

Neutrophilic Dermatoses: An Update

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Abstract Neutrophilic dermatoses constitute a heterogeneous group of dermatologic diseases, which are unified by the predominance of neutrophils within the inflammatory infiltrate on histopathology. The aims of this review were to provide an update on the clinical and histologic presentation of the main neutrophilic dermatoses and to develop a guide for clinical practice. A structured literature search of PubMed, Medline, and Embase was performed, using the key words “neutrophilic disorders”, “cutaneous small vessel vasculitis”, “Sweet’s syndrome”, “bowel associated dermatosis arthritis syndrome”, “Behcet’s”, “palisaded neutrophilic and granulomatous dermatosis”, “rheumatoid neutrophilic dermatitis”, and “pyoderma gangrenosum”. Related articles were screened for key terms and were included if appropriate. This group contains a wide spectrum of unique disorders, each with its own histologic and clinical

subtleties, making specific diagnosis of a given entity within the group diagnostically challenging. The fact that overlapping forms of neutrophilic dermatoses, which share features of multiple neutrophilic dermatoses, are not uncommon makes the diagnoses more challenging.

Key Points

Neutrophilic dermatoses are a heterogeneous group of disorders characterized by infiltration of neutrophils in active lesions.

The risk of association with underlying conditions attracts attention toward early diagnosis of neutrophilic dermatoses.

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1 Introduction

Neutrophilic dermatoses constitute a heterogeneous group of noninfectious dermatologic diseases, which are unified by the predominance of neutrophils within the inflammatory infiltrate of active skin lesions. While a publication by Jorizzo et al. in 1988 was the first to unify and describe a classification of neutrophilic reactions as distinct but related entities, subsequent research has shown that these entities have significant overlap in histopathologic and clinical findings, and can occur concurrently in the same patient [1]. Indeed, overlapping forms of neutrophilic dermatoses, which share features of multiple neutrophilic dermatoses, are not infrequently encountered [2]. A structured literature search of PubMed, Medline, and Embase from 1988 to the present was performed, using the key

Table 1 Characteristics of neutrophilic dermatoses

Disease	Clinical characteristics	Histologic characteristics
CSVV	Common locations: dependent areas, lower extremities Palpable purpura Constitutional symptoms Arthralgia Gastrointestinal, renal, and neurologic involvement	Angiocentric neutrophilic segmental inflammation Fibrinoid necrosis of vessel walls
Sweet's syndrome	Common locations: head and neck Acute onset of painful plaques or nodules Fever and arthralgia Leukocytosis Pathergy is present Different morphologies	Diffuse nodular and perivascular dermal infiltrate Superficial dermal edema True vasculitis is not common
BADAS	3 months to 5 years post-gastrointestinal surgery Polyarthralgia (episodic and peripheral), myalgia Panniculitis, pustular vasculitis, EN	Neutrophilic infiltration of mid-dermal venules Papillary dermal edema and then neutrophilic infiltration No true vasculitis
Behcet's disease	Recurrent oral and genital ulceration Ocular abnormalities (uveitis, retinal vasculitis) Variable skin lesions (acneiform, EN, panniculitis) Neurologic involvement	Systemic vasculitis (neutrophilic, lymphocytic) Occlusive perivasculitis and thrombosis
PNGD	Common locations: extensor surfaces of upper > lower extremities Symmetrical papules, nodules, plaques, linear bands Asymptomatic	Early lesions: leukocytoclastic vasculitis Late lesions: palisaded granuloma and degenerated collagen
RND	Common locations: hands and forearms Papulonodules and/or plaques distributed on the extensor surfaces of the extremities Different morphologies	Dense neutrophilic dermal infiltrate Mixed inflammatory infiltrate in the chronic stage No frank leukocytoclastic vasculitis
PG	Painful recurring lesions (pustules, bullae, ulcers) Arthralgia, myalgia Pathergy is present Ulcers with an active gunmetal border	Neutrophilic infiltrate The diagnosis is mainly clinical

BADAS bowel-associated dermatosis–arthritis syndrome, *CSVV* cutaneous small-vessel vasculitis, *EN* erythema nodosum, *PG* pyoderma gangrenosum, *PNGD* palisaded neutrophilic and granulomatous dermatosis, *RND* rheumatoid neutrophilic dermatitis

words “neutrophilic disorders”, “cutaneous small vessel vasculitis”, “Sweet’s syndrome”, “bowel associated dermatosis arthritis syndrome”, “Behcet’s”, “palisaded neutrophilic and granulomatous dermatosis”, “rheumatoid neutrophilic dermatitis”, and “pyoderma gangrenosum”. The abstracts and relevant full-text articles were reviewed. This review provides an update on the clinical and histologic presentations of the main prototypic neutrophilic dermatoses (Table 1).

