Acta Derm Venereol 2008; 88: 601–606

CLINICAL REPORT

Sweet's Syndrome: A Retrospective Clinical, Histopathological and Immunohistochemical Analysis of 11 Cases

Monica CORAZZA[1], Maria Michela LAURIOLA[1], Alessandro BORGHI[1], Andrea MARZOLA[2] and Annarosa VIRGILI[1]
[1]Department of Clinical and Experimental Medicine, Section of Dermatology, and [2]Pathological Anatomy Section, University of Ferrara, Ferrara, Italy

The aim of this paper is to report our clinical experience of Sweet's syndrome, a severe dermatological disease which may be extremely important to recognize for the early diagnosis of a neoplastic disorder. Eleven patients affected by Sweet's syndrome, treated at the Department of Dermatology, University of Ferrara, Ferrara, Italy, during 1998 to 2004, were evaluated. A retrospective analysis was performed. Data on age, sex distribution, clinical data, histopathological and immunohistochemical findings and therapy were collected. We observed one patient with idiopathic form, 5 patients affected by the para-inflammatory variant and 5 para-neoplastic cases (with haemoproliferative diseases). The cases with the para-inflammatory form were affected by minor infectious manifestations. Prolonged follow-up is necessary to verify that a case of idiopathic variant is not really a paraneoplastic form. Based on immunohistochemical analysis, we cannot exclude that true histiocytes, immunoreactive for CD68/PGM, infiltrate the dermis in Sweet's syndrome lesions. ***Key words: Sweet's syndrome; neutrophilic dermatosis; para-inflammatory form; paraneoplastic form.***

(Accepted May 20, 2008.)

Acta Derm Venereol 2008; 88: 601–606.

Monica Corazza, Department of Clinical and Experimental Medicine, Section of Dermatology, University of Ferrara, Via Savonarola 9, IT-44100 Ferrara, Italy. E-mail: czm@unife.it

Acute febrile neutrophilic dermatosis was described by Sweet in 1964 (1). This dermatosis, like subcorneal pustular dermatosis, pyoderma gangrenosum and erythema elevatum diutinum, is classified among the neutrophilic dermatoses, a distinctive group of inflammatory skin diseases with a significant link to disorders of the internal organs (2, 3).

Sweet's syndrome (SS) statistically presents most frequently between 30 and 50 years of age, with a predilection for females (F:M ratio 3:1) (4, 5).

Clinically, this dermatosis is characterized by an abrupt onset of tender, red or purple-red papules or nodules. The individual lesions may coalesce and form irregular, sharply bordered plaques with possible pseudo-vesiculations, pseudo-pustulations and pustules on the surface (4, 6). The face, neck, upper chest, back and extremities, notably the back of the hands, are frequently involved (4). The lesions may also appear on sites of biopsy or other traumas (6). Oral and genital manifestations have been reported (1). Eye involvement has been reported in 6–72% of patients (4).

Systemic symptoms accompanying the skin eruption are fever (48–83% of patients), arthralgia, general malaise, headache and myalgia (4, 7). Extracutaneous features of SS can affect bones, the central nervous system, kidneys, intestines, liver, heart, bronchi and lungs, muscles and spleen (6).

An elevated erythrocyte sedimentation rate and peripheral leukocytosis with neutrophilia are the most consistent laboratory findings in SS; however, they are not always present (4–6).

The most typical pathological features of SS are represented by oedema of the dermal papillae and by a dense infiltrate in the superficial dermis, predominantly composed of mature neutrophils (1, 6, 7). In addition, lymphocytes or histiocytes may be present in the inflammatory infiltrate (6), and their role has been debated by some authors (8–11). First Jordaan (8), in 1989, recognized three stages of the SS dermal infiltrate (a lymphocytic, a neutrophilic and a histiocytic stage). Instead, in a recent report, Requena et al. (11) described a variant of SS, which they named histiocytoid SS. Histopathological features of leukocytoclastic vasculitis in SS have also been reported, although generally they are not typical in this syndrome (12, 13).

