Neutrophilic dermatoses - Part I

Dermatoses neutrofílicas – Parte I

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Abstract: The authors present a review of neutrophilic dermatoses that have great impact on the health of patients: Sweet syndrome, pyoderma gangrenosum, Behçet's disease and neutrophilic urticaria. Major clinical aspects, histopathological changes and management options are discussed based on the results and conclusions of relevant studies recently published and on the authors' experience.
Keywords: Pyoderma; Behcet's Syndrome, Sweet Syndrome, Urticaria

Resumo: Os autores apresentam uma revisão das dermatoses neutrofílicas que possuem grande repercussão à saúde dos pacientes: síndrome de Sweet, pioderma gangrenoso, doença de Behçet e urticária neutrofílica. São discutidos, baseados nos resultados e conclusões de estudos relevantes publicados recentemente e na experiência dos autores, os principais aspectos clínicos, as importantes alterações histopatológicas e as opções para o manejo.
Palavras - chave: Pioderma; Síndrome de Behçet; Síndrome de Sweet; Urticária

INTRODUCTION

Neutrophilic dermatoses are a heterogeneous group of diseases which can occur with localized, generalized and systemic skin involvement.

Some deserve great attention due to major symptoms and the concept of reactive disease or for being a marker for other pathologies, especially neoplastic diseases. Common to all, there is a disorder of stimuli and proliferation of neutrophils, expressed by cellular skin infiltration. The clinical diagnosis, often with typical characteristics, should be ideally confirmed by histopathology (even with no pathognomonic patterns), and treatment is carried out according to disease severity and the underlying context.

The main clinical, histopathological and management features of the following diseases will be addressed in two parts: Sweet's syndrome, pyoderma gangrenosum, Behçet's disease and neutrophilic urticaria (Part 1), subcorneal pustular dermatosis, palmoplantar pustulosis, Hallopeau's continuous acrodermatitis, acute generalized exanthematous pustulosis, infantile acropustulosis and other pustuloses (Part 2).

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SWEET'S SYNDROME

Also called acute febrile neutrophilic dermatosis, Sweet's syndrome (SS) is characterized by a variety of symptoms, clinical and histological findings, which include fever, neutrophilia, erythematous and painful skin lesions, diffuse neutrophilic infiltrate in the dermis, and rapid response to therapy with corticosteroids. [1.2]

Despite the fact that the original description is attributed to Dr. Robert Douglas Sweet (1964), the diagnostic criteria were proposed by Su and Liu (1986) [4], and subsequently revised and modified by von den Driesch (1994) [5].

The pathogenesis of the disease is not fully understood. The association with infections, autoimmune diseases, neoplasms and drugs suggests a hypersensitivity reaction. Circulating autoantibodies, cytokines, dermal dendrocytes, HLA serotypes, immune complexes and leukotactic mechanisms have been suggested as factors that contribute to the pathogenesis of this syndrome. Cytokines appear to play an etiologic role in the development of lesions and symptoms of SS. Granulocyte colony-stimulating factor, macrophage colony-stimulating factor, interferon-gamma, interleukin-1, interleukin-3, interleukin-6, and interleukin-8 are potential candidates. [6] Elevated serum levels of IL-1, IL-2 and IFN-γ but not IL-4, suggest that the expression of Th1 cytokines $_{H}$ may be involved in the pathogenesis of this syndrome. [7] Although an increase in the frequency of HLA-B $_{w}$ 54 in Japanese patients with SS has been shown,[8] analysis of HLA antigens in the Caucasian population showed no association between this syndrome and certain HLA-ABC antigens. [9]

Clinical features, histopathological aspects and complementary evaluation

The classical or idiopathic variant affects more women, and the initial episode occurs between 30 and 50 years of age. When associated with malignancy, it affects both men and women. [1.6] Pediatric cases represent only 8% of the total, affecting both sexes equally. [10.11]

Clinical symptoms include painful papular-nodular lesions of erythematous and/or violaceous color. They may have a pseudovesicular appearance (secondary to edema on the upper dermis) (Figure 1). Ulcerated or bullous lesions are more common in the form associated with malignancy. [6.11] They are located mainly on the upper extremities, face and neck asymmetrically. [1.2] This syndrome can also present as a pustular dermatosis, characterized by pustules over an erythematous base or pustules on top of papules. [6] The "neutrophilic dermatosis of the dorsal hands" has been considered a localized variant of Sweet's syndrome. [12,13] The subcutaneous form of the disease presents with lesions that are usually painful, erythematous subcutaneous nodules, located on the extremities, similar to erythema nodosum. [6]

Fever, usually above 38 ^{O}C, is the most common sign and may precede the lesions or occur simultaneously. [1.6] Impairment of the oral mucosa, manifesting as ulcerated lesions, is more frequent in cases associated with hematologic diseases. Eye manifestations (conjunctivitis, episcleritis and iridocyclitis) can be the initial presentation of the syndrome. [3] Arthralgia or arthritis occurs in 33% to 62% of the cases, usually with asymmetric oligo-or polyarticular involvement of the upper or lower extremities. [11.14] Rarer extracutaneous manifestations include pulmonary, neurological, cardiac, hepatic, renal, bone and pancreatic involvement. [1.11] (Figure 1)

According to the clinical features of its occurrence, SS can be classified as idiopathic or classical, associated with malignancy or drug-induced (Table 1). [1.6]

Several conditions have been associated with Sweet's syndrome. Approximately 10-20% of the cases are related to neoplasms [15].Hematologic malignancies

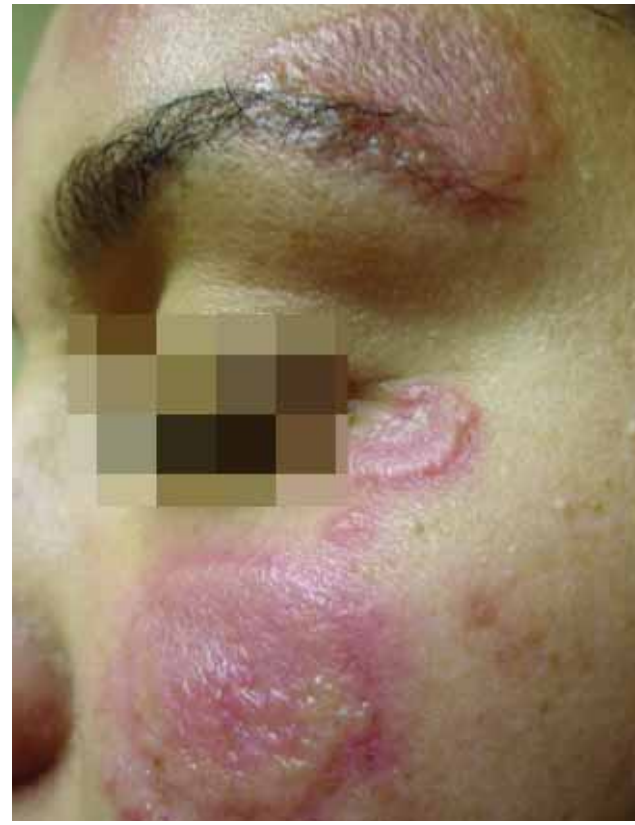

Figure 1: Sweet's syndrome: on the left, disseminated lesions in the trunk and, on the right, annular skin lesions on the face

