Sweet's syndrome: benign dermatosis or serious systemic disease?

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Abstract

Sweet's syndrome is an acute febrile neutrophilic dermatosis that due to its manifestations and systemic involvement, is commonly associated with infectious or inflammatory diseases or neoplasms, prompting hospitalizations in Internal Medicine or Rheumatology wards.

Six cases of Sweet's syndrome are retrospectively analyzed. The sex and age distribution and clinical symptoms are similar to those of the literature. Four patients had associated diseases. One patient had hepatic involvement, demonstrated histologically, which is an extremely rare situation.

The authors conclude that given the characteristics of this disease, the collaboration of the internist in the study and follow-up of these patients is necessary, and subsequently, their follow-up, to detect other situations such as neoplasias, enabling an earlier therapeutic intervention.

Key words: Sweet's syndrome, acute febrile neutrophilic dermatosis

Introduction

Sweet's syndrome, described by Sweet in 1964[1] as an *acute febrile neutrophilic dermatosis*, is characterized by the onset of acute fever; erythematous, violaceous, painful skin lesions located mainly in the limbs, trunk, face or neck; leukocytosis with neutrophilia; and dense dermal infiltrates consisting of neutrophils.

Being a predominantly dermatological disease, it is often seen in the area Internal Medicine and related areas, and admission rates in Rheumatology wards as high as 35% of cases have been reported. [2] The disease is often associated with infectious, inflammatory, and, in particular, neoplasic diseases. Of the infectious diseases, the most common are respiratory infections, with Yersinia enterocolitica[3] or a Cytomegalovirus[4] being reported as agents. In relation to inflammatory diseases, connective tissue diseases[5,6] and inflammatory bowel disease[7] are most commonly described. Neoplasms can occur in 15% to 20% of cases, hematological neoplasms being the most commonly observed. Besides the skin, the joints, eyes, lungs, kidneys or liver may also be involved.

In this paper, a retrospective analysis is carried out, of six patients with Sweet's syndrome admitted to the Internal Medicine and Rheumatology service, with a brief literature review.

Clinical cases

From January, 1988 to December, 1994 six patients with Sweet's syndrome were hospitalized in the Department of Medicine III and Rheumatology of the HUC.

Case 1

Female patient, aged 31, admitted with fever, chest pain and polyarthritis (elbows, MCP, PIJ, and wrists) with acute onset. During hospitalization, erythematous, painful and infiltrated cutaneous papules appeared in the lower limbs and trunk. On physical examination, reduced vesicular sounds were observed in the left base. Additional tests revealed: neutrophil leukocytosis (leukocytes 14.7 G/L, PMN 81%), erythrocyte sedimentation rate (ESR) of 115 mm in the first hour, positive rheumatoid factor and mode-

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rate pleural effusion in the left lung base. Skin biopsy revealed Sweet's syndrome. The patient was therefore diagnosed as having Sweet's syndrome and rheumatoid arthritis with associated pleuritis. No abnormalities were revealed in the bone biopsy. Treatment with indomethacin (100 mg/day) was begun, resulting in the disappearance of the skin lesions. Subsequently, the patient was treated with corticosteroids for the rheumatoid arthritis, and no recurrences of the skin lesion were recorded.

Case 2

Female patient, aged 43, admitted with acute symptoms, high fever (40ºC) and non-itchy erythematous, violaceous papules with blisters on the wrists, trunk and head. The patient presented arthritis of the left wrist, and aphtha of the mouth and vagina. Laboratory tests found a relative neutrophilia (leukocytes 9.5 G/L, PMN 76.5%) and ESR of 75 mm in the first hour. Immunological tests were all normal (autoantibodies, complement fractions and immunoglobulin) as well as the tumour markers. Skin biopsy revealed lesions characteristic of Sweet's syndrome. Bone marrow examination was normal. The patient was started with Methylprednisolone 32 mg/day, rapidly decreasing the dose, and terminating the treatment after two weeks. All the symptoms disappeared, without any relapses.

Case 3

Male patient, aged 27, admitted with hepatomegaly and alterations in liver function tests. The patient had a chronic erythema in the lower limbs, of unknown etiology. He also had recurrent acute skin lesions, associated with fever, for which histological examination revealed Sweet's syndrome. Physical examination revealed hepatosplenomegaly. Additional tests revealed: normochromic, normocytic anemia (Hb 6.5 g/dL), leukocytosis with neutrophilia (leukocytes 16.5 G/L, PMN 96%), ESR 90 mm in the first hour, AST 30 IU/L (normal <25 IU/L), normal ALT, alkaline phosphatase 109 IU/L (normal <69 IU/L), LDH 900 IU/L (normal <330 IU/L), 47% prothrombinemia and polyclonal hypergammaglobulinemia. Immunoglobulin assays showed increases in IgA, IgG and IgM. The test for circulating immune complexes was positive. Liver biopsy revealed a periportal inflammatory infiltrate, consisting predominantly of polymorphonuclear leukocytes, with sinusoidal distention and hepatocyte reactions, consistent with the liver impairment of Sweet's syndrome (*Fig. 1*). Bone biopsy revealed a hypercellular bone marrow without atypias.

