

PRIMARY CUTANEOUS NEUTROPHILIC DISORDERS

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ABSTRACT

The 'classical neutrophilic dermatoses' comprise a spectrum of disorders characterised by rash and neutrophilia. The defining histopathological finding is of a sterile neutrophilic infiltrate. Differentiation from cutaneous infection is essential to diagnosis. Triggers including drugs, infections, and malignant processes, and underlying systemic disorders including inflammatory bowel disease, account for the majority of cases; thorough investigation should be undertaken to exclude these. Steroid-responsiveness is an almost universal finding. We describe these disorders in detail and discuss the many rare presentations and appropriate management.

Keywords: Cutaneous neutrophilic disorders, neutrophilic dermatoses, Sweet's syndrome, pyoderma gangrenosum, neutrophilic dermatosis of the dorsal hands.

INTRODUCTION

The spectrum of cutaneous disorders which are histopathologically associated with a neutrophilic infiltrate is vast. Epidermal neutrophilic infiltrates typify subcorneal pustular dermatosis, acute generalised exanthematous pustulosis, transient neonatal pustulosis, and infantile acropustulosis. Skin biopsy from patients with bullous disorders including dermatitis herpetiformis, linear immunoglobulin A (IgA) disease, and epidermolysis bullosa acquisita commonly demonstrate a subepidermal blister with a predominantly neutrophilic inflammatory infiltrate. Neutrophilic vasculitis may be seen in medium and small vessel vasculitis including erythema elevatum diutinum, and in association with Behçet's disease (BD). Neutrophil-predominant eruptions are not uncommon in idiopathic autoimmune connective tissue diseases including lupus and rheumatoid arthritis (RA), and are well documented in association with periodic fever syndromes. In neutrophilic eccrine hidradenitis, a reaction pattern most commonly seen in patients receiving chemotherapy, eccrine necrosis is associated with a neutrophilic infiltrate. Among this vast spectrum

of disorders many overlapping clinical and histopathological features may be seen.

Within this array of disorders with varying pathogenesis, a small subset of disorders - Sweet's syndrome (SS), pyoderma gangrenosum (PG), and neutrophilic dermatosis of the dorsal hands - comprise the 'classical neutrophilic dermatoses (NDs)', which are the focus of this review. These conditions are generally considered to be reactive processes, often occurring in response to triggers including drugs, malignancy, and underlying systemic disorders such as infection, and frequently, inflammatory bowel disease. Any single patient may present with a combination of papules, plaques, pseudo-vesiculation (PV), or bullae and frank ulceration may be seen. Differentiating between the disorders can be difficult as more than one pattern of neutrophilic disorder may co-exist. Associated fever, circulating neutrophilia, and elevated inflammatory markers are often documented. The defining histopathological finding is of a sterile diffuse or perivascular neutrophilic predominantly dermal infiltrate. Steroid-responsiveness is an almost universal finding.

SWEET'S SYNDROME

SS (acute febrile ND) can be divided into three main types dependent on the aetiology. The most common is classic, followed by malignancy-associated and drug-associated. Classic SS is frequently associated with streptococcal upper respiratory tract infections, yersinial gastrointestinal (GI) infections, inflammatory bowel disease (IBD), and pregnancy.^{1,6} Less common associations include HIV, atypical mycobacteria, Bacillus Calmette-Guérin vaccination, cytomegalovirus, chlamydia, viral hepatitis, BD, erythema nodosum, sarcoidosis, RA, thyroid disease, and primary immunodeficiencies.¹ It is difficult to ascertain whether these are true associations due to the low numbers reported.

The cutaneous eruption in malignancy-associated SS may precede, follow, or occur concurrently with malignancy. The majority are haematological malignancies, especially acute myelogenous leukaemia.⁷ Solid tumours are most commonly of genitourinary organs, breast, and GI tract, and rarely prostate and larynx.⁸ Many drugs are associated with SS, with the eruption usually occurring around 2 weeks after exposure in a previously sensitised patient. The most commonly reported are granulocyte colony stimulating factor (G-CSF), nonsteroidal anti-inflammatory drugs (NSAIDs), co-trimoxazole, and carbamazepine. Other culprits include other antibiotics (minocycline [MC], nitrofurantoin, norfloxacin, and ofloxacin), antiepileptics (diazepam), antiretrovirals (abacavir), antihypertensives (hydralazine), antineoplastics (bortezomib, imatinib mesylate, and lenalidomide), antipsychotics (clozapine), anti-thyroid hormone synthesis (propylthiouracil), contraceptives, diuretics (furosemide), immunosuppressants (azathioprine), and retinoids.⁹

