

Sweet's Syndrome Associated with Systemic Sarcoidosis

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Introduction

Sweet syndrome (SS), or acute febrile neutrophilic dermatosis, was first introduced by Dr. Robert Douglas Sweet¹ in 1964. The main features of the syndrome include fever, leukocytosis of neutrophilic predominance in the peripheral blood, and skin lesions that exhibit neutrophilic infiltration of the dermis. The skin lesions usually take the form of erythematous papules, plaques, or nodules that are distributed mainly in the upper extremities and trunk, head, and neck. The disease is encountered equally frequently in men and women and can affect any race. The usual age at presentation ranges from 30 to 80 years, with a mean of 57 years, although SS has been encountered in children as well. Extracutaneous manifestations of SS have been described in most organs. Sweet syndrome can be classified to classic, malignancy-induced, or drug-induced. Classic SS has been associated with upper respiratory or gastrointestinal tract infections, inflammatory bowel disease, and pregnancy. Sweet syndrome has been less frequently associated with conditions such as erythema nodosum, rheumatoid arthritis, sarcoidosis, relapsing polychondritis, Behçet syndrome, and thyroid disease [1,2].

Observation

45 years old, with a history of pulmonary tuberculosis already treated, hospitalised several times in our department for a Sweet Bubble Syndrome with no etiological orientation, during her last hospitalisation, clinically she presented some erosive lesions on both hands (figure 1), biological examination objectified a moderate inflammatory syndrome, the dosage of antistreptolysin antibodies, the nasal swab in search of streptococcus, the quantiferon assay for tuberculosis, the polymerase chain reaction in the sputum were all negative, the conversion enzyme was high, in addition, the phosphocalcic balance and proteinuria of 24 were both without anomaly, the thoracic tomodensitometry objectified calcified nodules following granulomatosis associated with mediastinal adenopathy evoking pulmonary sarcoidosis. We then retained the diagnosis of a pulmonary sarcoidosis revealed by a sweet and sick syndrome was followed by the pneumology department.



Figure 1: Erosive lesions secondary to anterior bullous lesions of sweet's syndrome

Discussion and literature review

The diagnostic criteria for classic SS include 2 major features: (1) abrupt onset of painful or tender erythematous plaques or nodules and (2) a predominantly neutrophilic infiltration in the dermis without evidence of leukocytoclastic vasculitis, along with 4 minor features: (1) preceded by fever or infections; (2) accompanied by fever, arthralgia, conjunctivitis, or underlying malignancy; (3) leukocytosis; and (4) good response to systemic steroids and not to antibiotics. Two major and at least 2 minor criteria have to be met to support the diagnosis of SS. Malignancy-induced SS may precede, follow, or mark the recurrence of a predominantly hematologic or solid cancer. In a retrospective study that reviewed 77 patients with different types of SS, evidence of low hemoglobin in either sex was found to be associated with an underlying malignancy. Emergence of the syndrome has also been attributed to the effect of drugs, mainly to granulocyte colony-stimulating factor (G-CSF), all-trans retinoic acid, and certain vaccines. However, other less common offenders, such as minocycline, bortezomib, and TMP-SMX, have been described in a number of case reports. After the introduction of the classic major and minor criteria for SS by Su and Liu⁵ in 1986, Walker and Cohen have suggested adjusted criteria to diagnose DISS in 1996 [3-7]. The latter criteria share the following elements with the classic criteria: painful erythematous skin lesions (plaques and nodules), dense

neutrophilic infiltrate without evidence of vasculitis on pathology, and pyrexia. However, they differ from the classic criteria by incorporating a temporal relationship between drug ingestion (or drug rechallenge) and clinical presentation, and temporal resolution of symptoms after drug withdrawal or initiation of systemic corticosteroids [8-12]. All 5 criteria have to be fulfilled to diagnose DISS. Because of the inherent limitations of associating certain clinical presentations to specific drugs, other authors have proposed an expanded type of Naranjo scale for DISS to assess and review the literature on drug-induced cases of SS, which, however, has not been validated for this use. The original Naranjo scale (an adverse drug reaction probability scale), which was introduced in 1981, served as a systematic method of evaluating causality in adverse drug reactions with more limited intrarater and interrater variability compared to prior methods. Our patient fulfilled all 5 criteria of DISS per Walker and Cohen and scored 3 to 4 (possible probability category) based on the expanded Naranjo score for DISS. Although the classic pathologic finding of SS is infiltration of dermis with mature neutrophils, a histiocytoid SS variant has also been reported [13-17]. This is characterized by infiltration of dermis by immature myeloid cells that resemble histiocytes. In a series of 62 patients diagnosed as having SS, of whom 22 had the histiocytoid SS variant and 40 the classic neutrophilic SS pattern, infiltration of dermis with immature myeloid cells was associated with myelodysplastic syndrome and lymphoid malignancies compared with the neutrophilic SS variant. The authors also noted that in patients with myelodysplastic syndromes rash could precede the hematologic malignancy diagnosis.