Von den Driesch (4) proposed a new classification with the diagnostic criteria shown in Table I. SS can be subdivided into four groups: classic/idiopathic, para-inflammatory, para-neoplastic, and pregnancy-associated (4); a fifth possible variant is drug-induced (14).

SS belongs to the spectrum of the neutrophilic dermatoses, which comprises other cutaneous inflammatory disorders, such as pyoderma gangrenosum, subcorneal pustular dermatosis, and erythema elevatum diutinum. SS, like the other neutrophilic dermatoses, has been observed in association with infections (commonly of the upper respiratory tract), inflammatory bowel diseases and autoimmune disorders (15). Cancers include both haematological malignancies (acute myeloid leukaemia, but also myelodysplasia and Hodgkin's or non-Hodgkin's lymphomas) and solid tumours (carcinomas of the

 ISSN 0001-5555
doi: 10.2340/00015555-0526

Table I. *Diagnostic criteria of Sweet's syndrome according to von den Driesch (4)*

Major criteria	Minor criteria
1. Abrupt onset of tender or painful erythematous plaques or nodules occasionally with vesicles, pustules or bullae	1. Preceded by a non-specific respiratory or gastrointestinal tract infection or vaccination or associated with: (a) inflammatory diseases, such as chronic autoimmune disorders, infections; (b) haemoproliferative disorders or solid malignant tumours; (c) pregnancy.
2. Predominantly neutrophilic infiltration in the dermis without leukocytoclastic vasculitis	2. Accompanied by periods of general malaise and fever (>38ºC). 3. Laboratory values during onset: ESR >20 mm; C-reactive protein positive; segmented-nuclear neutrophils and stabs >70% in peripheral blood smear; leukocytosis >8000 (3 of 4 of these values necessary). 4. Excellent response to treatment with systemic corticosteroids or potassium iodide.

ESR: erythrocyte sedimentation rate.

genitourinary organs, breast, and gastrointestinal tract) (4, 5–7). Fett et al. (16), in an ample series of patients, observed SS in 54% of cases as a marker of underlying malignancy, mainly haemoproliferative diseases.

The drug-induced form has rarely been reported in the literature (17–19), above all in women. The agent most commonly associated with this form is granulocyte-colony stimulating factor; other medications include trimethoprim-sulphamethoxazole, ethinyl estradiol and levonorgestrel, all-trans-retinoic acid, hydralazine, diclofenac, carbamazepine, nitrofurantoin, and diazepam (7, 17).

Cutaneous and systemic symptoms of SS, usually respond rapidly to systemic steroids (2). Chlorambucil, cyclophosphamide, cyclosporine, dapsone, acitretin (etretinate) and interferon-alpha-2 have also been used alone or in combination with systemic corticosteroids (7).

We report here a series of 11 patients affected by SS, who were observed over a period of 6 years.

MATERIALS AND METHODS

Between 1998 and 2004, 11 patients (4 men, 7 women) affected by SS were observed. The median age at the time of diagnosis was 52.4 years (range 31–79 years). This retrospective study was based on critical re-evaluation of patients' clinical, histopathological and immunohistochemical data. In biopsy specimens exhibiting an infiltrate even partially composed of mononuclear/histiocytic cells, immunohistochemical studies with myeloperoxidase (expressed only in neutrophils and myeloid cells) and CD68/PGM1 (expressed only in monocytes/ histiocytes) were performed.

RESULTS

All patients presented an abrupt onset; the systemic symptoms varied (Table II). Tender, dull-red, erythematous papules, often coalescent in large circumscribed, infiltrated dermal plaques were always observed (Fig. 1). In 5 patients, pseudo-vesiculation, pseudo-pustulation and pustules on the surface of the plaques were noted. In 6 cases, nodules were observed. These clinical features reflect the localization of the neutrophilic cutaneous infiltrate (20). In vesicles and pustules infiltrates occupy a superficial position extending to epidermis, whereas in nodular lesions the neutrophilic infiltrates mostly involve the deep dermis. The lesions were predominantly located on the upper and lower limbs, but the head and trunk were also frequently involved. No ocular or oral mucosal lesions were noted. The clinical and laboratory data of the patients are summarized in Table II.