2 Cutaneous Small-Vessel Vasculitis

2.1 Clinical Presentation

Cutaneous small-vessel vasculitis (CSVV) is classified as a subset of vasculitis that predominantly affects small

vessels, including intraparenchymal arteries, arterioles, capillaries, and venules [3, 4]. While CSVV is frequently associated with a wide spectrum of systemic inflammatory conditions, malignancies, infections, or drug hypersensitivities [5], approximately half of all cases are idiopathic.

Clinically, CSVV presents as purpura, often palpable purpuric papules, or non-blanching macules, and favors dependent areas, areas of trauma, and areas of pressure, such as under tight-fitting clothing (Fig. 1a) [6–8].

In general, the presence of constitutional signs or symptoms—such as joint pain or swelling; abdominal pain, melena, frothy or discolored urine, or abnormal urinalysis; focal peripheral sensory or motor nerve problems or central nerve deficits—should all prompt consideration for systemic involvement in vasculitis. The presence of paresthesia or the absence of painful lesions and hypocomplementemia have been identified as risk factors

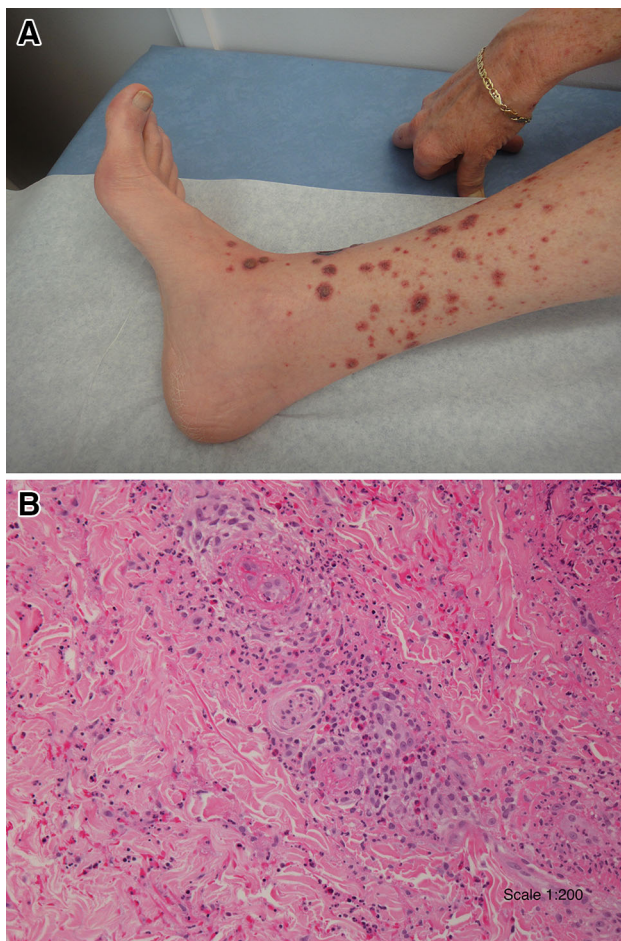


Fig. 1 Leukocytoclastic vasculitis: **a** palpable purpura, which may evolve to ulceration as superficial infarctions occur; **b** histology shows neutrophilic infiltration around and within dermal blood vessels and fibrinoid necrosis of blood vessel walls

for an associated systemic disease [6, 7, 9]. Given the above associations, all patients with CSVV must be evaluated for internal involvement, especially of the kidneys, gastrointestinal tract, and joints, which requires a thorough history, a detailed and targeted physical examination, and a thorough laboratory workup, which often includes urinalysis, a complete blood count with differential, creatinine level, complement 3 and 4 levels, and fecal occult blood.

2.2 Histopathology

The hallmark histopathologic pattern of CSVV is leukocytoclastic vasculitis, which is characterized by angiocentric segmental inflammation, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls (postcapillary venules). The cellular infiltrate around and within dermal blood vessel walls is composed mainly of neutrophils, many of which exhibit fragmentation of nuclei (karyorrhexis or leukocytoclasia) [Fig. 1b]. Palpable purpura can be explained by infiltration of leukocytes (palpability) and

the resulting extravasation of red blood cells from the damaged blood vessel (purpura).

Direct immunofluorescence is positive in around 80 % of cases, demonstrating deposition of complement C3, immunoglobulin (Ig)-M, IgA, and/or IgG (generally in that order of frequency) in a granular pattern within the vessel walls [10].