The pathogenesis is unknown; possible factors include a hypersensitivity reaction to bacterial, viral drug, or tumour antigens. This theory is supported by the association with infections, autoimmune diseases, IBD, malignancies, and the excellent response to glucocorticoids. Cytokines and chemokines have been demonstrated to be important effectors of tissue damage¹⁰ while G-CSF,¹¹ interleukins, and interferon gamma¹² play important roles. SS, as well as PG, have been considered in some studies to be prototypic autoinflammatory skin diseases.^{5,6} Genetic susceptibility has been reported, with sibling cases described, abnormalities

in chromosome 3q¹³ detected, and associations with HLA-Bw54.¹⁴ All ages can be affected but it usually occurs between 30-60 years of age,¹ with an older age of onset in the malignancy-associated subtype. There is a slight female predominance, with the greatest difference in the classic form (80%), followed by drug-associated (70%) and solid tumour-associated (60%), and with no difference found in those with a haematological malignancy.¹ There is a male predominance in children under the age of 3,¹⁵ but no difference in children over this age.

The cutaneous manifestations are varied (Figure 1). The typical presentation is of tender erythematous, or less commonly, violaceous papules which rapidly develop into deep red plaques and nodules. Size may vary widely, even within the same patient, but lesions typically measure 2-5 cm in diameter. Dermal oedema may lead to a pseudovesicular or pseudopustular appearance. Pustules, when seen, result from neutrophil migration into the epidermis. The lesions may appear targetoid with a central yellowish colour. They can be multiple or solitary and localised or widespread, and favour the head, neck, and upper limbs.¹ Pathergy, an exaggerated skin response to minor trauma, is common. Less common presentations include a bullous form with vesicles and bullae overlying erythematous plaques, which are most frequently in association with myelogenous leukaemia. A subcutaneous form presents with painful erythematous nodules with minimal superficial change that may resemble cellulitis. Oral lesions are uncommon but are described in 12% of patients with haematological malignancies.¹ Additional reports of mucosal involvement include bullae, vesicles, gingival hyperplasia, necrotising ulcerative periodontitis, and tongue swelling.



Figure 1: Pseudovesiculation seen in classical Sweet's syndrome affecting the lower back.

Associated fever occurs in 40-80% of patients but can be intermittent.¹ >50% of patients have leucocytosis. 20-50% of patients have arthralgias, arthritis, myalgias, and ocular involvement.¹⁶ Much less common extracutaneous manifestations include neutrophilic alveolitis, multifocal sterile osteomyelitis, and renal involvement. Rare systemic manifestations include hepatitis, acute myositis, aseptic meningitis, encephalitis, pancreatitis, GI involvement, or involvement of the spleen and heart. Investigations often reveal a peripheral leucocytosis with neutrophilia. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are frequently elevated. Perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) or cytoplasmic-ANCA are sometimes present. Typical histopathological features of SS are upper dermal oedema, a dense predominantly neutrophilic infiltrate in the mid-dermis, while neutrophils aggregate around vessels, but usually without vasculitis (Figure 2).

Diagnostic criteria have been proposed.¹⁷ Both major criteria and two of four minor criteria are required for a diagnosis of SS.

Major criteria:

