

Case report

Sweet's syndrome representing a flare of Behçet's disease

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Received on August 4, 2008; accepted in revised form on May 5, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 53): S88-S90.

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EXPERIMENTAL RHEUMATOLOGY 2009.

Key words: Sweet's syndrome, acute febrile neutrophilic dermatosis, Behçet's disease.

ABSTRACT

A case of Sweet's syndrome (SS) associated with Behçet's disease (BD) is presented. A 42-year-old Chinese woman was admitted for an eruption of tender, erythematous papules over the neck, which histological changes were typical of SS. She had a three-year history of oral and genital ulcers that was in remission for two months, but flared shortly after the eruption. SS in association with BD has been reported only in few cases. On reviewing the literature, some overlapping manifestations exist between BD and SS and it is possible that some common pathogenesis pathways may be shared by BD and SS.

Introduction

Sweet's syndrome (SS), featured with fever, acute eruption of erythematous plaques, leukocytosis, and a dense dermal infiltrate of neutrophils (1-3), has been reported in association with numerous diseases. However, SS in association with Behçet's disease (BD) has been reported only in few patients, which usually occurred during the acute phase of BD. Here we report the case of a woman in whom SS was present before the flare of BD.

Case report

A 42-year-old Chinese woman presented to our hospital for a fever and a painful rash on the left neck in October 2007. Five days earlier, the patient suddenly developed a painful erythematous eruption on her left neck accompanying with a fever of 38.7°C. Three days later, she developed mouth sores forming deep pits on her tongue, and erythematous subcutaneous nodules on the legs. The patient had a three-year history of recurrent oral aphthous ulcers, genital ulcers, skin lesions, and had been diagnosed as BD in July 2005. She had taken prednisone

and Chinese herbs intermittently, and experienced no symptoms during the past two months.

Physical examination revealed a 3.5cm in diameter pseudovesicular erythematous plaque on the left neck (Fig. 1), and erythema nodosum-like lesions on her legs, a 0.5cm ulcer on her tongue, and 1-3 mm erosions on the upper inner lips of her uvula. Findings were normal from examination of the pleuropulmonary and cardiovascular systems, abdomen, and nervous systems. Evaluation by an ophthalmologist disclosed no conjunctivitis and uveitis. Laboratory tests showed a white blood cells count of $8.4 \times 10^9/L$ with 84% neutrophils. The C-reactive protein (CRP) level was elevated at 27 mg/L (normal <8mg/L), as was the erythrocyte sedimentation rate (ESR) at 31 mm/h (normal <20 mm/h). No evidence of infection was found by serological tests for syphilis and HIV infection, bacterial throat cultures, blood cultures, or urine cultures at the time of admission. Serologic tests for autoimmune diseases, including rheumatoid factor, antinuclear antibodies (ANA), SS-A/SS-B antibodies, anti-dsDNA antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), were all negative. Serum C3, C4, IgA, IgG and IgM were within normal limits. Findings were also normal from a chest x-ray, an electrocardiogram, an ultrasound scan of the abdomen and pelvis, and a microscopic examination of bone marrow smears. HLA typing was negative for HLA-B27 and HLA-B51. Pathergy skin test yielded a 3mm papule after 48 hours. A skin biopsy specimen from her left neck plaque showed typical features of SS (Fig. 2).

She was therefore treated with prednisone 30mg daily and experienced a complete resolution of mucocutaneous lesions within twelve days. The prednisone was then tapered and immunomodulation with thalidomide was added.

Competing interests: none declared.

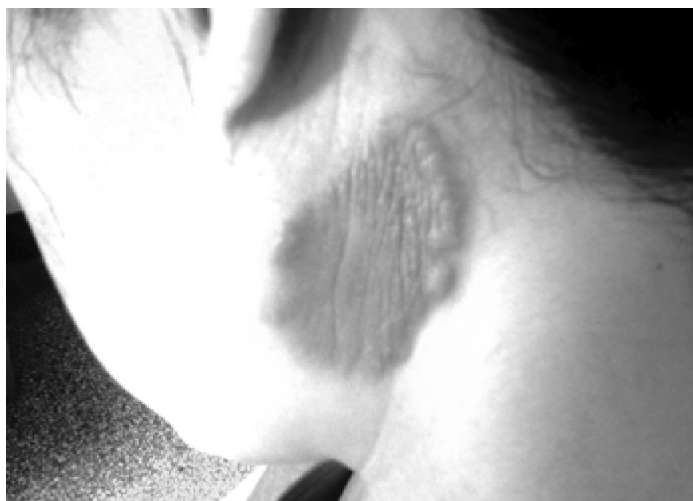


Fig. 1.
A pseudovesicular erythematous plaque on left side of neck.

