone marrow aspirate or biopsy should also be considered, especially in patients with constitutional symptoms or abnormalities on CBC, or those with the bullous subtype of PG. Hepatitis B and C panels may also be useful, particularly in high-risk populations, and serologic and/or radiographic examination may be helpful in patients with an accompanying arthritis.

Depending upon an individual patient's comorbidities and disease manifestations, additional workup to rule out alternative diagnoses may include: antinuclear antibody, antineutrophilic cytoplasmic antibodies, hypercoagulability studies (especially antiphospholipid antibody), rheumatoid factor, cryoglobulins, HIV testing, rapid plasma reagin, and a chest radiograph. In

addition, a Doppler ultrasound may help identify an underlying vasculopathy, and X-ray or magnetic resonance imaging may help exclude underlying osteomyelitis.

If there is a systemic disease associated with PG, as there is in most cases, it may or may not parallel the course of the cutaneous disease (with the exception of pustular PG, which usually flares along with the underlying IBD). Systemic conditions often precede the development of PG; however, associated conditions may also develop after the onset of PG, and therefore, a high index of suspicion for an underlying condition should be maintained in the follow-up of all patients with PG.

Principles of Management

The primary goal in the management of PG is to promote wound healing through inhibition of the underlying aberrant immune reaction. Given the rarity of PG and the lack of validated outcome measures, evidence for treatment is mostly derived from small case series and case reports, and there is no gold standard therapy. Ideally, treatment should include wound care measures along with topical and/or systemic therapy. Goals of therapy are to promote wound healing, control pain, and control inflammation. The algorithm chosen for any given patient depends upon the severity of the PG (considering depth, size, number of lesions, and location) as well as the presence of an underlying systemic condition.

The major goal of wound care in PG is to prevent superinfection without provoking pathergy, as wound care itself appears to have little impact on re-epithelialization [124, 139]. As in the management of other wounds, the choice of dressing is directed by lesion characteristics. For example, absorbent dressings are recommended over occlusive dressings for exudative lesions or peristomal PG [139, 140]. Wet-to-dry dressings should be categorically avoided because the mechanical debridement that occurs during dressing changes may pathergize lesions. Barrier creams or ointments should be used to help prevent skin breakdown and infection at wound edges [140].

Pain control should be addressed as soon as the diagnosis of PG is established, especially given that PG is often refractory to treatment, requiring multiple therapeutic trials before an effective therapy can be found. NSAIDs can be helpful for pain, as can opiates when appropriate. In patients with persistent pain, consultation with a pain specialist may be helpful. As effective therapy is established, pain will begin to resolve, often prior to the appearance of substantial visible improvement.

Once the diagnosis of PG is established, topical treatment may be sufficient for superficial disease that lacks a systemic association, as is the case in vegetative PG [133]. Topical therapy is also helpful adjunctively in severe PG, particularly at the inflamed borders. Options include potent topical or intralesional corticosteroids, topical tacrolimus or pimecrolimus, topical cyclosporine (ophthalmic preparation), and topical dapsone (an anti-neutrophilic agent). Topical tacrolimus was somewhat more effective than clobetasol in a comparison study [141]; however, topical tacrolimus must be used with caution given the potential for a large degree of systemic absorption. In one reported case, topical application of crushed dapsone tablets led to sustained resolution of peristomal PG without systemic side effects [142]. A branded topical formulation of dapsone is now available, and may be useful, particularly in superficial PG. Other topical medications that have been used successfully in isolated cases include: 5-aminosalicylic acid, becaplermin (a platelet-derived growth factor), sodium cromoglycate, and topical nitrogen mustard [140].

The majority of patients with PG require a combination of systemic and topical therapy [111]. Initial treatment should be directed towards the underlying disease if one is present, as this frequently results in improvement or complete remission [124]. For example, infliximab is considered first-line for IBD-associated PG. In the only randomized, double-blinded, placebo-controlled trial for PG, 46% of patients treated with 1 infusion of infliximab improved after 2 weeks,

compared with 6% in the placebo group ($p = 0.025$). By the fourth and sixth weeks, 69% of infliximab-treated patients (including those treated in an open-label fashion) had improved, 21% of whom had achieved complete remission [121].

Minocycline and other tetracyclines may be helpful in the treatment of PG, particularly while awaiting the results of cultures taken to exclude an infectious etiology. Minocycline has both anti-inflammatory and antimicrobial properties, including activity against some atypical mycobacteria. In a series of four patients with PG, minocycline proved effective within weeks when used at doses of 200–300 mg/day [143].

Other therapies that may be initiated while infection is being ruled out include IVIG, oral dapsone, and colchicine, which, like dapsone, has anti-neutrophilic properties. These medications are generally used in conjunction with immunosuppressive agents, which may be added once infection has been excluded. IVIG, for example, resulted in complete or nearly complete remission in 12 of 13 patients when used primarily as adjunctive therapy at 2 g/kg [144]. In another series, oral dapsone at 100–200 mg/day caused or contributed to resolution of recalcitrant PG in two of three patients [145].

Medium- to high-dose systemic corticosteroids and/or cyclosporine may be useful for PG refractory to topical treatment or treatment of an associated disease, PG that extends into underlying structures (i.e., muscles, tendons, ligaments), and extracutaneous PG [124]. A randomized, single-blinded trial of 121 patients with PG found that prednisolone and cyclosporine were equally effective, with each agent resulting in healing in about half of patients within 6 months [146]. Corticosteroids are generally initiated at 0.5–1 mg/kg/day of methylprednisolone or 1 g/day for 1–5 days if given as pulsed doses, and cyclosporine is typically started at 5 mg/kg/day [124]. Importantly, persistence of a lesion does not necessarily indicate treatment failure, as wounds may take time to heal despite successful immunosuppression. Signs of treatment response include loss of the undermined border and a halt in lesion growth (see Fig. 10.7).

For patients who require maintenance therapy or whose PG is refractory to the agents reviewed, monotherapy may be considered with other TNF-α inhibitors, granulocyte apheresis, or thalidomide. Alternatively, the following agents may be used as corticosteroid-sparing adjuncts: MTX, MMF, cyclophosphamide, IVIG, dapsone, and AZA [140, 147].

Recently, the successful use of platelet-rich plasma, or autologous plasma that is centrifuged to contain a high concentration of platelets, has been documented in PG. Platelet-rich plasma is thought to enhance wound healing due to the many growth factors it contains, which help promote the cell recruitment and proliferation necessary for proper wound healing [148]. Apremilast, a phosphodiesterase-4 inhibitor, has yet to be studied in PG, but it may be a potential therapeutic option given its inhibition of TNF-α [149] and its efficacy in a randomized, double-blinded, placebo-controlled phase II trial for Behçet disease, which, like PG, is a neutrophilic dermatosis [150].

Given the potential for pathergy, the role of surgery in the management of PG is controversial. Although the removal of necrotic tissue may help prevent superinfection, there are several case reports of worsening of PG following debridement [151], with sequelae ranging from disfiguring scars [152] to large tissue defects [153–155] to digital amputations [156]. Of note, PG was active at the time of debridement in each of these patients as none were treated with systemic immunotherapy either prior to debridement or concurrently. On the other hand, improvement with gentle debridement and/or grafting has been described in patients simultaneously being treated with systemic agents [154, 157–160]. These data suggest that the decision to pursue surgery for PG should be made with careful consideration of the risks and benefits, and that, if performed, surgical interventions should be limited to periods of disease quiescence or remission and pharmacologic immunosuppression. If patients with a history of PG need to undergo surgery for other reasons, these procedures should

be performed with caution, and perioperative systemic corticosteroids and/or cyclosporine should be considered to minimize the risk of pathergy [161].

