Sweet's Syndrome and relapsing polychondritis signal myelodysplastic syndrome

Síndrome de Sweet e policondrite recidivante reveladores de síndrome mielodisplásica

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Abstract: The emergence of certain skin conditions belonging to the group of mucocutaneous paraneoplastic syndromes may indicate the future appearance of a previously unknown malignancy. Sweet´s Syndrome and relapsing polychondritis are included in this group. Sweet´s Syndrome and relapsing polychondritis are very rarely found together in the same patient. This dual occurrence is more commonly found in cancer patients with associated hematological malignancies. We report the case of a 79-year-old male with Sweet´s Syndrome and relapsing polychondritis, who was subsequently diagnosed with a myelodysplastic syndrome.
Keywords: Polychondritis, relapsing; Sweet´s syndrome; Paraneoplastic syndromes

Resumo: Certas dermatoses, pertencentes ao grupo das síndromes paraneoplásicas mucocutâneas, podem ser o prenúncio de uma neoplasia previamente não conhecida. Tanto a síndrome de Sweet como a policondrite recidivante incluem-se neste grupo. A síndrome de Sweet e a PR são raramente encontradas em um mesmo paciente. A presença de policondrite recidivante e síndrome de Sweet em um mesmo paciente tem se revelado mais frequente em pacientes com neoplasias associadas, sobretudo hematológicas. Relata-se o caso de paciente do sexo masculino, 79 anos, com síndrome de Sweet e policondrite recidivante, em quem, subsequentemente, foi diagnosticada uma síndrome mielodisplásica.
Palavras-chave: Policondrite recidivante; Síndrome de Sweet; Síndromes paraneoplásicas

INTRODUCTION

Certain dermatoses in the group of paraneoplastic syndromes may herald the appearance of a previously unknown malignancy. A study of these may contribute to its early detection and treatment.

Sweet's Syndrome (SS), first described in 1964 by Robert Sweet, is a rare and acute febrile neutrophilic dermatosis, the pathogenesis of which is not entirely clear. The syndrome is characterized by sudden onset of erythematous infiltrated papules or plaques, located especially on the face, neck and upper extremities and associated with fever and neutrophilic leukocytosis. [1] It can be classified in five groups: idiopathic or classic, parainflammatory, paraneoplastic, linked to pregnancy and secondary to drugs. Relapsing polychondritis (RP) is a rare multisystemic disease of unknown etiology, probably of an immunologic nature, first described in 1923 by Jakch Wartenhorst. RP is characterized by recurrent inflammation and cartilage tissue destruction, including nasal, auricular tissues and the upper airways. [2] An increasing number of cases have been described as being linked to malignancies, particularly myelodys-

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plastic syndrome and, albeit less frequently, to solid tumors or other hematologic malignancies. [3]

Myelodysplastic syndrome (MDS) is a clonal disorder of the hematopoiesis characterized by dysplastic bone marrow and peripheral cytopenia.

The report below describes the case of a patient with Sweet's Syndrome and RP, who was subsequently diagnosed with MDS.

CASE REPORT

79-year-old male white patient, monitored in the Dermatology Department, suffering recurrent episodes of sudden onset of erythematous, pseudovesicular, circular plaques with slightly pink centers, painful, varying in size from 0.5 to 3 cm, located on the trunk, neck and upper limbs, always accompanied by fever (37.5 to 38º C) (Figure 1). The review of systems was normal, with no evidence of organomegalies or lymphodenomegalies. A skin biopsy showed edema of the papillary dermis, a dense perivascular inflammatory infiltrate consisting predominantly of neutrophils, many with leukocitoclasia (Figure 2). Histopathological findings were consistent with a diagnosis of SS. The laboratory tests showed leukopenia (3400/µL) and an increased erythrocyte sedimentation rate (50 mm/h). After steroid therapy was started (deflazacort 60 mg/day, with slow gradual withdrawal), initial remission was observed, but the lesions reappeared soon after suspension of therapy. In order to evaluate the associated etiology the following were performed: laboratory tests (liver, kidney and thyroid function, tumor markers, viral serology, ANA's, anti-DNA, anti-SSA, anti-SSB, anti-RNP, anti-SM), bone marrow tests, upper GI endoscopy, colonoscopy, simple chest X-rays, computerized axial tomography of the chest, abdomen and pelvis, and abdominal, prostate and thyroid gland ultrasound, which produced results within normal limits.