The histological features were consistent with the diagnosis of SS in all patients (Fig. 2). The infiltrate was mainly composed of neutrophils in 8 patients, whereas the histological composition of 2 cases comprised both histiocytes and neutrophils, and neutrophils were clearly outnumbered by mononuclear/histiocytic cells in one biopsy. Immunohistochemical studies with myeloperoxidase (which is expressed only in neutrophils and myeloid cells) and CD68/PGM1 (which is expressed only in monocytes/ histiocytes) were performed in 6 specimens and were consistent with these histological observations (Table III). The formation of subcorneal pustules accompanied by a diffuse exocitosis of neutrophils into the epidermis was observed in one patient. Some features of leukocytoclastic vasculitis were found in 5 cases.

We observed one patient with idiopathic SS, 5 patients affected by the para-inflammatory variant and 5 paraneoplastic cases (Table II). In 4 patients the underlying neoplasia was already known, while in patient number 7 chronic myelomonocytic leukaemia was diagnosed 2 months after the onset of SS.

All patients were treated with systemic steroids (Table II); the dose was gradually reduced. Considerable improvement or resolution of SS was achieved within 1–3 months. Only patient number 8 developed two relapses requiring further corticosteroid oral therapy.

DISCUSSION

Though the aetiopathogenesis remains unknown (4, 6, 21), the identification of a prevalent neutrophilic infiltrate suggests that neutrophils have a crucial role in the pathogenesis of the SS (1). Local and systemic activation of neutrophils and histiocytes could be explained by a stimulation of a cytokine cascade. Recent studies postulate that the pathogenesis of this disease is probably induced by T-helper cell type 1 cytokines (IL-2, γ-IFN) rather than T-helper T cell type 2 cytokines (IL-4) (7, 22).

SS is an uncommon disease; in the general population its estimated annual incidence ranges between 2.7

Table II. *Clinical and laboratory data of patients with Sweet's syndrome (n = 11)*

Patient	Age (years)/ Sex	Lesion location	Signs and symptoms	Laboratory findings	Associated disease	Treatment	Outcome
1	35/F	Arms, trunk, legs	Fever 39ºC, headache	WBC = 12×10^3/mm^3 Neu = 63.8% ESR = 55mm/h CRP = 7.3mg/dl	Otitis	MP 32 mg/day	Complete remission in 1.5 months
2	53/F	Arms, knees	Fever 38.5ºC pharyngodynia	WBC = 8.9×10^3/mm^3 Neu = 57.5 % ESR = 21mm/h	Pharyngitis	Pred 25 mg/day	Complete remission in 20 days
3	79/F	Arms, legs	Fever 37.8ºC pharyngodynia	WBC = 8.9×10^3/mm^3 Neu = 81.7% ESR = 75mm/h CRP = 5.4mg/dl	Pharyngitis	MP 40 mg/day	Complete remission in 2 months
4	54/M	Arms, trunk, legs	Fever 38.5ºC, headache, abdominal pain	WBC = 6.6×10^3/mm^3 Neu = 76.3% ESR = 37mm/h CRP = 0.7mg/dl	Parodontal disease	Bet 4 mg/day	Much improved in 15 days
5	51/F	Trunk	General malaise	WBC = 6.1×10^3/mm^3 Neu = 59.4% ESR = 18 mm/h Urine culture: E.coli ALAT = 92 γGT = 406U/l	Urinary infection	MP 16 mg/day	Complete remission in 1 month
6	68/M	Arms, legs	Fever 37ºC, arthralgia	WBC = 2.4×10^3/mm^3 Neu = 18.8% Lymphocytes = 79.7% Monocytes = 0.6% RBC = 2.9×10^6/mm^3 Hb = 10.9 g/dl MCV = 107fl ESR = 96 mm/h CRP = 4.30mg/dl	Myelodysplasia	MP 16 mg/day	Much improved in 3 months
7	35/F	Head, arms	Arthralgia, pharyngodynia, general malaise	WBC = 51.2×10^3/mm^3 Neu = 81.6% Lymphocytes = 4% ESR = 21mm/h CRP = 12.7mg/dl	Chronic myelomonocytic leukaemia	Pred 25 mg/day	Much improved in 20 days
8	49/M	Neck, arms	General malaise	WBC = 6.8×10^3/mm^3 Neu = 67% Lymphocytes = 16.1% ESR = 54 mm/h	Diffuse large B cell lymphoma	Pred 50 mg/day	Much improved in 1 month but 2 recurrences after stopping therapy
9	31/M	Head	Fever 37.5ºC	WBC = 11.5×10^3/mm^3 Neu = 76% ESR = 44 mm/h CRP = 5.2 mg/dl	Hodgkin's lymphoma	Pred 74 mg/dl	Complete remission in 1 month
10	69/F	Head	Fever 38ºC, abdominal pain	WBC = 6.7×10^3/mm^3 Neu = 89% (Lymphocytes = 9.6%) RBC = 3.2×10^6/mm^3 Hb = 8.2 g/dl	Hodgkin's lymphoma	MP 125 and 80 mg/day	Much improved in 5 days, then complete remission in 1.5 months
11	56/F	Arms, hands, trunk, legs, feet	Fever 37.6ºC, pharyngodynia, asthenia	WBC = 8.5×10^3/mm^3 Neu = 71.4% ESR = 54 mm/h	None (Idiopathic SS)	MP 16 mg/day, Bet 3 mg/day	Much improved in 20 days