Sweet Syndrome

Key Summary Capsule Bullets

- Presents with acute onset of fever, leukocytosis, and neutrophil-rich skin lesions, although fever and/or leukocytosis may be absent in the minority
- Lesions are brightly erythematous to violaceous, edematous or "juicy," tender papules, plaques, and/or nodules
- Three variants: classic/idiopathic, malignancy-associated, drug-induced
- Workup focuses on identifying underlying associations, including infection, medication, pregnancy, IBD, or malignancy
- Systemic corticosteroids are mainstay of therapy

Classification and Epidemiology

Sweet syndrome, or acute febrile neutrophilic dermatosis, is a rare inflammatory disorder with cutaneous and systemic manifestations. Classically, patients present with a tender, erythematous, edematous eruption, fever, and leukocytosis.

Sweet syndrome is one of the neutrophilic dermatoses, a group of inflammatory conditions that includes PG (see above), erythema elevatum diutinum (EED), and subcorneal pustular dermatosis (Sneddon-Wilkinson disease). These conditions are characterized by sterile, neutrophilic, cutaneous and extracutaneous infiltrates, as well as an association with systemic conditions (such as hematologic disorders and IBD). Other neutrophilic dermatoses include palmoplantar pustulosis, neutrophilic dermatosis of the dorsal hands, amicrobial pustulosis of the folds, Behçet disease, bowel-associated dermatosis-arthritis syndrome, and rheumatoid neutrophilic dermatitis. Although the classic features of these diseases are distinct from each other, many consider the neutrophilic dermatoses to exist along a spectrum, and there are several reports of multiple of these conditions coexisting in the same patient [162–172].

Sweet syndrome is generally divided into three categories: classic/idiopathic (associated with infection, vaccination, IBD, or pregnancy), malignancy-associated (hematologic or solid malignancies), or drug-induced. In a review of 77 patients with Sweet syndrome, 53% were affected by the classic subtype, 35% had malignancy-associated disease, and 12% had drug-induced Sweet syndrome [173]. Most commonly, adult women are affected, except in hematologic malignancy-associated cases, in which there is an equal sex distribution [174]. Patients with classic or drug-induced Sweet syndrome tend to be younger (with median ages of 46 and 45, respectively) than those with the malignancy-associated subtype (median age 71 years) [173]. Rarely, Sweet syndrome occurs in the pediatric population. In children under 3 years, the disorder is twice as common in males and is not associated with malignancy. In contrast, there is no sex predilection amongst children over 3 years, but a strong association with hematologic malignancy has been demonstrated [175].

Pathogenesis

The pathogenesis of Sweet syndrome is poorly understood. Currently, the most compelling hypothesis is that this condition represents a neutrophil-predominant inflammatory reaction, mediated in part by granulocyte-colony stimulating factor (G-CSF), a pro-neutrophil cytokine. Evidence for the role of G-CSF includes the finding that patients with active Sweet syndrome have significantly higher serum G-CSF than patients with inactive disease or healthy controls [176]. Moreover, G-CSF may represent the link between the heterogeneous conditions and states associated with Sweet syndrome, as the cytokine is elevated in infection [177, 178], pregnancy [179, 180], and ulcerative colitis [181], may be

produced by Sweet syndrome-associated malignancies [182], and is the most common cause of drug-induced Sweet syndrome [183]. Hypersensitivity reactions to antigens from bacteria, viruses, or tumors as well as genetic susceptibilities involving the MEFV gene, HLA-B54, and chromosome 3q have also been implicated in pathogenesis.

Clinical Features

Acute febrile neutrophilic dermatosis, the non-eponymous name for Sweet syndrome, reflects the disease's typical presentation with the acute onset of fever and neutrophil-rich skin lesions. The lesions are typically one or multiple, brightly erythematous to violaceous, tender papules, plaques, and/or nodules (see Fig. 10.8). The lesions characteristically appear edematous, or "juicy," due to significant interstitial edema in the upper dermis. Lesions typically present asymmetrically on the upper extremities but may also involve the head, neck, trunk, and (less likely in the classic subtype) lower extremities. Due to pathergy, the involved sites may correspond to areas of trauma. Mucosal involvement can occur and is variable, favoring the eyes in classic Sweet syndrome and oropharynx in the malignancy-associated subtype [174].

Patients with Sweet syndrome tend to appear ill, as fever usually accompanies the cutaneous manifestations or precedes the eruption by days to weeks. Fever, however, is not universal, and may spare roughly 10–20% of patients with the classic or malignancy-associated variants. Other constitutional symptoms, such as malaise, arthralgias, myalgias, and/or headache, may be present [174].

The morphology of Sweet syndrome may vary. An annular, arcuate, or target-like configuration may develop over time, as smaller lesions coalesce or central clearing develops. The malignancy-associated subtype may be vesiculobullous at first and then ulcerate (see Fig. 10.9). A subcutaneous variant presents as deep dermal to subcutaneous nodules that favor the lower extremities [169]. When a Sweet syndrome-like eruption including pustules occurs on the dorsal

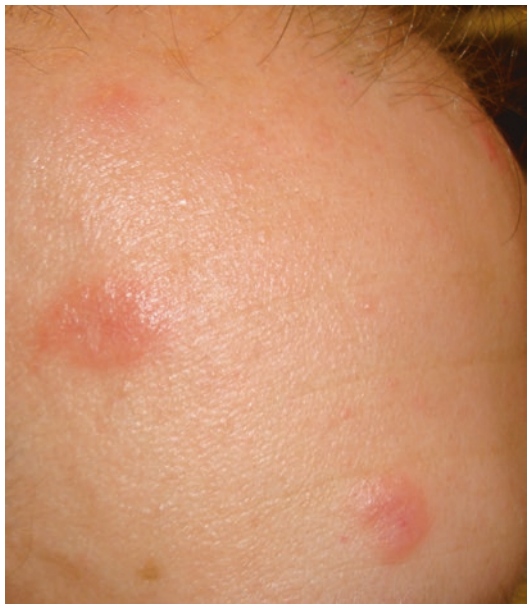

Fig. 10.8 Histiocytoid Sweet syndrome: erythematous and edematous papules and plaques on the forehead

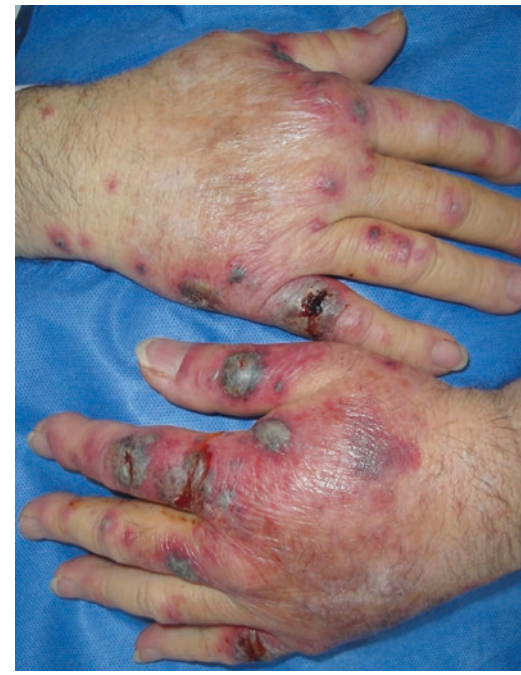

Fig. 10.9 Sweet syndrome: hemorrhagic vesicles and bullae, some of which have ruptured with resulting ulcerations, on the bilateral dorsal hands

hands, it is often termed neutrophilic dermatosis of the dorsal hands, but many consider it a variant of Sweet syndrome.

