

Sweet's syndrome: a study of 23 cases^{*}

Síndrome de Sweet: estudo de 23 casos

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Abstract: BACKGROUND: Sweet's syndrome or acute febrile neutrophilic dermatosis is a rare disease characterized by painful violaceous erythematous skin lesions, fever, neutrophilic leukocytosis and dense dermal neutrophilic inflammatory infiltrate. It shows excellent response to corticosteroids.

OBJECTIVES: To assess cases of Sweet's syndrome in a university hospital, identifying its clinical, laboratory and epidemiological characteristics and compare them with the data found on the literature.

METHODS: We conducted a retrospective epidemiological study by examining the medical records of 23 patients who met the diagnostic criteria for the disease from March 1995 to July 2009. We collected clinical and epidemiological data on the patients, such as lesion location, presence of cutaneous and extracutaneous manifestations, conditions associated with SS and some laboratory data, such as leukocyte count and ESR.

RESULTS: The age of the patients in the study ranged from 2 to 75 years. There were more females. The lesions mostly affected the trunk and upper limbs. Fever was the most common systemic manifestation, followed by arthralgia and myalgia, conjunctivitis and arthritis. The triggering factors most commonly identified were infections of the respiratory tract. Associated neoplasia occurred in 30% of the patients, especially hematologic neoplasia.

CONCLUSION: The clinical and epidemiological data found in our study are mostly similar to those found in the literature. Given the high prevalence of malignant diseases in patients with Sweet's syndrome, it is necessary to know how to perform the diagnosis, carry out a full investigation as well as do the patient's follow up.

Keywords: Epidemiology; Neutrophils; Sweet syndrome

Resumo: FUNDAMENTOS: A síndrome de Sweet (SS) é uma doença rara, caracterizada por lesões cutâneas eritematovioláceas dolorosas, febre, leucocitose com neutrofilia e derme com infiltrado inflamatório neutrofílico denso à histologia. Apresenta excelente resposta à corticoterapia.

OBJETIVOS: Avaliar os casos de SS em hospital universitário, identificando as características clínicas, laboratoriais e epidemiológicas e compará-las com os dados da literatura.

MÉTODOS: Realizou-se estudo epidemiológico, retrospectivo, mediante revisão de prontuários. Identificaram-se 23 pacientes que preencheram os critérios diagnósticos para a doença no período de março de 1995 a julho de 2009. Coletaram-se dados clínicos e epidemiológicos dos pacientes, tais como: localização das lesões, presença de manifestações cutâneas e extracutâneas, condições associadas à SS e alguns dados laboratoriais, como contagem de leucócitos e velocidade de hemossedimentação (VHS).

RESULTADOS: As idades variaram entre 2 e 75 anos. Houve predomínio do sexo feminino. As lesões acometeram, preferencialmente, tronco e membros superiores. Febre foi a manifestação sistêmica mais comum, seguida por artralgias e mialgia, conjuntivite e artrite. Os fatores desencadeantes mais comumente detectados foram infecções de vias aéreas. Neoplasias associadas ocorreram em 30% dos pacientes, principalmente hematológicas.

CONCLUSÕES: Os dados clínicos e epidemiológicos encontrados no presente estudo são, em sua maior parte, similares aos já disponíveis na literatura. Devido à alta prevalência de doenças malignas na SS é importante diagnosticá-la, realizar investigação sistêmica adequada e manter seguimento dos pacientes.

Palavras-chave: Epidemiologia; Neutrófilos; Síndrome de Sweet

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INTRODUCTION

Sweet's syndrome (SS) is an acute febrile neutrophilic dermatosis first described by Robert Douglas Sweet in 1964.¹ Sweet reported cases of eight women treated at Plymouth General Hospital from 1949 to 1964, thus describing four cardinal manifestations of the disease: fever, leukocytosis with polymorphonuclear predominance, painful elevated plaques on the face, neck and extremities, and histologically, dense dermal infiltration with mature neutrophils.¹ Later, Whittle et al. and Crow et al. were the first to use the term "Sweet's syndrome" as titles of their articles.²

Depending on its association with other diseases, SS can be divided into three groups: classic or idiopathic, malignancy-associated, and drug-induced.^{3,4}

Its distribution is universal and there is no racial predilection.^{2,3,4} Women are more commonly affected and, in particular, seem to be more affected by the idiopathic or drug-induced forms.⁴ The onset of the disease can occur at any age, but the peak incidence is usually from the forties to the seventies.^{2,5} There are few reports of children with SS. Among the earliest cases are children 10 to 15 days old. The incidence in women/men ranges from 2.3-3.7% to 1M regarding the classic form.²

