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Sweet´s syndrome: A review and update on new clinical and histological variants

López-Martínez Diego [1], García-Martínez Esther [1], Segado-Sánchez Marta [1], Parra-García Jose Juan [1], Martínez-Ortega Francisco Jose [1], Roman-Gómez Julia [1], Castillo-Landete Maria [1].

[1] Dermatology Service, Hospital Clínico Universitario Virgen de la Arrixaca, El Palmar, Spain

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ABSTRACT

Neutrophilic dermatoses involve a diverse range of conditions for which significant findings have been made in recent years. Despite the lack of comprehensive understanding of the pathophysiology of neutrophilic dermatoses, patients with pyoderma gangrenosum and Sweet's syndrome exhibit elevated levels of IL-1β, IL-17 and TNFα in the skin, accompanied by a dysregulation of the innate immune system. Furthermore, autoinflammatory diseases with the presence of neutrophilic infiltrates characteristic of neutrophilic dermatoses have also been described. Sweet's syndrome is a primary dermal neutrophilic dermatosis characterized by the presence of a sterile neutrophilic infiltrate without the presence of vasculitis in the superficial and mid dermis. This is de clinical form of neutrophilic dermatosis most frequently found in clinical practice. Depending on the etiology, we distinguish classic Sweet's syndrome, Sweet's syndrome associated with neoplasia, pharmacological Sweet's syndrome and Sweet's syndrome associated with lymphoedema. The clinical manifestations of SS are diverse, however cutaneous involvement is the most common organ affected. This typically presents as painful erythematous-edematous plaques or nodules on the upper third of the body. Recently, new variants of neutrophilic dermatoses have been described, which can be divided into clinical and histological variants. The new clinical variants are blistering Sweet's syndrome, cellulitis-like Sweet's syndrome, necrotizing Sweet's syndrome, and neutrophilic dermatosis of the dorsum of the hands. Histological variants found are divided into the next patterns: cryptococcal, histiocytic, subcutaneous/panniculitic, eosinophilic, lymphocytic and xanthomyzed normolipidemic. It is recommended that all patients with neutrophilic dermatoses receive systemic treatment to prevent recurrences, which occur in 30-50% of cases. The first-line treatment should be corticosteroids.

1. Introduction

Neutrophilic dermatoses (ND) are a group of heterogeneous inflammatory diseases that present a common histological pattern of neutrophilic infiltrate without evidence of secondary bacterial infection [1]. This abnormal accumulation is associated with a wide variety of pathologies, including Sweet's syndrome (SS), dermatitis herpetiformis or pyoderma gangrenosum, among others[1,2]. The pathogenesis of these diseases is complex and multifactorial, involving dysfunctions in the immune response, abnormalities in neutrophil chemotaxis, and alterations in the regulation of cytokines and growth factors [1,2].

The skin is not the only organ affected in these pathologies. For example, sterile neutrophilic infiltrate has been found in the heart and joints in VEXAS syndrome. It has therefore been proposed to change the term neutrophilic dermatoses to "neutrophilic diseases"[1–3].

ND is associated with underlying systemic diseases such as severe hematological malignancies, autoinflammatory diseases or autoimmune diseases, especially those affecting connective tissue. [3] It is important to achieve an accurate diagnosis and to introduce effective management strategies for ND, as the associated diseases often result in severe organ damage and even death [3].

The objective of this article is to provide a comprehensive and up-to-date review of ND, with particular emphasis on their classification based on clinical and histopathological features, underlying pathogenic mechanisms, detailed clinical manifestations, and the most effective management strategies to date [1–3]. The importance of a multidisciplinary approach to the diagnosis and treatment of these diseases will be discussed, given their potential association with underlying systemic disorders and their tendency to significantly affect patients' quality of life [1–3].