A search of MEDLINE (PubMed), beginning with the first description of SS in 1964 and continuing up to the present, together with a look at other relevant references, led us to identify 15 cases of SS associated with sarcoidosis in the English language literature. Two cases were excluded as one was incomplete and the other had insufficient data for the diagnosis of sarcoidosis. The latter case represented one of two cases reported in the same paper [18-19].

Common Mechanisms of Pathogenesis

Sweet Syndrome Pathogenesis Sweet syndrome has been categorized under neutrophilic dermatoses along with other disease entities such as pyoderma gangrenosum, subcorneal pustular dermatosis, erythema elevatum diutinum, and neutrophilic eccrine hidradenitis, which are all characterized by a predominantly neutrophilic infiltrate. The grouping of diseases that share this feature has served the purpose of searching for common pathogenic pathways and applying targeted treatments. From a larger viewpoint, it has been suggested that neutrophilic dermatoses may be closely related to autoinflammatory diseases and constitute aspects of the innate immune disorders spectrum. Nevertheless, the exact pathogenesis of SS remains largely unknown at this time and seems to be dictated by the underlying inciting factor (such as tumor, drug reaction, infection). It has been hypothesized that the manifestations of SS may be driven by helper T cell type 1 (TH1) [20,21]. In a study conducted in 8 patients with classic SS that fulfilled the Su and Liu5 criteria, serum levels of interleukin (IL) 1 α , IL-1 β , IL-2, and interferon γ were found to be elevated compared with control subjects, whereas levels of IL-4 were found to be normal, suggesting a TH1 predominance over TH2. Other investigators looked into the cytokine and chemokine expression within the skin rash of 6 patients with SS comparing it with 16 patients with pyoderma gangrenosum and 6 control subjects. The results showed elevated levels of IL-1 β , IL-1 receptor I (RI), tumor necrosis factor α , IL-17, and IL-17 receptor in patients with SS compared with

control subjects, all of which play a role in neutrophil recruitment. In addition, the chemokines IL-8, chemokine (C-X-C motif) ligand 1,2,3 (CXCL 1,2,3), and CXCL16 along with L-selectin were also elevated, indicating increased signals for neutrophilic diapedesis to tissues. Although it is known that DISS may occur with administration of G-CSF, the serum levels of this cytokine were found to be elevated irrespective of the cause of SS in all 5 patients examined, who had active SS compared with inactive SS or control subjects [22,23]. In addition, the neutrophils of patients with active SS exhibited decreased rate of apoptosis when cultured in the serum of patients with active SS versus fetal calf serum alone, providing a possible explanation to the neutrophilic predominance and skin infiltration that characterizes the syndrome. Another hypothesis that has been suggested attempting to explain the marked neutrophilic aggressiveness that manifests with infiltration is that of a "neutrophil recovery syndrometo". In this hypothesis, neutrophils that have been intensely stimulated for release from the bone marrow in an activated form (from a stimulus such as G-CSF) display augmented functional characteristics that result in the well-described skin manifestations. In patients with hematologic malignancies, it has been found that under certain circumstances when SS develops (in this case after use of G-CSF) the skin infiltrate consists of neutrophils originating from the predominant bone marrow neutrophilic clone16 and that those clones may have specific attributes (such as leukocyte adhesion molecules or integrins) that allow them to preferentially migrate to the skin. Sweet Syndrome and Sarcoidosis Sweet syndrome, although rarely, has also been associated with sarcoidosis. A review of 10 cases that examined the characteristics of patients with SS and sarcoidosis concluded that SS and sarcoidosis occur simultaneously with sarcoidosis presenting primarily within the context of Löfgren syndrome. Sweet syndrome and sarcoidosis tend to affect younger females compared to classic SS, have higher rates of presentation with fever, involve upper limbs rather than face or trunk, and present with the less typical skin lesions of SS (papules rather than plaques or nodules) [24,25]. Sincethen, additional case report has been published in the English literature reporting the concurrent presentation of SS with sarcoidosis. In that report, a 55-year-old woman presented with Löfgren syndrome, episcleritis, and a rash consisting of papules and plaques on her upper and lower extremities. Her angiotensin-converting enzyme level was normal, and she had peripheral leukocytosis and elevated CRP. Unlike the published cases, our patient's sarcoidosis was diagnosed 2 years prior to his DISS diagnosis. He did not share most of the aforementioned characteristics of patients who present with SS and sarcoidosis, strengthening the case of a DISS. The pathogenesis of sarcoidosis, irrespective of SS, is another field that remains under exploration. Sarcoidosis is a multiorgan disease characterized by noncaseating granulomas that are thought to be triggered by so far unspecified antigens. Factors such as occupational and environmental exposures (insecticides, molds) and infectious agents (such as P. acnes) have been associated with sarcoidosis. Although P. acnes may be found in lymph nodes and tissues of patients without sarcoidosis, it has been hypothesized that in predisposed patients P. acnes may cause a hypersensitivity reaction that triggers and preserves the formation of noncaseating granulomas through activation of TH1 immune response. TH1 immune response has also been implicated in development of SS. It is of interest that our patient's culture of the right axillary lymph node biopsy also grew P. acnes. The specimen was obtained by surgical means, making contamination of specimen by skin flora less likely [25,26]. Prior to initiation of TMP-SMX, he was experiencing a localized inflammatory process that forced him to seek medical attention. It can be speculated that a possible inflammatory reaction to P. acnes along with the introduction