Chart 1: Sweet's syndrome: clinical forms

Classical or idiopathic	- Upper respiratory tract infection - Gastro-intestinal infection - Inflammatory bowel disease - Pregnancy
Associated with malignancy	The temporal relationship of the development of lesions with the diagnosis of an unexpected malignancy or with tumor recurrence
Drug-induced	**Antibiotics** - Nitrofurantoin - Sulfamethoxazole / trimethoprim - Minocycline - Ofloxacin - Quinupristin / dalfopristin - Norfloxacin **Anticonvulsants** - Carbamazepine - Diazepam **Antihypertensive** - Hydralazine **Antiretroviral** - Abacavir **Antipsychotic** - Clozapine **Contraceptives** - Estradiol / levonorgestrel - Uterine levonorgestrel-releasing system **Antiinflammatory** - Diclofenac - Celebicox **Antineoplastic** - Bortezomib - Lenalidomide - Imatinib mesylate **Cytokines** - Granulocyte colony-stimulating factor - Macrophage colony-stimulating factor **Diuretics** - Furosemide **Anti-thyroid hormone** - Propylthiouracil **Retinoids** - Tretinoin

Fonte adaptada: Cohen & Kurzrock,[1] Cohen[6]

account for more than 85% of the cases, with acute myeloid leukemia being the most frequent. [16.17] The most common solid tumors are carcinomas of the genitourinary tract, breast and gastrointestinal tract [1.10]

The main infectious conditions associated with this syndrome are of the upper respiratory tract (streptococci) and gastro-intestinal tract (salmonellosis and yersiniosis). Other less frequent infectious agents, but that have already been mentioned, include: *Staphylococcus,* mycobacteria, cytomegalovirus, human immunodeficiency virus (HIV), hepatitis A, B and C and vaccination. [1.11]

Inflammatory bowel disease, Behcet's disease, erythema nodosum, rheumatoid arthritis, sarcoidosis, relapsing polychondritis, Graves' disease, and Hashimoto's thyroiditis are also associated with Sweet's syndrome. [1]

Granulocyte colony-stimulating factor is the drug most associated with the syndrome. Other drugs related to the onset of Sweet's syndrome are listed in

Table 1. [1.11]

Histopathology is characterized by a dense and diffuse dermal neutrophilic infiltrate. The infiltrate may be perivascular with leukocytoclasis and fragmentation of nuclei of neutrophil, but there is no true vasculitis. [10] Occasionally, the epidermis shows spongiosis, with the formation of subepidermal vesicles when edema is severe. [16.17] Recently described, histiocytic SS shows clinical findings identical to typical SS, but what differentiates this variant is the dermal inflammatory cell infiltrate composed of immature myeloid cells.[18]

Laboratory findings suggestive of SS include peripheral leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate or C-reactive protein. Particularly in cases in which Sweet's syndrome is associated with malignancy, leukopenia, anemia and thrombocytopenia have been reported. [11]

The diagnostic criteria for classical and drug-induced SS are shown in Table 2, which were elaborated based on a synthesis of the literature. [5.19]

The morphology of the lesions of SS may mimic various mucocutaneous and systemic diseases. The differential diagnosis includes inflammatory diseases (lymphangitis, panniculitis, pyoderma gangrenosum and thrombophlebitis) infectious diseases (bacterial sepsis, cellulitis, erysipelas, herpes simplex infection, leprosy, sporotrichosis, syphilis, tuberculosis, varicella-zoster virus infection and viral exanthem), neoplasms (chloroma , leukemia cutis, lymphoma, metastatic tumor), reactive erythema (erythema multiforme, erythema nodosum and urticaria), vasculitis (erythema elevatum diuntinum, leukocytoclastic vasculitis and polyarteritis nodosa), other skin diseases (acne, acral erythema, drug eruptions/allergies, eruptive xanthomas, granuloma facial and Halogenoderma) and other systemic diseases (Behçet's disease, intestinal *bypass* syndrome, dermatomyositis, lupus erythematosus, pustular eruption of ulcerative colitis, familial Mediterranean fever and vesicular eruption associated with hepatobiliary disease). [1.6]

Chronic recurrent neutrophilic dermatosis has been described as a possible variant of neutrophilic dermatosis. In the reported cases, patients had chronic and recurrent disease, absence of systemic symptoms and histopathological findings similar to those of Sweet's syndrome. [20]

Treatment

Without therapeutic intervention, lesions may persist for weeks or even months. Improvement of lesions in patients with the syndrome associated with neoplasms or drugs may occur after treatment of the neoplasm associated with the dermatosis or after discontinuing the offending drug [2].

In localized lesions, high-potency topical corticosteroids or intralesional corticosteroids may be used. [2.6] Systemic corticosteroids are the treatment of choice in most cases. Cutaneous and extracutaneous manifestations tend to improve within the first 72 hours of the start of therapy [11]. Prednisone can be used in the initial dosage of 30 to 60 mg daily or what corresponds to 0.5 to 1.5 mg / kg, with subsequent gradual reduction. [6] Potassium iodide tablets (900mg/dia) or colchicine solution (1.5mg/dia) are also considered first-line agents. Second-line systemic therapies include indomethacin (50-150mg/dia), clofazimine (100-200mg/day), dapsone (100-200mg/day) and cyclosporine (2-4mg/Kg day). [1,2,6,] Other drugs described include [11] doxycycline, metronidazole, interferon-·, etretinate, chlorambucil, cyclophosphamide, methotrexate, etanercept, infliximab and thalidomide. [6]

Recurrence of the lesions in cases associated with malignancies may indicate recurrence of the neoplasm.