Extracutaneous manifestations of Sweet syndrome may occur in virtually any organ. Musculoskeletal involvement is common and may manifest as arthralgias, acute sterile arthritis, pigmented villonodular synovitis, myositis, fasciitis, tendinitis, or tenosynovitis. The eyes are also frequently affected, with manifestations including conjunctivitis, episcleritis, glaucoma, peripheral ulcerative keratitis, and iritis; ophthalmologic evaluation in patients suspected to have Sweet syndrome is essential. Uncommonly, central nervous system involvement may manifest as encephalitis or aseptic meningitis. Patients may also develop sterile osteomyelitis or involvement of the ears, kidneys, intestines, liver, heart, lungs, or spleen [174]. Sweet syndrome may also be uncommonly associated with the systemic inflammatory response syndrome (SIRS), and such cases have even been reported to be fatal [184, 185].

The histopathologic features of Sweet syndrome include papillary dermal edema and a neutrophil-predominant dermal infiltrate in a perivascular to nodular and diffuse distribution. Although the absence of leukocytoclastic vasculitis (LCV) is a traditional diagnostic criterion of Sweet syndrome, evidence suggests that its presence should not rule out the diagnosis [186]. In fact, evidence of vasculitis may be seen in up to 29% of histopathology specimens in Sweet syndrome and is thought to be a secondary phenomenon due to the dense neutrophilic infiltrate [187]. Eosinophils may be present in classic or drug-induced Sweet syndrome [174]. New lesions of Sweet syndrome occasionally demonstrate a "histiocytoid" pattern characterized by a superficial to mid-dermal infiltrate predominated by histiocyte-like immature myeloid cells [188]. In subcutaneous Sweet syndrome, neutrophils predominate in the subcutaneous fat lobules, with minimal dermal involvement [189]. Lastly, in unusual cases of "necrotizing" Sweet syndrome, the neutrophil-predominant infiltrate extends into the fascia and skeletal muscle, with resultant fat necrosis and myonecrosis [190].

About 80% of patients with classic Sweet syndrome have peripheral leukocytosis with neutrophilia, compared with 47–60% with the malignancy-associated subtype and 38% with the drug-induced subtype [174]. Thus, the absence of neutrophilia does not exclude Sweet syndrome. In fact, patients with an underlying hematologic malignancy may develop Sweet syndrome despite being neutropenic [191].

Diagnostic Considerations

Diagnostic criteria for classic and malignancy-associated Sweet syndrome have been proposed [192] and revised [193]; the presence of both major criteria and two of four minor criteria are required for diagnosis (see Table 10.5). Guidelines also exist for the diagnosis of drug-induced Sweet syndrome, with five of five criteria required for diagnosis (see Table 10.6) [72].

Because Sweet syndrome classically presents with fever and leukocytosis, cutaneous and systemic infections are an important consideration in the differential diagnosis. Sweet syndrome may resemble bacterial (e.g., cellulitis, erysipelas, *carbunculosis*), fungal (e.g., coccidioidomy-

Table 10.5 Diagnostic criteria for classic and malignancy-associated Sweet syndrome [195]

Major criteria (both required)
Abrupt onset of tender or painful erythematous plaques or nodules occasionally with vesicles, pustules, or bullae
Predominantly neutrophilic infiltration in the dermis without leukocytoclastic vasculitis (LCV)
Minor criteria (2 of 4 required)
Preceded by a nonspecific respiratory or gastrointestinal tract infection, vaccination, or associated with inflammatory diseases such as chronic autoimmune disorders, infections, hemoproliferative disorders or solid malignant tumors, or pregnancy
Accompanied by periods of general malaise and fever (>38 °C)
3 of 4 of the following laboratory values during onset: ESR >20 mm; positive C-reactive protein; >70% neutrophils and bands in the peripheral blood smear; >8000 leukocytes
Excellent response to treatment with systemic corticosteroids or potassium iodide

Table 10.6 Diagnostic criteria for drug-induced Sweet syndrome (all required) [196]

1. Abrupt onset of painful erythematous plaques or nodules
2. Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis (LCV)
3. Pyrexia >38 °C
4. Temporal relationship between drug ingestion and clinical presentation, or temporally related recurrence after oral challenge
5. Temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids

cosis, sporotrichosis), or atypical mycobacterial infections. Necrotizing Sweet syndrome may also mimic necrotizing fasciitis and should be considered in patients with clinicopathologic features consistent with necrotizing fasciitis as well as risk factors for Sweet syndrome. The distinction between the two disorders is crucial because surgical debridement, the mainstay of treatment for necrotizing fasciitis, can exacerbate Sweet syndrome due to pathergy. The presence of myonecrosis, which is usually present in necrotizing Sweet syndrome but absent until the final stages of necrotizing fasciitis, may help differentiate the two conditions [190].

When the lesions of Sweet syndrome are target-like, the clinical differential diagnosis may include erythema multiforme [194]. Features favoring erythema multiforme include oral mucosal involvement and the absence of fever, flu-like symptoms, leukocytosis, or highly elevated inflammatory markers. Moreover, Sweet syndrome and erythema multiforme are histopathologically distinct.

Both Sweet syndrome and neutrophilic eccrine hidradenitis occur in patients with AML and have a similar clinical presentation, but only in the latter does the neutrophilic infiltrate surround eccrine glands. EED is distinguished from Sweet syndrome by its asymptomatic, firm lesions with a predilection for extensor surfaces and histopathology predominated by LCV or dermal fibrosis and mucin. The abrupt-onset, erythematous plaques of Wells' syndrome are differentiated by their symmetric, widespread distribution, their association with peripheral eosinophilia, and the histopathologic finding of "flame figures" (masses of collagen and eosinophils).

Malignancy-associated Sweet syndrome may be vesiculobullous and ulcerate (see Fig. 10.9), thus, mimicking bullous PG. Leukemia cutis presents with firm papules, plaques, and nodules and can be distinguished histologically from Sweet syndrome; immunophenotyping enables differentiation of the histiocytes of leukemia cutis and the histiocyte-like immature myeloid cells of histiocytoid Sweet syndrome [188, 195]. The nodules of subcutaneous sarcoidosis, unlike those of subcutaneous Sweet syndrome, favor the upper extremities and histopathologically feature noncaseating granulomas. When subcutaneous Sweet syndrome occurs on the shins, it may be indistinguishable from EN; however, the neutrophilic infiltrate is predominantly lobular in subcutaneous Sweet syndrome but septal in EN. Moreover, EN is characterized by Miescher granulomas (small, nodular aggregates of histiocytes around a central stellate cleft), while this feature is absent or rare in subcutaneous Sweet syndrome [189].

Disease and Comorbidity Assessment

The evaluation of patients with suspected Sweet syndrome includes a history, physical examination, and laboratory studies, including a skin biopsy, to confirm the diagnosis and identify any underlying association.

