Sweet's syndrome: clinicopathological features of patients treated from 1997 to 2009 at Cassiano Antonio Moraes University Hospital - Vitoria (Espirito Santo) *

Síndrome de Sweet: achados clínico-patológicos nos pacientes atendidos de 1997 a 2009 no Hospital Universitário Cassiano Antônio Moraes - Vitória (Espírito Santo)

Itamara Assini Eleuterio[1]
Delio Delmaestro[1]
Elton Almeida Lucas[4]
Ricardo Montibeler Tiussi[2]
Lucia Martins Diniz[3]

Abstract: Sweet's syndrome or acute febrile neutrophilic dermatosis is rare in Brazil. It is clinically characterized by painful erythematous nodules, papules or plaques that occur mainly on the neck and upper limbs. Its cause may be unknown (idiopathic form) or it may be associated with malignancies, usually hematologic, or drugs. The authors describe 16 cases of the syndrome. The median age was 36 years, and all patients were white and presented solid lesions, predominantly on the upper limbs and trunk. Histopathological examination of the dermis of all patients revealed predominance of moderate to intense, superficial and deep, diffuse inflammatory infiltrate, mainly consisting of polymorphonuclear neutrophils, with leukocytoclasia. It also revealed changes in the epidermis and hypodermis (neutrophilic hypodermitis), but with no signs of vasculitis in most patients, which was not considered an important finding for diagnosis. Presence of exocytosis of neutrophils was common, favoring the diagnosis of Sweet's syndrome when accompanied by diffuse interstitial neutrophilic dermatitis.
Keywords: Fever; Pathology; Sweet syndrome

Resumo: A Síndrome de Sweet ou dermatose neutrofílica febril aguda é rara no Brasil, caracterizada clinicamente por pápulas, placas ou nódulos eritematosos, dolorosos, principalmente na região cervical e membros superiores. Pode surgir sem fator desencadeante (forma idiopática) ou associar-se a neoplasias, comumente hematológicas, ou a drogas. Os autores descrevem 16 casos da Síndrome, idade mediana de 36 anos, todos da raça branca, com lesões sólidas predominantes nos membros superiores e no tronco. O histopatológico da derme observou, em todos os pacientes, predomínio de infiltrado inflamatório difuso, superficial e profundo, de moderado a intenso, composto principalmente por polimorfonucleares neutrófilos, com leucocitoclasia, além de alterações na epiderme e na hipoderme (hipodermite neutrofílica), mas sem sinais de vasculite na maioria dos pacientes, não sendo considerada achado importante para o diagnóstico. A presença de exocitose de neutrófilos foi frequente, favorecendo o diagnóstico de Síndrome de Sweet quando acompanhada por dermatite intersticial neutrofílica difusa.
Palavras-chave: Febre; Patologia; Síndrome de Sweet

Received on 17.10.2010.
Approved by the Advisory Board and accepted for publication on 14.02.2011.
* Work conducted at Cassiano Antonio Moraes University Hospital - Federal University of Espirito Santo (HUCAM-UFES) - Vitoria (ES), Brazil.
Conflict of interest: None
Financial funding: None

[1] Physician at the Dermatology Service, Cassiano Antonio Moraes University Hospital (Hospital Universitário Cassiano Antônio Moraes) - Federal University of Espirito Santo (HUCAM-UFES) - Vitoria (ES), Brazil.
[2] Medical Resident at the Dermatology Service, Cassiano Antonio Moraes University Hospital - Federal University of Espirito Santo (HUCAM-UFES) - Vitoria (ES), Brazil.
[3] Ph.D. in Dermatology, Federal University of Rio de Janeiro – (UFRJ) - Head of the Dermatology Residency Program and Professor at the Department of Internal Medicine, Area of Dermatology, Federal University of Espirito Santo (UFES) - Vitoria (ES), Brazil.
[4] Professor of Pathology, Federal University of Espirito Santo (UFES) - Pathologist, Cassiano Antonio Moraes University Hospital - Federal University of Espirito Santo (HUCAM-UFES) - Vitoria (ES), Brazil.

