

# NEUTROPHILIC DERMATOSES REVISITED

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**Disclosure:** No potential conflict of interest.

**Received:** 24.07.14 **Accepted:** 15.09.14

**Citation:** EMJ Dermatol. 2014;2:77-85.

## ABSTRACT

The neutrophilic dermatoses (ND) comprise a group of heterogeneous disorders characterised by inflammatory skin lesions that histologically show an intense inflammatory infiltrate composed primarily by neutrophils, with no evidence of infection. Although there are distinct clinical differences in the classical lesions of these disorders, many patients have overlapping features. In this mini-review we describe the clinical aspects of the main NDs, including: Sweet's syndrome, neutrophilic dermatosis of the dorsal hands, pyoderma gangrenosum, erythema elevatum diutinum, subcorneal pustular dermatosis, neutrophilic eccrine hidradenitis, rheumatoid neutrophilic dermatitis, neutrophilic panniculitis, and aseptic abscesses, their association with underlying diseases, differential diagnosis, treatment options, and prognosis.

**Keywords:** Neutrophilic dermatoses, Sweet's syndrome, pyoderma gangrenosum, subcorneal pustular dermatosis, erythema elevatum diutinum, neutrophilic eccrine hidradenitis, rheumatoid neutrophilic dermatitis, neutrophilic panniculitis, aseptic abscesses.

## INTRODUCTION

The neutrophilic dermatoses (NDs) are a heterogeneous group of disorders that have in common the presence of an inflammatory infiltrate of polymorphonuclear neutrophils without associated infectious cause. Although the main expression of these pathologies is in the skin, they may present with sterile neutrophilic infiltrates in various organs. The frequent involvement of multiple systems has led us to consider the NDs as a group of systemic disorders.<sup>1</sup> They also share the characteristic of being associated with underlying diseases.<sup>1,2</sup> As suggested by some researchers, the authors proposed a classification (Table 1) based on the histological location of the neutrophilic infiltration.<sup>3</sup> The location influences the clinical manifestation of the disease. If the infiltrates are epidermal, pustules are the main clinical feature, and are suggestive of the well-defined clinical entity subcorneal pustular dermatosis (SPD). The neutrophilic infiltrates in the dermis present as papules and plaques, and may represent two clinical entities: acute febrile neutrophilic dermatosis (Sweet's syndrome

[SS]) and rheumatoid neutrophilic dermatosis (RND). Nodules and ulcers are present when the neutrophilic infiltrates are deeper (dermo-hypodermic), and are representative of pyoderma gangrenosum (PG). Nevertheless, several of those conditions may display similar clinical and/or histopathological features and assume transitional and overlap forms.

## SWEET'S SYNDROME

SS is the most common, and considered the prototype, of the NDs. It usually affects middle-aged women (30-60 years) and there is no racial or geographic preference.<sup>4</sup> Some diagnostic criteria have been proposed for SS (Table 1); the abrupt onset of characteristic skin lesions and histopathology being the major criteria.<sup>4,5</sup> Some of the criteria must be carefully analysed; for example, in cancers that induce neutropaenia, leukocytosis may not occur. Therefore, some authors consider such criteria less useful in clinical practice. Variants of the SS include: the classic presentation, which may be associated with upper respiratory tract or gastrointestinal

(GI) infection, pregnancy, and inflammatory bowel disease (IBD); the paraneoplastic presentation, in which SS is the presenting manifestation or the marker of recurrence of malignancy; and the drug-induced SS, when a drug can be implicated.<sup>6-8</sup>

### Clinical Features

After a prodrome of a flu-like syndrome, an abrupt onset of painful red-purple papules that tend to coalesce, forming well-demarcated plaques, is observed many times with a pseudo-vesiculation appearance as a result of the extensive oedema on the dermis (Figure 1A). A clinical variant with tender erythematous dermal or subcutaneous nodules that clinically resembles erythema nodosum has been described.<sup>9</sup> Lesions are located asymmetrically on the face, neck, upper extremities, and rarely on the trunk and lower limbs. Sometimes a photo-distributed pattern may be seen.<sup>10</sup> Mucosal involvement is rare, usually associated with paraneoplastic SS,<sup>4</sup> and is more frequent in extensive disease. In rarer cases, atypical forms are observed with circinate, haemorrhagic, or ulcerated vesiculopustular features, and are considered by some authors as transitional forms to other types of NDs. Lesions may appear at sites of trauma. The extra-cutaneous manifestations are very common and result from organ infiltration by neutrophils.