In classic Sweet syndrome, patients may report an infection in the 1–3 weeks prior to onset, usually of the upper respiratory tract (streptococcosis) or gastrointestinal tract (salmonellosis or yersiniosis). Alternatively, classic Sweet syndrome can develop in the setting of vaccination, pregnancy, or known or new IBD (Crohn disease or ulcerative colitis). A possible association exists between Sweet syndrome and Behçet disease, EN, relapsing polychondritis, RA, sarcoidosis, Grave's disease, and

Hashimoto's thyroiditis. In addition, over 30 cases have been reported of Sweet syndrome associated with LE, including SLE, subacute cutaneous lupus, neonatal lupus, and drug-induced lupus [174]. In one review of 30 such patients, 9 carried a diagnosis of lupus preceding the onset of Sweet syndrome, and 21 were diagnosed concomitantly. In these patients, a higher male-to-female ratio was seen (1:2) as compared with SLE and Sweet syndrome alone [196].

Malignancy-associated Sweet syndrome typically reflects an underlying hematologic malignancy (especially AML), but solid malignancies (most often genitourinary, breast, and gastrointestinal carcinomas) have also been reported [197]. In a review of 77 patients with Sweet syndrome, 78% of malignancy-associated cases were due to hematologic malignancies or myelodysplastic/myeloproliferative disorders, while the remainder were associated with solid tumors [173]. Subcutaneous Sweet syndrome may be particularly associated with hematologic disorders [169]. Sweet syndrome may signify a new or recurrent malignancy and is the presenting sign of malignancy in roughly two-thirds of patients [198].

Drug-induced Sweet syndrome has been attributed to several medications, but a systematic review determined that there is sufficient evidence for only G-CSF and tretinoin to be implicated as causes [183]. Use of these agents generally precedes the onset of Sweet syndrome by 1–2 weeks [183].

The initial physical examination for patients with Sweet syndrome involves the measurement of vital signs (to evaluate for fever and exclude SIRS or sepsis), as well as examination of the skin, mucosal surfaces, lymph nodes (to evaluate for lymphadenopathy suggestive of a hematologic malignancy), and other organ systems as directed by a patient's symptoms (to evaluate for extracutaneous disease).

Skin biopsy is obtained in almost all cases to confirm the diagnosis. If infectious etiologies are considered likely in the differential, skin biopsies for bacterial, fungal, and mycobacterial cultures may be obtained. Incisional biopsies are preferred if subcutaneous or necrotizing Sweet syndrome is suspected, in order to ensure adequate sampling of the subcutaneous tissue.

A CBC with differential is recommended in all patients to screen for hematologic disorders, and if abnormal, consideration should be given to a bone marrow biopsy. Patients with anemia identified on CBC are more likely to have a malignancy. Other initial laboratory studies include antistreptococcal antibodies and throat culture, as well as a pregnancy test in women. Erythrocyte sedimentation rate and CRP serum levels are generally also obtained; ESR is elevated in the large majority of patients. Chest radiograph should be obtained in any patient with pulmonary symptoms, as lung involvement may occur in Sweet syndrome and is responsive to therapy.

Depending on the initial workup, further assessment for IBD or malignancy may be warranted. As there are no established guidelines for malignancy screening in patients with Sweet syndrome, one option is to begin with age-appropriate screening. Some have proposed that the malignancy workup include the following: digital rectal examination (including prostate examination in men); thyroid examination; breast and pelvic exam (including cervical cancer screening) in women; testicular exam in men; carcinoembryonic antigen level; complete metabolic panel; urinalysis and cytology; chest radiograph; sigmoidoscopy in patients over 50 years; and endometrial biopsy in menopausal women or those with a history of abnormal uterine bleeding, estrogen therapy, infertility, or obesity [197]. In addition, positron emission tomography (PET) and PET-computed tomography (PET-CT) have been used to screen for malignancies in patients with Sweet syndrome and are particularly helpful in the evaluation of hematologic disorders [199, 200].

In patients in whom an underlying condition is not apparent after screening, and particularly in young women, the diagnosis of SLE should be

considered. A recent literature review including 47 patients with both SLE and neutrophilic dermatoses found that the neutrophilic dermatosis was the initial presentation in 15 patients (32%) [201].

If, after extensive workup, no underlying cause is identified for Sweet syndrome, a CBC with differential may be repeated annually or twice yearly, as hematologic malignancies have developed as late as 11 years after initial presentation of Sweet syndrome. On the other hand, a solid malignancy is unlikely to develop if one has not been detected within the first year after the onset of Sweet syndrome [197].

Principles of Management

Systemic corticosteroids are the mainstay of therapy for Sweet syndrome. Oral prednisone is generally initiated at 1 mg/kg/day, results in remission within 2–5 days, and is tapered over 4–6 weeks. Recurrences are common, and some patients may require a corticosteroid taper over 2–3 months or repeated pulses of intravenous methylprednisolone (up to 1 g/day for 3–5 days) [174].

For patients with multiple recurrences requiring long-term therapy, several corticosteroid-sparing agents may be used. Colchicine has been shown to be beneficial, likely due to its anti-neutrophilic effect. In a retrospective study, colchicine (1.5 mg/day for 10–21 days) was found to lead to resolution of classic Sweet syndrome in 18 of 20 patients. Defervescence occurred within 1–3 days, and cutaneous lesions and arthralgias began to improve within 2–5 days. There was no evidence of recurrence during a median follow-up of 8.5 years [202]. Potassium iodide has also been reported as effective; when used at 900 mg/day in a prospective study, 7 of 8 patients had resolution of fever, lesional tenderness, and arthralgias within 1–2 days, and resolution of cutaneous lesions within 3–4 days. The five patients who were treated for 2 weeks did not subsequently relapse [203].

Other potential therapies include indomethacin, clofazimine, cyclosporine, and dapsone. In an open-trial of indomethacin (150 mg/day for 1 week, then 100 mg/day for 2 weeks) for classic or malignancy-associated Sweet syndrome, 18 of 19 adults had resolution of fever and arthralgias within 2 days and resolution of cutaneous disease within 1–2 weeks. None relapsed during a mean follow-up of 20.1 months [204]. In a series including six patients with classic or malignancy-associated Sweet syndrome who flared upon discontinuation of methylprednisolone, clofazimine (200 mg/day for 4 weeks, then 100 mg/day for 4 weeks) resulted in "almost complete remission" without the need for subsequent systemic therapy [193]. Cyclosporine (2–10 mg/kg/day) or dapsone (100–200 mg/day) therapy may also be successful, but evidence is limited to case reports [174].

Pregnant patients with Sweet syndrome are generally treated with systemic corticosteroids [205–207]. Avoidance of potassium iodide and indomethacin at or after 30 weeks of gestation is important, as both are category D medications. Decisions regarding treatment in pregnant patients should be made in conjunction with an obstetrics specialist.

In addition to the above therapies, the treatment of drug-induced Sweet syndrome involves discontinuation of the suspected triggering agent. Recurrence upon rechallenge has been reported in 67% of patients [174]. When readministration of the drug is necessary, premedication with oral prednisone (0.5 mg/kg/day for 5 days) has been reported to prevent the recurrence of Sweet-like lesions, but this approach has not been formally evaluated in Sweet syndrome [208].