INTRODUCTION

Sweet's syndrome, also called acute febrile neutrophilic dermatosis, is rare in Brazil. It is often accompanied by systemic manifestations such as poor general condition, myalgia, ocular, bone, liver, and spleen involvement.[1] In general, the disease is more common in women between 30 and 60 years old. [2,3]

Skin lesions appear as painful erythematous nodules and papules of sudden onset on the neck and upper extremities.[4] Laboratory abnormalities may be found, such as increased erythrocyte sedimentation rate (ESR), elevated C-reactive protein and leukocytosis. [1,2]

Sweet's syndrome may be associated with hematologic malignancies, particularly acute myelogenous leukemia or solid tumors, such as those of the gastrointestinal tract.[1] About 21% of cases are associated with malignancies, and the presence of ulcerations in the lesions are a common sign. These cases are especially associated with the following hematologic malignancies, in descending order of frequency: acute myelogenous leukemia, myeloproliferative diseases, chronic lymphocytic leukemia, myelodysplastic syndromes. [5] It may be associated with melanoma. [6]

Etiologically, Sweet's Syndrome may be associated with the use of drugs (trimethoprim-sulfamethoxazole, antiepileptic drugs, granulocyte colony-stimulating factor). When no triggering factor is found, the disease is called classic or idiopathic. [1,2] When associated with infections or inflammatory conditions, it belongs to the para-inflammatory subgroup of the disease. [7]

Histopathological criteria for the diagnosis of the disease include presence of diffuse neutrophilic infiltrate in the dermis, edema, and fragmentation of the nuclei of neutrophils (leukocytoclasia). Lymphocytes and histiocytes may be present. [7,8] The neutrophilic infiltrate may compromise the epidermis, forming subcorneal pustules, and the hypodermis, affecting lobules of adipocytes and/or septa. Some neutrophils may be located around small blood vessels in the dermis, leading to leukocytoclastic vasculitis. [1,8] The signs of vasculitis, which are not always seen on histopathological examination, are inflammatory infiltrate around postcapillary venules, with a predominance of neutrophils, nuclear dust, extravasation of erythrocytes, fibrin deposition in vessel walls, necrosis, and granuloma formation. [4,8]

Although the disease is primarily a dermal process, the inflammatory infiltrate may lead to neutrophilic panniculitis in up to 38% of cases. Absence of necrosis of adipocytes is clear, despite the large number of neutrophils. Lymphocytes, monocytes, and multinucleated giant cells may be found. [9]

Histopathological analysis is important for the diagnosis of the disease, since the differential diagnosis of Sweet's syndrome is extensive (leprosy, syphilis, tuberculosis, etc.). This makes a clinicopathological association essential for confirming the diagnosis. [10]

The disease responds well to oral corticosteroids. However, relapses may occur in the forms associated with malignancies and with intake of drugs, if the triggering factor remains. [1,2,4]

PATIENTS AND METHODS

This retrospective, descriptive study was based on the analysis of the medical records of patients diagnosed with Sweet's syndrome and subjected to skin biopsy and to clinicopathological discussion at dermatopathology meetings. The study was carried out from January 1997 to June 2009 at the Dermatology Service of Cassiano Antonio Moraes University Hospital (HUCAM), Vitoria, Espirito Santo.

A patient database on epidemiology, clinical manifestations, associated diseases, treatment, and clinical response to therapy was organized.

For the study of the histopathological features of skin lesions, we reviewed the slides and/or blocks of patients with positive diagnosis of the disease.

We used the SPSS 13.0 statistical software to analyze the variables (age, sex, race, clinical forms of Sweet's syndrome and histopathological aspects) and determine the descriptive analysis of the data and the correlation between the variables (sex and diagnostic hypothesis, sex and clinical forms of Sweet's syndrome, sex and histopathological examination, Sweet's syndrome classification and histopathological examination). The significance level adopted was 5%.

The study design was approved by the Research Ethics Committee on September 30, 2009.

RESULTS

After examining the files of the Dermatology Service at HUCAM, we found 27 cases of patients diagnosed with Sweet's syndrome from 1997 to 2009, which resulted in a frequency of 0.85% among 3,176 patients subjected to the clinicopathological meetings at the hospital. Ten medical records were not available at the Medical Records and Statistics Service of the hospital, due to their inexistence. Thus, the study was based on the analysis of 17 medical records. A review of the histopathological slides was possible in 12 cases, since the material of the other five patients (slides and paraffin blocks) had deteriorated.

Of the 12 patients histopathologically reviewed, one case was consistent with drug reaction (predominance of eosinophils in the inflammatory infiltrate) and was excluded. The clinical records of the five cases whose slides were not reevaluated showed clinical and histopathological characteristics of the syndro-

me. Therefore, the study analyzed 16 cases diagnosed with Sweet's syndrome.