of TMP-SMX, which is also known to cause a hypersensitivity reaction and stimulation of T-cell response through the metabolite of sulfamethoxazole, may have resulted in emergence of SS.

Histological findings

In all of the cases, the diagnosis of SS was made on the basis of the presence of compatible clinical and laboratory features in combination with lesion biopsy demonstrating infiltration of the dermis with neutrophils without evidence of vasculitis.

A final histological diagnosis of sarcoidosis was made in nine patients. One patient who had non-diagnostic transbronchial biopsy refused mediastinoscopy. In all nine patients the biopsy showed sarcoid-type granulomata. In only three cases were the findings diagnostic for sarcoidosis. In the remaining three

cases, the findings were either nonspecific or non-diagnostic for sarcoidosis. The findings of mediastinal lymph node biopsy were compatible with sarcoidosis in four patients. Two of the mediastinal lymph node biopsies were performed after getting non-diagnostic findings on transbronchial biopsy. In one patient the diagnosis of sarcoidosis was made by cervical lymph node biopsy as the only procedure. In another patient sarcoidosis was diagnosed by the Kveim test, which produced 10 mm violaceous patch at 6 weeks and, on biopsy, epithelioid cell granulomata with multinucleated giant cells were found. Other sites that were biopsied were minor salivary glands and the lungs, both of which provided evidence of sarcoidosis. Transbronchial and mediastinal lymph node biopsy, respectively, were also diagnostic in these patients. Bronchoalveolar lavage was performed in two patients and was normal [2,25,26].

