Sweet's syndrome: study of 73 cases, emphasizing histopathological findings *

Síndrome de Sweet: estudo de 73 casos, com ênfase nos achados histopatológicos

Mayra Carrijo Rochael[1]
Enoï A. Guedes Vilar[3]
Eduardo Quelhas Spada[5]
Karla Strong Rodrigues[7]
Luciana Pantaleão[2]
Luciana Helena Zacaron[4]
Marcus H. S. B. Xavier[6]

Abstract: BACKGROUND: Sweet's syndrome refers to a set of cutaneous, systemic and histopathological alterations that occur in response to different stimuli, in a similar way to that occurring in erythema nodosum, erythema multiforme and leukocytoclastic vasculitis. The syndrome has been described in association with conditions such as infections, pregnancy, the use of certain medications and malignancy.
OBJECTIVES: To evaluate the clinical and histopathological alterations occurring in this syndrome and to assess the association between these alterations and other conditions.
METHODS: A retrospective study of 73 cases was conducted, evaluating data on the microscopic examination of skin lesions, as well as clinical and laboratory data.
RESULTS: The majority of the patients were female (83.0%), white (49.2%) and between 30 and 60 years of age (73.8%). The principal alterations found were: erythymatous plaques (76.9%), papules (43.0%), pseudo-vesiculation (PV) (38.4%) and target lesions (18.5%). With respect to the associated conditions, upper respiratory tract infections (15.4%) and the use of medication (10.8%) were the most common. Other associations, albeit represented by only one case each, were: Hodgkin's lymphoma, pregnancy, ulcerative colitis, polycythemia vera and lupus erythematosus in a patient with acquired immune deficiency syndrome (AIDS). The principal microscopic findings were: neutrophils with leukocytoclasia (98.6%), collagen degeneration (87.7%), edema (74.0%) and PV (38.4%). The presence of eosinophils (41.1%) ranged from rare to abundant and was usually unrelated to the use of medication. Inflammatory infiltrate reached the deep epidermal layer in 47.9% of cases and panniculitis was found in 80.0% of cases in which the hypodermis was affected (10 cases).
CONCLUSIONS: In general, these findings are in agreement with results published in the literature, emphasizing the frequent finding of eosinophils unrelated to drug use, panniculitis and the rare association with Hodgkin's lymphoma. This is the fifth report of an association between Sweet's syndrome and Hodgkin's disease.
Keywords: Erythema Multiforme; Hodgkin's Disease; Panniculitis; Sweet's Syndrome.

Resumo: FUNDAMENTOS: A síndrome de Sweet corresponde a um conjunto de alterações cutâneas, sistêmicas e histopatológicas como resposta a diversos estímulos, semelhantes ao eritema nodoso, ao eritema multiforme e à vasculite leucocitoclásica. São descritas condições associadas como infecção, gravidez, uso de drogas e malignidades.
OBJETIVOS: Avaliar as alterações clínicas e histopatológicas da síndrome, relacionando-a a outras condições.
MÉTODO: Estudo retrospectivo de 73 casos com avaliação microscópica de lesões cutâneas, dados clínicos e laboratoriais.
RESULTADOS: Houve predomínio de mulheres (83,0%), brancas (49,2%), entre a quarta e a sexta décadas de vida (73,8%). Placas eritematosas (76,9%), pápulas (43,0%), pseudovesiculação (PV) (38,4%) e lesões em alvo (18,5%) foram as principais alterações. Entre as condições associadas, infecções de vias aéreas (15,4%) e uso de drogas (10,8%) foram as mais frequentes. Outras associações, representadas por um caso cada, foram: linfoma de Hodgkin, gravidez, colite ulcerativa, policitemia vera e lúpus eritematoso em paciente com Aids. Neutrófilos com leucocitoclasia (98,6%), degeneração do colágeno (87,7%), edema (74,0%) e PV (38,4%) foram os principais achados microscópicos. Eosinófilos estiveram presentes (41,1%) de raros a abundantes e, em geral, não relacionados ao uso de drogas. O infiltrado inflamatório atingiu a derme profunda em 47,9% das vezes e encontrou-se paniculite em 80,0% dos casos nos quais a hipoderme estava representada (10 casos).
CONCLUSÕES: Os achados, de modo geral, coincidem com os da literatura, destacando-se: frequente participação de eosinófilos sem correlação com a ingestão de medicamentos, paniculite e rara associação com linfoma de Hodgkin, sendo este o quinto relato de tal ocorrência, segundo o conhecimento dos autores.
Palavras-chave: Doença de Hodgkin; Eritema multiforme; Paniculite; Síndrome de Sweet