Fever and leukocytosis are present in >50% of cases, and therefore, infectious diseases must be ruled out.

### Diagnosis

Skin biopsy shows a diffuse infiltrate of mature neutrophils in the superficial dermis and is one of the major diagnostic criteria for SS. It may extend into the subcutaneous tissue, especially if associated with myeloid disorders (neutrophilic panniculitis [NP] or subcutaneous SS).<sup>11</sup> Dermal papilla oedema, and occasional eosinophils (mainly in the drug-induced SS) and lymphocytes may be seen. Features of primary leukocytoclastic vasculitis are typically absent, but can occur as an epiphenomenon in old lesions. Direct immunofluorescence is not specific of the disease. The analytical study usually reveals neutrophilic leukocytosis (but this is not always present), an increased sedimentation rate (SR), and C-reactive protein (CRP). Once the diagnosis is established, it is essential to investigate associated systemic diseases (Table 2). It can occur in the setting of an underlying malignancy (10-20%),<sup>4</sup> namely haematological diseases, and in rarer cases with solid tumours. SS has a *bona fide* association with IBD, rheumatoid arthritis (RA), thyroid disease, Behçet disease (BD), or relapsing polychondritis.

**Table 1: Classification of neutrophilic dermatoses.**

Histopathological location of the neutrophilic infiltrates	Clinical entities
Epidermis	Subcorneal pustular dermatosis
Dermis	Sweet's syndrome Rheumatoid neutrophilic dermatitis
Dermis and vessels	Eritema elevatum diutinum
Dermis and eccrine glands	Neutrophilic eccrine hidradenitis
Dermis and hypodermis	Pyoderma gangrenosum
Hypodermis and fatty lobules	Neutrophilic paniculitis
Hypodermis and adjacent tissues	Aseptic abscesses
SWEET'S SYNDROME DIAGNOSTIC CRITERIA <sup>3,4</sup>	
<b>MAJOR</b>	
1. Abrupt appearance of papules and/or painful erythematous plaques	
2. Predominantly neutrophilic infiltrate with no signs of leukocytoclastic vasculitis	
<b>MINOR</b>	
1. Association with malignancies, infections, inflammatory diseases, and pregnancy	
2. Fever (>38 °C)	
3. Leukocytosis	
4. Rapid response to steroid therapy but not to antibiotic therapy	
<b>Two MAJOR plus two MINOR criteria are required for the diagnosis</b>	

**Table 2: Systemic diseases associated with Sweet's syndrome and pyoderma gangrenosum.**

	Sweet's syndrome	Pyoderma gangrenosum
Malignancies	<b>Haematological</b> Acute myeloid leukaemia Monoclonal gammopathies Myeloma Myelodysplastic syndrome <b>Solid tumours</b> Digestive, breast, genitourinary carcinoma	<b>Haematological</b> Myelodysplasia Acute myeloid leukaemia Hodgkin's disease Monoclonal gammopathies: IgA
Infections	Gastrointestinal - Yersiniosis Respiratory tract - <i>Streptococcus</i> Atypical mycobacteria, CMV, HIV	HIV, HCV
Inflammatory diseases	Crohn's disease, ulcerative colitis	Crohn's disease, ulcerative colitis
Drugs	Retinoic acid, carbamazepine, hydralazine, minocycline, nitrofurantoin, Trimethoprim-sulfamethoxazole, G-CSF, GM-CSF, furosemide, BCG vaccine Levonorgestrel/ethinylestradiol	G-CSF, interferon, Antipsychotic drugs
Other	Trimethoprim-sulfamethoxazole disease Sarcoidosis Hashimoto's thyroiditis Graves' disease Systemic lupus erythematosus Rheumatoid arthritis Pregnancy	Behçet's disease Systemic lupus erythematosus Antiphospholipid syndrome Rheumatoid arthritis Sarcoidosis Gastric and duodenal ulcer Diabetes mellitus Non-destructive oligoarticular arthritis Spondylitis
Hepatic disease	Chronic hepatitis	Primary biliary cirrhosis Chronic hepatitis

CMV: cytomegalovirus; HIV: human immunodeficiency virus infection; HCV: hepatitis C virus infection; G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; BCG: Bacille de Calmette et Guérin.