WBC: white blood cells; Neu: neutrophils; ESR: erythrocyte sedimentation rate; MP: methylprednisolone; Pred: prednisone; Bet: betamethasone; CRP: C-reactive protein; F: female; M: male; ALAT: alanin aminotransferas; RBC: red blood cells Hb: hemoglobin; MCV: mean corpuscular volume.

and 3/10^6 cases (5, 23). Over a period of 6 years we diagnosed SS in 11 patients on the basis of the revised criteria proposed by von den Driesch (4). As reported in the literature, in our study females were the most frequently affected (F:M ratio 7:4). Some authors (4, 24–26) suggest that male patients have a higher risk of being affected by paraneoplastic SS; we observed this variant in 3 males and 2 females.

Dermatological examination was always significant and histopathology was explanatory. As regards the clinical and laboratory findings characteristic of the syndrome, fever and neutrophilia were not always present (fever 8/11, neutrophilia 6/11).

In this study, we reviewed the biopsy specimens in the light of the latest reports in the literature concerning the presence of histiocytes in SS inflammatory infiltrate.

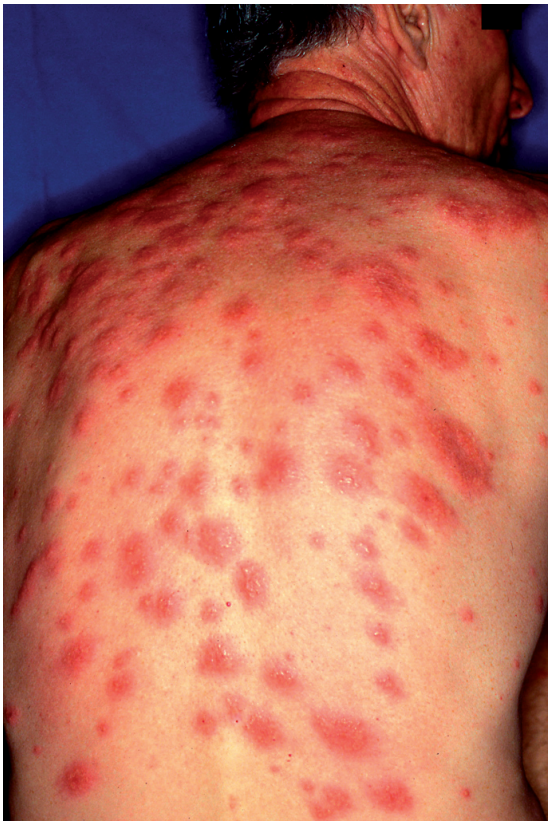

Fig. 1. Sweet's syndrome in a patient with parodontal disease (case 4).