2. The pathophysiology of neutrophilic dermatoses.

Neutrophils play a pivotal role in the innate immune response[4]. Upon activation within the tissue, they perform a variety of functions to combat pathogens, including phagocytosis, cytokine release and neutrophil extracellular traps [2,4]. It has recently been proposed that neutrophils also play a crucial role in regulating inflammatory and immune responses[1,2,4]. Nevertheless, an increase in neutrophil extracellular traps has been observed in skin lesions of certain conditions, including pyoderma gangrenosum, SS and urticarial neutrophilic dermatosis[4].

Recent evidence suggests that three key elements are involved in the development of ND: changes in the expression of inflammatory molecules, neutrophil dysfunction and genetic predisposition[4].

The pathophysiology of ND is currently not well understood. Patients with pyoderma gangrenosum and SS exhibit elevated levels of IL-1β and its receptor, IL-17, as well as TNFα in the skin[4]. There is evidence of dysregulation of the innate immune system, with a significant increase in serum IL-1, IL-8, Fas/Fas ligand, CD40/CD40 ligand, IFN-γ and G-CSF observed in SS patients. Furthermore, studies of subcorneal pustular dermatosis (SPD) have identified the presence of sterile collections of neutrophils accompanied by IL-1β and TNFα in the superficial layers of the epidermis[3,4]. These findings provide insights into pathogenesis of ND and suggest a common IL-1-mediated mechanism[2,3].

Proinflammatory protein complexes diffdesignated inflammasomes, exhibit dysregulation or aberrant activation, resulting in an elevation of proinflammatory cytokines, including IL-1 and IL-36[1,3,4]. This is exemplified by DITRA syndrome (interleukin-36 receptor antagonist deficiency) or DIRA syndrome (interleukin-1 receptor antagonist deficiency), which typically present with generalized pustulosis[4].

Some studies propose that they should be considered as autoinflammatory diseases, such as CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), TRAPS (tumor necrosis factor receptor 1 associated periodic syndrome) or FCAS (familial cold autoinflammatory syndrome)[4]. That is the reason why they share a number of clinical, histological, biochemical and therapeutic features[4].

For instance, SS is observed in CANDLE, while erysipelas-like skin lesions (SS-like) manifest in patients with familial Mediterranean fever. Similarly, pyoderma gangrenosum can occur in the context of autoinflammatory syndromes induced by mutations in the gene encoding proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1), such as pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), PASH (pyoderma gangrenosum, acne and hidradenitis suppurativa) and PAPASH (combination of both) syndrome[4].

3. The classification of neutrophilic dermatoses.

ND are distinguished according to several different criteria, including clinical characteristics, histological findings, laboratory tests and prognosis. In 2006, Vignon-Pennamen and Wallach proposed the most widely accepted classification of ND, which is mainly based on the location of the neutrophilic infiltrate (Table 1)[1–3].

Given the greater frequency of the clinical presentation of Sweet´s syndrome we are going to focus on this entity

Epidermal
Pustular psoriasis, Sneddon-Wilkinson disease, IgA pemphigus, infantile acropustulosis.
Primary dermal
• **No vasculitis and no blisters**
Sweet's syndrome, Pyoderma gangrenosum, Behçet's disease, Gut-associated dermatosis-arthritis syndrome.
• **No vasculitis and blistering**
Dermatitis herpetiformis, Linear IgA bullous dermatosis, Systemic Lupus Erythematosus Bullous.
• **With vasculitis**
Neutrophilic dermatosis of the dorsum of the hands, Leukocytoclastic vasculitis, Urticarial vasculitis, Erythema elevatum diutinum.

Table 1: *Classification of neutrophilic dermatoses.*

4. Sweet's syndrome.

SS is the classical clinic presentation, initially delineated in 1964 by Dr. Robert Douglas Sweet, who described eight cases of what he designated "acute febrile neutrophilic dermatosis"[5].

4.1 EPIDEMIOLOGY.

It is a pathology with a low incidence, with a higher percentage of cases described in Japanese. It occurs around the age of 30-60 years (although it also can appear in childhood and in the elderly). There is a 4:1 female predilection, although some articles show an almost equal gender distribution[5,6].