Pyoderma Gangrenosum

In 1908 Louis Brocq described a series of patients with skin lesions that would be later called pyoderma gangrenosum. [21]

Phagedena geometric, gangrenous dermatitis and phagedenic pyoderma are synonymous terms with historical value for Pyoderma Gangrenosum (PG), which is defined as an inflammatory and neutrophilic disease, which usually evolves to ulcerative skin lesions and systemic involvement, being associated with the pathergy phenomenon in many cases and with systemic diseases in 30-70% of the cases. [21-23]

Pyoderma Gangrenosum is considered a neutrophilic dyscrasia. Initially, following a context that triggers a reaction in the immune system (of different origin) that results in the release of interleukin -1 beta by cell lymphocytes, there is a clonal expansion of T lymphocytes. This cell expansion is followed by another of neutrophilic cells. Arrival of neutrophils occurs in the dermis, affecting large areas of the involved region. Pustular lesions observed on earlier cases of pyoderma gangrenosum correspond to the accumulation of neutrophils. [24]

The number of inflammatory cells, under abnormal activity, causes the release of large amounts of anti-matrix metalloproteinases 9 and 10, as well as tumor necrosis factor alpha. These mediators cause the initial ulceration and are responsible for its progressive increase. [25]

Moreover, there are modest amounts of anti-matrix metalloproteinase 1 and 26 on the borders of

Chart 2: Diagnostic criteria for Sweet's syndrome

CLASSICAL SWEET'S SYNDROME

Major Criteria

1. Abrupt onset of painful erythematous nodules or plaques
2. Histopathological findings of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis

Minor Criteria

3. Fever> 38 ° C
4. Association with hematologic or visceral malignancy, inflammatory disease or pregnancy, or preceded by upper respiratory tract infection, gastro-intestinal infection or vaccination
5. Excellent response to treatment with systemic corticosteroids or potassium iodide
6. Abnormalities in laboratory tests (three of four): erythrocyte sedimentation rate> 20mm/Hr; high C-reactive protein, leukocytes> 8,000, with> 70% neutrophils.

The presence of both major criteria (1 and 2) and two minor criteria (3,4,5 and 6) is needed to establish the diagnosis of classical Sweet's syndrome.

Drug-induced Sweet's syndrome

A. Abrupt onset of painful erythematous plaques or nodules
B. Histopathological findings of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
C. Fever> 38 ° C
Temporal relation between use of medication and clinical presentation or relapse with readministration
E. Disappearance of lesions after drug discontinuation or treatment with systemic corticosteroids

All five criteria are necessary for the diagnosis of drug-induced Sweet's syndrome.

the lesions, which makes the healing process more difficult. [25]

Pathergy is a phenomenon that occurs in approximately 30% of the patients with PG. It is characterized by the appearance of a skin lesion that is clinically and histopathologically identical to the original disease, being erythematopapular, sometimes pustular, with small ulcer formation after dermal injury, which may be minor such as, for instance, the insertion of a fine needle to perform venipuncture, or even after surgery of any size, such as injuries arising from surgical wounds. The occurrence of severe aggravation of pre-existing lesions is also due to the pathergy phenomenon. This is common when debridements of lesions interpreted as having a bacterial origin are conducted. [23,26,27]

The abnormal immune reactivity and reaction of antibodies against common antigens found on the skin, gastrointestinal tract and joints would be a basic explanation for the interpretation of symptoms in some patients. [28]

Pyoderma gangrenosum included in PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne) has been considered a part of auto-inflammatory dermatoses. These are immune, but not autoimmune, disorders (there are no high titers or presence of autoantibodies and there is no specific antigen stimulation). There is a primary dysfunction of the innate immune system and, in origin, there is genetic and protein alterations. Activation of neutrophils and / or monocytes and macrophages occurs together with inflammatory processes and apoptosis.

Besides the PAPA syndrome, the following are also examples of auto-inflammatory diseases: periodic syndrome associated with cryopyrin, familial Mediterranean fever, chronic recurrent multifocal osteomyelitis, periodic syndrome associated with necrosis factor alpha tumoral receptor, mevalonate kinase deficiency. The genetic alterations of the PAPA syndrome occur on chromosome 15, gene PSTPIP 1/CD2BP1, with the presence of the E250Q mutation. [28, 29]

Clinical features, histopathological aspects and complementary evaluation

PG slightly predominates in women, it is more common between 20-60 years of age, but occurs in children 4% of the time. [23,30,31]

Clinically, it presents with a papular-pustular lesion with occasional hemorrhagic content and rapid progression to ulceration, with varying levels of depth extension. It may affect tendons and/or muscles. The borders are elevated, well demarcated, erythematous, violaceous and undermined (derived from the necrotizing inflammatory process)(Figure 2). [23,26,27,30-32]

There is a wide clinical variability, but the morphology of PG is the following: a) pustular b) ulcerated c) vesico-bullous, d)-verrucous vegetating. In general, there is predominance of one of the clinical forms, which can coexist in the same patient. The ulcerative form may be mainly related to

inflammatory bowel diseases, arthritis, monoclonal gammopathy and malignancies. The bullous form is more associated with hematologic diseases (Figure 3) and the generalized, pustular form, with inflammatory bowel diseases (Figure 4). The vegetative form, the rarest and also known as superficial granulomatous pyoderma, has hardly any relationship with systemic diseases (except for risk of association with chronic kidney disease) and its therapeutic management is recognized as being the least complex. [23,32,33]

In addition to the fact that clinical variability leads to the classification above, PG has, as an alternative spectral description, the classical features (initial papular-pustular lesion that ulcerates and forms undermined borders) and the following variants: [34-38]

Periostomal: the disease occurs after the formation of an ostomy (less than 1% of ostomized individuals). Overall, PG is associated with inflammatory bowel disease (Crohn's disease and ulcerative colitis). [34-37]

Pyostomatitis vegetans: it is a condition that presents with a pustular eruption affecting the oral mucosa, with multiple small friable superficial lesions, some being considered true abscesses.They are recognizably associated with inflammatory bowel diseases. [38]

Atypical (or *bullous),* bullous lesions (most often in the lower extremities) and constitutional symptoms are the characteristics of this variant, which is related to hematologic and / or malignant diseases. [39]

In 30% of the patients, there are multiple lesions and pain is the main symptom, though some do not report specific symptoms. [40]

The location of the lesions is variable, with a preferential topography: the lower extremities, abdomen, upper extremities, breasts, buttocks, genitals and face. In children, lesions are mostly found in the head, neck and perineum. [26,27,30-32,40]

The most common extracutaneous clinical manifestations occur in the lungs, joints and digestive tract and are due to the general inflammatory process. Pulmonary involvement may lead to the development of pleural effusion, nodules, cavitation, bronchial pneumonia and abscess. Other changes are found in the eyes (necrotic sclerokeratitis), liver (hepatitis, granulomas), spleen, bones, bone marrow (alterations in red blood cells, white cells and platelets). [26,27,32,40-44]

Death can occur, albeit rarely. In general, it occurs in patients with severe associated diseases. In addition to the underlying disease, secondary infections in ulcerations and sepsis constitute the leading cause of death, but respiratory failure and morbidities due to therapy are also important. [26,27,32,40,41]

The main diseases and/or clinical contexts related to Pyoderma Gangrenosus are listed in Table 3. [44-56]