Liver Biopsy: periportal inflammatory infiltrate, consisting predominantly of polymorphonuclear leukocytes with sinusoidal distension and hepatocyte reactions

FIG. 1

Subsequently, although intestinal biopsy was normal, the patient was diagnosed with intestinal malabsorption syndrome, compatible with the d-xylose test. A nephrotic syndrome was later diagnosed, and renal biopsy showed lesions associated with secondary renal amyloidosis. At this point, thrombocytopenia emerged, which continued.

During the evolution of the disease, skin lesions reappeared, but were successfully controlled with oral corticosteroids used for short periods of time. At the time of diagnosis of nephrotic syndrome, prolonged corticosteroid therapy was initiated. The patient underwent a further two liver biopsies. The second one showed results similar to the first, but the last biopsy, which was performed after the diagnosis of nephrotic syndrome, during the corticosteroid therapy, did not reveal PMN infiltration.

Finally, the patient suffered lower gastrointestinal

bleeding, with symptoms of colic angiodysplasia which, in the presence of thrombocytopenia, led to a potential splenic embolization. The patient died as a result of gastrointestinal bleeding.

Case 4

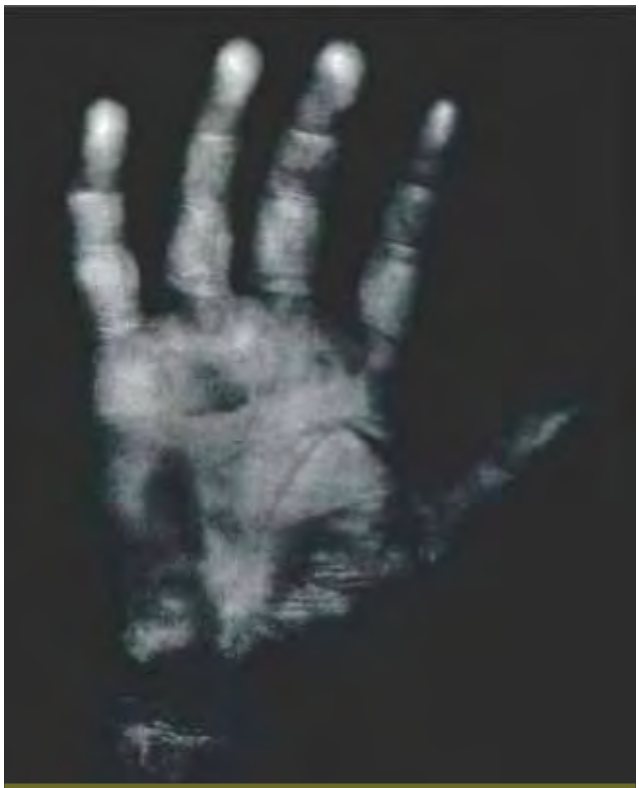
Male patient, aged 63, admitted with acute symptoms including high fever (39ºC); non-itchy erythematous, violaceous skin lesions on the limbs (Fig. 2), and productive cough. On physical examination, in addition to skin lesions, a decrease in vesicular sounds in the right lung base was observed, with rales. Leucopenia with relative neutrophilia (leukocytes 3.3 G/L, PMN 73%) was also present. The ESR was 24 mm showing a polyclonal hypergammaglobulinemia. Chest X-ray revealed pneumonia of the right lung base, and the skin histology was consistent with Sweet's syndrome. Bone biopsy was inconclusive, due to a lack of sufficient material. The patient was treated with antibiotics for pneumonia, and the skin lesions cleared up spontaneously. Later, after hospitalization the patient suffered thrombocytopenia, the cause of which was not investigated, and the leucopenia persisted. There were no recurrences of the skin lesions.

