Sweet's syndrome – a case report

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Abstract

Although rare, the association of Sweet's syndrome with Crohn's disease is established and is considered an extra-intestinal manifestation of the disease.

The authors describe a case of this neutrophilic dermatosis in a 65-year-old male with a background of ankylosing spondylitis and Crohn's disease, undergoing immunosuppressive therapy, who suddenly developed fever, arthralgias and a widespread reddish-purple papular rash. Laboratory data revealed high inflammatory markers. No cause of infection was found. The biopsy of two skin lesions showed subepidermal edema and perivascular neutrophilic infiltrate with no signs of vasculitis. Both the symptoms and the rash gradually subsided about one week later, after initiation of Ibuprofen alongside the continuation of immunosuppressive therapy. Clinical, laboratory and histological findings suggested the diagnosis of Sweet's syndrome, and no extracutaneous manifestations were found.

Key words: neutrophilic dermatosis, Sweet's syndrome, ankylosing spondylitis, Crohn's disease.

INTRODUCTION

The term acute febrile neutrophilic dermatosis was initially proposed by Robert Douglas Sweet in 1964, describing the clinical cases of eight women with cutaneous lesions presenting polymorphonuclear infiltrates in association with leukocytosis and neutrophils in the peripheral blood, known from that time on as Sweet's syndrome (SS). In 1983, a case of clinical overlapping and histopathology of SS with the already-known gangrenous pyoderma (GP) was reported for the first time, suggesting for the first time the existence of a continuous pathological spectrum. These dermatoses also have in common the fact that they are associated with systemic diseases, which contributes to being considered as clinical variants of the same disease: neutrophilic dermatosis (ND). Using the same criteria (neutrophilic cutaneous infiltration, existence of forms of overlapping/transition and association with systemic diseases), other entities have now been included in this group, such as erythema elevatum diutinum, a subcorneal pustular dermatosis and neutrophilic eccrine hidradenitis.[1]

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ND are often accompanied by non-specific systemic symptoms and polymorphonuclear infiltrates in the visceral organs, and are the visible manifestation of a reactive aseptic inflammatory process that affects other organ systems, which led to a proposed concept of neutrophil disease in 1991.[2,3]

SS is the most common entity within this group, and may manifest in various clinical contexts:

- Classical or idiopathic SS affects mainly women between 30 and 50 years of age, and may be preceded by infections, more commonly of the upper respiratory tract (the isolation of *Streptococcus* has been described) but also gastrointestinal infections (the isolation of Yersinia and Salmonella has been described);
- SS associated with neoplasia – paraneoplastic manifestations of hematological or solid neoplasia, the most commonly reported is acute myeloid leukemia;
- SS associated with drugs – the most commonly reported is the growth factor of colonies of granulocytes and macrophages, GM-CSF, but also co-trimoxazole, carbamazepine, hydralazine, levonorgestrel/ethinylestradiol, among others;
- SS associated with systemic inflammatory diseases – with a prevalence of DII;
- SS associated with pregnancy.[4,5]

Generally, the clinical symptoms include sudden onset of fever and general malaise, which may be accompanied by myalgias, arthralgias and migraines. The exanthema is erythematous-purple, papular or nodular, and can coalesce to form plaques, which are asymmetrically distributed all over the face, neck and limbs. The lesions can be painful but are not itchy.1,[4,5]

Due to the extensive subepidermal edema, the lesions may have a falsely vesicular or pseudovesicular appearance. In SS associated with neoplasm, atypical forms are described (vesicles, blisters and ulceration) mimicking or overlapping with the GP. There are also clinical variants such as pustular dermatosis (erythematous papule with small pustules on top, or pustules with an erythematous base), previously known as neutrophilic dermatosis of the dorsal hands or pustular vasculitis of the dorsal hands.[6] In the absence of treatment, the exanthema can last several weeks or months, and disappears without scarring.[1] Other more consistent laboratory findings are leukocytosis with neutrophils and increase in ESR.[4,5] Other findings include high protein levels in the acute phase.