1. Abrupt onset of typical cutaneous lesions.
2. Histopathology consistent with SS.

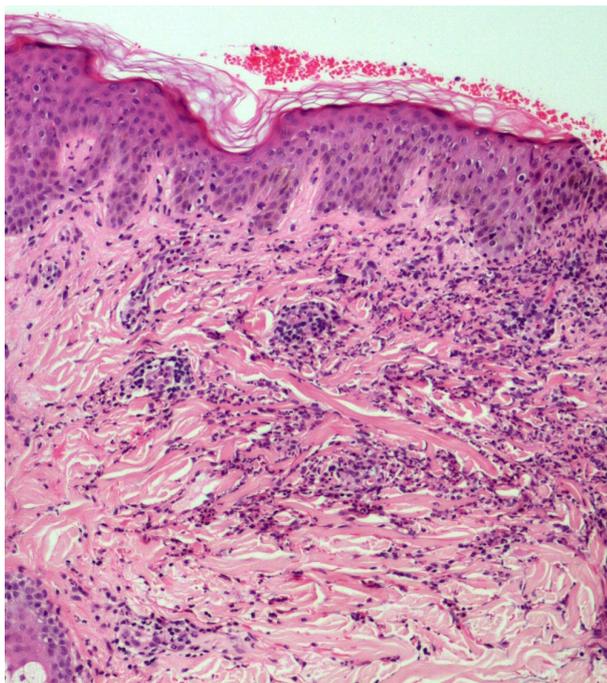


Figure 2: Sterile neutrophilic infiltrate seen in Sweet's syndrome.

Minor criteria:

1. Pyrexia >38 °C and constitutional signs and symptoms.
2. Association with underlying haematological or visceral malignancy, inflammatory disease or pregnancy, or preceded by upper respiratory infection, GI infection or vaccination, or association with a drug.
3. Abnormal laboratory values at presentation (three of four of the following: ESR >20 mm/hr, positive CRP, >8,000 leucocytes, >70% neutrophils).
4. Excellent response to systemic corticosteroids.

Systemic glucocorticoid therapy is first-line treatment with rapid improvement usually occurring within days. The extracutaneous manifestations also respond to systemic corticosteroid therapy. High potency topical corticosteroids, or intralesional corticosteroid injections, can be used as an adjunctive therapy or alone in mild cases. Colchicine, dapsone, or potassium iodide can be used as alternative first-line treatments in those who cannot be treated with systemic glucocorticoids. Other reported treatments include NSAIDs, cyclosporine, anti-tumour necrosis factor alpha (TNF- α) biologic agents, tetracyclines, mycophenolate, clofazimine, and thalidomide. Severe ulcerated cases associated with malignancy may persist despite treatment.

PYODERMA GANGRENOSUM

PG occurs due to intense neutrophilic inflammation inducing skin destruction, usually resulting in a painful necrotic ulcer. It occurs rarely with an estimated incidence of 3-10 cases per million people per year.¹⁸ The average age of onset is between 40-60 years of age, and once again a female predilection has been noted.¹⁹ Suggested pathogenic mechanisms include abnormalities in neutrophil function and dysregulation of the innate immune system. Familial cases have been reported and PAPA syndrome, which is characterised by pyogenic sterile arthritis, PG, and acne, has been linked to mutations in the *PSTPIP1/CD2BP1* gene on chromosome 15q.²⁰

Approximately 50% of cases are associated with an underlying systemic disease^{19,21} such as: IBD, RA or seronegative arthritis, IgA monoclonal gammopathy, haematological malignancy (myeloid leukaemias and multiple myeloma), chronic active

hepatitis, and Wegener's granulomatosis. Other rare but not verified associations include pulmonary disease, systemic lupus erythematosus, thyroid disease, solid organ cancers, viral and autoimmune hepatitis, sarcoidosis, and major depression.^{19,22} Although not formally validated, diagnostic criteria have been proposed.²³

Major criteria (both required):

1. Rapid (usually 1 cm/day) progression of painful, necrolytic ulceration with an irregular, undermined, violaceous border—usually with a preceding papule, pustule or bulla, and pain out of proportion to the size of the ulcerated area.
2. Exclusion of other causes of ulceration.

Minor criteria (at least two required):

1. A history of pathergy, or presence of cribriform scarring.
2. Presence of a disease known to be associated with PG (IBD, polyarthritis, myelodysplasia, leukaemia, monoclonal gammopathy).
3. Appropriate histopathological findings (again, specifically excluding infective causes).
4. Rapid response to oral corticosteroid therapy (usually interpreted as at least 50% reduction in size using 1-2 mg/kg/day).