Case 5

Female patient, aged 60, admitted with fever and erythematous, violaceous and painful maculopapular rashes of sudden onset in the lower limbs. History of a similar episode four years earlier, which was successfully treated with corticosteroids. Physical examination revealed rales in the lung bases. The ESR was 82 mm in the first hour. The blood count and chest X-rays were normal. The skin biopsy was consistent with Sweet's syndrome. The patient was treated with Prednisolone at an initial dose of 80 mg/day, discontinued after 3 weeks, and the skin lesions disappeared quickly. This case was followed-up at the clinic, and no relapses or other changes were observed.

Case 6

Female patient, aged 52, with asthenia and polyarthralgias for 10 days, aphtha of the mouth and vagina, and more recently, bartholinitis. The axillary temperature was 40ºC and she had painful maculopapular rashes on all four limbs. Neutrophil leukocytosis (leukocytes 18.4 G/L, PMN 81%) and an ESR of 60 mm in the first hour were observed. Bone biopsy revealed reactive bone marrow. Skin biopsy revealed lesions characteristic of Sweet's syndrome. The patient underwent marsupialization and received Methylprednisolone at 40 mg/day, which was gradually reduced over several weeks. The skin lesions disappeared without recurrences.



Skin lesions in Sweet's syndrome.

FIG. 2

Discussion

Although the disease was first referred to as acute febrile neutrophilic dermatosis, the current name of Sweet's syndrome is adopted by most authors. Skin lesions and specific histological aspects are normally the most suggestive signs of the disease. Su and Liu suggested, in 1986, some criteria that are usually used as a guide for the diagnosis of this syndrome.[8] The major criteria are: 1) acute onset of painful, erythematous or violaceous skin plaques or nodules; 2) predominantly neutrophilic infiltrates in the dermis, without leukocytoclastic vasculitis. The minor criteria are: 1) fever or previous infection; 2) arthralgia, conjunctivitis or concomitant malignant disease; 3) leukocytosis; 4) a favorable response to corticosteroi-

ds, but not to antibiotics. In 1989, Von den Driesch and colleagues proposed a fifth minor criterion - the existence of high erythrocyte sedimentation rate. [9] The definitive diagnosis is established in the presence of all the major criteria and two minor criteria. Hence the need for skin biopsy when studying these patients.

By analyzing the cases presented here, we find several points in common with those described in the literature, and some aspects worth highlighting.

The prevalence of female patients (4 out of 6 cases) is consistent with the cases usually reported in adults, [2,10,11,12] in which the prevalence of female patients is as high as 80%. [13] Similarly, the average age of our patients is similar to the age range generally described for this disease - between 30 and 60 years, [7,10,11,12] cases involving older patients or children are rare. [14]

The high fever recorded in all our patients is consistent with the symptoms described in the literature, with prevalence varying from 48% to 100%. [10] Joint complaints are also common, as is well-known. In our patients, joint complaints occurred in 5 out of 6 cases, a higher than normal incidence. Arthralgias were described in 33% of the cases, with arthritis in approximately 15%, nearly always in the form of a migratory monoarthritis. [11]

Skin manifestations were the prevalent symptoms. However, all the reported case series suggest a possible systemic involvement. In our group of patients, one case in particular deserves special mention, as both liver and kidney involvement were present. The liver lesion was confirmed by biopsy, and histological tests revealed changes similar to those found in the skin, with infiltration of leukocytes, predominantly neutrophils. Of the two further liver biopsies, the second one showed a decrease in PMN infiltration, as the patient was receiving corticosteroids to treat a diagnosed nephrotic syndrome. The kidney biopsy showed no aspects resembling the skin lesions in Sweet's Syndrome, but only revealed secondary amyloidosis.

Reported cases with histologically proven renal and hepatic involvement are extremely rare, [15] which further emphasizes the value of the findings in this case. However, there have been several cases in which suggestive changes are reported, whether involving lesions of the liver or the kidneys. In the case of liver lesions, transitory elevation of aspartate aminotransferase (AST) and gamma-glutamyltranspeptidase were reported in some patients, as well as of alkaline phosphatase in 83% of patients in the same case series.[7] Renal involvement is manifested mainly by changes in the urine sediment, which are reported in 11% -72% of patients, depending on the series. [11,13,16] Usually these changes are characterized by the appearance of proteinuria, hematuria, urinary casts (erythrocyte and granular), or alterations in creatinine clearance. In our case series, only one patient had signs of renal involvement.

Besides the kidney and liver, involvement of other organs has also been reported. These include, the lungs, in rare cases, [17] and the eyes, with highly variable rates of involvement, as high as 75%. [7,10,11,18] The most common alterations are conjunctivitis or episcleritis. In the cases presented here, no eye alterations were observed. Only one patient had oral lesions (aphtha). Although these lesions are common, for many authors their presence is associated mainly with neoplasms. [19,20,21]

Our patients also presented other associated pathologies. One patient had bartholinitis, one had rheumatoid arthritis with pleural effusion, a third patient had pneumonia, and a fourth, whose condition was more severe, had hepatic involvement, intestinal malabsorption syndrome, and subsequently, nephrotic syndrome. So far, no case of neoplasm has been detected.