4.2 ETIOLOGY.

Depending on the etiology, we can differentiate:

- Classic Sweet's syndrome (60-70%).
The majority of classical SS is usually idiopathic, around 50% (no causative agent identified), and is the most frequent cause. A 10-20% of cases are due to concomitant infection, most commonly upper respiratory tract viral infections, cytomegalovirus, hepatitis B virus, bacteria such as Yersinia and even mycobacterial infections. The remainder 5-10% are associated with inflammatory bowel disease or autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis or sarcoidosis[7].

- Sweet's syndrome associated with neoplasia (20-30%).
The most malignant neoplasm associated are acute myeloid leukemia and myelodysplastic syndrome. In smaller proportions, SS occurs in the context of solid organ neoplasia, mainly breast, colon and lung carcinomas[6,7].

It should be clarified that SS associated with hematological malignancies is caused by a clonal infiltration of tumor cells into the skin. However, SS associated with solid organ malignancies appears to be secondary to a reactive process, as no tumor cells have been found in biopsies of these patients[7].

- Pharmacological Sweet's syndrome (10%).
There are several drugs that can cause SS. The most frequently associated is granulocyte colony stimulating factor (G-CSF), followed by FMS-like tyrosine kinase 3 (FLT3) inhibitors[8]. There are criteria for the diagnosis of pharmacological SS proposed by Walker and Cohen (Table 2)[9,10].

1.	Rapid onset of painful erythematous plaques or nodules.
2.	Histology with presence of neutrophilic infiltrate without leukocytoclastic vasculitis.
3.	Fever >38ºC
4.	Temporal relationship between taking the drug and the onset of symptoms, or the recurrence of the symptoms after taking the drug again.
5.	Disappearance of lesions after drug withdrawal.

Table 2: Diagnostic criteria for pharmacological SS proposed by Walker and Cohen. The presence of all of them is necessary for diagnosis.

A multitude of drugs associated with SS have been described, the most common of which are listed in the following table (Table 3)[1,3].

Antibiotics	Analgesics	Anticonvulsants	Antineoplastics	Immunological agents
Trimethoprim-sulfamethoxazole	Aceclofenac	Carbemazepine	Ipilimumab	G-CSF
Doxycycline	Diclofenac	Diazepam	Vemurafenib	Tocilizumab
Minocycline	Ibuprofen	Gabapentin	Lenalidomide	Azathioprine
Ciprofloxacin	Metamizole	Lamotrigine	Capecitabine	Adalimumab
Amoxicillin	Celecoxib		Sorafenib	Infliximab

Table 3: Most common SS-related drugs.

- Sweet's syndrome associated with lymphoedema.

It has been observed that Sweet's syndrome is associated with lymphoedema[11,12].The hypothesis that would explain the appearance of SS lesions is that there has been an alteration in lymphatic drainage that occurs mainly after oncological surgery such as lymphadenectomies [11,12]. The accumulation of lymph would be accompanied by the presence of higher concentrations of inflammatory cytokines, which would act as a stimulus for the migration of neutrophils. A significant advantage of this hypothesis is that it does not involve a relapse of the neoplasm, as no evidence of satellitosis or in-transit metastasis has been identified in these cases [11,12].

4.3 CLINICAL MANIFESTATIONS

The most common lesions in SS are erythematous papules, plaques, or erythematous-edematous nodules with an irregular surface. These lesions are typically non-pruritic and painful[5,6,13]. The lesions are typically distributed over the upper third of the body, affecting the face, neck region, neckline, and arms[14]. However, they can appear in any location (Figure 1). The greater the area of the body affected, the greater the likelihood of a concomitant malignant neoplasm[14]. Mucosal lesions are not typically observed, although ulcers or aphthae may manifest in patients with hematological disease. Systemic corticosteroids are effective in improving lesions within days, while spontaneous improvement takes 1-3 months and recurrence occurs in up to one-third of patients[7,10,13].