The differential diagnosis of SS is extensive, and is one of exclusion; it includes the other NDs. Fever and leukocytosis are present in septic processes that need to be ruled out. It is also important to exclude erythema multiforme (targetoid lesions and greater mucosal involvement). The pseudo-vesicular appearance may mimic herpes simplex infection.

### Treatment and Prognosis

SS is usually an acute, self-limited disease. It is corticosteroid-responsive, and a 2-week tapering course of oral prednisone in a dose of 40-60 mg/d is effective in controlling the cutaneous and extra-cutaneous manifestations. In some cases,

a more chronic relapsing course is observed and requires longer periods of systemic corticotherapy in conjunction with steroid-sparing agents. Potassium iodide (total daily dose of 900 mg) and colchicine (total daily dose of 1.5 mg) are also first-line therapies.<sup>6</sup> Dapsone is also useful for most NDs since it prevents neutrophil chemotaxis and binding to adhesion molecules. High-potency topical corticosteroids can be applied to the lesions. The prognosis of the dermatological disease itself is good, with a resolution of the lesions without scarring. Recurrences may occur in up to 33% of cases (with or without treatment), especially when there are associated diseases.

## NEUTROPHILIC DERMATOSIS OF THE DORSAL HANDS (NDDH)

NDDH is a rare disorder regarded as a subset of NDs, similar to superficial PG, pustular vasculitis of the dorsal hands, and atypical SS. It seems that they are both points on a spectrum of the same entity, which is best named NDDH. Nowadays, it is recognised as a localised variant of SS.<sup>12,13</sup> NDDH is more common in women. The dermatological lesions are similar to SS, with lesions being located exclusively on the dorsum of the hands, with no associated systemic symptoms.<sup>12</sup> The most effective systemic treatments include: corticosteroids, colchicine, and dapsone. Less frequently cyclosporine, azathioprine, methotrexate, potassium iodide, indomethacin, and minocycline have been used.

## PYODERMA GANGRENOSUM

PG is a rare disease of unknown aetiology. It appears at any age, with 4% occurring in children.<sup>14</sup> It can be idiopathic or associated with several diseases (>50%),<sup>15</sup> namely IBD (up to 41%),<sup>16</sup> RA, seronegative arthritis, haematological malignancy, paraproteinaemia, and less often solid tumours. It has been associated with hepatitis C infection, PAPA syndrome (pyogenic, sterile arthritis, pyoderma gangrenosum, severe cystic acne), and may be drug-induced (interferon- $\alpha$  2b, granulocyte colony-stimulating factor, gefitinib, propylthiouracil).<sup>6,17</sup> Besides the classic (ulcerative)

form, several variants have been described: pustular, bullous, vegetative, and peristomal PG.

### Clinical Features

The lesion begins as a follicular papule on an erythematous base, which rapidly expands and ulcerates, leading to a painful ulcer. The ulcer borders are well-defined, violaceous, and undermined. Its base is necrotic and often covered with purulent exudates. There is inflammation on the perilesional skin (Figure 1B). Healing results in cribriform scars. Lesions are usually solitary, but clusters can appear on different parts of the body. The most common location is the lower limbs, namely the pretibial area, but other skin areas (head, neck, breasts, genitalia, and upper extremity) can be involved.<sup>18,19</sup> Non-cutaneous sites such as eyes, larynx, pharynx, vulva, and oral mucosa may be affected in the form of aphthous lesions. In children, the clinical appearance of PG is similar to adults, but tends to involve the head, genital, and perianal areas.<sup>18</sup> Pathergy phenomenon may occur. Pustular PG is commonly associated with IBD and presents as multiple pustules on the extensor surface of the extremities and the upper trunk; bullous PG is associated with haematological malignancies and has features that overlap with bullous SS;<sup>6,18</sup> vegetative PG presents as superficial ulcers or solitary erosions on the trunk; peristomal PG occurs around abdominal stoma.<sup>6,7,16</sup> As with SS, PG can be associated with systemic symptoms and extracutaneous manifestations (articular, GI, ocular, and pulmonary).<sup>20</sup>