Clinically, Sweet's syndrome is acute and accompanied by fever, malaise and headache.^{3,4,6} The skin typically presents multiple erythematous or violaceous plaques that are well demarcated and often painful. The surface of these plaques can have a vesicular/transparent appearance due to intense edema of the upper dermis (Figures 1 and 2).^{3,7} With progression of the lesion, there may be central clearing, giving the lesion an annular pattern similar to erythema multiforme.^{2,3,6} The areas primarily affected are face, neck, chest, back and upper extremities.^{2,3,4,5,7}

Histologically, the disease is characterized by the presence of a dense dermal predominantly neutrophilic inflammatory infiltrate associated with subepidermal edema of variable intensity and nuclear dust (Figures 3 and 4). Although the criteria for defining the disease include absence of leukocytoclastic vasculitis, there are reports of SS associated with vasculitis.⁵

Often, the syndrome may be preceded by an infection (of the upper respiratory tract, which is more common, or gastrointestinal tract) or even be associated with inflammatory bowel disease or pregnancy.^{3,4,6,8} An association between Sweet's Syndrome and the pathergy phenomenon - hypersensitivity of the skin more common in Behçet's disease and pyoderma gangrenosum - has also been described.^{2,3}

Extracutaneous manifestations include constitutional symptoms such as fever, malaise, diffuse pain, arthralgia, and myalgia. However, neutrophilic dermatosis



FIGURE 1: Well-demarcated erythematous edematous plaques on the upper back

can affect any organ, with reported cases involving the oral mucosa, intestines, lungs, kidneys, heart, blood vessels, liver, spleen, pancreas, bones, muscles, joints, lymph nodes, eyes, and even the CNS.^{2,3,4,6,9-11}

In 21% of the patients with SS, there is an association with malignant diseases, usually a hematologic disorder.¹² The neoplasm most commonly associated with SS is acute myelogenous leukemia (AML). There are also reports of association with solid tumors.^{2,3} Buck et al. found a similar prevalence of SS in patients with AML and myelodysplastic syndromes.¹² SS may precede or occur concurrently with the underlying disease and, according to some authors, is a factor of poor prognosis.^{2,4}

There are reports of SS as a side effect of drugs such as granulocyte colony stimulating factor (G-CSF), trans retinoic acid, trimethoprim-sulfamethoxazole, radiocontrast agents, dipyrrone, minocycline,



FIGURE 2: Lesion detail showing marked erythema and edema

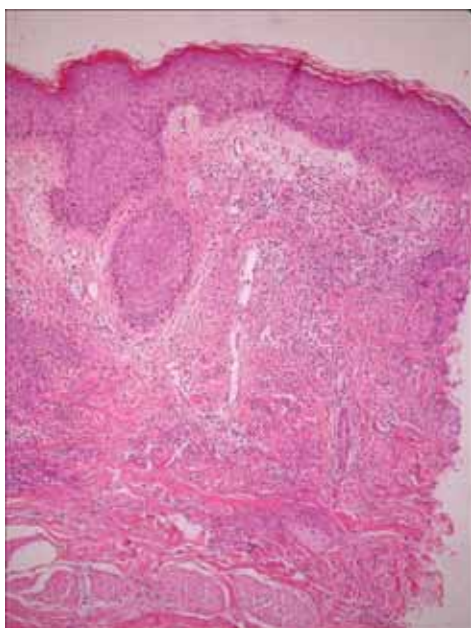


FIGURE 3: Skin presenting dermal edema and diffuse neutrophilic infiltrate. HE 100x, zoom 1,5x

quinolones, carbamazepine, oral contraceptives, diclofenac, diazepam, among others.^{3,4,7,13-15}

In terms of epidemiology, Cohen et al. reported prevalence of the paraneoplastic form in men and women of 1:1, unlike what occurs in its classic form; thus men, when affected, are at higher risk of having a paraneoplastic manifestation.^{2,3}

Diagnostic criteria for SS were proposed by Su and Liu in 1986 and modified by von den Driesch in 1994.² The disease is defined by the presence of two major criteria: abrupt onset of nodules or painful erythematous plaques associated with histopathologic evidence of a dense neutrophilic infiltrate in the dermis without leukocytoclastic vasculitis, and at least two minor criteria, among which are the following:

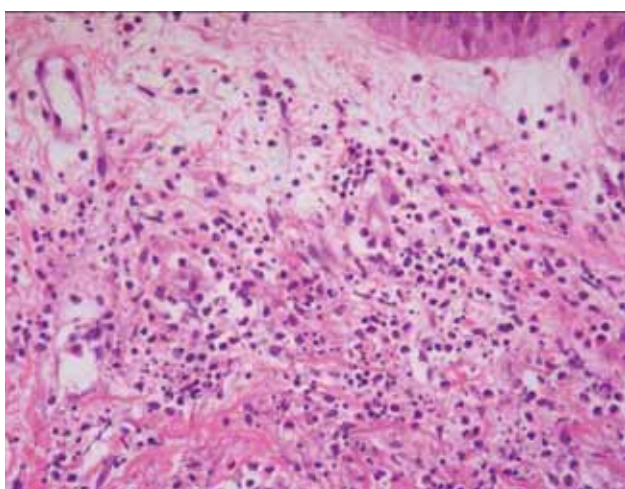


FIGURE 4: Skin presenting dermal edema and diffuse neutrophilic infiltrate. HE 400x, zoom 1,5x

fever above 38°C; infection of the respiratory tract or gastrointestinal tract preceding the medical condition or association with vaccination, inflammatory disease, neoplasia or pregnancy; presence of the following laboratory findings (3 of 4): ESR above 20 mm; positive C-reactive protein; leukocyte count above 8,000, neutrophil blood count over 70% and excellent response to treatment with corticosteroids or potassium iodide.

Systemic corticosteroid therapy is considered the gold standard treatment for SS: prednisone or prednisolone at an initial dose of 0.5 to 1.5 mg / kg / day, tapering in 2 to 4 weeks. Response is excellent, with rapid remission of both cutaneous and extracutaneous symptoms. Other options considered as first line therapy by some authors are potassium iodide and colchicine. Localized lesions can be managed with intralesional or high potency topical corticoids.^{2,3,4,7} In cases associated with malignancy or drug-induced SS, treatment of the underlying disease and discontinuation of the drug, respectively, are associated with improvement of the condition.^{2,3,7}

Without treatment, SS lesions usually persist for several months, some, however, may have spontaneous resolution. The disease is characterized by frequent recurrences, which occur in both patients who have been treated and patients who had spontaneous remission.^{2,3,7} In patients with SS associated with malignancy, relapses are more common and can be an early sign of recurrence of the underlying disease.^{3,7}

MATERIALS AND METHODS

We conducted a retrospective observational study based on the analysis of the medical records of 23 patients diagnosed with Sweet's syndrome (according to Su and Liu's modified criteria) who were treated at the Clinics Hospital of Curitiba from March 1995 to July 2009. We collected clinical and epidemiological data on these patients, such as lesion location, presence of cutaneous and extracutaneous manifestations, conditions associated with SS and some laboratory data, such as leukocyte count and ESR.

RESULTS

The patients' data are found in Table 1.

Of the patients included in this study, approximately 74% were female (17 women and 6 men) (Graph 1). Their ages ranged between 2 and 75 years with a mean of 44.5 years. Excluding the pediatric cases, the mean age rises to 48.57 years. Only two children presented the disease during the period of the investigation, totaling 8% of the sample.

The most affected sites in descending order were: upper limbs (78% of the patients), lower limbs and trunk (52%), face (21.7%), and neck (17%) (Graph 2).

The most common systemic manifestation was fever (65% of the cases), followed by arthralgia and myalgia (17%), conjunctivitis (13%), and arthritis (8.6%) (Graph 3).

Of the patients whose data were available, 80% had leukocyte counts above 8,000 cells / mm³ and 66% above 10,000 leukocytes / mm³. Neutrophilia was observed in 70% of these patients (neutrophil blood count above 70%). Leukocyte count ranged from 42,000 leukocytes / mm³ to less than 900 leukocytes / mm³. ESR was above 20 mm in 94.7% of the 19 patients analyzed and its mean value was 65 mm (Graph 4).

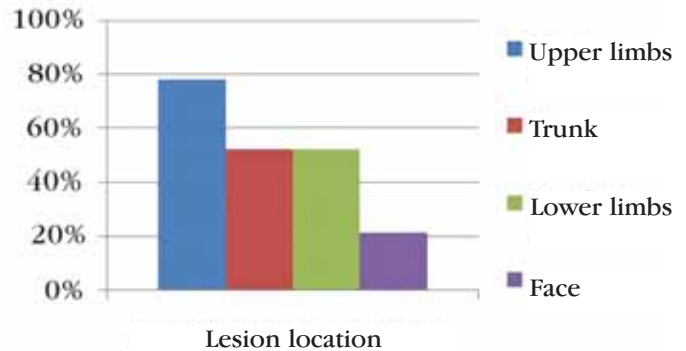
In the study of associated causes (Graph 5), 43% of the patients presented associated inflammatory or infectious diseases, most commonly respiratory infections (60% of the cases). Among the inflammatory conditions found in association with the disease in this sample, we can cite ulcerative colitis, erythema nodosum, and systemic lupus erythematosus as the most commonly reported in association with the syndrome. These were followed by neoplasms (30%), of which 70% were hematological, with chronic myeloid leukemia (CML) as the most prevalent.