2.3 Pathogenesis

The pathogenesis of CSVV has not been fully elucidated, but it includes circulating immune complex deposition, increased adhesiveness between inflammatory cells and the endothelium, and neutrophil-mediated damage to postcapillary venules. Although 50 % of cases are idiopathic and follow a benign, self-limited course, an attempt to address underlying systemic involvement or causes should be made. This is best done through a multidisciplinary, collaborative approach.

2.4 What's New?

In recent decades, additional etiologies have been implicated and associated with CSVV, including drugs [11, 12], infections, malignancies [13], herbal supplements [14], and systemic diseases. It is worth remembering that association does not prove causation. Therefore, each patient's history needs to be assessed carefully.

The Chapel Hill Consensus Conference statement replaced the name “Henoch–Schönlein purpura” with “IgA vasculitis” because of evidence that IgA deposits in vessel walls are the defining feature [4]. Also, the new category of single-organ vasculitis can occur with IgA vasculitis. Recent studies have suggested that IgA vasculitis in adults may represent a paraneoplastic vasculitis, with renal cancer being the top culprit [15].

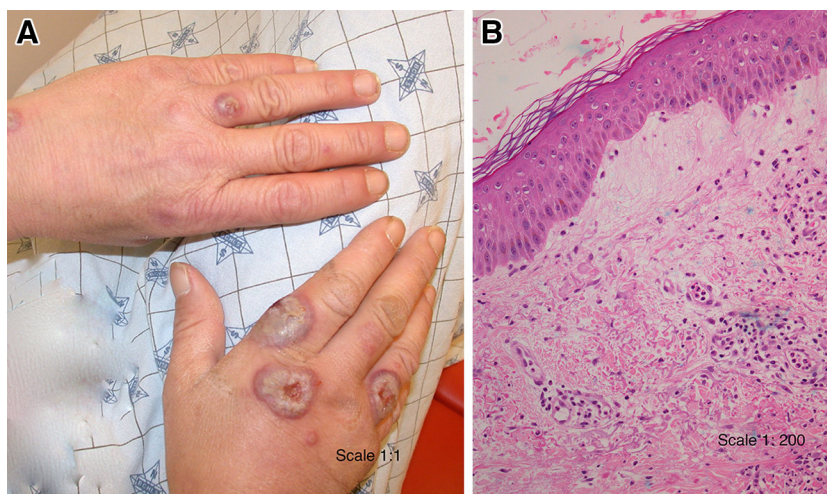
Notably, a lymphocytic form of small-vessel vasculitis has also been described in cases of collagen vascular disease [14, 16, 17]. In a study by Bahrami et al. [18] in 60 patients with CSVV, marked tissue eosinophilia was suggested as a reliable indicator of drug-induced cases [19, 20].

3 Sweet's Syndrome

3.1 Clinical Presentation

Sweet's syndrome, or acute febrile neutrophilic dermatosis, is the prototypic member of the neutrophilic dermatoses. While up to 50 % of cases are idiopathic, up to 35 % of patients have underlying internal malignancies [21]. These are predominantly hematologic malignancies, particularly

Fig. 2 Febrile neutrophilic dermatosis: **a** tender erythematous plaques on the hands; **b** characteristic histopathology findings include significant edema with diffuse nodular and perivascular neutrophilic infiltration



myelodysplastic syndrome and acute myelogenous leukemia, although 7–15 % of these patients have solid malignancies, the most common of which are genitourinary tumors [22, 23]. Other associations include postinfectious, inflammatory autoimmune disorders, as well as reactions to an ever increasing list of medications.

Clinically, Sweet's syndrome typically develops several days after an upper respiratory tract infection or occasionally after acute viral gastroenteritis. It typically presents as bilateral, edematous, tender plaques or nodules in the setting of fever and arthralgia. Interestingly, a recent study of 77 patients found that only 39 and 27 % of patients reported a fever and arthralgia, respectively [21]. The lesions favor the head, neck, and upper and lower extremities, and occasionally display a central yellowish discoloration, which may create a targetoid appearance (Fig. 2a). Cohen [24] has noted that multiple neutrophilic dermatoses may exhibit an annular pattern. Pathergy may be observed, with the appearance of new lesions at the site of trauma. Sweet's syndrome lesions can uncommonly involve internal organs, especially in the setting of an underlying malignancy. The most commonly affected areas include the eyes,

neuromuscular system, joints, kidneys, lungs, heart, and liver [23, 24]. Patients with the presence of (a) vesiculobullous lesions, particularly ones that progress to pyoderma gangrenosum (PG)-like ulcers; (b) a histiocytoid clinicopathologic variant; or (c) extensive, asymmetrical distribution of lesions appear to have a higher propensity for an underlying malignancy. The criteria for the diagnosis of Sweet's syndrome are listed in Tables 2 and 3 [25, 26].