**Figure 1: A) Erythematous violaceous papules and plaques in Sweet's syndrome; B) irregular, well defined, undermined, and violaceous border of the pyoderma gangrenosum ulcer.**

## Diagnosis

There are no specific tests for the diagnosis of PG. Histopathology is useful to rule out other causes of ulcers, and a specimen should be sent for culture. The histological findings vary depending on the site and timing of the skin biopsy. Initial lesions show a dermal perivascular lymphocytic infiltrate with endothelial cell swelling. In older lesions a neutrophilic infiltrate is seen in the dermis and hypodermis.<sup>6,7,17</sup> The histopathological changes also vary with the PG variant. Therefore, the diagnosis is clinical and requires exclusion of other causes of skin ulceration.<sup>19,21</sup> The analytics usually show leukocytosis and an elevation in the SR and CRP. After the diagnosis, it is necessary to investigate the association with systemic diseases, which can occur in 50-80% of the cases (Table 2).<sup>19</sup> For a differential diagnosis, other causes of cutaneous ulceration include: infections (ecthyma gangrenosum, deep mycoses, and infection with atypical mycobacteria), vascular disease (venous or arterial insufficiency), vasculitis, facticia, and neoplasms.

## Treatment and Prognosis

The ulcer may heal spontaneously, but most cases require local and systemic treatment. Ulcer debridement is not recommended as it can aggravate the lesions. Hydrocolloid dressings may be used.<sup>14,20</sup> Intralesional corticosteroids on the edges may control the disease<sup>18</sup> and there are reports of good results with topical tacrolimus.<sup>20</sup> Topical treatments alone are usually inefficient.<sup>20</sup> Oral corticosteroids seem to be the first-line therapy. The best strategy is to start with high doses (ranging from 0.5-2.0 mg/kg/day) of oral prednisone.<sup>6,19</sup> Disease stabilisation usually occurs within 24 hours.<sup>20</sup> Tapering or discontinuation of the drug should be taken only when the new epithelial growth connecting the ulcer bed to the surrounding normal skin is observed (Gulliver's sign)<sup>21</sup> or when the ulcer is healed, respectively. The sulpha drugs may be beneficial, but not all patients will have a favourable response. Sulfasalazine is the most effective sulpha drug, especially in patients with PG associated with ulcerative colitis and in idiopathic PG. Adalimumab, etanercept, and infliximab seem to be effective, particularly if there is IBD.<sup>6,20</sup> Cyclosporine (2-5 mg/kg), either alone or in combination with systemic corticosteroids dapsone (50-200 mg/day), may be used.<sup>6,7</sup> Pain is sometimes so severe that narcotics may be required.<sup>7,20</sup> PG may resolve after treatment of the associated systemic disease. Lesions heal with cribriform scars.

EED is a rare condition with an unclear pathogenesis. It is believed to be mediated by the deposition of circulating immune complexes in the perivascular dermis, secondary to streptococcal infections and haematological or autoimmune diseases, inducing an inflammatory cascade that damages the vascular walls.<sup>22</sup> Initially classified within NDs, it is now considered as a leukocytoclastic vasculitis according to its histopathological pattern. EED can occur at any age with a peak in the sixth decade, and has no gender predilection.<sup>23</sup>

## Clinical Features

EED presents as erythematous and violaceous plaques, papules, and nodules occurring symmetrically over extensor surfaces of the hands, feet, elbows, knees, and buttocks. Older lesions have cholesterol deposits, which gives them a yellow-brown coloration that resembles xanthomas (Figure 2A). Nodules are soft and mobile, but over time they can become fibrotic or atrophic with hyper/hypopigmented scars.<sup>24</sup> Lesions of EED are usually asymptomatic, but pruritus, pain, and a burning sensation, as well as constitutional symptoms, have been reported.<sup>23,24</sup> Joint pain is the most common systemic symptom.

## Diagnosis

The pathologic features correlate with the lesion age. Acute lesions show signs of a leukocytoclastic vasculitis, with fibrin, neutrophils infiltrates, and leukocytoclasia in the wall of the small vessels of the middle and superficial dermis.<sup>25</sup> Older lesions show dermal aggregates of neutrophils, granulation, or scar tissue along with proliferation of fusiform cells in the dermis, and sometimes multinucleated giant cells.<sup>26</sup> Several diseases have been associated with EED, including recurrent infections (pharyngeal or sinopulmonary) such as syphilis, hepatitis, HIV, IBD, RA, and haematological diseases (multiple myeloma [MM], monoclonal gammopathy immunoglobulin (Ig)G or IgA, and myelodysplastic syndrome).<sup>25</sup> The differential diagnosis includes: xanthomas, SS, PG, facial granuloma, Kaposi's sarcoma, bacillary angiomatosis, angiosarcoma, and erythema multiforme.