We found histiocytes in a moderate amount in 2 cases (in addition to neutrophils), whereas in only one case was there a predominant histiocytic infiltrate (Table III). In the other specimens, the infiltrate was classically neutrophilic. No relationship was established between the duration of the lesions and the composition of the infiltrate, as suggested by Jordaan (8). We also studied

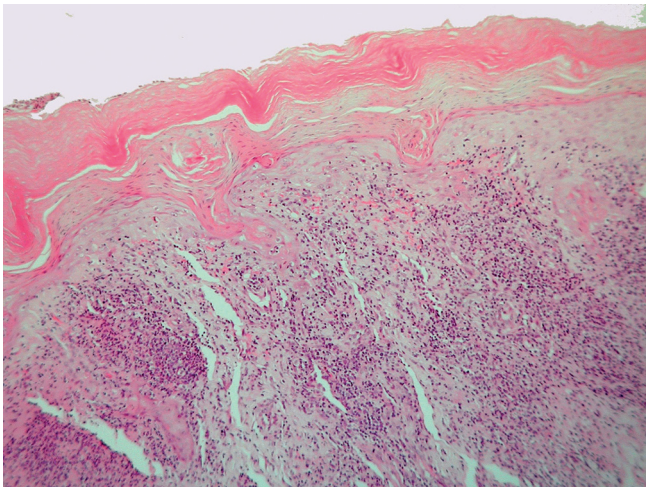

Fig. 2. Skin biopsy showing a dense infiltrate of neutrophils in the dermis (haematoxylin and eosin stain ×10).

the immunophenotypical expression of these cells of SS infiltrate, and particularly the myeloperoxidase for neutrophils/myeloid cells and the CD68/PGM1 for monocytes/ histiocytes.

Delabie et al. (9) described abundant histiocytes in SS, expressing pan-histiocytic markers (CD68/KP1, CD14, α1-antichymotrypsin and factor XIIIa). Subsequently, Bourke et al. (10) described CD68/PGM1-positive histiocytes in SS, but still lower than the neutrophils. Nevertheless, none of these authors studied myeloperoxidase expression. Finally, in a recent study, Requena et al. (11) described an intense myeloperoxidase reactivity of the monocytic-histiocytic infiltrate sometimes found in SS. Most of these cells expressed reactivity with CD68/KP1 (expressed in monocytes/histiocytes and also in neutrophils), but only a few cells co-expressed CD68/PGM1 (expressed only in monocytes/histio-

Table III. *Histopathological and immunohistochemical findings of patients with Sweet's syndrome (SS) (n = 11)*

Patient	SS group	Infiltrate composition	Immunohistochemical study/ expressed immunophenotypes	Signs of (secondary) vasculitis
1	Para-inflammatory SS	N	---	Yes
2	Para-inflammatory SS	N	---	Yes
3	Para-inflammatory SS	N	MPO +++ CD68/PGM1 +	No
4	Para-inflammatory SS	H/N	MPO ++ CD68/PGM1 ++	Yes
5	Para-inflammatory SS	N	---	No
6	Para-neoplastic SS	H/N	MPO ++ CD68/PGM1 ++	Yes
7	Para-neoplastic SS	N	MPO +++ CD68/PGM1 +	No
8	Para-neoplastic SS	H	MPO + CD68/PGM1 +++	No
9	Para-neoplastic SS	N	MPO +++ CD68/PGM1 +	Yes
10	Para-neoplastic SS	N	---	No
11	Idiopathic SS	N	---	No

H: prevalently histiocytes; N: prevalently neutrophils; H/N: mixed histiocytes and neutrophils; MPO: myeloperoxidase, expressed only in neutrophils and myeloid cells; CD68/PGM1: expressed only in monocytes/ histiocytes.