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[1] Doutora em Patologia - Professora Associada da Universidade Federal Fluminense (UFF) – Niterói (RJ), Brasil.
[2] Mestre em Patologia - Professora Assistente da Universidade Federal Fluminense (UFF) – Niterói (RJ), Brasil.
[3] Mestre em Patologia - Professora Adjunta da Universidade Federal Fluminense (UFF) – Niterói (RJ), Brasil.
[4] Patologista - Clínica Particular - Rio de Janeiro (RJ), Brasil.
[5] Patologista - Hospital de Clinicas Caieiras – São Paulo (SP), Brasil.
[6] Dermatologista – Clínica Particular - Belo Horizonte (MG), Brasil.
[7] Dermatologista - Centro de Transplante de Medula Óssea do Instituto Nacional do Câncer (INCA) – Rio de Janeiro (RJ), Brasil.

INTRODUCTION

The classic presentation of Sweetís syndrome includes skin lesions and systemic manifestations of acute disease, generally following an upper respiratory tract infection. The abrupt onset of erythematous or violaceous papules, plaques and nodules and neutrophilic infiltration in the dermis with leukocytoclasia (but without leukocytoclasic vasculitis) constitute the major diagnostic criteria. Fever or infection prior to malaise; accompanying fever, arthralgia, conjunctivitis or underlying malignancy; leukocytosis with neutrophilia; and a good response to systemic corticoids constitute the minor criteria, according to the definitions of Su and Liu, who proposed the presence of two major criteria and at least two of the minor criteria for confirmation of a diagnosis of Sweetís syndrome. [1] Some authors such as Ackerman et al. believe that the condition represents a reactive phenomenon and not a specific entity, as with erythema multiforme and leukocytoclastic vasculitis, and it has been suggested that Sweetís syndrome is the result of a hypersensitivity reaction to antigens, its sources being diverse: bacteria, viruses, tumors. [2] The response to corticoids gives strength to this hypothesis. Relapses may occur and are more common when the syndrome is associated with malignancy. Contradictory findings with respect to the composition of the inflammatory infiltrate, its location and the presentation of a histiocytoid Sweetís syndrome have attracted the interest of investigators, justifying the evaluation of a larger number of cases. [3,4]

The objective of the present study was to evaluate the demographic, clinical and histopathological aspects and associated conditions of patients with Sweetís syndrome receiving care at a general hospital between January 2002 and March 2007.

MATERIAL AND METHODS

Seventy-three biopsies of Sweetís syndrome were identified in the archives of the Anatomopathology Department of the Antonio Pedro Teaching Hospital, Federal Fluminense University, Niteroi, Rio de Janeiro, Brazil between January 2002 and March 2007. This hospital has both general and specialist clinics, including a dermatology clinic. The hospital catchment area covers an extensive region that includes not only the city of Niteroi but also several neighboring cities. The patient charts and medical requests for skin biopsies were the source of the clinical and demographic data. Histopathology was carried out using routine hematoxylin-eosin staining.