All 16 patients were white, 14 female and two male (seven women for each man), and their age ranged from 22 to 70 years, with a median age of 36 years and five months (standard deviation of 14 years and two months).

In the first consultation, a diagnostic hypothesis of Sweet's syndrome was raised in five cases, while 11 patients were diagnosed with a drug reaction. In the case of these 11 patients, erythema nodosum, lupus erythematosus, leprosy, vasculitis, bullous disease, and paraneoplastic syndrome were presented as a second option.

Clinically, all patients presented solid skin lesions, which varied among papules (9/16), plaques (6/16), infiltration (5/16), and nodules (3/16). Three patients had vesicles, three presented purpuras, and two presented targetoid lesions between the solid lesions. As for local symptoms, eight patients (50%, 95% CI 36.8 to 63.2) presented pruritus, one (6.2%, 95% CI 1.4 to 11) presented burning, and seven (43.8%, 95% CI 31.3 to 56.3) were asymptomatic. Two patients presented symptoms in the mucosae: one had xerostomia and xerophthalmia, and another presented vulval and oral thrush.

The locations of the lesions were upper limbs (11/16), trunk (10/16), lower limbs (7/16), and neck (3/16). One patient presented lesions spread over the integument.

Fever was present in four patients (25%, 95% CI 15.4 to 34.6), and arthralgia and myalgia were present in three patients for each symptom (18.7%, 95% CI 10.3 to 27).

In the clinical classification of patients, 12 (75%, 95% CI 57.8 to 92.1) corresponded to the classic form, three (18.7%, 95% CI 10.3 to 27) presented the syndrome associated with a neoplasm (infiltrating lobular carcinoma of the breast, anal cancer and myelodysplasia), and one (6.2%, 95% CI 1.4 to 11) presented the form associated with drugs (trimethoprim-sulfamethoxazole).

As for the laboratory findings, anemia (hemoglobin less than 13g/dl in males and 12g/dl in females) was found in six patients, leukocytosis (white blood cell count above 8,000/mm^3) was found in eight patients, neutrophilia (neutrophils above 70%) in four patients, leukopenia (white blood cell count below 5,000/mm^3) in one patient, thrombocytopenia (platelet count less than 150,000/microliter) in one patient, and high ESR (higher than 20mm in the first hour) in four patients.

The histopathological analysis revealed that the slides of 11 patients (91.6%, 95% CI 73.9 to 109.3) were consistent with Sweet's syndrome, with epidermal, dermal and hypodermal changes being observed, as shown in table 1.

Among the epidermal changes, which were seen in seven cases, we found exocytosis of neutrophils, formation of subcorneal pustules, spongiosis and subepidermal edema. Dermal alterations were found in all patients, with a predominance of moderate to intense, superficial and deep, diffuse inflammatory infiltrate composed mainly of polymorphonuclear neutrophils with leukocytoclasia. Changes in the hypodermis were present in three patients. One case showed septal and lobular neutrophilic and lymphocytic infiltrate, another presented lobular macrophages and neutrophils, and one had only septal neutrophilic infiltrate. (Figures 1 to 4).

In most cases, treatment consisted of a systemic corticosteroid therapy with oral prednisone, varying from 20 to 60 mg/day, with subsequent gradual reduction of the drug for eight patients (50%, 95% CI 36.7 to 63.3). Of these patients, four had recurrence of the dermatosis.

Data comparison was not statistically significant: sex and diagnostic hypothesis (p = 0.54), sex and classification of Sweet's syndrome (p = 0.37), sex and histopathology (p = 0.16), classification of Sweet's syndrome and histopathology (p = 0.75).

DISCUSSION

Sweet studied for 15 years (1949-1964) eight cases of the syndrome that he described. [1] In this study, 16 patients were identified over a shorter