Currently, post-surgical PG (PSPG) can be considered a specific subtype of pyoderma gangrenosum, which has the essential phenomenon of pathergy. In PSPG, after a period of normal appearance (between 4 days and 6 weeks), the surgical wound shows many small dehiscences, which often coalesce to large areas of ulceration in a process that goes beyond the wound. Granulation tissue is almost nonexistent and the pain is not constant. It can

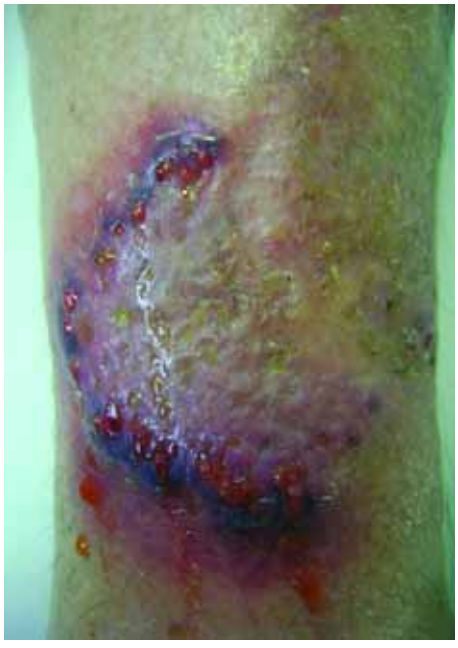

Figure 2: Pyoderma gangrenosum: on the left, an ulcerative lesion and, on the right, bullous lesions, with necrosis

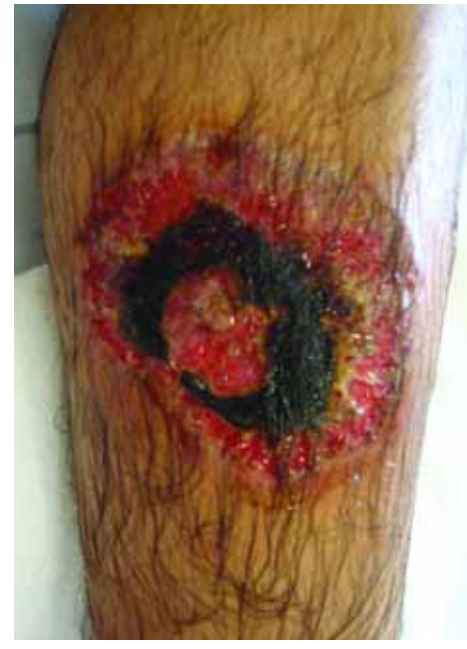

Figure 3: Pyoderma gangrenosum: papulo-pustular lesions

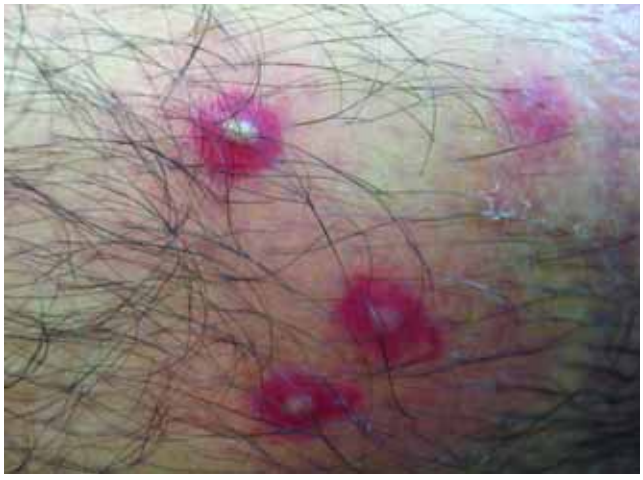

Figure 4: Post-surgical pyoderma gangrenosum

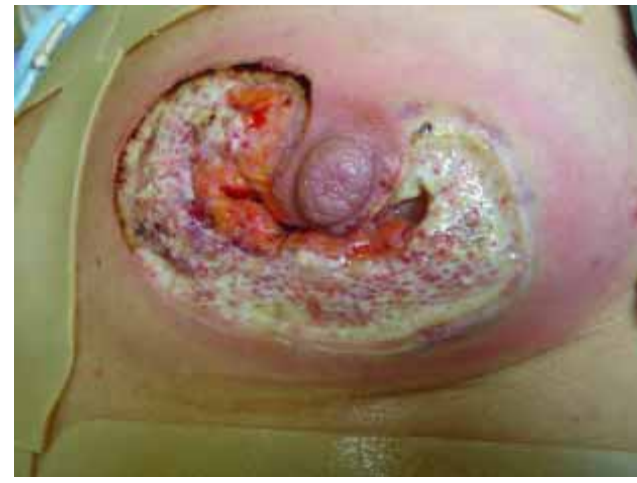

Figure 5: Post-surgical pyoderma gangrenosum

affect any anatomical site; in the breast, the nipple is spared (Figure 5). Local treatment and antibiotics do not result in improvement and a dramatic response to the immunomodulator is the rule. [57,58]

Histopathological findings are nonspecific, but may be important in defining certain cases. Initially there is neutrophil infiltration (with or without lymphocytes), which often occurs diffusely in the dermis and involves follicular structures. There are varying degrees of vascular damage, but usually without fibrinoid necrosis. Focal vasculitis is observed in fully developed lesions, which is apparently a secondary phenomenon. The infiltrate tends to be located in deeper levels of the dermis. A mixed inflammatory process and areas of necrosis are observed in fully developed lesions. Involvement of the reticular dermis and subcutaneous tissue may show mononuclear cells and granulomatous reactions. [59, 60]

Direct immunofluorescence may be positive for various markers (no specificities), mainly in the vicinity of the dermal vessels. [59, 60]

In the evaluation of a patient with PG, it is important to consider the possibility of an underlying disease and investigate specific suspicions.

Generally speaking, if after anamneses and physical examination there is no evidence of an associated disease, further examination should include: complete blood count, platelet count, erythrocyte sedimentation rate, kidney/liver function, coagulation tests, protein electrophoresis, rheumatoid factor, antineutrophil cytoplasmic antibodies (pANCA and cANCA), chest radiography and abdominal ultrasound, direct examination and culture for bacteria, mycobacteria and fungi (preferably from skin biopsy).

If additional assessment does not reveal changes, further tests may be important. The major ones include: blood culture, cryoglobulins and cryoagglutinins, cryofibrinogen, serology for hepatitis and HIV, VDRL, tomographic studies, vascular studies and bone marrow aspirate /biopsy.