About 12 months after initial diagnosis of SS, the patient complained of pain and swelling of the left pinna. Physical examination revealed swelling, redness and heat, except for the lobule (Figure 3A). An auricular cartilage biopsy showed dense inflammatory infiltrate in the subcutaneous cartilage and degeneration of marginal chondrocytes consistent with chondritis (Figures 3B, 3C and 3D). Concomitant episodes of conjunctival injection (Figure 4) were diagnosed by an ophthalmologist as bilateral peripheral superficial corneal ulcers. The patient was medicated symptomatically.

The patient was monitored at the Dermatology Clinic for 15 months. During this period he presented with recurrent skin lesions consistent with SS, as well as recurring episodes of inflammation in the eyes and both ears. Received oral corticosteroids to deal with the outbreaks, with complete remission of symptoms until after completion of treatment. More recently the patient has suffered weight loss and asthenia. Periodic laboratory tests have detected non-megaloblastic macrocytic anemia and neutropenia. Amyelogram and bone marrow biopsy were done, with findings consistent with Myelodysplastic Syndrome. The patient was referred to the Hematology/Oncology Department.

DISCUSSION

Paraneoplastic dermatoses are non-neoplastic, tumor-related visceral or hematologic skin disorders. The possibility of predicting the coexistence of a neo-

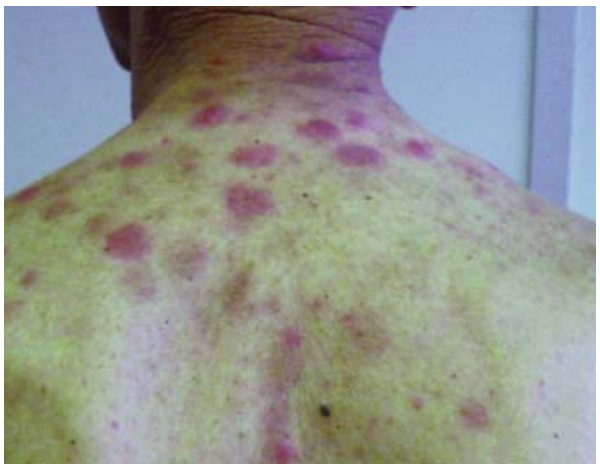

Figure 1: Clinical manifestations of Sweet's Syndrome: erythematous plaques with annular configuration and pseudovesiculation, located on the back

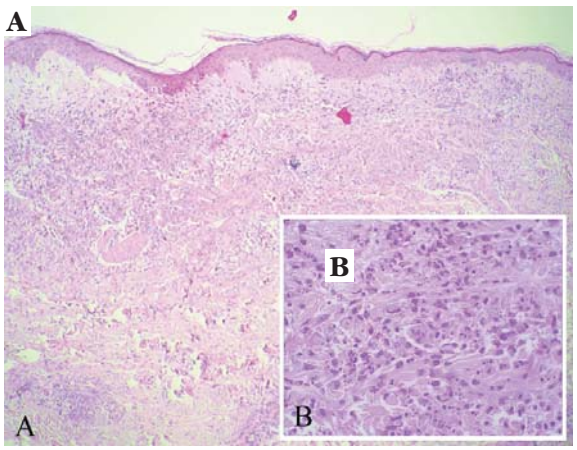

Figure 2: A. Sweet's Syndrome (H&E x 40): Edema in the papillary dermis and a dense perivascular inflammatory infiltrate; **B.** Infiltrate composed of neutrophils with leukocitoclases (H&E x 400)