The skin lesions of Sweet syndrome heal without scarring. Malignancy-associated Sweet syndrome recurs at a rate similar to that of the drug-induced subtype (69%), usually in association with hematologic relapse. Recurrences of Sweet syndrome occur in 41% of patients whose disease is associated with solid malignancy, often due to recurrence of the malignancy itself (41%) [174]. Recurrence may be seen in up to 30% of patients with the classic subtype, often upon tapering of corticosteroids [174].

Palisaded Neutrophilic Granulomatous Dermatitis and Interstitial Granulomatous Dermatitis

PNGD and interstitial granulomatous dermatitis (IGD) are two granulomatous conditions that often present in patients with underlying autoimmune disease. RA is the most commonly reported autoimmune association with PNGD and IGD; however, SLE and other connective tissue diseases have been associated with these conditions as well. Medications, particularly TNF-α inhibitors, have also been associated with an IGD-like eruption, and when this occurs, the term IGDR is applied. While PNGD and IGD have been traditionally classified as distinct clinical and histological entities, and each is known to have its own characteristic features [209–214], the two conditions feature many similarities and, in many cases, there is a large degree of clinical and histologic overlap. Furthermore, the two entities share similar disease associations and therapeutic algorithms. In this section, we have described PNGD and IGD separately in order to fully encompass disease characteristics and associations. Nevertheless, we recognize the potential for overlap between these entities, and like many others, regard these entities as existing along a spectrum [215, 216].

Palisaded Neutrophilic Granulomatous Dermatitis

Key Summary Capsule Bullets

- Presents with skin-colored to red-violet umbilicated papules and/or nodules symmetrically on extensor elbows and fingers, but cutaneous findings may vary considerably
- Almost always associated with a systemic condition, most often RA, SLE, and ANCA-positive vasculitides, which may be active or quiescent
- Histopathology shows pan-dermal LCV, dense neutrophils, and degenerated collagen (early lesions) or palisading granulomas surrounding degenerated collagen and mucin (late lesions)
- May be challenging to differentiate from IGD due to clinicopathologic overlap

Classification and Epidemiology

PNGD is a cutaneous manifestation of RA, SLE, and other immune complex-mediated systemic diseases. Before the term PNGD was described, the condition was referred to by names such as rheumatoid papules, Churg-Strauss granuloma, cutaneous extravascular necrotizing granuloma, and superficial ulcerating rheumatoid necrobiosis [217].

Although PNGD is considered rare, the prevalence was found to be 6.5% in one study of 215 patients with RA [218]. Adult women are most frequently affected [219], which likely reflects the age and sex predilection of the systemic conditions often associated with PNGD.

Pathogenesis

The pathogenesis of PNGD is poorly understood, but it is thought to be related to the underlying systemic disease. Supporting this theory is the finding that patients with RA and PNGD have higher Disease Activity Score 28 (DAS28) scores than those without PNGD [218], suggesting that in some patients, PNGD and the underlying systemic disease may run a parallel course. Specifically, the underlying disease is believed to generate large immune complexes which, due to their size, deposit within dermal vessel walls, inciting a LCV [217]. This hypothesis is supported by the presence, in some patients, of immunoreactants within the vasculature of lesional skin [217, 220–223]. Ischemic tissue injury to the dermis is thought to occur from LCV, resulting in degenerated collagen, which

may trigger a granulomatous reaction that ultimately resolves with fibrosis [217].

Clinical Features

PNGD was originally described as multiple, skin-colored to red-violet papules and/or nodules symmetrically distributed on the extensor surfaces of the elbows and fingers (see Fig. 10.10). Early in the course, lesions may be erythematous or urticarial-like annular plaques, and as the disease evolves, an infiltrative or waxy quality with a violaceous hue may develop. Umbilication due to a central ulcer and/or crust is characteristic of the papules (see Fig. 10.10) [217, 220, 223]. Despite this characterization, PNGD may vary considerably in terms of color (e.g. yellow-red [224], red-brown [225]), shape (e.g. macules, patches, plaques, pustules [226], vesicles [225]), secondary skin features (e.g. edema [227]), and symptoms (e.g. none, pain, pruritus). Moreover, PNGD can occur on virtually any skin surface, although the upper extremities are the most common site, followed by the lower extremities, trunk, and head and neck [219]. Lesions in atypical areas should prompt examination of the extensor surfaces, which, if affected symmetrically, may aid in the diagnosis [226, 228, 229].

The histopathology of PNGD varies with lesion age, with gradual resolution of the initial LCV and neutrophilic infiltrate and organization of histiocytes into granulomas [217, 223, 226]. Early (i.e., days to weeks old) lesions classically demonstrate LCV, a dense neutrophilic infiltrate, and basophilic degenerated collagen throughout the dermis [217, 226]. Interstitial histiocytes may also be present throughout the dermis [217, 222, 226, 228, 230–233]. Fully developed (i.e., weeks to months old) lesions are characterized by histiocytes organized into granulomas and palisaded around fibrin, degenerated collagen, and mucin. Leukocytoclasia with or without vasculitis may be present [217, 226]. Finally, in resolving lesions, palisaded granulomas have little leukocytoclasia, lack mucin, and are separated by dermal fibrosis [217].

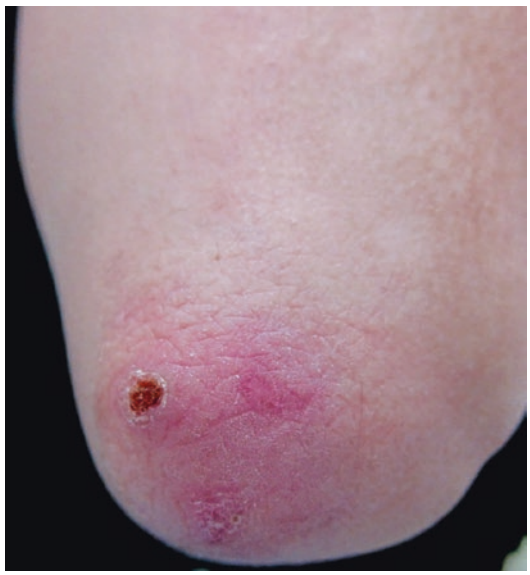

Fig. 10.10 Palisaded neutrophilic granulomatous dermatitis (PNGD): violaceous papules on the elbow, one with a central hemorrhagic crust

Diagnostic Considerations

An important consideration in the differential diagnosis of PNGD is IGD. Unlike PNGD, IGD classically presents with indurated cords or annular plaques. Histologically, IGD is concentrated in the mid to deep dermis ("bottom heavy") as compared with PNGD, which tends to be more superficial. Moreover, the histopathology of IGD is not classically thought to evolve over time [211]. Nevertheless, differentiating PNGD from IGD may be challenging if lesions are clinically consistent with PNGD but histologically consistent with IGD [210, 234, 235] or vice versa [236–238]. In some cases, the histopathology combines features of IGD (e.g. "bottom heavy" histiocytic infiltrate) and PNGD (e.g. pan-dermal mucin [230] or leukocytoclasia [226, 239]). Thus, the differentiation between PNGD and IGD may be difficult both clinically and histopathologically.