The differential diagnosis of PG should be performed with major diseases, most of which develop into skin ulcers: [59,60] bacterial skin infections (folliculitis, furunculosis, carbuncle, ecthyma, gangrenous cellulitis, necrotizing fasciitis), sexually transmitted diseases (syphilis, donovanosis , chancroid), mycobacteriosis, accidents with animals and insect bites, leishmaniasis, deep mycoses (sporotrichosis, criptococosis, paracoccidioidomycosis, chromomycosis, mucormycosis, histoplasmosis, and aspergillus and *Rhyzopus* infection*),* amebiasis, herpes simplex, small-vessel vasculitis, Wegener's granulomatosis, polyarteritis nodosa, erythema multiforme, pustular psoriasis,

Chart 3: Diseases associated with pyoderma gangrenosum

- Inflammatory bowel disease: [26,27,45-48] ulcerative colitis, Crohn's disease, collagenous colitis;
- Artrite reumatóide;[26,27,41] Myeloproliferative and lymphoproliferative diseases: [26,27,32,41,49-51]leukemia (myelocytic), lymphoma, myelodysplastic syndromes, polycythemia vera; Paraproteinemias[41;] Gammopathies;[39,41,52] Takayasu's arteritis;[53] Wegener's granulomatosis;[39,41] Infection with hepatitis C and hepatitis B;[54] Use of interferon and ribavirin in hepatitis C;[54] Dysfibrinogenemia;[55] Renal failure; diabetes *mellitus*, Graves disease; [56] Pregnancy. [32,93,41,56]

pustular drug eruptions, autoimmune bullous diseases, venous ulcers, arterial ulcers, antiphospholipid syndrome, specific thrombopathies, Sweet's syndrome, Behcet's disease, calciphylaxis, psychodermatosis, primary and metastatic skin cancer

Treatment

There are few clinical trials and there is no universally accepted treatment regimen.

Systemic corticosteroids (prednisone or prednisolone) 0.5-1 mg/kg/day, orally, cyclosporine in doses of 5mg/kg/day and tacrolimus 0.1% topical use are the drugs with greater historical evidence and current scientific recommendation for the treatment of PG. [61]

The dramatic response to treatment with corticosteroids or immunosuppressants is considered one of the keys to the diagnosis of PG.

There are other options, with varying degrees of evidence and recommendations, but that might be useful: topical corticosteroids, preferably medium to high power, [61] triancinolone acetonide (10mg/ml, intralesional, in the borders of the lesion), topical cromoglycate [62] (in ulcers), [63] tacrolimus (0.15 mg / kg / d), [64-66] Intralesional cyclosporine (35 mg), [67] azathioprine (100-150 mg / d), prednisone [68] / oral prednisolone (40-100 mg / day) , [69] methylprednisolone pulse therapy, oral cyclosporine [70, 71] methotrexate (15 mg / week), [72] clofazimine (100-300 mg / d), [73.74] dapsone (100-300 mg / d), [75] colchicine (1 mg / d), [76] thalidomide (100-400 mg / d), [77] chlorambucil (2-4 mg / d), [78] mycophenolate mofetil (1 to 2.5 g / d), [79] minocycline (100-200 mg / d), [80] sulfasalazine (1 g-4 g / d), [68] cyclophosphamide (50-100 mg / d or 500 mg m^2 5-7 pulses for 1-4 months), [81] to anticoagulants, [55] granulocyte apheresis, [82] nitrogen mustard (20 mg/100 ml), [83] grafting, transplantation of keratinocytes [84, 85] platelet growth factor, [86] granulocyte colony stimulating factor, [87] hyperbaric oxygen therapy, intravenous human immunoglobulin [88, 89] plasmapheresis [61].

The following may also be cited as recent and promising acquisitions for the treatment of PG: endovenous infliximab (5 mg / kg), intramuscular etarnacept (25-50 mg) and adalimumab (40-80 mg / kg). [89-91]

Receptor antagonists of interleukin-1 are being studied in the control of auto-inflammatory diseases. They may eventually be recommended for the treatment of PG. [92]

It is important to stress that the use of polytherapy is common and necessary to control certain cases of PG. Thus, regimens using systemic corticosteroids and antineutrophil drugs are often prescribed.

There are certain cases that do not evolve properly. These are patients who have forms of the disease that are resistant to therapy. In general they are men, of advanced age and with serious underlying diseases. The bullous form has worse prognosis.

Behcet's Disease

Behcet's disease (BD), also called Adamantiades-Behçet, is related to genetic and geographical aspects, with a multisystemic and inflammatory profile and chronic relapsing behavior. It is histopathologically characterized by vasculitis and vascular thrombi. [93]

The first description was probably given by Hippocrates, but it was in 1937 that the Turkish doctor and professor of dermatologist Hulusi Behcet called it a syndrome of unknown etiology that presented with recurrent oral ulcers, genital ulcers and uveitis. [94.95] In the decades following the original description, joint, vascular, gastrointestinal, cardiopulmonary, neurological and psychiatric alterations were cited as manifestations of the disease. [93.96]

There are still some gaps in the understanding of the complex etiopathogenesis of BD. The higher frequency of the disease among Mediterranean populations and the increased risk among carriers of HLA-B51, grant a genetic and geographical particularity to the disease. [97]

Immunological abnormalities are found in patients with BD, such as the presence of immune complexes. However, the set of all changes found in the disease is not explained by the presence of immune complexes. There is report of a decrease in the number of CD3 cells and increase of *natural killer* cells, but their activity is reduced, possibly due to elevated levels of PGE2. There is no increase in the number of B cells, but there may be a hyperfunction of these cells. [98.99]

Without definite proof, there was also a proposition about a possible pathogenic mechanism of BD involving antigenic bacterial stimuli (especially *Streptococcus sangius)* and / or viral stimuli (particularly of the *herpes simplex virus)* in predisposed patients. [98.99]

In fact, there is production of heat shock proteins (increase of IgA antibodies against 65 kDa heat shock proteins) and neutrophil chemotaxis from lymphocytic hyperfunction.

Leukocyte adhesion molecules (L-selectin, Mac-1 and CD44) are expressed in peripheral leukocytes and may participate in leukocyte chemotactic activity and in adhesions (neutrophil adhesions to the endothelium are high, and there is elevation of ICAM-1). The stimulation of mononuclear cells induces the release of tumor necrosis factor and interleukin-1, -6

and -8. [98.99]

Patients with neurological disorders have elevated IL-6, and marked elevation of IL-2 is present in patients with uveoretinitis. Levels of IL-10 are correlated with the degree of disease activity. [98,99]

Lesions of BD have decreased fibrinolytic potential, as attested by decreased circulating levels of factor XII and by the prolongation of euglobulin lysis time. [98.99]

Anti-endothelial cell antibodies are present in patients with BD, being important in the pathogenesis of the disease. Endothelial damage causes oxidative changes and release of free radicals. Autoantibodies against low-density lipoproteins may be a cofactor of endothelial damage. The decreased synthesis of prostacyclin and elevation of thromboxane B2 and prostaglandins may contribute to the formation of thrombosis in the course of BD. Sporadic changes of protein S and of fibrinolysis are associated with thrombotic manifestations of the disease. Elevated plasma endothelin-1 (ET-1) found in patients with active BD may result from increased synthesis by endothelial damage. Thrombomodulin (TM), a cell surface glycoprotein of the endothelium, is present in very high levels in all patients with BD and is related to the pathogenesis of vasculopathy. It is speculated that atherogenic lipoproteins could contribute to the process of thrombogenesis in BD. [98.99]