The classic histopathological pattern describes a dense infiltrate of mature polymorphonuclears in the superficial dermis, with sub-epidermal edema and leukocytoclastic nuclear fragments. The epidermis is generally spared, and the signs of leukocytoclastic vasculitis are generally absent. Occasionally, lymphocytes, eosinophilia and histiocytes are also present in the infiltrate. The histopathological spectrum has expanded to include leukemia cutis, vasculitis and variability in the composition and localization of the inflammatory infiltrate (such as subcutaneous SS or subcorneal pustules).[5]

The etiology of SS is still unknown, but is probably multifactorial. Epidemiological, clinical and histopathological data support the hypothesis of a reaction of hypersensitivity to a viral, bacterial or tumoral agent. On the other hand, the cytokines appear to have an etiological role, with high levels being been detected in some cases.[5,6]

A characteristic aspect of SS is its rapid and excellent response to systemic corticotherapy, considered the cornerstone of therapy. However, its recurrence is anticipated in up to 30% of cases.[4]

CLINICAL CASE

Male patient, aged 65 years, Caucasian, with a history of ankylosing spondylitis HLA B27+ diagnosed in 1981, Crohn's disease (CD) diagnosed in 2001 and left uveitis diagnosed in November 2008. The patient was medicated with Salazopyrin (750 mg/day), and there have been no recent gastrointestinal manifestations. He was also medicated with Azathioprine (150 mg/day) and was in the phase of being weaned off Prednisolone (25 mg/day), initiated due to the uveitis, which had improved.

TABLE I

Diagnostic criteria of SS*

Major Criteria
Sudden onset of painful erythematous plaques or nodules
Dense neutrophilic infiltrate in, without leukocytoclastic vasculitis
Minor Criteria
Association with inflammatory disease, hematological disease, solid malignant tumors, vaccination, pregnancy, or preceded by non-specific gastrointestinal or upper respiratory infections
Fever (T >38ºC)
Laboratory analyses with ESR >20 mm; increased CRP, leukocytosis(>8000/µL), >70% of neutrophils (3 of these 4 criteria must be met)
Excellent response to treatment with systemic corticoids or potassium iodine
2* major and 2 minor criteria must be present.

On 9th March, patient showed onset of clinical symptoms characterized by fever (39ºC), arthralgias of the major joints, predominantly in the lower limbs, painless, non-itchy widespread exanthema, asthenia, and dyspnea on medium effort. There were no other complaints, such as gastrointestinal or ophthalmological complaints.

The patient was admitted for further tests on 11th March. On objective examination, the following were highlighted: erythematous-purple papular exanthema in the frontal region, anterior side of the chest, and limbs, slightly painful to touch, without involvement of the palms of the hands or soles of the feet, or the mucosa (*Fig. 1-3*), and crackles in both bases in the lung auscultation.

The analyses revealed leukocytosis (16,500/µL) with neutrophils (94%), ESR-52 mm/h and CRP-US--41.5mg/dL. Chest X-ray showed a bilateral hypotransparency with interstitial pattern.

The viral serologies (HIV1 and 2, EBV, CMV) and bacterial serologies (*Yersinia, Chlamydia trachomatis* and *pneumoniae, Mycoplasma pneumoniae*), as well as the tests for AS(L)OT, VDRL, ANN, ECA, and the blood cultures, were all negative. ALT, AST, creatinine and urea levels were within the reference values.

Chest CT showed aspects of emphysema, parti-

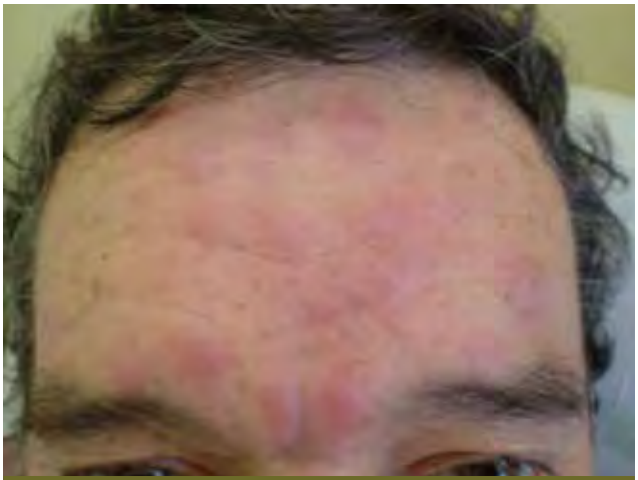

Image of the exanthema in the frontal region.