The clinical differential diagnosis of PNGD also includes papular eruptions that favor the bilateral elbows, knees, and other extensor surfaces. Rheumatoid neutrophilic dermatitis is a rare condition that, like PNGD, classically presents with erythematous, umbilicated papules or annular plaques that may affect the extensor surfaces. However, unlike PNGD, rheumatoid neutrophilic dermatitis typically lacks LCV or granulomas on skin biopsy. Rheumatoid nodules are granulomatous nodules that typically affect extensor surfaces; however, these nodules are situated deep in the subcutis, as compared with the dermal location of PNGD. EED is a rare form of vasculitis that presents with papules and nodules primarily overlying extensor surfaces. In contrast to PNGD, the lesions of EED typically darken over time, from yellow-pink to red, brown, or purple, and typically heal with extensive dermal fibrosis, resulting in firm papules overlying extensor surfaces even once the inflammation is quiescent. Histologically, EED lesions lack palisaded granulomas. Xanthoma tuberosum is another cause of subcutaneous nodules on the extensor surfaces; however, this entity is distinguished by its pink-yellow color, usual association with a personal or family history of hyperlipidemia, and histopathologic evidence of foamy macrophages and cholesterol clefts. Lastly, tendinous xanthomas are subcutaneous, while PNGD is a dermal process.

The histopathologic differential diagnosis of PNGD depends upon lesion age. In early PNGD, the histology may resemble that of cutaneous LCV; however, the two may be differentiated by the greater amount of extravasated erythrocytes and lack of an interstitial neutrophilic infiltrate or degenerated collagen in LCV [217]. Moreover, cutaneous LCV is characterized on exam by petechiae and/or palpable purpura in dependent areas such as the lower legs, which are typically absent in PNGD.

The histopathologic differential diagnosis of later stage PNGD (i.e., fully developed or resolving lesions) includes other conditions characterized by palisading granulomas. GA is distinguished by more mucin, less vasculitis, thinner bundles of degenerated collagen, and fewer neutrophils and fibrin [220]. Moreover, GA most commonly presents as asymptomatic, skin-colored or erythematous, annular or arciform plaques on the wrist, ankle, or dorsal hand or foot, without overlying scale. In eosinophilic granulomatosis with polyangiitis, granulomas surround eosinophils, not neutrophils [217]. Furthermore, granulomatosis with polyangiitis most commonly presents as palpable purpura. Finally, the degenerated collagen and palisading granulomas of necrobiosis lipoidica are differentiated from PNGD by a "layered cake" pattern that extends into the subcutaneous fat septae. Plasma cells are typically seen, while neutrophils and mucin are absent. Moreover, necrobiosis lipoidica is clinically distinct from PNGD, as it is typified by yellow-brown, atrophic plaques with central telangiectasias on the bilateral shins.

Disease and Comorbidity Assessment

The diagnosis of PNGD generally requires clinicopathologic correlation with one or multiple biopsies, given the potential for variable and overlapping clinical and histopathologic features. The workup should aim to identify an underlying cause, as the vast majority of reported cases have an associated systemic condition that precedes, occurs with, or follows the diagnosis of PNGD [219, 220, 223]. The most common association is RA, followed by SLE. ANCA-positive vasculitides are also often reported as associated with PNGD [219]. Other reported underlying diseases include other systemic vasculitides, malignancy (particularly immunoproliferative disorders), IBD, other connective tissue diseases, and infectious diseases (see Table 10.7).

In exceptional cases, patients with PNGD lack an underlying association [240] or have extracutaneous features (e.g. fatigue, fever, diffuse polyarthralgia, reactive lymphadenopathy, abnormal

Table 10.7 Systemic conditions associated with palisaded neutrophilic granulomatous dermatitis (PNGD)

Arthritides	Rheumatoid arthritis (RA) [226, 227, 232, 248] Ankylosing spondylitis [248]
Connective tissue diseases	Systemic lupus erythematosus (SLE) [225, 233, 237, 249, 251] Systemic sclerosis (SSc) [222] Mixed connective tissue disease [236] Undifferentiated connective tissue disease [220, 227]
Systemic Vasculitides	Eosinophilic granulomatosis with polyangiitis [226] Granulomatosis with polyangiitis [226, 252] Behçet's disease [240] Takayasu arteritis [226, 253] Polyarteritis nodosa [223] Microscopic polyangiitis [229] Unclassified vasculitis [223]
Immunoproliferative disorders	Myelodysplastic syndrome (MDS) [226] Leukemia [223, 226] Lymphoma [223] Multiple myeloma [223]
Infectious diseases	Cellulitis [249] Subacute bacterial endocarditis [223] Hepatitis [223] Streptococcal infection [226] Acquired immunodeficiency syndrome [222]
Other	Sjögren's syndrome [228] Polymyalgia rheumatica [254] Adult-onset Still's disease [232] Sarcoidosis [235, 255, 256] Ulcerative colitis [223, 242] Type 1 diabetes mellitus [257] Celiac disease [257] Mixed cryoglobulinemia [226] Metastatic prostate adenocarcinoma [226] Multiple sclerosis [226] Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [226]

liver chemistries) that cannot be accounted for by another condition. These extracutaneous manifestations follow the course of cutaneous disease in PNGD, resolving spontaneously or in response to the same treatment [234, 241]. Additionally, PNGD has been attributed to medications, such as penicillin [223], allopurinol [242], MTX [229], and adalimumab [231, 243]. However, these rare reports may be confounded by the fact that the patients were often taking these medications (with the possible exception of allopurinol) for underlying systemic diseases known to be associated with PNGD. Furthermore, although lesions resolved with discontinuation of the suspected medication, immunosuppressive therapy directed at the underlying condition was often initiated at the same time, which may have affected PNGD activity. There are no reported cases in which re-challenge of a medication thought to provoke PNGD has been attempted.

Given the strong association between PNGD and systemic disease, screening for underlying conditions should be performed in conjunction with the patient's primary pare condition and relevant specialists. Evaluation should include a thorough history (including medication review), review of systems, physical examination, and basic laboratory panels including CBC and complete metabolic panel. In patients with arthralgias or arthritis, joint radiographs as well as serum rheumatoid factor and anti-citrullinated protein antibodies should be considered. Age- and sex-appropriate malignancy screening is important in all patients.

If an underlying condition is not readily identified, additional tests to consider include serum

anti-nuclear antibody titers and additional autoimmune serologies, serum and urine protein electrophoresis and immunofixation, and a chest radiograph. A computed tomography (CT) scan of the chest, abdomen, and pelvis should also be considered to screen for underlying malignancy.

If, despite this expanded workup, an underlying condition cannot be identified, long-term, symptom-directed screening is warranted, as PNGD may predate the onset of systemic disease by several years [220]. It is important to note that PNGD may manifest during flares [220, 222, 226, 237, 244] or periods of quiescence of the underlying disorder [219, 221, 234, 239, 245].

Principles of Management

Data on the treatment of PNGD are limited to case reports and case series and confounded by the occurrence of spontaneous resolution in about 20% of patients [219]. In the remaining 80%, PNGD generally responds to systemic treatment of the underlying disease [219], most often with the initiation [223, 246] or continuation of systemic corticosteroids [217, 220, 223, 228, 232, 234, 242]. Dapsone [65, 222, 224, 226, 239, 241, 247], MMF [236], hydroxychloroquine (HCQ) [220], colchicine [237], or cyclophosphamide [230] have been used in combination with corticosteroids or as monotherapy, with some success. MTX is often used for granulomatous conditions and may be attempted; however, to date, the only two cases in the literature on MTX for PNGD report no to partial efficacy [225, 241]. Recurrence has been reported after tapering corticosteroids [224] or dapsone [226, 239]. Other treatment options include AZA [236], TNF-α inhibitors [228, 244], antimicrobials for an associated infection [234, 248], and insulin replacement therapy for diabetes mellitus [249]. Intralesional corticosteroids may be useful as adjunctive therapy for localized disease [223, 226, 247, 250]. Topical corticosteroids yield mixed results as they are unlikely to sufficiently penetrate the dermis [65, 223, 228, 229, 231, 239, 244, 246].