Clinical features, histopathological aspects and complementary evaluation

Behcet's disease is endemic in the Eastern Mediterranean and in the Eastern and Middle Eastern countries. The highest prevalence is found in Turkey (80-370 cases per 100,000 individuals), with family events. [97] Other available data regarding the prevalence: 13.5 to 20 per 100,000 individuals in Japan, South Korea, China, Iran, Iraq, and Saudi Arabia. The prevalence is significantly lower in northern European countries and the United States of America. [98.99]

It occurs more commonly in men, but in northern European countries it is more frequent in women. The predominant age range for onset of disease is between 20 and 40 years and it is rare in childhood. The more aggressive forms of the disease are observed in young adults. [100.101]

BD is recognized as a complex, multisystemic disease, with primary vasculopathic damage and an extensive range of clinical manifestations. [96,99,102]

- Manifestations of the cutaneous-mucous coat (Figure 6): oral aphthae (oral mucosa, tongue, gums, palate) of *major, minor* or herpetiform type, genital aphthae (vulva, vagina, cervix, foreskin, scrotum, glans) similar to oral aphthae (but tending to be deeper); genital scars of genital ulcers, lesions of erythema nodosum (lower limbs, upper limbs, face and cervical region); papular-pustular eruptions called pseudofolliculitis; pathergy reaction (papulopustular reaction 24-48 h after minor trauma produced by fine-needle puncture in the dermis), which occurs in approximately 40% of the patients. Other less frequent cutaneous manifestations are lesions similar to those of Sweet's syndrome, pyoderma gangrenosum and erythema multiforme, as well as purpuric lesions, hemorrhagic blisters, extra-genital ulcerations, and subungual infarctions. [96,99,102]

- Ophthalmologic manifestations: they occur in up to 70-85% of the patients. Hypophonic posterior uveitis is the most common manifestation, but vitreous deposits, choroiditis, retinitis may also occur. Reduction of visual acuity is an important problem. [96,99,102]

- Articular manifestations: seronegative arthritis is the most common finding. There is often a monoarticular synovitis of the knee. Up to 10% of ankylosing spondylitis and 34% of sacroiliitis are described. [96,99,102]

- Vascular and cardiac manifestations: deep and superficial thrombophlebitis are the most common vascular abnormalities. Thrombotic events can occur at any topography and may even occur in individuals not at risk. The following are reported: pericarditis, cardiomyopathy, aneurysm, endomyocardial fibrosis, conduction abnormalities (in particular, QT dispersion). Vasculitis of the coronary arteries can cause heart attack or aneurysm and often require surgical intervention. Arterial lesions are at risk for rupture (especially the pulmonary arteries). Patients with heart and atrial disease have worse prognosis. [96,99,102]

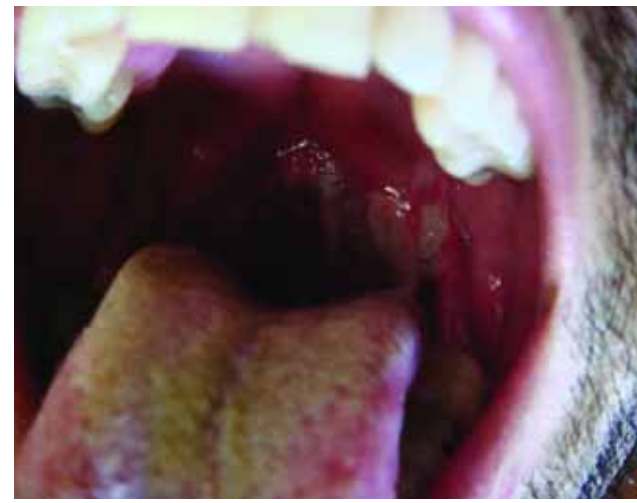

Figure 6: Behcet's disease: on the left, aphthous ulcer in oral mucosa and, on the right, pseudofolliculitis lesions

- *Pulmonary manifestations* - the following are described as rare, but important findings: pleural effusion, embolism, pulmonary arterial aneurysm, parenchymal abnormalities and fibrosis. [96,99,102]

- *Renal manifestations:* rarely reported, glomerulonephritis and systemic amyloidosis. [96,99,102]

- *Gastrointestinal manifestations:* aphthous ulcerative lesions may occur in the large intestine, especially in the terminal portion of the ileum and cecum, and in the stomach and small intestine. [96,99,102]

-*Neurological and psychiatric manifestations:* manifestations of the central nervous system occur in approximately 1% of the patients. Major ones are related to meningoencephalitis, vasculitis with peripheral nerve involvement, cranial nerve palsies and hemiplegia and paralysis. Thrombosis and cerebral aneurysms may occur. Vestibular disorders are described. Fibromyalgia, migraine, anxiety, depression and other psychological disorders occur in at least 50% of the patients in the course of the disease. It has been reported that stressful events may trigger the clinical manifestations of the disease. [96,99,102]

- *Other clinical manifestations* - the following are also mentioned, probably related to vasculitis and/or inflammatory mediators: hearing disorders, dermographism, epididymitis, erectile dysfunction and amyloidosis. [96,99,102]

The various tissues affected by BD have both vasculitis and thrombosis. There is perivascular lymphocytic infiltrate and neutrophilic vascular reaction. Pathergy lesions reveal leukocytoclastic vasculitis or neutrophilic vascular reaction. The histopathologic aspect of initial lesions is that of neutrophilic vascular response, while perivascular lymphocytic infiltrate predominates in older lesions. [98.103]

There are no specific laboratory tests which may be conclusive regarding diagnostic suspicion. In situations of active disease, the acute phase response is evidenced by elevated erythrocyte sedimentation rate, C-reactive protein, complement components (C3, C4, C9), interleukin-8 and immunoglobulins (IgA, IgM) and alpha 2 -globulin. [96-99.103]

Scintigraphy shows arthritis in approximately 50% of the patients. Magnetic resonance imaging may show atrophic changes in the brain; the EEG detects diffuse alpha waves and angiographic changes can be viewed. [96-99,102,103]

Positive pathergy tests were observed in 30-40% of the patients, but in Asian and Middle Eastern countries the majority of patients have this reaction. The histopathology of a positive pathergy test can be very useful to determine the diagnosis. [93,98,102,103]

For the diagnosis, the *International Study Group of Behcet's Disease* established the criteria (Table 4): a major criterion (essential) and four more minor criteria (it requires at least 2 more minor criteria to complete the diagnosis): [104]