PG classically presents as an exquisitely painful red/blue papule, nodule, vesicle, or haemorrhagic pustule, which breaks down to form a painful ulcer with an undermined violaceous margin. The base can be granulating, purulent, or necrotic. The ulcer often extends into the subcutaneous fat and occasionally to the fascia. It usually resolves with atrophic, cribriform scars. Several ulcers may develop simultaneously. The surrounding skin is red and indurated. Pathergy with induction or exacerbation at sites of incidental or iatrogenic trauma is described but does not occur in all patients. The lower legs are the most frequently affected¹⁸ (Figure 3). Associated symptoms include fever, malaise, myalgia, and arthralgia. Variants include bullous, pustular, superficial granulomatous, peristomal, and extracutaneous PG. Bullous PG, characterised by blue-grey inflammatory bullae, most commonly occurs in patients who have underlying haematological disease.^{18,24} The lesions erode resulting in superficial ulcers. Pustular PG is more commonly associated with IBD and tends to occur

with flares of the bowel disease. Painful pustules with surrounding erythema, associated fever, and arthralgia are characteristic. It usually resolves with control of the bowel disease but can evolve into the ulcerated classic form.²⁵ Pyostomatitis vegetans also has a strong link with IBD and presents with multiple small pustules on the oral mucosa.¹⁸

Superficial granulomatous pyoderma (vegetative PG) is a solitary, localised, mildly tender nodule, plaque, or ulcer without an undermined border or purulent base, often occurring on the head, neck, or trunk. It is slowly progressive and is not usually associated with systemic disease.¹⁸ Peristomal PG describes the development of ulcerative PG around a stoma site. This typically occurs in association with IBD, and can develop months or many years after the placement of a stoma.¹⁸ PG can rarely involve extracutaneous sites such as the lungs, intestine, cornea, liver, spleen, heart, bones, muscle, and central nervous system. Investigations are most useful to rule out other disorders and to assess for associated disease. The wound should be swabbed and cultured for microorganisms. Classic histopathological findings are much less specific than SS, although the findings may overlap, and include sterile neutrophilic inflammation with abscess formation; a lymphocytic or leukocytoclastic vasculitis is sometimes also seen.

Super potent topical corticosteroid ointment under non-adherent dressings with gentle compression bandaging, if tolerated, should be applied. Wounds should be cleansed gently to avoid pathergy, and barrier creams should be used around the edge of the wound to prevent further breakdown.



Figure 3: Pyoderma gangrenosum affecting the lower leg.

High-dose systemic corticosteroids reducing with response are usually needed, particularly for more extensive disease. Treatment is usually successful in preventing further progression but complete healing may take weeks or months, and treatment should be tapered slowly over many months, rather than stopped abruptly, to avoid recrudescence of the disorder. For recalcitrant disease, alternative immunosuppressants may be necessary as an alternative or adjunctive treatment; these include cyclosporine, intravenous Ig, dapsone, tetracyclines, or an anti-TNF biologic agent (e.g. infliximab). Surgery should be avoided if possible due to the risk of pathergy. Once the diagnosis of PG has been made, investigations should be directed to identify an associated systemic disease.

ND OF THE DORSAL HAND

Classically presenting with clinical features of SS, cutaneous involvement is restricted almost entirely to the dorsum of one or both hands. In contrast to SS, ulceration is common. This entity is frequently misdiagnosed as infection due to the clinical appearance, which may be unilateral, the frequent presence of fever, neutrophilia, and elevated ESR. The absence of microorganisms on blood and tissue culture and the lack of response to anti-microbial therapy, in addition to neutrophilic vasculitis, which is frequently seen on histopathology, are clues to diagnosis. ND of the dorsal hand, which

may be considered to be a localised variant of SS, appears to be less frequently associated with systemic malignancy than either SS or PG,^{26,27} although investigations should be undertaken in a similar manner to identify a potential trigger. After investigation for and elimination of triggering infection, drugs, or malignancy, treatment approach is identical to that of SS and includes appropriate wound care, topical and systemic steroids, and less frequently systemic immunosuppression with the agents described above.

CONCLUSION

The 'classical NDs' comprise a spectrum of eruptions typified by a prodrome of fever and malaise, followed by the onset of papules, plaques, PV, or bullae and frank ulceration. Systemic upset including fever, circulating neutrophilia, and elevated inflammatory markers are often seen. The defining histopathological finding is of a sterile diffuse or perivascular neutrophilic predominantly dermal infiltrate. Differentiation from cutaneous infection is essential to diagnosis. Systemic disorders such as infection, IBD, and malignancy, along with drug triggers, account for the majority of cases, and thorough investigation should be undertaken to exclude these. Steroid-responsiveness is an almost universal finding, although second-line immunosuppression may sometimes be required.

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