Interstitial Granulomatous Dermatitis and Interstitial Granulomatous Drug Reaction

Key Summary Capsule Bullets

- Two clinical variants of IGD: plaque-variant (most patients) and cutaneous cord-variant
- IGD is associated with arthritis or arthralgias in more than half of patients; also associated with various autoimmune conditions and in some cases, malignancy
- IGDR is caused by chronic use of TNF-α inhibitors, calcium channel blockers, and other medications
- Mainstay of treatment is systemic immunosuppressive agents in IGD and drug withdrawal in IGDR

Classification and Epidemiology

IGD is a disorder with cutaneous and often articular manifestations that may be associated with an underlying systemic disease. IGD is also known as interstitial granulomatous dermatitis with arthritis (IGDA) or Ackerman's syndrome. When IGD occurs in the setting of exposure to medications, such as TNF-α inhibitors, the term IGDR is applied.

IGD predominates in women by a ratio of 3:1 [212]. IGDR has been reported only in adults, which may reflect the tendency of the implicated medications to be used in this age group.

Pathogenesis

IGD has been posited but not proven to be initiated by circulating immune complexes that are small enough to diffuse into the interstitial dermis, where they deposit and incite a granulomatous reaction [217]. The formation of these immune complexes may be related to an underlying systemic disease. In IGDR, the antigenic trigger is unknown but may be the triggering medication itself or another molecule that

becomes immunogenic as a result of exposure to the medication [213].

Clinical Features

Interstitial Granulomatous Dermatitis

IGD has two major clinical variants: IGD with plaques and IGD with cutaneous cords. Approximately 90% of patients with IGD have the plaque variant [212], which classically manifests with multiple, skin-colored to tan or erythematous, waxy, papules and plaques. As IGD is a dermal process, there is no associated scale. The lesions may be annular and are usually asymptomatic but may be minimally pruritic or painful [212]. Typical sites of involvement include the lateral trunk and proximal, medial extremities in a symmetric distribution [212]. Uncommon sites include the face [251], breasts [252], and palms [253]. Widespread involvement may occur [254].

The remaining 10% of patients with IGD have the variant with cutaneous cords. In this variant, the clinical picture is characterized by linear or arciform, erythematous, indurated cords on the lateral trunk, which correspond to the so-called "rope sign." This "rope sign" has traditionally been considered pathognomonic of IGD [212].

In more than half of patients, the cutaneous lesions of IGD are associated with prior, concurrent, or subsequent arthritis or arthralgias [212]. Characteristically, the arthritis manifests as either RA or a symmetric, seronegative, non-erosive, oligo- to polyarthritis of small and/or large joints. Similarly, the arthralgias are symmetric, polyarticular, favor peripheral over central joints, and may be migratory [212, 255–257]. These articular symptoms generally respond to treatment of the cutaneous disease [255, 257]. Antinuclear antibody titers are positive in about half of patients with IGD [212].

Both clinical variants of IGD share the same histopathologic features: interstitial and palisading histiocytes diffusely throughout the dermis, small foci of degenerated collagen ("piecemeal fragmentation") that are surrounded by an empty space, and, thus, appear "free floating" ("floating sign"), and perivascular and interstitial lymphocytes. The histiocytic infiltrate may be concentrated in the mid to deep reticular dermis ("bottom heavy"), and extension into the subcutaneous tissue occurs in about 30% of patients. Mucin, vasculitis, neutrophils, and eosinophils tend to be sparse or absent [212].

Interstitial Granulomatous Drug Reaction

IGDR presents similarly to IGD but may be distinguished by its predilection for intertriginous areas and a weaker association with constitutional and articular symptoms and autoantibodies. For example, the original series of patients with IGDR, which remains the largest to date, found that 10% of patients had an underlying arthropathy [213], compared with more than half of patients with IGD [212]. The lesions of IGDR may be pruritic [213]or tender [258–260]. Variations in morphology (e.g., papules [213] and nodules [260]) and configuration (e.g. livedoid [213]) have been reported.

Like PNGD and IGD, IGDR may atypically manifest on virtually any skin surface (e.g. trunk, lower extremities [213], palms and soles [259, 261], head [258, 262], neck [263]). In one reported case, IGDR presented with erythroderma [264].

The medications most commonly associated with IGDR are TNF-α inhibitors and calcium channel blockers, although several other medications have also been reported (see Table 10.8). TNF-α inhibitors have caused IGDR in patients being treated for both RA and psoriatic arthritis [265–267]. The eruption most often occurs years after the initiation of the causative medication but may occur as soon as weeks or months into therapy. IGDR tends to resolve after discontinuation of the triggering medication [213].

Histopathologically, IGDR shares the diffuse, interstitial lymphohistiocytic infiltrate of IGD, and the two entities cannot be definitively distinguished based on histopathology alone. Features favoring IGDR include a vacuolar interface

Table 10.8 Agents implicated in interstitial granulomatous drug reaction (number of cases)

TNF-α inhibitors: infliximab (2), adalimumab (2), etanercept (2), thalidomide (1), lenalidomide (1) [271, 274–276]
Calcium channel blockers: diltiazem (4), verapamil (2), nifedipine (1) [216]
Angiotensin converting enzyme inhibitors: enalapril (5), lisinopril (1) [216, 273, 283]
HMG-CoA reductase inhibitors: atorvastatin (1), simvastatin (1), lovastatin (1), pravastatin (1) [216, 279]
H1- and H2-receptor antagonists: ranitidine (1), famotidine (1), cimetidine (1), brompheniramine (1) [216]
Furosemide (3) [216, 283]
Beta-blockers: propranolol (1), atenolol (1) [216]
Herbal supplements including Panax notoginseng (3) [277, 284, 285]
Candesartan (1) [283]
Carbamazepine (1) [216]
Bupropion (1) [216]
Diazepam (1) [216]
Gemfibrozil (1) [216]
Febuxostat (1) [278]
Ganciclovir (1) [269]
Trastuzumab (1) [267]
Sorafenib (1) [268]
Darifenacin (1) [272]
Fluindione (1) [283]
Anakinra (1) [286]
Sennoside (1) [270]
Strontium ranelate (1) [280]

dermatitis, atypical lymphocytes, and abundant eosinophils [213]. However, the histiocytes may be palisaded [264], and lymphocyte atypia [213] and interface dermatitis [267–271] may be absent. Of note, three cases have been reported in which patients presented with clinical features of drug-induced hypersensitivity syndrome, but histopathology consistent with IGDR [272, 273].