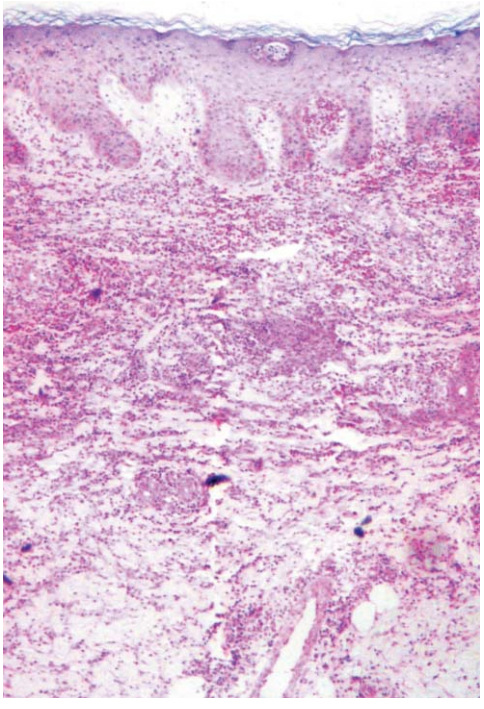

Figure 1: Exocytosis of neutrophils, subcorneal pustules, and intense and diffuse neutrophilic inflammatory infiltrate in the superficial and deep dermis. (HE)

Table 1: Epidermal, dermal and hypodermic changes observed in the slides reviewed in the histopathological study

N	Epidermis	Edema + subepidermal vesicle	Dermis: inflammatory infiltrate	Superficial or deep infiltrate	Intensity of the infiltrate	Predominant cells in the infiltrate	Leukocytoclasia	Vasculitis	Hypodermis	Histopathological diagnosis
1	Exocytosis of Neutrophils	Yes	Diffuse	Both	Moderate	Neutrophils	Yes	No	No change	Sweet
2	Exocytosis of Neutrophils	Yes	Diffuse	Both	Moderate	Neutrophils	Yes	No	No change	Sweet
3	No change	No	Diffuse	Both	Moderate	Neutrophils	Yes	No	No change	Sweet
4	No change	No	Diffuse	Both	Moderate	Neutrophils	Yes	No	Lobular and septal hypodermitis	Sweet
5	Exocytosis of Neutrophils	Yes	Diffuse	Both	Intense	Neutrophils	Yes	No	No change	Sweet
6	Exocytosis of Neutrophils + pustules	No	Diffuse	Both	Intense	Neutrophils	Yes	Yes	Septal hypodermitis	Sweet
7	No change	No	Diffuse	Superficial	Discrete	Neutrophils	No	No	No change	Sweet
8	Exocytosis of Neutrophils	No	Diffuse	Both	Intense	Neutrophils	Yes	No	No change	Sweet
9	Exocytosis of lymphocytes	No	Perivascular	Both	Moderate	Eosinophils	No	No	No change	Drug reaction
10	No change	Yes	Diffuse	Both	Moderate	Neutrophils	Yes	No	No change	Sweet
11	Acanthosis + hyperorthokeratosis	No	Diffuse	Both	Intense	Neutrophils	Yes	Yes	No change	Sweet
12	Exocytosis of Neutrophils + pustules	Yes	Diffuse	Both	Intense	Neutrophils	Yes	Yes	Lobular hypodermitis	Sweet

Note: N = Slides of patients with Sweet's Syndrome reviewed

period of time (12 years). All patients were white, but the literature shows no racial difference in relation to the clinical forms of the syndrome. [1]

The disease was more frequent in females (7:1), corroborating the data in the literature. [4,7] In relation to age, the median was 36 years and five months, which was lower than the median age of 60 years found by Zamanian et al. in their analysis of 15 patients with the syndrome. [4] In HIV-associated cases of the disease, the mean age concerning the dermatological symptoms is 43 years, and it is more frequent in men.

The most common initial diagnosis was drug reaction, especially erythema multiforme, the main differential diagnosis of Sweet's syndrome. In a retrospective study by Ratzinger et al., the clinical diagnosis of 28 cases was Sweet's syndrome, out of 31 cases. [11]

The classic form of the disease was the most frequent in the study (12/16), followed by Sweet's syndrome associated with a neoplasm and the drug-related form, corroborating the data in the literature. [1,2,7] Concerning the malignancy-related form, one case was associated with a hematologic disorder (myelodysplasia), unlike what was reported in other studies, which show a predominance of acute myelogenous leukemia followed by myelodysplastic syndromes. [5] As for the drug-related form, the drugs more commonly found in association with the disease are granulocyte colony-stimulating factor and trimethoprim- sulfamethoxazole, found in around 4.8% of cases. In our analysis at HUCAM, we registered one case associated with trimethoprim-sulfamethoxazole. [2]

All patients in the study presented solid skin lesions, and three patients also presented vesicles, corroborating the findings of a retrospective study conducted in Italy, which showed presence of papules and plaques in all 11 patients analyzed and presence of vesicles and pustules on the surface of the lesions in five patients. [7]