DISCUSSION

Most national studies about SS are case reports. There are few Brazilian studies addressing the clinical and epidemiological characteristics of SS in Brazil and if these are consistent with the data found in the world literature.

In this study, the mean age of the patients affected was consistent with that found in the literature, with preferential involvement of those in their forties to seventies.^{2,5} Only two patients were in the pediatric age group, which confirms that the disease is rare among children; in this sample, the total number of children corresponded to 8% of the patients.

Regarding sex, we found a higher incidence of

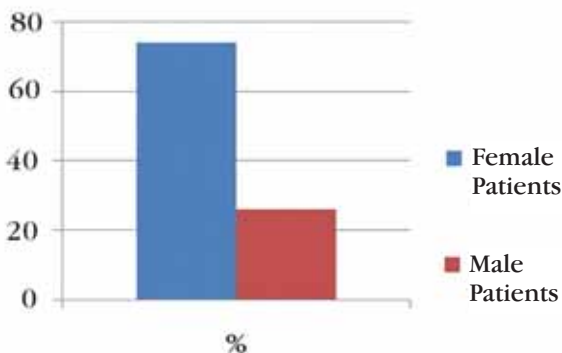


GRAPH 2: Lesion distribution

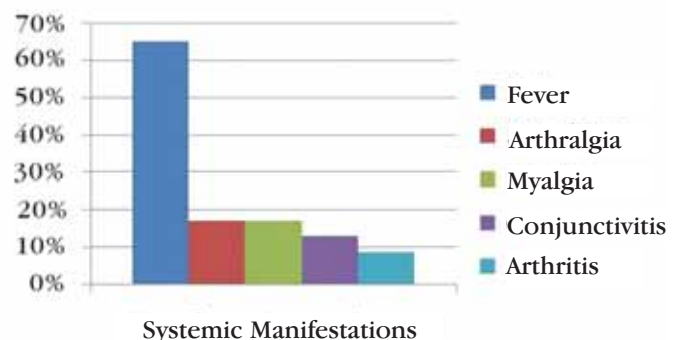
the disease among women (who represented 73.9% of the total), which is consistent with the literature. Lesion location was also found to be in accordance with other studies, mainly affecting the upper limbs. The percentage of patients who had lesions on the trunk was higher than that found in some other studies.³ On the other hand, face and neck, which are quite affected by Sweet's syndrome according to the literature, were not affected in our study.

Fever was the main systemic manifestation, as reported in other studies. Myalgia and arthralgia, other very common symptoms, affected 17% of our patients. As for eye symptoms, which can occur in 30 to 75% of the patients with SS,¹¹ they occurred in only three patients (13%) in our study. Two of them presented conjunctivitis and one had visual blurring with eyelid edema and scleral hyperemia. Although the statistics do not correspond exactly to those found in several studies, the symptoms presented by our patients are among those most commonly described in association with the disease.

Infection of both upper and lower airways was the associated condition that was more prevalent in



GRAPH 1: Percentage of female and male patients in the sample



GRAPH 3: Systemic manifestations

our patients, which is consistent with the literature. One patient was diagnosed with ulcerative colitis. Inflammatory bowel diseases are commonly associated with SS, second only to infections and neoplasms. Seven (30%) of the 23 patients presented malignancy associated with SS, and chronic myeloid leukemia was the most prevalent (8% of total). Acute myeloid leukemia, which is cited in the literature as the most common neoplasm in patients with Sweet's syn-

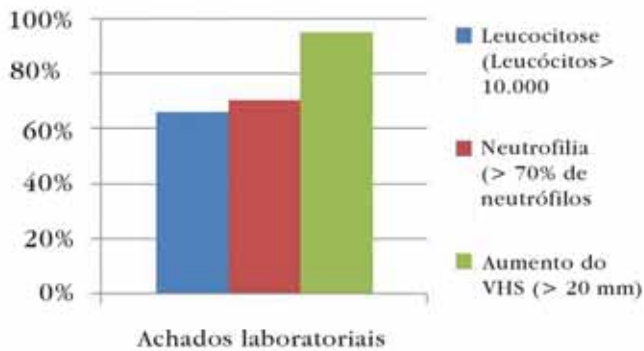
drome, occurred in only one of our patients. Other neoplasms presented were hairy cell leukemia, papillary thyroid cancer and breast cancer.