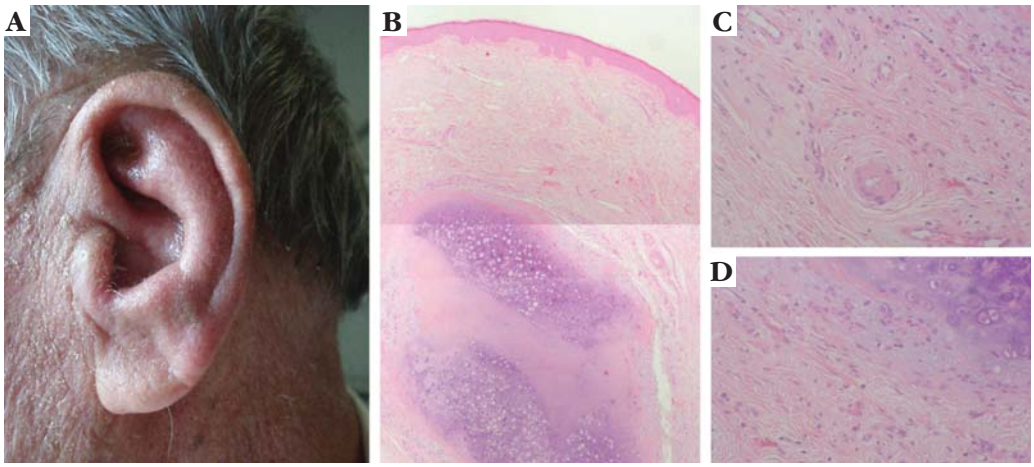

Figure 3: A. Left pinna with hyperemia and edema in the region cartilage, not affecting earlobe: **B.** Biopsy of cartilage (H&E x 40); **C.** Lymphoplasmacytic inflammatory infiltrate in the dermis underlying the cartilage (H&E x 100); **D.** Degeneration of marginal chondrocytes (H&E x100)

plasm from the study of mucocutaneous lesions with certain characteristics arouses particular interest in these dermatoses.

SS is related to cancer in 20% of cases, with 85% of these linked to hematological disorders and 15% to solid tumors. Association with MDS is common and may signify a poor prognosis given the possibility of conversion to acute myeloid leukemia.

The diagnosis of SS is based on clinical findings, histology and laboratory tests, according to the diagnostic criteria adapted by Su and Liu [1] (Table 1). Our patient presented two major criteria (clinical aspect of lesions and dense neutrophilic infiltrate in the biopsy) and three minor criteria (fever, associated sickness and response to corticosteroid therapy).

The paraneoplastic form of SS tends to present more severe and atypical manifestations than the classic form. There is no predilection for either sex. The skin lesions tend to be vesicular, bullous and sometimes necrotic and ulcerative. In addition to the usual locations, the lesions also affect the lower limbs, trunk and back. Systemic signs of neutrophilic leukocytosis and fever may be absent, while clinical recurrences are frequent. [4]

Recurrent episodes of painful, well-demarcated plaques, with pseudovesiculation, predominantly located on the trunk, without neutrophilia, drew our attention to a possible connection to underlying disease and we decided to monitor the patient closely. MDS was diagnosed around two years after the onset of the skin symptoms. The clinical and patient outcomes reported confirm the data available in the literature. In a published review of 9 cases (all male patients with atypical and recurrent skin lesions) MDS was eventually diagnosed at all, 3.5 years (on average) after onset of SS. [4]