RESULTS

Evaluation of the 65 cases for which clinical data were complete showed that the majority of patients affected by the disease were women (83%), white (49.2%) and of 30 to 60 years of age (73.8%). The disease was preceded by an upper respiratory tract infection in 10 cases (15.4%). A 12-year old child was the youngest patient, while a 72-year old man was the oldest. The duration of the disease was 15 days in 65.5% of cases and 5 days in 30.7% of the cases. In these 65 individuals, the most significant clinical manifestations were: erythematous plaques (76.9%), papules (43.0%), pseudo-vesicles (38.4%) and target lesions (18.5%). The most common sites of the lesions were: the upper limbs (87.7%), trunk (58.4%) and lower limbs (49.2%) (Figure 1). With respect to the involvement of other sites, the oral mucosa was affected in three cases (4.6%), while two patients reported episcleritis. These findings are shown in Table 1. The diagnostic hypotheses raised were Sweetís syndrome in 72 patients (99%) and erythema multiforme and Sweetís syndrome in 43 cases (66%). Other hypotheses and their frequencies are shown in Figure 1. Figure 2 shows the microscopic data: neutrophilic infiltratation with leukocytoclasia was found in 98.6% of the cases, as well as lymphocytic infiltration. Eosinophils were present in 41.1% of the biopsies. In 47.9% of the cases, the infiltration extended as far as the deep dermal layer and 63% presented exocytosis. Collagen degeneration, edema, spongiosis and pseudo-vesicles were found in 87.7%, 74%, 42.5% and 38.4% of biopsies, respectively (Figures 2-6). Associated conditions included: upper respiratory tract infections (15.4%), the use of certain drugs (10.8%) and other rarer conditions represented by only one case of each: pregnancy, ulcerative colitis, polycythemia vera, Hodgkinís lymphoma and systemic lupus erythematous in a patient with acquired immunodeficiency syndrome (AIDS). The remaining cases

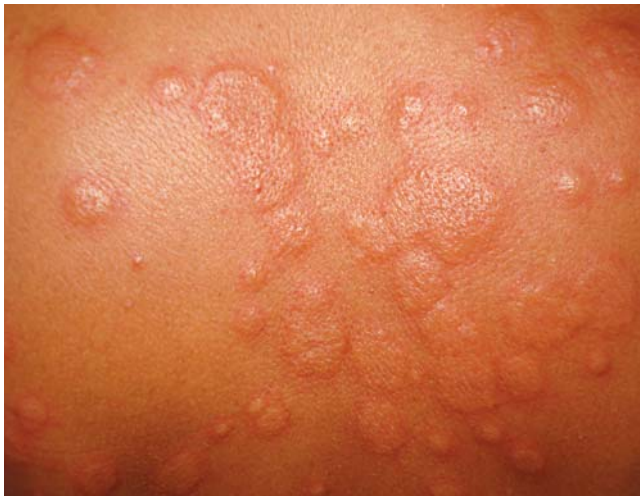


Figure 1: Papules and erythematous plaques with pseudo-vesicles

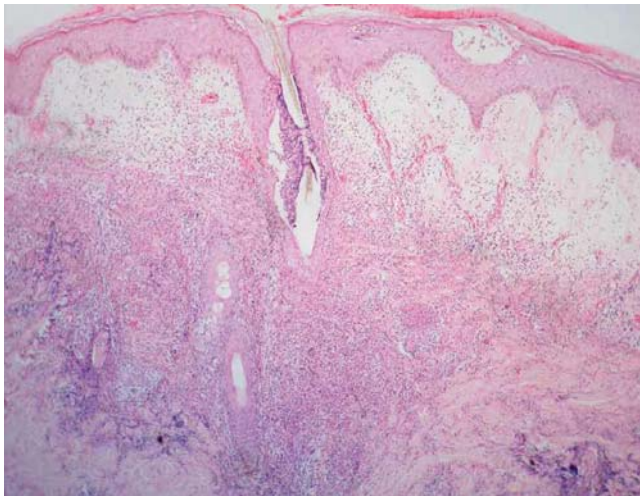


Figure 2: Dense inflammatory infiltrate in the upper dermal layer and pseudo-vesicles (Hematoxylin-eosin, magnification 40x)