Among laboratory abnormalities, neutrophilic leukocytosis and increased ESR are the most consistent findings.^{3,7} Leukocytosis, neutrophilia and increased inflammatory activity tests were consistent findings in this study, which is in accordance with the data reported in the literature.

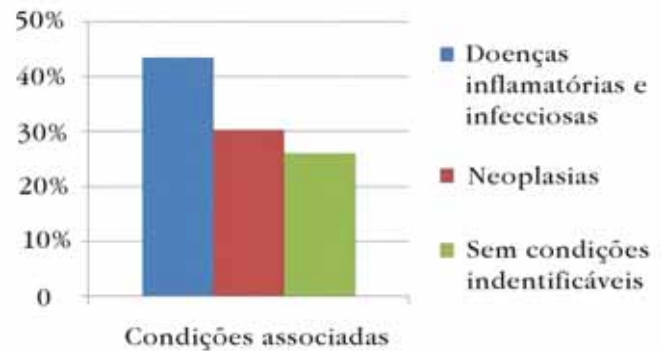
TABLE 1: Data on the patients

Age (years)	Gender	Leukocyte count (X10 ⁹ /L)	ESR (mm/h)	Lesion location	Systemic manifestations	Associated conditions
74	M	42	30	face	absent	LMC
52	M	29.9	121	face, trunk, UL	fever	myeloproliferative syndrome
47	F	14.1	83	neck, trunk, UL and LL	fever, arthralgia, myalgia	none
30	F	13.4	60	trunk, UL	fever	UC
2	F	9.3	52	trunk, abdomen, UL and LL	fever	none
2	M	30.4	44	trunk, LL	fever	MCL
50	F	18.8	41	UL	none	AML
47	M	0.9	94	trunk, UL	fever	hairy cell leukemia
45	F	6.8	18	UL	fever	papillary thyroid cancer
41	F	9.4	98	neck, trunk, UL and LL	fever, arthralgia, myalgia, conjunctivitis	URI
44	F	27.4	76	LL, UL	absent	URI
37	M	13.9	27	UL, back, neck, face	fever, scleral hyperemia, visual blurring, myalgia, eyelid edema	none
61	F	12.5	30	LL, UL	absent	psoriasis
47	F	12.6	112	UL, LL	fever, arthralgia, arthritis in knees and ankles	URI, erythema nodosum
29	F	10.8	42	UL, trunk	absent	leprosy, URI
61	F	9.9	82	UL, LL, trunk	fever, arthritis in the knees	invasive ductal carcinoma of the breast
47	F	22.8	56	trunk, UL, LL	fever	none
75	F	-	-	face	absent	DM
29	F	15.6	125	UL, LL, face	conjunctival hyperemia, proteinuria	URI
43	F	-	-	neck, UL, LL	fever	URI/pneumonia
52	M	7.6	59	back	absent	DM, hypertension, atrial fibrillation
64	F	5.3	-	LL	fever, myalgia, arthralgia	SLE, gastroenteritis
45	F	15.3	-	UL	fever	membranoproliferative glomerulonephritis, hepatitis C, DM, hypertension, pulmonary sepsis

Legendas: M - male | F - female | L - upper limbs | LL - lower limbs | URI - upper respiratory infection | SLE - systemic lupus erythematosus | DM - diabetes mellitus | CML - chronic myeloid leukemia | AML - acute myeloid leukemia | UC - ulcerative colitis



GRAPH 4: Laboratory findings



GRAPH 5: Associated diseases

CONCLUSION

Most of the data found in this study can be correlated with data from the literature. Prevalence in women, age group, laboratory findings, predominance of fever as the most common systemic manifestation, association with respiratory diseases are all findings consistent with those found in the Anglo-Saxon literature in the field. Prevalence of SS associated with neoplasms was higher in this group of patients when compared to data reported in other studies, which are around 20%. CML was more commonly reported, which differs from the literature, since the literature reports AML as the most commonly associated disease. The service in which this study was conducted belongs to a reference hospital for hematologic diseases, which may have contributed to these numbers and which may justify them. In previous studies in this same service, we found¹⁰ more cases of SS associated with malignancies; in this study,

the proportion of patients with the classic or idiopathic form exceeded the cases of SS associated with malignancies.

It is important that physicians in general and especially dermatologists know how to diagnose SS. Due to the high association of the syndrome with malignant diseases, it is essential that malignancies be discarded and that the patient follow-up be maintained. □

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