(Evaluation and revision of the International Criteria for Behcet's Disease - ICBD), a score of 3 points was suggested for diagnosis, considering the following criteria: [105]

1 point - oral aphthae
1 point - cutaneous manifestations (pseudofolliculitis, cutaneous aphthae)
1 point - vascular lesions (phlebitis, venous thrombosis, aneurysm, arterial thrombosis)
1 point - positive pathergy test
2 points - genital aphthae
2 points - eye injuries

Alternatively, also in an attempt to improve the sensitivity and specificity of conventional criteria, the *Behçet Disease Research Committee of Japan* proposed the existence of major symptoms - recurrent oral aphthous ulcers, skin lesions (erythema nodosum, superficial thrombophlebitis, hypersensitivity papules), eye injuries (iridocyclitis or sequela, posterior uveitis or sequela) and genital ulcers. The following are additional symptoms: arthritis without deformity or sclerosis, epididymitis, gastrointestinal ulcerations (ileocecal), vascular lesions, lesions of the central nervous system. The systematization of the diagnosis, considering these symptoms, is as follows: [106]

- **Complete types:** 4 major symptoms

- **Incomplete types:** 2 or 3 major symptoms and two additional symptoms or typical eye lesions and one major symptom or two additional symptoms.

- **Suspected disease:** typical major symptoms without meeting criteria for the incomplete type.

- **Special lesions** certain gastrointestinal and vascular lesions and lesions of the central nervous system.

According to the Committee, the laboratory data that may contribute to the diagnosis are the pathergy test, *prick test* for streptococcal vaccination, tests that show inflammatory response, HLA-B51 positivity, histopathological findings.

Important diseases for the differential diagnosis are: [107]

EAR (recurrent aphthous stomatitis) and aphthae, cyclic neutropenia, viral infections, herpes simplex infection, cytomegalovirus infection, ulcers caused by other sexually transmitted diseases, systemic lupus erythematosus, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, multiple sclerosis, sarcoidosis, Sweet's syndrome, autoimmune bullous diseases, lichen planus, tuberculosis, yersiniosis, Reiter's syndrome, Vogt-

Chart 4: Diagnostic criteria for Behcet's Disease

Major criterion
Recurrent oral lesions: minor or major or herpetiform aphthous ulcers seen by a doctor or patient, with recurrence of at least three times a year.

Minor criteria:
Recurrent genital ulceration: aphthous ulceration or scarring observed by physician or patient.
Eye lesions: anterior or posterior uveitis or vitreous cells on slit-lamp examination or retinal vasculitis observed by an ophthalmologist.
Skin lesions: erythema nodosum observed by physician or patient, or pseudofolliculitis or papular-pustular lesions or acneiform nodules observed by physician in post-adolescent patients in the absence of treatment with systemic corticosteroids.

Koyanagi-Harada syndrome, MAGIC syndrome (mouth and genital ulcers with cartilage inflammation), drug eruptions, erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis, acneiform eruptions, pyoderma gangrenosum, vasculitis, inflammatory bowel disease, uveitis from other causes, neoplasms.

Treatment

Behcet's disease can be treated with different drugs, depending on its clinical presentation. [107-109]

Important non-pharmacological recommendations are to avoid very salty and spicy diets, alcoholic beverages and dental or oral hygiene cleaning agents which can be irritating. [107-109]

In the treatment of oral lesions anti-inflammatory and antiseptic drugs may be prescribed: mouthwash solutions with chamomile, chlorhexidine 1.2%, triclosan 0.1%, tetracycline 250mg/5ml and diclofenac 3% (hyaluronic acid 2.5%). Gel anesthetics such as lidocaine 2-5% and mepivacaine 1.5% and the use of amlexanox paste and 5-aminosalicylic acid 5% cream may temporarily relieve pain. Triamcinolone, dexamethasone and betamethasone, paste or ointment, may be useful, as well as intralesional triamcinolone suspension 40mg/ml (0.1-0.5 ml in each injury or 5mg/ml). The use of cyclosporine solution (100 mg/5 ml three times daily) for mouthrinsing, tacrolimus 0.1% ointment, and sulcralfate suspension are alternatives to the use of topical corticosteroids. [107-135]

For patients with extensive disease, with higher levels of clinical morbidity, systemic involvement and lesions resistant to topical treatment, the use of systemic drugs is essential, often in combination with topical treatment.

The following alternatives have a relevant scientific basis for treatment recommendation: prednisone and prednisolone (preferable for pregnant women) 1 mg/day, methylprednisolone 40 mg IM per week (3 weeks), colchicine 1-2 mg / day, dapsone 100-200 mg / day , thalidomide 100-300 mg / day, cyclosporine 5-10 mg / kg / day, azathioprine 2-2.5 mg / kg / day, interferon-alpha 6 x 10^6 IU 3 days/week SC, etanercept 25 mg 2 days / week IM, rebamipide 300 mg/ day p.o. [107-135]

With less evidence than the previous drugs mentioned, but cited as useful, we have sulfasalazine, methotrexate, penicillin, minocycline, indomethacin, etretinate, cyclophosphamide, chlorambucil, plamaferese, prostaglandin E1, intravenous human immunoglobulin, anti-tumor necrosis factor-alpha, levamisole , peptide linked to cholera toxin, granulocyte and monocyte apheresis, and anti-CD52. Often there is the need to combine two drugs for better control of the disease. The synergistic effect between systemic corticosteroids and cyclosporine in cases of ocular involvement is reported. [96.107-136]

Patients with severe recurrent aphthous ulcers, particularly those with family history of BD, should be monitored at long term in case other signs and symptoms of the disease develop. Spontaneous remission of symptoms may occur.

The main complications that can have the worst outcome occur in the central nervous system, lungs, gastrointestinal tract and great arteries. Moreover, blindness should not be overlooked as a possible major complication.

Death occurs in up to 6% of patients, depending on the severity of systemic involvement. In particular, HLA-B51 positive men, with serious illness and / or clinical manifestations early in life, should be monitored very carefully because they have a worse prognosis.