The skin lesions appeared on the following

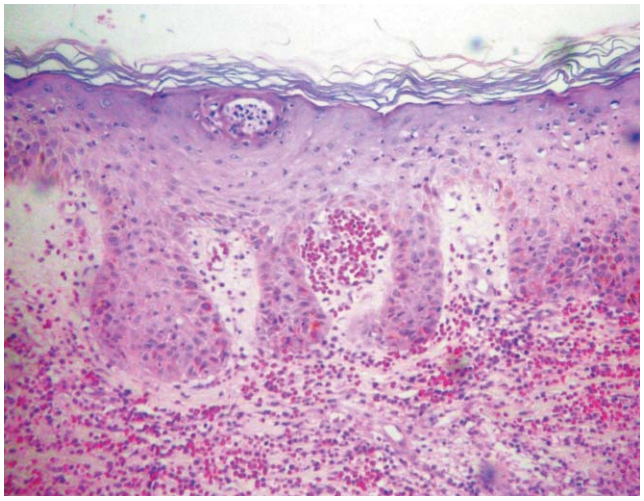

Figure 2: Exocytosis of neutrophils and subcorneal pustule

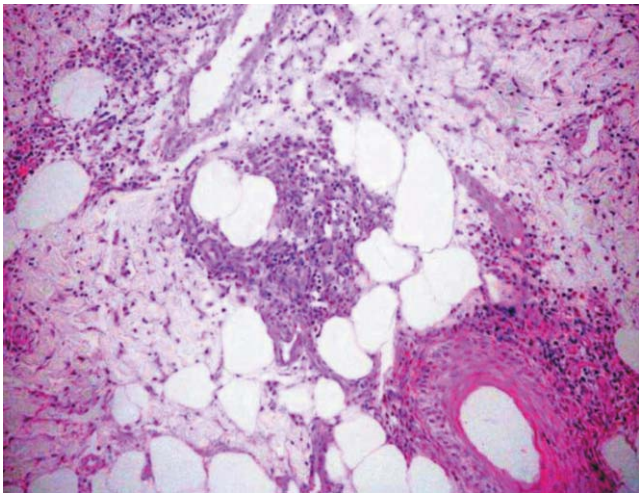

Figure 4: Septal neutrophilic hypodermitis

sites, from most to least frequent: upper limbs, trunk, lower limbs and neck; however, previous studies suggest greater involvement of the face, neck, upper limbs and, less frequently, the lower limbs. [1,4] Unlike these data, some authors found an involvement of the lower limbs in 54.5% and 64% of cases, [2,7] which is closer to the data found in this study. When the syndrome is exclusively subcutaneous, the lesions are more frequent on the lower limbs, but this form was not observed among the patients in this study. [9]

Our findings concerning local symptoms are in disagreement with those found by other authors, since there was no report of pain, which is considered a common symptom, unlike pruritus, which was the predominant symptom in this study. [1] Fever was present in four cases. This frequency was lower than that reported by most authors, who reported frequency of 33% to 90% of patients. [1,2]

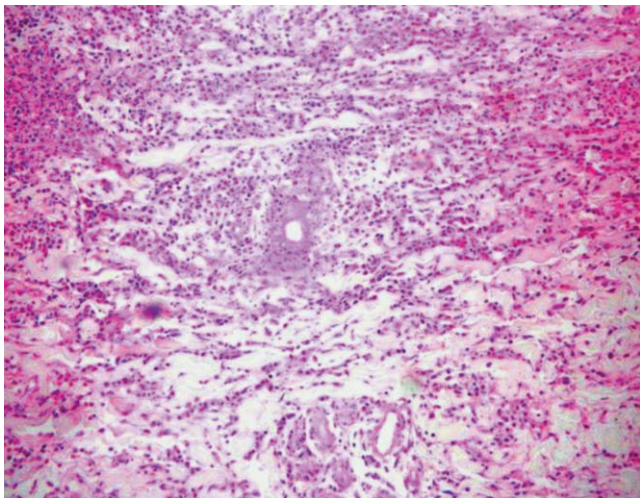

Figure 3: Leukocytoclasia and vasculitis (center)

One patient presented xerophthalmia, but the literature shows conflicting data, with frequency of ocular involvement varying from 0% to 72%, especially in the form of conjunctivitis. [1,2,4,7]