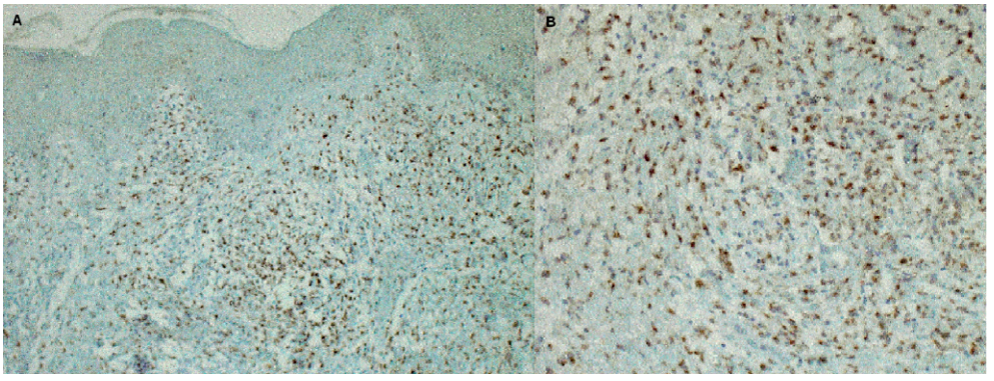

Fig. 3. (A) Immunohistochemical findings in patient 8: dermal infiltrate expressed strong immunoreactivity for CD68/PGM1 (CD68/PGM1 strain, original magnification ×10); (B) ×20 magnification of the same immunostaining result.

cytes, but not in neutrophils). Therefore, they conclude that these cells, misinterpreted as histiocytes, are in fact immature myeloid cells. They also named this histopathological variant histiocytoid SS.

We cannot confirm these conclusions about the correct nature of these mononuclear cells: in fact, we cannot exclude that they are true histiocytes, considering the positivity of infiltrate for CD68/PGM1 (expressed only in monocytes/histiocytes) (Fig. 3).

In our study, it is noteworthy that some features of leukocytoclastic vasculitis were found in 5 cases out of 11: this observation is consistent with other recent reports of secondary vasculitis in typical lesions of SS (12, 13).

A review of the literature evidences a major frequency of the classic/idiopathic form (75%), in comparison with the para-inflammatory form (15–16%), the paraneoplastic variant (10–20%), the iatrogenic form (5%) and the pregnancy-associated variant (2%) (4, 5, 21). However, only one of our cases was idiopathic, while 5 patients were affected by the para-inflammatory form and 5 by the para-neoplastic variant. In these last 5 patients, SS was correlated with haemoproliferative diseases. The cases affected by the para-inflammatory form presented minor infectious manifestations of the ears (patient number 1), buccal cavity (patient number 4), upper respiratory tract (2 patients) or urogenital tract (patient number 5).

According to the literature, patients affected by paraneoplastic SS frequently have more relapses. Short-term recurrences after therapy appear in 25% of cases; relapses after a disease-free interval of more than one year in 8% of patients (4).

In our study, we observed complete clinical remission in 6 of our patients. One patient with large B-cell lymphoma presented two relapses after stopping steroid treatment; the others were much improved at discharge from hospital

It is not yet clear if what appears to be the high prevalence of the idiopathic variant is in fact due to our limited knowledge of the correlations of SS with internal diseases and to the consequent inadequate laboratory tests. For this reason, we consider a prolonged follow-up (of 6–12 months) necessary to verify that a case of idiopathic variant is not really a para-neoplastic form.

In conclusion, this study of a large number of patients not only confirms that SS syndrome is a severe dermatological disease, but underlines the fact that its recognition may be extremely important for an early diagnosis of a neoplastic disorder. In addition, SS may be the presenting symptom of a relapsed neoplasia.