Neutrophilic urticaria (neutrophilic urticarial dermatosis)

Initially described in 1985 as a variant of

physical urticaria due to the presence of dermographism, normocomplementenemia and negative immunofluorescence, [137] neutrophilic urticarial dermatosis or neutrophilic urticaria has been suggested as a new disease, which belongs to the spectrum of neutrophilic diseases, with significant association to systemic diseases. [138]

Neutrophilic urticaria is clinically characterized by erythematous, pale, non-pruritic macules, papules or plaques. These lesions resolve within 24 hours. [138]

The patients do not present angioedema or purpura, but there may be dermographism and history of atopic disease. [138-139] Fever and polyarthritis are among the systemic symptoms, and in WBC, there is leukocytosis.[138]

Increased tissue expression of tumor necrosis factor alpha and interleukin-3 suggests that these inflammatory cytokines are involved in the dermal influx of neutrophils. [140.141]

Histopathology of the skin lesion shows neutrophil infiltration with intense leukocytoclasia, but without vasculitis and dermal edema. [137,138,140]

Patients with neutrophilic urticaria should be evaluated for the presence of systemic diseases, especially Still's disease, systemic lupus erythematosus, Schinzler's syndrome. [138]

Some studies about this dermatosis that associate histopathological findings with the therapeutic response demonstrated that drugs with antineutrophil action (e.g. dapsone) may be effective, with long periods of remission after discontinuation. [142.143] ❑

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QUESTIONS

1. Mark the correct statement(s) in relation to the pathogenesis of Sweet's syndrome (SS):
I. Association with infections, autoimmune diseases, neoplasms and drugs suggests a hypersensitivity reaction.
II. Cytokines appear to play an important etiologic role.
III. Elevated levels of IL-4 indicate that the expression of Th1 cytokines may be involved.
a) Only II
b) I and II
c) II and III
d) All of the items

2. Regarding the epidemiology of SS, it is correct to state the following:
a) The classical or idiopathic variant affects both sexes equally.
b) the form associated with malignancy affects more women.
c) The initial episode of the idiopathic or classical variant occurs between 30 and 50 years of age.
d) Pediatric cases represent 18% of the total.

3. Mark the correct option in relation to the clinical features of SS:
a) erythematous and/or violaceous papular-nodular lesions, located mainly in the lower limbs.
b) bullous or ulcerated lesions are more frequent in the classic variant associated with infection.
c) Fever> 38 o C is the most common sign.
d) Eye and joint manifestations are rare.

4. It is correct to state the following about SS:
a) Most cases are related to cancer.
b) The most common hematologic malignancy is chronic myeloid leukemia.
c) The main associated infectious condition is that of the genitourinary tract.
d) Granulocyte colony-stimulating factor is the medication most implicated in drug-induced SS.

5. Mark the correct statement about the laboratory findings of SS:
a) The histopathology is characterized by dense and diffuse dermal neutrophil infiltrate, with leukocytoclastic vasculitis.
b) Peripheral leukocytosis with lymphocytosis occurs.
c) The erythrocyte sedimentation rate is <20mm/Hr and / or C-reactive protein is low.
d) Leukopenia, anemia and thrombocytopenia may occur in cases related to malignancies.

6. It is true regarding the treatment of SS:
a) systemic corticosteroids are the treatment of choice in most cases.
b) Intralesional or topical corticosteroids are never used.
c) Indomethacin is considered a first-line agent.
d) Colchicine and potassium iodide are second-line therapies.

7. The pathogenic mediator that favors the expansion of the ulcerated lesion of pyoderma gangrenosum are:
a) metalloproteinase-9
b) metalloproteinase-10
c) tumor necrosis factor
d) all of the above

8. The pathergy phenomenon occurs in pyoderma gangrenosum:
a) In all cases
b) In rare cases (<1%)
c) In approximately 30% of the cases
d) Only if there is an association with lymphoproliferative disease

9. Pyoderma gangrenosum can be associated with autoinflammatory diseases, including PAPA syndrome, which evolves with:
a) Pyogenic arthritis, alopecia
b) Pyogenic arthritis, acne
c) pancreatitis, acne
d) pancreatitis, alopecia

10. The clinical form of pyoderma gangrenosum most often associated with hematologic diseases is:
a) bullous
b) ulcerated
c) superficial
d) vegetating

11. In general terms, it is correct to state the following about pyoderma gangrenosum:
a) It occurs less frequently in children than in adults
b) It is primarily associated with infectious processes
c) It has a fatal outcome
d) In its treatment, it is always necessary to perform surgical debridement

12. Regarding the histopathological aspects of pyoderma gangrenosum, it is correct to state the following:
a) There is neutrophil infiltration and varying degrees of dermal vasculopathy
b) There is generally fibrinoid necrosis of vessels
c) Granulomas with caseous necrosis are the rule
d) Direct immunofluorescence is pathognomonic

13. The histopathogenesis of Behcet's disease mainly includes:
a) granuloma, vasculitis, elastosis
b) thrombosis, granuloma, neutrophil infiltration
c) neutrophil infiltration, thrombosis, vasculitis
d) atypical lymphocytes, thrombosis, vasculitis

14. The typical HLA of Behcet's Disease is:
a) HLA-B52
b) HLA-B51
c) HLA-DW5
d) all of the above

15. According to the criteria established by the International Study Group of Behcet's Disease published in 1990, the major criterion for diagnosis of Behcet's Disease is:
a) recurrent genital ulcer (3 or more episodes per year)
b) recurrent uveitis (3 or more episodes per year)
c) recurrent cutaneous vasculitis (3 or more episodes per year)
d) recurrent oral ulcers (3 or more episodes per year)

16. According to the criteria established by the Behçet Disease Research Committee of Japan published in 1994, which of the following clinical features constitute diagnosis of the complete form of BD?
a) oral ulcer, uveitis, depression, ileocecal ulcer
b) genital ulcer, erythema nodosum, thrombophlebitis, oral ulcer
c) uveitis, oral ulcer, genital ulcer, pseudofolliculitis
d) ileocecal ulcer, oral ulcer, uveitis, erythema nodosum

17. Regarding the treatment of Behcet's Disease it is correct to state the following:
a) sulfasalazine is the drug of choice
b) topical therapy is sufficient
c) therapy in critically ill patients may require more than one drug
d) None of the above

18. Regarding the prognosis of Behçet's disease, it is correct to state the following :
a) Evolution is always serious
b) It tends to be more severe in men, HLA-B51 positive and with early manifestations of the disease in life
c) It tends to be more severe in women, HLA-B51 positive, with early manifestations in life
d) it tends to be more severe in women, HLA-B51 positive and with late manifestations in life

19 In relation to neutrophilic urticaria we can state the following:
a) There are systemic manifestations such as fever and leukocytosis
b) The inflammatory cytokines involved in its pathogenesis are C3 and TNF-alpha
c) Anti-neutrophil drugs are a good therapeutic option
d) All of the above

20 Among the diseases that should be investigated related to neutrophilic urticaria we have:
a) Still's Disease
b) Tuberculosis
c) Neoplastic diseases
d) None of the above.

Answer Key

Sexually transmitted diseases during pregnancy: a synthesis of particularities. An Bras Dermatol. 2010;85(6):767-85.

1) b	6) c	11) c	16) a
2) d	7) a	12) b	17) c
3) d	8) a	13) d	18) a
4) b	9) b	14) c	19) d
5) a	10) c	15) a	20) c

Papers

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 60 days from the date of online publication.