## Treatment and Prognosis

The treatment is difficult and the dermatosis has a chronic and recurring course. The most effective treatment is dapsone, but lesions usually

recur after its suspension.<sup>25</sup> Oral corticosteroids are not effective, but topical and intralesional corticosteroids can decrease the size of the lesions.<sup>25</sup> Treatment of the underlying disease results in improvement of the lesions. Other treatment options are colchicine and niacinamide associated with tetracycline.<sup>25</sup> Reports of spontaneous resolution with atrophic scars have been described.

## SUBCORNEAL PUSTULAR DERMATOSIS

SPD is a rare, relapsing symmetric pustular dermatosis of unknown aetiology that occurs mainly in women between the ages of 40-70 years.<sup>27</sup> It is accepted that SPD results from an abnormal cytokine profile secondary to immunological dysfunction.

### Clinical Features

The primary lesion is a small sterile pustule arising on normal skin or slightly erythematous base (Figure 2B). Pustules are described as half-pustular (lower half), half-clear fluid blisters that coalesce to form annular or serpiginous patterns. Afterwards, rupture scaling, crusting, and hyperpigmentation are observed. Lesions are characteristically symmetrical and involve intertriginous areas, flexural sites of the trunk, and flexor aspects of the limbs. The face, palms, soles, and mucous membranes are usually spared. There are no systemic symptoms or abnormal laboratory findings. SPD may be associated with underlying malignancy (IgA or IgG monoclonal gammopathies, MM, chronic lymphocytic leukaemia, and solid tumours),

autoimmune disorders (such as systemic lupus erythematosus), IBD, RA, thyroid disease, and *Mycoplasma pneumoniae* respiratory infection, that must be excluded.<sup>6,27</sup>

### Diagnosis

Histopathology shows a subcorneal accumulation of neutrophils with the absence of spongiosis or acantholysis. There is a superficial split between the stratum corneum and the layers of epidermis beneath. Few eosinophils may be seen with the neutrophils in the blister.<sup>27</sup> Direct and indirect immunofluorescence are negative, which is important for the differential diagnosis with IgA pemphigus, subcorneal pustular subtype. The latter may be only distinguished through a positive IgA immunofluorescence; some consider it a continuum between neutrophilic dermatoses and autoimmune bullous disease.<sup>28</sup> Differential diagnosis include the subcorneal-type of IgA pemphigus, pemphigus foliaceus, dermatitis herpetiformis, pustular psoriasis, generalised pustulosis, generalised exanthematous pustulosis, and bacterial impetigo.

### Treatment and Prognosis

Dapsone (50-200 mg/day) is the treatment of choice, and long-term therapy is usually required to control the dermatosis.<sup>6,29</sup> Sulfapyridine (1.0-3.0 g/day), prednisone (50-100 mg/day), etretinate (0.25-1.0 mg/kg/day), tumour necrosis factor- $\alpha$  antagonists, and phototherapy have been successfully used.<sup>6</sup> The disease runs a chronic, benign, relapsing course.



**Figure 2: A) Symmetrical violaceous nodules and plaques on the toes in erythema elevatum diutinum; B) pustules on normal skin or slightly erythematous base in subcorneal pustular dermatosis.**

## NEUTROPHILIC ECCRINE HIDRADENITIS (NEH)

NEH usually occurs in patients receiving chemotherapy regimens, namely with cytarabine or daunorubicin, for acute myelogenous leukaemia.<sup>30-32</sup> It has been reported in association with haematological malignancies (without chemotherapy)<sup>31</sup> and solid tumours (lung and breast carcinomas),<sup>33,34</sup> BD,<sup>35</sup> HIV,<sup>31</sup> *Staphylococcus* or *Streptococcus* infections, haemodialysis,<sup>32</sup> granulocyte colony-stimulating factor,<sup>30</sup> zidovudine,<sup>36</sup> and acetaminophen.<sup>30</sup> The pathogenesis is unclear and may be the consequence of a direct toxic effect of a drug secreted in the sweat from eccrine coils and duct cells (at least in chemotherapy-related cases), or may be a hypersensitivity reaction within the spectrum of NDs, such as SS.<sup>30,37,38</sup>