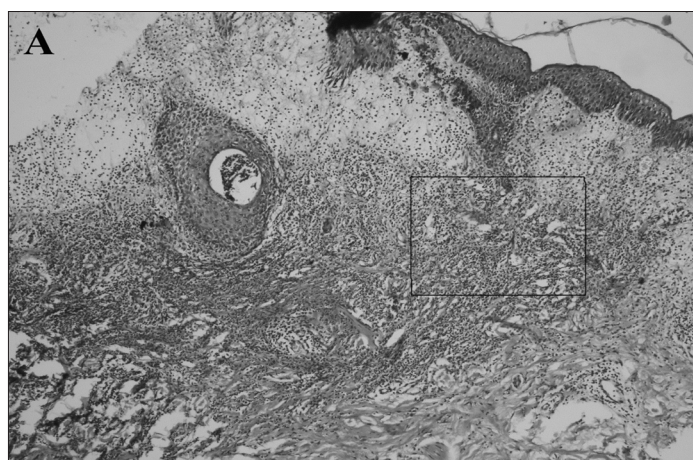
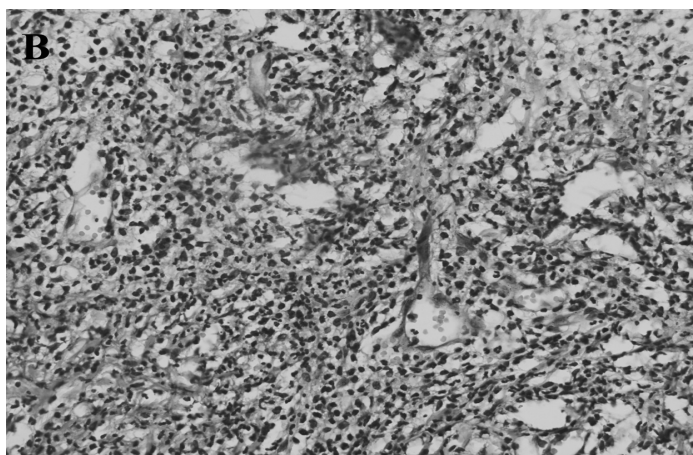


Fig. 2.
Skin biopsy revealing a dense infiltrate composed predominantly of neutrophils.
A: hematoxylin-eosin, $\times 100$;
B: hematoxylin-eosin, $\times 400$.



Discussion

Our patient met the criteria for SS developed by Su and Liu and modified by von den Driesch (4). She fulfilled two major criteria: 1. an abrupt onset of tender, painful erythematous plaques with vesicles; and 2. a predominantly neutrophilic infiltrate in the dermis without leucocytoclastic vasculitis. She also fulfilled the three minor criteria: 1. pyrexia

$>38^{\circ}\text{C}$; 2. laboratory abnormalities (ESR $>20\text{mm/h}$, elevated CRP levels, and neutrophils $>70\%$); and 3. a good response to treatment with systemic corticosteroids. The diagnosis of BD in our patient was based upon the recurrent oral and genital ulcers, erythema nodosum-like lesions, and a positive result of

skin pathergy test, which met the criteria for BD established by the International Study Group on BD in 1990 (5).

There have been case reports on SS combined with other inflammatory diseases such as inflammatory bowel disease, lupus erythematosus, rheumatoid arthritis and relapsing polychondritis (3). However, to our knowledge, only a few cases of SS have been reported in patients with BD (7-12).

Skin involvement in BD includes various lesions such as erythema nodosum, pustules, papules, pseudofolliculitis, acneiform folliculitis, or pyoderma gangrenosum (2, 3). SS-like lesions have also been addressed in BD (2, 6). The histopathology of the papulopustular lesions usually shows vasculopathy that is characterized by the perivascular infiltration of mononuclear cells, and this infiltrate is mainly composed of lymphocytes. The erythema nodosum-like lesion is known to be characterized by extravascular neutrophilic infiltration and panniculitis, and this can be followed by lymphocyte infiltration during the evolution of the skin lesions. The SS-like lesions also show vascular injury that is featured by a dense infiltrate of leucocytes around blood vessels, with necrosis of vascular endothelium and extravasation of red blood cells. The infiltrate consisted of lymphocytes, histiocytes and a few neutrophils with some nuclear dust (6). In our case, the main histopathologic finding of the skin lesions was a diffuse infiltration of the dermis by mature neutrophils, with no features of vasculitis, which are the characteristic findings of SS.