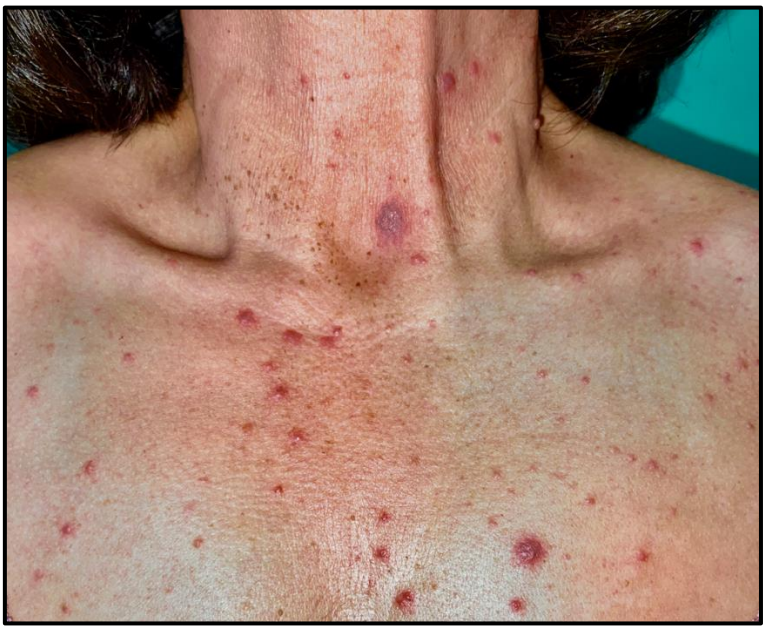

Figure 1: Erythematous and edematous papules and plaques on the neckline and anterior cervical region in a woman with Sweet's syndrome.

The lesions may present a vesicular appearance or develop true blisters within the plaque resembling a dianiform morphology[5,7]. In the case of lesions affecting the lower limbs, they typically manifest as painful papulo-nodules, which may simulate erythema nodosum. This is known as the subcutaneous or panniculitic variant of SS[9,10].

Patergia is a phenomenon observed in SS, as in other NDs. Consequently, in approximately 20-25% of cases, new lesions will emerge in areas where trauma with epidermal disruption has occurred[10,13].

4.4 EXTRA-CUTANEOUS MANIFESTATIONS.

The skin is the most frequently affected organ, although SS also presents alterations at other levels[9,10]. Fever and leukocytosis are observed in more than 50% of cases. Between 20 and 50% of patients present with musculoskeletal pathology (including arthralgias, arthritis and myositis) as well as ocular disorders, such as conjunctivitis and scleritis. About 10% of cases exhibit neutrophilic alveolitis, osteomyelitis or renal involvement (glomerulonephritis) [3,5].

Additionally, cases of patients with neurological involvement, designated "neuro-Sweet," have been documented, most commonly manifesting as meningitis, encephalitis, and SS-like skin lesions. There is a potential correlation with human leukocyte antigen (HLA) Cw1 or B54[7]. As fewer common manifestations observed we can include acute myositis, hepatitis, bronchiectasis, diffuse alveolar hemorrhage, pancreatitis and encephalitis[6,10,13].

4.5 HISTOLOGY.

The most common microscopic finding is a perivascular neutrophil infiltrate, which is predominantly observed in the superficial-medium dermis. This differs from pyoderma gangrenosum, where the infiltrate affects the superficial and deep dermis. On rare occasions, leukocytoclastic vasculitis without fibrinoid necrosis is observed, although this is not a common occurrence[10].

In the epidermis, spongiosis, reticular degeneration and even intraepidermal and subepidermal vesicles are typically observed. Neutrophils typically respect the epidermis, although subcorneal pustules or infiltration of the adnexa by polymorphonuclear cells may be observed [9,14].

New histological variants of SS have recently been described according to the predominant cellularity, which are described in detail later.