### Clinical Features

The cutaneous lesions are polymorphic. They are presented as asymptomatic or painful erythematous to violaceous macules, papules, plaques, pustules, and nodules that may be purpuric or hyperpigmented. Lesions may be single or multiple and are always accompanied by a limited period of pyrexia.<sup>30</sup> Lesion distribution appears to be related to differences in the metabolic activity of the eccrine glands and to trauma.<sup>39</sup> The lesions are predominantly located on the face, neck, trunk, and limbs, and pathergy phenomenon may occur.<sup>38</sup>

### Diagnosis

The diagnosis is made by a skin biopsy. Histopathology shows a dense neutrophilic infiltrate within and around eccrine glands, which may be accompanied by necrosis of eccrine epithelial cells. In some neutropaenic patients, neutrophils may be scarce or absent. The epidermis is usually normal.<sup>38</sup> The differential diagnosis is with idiopathic palmoplantar hidradenitis, which occurs in children and has similar histological and morphological characteristics, but is not associated with underlying diseases.<sup>39,40</sup> It is also necessary to exclude infection, namely cellulitis, as there may be associated fever.<sup>41</sup>

### Treatment and Prognosis

Spontaneous resolution occurs within 1-3 weeks after cessation of the drugs, and without residual

scarring.<sup>30,38</sup> Anti-inflammatory treatment may be used in symptomatic disease. Recurrence is observed in the majority of the cases (up to 60%) with reinstatement of chemotherapy.<sup>42</sup>

## RHEUMATOID NEUTROPHILIC DERMATOSIS

RND is a rare cutaneous manifestation of RA and very few cases have been described.<sup>43,44</sup> It occurs most frequently in middle-aged women with severe seropositive forms of the disease.<sup>43,44</sup> It presents as asymptomatic erythematous papules, plaques, nodules, and urticarial-like lesions that are symmetrically distributed on the extensor surfaces of the extremities, trunk, shoulders, and neck. Annular, vesicular, bullous, and ulcerative lesions are less commonly observed.<sup>43,44</sup> Histopathology reveals a dense dermal neutrophilic infiltrate without vasculitis. Mild leukocytoclasia may be observed. Papillary dermal microabscesses are common and may mimic dermatitis herpetiformis.<sup>45,46</sup> However, direct immunofluorescence shows no granular IgA deposits within the dermal papilla in RND. The differential diagnosis includes the other NDs, urticarial vasculitis, and BD. Treatment is often challenging and is limited to the few cases reported. It includes topical and systemic corticosteroids, dapsone, hydroxychloroquine sulphate, methotrexate, and cyclophosphamide.<sup>47</sup> Colchicine and etretinate were used with varying success. The lesions may resolve spontaneously or with the improvement of RA.<sup>43,44</sup>

## NEUTROPHILIC PANNICULITIS

NP is a very rare entity that presents as painful, inflammatory, subcutaneous nodules, mainly located on the limbs. Fever, arthralgia, and fatigue are almost always present. Histological examination reveals neutrophilic infiltrates in the fatty lobules (lobular panniculitis) and hypodermis.<sup>47</sup> Vasculitis is also observed. Hypodermal neutrophilic infiltrates can be found in some cases of SS and PG, but they are considered as a secondary phenomenon.<sup>47</sup> The disease is usually associated with myelodysplastic syndromes. It is corticosteroid-responsive and improvement occurs within a few days after its introduction.<sup>47</sup> This condition is most probably underdiagnosed because it is wrongly confused with erythema nodosum.

The AAS is a rare inflammatory condition characterised by deep, well-defined, sterile collections of polymorphonuclear neutrophils, usually associated with pain, high-grade fever, and

leukocytosis.<sup>2</sup> The cause is unknown, but is closely related to NDs (namely SS and PG) and IBDs.<sup>3</sup> It presents as relapsing subcutaneous painful nodules that drain sterile pus. The lesions are not influenced by antibiotic therapies, but they respond well to systemic corticosteroids and immunosuppressors.<sup>2</sup>

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