Diagnostic Considerations

IGD and IGDR may be distinguished by factors elicited on history (with exposure to a known medication trigger suggestive of IGDR and constitutional or articular symptoms more likely in IGD); physical examination (IGDR has a tendency to occur in intertriginous zones); histopathology (IGD lacks a vacuolar interface dermatitis and lymphoid atypia and has more completely degenerated collagen); and serology (IGD is more likely to be associated with autoantibodies). However, differentiation may be challenging in cases in which IGDR lacks characteristic clinical and histopathologic features [260], especially as patients may take drugs implicated in IGDR for conditions associated with IGD, given that IGDR can occur years after initiation of the offending medication. In uncertain cases, a trial off a potentially triggering medication may be warranted. Whether patients with IGDR due to TNF-α inhibitors may tolerate other medications in the same class has yet to be documented in the literature.

The differential diagnosis of IGD and IGDR includes interstitial GA and PNGD. Although it is characterized by annular plaques, interstitial GA favors the wrists, ankles, and dorsal hands and feet, and it is not associated with articular symptoms and autoantibodies (as in IGD) or medication exposure (as in IGDR). Histopathologically, interstitial GA features more mucin than IGD or IGDR, as well as histiocytes concentrated in the upper to mid dermis ("top heavy"). Neutrophils, vacuolar interface dermatitis, and atypical lymphocytes are generally absent.

Both IGD and IGDR typically lack the LCV, leukocytoclasia, and predominant neutrophils seen in early PNGD as well as the palisaded granulomas and neutrophilic debris seen in late PNGD [213]. Moreover, unlike PNGD, neither IGD nor IGDR are thought to evolve histopathologically over time [211].

The clinical differential diagnosis of IGD with cutaneous cords also includes superficial thrombophlebitis of the breast (Mondor disease), which typically follows breast trauma or surgery. The plaques of cutaneous larva migrans, which is caused by the hookworms *Ancylostoma braziliense* or *Ancylostoma caninum*, may resemble the cutaneous cords seen in IGD., but they are characteristically serpiginous, and, unlike IGD, they favor the feet, are pruritic, and occur after travel to a tropical or subtropical country. Granulomatous mycosis fungoides and

its variant granulomatous slack skin present with violaceous, intertriginous plaques; this condition can be distinguished from IGD with cutaneous cords on skin biopsy.

The differential diagnosis of IGD with plaques includes rheumatoid neutrophilic dermatitis, which is histopathologically distinguished by its dense neutrophilic dermal infiltrate and abundant leukocytoclasia.

Disease and Comorbidity Assessment

The evaluation of patients with suspected IGD begins with a thorough history (with careful attention to medications), review of systems, physical examination, and routine laboratory studies.

As described above, more than half of patients with IGD have arthritis (rheumatoid or non-erosive and seronegative) or polyarthralgias that can predate, manifest with, or follow the cutaneous disease [212]. In addition to RA, other autoimmune conditions have been reported as associated with IGD, most commonly autoimmune thyroiditis [253, 257, 274] and SLE [257, 275–278], and less frequently undifferentiated connective tissue disease [279], antiphospholipid antibody syndrome [280], autoimmune hepatitis [235], vitiligo [257], hemolytic anemia [257], and autoimmune thrombocytopenia [212]. Other underlying conditions include hematologic dyscrasias (e.g., monoclonal gammopathy of undetermined significance [212, 251], MDS [254], acute *myeloid leukemia* [254, 281]) and solid malignancies (e.g. bronchial [282] and hypopharyngeal [212] squamous cell carcinomas, and breast cancer [212]).

Antinuclear antibody titers are positive in about half of IGD patients [212]. Thus, the workup should generally include autoimmune serologic testing in addition to thyroid function studies, age- and sex-appropriate malignancy screening, and serum and urine protein electrophoresis and immunofixation. Consideration may be given to a CT scan of the chest, abdomen, and pelvis and/or additional "blind" malignancy screening in patients in whom an underlying condition is not readily identified.

The diagnosis of IGDR requires clinicopathologic correlation as well as a history of generally chronic exposure to one or multiple medications identified as triggers for this condition. If the cutaneous eruption does not resolve within months of medication discontinuation, consideration should be given to a workup directed at excluding cutaneous T-cell lymphoma [213].

Principles of Management

In the majority of reported cases, IGD completely remits after a mean of 8.8 months [212]. In the remaining patients, IGD tends to follow a chronic, relapsing course [212]. Progression of IGD to localized acquired cutis laxa despite systemic treatment was reported in one patient with a chronic, relapsing course in whom the initial IGD biopsy showed elastophagocytosis [283]. Treatment for IGD may not be required if symptoms are absent or mild and the extent of involvement is limited.

When treatment is desirable, data from case reports suggest that the cutaneous and/or articular manifestations of IGD may be treated with systemic corticosteroids [235, 255, 275, 277, 284], TNF-α inhibitors (infliximab [252], adalimumab [285]), HCQ [279], MTX [279, 286], and narrow-band ultraviolet B phototherapy [287]. Recalcitrant IGD has been successfully treated with IVIG [251], tocilizumab [288], lenalidomide [254], cyclosporine [289], and combination therapy (MTX and etanercept [290]; systemic corticosteroids, MTX, and AZA [283]). For localized disease, resolution has been reported with intralesional triamcinolone [276], but topical corticosteroids have not been consistently reported to be effective [284, 285, 291, 292]. When associated with autoimmune thyroiditis, IGD did not improve despite normalization of thyroid function [253].

The mainstay of treatment of IGDR is discontinuation of the offending agent(s), with resolution occurring in most patients within weeks to months. Reintroduction of the same medication or substitution with another in the same class generally leads to recurrence [213].

Summary

The evaluation of patients with reactive erythemas requires an interdisciplinary approach, relying on collaboration between dermatologists, rheumatologists, and other specialists. The main goals of this evaluation are generally twofold: (1) to exclude disease mimickers, and (2) to identify an underlying systemic disease, if one is present. Given the rarity of the reactive erythemas, no formal guidelines exist to direct the assessment of patients who develop them. However, the tenets of evaluation are a thorough history, review of systems, and physical examination of the skin, mucosal surfaces, lymph nodes, and other organ systems. Comprehensive laboratory and radiologic evaluations should be directed towards any identified abnormalities and further testing based upon the specific disease associations of the reactive erythema in question. A skin biopsy is often a key diagnostic component; however, in some cases, such as in classic EN, a skin biopsy may not be necessary.

Given that a reactive erythema may precede the clinical onset of an underlying disease, ongoing surveillance for associated conditions should be performed in patients in whom an underlying condition is not initially identified. For example, in a patient with LEP, but not SLE, clinical monitoring for the subsequent development of SLE is warranted, although SLE will develop only in the minority. Similarly, an increased index of suspicion for an underlying condition should be maintained in the follow-up of all patients with PG, Sweet syndrome, PNGD, and IGD.

Management of reactive erythemas may include supportive care, targeted treatment of the underlying disorder, and/or systemic immunomodulatory therapy directed towards the skin disease. Because reactive erythemas generally involve the dermis and/or subcutaneous tissues, topical therapies are unlikely to sufficiently penetrate the skin, and, thus, systemic therapies are often required. In cases where extracutaneous manifestations are present, these symptoms may respond to treatment of the cutaneous disease. If a drug etiology is suspected, the causative agent should be discontinued. Importantly, if patients are pregnant or have an underlying disorder such as RA, IBD, or a malignancy, treatment of the cutaneous disease should be performed in collaboration with the specialists managing the pregnancy or underlying condition. Overall, recognition of the interdisciplinary nature of the reactive erythemas is imperative for proper management and long-term care.

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