4.6 DIAGNOSTIC CRITERIA

In 1986, Su and Liu et al. proposed the following major and minor criteria for the diagnosis of SS [15]. To make a diagnosis, one major and at least two minors of the following criteria had to be met:

- Major criteria:
  - Painful erythematous erythematous-edematous papules or plaques with abrupt onset.
  - Histological findings of neutrophilic infiltrate

- The minor criteria include:
  - Associations: infection, previous vaccination, associated malignancy, associated inflammatory disorder, drugs.
  - Fever and symptoms or signs of systemic involvement.
  - Excellent response to systemic corticosteroids.
  - Leukocytosis.

These criteria were subsequently modified by von den Driesch et al. in 1994 (Table 2). In this instance, two major and two minor criteria must be fulfilled [15].

Minor criteria	Major criteria
1. Painful erythematous plaques or nodules of rapid onset.	a. Fever >38°C. b. Hematological malignancy or associated solid organ neoplasm. c. Rapid response to systemic corticosteroids or potassium iodide. d. Elevation of 3 of the following: - Erythrocyte sedimentation rate (ESR) > 20mm/h. - Elevated C-reactive protein (CRP). - Leukocyte count > 8000 x10^6. - Neutrophils > 70%.
2. Histological findings of dense neutrophilic infiltrate without leukocytoclastic vasculitis.	

Table 4: Diagnostic criteria for SS proposed by von den Driesch in 1994.

4.7 DIFFERENTIAL DIAGNOSIS.

It is necessary to consider a broad spectrum of inflammatory, autoimmune and infectious dermatoses in order to make a differential diagnosis of SS (Table 2)[2,4,10].

The most useful diagnostic test for the diagnosis of SS is a skin biopsy. No specific laboratory findings are present, although leukocytosis at the expense of neutrophils and elevated acute phase reactants (ESR and C-reactive protein) are commonly observed.

Neutrophilic dermatoses	Urticarial dermatoses	Vasculitis	Connectivopathies	Infections	Neoplasms
Pyoderma gangrenosum	Neutrophilic urticaria	Small vessel vasculitis	Acute Lupus Erythematosus	Erysipelas	Cutaneous T lymphomas
Neutrophilic dermatosis of the dorsum of the hands	Urticarial vasculitis	Erythema elevatum diutinum	Lupus erythematosus tumidus.	Cellulite	Cutaneous B lymphomas
Neutrophilic eccrine hydradenitis		Granulomatosis with polyangiitis.	Dermatomyositis	Mycobacterial infections	Cutaneous metastasis

Table 5: *Differential diagnosis of SS.*

4.8 SWEET'S VARIANTS.

A multitude of variants of SS have been delineated in recent years, exhibiting both clinical and histopathological differences. It has been documented that patients with SS may present with different subtypes of the disease over the course of their illness. For the sake of clarity, they are divided into clinical and histopathological variants[10].

4.8.1 Clinical variants of Sweet's Syndrome.

The clinical variants of SS comprise five subtypes, which will be developed below. The following clinical variants of Sweet's syndrome (SS) have been described: classical SS, bullous SS, cellulitis-like SS, necrotizing SS, and neutrophilic dermatosis of the dorsum of the hands.

4.8.1.1 Bullous Sweet's syndrome.

Bullous SS is a rare form of presentation. It presents as either flaccid or tense blisters at classical SS sites, including the extremities, trunk, and face. Histologically, dermoepidermal detachment is associated with a dense dermal neutrophilic infiltrate, without the presence of vasculitis. Cases of bullous SS have been reported in the context of acute myeloid leukemia and ulcerative colitis, suggesting that this form of presentation may be more frequent in this subgroup of patients. Some cases have been reported in the literature of an association between bullous SS and the presence of antineutrophil cytoplasmic antibodies (ANCA) in the absence of vasculitis[1,10,16].