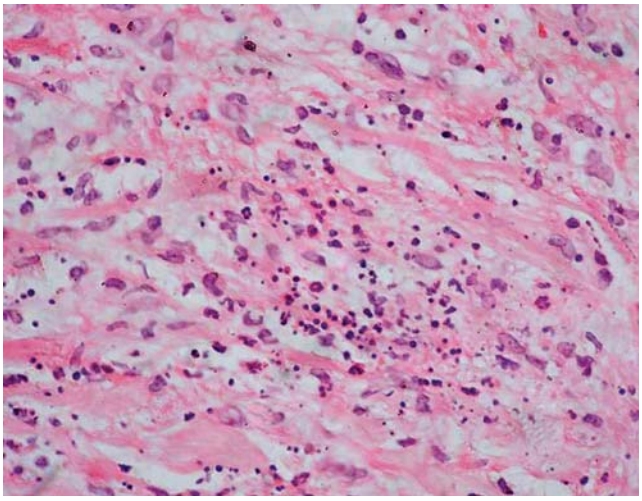


Figure 4: Eosinophils and neutrophils with interstitial leukocytoclasia (Hematoxylin-eosin, magnification 400x)

were considered idiopathic. Eight patients had relapses unrelated to malignancy.

DISCUSSION

The classic presentation of this syndrome, as described by Robert Douglas Sweet in 1964, is well established and consists of fever, neutrophilia, papules, plaques and erythematous and painful nodules that involute immediately following the introduction of corticoids. [5,6] Sweetís syndrome generally affects women of 30 to 60 years of age, predominantly in the spring or fall. Its etiology is unknown; however, an unusual hypersensitivity reaction mediated by cytokines may be involved, followed by infiltration of neutrophils, probably activated by interleukin (IL)-1. This reaction may be triggered by a wide variety of antigens including bacteria, viruses, medication and malignancies. The presence of IL-1±, IL-1≤, IL-2 and interferon-gamma but not IL-4 suggests that type 1 T helper cells may play a role in the pathogenesis of this disease. [7] Recently, new aspects have been mentioned and proposed as part of the set of signs and symptoms that constitute the syndrome. These include variability in the composition of the inflammatory infiltrate, the location of this infiltrate, vascular involvement, extracutaneous sites of the lesions, an association with new drugs and successful new therapeutic proposals. [3,8]

The findings of the present study are in agreement with data published in the literature with respect to the clinical and histopathological data. Nevertheless, some of the clinical findings merit further comment, particularly the rare mucosal involvement and episcleritis, with three and two cases, respectively, and no lesions in any other of the organs described in the literature (bones, brain, kidneys, bowel, liver, heart and others); however, these data

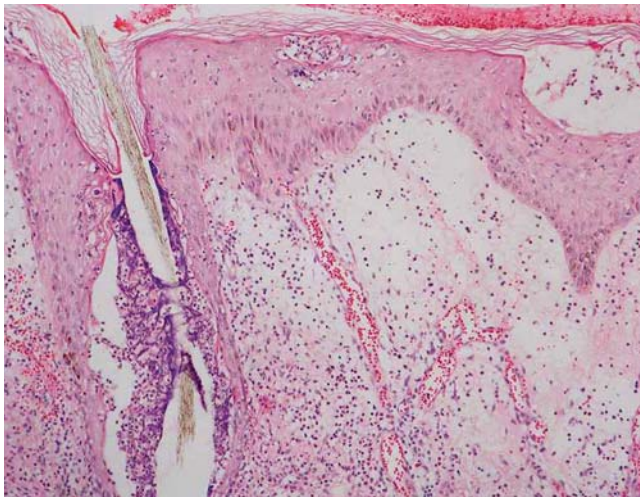


Figure 3: Detail of the previous photograph with follicular pustule (hematoxylin-eosin; magnification 100x)

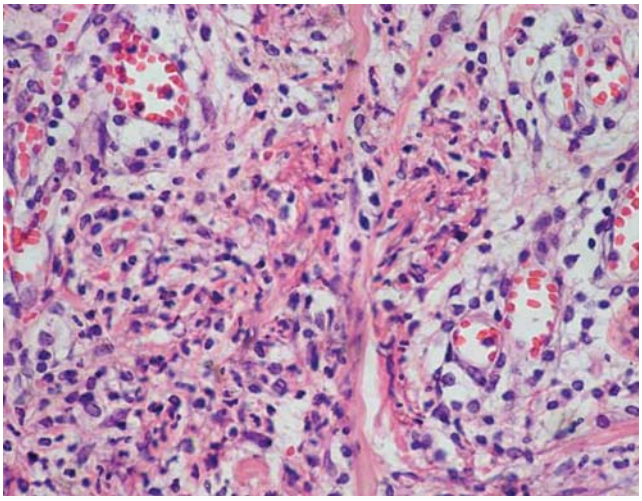


Figure 5: Neutrophilic infiltrate, leukocytoclasia and fibrin (hematoxylin-eosin; magnification 400x)