As neither the etiology nor the pathogenesis of Sweet's syndrome are known, some explanations have been proposed. The most frequent are related to the role of interleukin-1, [22] with various alterations in function of neutrophils, such as an increase in its chemotaxis or phagocytosis, [12,21] or more rarely, reactions of hypersensitivity to external stimuli. [21] More recently, a role for autoantibodies has been suggested, and in particular, for anti-neutrophil cytoplasmic antibodies (ANCA). [23] The significantly high percentage of respiratory infections is notable, among the prodromal symptoms of the disease, and can be as high 75% in so-called idiopathic cases. [16]

But although the etiology is unclear, the association with neoplasms is a generally accepted fact. Between 10% and 20% of patients with Sweet's syndrome suffer or will suffer from a neoplasm. [11,20,24] The most frequent neoplasms are malignant hemopathies, and of these, the most common is acute myeloid leukemia, present in 42% of patients with Sweet's syndrome and malignant disease. [21] Chronic myeloid leukemia, chronic lymphocytic leukemia, lymphomas and

myelodysplastic syndromes[25] are also described. The presence of solid neoplasms is less common. The most frequent are those affecting the urogenital (especially prostate and testicle) and gastrointestinal tracts, and the breast. Cervical and lung cancer, or even hidden neoplasms, are rarer. The most common histological type is adenocarcinoma. [20] The extent to which these conditions are related with the onset of the disease has not been determined, therefore theories that consider Sweet's syndrome as a paraneoplasic condition have yet to be proven. Nevertheless, even in patients with neoplasm, many respiratory infections occur in the preliminary stages of the disease. Also in relation to such cases, associated with the neoplasm are some peculiarities that should be pointed out: a similar incidence between gender, a higher frequency of lesions of the oral mucosa, and a lower incidence of leukocytosis and thrombocytopenia, especially in patients with malignant hemopathy. The response to treatment is similar to that of other patients, but the relapse rate may be a little higher.

The investigation of the skin lesions is essential for the diagnosis: the lesions are usually restricted to the dermis and the most characteristic aspect is the presence of inflammatory infiltrate, basically composed of PMN in the middle and deep layers, and around the veins. Lymphocytes, eosinophils, or even mast cells, are rare. Sometimes karyoklasis may occur, but the occurrence of vasculitis is uncommon. There may be papillary edema or even cases of spongiosis and exocytosis. [10,11,26] The differential diagnosis of skin lesions occurs with polyform erythema, erythema nodosum, erythema elevatum diutinum, leukocytoclastic vasculitis and granuloma faciale, among others. [10]

As mentioned earlier, these patients respond very favorably to corticosteroids, whether for skin lesions or systemic manifestations. [27] Usually, the skin lesions do not leave scars and, even without treatment, they tend to disappear spontaneously within 2 to 4 weeks.[16] Relapses may occur in 30% to 50% of the cases, responding equally well to corticosteroids. However, this fact does not alter the favorable prognosis of the disease itself. In the group of patients presented here, only two suffered relapses, and in both of them there were multiple episodes.

Conclusions

Although skin lesions are determining factors in the clinical symptoms of Sweet's syndrome, the presence of systemic manifestations such as fever or leukocytosis, the frequent involvement of other organs, and the high probability of occurrence of other diseases, either before or after the diagnoses of Sweet's Syndrome (including inflammatory diseases and neoplasms), led us to conclude that this syndrome should be considered within the scope of Internal Medicine.

Of the cases reported here, we emphasize, firstly, the association of most of them (4 of 6) with other pathologies and, secondly, liver involvement in one of them, which is extremely rare.

By analyzing these cases and those described in the literature, we infer that it is essential to work closely with the internist in the investigation and follow-up of these patients. The follow-up should be carried out for long periods, as previously reported by other authors, [20] since malignant neoplasms can occur later on. A malignant hemopathy, for example, occurred 11 years after the initial diagnosis of Sweet's syndrome. [20]

Finally, we draw attention to the fact that although skin lesions in the Sweet's syndrome is recognized as a benign entity, the syndrome, due to its potential consequences described in the literature and verified in some of our cases, requires a thorough and extended study over time, as the prognosis can be unclear in the short or long term. ■

References

1.Sweet RD. An acute febrile neutrophilic dermatosis. Br J Dermatol 1964; 76: 349 – 356.