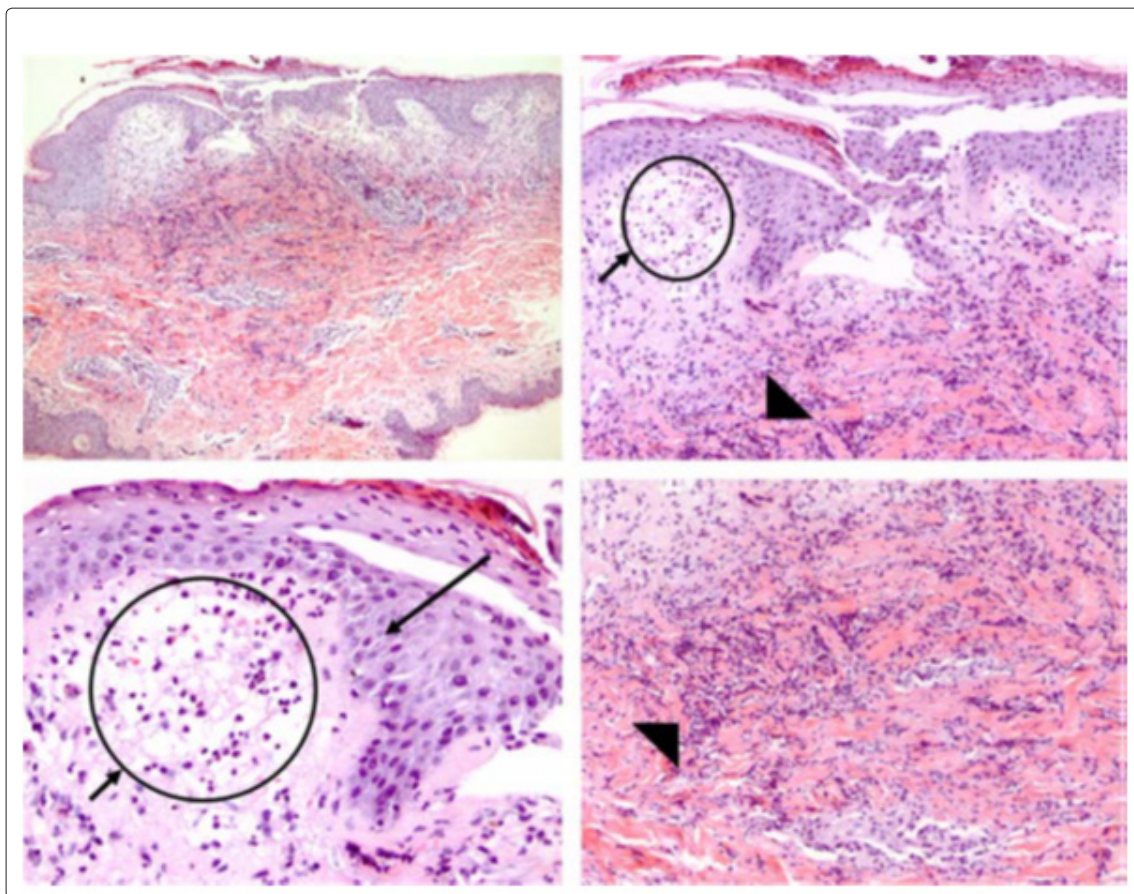


Figure 2: Biopsy of the skin showing normal epidermis with slight spongiosis (long arrow), diffuse neutrophilic dermal infiltration in reticular dermis (arrowhead), and marked edema in papillary dermis.

Treatment and outcome

In our patient and in all of the patients reported, the two disorders were characterized by acute onset with benign course and self-limiting disease. Thus, SS in association with sarcoidosis could be considered a favorable prognostic factor. In contrast to the high rate of recurrence in the general SS population (21–37%), no recurrence was detected in the patients with SS and associated sarcoidosis during a follow-up of 3 weeks to 15 months. Repeat chest X-ray in six patients revealed the resolution of findings in our patient and three others after 5–17 months of follow-up. One patient had a decreased size of hilar adenopathy at 6 weeks of follow-up, while another showed persistent hilar adenopathy at 9 months of follow-up.

Nine patients were initially treated with NSAIDs, leading to rapid improvement within few weeks in four. One patient developed new lesions while on indomethacin; adding a tapering dose of prednisone led to improvement over a period of 2 weeks. Another patient initially treated with NSAIDs and erythromycin without improvement was placed on prednisone and doxycycline with gradual improvement over 6 weeks [1-4,16].

Colchicine for 3 weeks was prescribed for three patients and was successful. Systemic prednisone treatment as first-line therapy was prescribed for two patients, while another patient was prescribed a topical corticosteroid. Skin lesions in SS may resolve spontaneously. Corticosteroids remain the treatment of choice. Prednisone 20–60 mg daily leads to rapid, symptomatic relief within hours, and subsequent clearing of the skin lesions within 3–5 days. In order to reduce the rate of recurrence, prednisone should be tapered over 4–6 weeks. Indomethacin, colchicines, and potassium iodide have all been used in the treatment of SS, but they have no particular advantages over corticosteroids [17,18,25,26].

Conclusion

The combination of SS and sarcoidosis is rare. Both disorders are diagnosed simultaneously and are characterized by a benign course and favorable outcome without recurrence. In this group of patients, we found a trend toward less involvement of the face and trunk, more involvement of the upper limbs, and more atypical skin lesions, particularly papules. The association of both diseases seems to be particularly related to Lofgren's syndrome and especially to the presence of erythema nodosum. Due to the high rate of malignancy associated with SS, the discovery of mediastinal lymphadenopathy may raise the suspicion of an underlying malignancy and lead to aggressive invasive tests. However, considering sarcoidosis, particularly in the presence of erythema nodosum, may save unnecessary procedures.