3.2 Histopathology

The characteristic histopathologic finding of a classic lesion is a diffuse pan-dermal or nodular and perivascular dermal neutrophilic infiltrate, although infiltration of the appendages may also be seen. Superficial dermal edema is usually seen (Fig. 2b). While most cases of Sweet's syndrome present with leukocytoclasia, dilation of small blood vessels, fragmentation of neutrophil nuclei without fibrin deposition, and neutrophils within vessel walls [27], true vasculitis has been seen in several cases [10, 11], and its presence should not rule out the diagnosis of Sweet's syndrome.

Table 2 Diagnostic criteria for classic Sweet's syndrome; the diagnosis requires all major criteria and at least three minor criteria

Major criteria

1. Abrupt onset of cutaneous lesions consistent with Sweet's syndrome
2. Histopathology compatible/consistent with Sweet's syndrome

Minor criteria

1. Preceded by associated systemic findings, such as infection, pregnancy, drugs, malignancy, or other inflammatory conditions
2. Fever and constitutional signs and symptoms
3. Excellent response to corticosteroids
4. Laboratory abnormalities:
 - a. Elevated white blood cell count ($>8 \times 10^9$, of which >70 % are neutrophils)
 - b. Elevated erythrocyte sedimentation rate or C-reactive protein levels

Adapted from Marzano et al. [25]

Table 3 Diagnostic criteria for drug-induced Sweet's syndrome; requires all of the criteria to be positive

1. Abrupt onset of cutaneous lesions consistent with Sweet's syndrome
2. Histopathology compatible/consistent with Sweet's syndrome
3. Fever with constitutional signs and symptoms
4. Drug ingestion temporarily associated with onset of clinical findings with recurrence after oral rechallenge
5. Resolution with drug withdrawal
6. Excellent response to corticosteroids

Adapted from Walker and Cohen [26]

3.3 Pathogenesis

While the exact etiology of Sweet's syndrome remains unknown, circulating autoantibodies, cytokines, dermal dendrocytes, immune complexes, and genetic predisposition [28] have been discussed in the pathogenesis of Sweet's syndrome [29] and suggest an underlying hypersensitivity reaction to a variety of stimuli. Indeed, numerous associations capable of inducing these responses, including hematologic malignancies (lymphoma, myeloma) and solid organ malignancies, drugs, and inflammatory diseases (inflammatory bowel disease, autoimmune connective tissue disorders, Behcet's disease, thyroid disease, sarcoidosis) have been described [30].

3.4 What's New?

Sweet's syndrome has been expanded in terms of the spectrum of its etiologic, clinical, and histologic manifestations. There are now numerous recognized skin variants of Sweet's syndrome, and several internal organs have been shown to develop lesions consistent with Sweet's syndrome. A variant of Sweet's syndrome, termed "histiocytoid Sweet's syndrome" [31, 32], has recently been described, though that entity may be better characterized as a form of leukemia cutis with immature cells [33]. Currently, Sweet's syndrome is classified as either idiopathic or secondary to drugs, autoimmune conditions, or malignancies. Diagnostic criteria have been formulated for classic as well as drug-induced Sweet's syndrome (Tables 2, 3) [25, 26]. In addition, several new treatment modalities have been described, which include potassium iodide, dapsone, colchicine, indomethacin, clofazimine, cyclosporine, interferon- α , and tumor necrosis factor (TNF)-blocking biologics [34].

Overall, Sweet's syndrome typically follows a benign course, which, if untreated, can involute spontaneously without scarring in 5–12 weeks. However, there is a significant proportion of patients in whom the disease affects vital internal organs or is associated with an increasing

number of malignancies or drugs. Given the febrile nature of Sweet's syndrome, patients are often uncomfortable, and treatment may be necessary for symptomatic relief. Patients with malignancy-associated Sweet's syndrome, particularly patients with myelodysplastic syndrome/acute myelogenous leukemia, may be mistakenly diagnosed with infection. In these cases, diagnosis and treatment of Sweet's syndrome may be important to resolve the fever. Sweet's syndrome is rapidly and strikingly responsive to systemic corticosteroids (as one of the minor criteria), and treated patients will often defervesce within 24 h. Patients who fail to respond warrant consideration for alternate diagnoses. In all patients with Sweet's syndrome, it is important to perform a careful review of systems, along with a targeted investigation.