Leukocytosis, neutrophilia and increased ESR are considered the most common changes caused by the disease. In this study, half of the patients presented leukocytosis and there were four cases of neutrophilia and elevated ESR. [1]

The histopathological findings were similar to those found in the literature and included presence of exocytosis of neutrophils, subcorneal pustules, and subepidermal edema, in addition to moderate to intense nodular or diffuse inflammatory infiltrate of predominantly neutrophils in the dermis with leukocytoclasia. [1,8] However, this study was not in accordance with the literature in relation to vasculitis. This finding was not frequent at HUCAM, but was found in 74% of the 31 cases in the histopathologic study by Ratzinger et al. [8] The hypodermis was affected by the neutrophilic infiltrate in three cases, but it was not restricted to the adipose tissue in any case, demonstrating how rare this form is. To date, it has been observed in nine cases in the world literature. [9]

Of the eight patients treated with corticosteroids, four had recurrence of the lesions. One of these patients had cancer and three presented the classic form of the syndrome. However, studies show that patients with the classic form, when treated accordingly, present recurrence of the lesions from 4.7% to 13% of cases, with patients with malignancies having a higher chance of presenting recurrence, around 25% of cases. [2,4,7]

CONCLUSION

In this study, Sweet's syndrome was more frequent in white individuals of the female sex, and the most common laboratory abnormality was leukocytosis. The classic form of the disease was the most common, followed by the malignancy-related and the drug-induced forms. Erythema multiforme was the main differential diagnosis.

The slides evaluated showed similar histopathological changes, such as moderate to intense, superficial and deep, dermal neutrophilic infiltrate with leukocytoclasia, in addition to changes in the epidermis and hypodermis, but with no signs of vasculitis in most patients. Presence of exocytosis of neutrophils was common, favoring the diagnosis of Sweet's syndrome when accompanied by diffuse interstitial neutrophilic dermatitis. ❑

REFERENCES

1. Cohen P. Sweet's syndrome - a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis. 2007;2:34.
2. Borges da Costa J, Silva R, Soares de Almeida L, Filipe P, Marques Gomes M. Sweet's syndrome: a retrospective study of 42 admitted patients in a Portuguese hospital. Int J Dermatol. 2009;48:953-5.
3. Sampaio SAP, Rivitti EA. Afecções dos vasos. In: Sampaio SAP, Rivitti EA. Dermatologia 3. ed. São Paulo: Artes Médicas; 2001.p.542-3.
4. Zamanian A, Ameri A. Acute febrile neutrophilic dermatosis (Sweet's syndrome): a study of 15 cases in Iran. Int J Dermatol. 2007;46:571-4.
5. Buck T, González LM, Lambert WC, Schwartz RA. Sweet's syndrome with hematologic disorders: a review and reappraisal. Int J Dermatol. 2008;47:775-82.
6. Anacleto EB, Petri V. Dermatose neutrofílica aguda febril – Síndrome de Sweet. An Bras Dermatol. 1991;66:259-60.
7. Corazza M, Lauriola MM, Borghi A, Marzola A, Virgili A. Sweet's syndrome: a retrospective clinical, histopathological and immunohistochemical analysis of 11 cases. Acta Derm Venereol. 2008;88:601-6.
8. Ratzinger G, Burgdorf W, Zelger B. Sweet syndrome: vasculitis or not? Br J Dermatol. 2006;155:1099-101.
9. Guhl G, García-Díez A. Subcutaneous Sweet Syndrome. Dermatol Clin. 2008;26:541-51.
10. O' Brien, MC. Sweet's Syndrome. J Emerg Med. 2005;29:341-2.
11. Ratzinger G, Burgdorf W, Zelger BG, Zelger B. Acute Febrile Neutrophilic Dermatosis: a histopathologic study of 31 cases with review of literature. Am J Dermatopathol.

MAILING ADDRESS:
Itamara Assini Eleuterio
Avenida Marechal Campos s/nº
29040-191 Maruípe - Vitória, ES
E-mail address: itamara_assini@hotmail.com

How to cite this article: Eleuterio IA, Tiussi RM, Delmaestro D, Diniz LM, Lucas EA. Sweet's syndrome: Clinicopathological features of patients treated from 1997 to 2009 at Cassiano Antonio Moraes University Hospital - Vitoria (Espirito Santo). An Bras Dermatol. 2012;87(3):455-5.