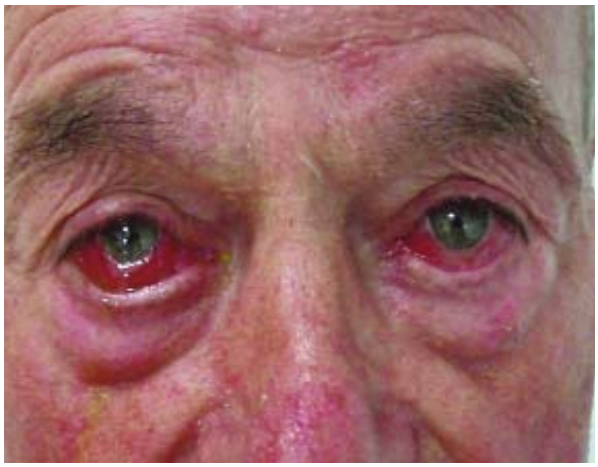

Figure 4: Eye inflammation

Chart 1: Diagnostic criteria for Sweet's Syndrome - 2 major and 2 minor criteria required

Major criteria	1 - Abrupt onset of painful erythematous plaques or nodules 2 - Dense neutrophilic exudate in the biopsy
Minor criteria	1 - Fever with temperature over 38° C 2 - Association with hematologic malignancy, inflammatory disease, pregnancy, prior respiratory or grastrointestinal infection 3 - Excellent response to treatment with systemic steroids 4 - Abnormal lab values

Our patient was referred to the Oncology Department for more aggressive treatment of MDS, in the expectation of controlling the skin disease more effectively.

The classic manifestation of RP is acute unilateral or bilateral auricular chondritis with the presence of inflammatory signs sparing the earlobe, present in 39% of cases at diagnosis and manifested in 85% of patients at some stage of the disease. Other frequently encountered clinical manifestations include nasal cartilage alterations, arthritis, eye and tracheobronchial tree symptoms. Approximately 30% of RP is associated with an autoimmune or hematological disease. [2]

The diagnosis of RP is mainly clinical, embodying the criteria established by Damiani and Levine [2] (Table 2). The patient described had bilateral chondritis of the pinna, superficial peripheral corneal ulcers and ocular inflammation and compatible histopathologic findings - all of which fitted the RP criteria. Eye symptoms are the most common (present in 60% of patients), with scleritis and episcleritis the most frequently observed. In the literature we also found cases associated with corneal ulcers, although these are less common. [5]

RP and SS are rarely found in the same patient. Only 23 cases have been reported to date in the literature. Three of these cases concerned were from a group of 48 Mayo Clinic patients with SS. [6] In a French study involving 200 patients with RP, seven had SS. [7] In a review of nine patients with SS and MDS, four of them developed RP [4].

Le Gal *et al* describe two cases of SS associated with RP - one case associated with myelodysplasia and the other preceding RP. [8] The other seven cases were published separately. In these, SS preceded the appearance of PR in two cases, occurred after its appearance in four cases and was concomitant in one case. [9-15] Twelve patients with SS and PR had associated neoplasia: MDS in 11 cases and bladder cancer in one case.

Chart 2: Diagnostic criteria for relapsing polychondritis (McAdam et al consider that it is necessary to take into account the presence of 3 or more of the 6 items below; Damiani and Levine consider the need for one McAdam et al criterion + confirmatory histology)

1 - Chondritis of pinna
2 - Nonerosive seronegative inflammatory polyarthritis
3 - Nasal chondritis
4 - Eye inflammation
5 - Respiratory tract chondritis
6 - Cochlear and/or vestibular dysfunction

McAdam *et al* consideram necessária a presença de 3 ou mais dos seguintes 6; Damiani e Levine: 1 critério de McAdam *et al* + histologia confirmatória

Both SS and RP are included in the group of mucocutaneous paraneoplastic syndromes associated with hematologic malignancies. Our patient who was diagnosed with SS and PR developed MDS. Although uncommon, more than one paraneoplastic syndrome has been described as affecting the same patient. [3] The knowledge that both SS and RP could be the first signs of progression to MDS should prompt clinicians seriously to consider this hypothesis.

There has been some speculation in the literature as to whether the association of SS and PR could be simply a coincidence in patients with hematologic malignancies or whether both conditions might be etiologically related. [13] For the moment, we await reports on a larger number of cases documenting the occurrence of SS and RP in patients with MDS before affirming that a significant link indeed exists between them. ❑

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