4.8.1.2 Sweet cellulitis-like syndrome.
This presents as large, infiltrated, erythematous, edematous plaques with poorly defined borders, clinically indistinguishable from bacterial cellulitis. Diagnosis is typically made following the failure of multiple cultures to yield a positive result and the absence of clinical improvement with antibiotic treatment. Histological examination reveals a neutrophilic infiltrate affecting the superficial and dermis, with a significant dermal oedema component[17].

4.8.1.3 Necrotizing Sweet's syndrome.
The condition was first described in 2012 by Kroshinsky et al. Clinically, it is indistinguishable from necrotizing fasciitis[18,19]. The lesions evolve rapidly, presenting as erythematous and edematous skin lesions accompanied by necrosis of the subcutaneous cellular tissue. A negative bacterial culture and histological findings of a dense neutrophilic infiltrate in the dermis with involvement of the subcutaneous cellular tissue are essential for the diagnosis[18,19].

The cases published in the literature to date demonstrate an excellent response to systemic corticosteroids, although in some cases they have been used in combination with dapsone. It is of great importance to distinguish necrotizing SS from necrotizing fasciitis, as surgical debridement induces worsening and increased aggressiveness in necrotizing SS and should be avoided in this case[18,19].

4.8.1.4 Neutrophilic dermatosis of the dorsum of the hands.
The first case description was published in 1995 by Strutton et al., but it was not until 2000 that Galaria et al. gave it the name neutrophilic dermatosis of the dorsum of the hands [6]. This variant is most observed in women, with a mean age of over 60 years. The lesions present as erythematous, infiltrated, hard-to-the-touch plaques that may ulcerate or form pustules. As the name implies, the most prevalent site is the dorsum of the hands bilaterally. Cases of Koebner's phenomenon have been documented in the medical literature[6,20].

Approximately 30-40% of cases are associated with systemic disease, with hematological malignancies being the most common, followed by solid organ malignancies and infections. The histopathological findings are identical to those observed in classical SS[20].

4.8.2 Histological variants of Sweet's syndrome.
The histological variants of Sweet's syndrome are divided into the following categories: cryptococcal SS, histiocytoid SS, subcutaneous/panniculitis SS, eosinophilic SS, lymphocytic SS, and xanthomyzed normolipidemic SS are the various histological variants of Sweet's syndrome.

4.8.2.1 Cryptococcal Sweet's syndrome.
This is a relatively uncommon form of SS. The first case to be reported in the literature was detailed by Ko et al. in 2013, and subsequently by Wilson in 2017[21]. While the lesions may clinically resemble those of classic SS, cases reported in the literature demonstrate a pattern of lesions with a tendency to form ulcers, vesicles, blisters, and even necrotic lesions[21].

The typical histopathological finding is a dermal infiltrate of vacuolated mononuclear cells with basophilic bodies inside, which simulates fungal structures. However, periodic acid Schiff (PAS) and Grocott stains are negative. Some authors postulated that these structures may be degraded neutrophils, as they are positive for myeloperoxidase (MPO) staining[10,21].

The cases described have demonstrated a favorable response to systemic hydrocortisone, with an unfavorable response to systemic antifungal agents[21].

4.8.2.2 Histiocytoid Sweet's syndrome.
The condition was first described in 2005 by Requena et al. It is a rare form of SS, affecting males and females equally, and is not usually associated with extracutaneous manifestations. However, it is more frequently associated with underlying neoplasms than with classical SS[22,23].

Histological examination of this variant reveals an intense infiltrate of immature neutrophils in the dermis, accompanied by positive immunohistochemical staining for CD68 and myeloperoxidase[23,24].

The initial treatment is systemic steroids, although there are cases in the literature that do not respond to these[24].

4.8.2.3 Subcutaneous/panniculitic Sweet's syndrome.
In clinical settings, patients present with painful erythematous infiltrated nodules or plaques on the trunk and limbs. It is most often associated with hematological malignancies, with the most common being acute myeloid leukemia and myelodysplastic syndrome. Additionally, there are cases associated with Behçet's disease[25–27].