4 Bowel-Associated Dermatitis–Arthritis Syndrome

4.1 Clinical Presentation

Bowel-associated dermatitis–arthritis syndrome (BADAS), previously known as bowel bypass syndrome, is usually seen subsequent to gastrointestinal pathology [35]. The first cases were reported in 1971 following jejunioileal bypass surgery. Dicken and Seehafer in 1979 coined the term "bowel bypass syndrome" and related the pathogenesis to the bacterial overgrowth in blind loops of bowel [36, 37]. Subsequently, following the reporting of cases of this syndrome in patients who had no previous history of intestinal bypass surgery but had inflammatory bowel disease or Bilioth II surgery with blind loops of bowel, Jorizzo introduced the term "bowel-associated dermatitis–arthritis syndrome" [38].

BADAS typically presents with polyarthralgia, polyarthritis, myalgia, and a variety of cutaneous manifestations, in conjunction with significant bowel symptoms, including diarrhea and malabsorption. Skin manifestations include panniculitis, ecchymosis, pustular vasculitis, and erythema nodosum (EN). Skin lesions often present rapidly within days and may recur over several weeks. The polyarthritis is episodic and migratory, and involves predominantly peripheral joints [39].

4.2 Histopathology

Early lesions demonstrate infiltration of neutrophils in mid-dermal venules and a perivascular mononuclear cell infiltrate. In older lesions, the edema in the papillary dermis increases to form a vesicle and the density of the dermal neutrophil infiltrate increases to form a pustule. There is no endothelial necrosis, infarction, or fibrinoid degeneration characteristic of a true leukocytoclastic vasculitis [39].

4.3 Pathogenesis

The pathogenesis of BADAS is poorly understood, but it is believed that blind loops of bowel and microbial overgrowth lead to an immune complex disease due to bacterial antigens. The disease is purported to be associated with entities that predispose to bacterial overgrowth secondary to bowel insults that promote stasis. These include surgery (gastric resection, jejunioileal bypass, biliopancreatic diversion, blind loops of bowel) or inflammatory conditions (inflammatory bowel disease, diverticulitis, peptic ulcer disease), and there have even been reports after appendicitis [40]. BADAS has been described between 3 months to 5 years post-surgery and with a reported incidence of up to 20 %. Typically, flu-like symptoms precede the development of the skin rash and arthritis by 12–36 h [39].

4.4 What's New?

In recent decades, multiple cases of BADAS have been reported, and the characteristics and etiology have been expanded and better defined. With the increase in the incidence of obesity and bariatric surgeries related to this, case reports of BADAS following this type of surgery have been reported rarely [37, 40]. The delayed period of time between surgery and development of BADAS can hinder prompt diagnosis and treatment of the disease.

5 Behcet's Disease

5.1 Clinical Presentation

Behcet's disease is an inflammatory multisystem disease, which can have an extremely variable course with unpredictable exacerbations and remissions. The exact pathogenic mechanism is unknown, but it is believed to involve genetic and environmental factors, with the *HLA-B*51* allele being strongly associated with the disease in Asian populations [41]. Behcet's disease is typified by the presence of recurrent oral and genital ulceration, ocular abnormalities (uveitis, retinal vasculitis), and skin lesions [42]. Cutaneous findings have been reported in 80 % of patients, commonly on the face and acral sites [2]. Recurrent oral and genital ulcers, pseudo-folliculitis, pustular and purpuric papules, PG, and EN-like lesions may be seen. EN-like lesions may be seen on the buttocks and legs, particularly in women, as well as on the face and neck, and can resemble thrombophlebitis—which itself can affect 30 % of patients with Behcet's disease. The various systems are affected by both vasculitis and thrombotic events. A pathergy test is positive in 30–40 % of patients with

Behcet's disease and more commonly in patients of Asian or Middle Eastern ethnicity [29, 43, 44].

5.2 Histopathology

Behcet's disease is a systemic perivascularitis with a variety of histologic findings. In early lesions, significant neutrophil infiltration is seen, including in mucocutaneous aphthae, the skin pathergy reaction, nodular lesions of the skin, and ocular lesions [41].

5.3 Pathogenesis

The exact pathophysiologic mechanism is still undetermined; however, studies have demonstrated the potential role of impaired fibrinolytic kinetics in generation of the hypercoagulable/prothrombotic state in Behcet's disease [41]. Molecular mimicry following infection with various pathogens and immunologic abnormality likely play a significant role [29]. Multiple cytokines and chemokines play a substantial role in the disease pathogenesis and even in organ lesions, which may provide essential clues to the target therapy regimen of cytokine agents [45]. Interleukin (IL)-6 has been shown to be associated with disease activity in several studies [45].