2. Harms M, Saurat JH. Syndrome of Sweet. Ann Dermatol Venerol 1983; 110 (5): 461 – 468.

3. Elsner P, Hartmann AA, Lechner W. Sweet's syndrome associated with Yersinia enterocolitica infection. Dermatologica 1986; 173: 85 – 89.

4. Planty P, Le Guillon, Le Roux P, Guillet G. Syndrome de Sweet. 2 cas d'origine probablement infectieuse. La Presse Medicale 1987; 16 (27): 1333 – 1334.

5. Prystwosky Sd, Fye KH et al. Acute febrile neutrophilic dermatosis associated with Sjogren's syndrome. Arch Dermatol 1978; 114: 1234 – 1235.

6. Frayhey R, Matta M and Kurben A. Sweet's Syndrome simulating systemic lupus erythemathous. Dermatologica 1972; 144: 321 - 324.

7. Kemmett D, Hunter J. Sweet's syndrome: the clinical review of 29 cases. J Am Acad Dermatol 1990; 23: 503 – 507.

8. Su PD, Liu H-NH. Diagnostic criteria for Sweet's syndrome. Cutis 1986; 37: 167 - 174.

9. Van den Driesch P, Gomez RS, et al. Sweet's syndrome: clinical spectrum and associated conditions. Cutis 1989; 44: 193 – 200

10. Machado A, Duarte Freitas J and Baptista P. Dermatose aguda febril neutrofilica. Síndroma de Sweet. Separata do Jornal do Médico CXVII (2116): 393 – 400.

11. Moreland LB, Brick JE, Kovach E et al. Acute febrile neutrophilic dermatosis (Sweet's syndrome): a review of the literature with emphasis on musculoskeletal manifestations. Sem Art Rheum 1988; 17 (3): 143 – 155.

12. Fett D, Gibson L, Su D. Sweet's syndrome: systemic signs and symptoms and associated disorders. Mayo Clin Proc 1995; 70:234 – 240.

13. Storer JM, Nesbitt LT, Galen WK, Dello VA. Sweet's syndrome. Int J Dermatol 1983; 22: 8 – 12.

14. Collins P, Rogers S et al. Acute febrile neutrophilic dermatosis in childhood (Sweet's syndrome). BR J Dermatol 1991; 124: 203 – 206

15 Matta M, Malak J, Tabet E, Kurben A. Sweet's syndrome: systemic associations. Cutis 1973; 12: 561 – 565.

16 Cooper PH, Innes DJ, Geer KE: Acute febrile neutrophilic dermatosis (Sweet's syndrome) and myeloproliferative disorders. Cancer 1983; 51: 1518 – 1526.

17.Lazarus A, McMillan M, Miramadi A. Pulmonary involvement in Sweet's syndrome. Preleukemic and leukemic phases of acute myelogenous leukemia. Chest 1986; 90 (6); 922 – 924.

18.kernel Morston GP, Col Warden TE it all.the clinical spectrum of sweeps syndrome (acute febrile neutrophil leak Dermot houses): a report of 18 cases. BR J dermatology 1975; 92:363 – 373.

19.driven NE, I'll varies N a.oral manifestations of sweeps syndrome.dermatology 1984; 169:102 – 103.

20.Cohan the art, Holder W it talk.sweeps syndrome in patients with solid tumours.cancer 1993; 72:2723 – 2731.

21.Cohan PR, help us and, close rock R.believe Nancy associated, sweeps syndrome: review of the Walch literature.J clean oncology 1988; 6:1887 – 1897.

22.going JJ darts is the pathogenesis of sweeps syndrome mediated by interleukin one? BR J dermatology 9087; 116:282 – 283.

23.G, Harrison GJ, Hunter G a.antibodies to neutrophil leak said the plans make a antigen is: serology marker for sweeps syndrome.J a M dermatology 1991; 24:97 – 969.

24.Cohan PR, K rock R, sweeps syndrome and malignancy.HM J met 1987; 82:1220 – 1226.

25.Clementson LJ, minute see it all.acute febrile Dermot loses: a marker of malignancy? Act their venereal (star call) 1989:69:52 – 58.

20 6V Newell – Bannerman empty.Wallis the.could cutaneous manifestations of neutrophil leak disease.study of seven gazes.dermatology 1991; 183:255 – 264.

27.Larson LG, bound J.acute febrile neutrophil experiment poses (sweeps syndrome).successful treatment with short-term corticosteroids.J rheumatology 1985; 12:1000 – 1003.