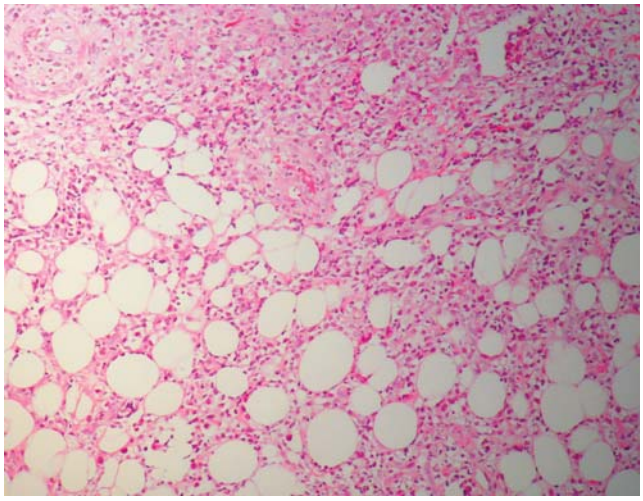
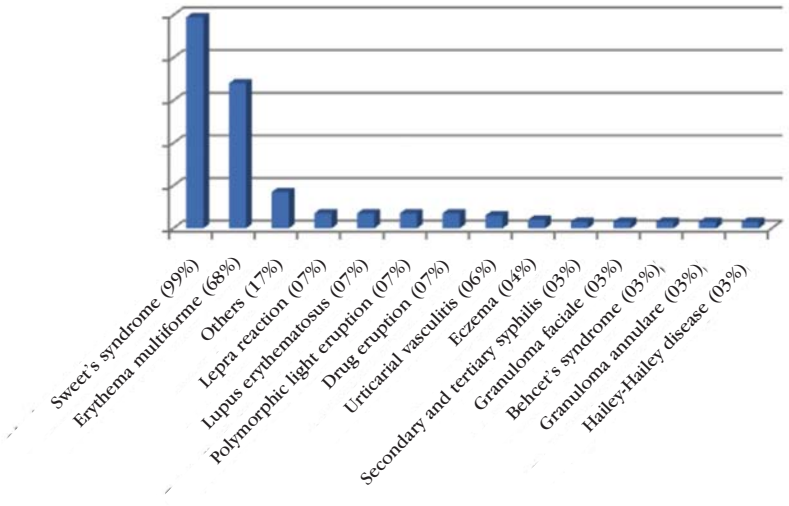


Figure 6: Mixed inflammatory infiltrate affecting adipose tissue (hematoxylin-eosin, magnification 100x)

are negatively affected by the fact that in a large number of cases data were missing from the charts. Target lesions were found in 12 patients (18.5%), justifying the persistent diagnostic hypothesis of erythema multiforme, as described by Mendonça (1997), who evaluated 21 cases of Sweetís syndrome in a study conducted at the same hospital. In 13 of these patients (61.9%) the diagnostic hypothesis was erythema multiforme. [9] Fever, vesicopustules and pseudo-vesicles were features whose description was incomplete in the majority of cases. Subungual hemorrhage was found in two patients, while upper respiratory tract infection was the most common preceding condition (15.4%). Of the drugs reported by the patients, orphenadrine citrate (5 cases), oral contraceptives (4 cases) and antiretroviral drugs (2 cases) were the most common, although their role in triggering Sweetís syndrome is difficult to evaluate due to the small number of cases. In the present sample, no association was found with granulocyte colony-stimulating factor (G-CSF), reported to be the therapy most commonly associated with Sweetís syndrome. In those patients who had an upper respiratory tract infection prior to developing the syndrome, no evidence was found in their charts confirming the use of any symptomatic drugs that may have been used during the infectious condition. Therefore, the role of these infections and that of anti-inflammatory drugs in the genesis of the disease could not be evaluated. Other associated conditions found in this sample include pregnancy, ulcerative colitis, polycythemia vera, Hodgkinís lymphoma and systemic lupus erythematosus in a patient with AIDS.