5.4 What's New?

In the revised Chapel Hill Consensus Conference classification, Behcet's disease has been classified as variable vessel vasculitis (VJV), with multiple presentations such as small-vessel vasculitis, arteritis, arterial aneurysms, and venous and arterial thromboangiitis and thrombosis [4]. Recent studies have demonstrated the role of cytokines in the pathogenesis of Behcet's disease. The cytokines involved can be categorized as T helper (Th)-1, Th2, and Th17 types, chemokines, and other proinflammatory cytokines [45]. The IL-10 and IL-23/IL-17 pathways are crucial in the pathogenesis of the disease, and new treatments have been used with success, such as anti-IL-1 targeted inhibitors [46], anti-IL-6 receptor inhibitors [47], and anti-CD20 monoclonal antibodies, intravenous immunoglobulin, and stem cell treatment [48].

6 Palisaded Neutrophilic and Granulomatous Dermatitis

6.1 Clinical Presentation

Palisaded neutrophilic and granulomatous dermatosis (PNGD) is a rare neutrophilic dermatosis, with varied clinical presentations. It usually presents in patients with an

underlying systemic condition, such as a connective tissue disease, inflammatory arthritis, lymphoproliferative disorder, or infection; in rare cases, it may be medication induced [49].

The most common clinical presentation is that of erythematous papules, which may appear to be umbilicated or crusted, and symmetrically distributed on extensor surfaces of the upper extremities, especially the fingers and elbows [50–54]. These have been reported as ranging from urticarial papules to more fixed pink-red papules to more flesh-colored fibrotic papules. In a review of 81 patients [51], the extremities were the most common presenting location, with 51.1 % involving the upper extremities and 27.7 % involving the lower extremities. The trunk and head and neck regions were involved in 21.2 % of patients [55–57].

While erythematous papules around the elbows are the classic description, the breadth of lesions now described as PNGD is quite varied and can also include patches, plaques, or nodules.

6.2 Histopathology

Like its clinical presentation, the histopathologic features of PNGD vary. Chu et al. [58] have suggested that it represents a histologic continuum. Early lesions show evidence of leukocytoclastic vasculitis, with diffuse peridermal infiltrates composed of neutrophils, nuclear debris, and strands of amorphous basophilic material. Late lesions usually lack leukocytoclasia [16], with palisaded granulomas and degenerated collagen being the predominant findings [58]. Each stage of development can elicit a different differential diagnosis; thus, clinicopathologic correlation is compulsory.

6.3 Pathogenesis

The responsible underlying mechanisms for development of PNGD remain poorly understood. Direct immunofluorescence studies have demonstrated the presence of immunoglobulins and C3 deposits in vessel walls [50, 58]. PNGD may be a cutaneous marker of systemic disease, especially diseases with a suspected autoimmune pathogenesis [54]. PNGD can occur in the setting of rheumatoid arthritis [51, 54]. The presence of PNGD, like rheumatoid nodules and rheumatoid vasculitis, has been associated with higher disease activity scores and greater disease severity [59].

6.4 What's New?

Different terms were used to describe this condition until the description “palisaded neutrophilic and granulomatous dermatitis of immune-complex disease” was coined in 1994.

Systemic lupus erythematosus and rheumatoid arthritis have been more commonly reported as underlying causes [54, 60]. PNGD and other reactive granulomatous skin findings have been reported in the setting of malignancies, particularly hematologic malignancies (myelodysplastic syndrome, leukemia, lymphoma, and paraproteinemia). If the underlying disease is not known, then the history, physical examination, and laboratory tests should be directed toward diagnosing the underlying conditions. There is confusion in the literature between PNGD and a related reactive granulomatous process, interstitial granulomatous dermatitis (IGD). Some authors consider PNGD to be a subtype of IGD, whereas others consider PNGD and IGD to be distinct reactive processes, which may be similar to or distinct from rheumatoid neutrophilic dermatitis (RND).

7 Rheumatoid Neutrophilic Dermatitis

7.1 Clinical Presentation

RND is an uncommon skin condition, which was first described by Ackerman in 1978 [59, 61, 62]. While most described cases are associated with RA, RND can also be observed in patients with seronegative arthritis [62, 65].

Patients classically present with papulonodules and/or plaques distributed on the extensor surfaces of the extremities (Fig. 3), particularly the hands and forearms, as well as the neck and trunk. Overall, the lesions tend to be asymptomatic, and patients do not display constitutional symptoms [63].