In histological terms, subcutaneous Sweet's syndrome is characterized by a dense neutrophilic infiltrate of the subcutaneous cellular tissue and findings of panniculitis[25,26].

4.8.2.4 Eosinophilic Sweet's syndrome.
In terms of clinical presentation, the lesions are like those observed in classical SS. Histological examination reveals an infiltrate comprising neutrophils and eosinophils. In instances where there is a high prevalence of eosinophils in the biopsy, it is advisable to conduct a screening for hematological malignancy, as there is an increased risk associated with this[10,28].

Some authors have proposed that cases where there is a predominance of eosinophils over neutrophils should not be classified as eosinophilic SS[28].

4.8.2.5 Lymphocytic Sweet's syndrome.
The clinical presentation of the lymphocytic variant is characterized by the presence of painful papules and nodules on the dorsum of both hands and feet, as well as on the palms and soles. To date, no association with malignant neoplasms has been identified[29,30].

The biopsy revealed oedema in the dermis with a predominantly mononuclear cell infiltrate, without

evidence of vasculitis. A differential diagnosis should be made with neutrophilic eccrine hidradenitis, perniosis, persistent reaction to stings, and other similar conditions[29,30].

The cases described demonstrated a significant improvement following the administration of oral prednisone for a period of seven days[29,30].

4.8.2.6 Xanthomyzed normolipidemic Sweet's syndrome.

Xanthomized normolipidemic Sweet's syndrome has recently been described by Ferris et al. and Kamimura et al. The form of presentation is characteristic, with lesions having a yellowish-brown appearance, sometimes with a ring-like morphology[31].

The disease is characterized by a biopsy demonstrating a neutrophilic infiltrate in the deep dermis, accompanied by xanthomatoid cells with foamy cytoplasm and positivity for MPO, CD 68 and CD163, with the latter being the most prevalent. The cases described have been associated with hematological malignancies[31].

4.9 TREATMENT.

It is recommended that all patients with SS commence systemic treatment. Although most cases of SS are self-resolving and resolve within 1-2 months without treatment, early initiation of treatment has been shown to prevent recurrence, with a recurrence rate of 30-50% in patients who do not receive treatment [9,10].

If the skin lesions are mild and localized to a specific area, the use of high-potency topical corticosteroids may be beneficial. However, due to the potential for extracutaneous involvement, it is preferable to administer systemic steroids [7].

In the event of more extensive cutaneous involvement or the presence of extracutaneous manifestations, the treatment that has demonstrated the most efficacious outcomes is oral prednisone at a dosage of 0.5-1 mg/kg/day. The response of the lesions to systemic treatment with corticosteroids is rapid, with improvement being observed within 48 to 72 hours of the start of treatment[5,7,32].

Other immunosuppressive drugs, such as dapsone, colchicine, or potassium iodide, represent the second line of treatment. Some small case series have described improvements with indomethacin, cyclosporine, thalidomide, methotrexate, or anti-TNF[10,25].

5. Differential diagnosis.

5.1 PYODERMA GANGRENOSUM.

Pyoderma gangrenosum (PG) is a rare inflammatory skin disorder, characterized by rapidly progressing painful ulcers with undermined and irregular edges [33,34]. Classified as a deep neutrophilic dermatosis, PG has an estimated global incidence of 3-10 cases per million people per year[33,34].

The pathogenesis of PG is complex, involving significant dysfunction of both innate and adaptive immunity, with

the follicular unit increasingly recognized as the initial target[35]. There is a skewed inflammation towards T helper 17/T helper 1 cells and exaggerated inflammasome activation, leading to a predominantly neutrophilic environment[35]. Genetic factors play an important role, with pathogenic variants of genes involved in inflammasome formation (PSTPIP1, MEFV, NLRP3, NLRP12, and NOD2) documented in both syndromic and sporadic cases. Excessive release of IL-1β is a common feature in these cases[35]. Additionally, triggering factors such as trauma (pathergy phenomenon) can induce the release of pro-inflammatory cytokines, exacerbating the disease in genetically predisposed individuals.