Sweetís syndrome may be associated with a malignancy in as many as 20% of cases and the skin manifestation may either precede or follow manifestation of the malignancy. [10,11] In the present sample, however, neoplasia (Hodgkinís lymphoma) was found in only one case (1.5%). In this case, the diagnosis of lymphoma preceded that of Sweetís syndrome and no recurrence has been recorded. The association between Sweetís syndrome and leukemia is well-known and corresponds to the majority of cases of malignancy; however, lymphoma is rare. [10-15] The association between Hodgkinís lymphoma and Sweetís syndrome is even rarer. To the best of our knowledge, this is only the fifth report of such a case. [14,15] According to the literature, solid tumors correspond to 15% of cases of associated malignancy, principally carcinomas of the breast, genitourinary tract and gastrointestinal tract. [14,16] There have also been some recent, less well-known reports of Sweetís syndrome in areas of post-lymphadenectomy lymphedema in patients mastectomized following breast cancer. [17,18] According to Gille and Woodrow, there are no well-established criteria to



Graph 1: Principal diagnostic hypotheses in 73 cases of Sweet's syndrome

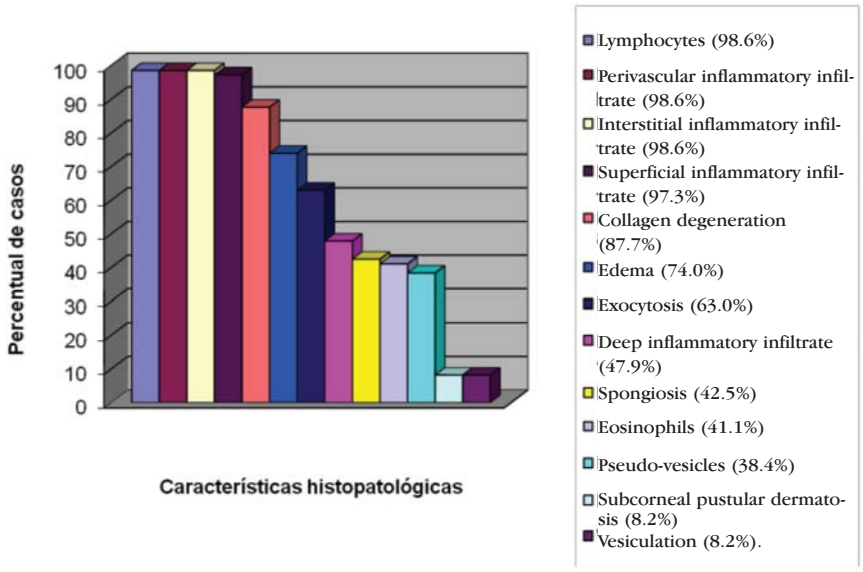


Gráfico 2: Achados histopatológicos de 73 casos de síndrome de Sweet

identify patients with a risk of neoplasia in individuals with Sweetís syndrome; however, these authors recommend further investigation in the following situations: [6,10]

Episodes of recurrence
Painful or polymorphic skin lesions
Involvement of the oral mucosa
Alterations in full blood count
Absence of fever or neutrophilia

Table 1: Relevant clinical and demographic aspects of 65 patients with Sweet's syndrome

	Sex	Female 83.0%
		Male 15.4%
		Data missing 1.5%
Demographic	Age	30-60 years 73.8%
Data	Ethnicity	White 49.2%
		Brown 20.0%
		Black 1.5%
		Data missing 30.8%
	Fever	27.7% (data missing in 69.2% of cases)
	Erythematous plaques	76.9%
	Papules	43.0%
	Pseudo-vesicles	40,0%
	Target lesions	18.5%
Clinical data	Site	Upper limbs 87.7%
		Trunk 58.4%
		Lower limbs 49.2%
	Duration	≤ 5 days 30.7%
		6 – 10 days 18.5%
		11 – 15 days 16.9%
	Associated conditions	Upper respiratory tract infection 15.4%
		Drugs 10.8%
		Pregnancy 1.5%
		Neoplasia 1.5%

In the present sample, however, pain (18.5%), relapses (12.7%) and lesions of the oral mucosa (3%) were not associated with malignancy.