7.2 Histopathology

Histologically, one observes a dense neutrophilic dermal infiltrate, which is accentuated in the upper and middle

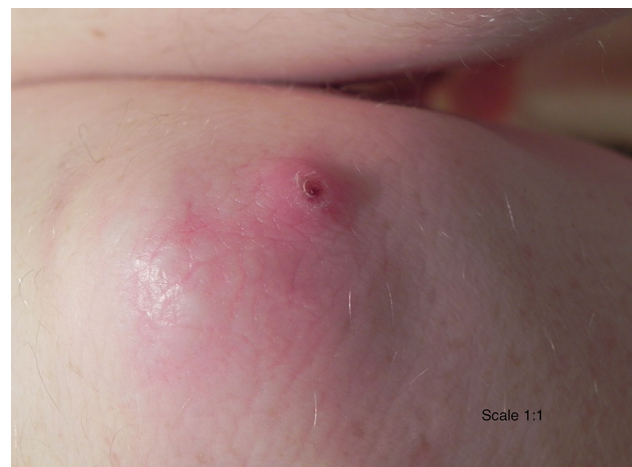


Fig. 3 Rheumatoid neutrophilic dermatitis, presenting as papulonodules on the extensor surface of the hand

levels. Indeed, in late lesions, this last finding may be the only evidence of a neutrophilic dermatosis; thus, this may make the diagnosis more difficult [63, 64]. Overall, histologic features of both Sweet's syndrome and dermatitis herpetiformis, along with plasma cells, all in the context of rheumatoid arthritis, should lead to the diagnosis.

7.3 Pathogenesis

The pathogenesis and etiology of RND is not completely understood, though it has been suggested that it is likely an immune-complex-mediated disease [65].

7.4 What's New?

Numerous skin variants of RND have been described. Overall, RND typically follows a benign course, and while the lesions may resolve spontaneously, the norm for this condition is to be persistent, symmetrical, and chronic. Some authors also view PNGD as yet another histologic variant of RND [54], though in the absence of visible granulomas on histology, it seems reasonable to suggest that the two represent separate entities.

8 Pyoderma Gangrenosum

8.1 Clinical Presentation

PG is a rare, recurring, chronic, and painful disease, with four distinct clinical variants: ulcerative, bullous, pustular, and superficial granulomatous (or vegetative). Although the cause of PG is unknown, between 45 and 75 % of cases are associated with systemic disease, including

inflammatory bowel disease, myeloproliferative disorders, connective tissue disease, and rheumatoid arthritis [25, 43, 66, 67].

The clinical course of PG is unpredictable—from a precipitous onset with rapid spread to a more indolent pattern. PG lesions comprise one or more central papulopustules surrounded by an erythematous or violaceous gunmetal induration, a bulla on a violaceous base, or erythematous nodules (Fig. 4a). Pathergy is present in 25–30 % of patients with PG and presents as extension of existing PG lesions or appearance of new lesions following dermal injury [27, 43]. The vesiculobullous variant of PG has been associated with myeloproliferative disorders in as many as 70 % of cases and has an increased incidence of occurrence on the face and the dorsum of the hands; this may show significant overlap with Sweet's syndrome and the subtype neutrophilic dermatosis of the dorsal hand [43, 68]. The pustular form is commonly associated with inflammatory bowel disease [69]. The vegetative form of PG is not usually associated with the underlying disease and is found predominantly on the head and neck [25, 43]. Very rarely, as in Sweet's syndrome, extracutaneous sterile neutrophilic infiltrates can be observed in the bones, liver, lungs, pancreas, spleen, kidneys, and central nervous system of patients with PG. PG is often a diagnosis of exclusion, and frequently it is misdiagnosed [67]. The proposed diagnostic criteria for classic ulcerative PG are listed in Table 4 [70].

8.2 Histopathology

The hallmark of PG is accumulation of neutrophils in the skin and, rarely, in internal organs (Fig. 4b). Although PG is characterized by the presence of inflammatory dermal

Fig. 4 Pyoderma gangrenosum (PG): **a** painful ulcer with a purulent base and a gunmetal border; **b** neutrophilic infiltration of the dermis, which is characteristic of PG on histology