Although cases of BD combined with SS have rarely been reported, BD and SS do not seem to be separate entities. Suehisa *et al.* (13) reported three cases of SS which had oral aphthosis, leukocytoclastic vasculitis and thrombophlebitis, and suggested that there may be a link between SS and BD. Some overlapping manifestations exist between BD and SS. Oral ulcers, Ocular and articular involvement, erythema nodosum-like lesions, papulopustular lesions and acneiform eruptions, which are commonly found in BD, have also been described in SS. Pathergy, which is one of the diagnostic criteria for BD,

has also been demonstrated in SS (8). These similarities between the clinical manifestations of BD and SS imply that there seems to be something in common for the pathogenesis of BD and SS.

The pathogenesis of both SS and BD remains unknown. Indeed, there may be multifactorial and many etiologies. Immunohistochemical evaluation of the epidermis of SS lesions suggests an important role of cytokines in the development of SS (2, 4). Increasing evidence suggests that SS results from local or even systemic cytokine and chemokine recruitment and activation of neutrophils (2). Cohen *et al.* (14) hypothesized that the causative agent of SS may stimulate the production of various cytokines, such as interleukin (IL) 1, IL-6, IL-8 (CXCL8), or granulocyte colony-stimulating factor (G-CSF). von den Driesch (15) described SS patients with IL-8-reactive dendritic cells in the dermis. Reuss-Borst *et al.* (16) reported a patient during the acute phase of SS with markedly elevated serum levels of G-CSF and IL-6. In acute myelocytic leukemia (AML) associated SS, it was found that increased G-CSF expression, which is consequently induced by IL-1 produced by AML cells, played a role in the pathogenesis of SS (17, 18). This is further documented by the fact that SS can occur after G-CSF treatment (19, 20). Moreover, significantly elevated levels of helper T-cell type 1 (Th1) cytokines (IL-2 and interferon-gamma) were observed in the immunohistochemical studies of SS patients' serum (21). In patients with BD, an overactivated cytokine cascade through IL-1, IL-6, IL-8 (CXCL8), IL-18, TNF- α is also prominent, especially during the active phase of the disease (1, 22, 23). However, patients with inactive BD have also shown increased production of IL-1, IL-6 and IL-8 from monocytes following lipopolysaccharide stimulation (24). Recent studies have revealed the central of T-cell mediated immune response in the pathogenesis of BD. Increased entry of CD4+ T cells into the Th1 subset and predominance of Th1 cytokine production have been observed in BD (25, 26). Moreover, skin-derived T-cell clones from BD patients

were shown to produce CXCL-8 and GM-CSF (27). These data suggested that the overactivated cytokine cascade and Th1 responses could be the common mechanism of BD and SS.

In the cases reported in the literature, SS usually developed during the acute phase of BD. Horiguchi *et al.* (12) described a case with SS as initial signs of BD. Our patients developed SS in the inactive stage of BD, but shortly followed by a flare of the disease. These cases suggest that the occurrence of SS in BD may indicate active disease or flare of the disease.