The most frequent clinical manifestation of PG is rapidly expanding, painful ulcers with irregular, violaceous-red borders, most located on the lower limbs, although they can appear anywhere on the body[33,36]. There are several clinical variants of PG, including classic ulcerative, bullous, pustular, vegetative, peristomal, and postoperative forms. PG is also associated with systemic diseases such as inflammatory bowel disease and certain hematological malignancies[36].

Systemic corticosteroids are the first-line treatment due to their rapid anti-inflammatory action, with initial doses of 0.5-1 mg/kg/day. In severe cases, calcineurin inhibitors like cyclosporine can be used[37]. Studies show that cyclosporine and prednisolone have similar efficacy in treating PG. Other treatments include methotrexate, IL-1 inhibitors (anakinra, canakinumab), IL-17 inhibitors, JAK inhibitors (tofacitinib, baricitinib), and phosphodiesterase 4 (PDE4) inhibitors[37].

Managing PG remains a challenge as treatments largely depend on clinical experience. Limited evidence from studies and the lack of validated diagnostic and response criteria have hindered the investigation of effective treatments. However, the growing understanding of the molecular basis of PG is promising for the emergence of targeted therapies[37].

5.2 NEUTROPHILIC ECCRINE HIDRADENITIS (NEH)

Neutrophilic eccrine hidradenitis (NEH) is an uncommon, indolent condition first identified in patients with acute myeloid leukemia[38]. It is considered a reactive disorder and is frequently associated with malignant neoplasms, including other leukemias, Hodgkin lymphoma, and solid tumors. Since its initial description in 1982, NEH has been classified among neutrophilic dermatoses, a group of skin disorders characterized by neutrophilic infiltrates in the dermis without a clear infectious source[38].

The frequency of NEH is not well documented. It has a slight male predominance and has been reported in individuals aged from six months to 79 years[38,39]. NEH has been associated with the use of several medications, such as acetaminophen, minocycline, granulocyte colony-stimulating factors, cyclophosphamide, methotrexate, carbamazepine, cetuximab, BRAF inhibitors, bleomycin, 5-fluorouracil, and antiretrovirals[39,40]. Before diagnosing

NEH, the most common infectious causes must be ruled out. However, biopsies from some cases of active bacterial and viral infections have shown histological changes consistent with NEH. In children, heat damage to the eccrine glands can also trigger NEH[40].

Biopsies reveal a dense neutrophilic infiltrate around and within the eccrine glands, with necrotic epithelial cells. Intraductal abscess formation may also be observed. In neutropenic patients, neutrophils may be sparse or absent in the dermis, but necrosis of the eccrine glands is evident[40].

The classic presentation of NEH is seen in AML patients receiving chemotherapy, commonly with cytarabine. NEH can manifest from two days to two years after the initiation of chemotherapy. Clinically, patients present with erythematous papules and plaques, frequently on the face, back, trunk, and extremities. Fever and lesions described as dark red to violaceous macules, papules, nodules, or plaques are also common[40,41].

There is no widely accepted treatment for NEH; supportive care is recommended. Generally, NEH is a self-limiting condition and does not require therapy. In most cases, the lesions resolve spontaneously within a month. The use of corticosteroids, both topical and systemic, is debatable. Symptomatic management of fever and pain is highly recommended. Colchicine has been used successfully in otherwise healthy patients with NEH[40,41].

7.Conclusions

In recent years, multiple variants of SS have been described, broadening our understanding of this condition and its clinical and histopathological manifestations. These variants serve to illustrate the complexity and diversity of SS, thereby underscoring the importance of a personalized diagnostic and therapeutic approach. These variants not only illustrate the phenotypic diversity of SS, but also highlight the necessity for accurate diagnosis and appropriate treatment to improve clinical outcomes. The identification of the specific characteristics of each variant facilitates a more comprehensive understanding of the pathophysiology of SS and provides avenues for the development of more efficacious and targeted therapies.

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