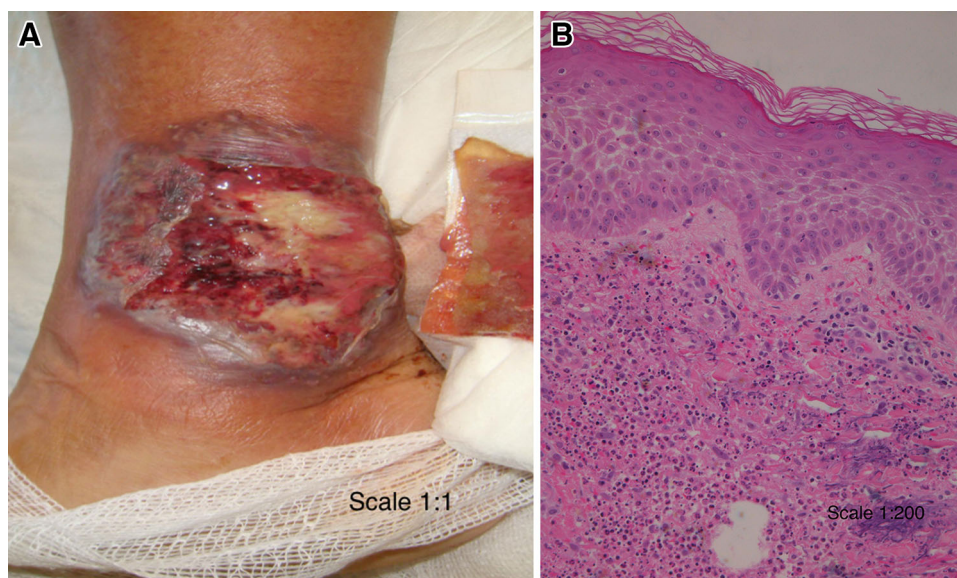


Table 4 Proposed diagnostic criteria for classic ulcerative pyoderma gangrenosum (PG); the diagnosis requires both major criteria and at least two minor criteria

Major criteria

1. Rapid progression of a painful, necrolytic cutaneous ulcer with an irregular, violaceous, and undermined border
2. Exclusion of other causes of cutaneous ulceration

Minor criteria

1. History suggestive of pathergy or clinical findings of cribriform scarring
2. Systemic diseases associated with PG
3. Histopathologic findings
4. Treatment response to systemic steroids

Adapted from Su et al. [70]

infiltrates composed of mature neutrophils on histology, the diagnosis is based on clinical correlation and exclusion of other causes.

8.3 Pathogenesis

Immunohistochemical studies have demonstrated the expression of CD3-positive T cells and CD163-positive cells (macrophages) at the wound edge, while, in contrast, the wound bed has mainly contained neutrophil markers. These findings demonstrate that activated T cells and macrophages at the wound edge may pave the way for extension of the ulcer [25].

8.4 What's New?

The role of inflammasomes in the pathogenesis of some cases of PG has been highlighted in recent literature. There have been reports of PG being treated with biologics. New medications including anti-TNFs, such as infliximab (chimeric anti-TNF- α monoclonal antibody), adalimumab (humanized anti-TNF- α monoclonal antibody), and etanercept (fusion protein human p75 TNF- α receptor IgG1), have been used as treatment options, with some success [67].

Brooklyn et al. [71] demonstrated that infliximab at a dose of 5 mg/kg was superior to placebo for treatment of PG in a randomized, placebo controlled trial, where 29 patients received infliximab. At week 6, 20 patients (69 %) demonstrated a beneficial clinical response, with remission in 6 patients (21 %), while the control group had no response. PG has been listed in some literature as an auto-inflammatory disorder, especially in the context of PAPA (pyogenic arthritis, PG, and cystic acne) syndrome [2, 24]. In PAPA syndrome, different mutations induce assembly of inflammasomes through increased binding affinity to

pyrin. Overproduction of IL-1 β [27] triggers release of several proinflammatory cytokines and chemokines, which recruit and activate neutrophils and lead to neutrophil-mediated inflammation [25, 72].

Hadi and Lebwohl [73] showed that clinical clues to PG are undervalued. In the absence of clinical characteristics, pathologic features should not be the sole grounds for diagnosing an ulcer appearing at an atypical site. Misdiagnosis of PG is common. In a study by Weenig et al. [74], a retrospective chart review of 240 patients demonstrated a large number of cases of skin ulcers with resemblance to PG. These findings highlight the need for thorough evaluation in all patients with a diagnosis of PG in order to rule out alternative diagnoses.

9 Conclusion

Neutrophilic dermatoses are a heterogeneous group of reactive diseases, which are unified by the predominance of neutrophils within the inflammatory infiltrate of active skin lesions. A comprehensive review of the treatment options is beyond the scope of this article. The first intervention consists of supportive care and avoidance of possible triggers, which may be the only intervention needed by some patients. Additional treatments should be prescribed according to the severity of the cutaneous involvement, chronicity, and whether or not systemic involvement is present. Careful management of chronic underlying diseases—for example, rheumatoid arthritis or inflammatory bowel disease—can prevent rebound flares [3]. Despite the clinical overlap, each entity shows unique differences in the frequency and/or the hierarchy of associated systemic findings. These associations highlight the need for more attention toward this group of inflammatory diseases.

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