The histopathological features found in this study were, in general, those well-established in the literature, with neutrophilic infiltrate with leukocytoclasia, considered one of the major criteria for diagnosis of this syndrome, being observed in approximately 100% of cases. Nevertheless, other aspects merit further comment, including the fact that the condition extended as far as the deep dermal layer in half the biopsies, the presence of collagen degeneration in 87.7% of cases, perivascular lymphocytes and eosinophils. According to Cohen, eosinophils may be present both in the classic and drug-induced forms of the disease. [19] Eosinophils were found in 41.1% of the tissue samples in the present study, ranging from rare to abundant. In 19.1% of cases, eosinophils were detected in a proportion of 2 to 4 ± 4. Only one of these patients was in use of retroviral drugs and sulfa; therefore, it was impossible to establish any correlation between the presence of eosinophils and the use of medication, since this HIV-positive patient had opportunistic infections.

According to the majority of authors, the vasculitic lesions consist of fibrin deposits on the vessel walls and are considered secondary, constituting an epiphenomenon to the inflammatory process present in the dermis. Of the 73 cases evaluated in this study, this deposit was found in 6.8% of the biopsies, always in vessels that were totally surrounded by the neutrophillic infiltrate and by the leukocytoclasia, appearing to occur secondary to an inflammatory process rather than as primary vasculitis. [19,20]

Cellular infiltrate, consisting principally of cells that resemble histiocytes, was described by Requena

et al. and later by Chow et al. in cases referred to by the authors as histiocytoid Sweetís syndrome. [4,21] In the cases reported by Requena et al., these cells showed strong reactivity to the anti-myeloperoxidase antibody, suggesting that they are immature myeloid cells, precursors of neutrophils, which are found in early lesions. [4] In these cases, myeloid leukemia was not confirmed, despite the immature appearance of the cells composing the cellular infiltrate in the dermis and hypodermis. The same occurred in the majority of the cases evaluated by Chow et al., in which, however, there was a case of leukemia cutis that was later confirmed. [21] Involvement of the subcutaneous cellular tissue, alone or associated with dermal involvement, has been described in the form of painful nodules on the limbs, represented microscopically by neutrophillic infiltration of the septum and/or lobule. [3] In the present sample, the hypodermis was affected in only 10 cases (13.7%). Of these, the high incidence of cases with inflammatory infiltrate (80.0%), composed in most cases by lymphocytes, was noteworthy. These findings are in agreement with reports by Jordan but contradictory to the original report by Sweet and that of Cohen and Kurzrock, who found a predominance of neutrophils. [5,3,22] This discrepancy suggests that deeper biopsies are required whenever Sweetís syndrome is suspected to enable a better evaluation of the panniculus adiposus to be conducted.

CONCLUSIONS

The clinical characteristics of Sweetís syndrome are well known. However, its less common features are relatively unknown and include the histiocytoid appearance of the inflammatory infiltrate and involvement of the subcutaneous cellular tissue, which was found in 80% of the present cases in which the hypodermis was affected. These findings justify performing biopsies in all cases in order to study the common and less usual histopathological characteristics of the disease, to correlate them with clinical and laboratory data, and to increase knowledge on what triggers the condition and its associated conditions. We also report a rare case of Sweetís syndrome in a patient with Hodgkinís lymphoma. To the best of our knowledge, this is the fifth report of this association in the literature. ❑

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Mailing Address / Endereço para correspondência:
Mayra Carrijo Rochael
Rua Lopes Trovão, 134 – Ap. 1.901 Bl. 2 – Icaraí
24220-071 Niterói - RJ, Brazil
E-mail: mayra@dermatopatologia.com.br

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