FIG. 1

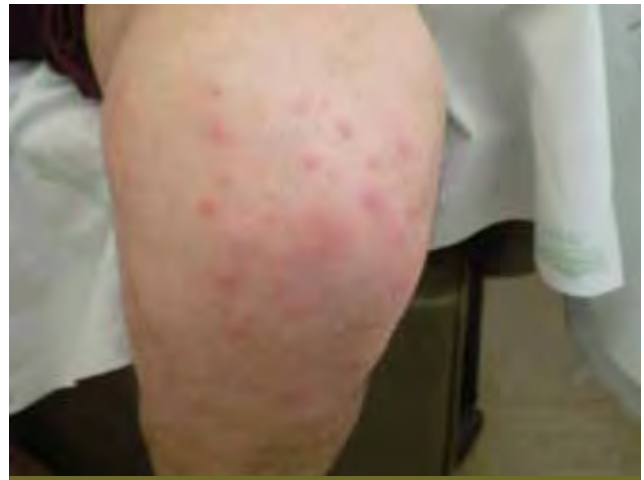

Image of the exanthema in the left knee - biopsied lesion.

FIG. 3

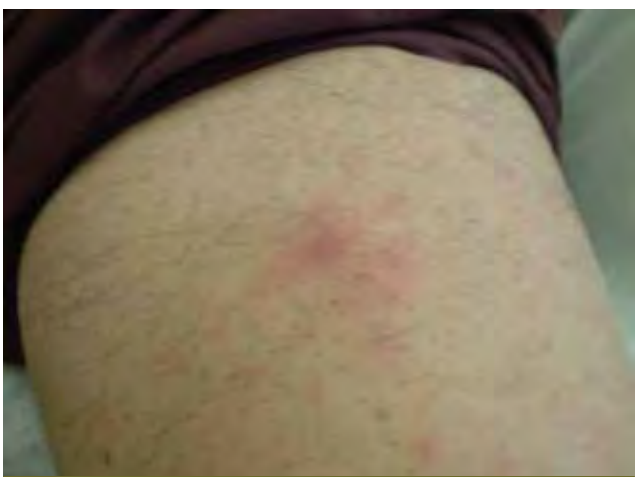

Image of the exanthema in the left thigh – biopsied lesion.

FIG. 2

cularly in the upper lobes, ground-glass densification, and thickening of the secondary interlobular septum, suggesting involvement of the pulmonary interstitium, minor bilateral lung effusion, and mediastinal adenopathies. The study continued with bronchofibroscopy, which did not reveal any macroscopic lesion; and bronchoalveolar lavage (BAL), showing habitual cell constitution with a prevalence of macrophages and absence of neoplastic cells. Immunophenotype study of the lymphocytes in the BAL was normal. Mycobacterium study was negative. It was suggested a hypothesis of chronic pulmonary interstitial involvement in association with ankylosing spondylitis.

Ophthalmological evaluation showed vitritis of the left eye, in regression compared with previous assessments.

Skin biopsy of two lesions in the left thigh and knee (*Fig. 2 and 3*), showed sub-epidermal edema and perivascular neutrophilic infiltrate without signs of vasculitis.

During hospitalization, the patient was apyretic, and the medication and dosage given in the outpatient clinic were maintained, except for topical treatment of the vitritis and the introduction of Ibuprofen 1200 mg/day. The clinical symptoms and laboratory alterations reverted at the end of approximately one week, without the formation of scarring in the cutaneous lesions.

The patient was discharged on 26th May, in improved condition, and was placed once again on the outpatient therapeutic regimen.

In view of the results of the skin biopsy, and given the clinical context and macroscopic findings, a hypothesis of Sweet's syndrome was proposed, in consensus with the Pathological and Pathological Anatomy.

DISCUSSION

In this patient, the clinical symptoms, the characteristics of exanthema, the laboratory findings and the biopsy of the cutaneous lesions are compatible with

the diagnosis of SS, fulfilling the diagnostic criteria proposed by Von Den Driesch.[7]

Around 15% of cases of SS are associated with systemic inflammatory disturbances, most commonly DII.[8] Meanwhile, and according to a Portuguese study, DII tends to present extra-intestinal cutaneous manifestations, in incidences that affect 10% of cases at the time of diagnosis, and 20% over the course of the disease. The most common cutaneous presentations are erythema nodosum and gangrenous pyoderma.[9] Although it has been described in few cases of CD, SS is an established cutaneous manifestation, and its incidence is higher among females, in cases with involvement of the colon, and in patients with other extra-intestinal manifestations. Outbreaks of SS most commonly occur in phases of active disease, although it has been described in other states, and may even precede the intestinal symptoms.[10] In view of the absence of gastrointestinal complaints in this patient, we opted not to carry out endoscopic study, therefore the activity of CD was not documented.