References

1. COHEN PR, KURZROCK R: Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol* 2003; 42: m761-78.
2. COHEN PR: Sweet's syndrome--a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; 2: 34.
3. KRAUSE I, WEINBERGER A: Behçet's disease. *Curr Opin Rheumatol* 2008; 20: 82-7.
4. COHEN PR, KURZROCK R: Sweet's syndrome: a neutrophilic dermatosis classically associated with acute onset and fever. *Clin Dermatol* 2000; 18: 265-82.
5. TUNÇ R, ULUHAN A, MELIKOĞLU M, OZYAZGAN Y, OZDOĞAN H, YAZICI H: A reassessment of the International Study Group criteria for the diagnosis (classification) of Behçet's syndrome. *Clin Exp Rheumatol* 2001; 19 (Suppl. 24): 545.
6. CHO KH, SHIN KS, SOHN SJ, CHOI SJ, LEE YS: Behçet's disease with Sweet's syndrome-like presentation--a report of six cases. *Clin Exp Dermatol* 1989; 14: 20-4.
7. HASSIKOU H, TABACHE F, BAAJ M, SAFI S, HADRI L: Sweet's syndrome in Behçet's disease. *Joint Bone Spine* 2007; 74: 495-6.
8. LEE MS, BARNETSON RS: Sweet's syndrome associated with Behçet's disease. *Australas J Dermatol* 1996; 37: 99-101.
9. UYSAL H, VAHABOĞLU H, INAN L, VAHABOĞLU G: Acute febrile neutrophilic dermatosis (Sweet's syndrome) in neuro-Behçet's disease. *Clin Neurol Neurosurg* 1993; 95: 319-22.
10. OĞUZ O, SERDAROĞLU S, TÜZÜN Y, ERDOĞAN N, YAZICI H, SAVAŞKAN H: Acute febrile neutrophilic dermatosis (Sweet's syndrome) associated with Behçet's disease. *Int J Dermatol* 1992; 31: 645-6.
11. MIZOGUCHI M, CHIKAKANE K, GOH K, ASAHINA Y, MASUDA K: Acute febrile neutrophilic dermatosis (Sweet's syndrome) in Behçet's disease. *Br J Dermatol* 1987; 116: 727-34.
12. HORIGUCHI M, HORIGUCHI Y, HOHO T *et al.*: A case of Behçet's disease beginning as Sweet's disease. *Hifukanorinsho* 1983; 25: 1095-101 (in Japanese).
13. SUEHISA S, TAGANII H, INOUE F *et al.*: Colchicine in the treatment of acute febrile neutrophilic dermatosis (Sweet's Syndrome). *Br J Dermatol* 1983; 108: 99-101.
14. COHEN PR, HOLDER WR, RAPINI R: Concurrent Sweet's syndrome and erythema nodosum: a report, world literature review, and mechanism of pathogenesis. *J Rheumatol* 1992; 19: 814-20.
15. VON DEN DRIESCH P: Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol* 1994; 314: 535-56.
16. REUSS-BORST MA, PAWELEC G, SAAL JG, HORNY HP, MULLER CA, WALLER H: Sweet's syndrome associated with myelodysplasia: possible role of cytokines in the pathogenesis of the disease. *Br J Dermatol* 1993; 84: 356-58.
17. GRIFFIN JD, RAMBALDI A, VELLENGA E, YOUNG DC, OSTAPOVICZ D, CANNISTRA S: Secretion of interleukin-1 by acute myeloblastic leukemia cells *in vitro* induces endothelial cells to secrete colony-stimulating factors. *Blood* 1987; 70: 1218-21.
18. BOURKE JF, KEOHANE S, LONG CC *et al.*: Sweet's syndrome and malignancy in the UK. *Br J Dermatol* 1997; 137: 609-13.
19. FUKUTOKU M, SHIMIZU S, OGAWA Y *et al.*: Sweet's syndrome during therapy with granulocyte colony-stimulating factor in a patient with aplastic anemia. *Br J Haematol* 1994; 86: 645-8.
20. WHITE JM, MUFTI GJ, SALISBURY JR, DU VIVIER AW: Cutaneous manifestations of granulocyte colony-stimulating factor. *Clin Exp Dermatol* 2006; 31: 206-7.
21. GLASUDDIN ASM, EL-ORFI AHAM, ZIU MM, EL-BARNAW NY: Sweet's syndrome: is the pathogenesis mediated by helper T cell type 1 cytokines? *J Am Acad Dermatol* 1998; 39: 940-3.
22. SAKANE T, SUZUKI N, NAGAFUCHI H: Etiopathology of Behçet's disease: immunological aspects. *Yonsei Med J* 1997; 38: 350-8.
23. KAWAKAMI T, OHASHI S, KAWA Y *et al.*: Elevated serum granulocyte colony-stimulating factor levels in patients with active phase of Sweet's syndrome and patients with active Behçet's disease: implication in neutrophil apoptosis dysfunction. *Arch Dermatol* 2004; 140: 570-4.
24. MEGE JL, DILSEN N, SANGUEDOLCE V *et al.*: Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects. *J Rheumatol* 1993; 20: 1544-9.
25. FRASSANITO MA, DAMMACCO R, CAFFORIO P, DAMMACCO F: Th1 polarization of the immune response in Behçet's disease: a putative pathogenetic role of interleukin-12. *Arthritis Rheum* 1999; 42: 1967-74.
26. ILHAN F, DEMIR T, TÜRKÇÜOĞLU P *et al.*: Th1 polarization of the immune response in uveitis in Behçet's disease. *Can J Ophthalmol* 2008; 43: 105-8.
27. KELLER M, SPANOU Z, SCHAEERLI P *et al.*: T cell-regulated neutrophilic inflammation in autoinflammatory diseases. *J Immunol* 2005; 175: 7678-86.