REFERENCES

1. Fitzgerald RL, McBurney EI, Nesbitt LT Jr. Sweet's syndrome. Int J Dermatol 1996; 35: 9–15.
2. Wallach D. Neutrophilic dermatoses: an overview. Clin Dermatol 2000; 18: 229–231.
3. Caughman W, Stern R, Haynes H. Neutrophilic dermatosis of myeloproliferative disorders. J Am Acad Dermatol 1983; 9: 751–758.
4. von den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). J Am Acad Dermatol 1994; 31: 535–556.
5. Djien V, Wallach D. Sweet's syndrome: practical conduct. Ann Dermatol Venereol 1999; 126: 343–347.
6. Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. Int J Dermatol 2003; 42: 761–778.
7. Cohen PR, Kurzrock R. Sweet's syndrome: a neutrophilic dermatosis classically associated with acute onset and fever. Clin Dermatol 2000; 18: 265–282.
8. Jordaan HF. Acute febrile neutrophilic dermatosis: a histopathological study of 37 patients and a review of the literature. Am J Dermatopathol 1989; 11: 99–111.
9. Delabie J, de Wolf-Peeters C, Morren M, Marien K, Roskams T, Desmet V. Histiocytes in Sweet's syndrome. Br J Dermatol 1991; 124: 348–353.
10. Bourke JF, Jones JL, Fletcher A, Graham-Brown RA. An immunohistochemical study of the dermal infiltrate and epidermal staining for interleukin 1 in 12 cases of Sweet's syndrome. Br J Dermatol 1996; 134: 705–709.
11. Requena L, Kutzner H, Palmedo G, Pascual M, Fernández-Herrera J, Fraga J, et al. Histiocytoid Sweet syndrome – a dermal infiltration of immature neutrophilic granulocytes. Arch Dermatol 2005; 141: 834–842.
12. Malone JC, Slone SP, Wills-Frank LA, Fearneyhough PK, Lear SC, Goldsmith LJ, et al. Vascular inflammation (vasculitis) in Sweet syndrome: a clinicopathologic study of 28 biopsy specimens from 21 patients. Arch Dermatol 2002; 138: 345–349.
13. 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 2007; 29: 125–133.
14. Prevost-Blank PL, Shwayder TD. Sweet's syndrome secondary to granulocyte colony stimulating factor. J Am Acad Dermatol 1996; 35: 995–997.
15. Aste N, Pau M, Loddo G, Biggio P. Sindrome di Sweet – descrizione di 10 casi [Sweet's syndrome – description of 10 cases]. G Ital Dermatol Venereol 2000; 135: 469–473 (in Italian).
16. Fett DL, Gibson LE, Su WP. Sweet's syndrome: systemic signs and symptoms and associated disorders. Mayo Clin Proc 1995; 70: 234–240.
17. Saez M, Garcia-Bustinduy M, Noda A, Dorta S, Escoda M, Fagundo E, et al. Drug–induced Sweet's syndrome. J Eur Acad Dermatol Venereol 2004; 18: 233.
18. Saez M, Garcia-Bustinduy M, Noda A, Guimera F, Dorta S, Escoda M, et al. Sweet's syndrome induced by oral contraceptive. Dermatology 2002; 204: 84.
19. Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. J Am Acad Dermatol 1996; 34: 918–923.
20. Wallach D, Vignon-Pennamen MD. From acute febrile neutrophilic dermatosis to neutrophilic disease: forty years of clinical research. J Am Acad Dermatol 2006; 55: 1066–1071.
21. Vignon-Pennamen MD. Syndrome de Sweet. Encycl Méd Chir (Editions Scientifiques et Médicales Elsevier SAS, Paris), Dermatologie 98-540-B-10; 2000; 7p.
22. Giasuddin ASM, El-Orfi AHAM, Ziu MM, El-Barnawi NY. Sweet's syndrome: is the pathogenesis mediated by helper T cell type 1 cytokines? J Am Acad Dermatol 1998; 39: 940–943.
23. Kemmet D, Hunter JA. Sweet's syndrome: a clinicopathologic review of twenty-nine cases. J Am Acad Dermatol 1990; 23: 503–507.
24. Cohen PR, Kurzrock R. Sweet's syndrome and cancer. Clin Dermatol 1993; 11: 141–148.
25. Bourke JF, Keohane S, Long CC, Kemmet D, Davies M, Zaki I, et al. Sweet's syndrome and malignancy in the UK. Br J Dermatol 1997; 137: 609–613.
26. Clemmensen OJ, Menné T, Brandrup F, Thomsen K, Lange Wantsin G. Acute febrile neutrophilic dermatosis – a marker of malignancy? Acta Derm Venereol 1989; 69: 52–58.