SS is associated with neoplasias in 21% of cases, therefore a structured diagnostic approach is recommended, to study the undiagnosed neoplasia, as well as long-term follow-up, given that the SS preceded the occurrence of neoplasia in time intervals as long as 11 years.6 In the patient in question, no signs suggestive of neoplasia were observed in the anamnesis, clinical presentation, or laboratory and imaging studies carried out. Therefore, no targeted study was carried out according to the recommendations, notably, research of thyroid, prostate or testicular pathologies; the tumor marker test (CEA) and sigmoidoscopy (although the patient was followed up in Gastroenterology). According to the same recommendations, the patient will be monitored periodically by the Medical and Gastroenterology clinics.

More commonly than other neutrophilic dermatoses, SS may be accompanied by systemic manifestations - neutrophilic disease - which can affect any organ. Extracutaneous involvement has been described in the eyes, lungs, heart, aorta, bones, joints, muscles, liver, pancreas, spleen, digestive tube, lymphatic ganglions and central nervous system.4,11 Besides specific organic complaints, there may also be concomitant laboratory alterations and respective imaging findings. In histological terms, the presence of neutrophilic infiltrate or aseptic abscesses in the affected organs is observed.3,[11] These manifestations may occur in the absence, or precede the cutaneous involvement, are difficult to diagnose, and are probably underdiagnosed. They are important because a correct understanding of them, in the context of ND, can prevent unnecessary invasive investigations.11 During our clinical investigation, it was not possible to demonstrate systemic involvement of the dermatosis. Alveolar lavage did not show a prevalence of neutrophils. Ophthalmological observation did not show any recurrence of uveitis or new ocular involvement. We opted not to investigate possible joint involvement. The patient did not present any other complaints or clinical or laboratory alterations compatible with extra-cutaneous manifestations.

Systemic corticotherapy is considered the cornerstone of therapy in SS. Besides surgical or pharmacological treatment of the underlying cause, there are other therapeutic options, including: Lugol solution, Colchicine, Indomethacin and Dapsone. There have been reports of a good response to non-steroid antiinflammatories, although there have also been reports of a new outbreak of SS while taking these drugs.[12] The patient was in the phase of being weaned off corticotherapy which, on one hand, may have led to the development of the dermatosis, and on the other, may have given rise to the less exuberant clinical symptoms and exanthema of shorter duration. On the other hand, the administration of Ibuprofen, together with maintenance of the Prednisolone and Azathioprine regimen, may have contributed to the symptoms clearing up more quickly. ■

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References

1. Wallach D. Les dermatoses neutrophiliques. Rev Med Interne 2005; 26:41-53.

2. Vignon-Pennamen MD, Wallach D. The cutaneous manifestations of neutrophilic disease. Dermatologica 1991;183:255-264.

3. Leitão J et al. Síndrome de Sweet, afecção cutânea benigna ou sistémica grave? Revista Portuguesa de Medicina Interna 2006; 3 (1): 24-28.

4. Cohen PR, Kurzrock R. Sweet's syndrome: a neutrophilic dermatosis classically associated with acute onset and fever. Clin Dermatol 2000;18:265-282.

5. Cohen Philip R. Sweet's syndrome – a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis. 2007;2:34. doi: 10.1186/1750-1172-2-34.

6. Cohen Philip R et al. "Chapter 31. Acute febrile neutrophilic dermatosis (Sweet's syndrome)" (Chapter). Wolff K et al: Fitzpatrick's Dermatology in General Medicine, 7e: http://www.accessmedicine.com/content.aspx?aID=2952280

7. Von Den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). J Am Acad Dermatol 1994;31:535-556.

8. Timani S, Mutasim D. Skin manifestation of inflammatory bowel disease. Clin Dermatol 2008; 26: 265-273.

9. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol 1996; 23: 29-34.

10. Travis l et al. Sweet's syndrome: an unusual cutaneous feature of Crohn's disease or ulcerative colitis. The South West Gastroenterology Group. European journal of gastroenterology and hepatology. Eur J Gastroenterol Hepatology 1986; 9(7):715-720.

11. Vignon-Pennamen MD. The extracutaneous involvement in the neutrophilic dermatoses. Clin Dermatol 2000;18:339-347.

12. Cohen PR, Kurzrock R. Sweet's Syndrome - A Review of Current Treatment Options. Am J Clin Dermatol 2002; 3 (2): 117-131.