References

1. Sweet RD (1964) An acute febrile neutrophilic dermatosis. *Br J Dermatol* 76: 349-356.
2. Rochet NM, Chavan RN, Cappel MA (2013) Sweet syndrome: clinical presentation, associations, and response to treatment in 77 patients. *J Am Acad Dermatol* 69: 557-564.
3. Halpern J, Salim A (2009) Pediatric Sweet syndrome: case report and literature review. *Pediatr Dermatol* 26:452-457.
4. Cohen PR (2007) Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2:34.
5. Su WP, Liu HN (1986) Diagnostic criteria for Sweet's syndrome. *Cutis* 37:167-174.
6. Thompson DF, Montarella KE (2007) Drug-induced Sweet's syndrome. *Ann Pharmacother* 41:802-811.
7. Walker DC, Cohen PR (1996) Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol* 34: 918-923.
8. Naranjo CA, Busto U, Sellers EM (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30:239-245.
9. Requena L, Kutzner H, Palmedo G (2005) Histiocytoid Sweet syndrome: a dermal infiltration of immature neutrophilic granulocytes. *Arch Dermatol* 141:834-842.
10. Ghoufi L, Ortonne N, Ingen-Housz-Oro S (2016) Histiocytoid Sweet syndrome is more frequently associated with myelodysplastic syndromes than the classical neutrophilic variant: a comparative series of 62 patients. *Medicine (Baltimore)* 95:e3033.
11. Navarini AA, Satoh TK, French LE (2016) Neutrophilic dermatoses and autoinflammatory diseases with skin involvement—innate immune disorders. *Semin Immunopathol* 38:45-56.
12. Giasuddin AS, El-Orfi AH, Ziu MM (1998) Sweet's syndrome: is the pathogenesis mediated by helper T cell type 1 cytokines? *J Am Acad Dermatol* 39:940-943.
13. Marzano AV, Fanoni D, Antiga E (2014) Expression of cytokines, chemokines and other effector molecules in two prototypic autoinflammatory skin diseases, pyoderma gangrenosum and Sweet's syndrome. *Clin Exp Immunol* 178:48-56.
14. Kawakami T, Ohashi S, Kawa Y (2004) Elevated serum granulocyte colony-stimulating factor levels in patients with active phase of Sweet syndrome and patients with active Behçet disease: implication in neutrophil apoptosis dysfunction. *Arch Dermatol* 140: 570-574.
15. Dereure O, Hillaire-Buys D, Guilhou JJ (2004) Neutrophil-dependent cutaneous side-effects of leucocyte colony-stimulating factors: manifestations of a neutrophil recovery syndrome? *Br J Dermatol* 150: 1228-1230.
16. Magro CM, De Moraes E, Burns F (2001) Sweet's syndrome in the setting of CD34-positive acute myelogenous leukemia treated with granulocyte colony stimulating factor: evidence for a clonal neutrophilic dermatosis. *J Cutan Pathol* 28: 90-96.
17. Vignon-Pennamen MD, Aractingi S (2003) Sweet's syndrome and leukemia cutis: a common skin homing mechanism? *Dermatol* 206: 81-84.
18. Saliba WR, Habib GS, Elias M (2005) Sweet's syndrome and sarcoidosis. *Eur J Intern Med*. 16: 545-550.
19. Dadban A, Hirschi S, Sanchez M (2009) Association of Sweet's syndrome and acute sarcoidosis: report of a case and review of the literature. *Clin Exp Dermatol* 34: 189-191.
20. Newman LS, Rose CS, Bresnitz EA (2004) A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med* 170: 1324-1330.
21. Eishi Y, Suga M, Ishige I (2002) Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. *J Clin Microbiol* 40:198-204.
22. Ishige I, Eishi Y, Takemura T (2005) Propionibacterium acnes is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 22:33-42.
23. Castrejon JL, Berry N, El-Ghaiesh S (2010) Stimulation of human T cells with sulfonamides and sulfonamide metabolites. *J Allergy Clin Immunol* 125:411-418.e4.
24. Castrejon JL, Lavergne SN, El-Sheikh A (2010) Metabolic and chemical origins of cross-reactive immunological reactions to arylamine benzenesulfonamides: T-cell responses to hydroxylamine and nitroso derivatives. *Chem Res Toxicol* 23:184-192.
25. Bidinger JJ, Sky K, Battafarano DF (2011) The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome. *J Am Acad Dermatol* 65:184-191.
26. Maria A, Guilpain P, Forestier A (2012) Syndrome de Sweet et sarcoïdose: une association inhabituelle. *Rev Med Interne* 33: S175-S176.
27. Myriem Bricha, Fatimazzahra Sqalli, Sanae Hammi, Jamal Eddine Bourkadi (2016) Un mode révélateur original de la sarcoïdose: syndrome de sweet An original revealing mode of sarcoidosis: Sweet's syndrome. *Pan African medical Journal*.

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