Sweet's syndrome in a patient with Crohn's disease

W. Carpels, C. Mattelaer[1], K. Geboes[1], G. Coremans, J. Tack

Department of Internal Medicine Division of Gastroenterology ; (1) Department of Pathology, University Hospital Gasthuisberg University of Leuven, Leuven, Belgium.

Abstract

Crohn's disease is rarely associated with Sweet's syndrome. We report a 32-year old woman who presented with diarrhea, fever and disseminated erythematous plaques on the arms and the trunk. After colonoscopy with biopsies, Crohn's disease was diagnosed. Skin biopsy showed a dense infiltration of neutrophilic polymorphonuclear leukocytes, establishing also the diagnosis of Sweet's syndrome. Crohn's disease is one of several systemic diseases that may underlie Sweet's syndrome. Treatment with methylprednisolone resulted in a rapid improvement of both gastro-intestinal symptoms and skin lesions. (Acta gastroenterol. belg., **1999**, 62, **372-374**).

Key words : inflammatory bowel disease, Crohn's disease, Sweet's syndrome, Neutrophilic dermatosis.

Introduction

Inflammatory bowel diseases can be accompanied by a number of systemic complications, including several skin disorders such as erythema nodosum, pyoderma gangrenosum, aphtous ulcers, vasculitis and epidermolysis bullosa acquisita.

Sweet's syndrome is a neutrophilic dermatosis, characterized by the acute onset of fever and cutaneous lesions ranging from dark red plaques to papules and pustules, mostly on the arms, neck and face. In the majority of patients with Sweet's syndrome, an underlying malignant or inflammatory disease is present (3). Sweet's syndrome has frequently been described in association with ulcerative colitis and, more recently, the association of Sweet's syndrome with Crohn's disease has also been reported (1 to 8). We report on a patient with Crohn's disease who presented with cutaneous lesions, diagnosed as Sweet's syndrome.

Case report

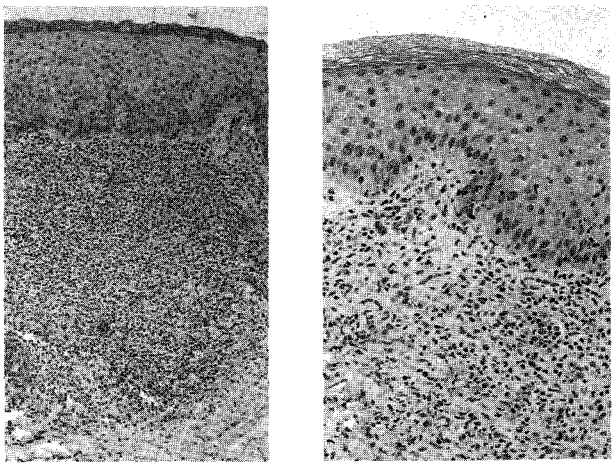
A 32-year old women was admitted to the hospital with symptoms of diarrhea, vomiting, fever and increasing fatigue. Her medical history included schizophrenia and a resection of a lung cyst. The patient had been well until one month earlier, when she developed skin lesions which were characterized by the presence of infiltrated erythematous plaques on both hands and fore-arms. There was a longer standing history of diarrhea, which worsened approximately two weeks prior to admission. She also complained of a sore throat and she developed a high fever (39.3° C).

On admission, the patient's temperature was 38.3° C, the pulse was 96 bpm and the blood pressure was 110/60 mm Hg. Clinical examination revealed skin lesions on both arms and on the trunk and the presence of white plaques in the oropharynx, which were reminiscent of a Candida infection. No lymphadenopathy was found. The abdomen was slightly tender in the umbilical region and in the right lower quadrant. Laboratory studies revealed iron deficiency anemia and signs of inflammation. The hemoglobin level was 8.1 g/dl. The white blood cell count was $7.4*10^9$/l with 55.3% neutrophils. The C-reactive protein serum level was 222.9 mg/l. Stool cultures revealed no pathogenic organisms. A plain abdominal X-ray was normal. Ultrasound examination of the abdomen revealed no abnormalities. A colonoscopy was performed which showed inflammation of the left and right colon with edema and ulceration. The terminal ileum appeared macroscopically normal. Microscopic examination of ileal and colonic biopsies showed a transmucosal and submucosal lymphoplasmocellular inflammatory infiltrate with numerous neutrophilic granulocytes. A diagnosis of Crohn's disease was made and treatment was started with mesalamine, 500 mg t.i.d.

However, after a few days, aphthous ulcers in the throat became apparent. Steroids were withheld because of the uncertainty regarding the diagnosis of the skin lesions. A viral skin rash was thought most likely. Histological examination of the skin biopsy showed a dermal infiltrate composed of both neutrophils and mononuclear cells forming Miescher's granulomes. Focal invasion of the inflammatory cells into the epidermis was seen. There was a marked edema of the upper dermis (Fig. 1). These features are characteristic for a Sweet's syndrome. Laboratory studies at that time were : hemoglobin 9.0 g/dl, white blood cell count $7.7*10^9$/l with 66.7% neutrophils and C-reactive protein 255.1 mg/l.

After the initiation of treatment with methylprednisolone 40 mg I.V., the patient's temperature dropped within 24 hours and there was a rapid improvement of the cutaneous, the mucosal as well as the digestive symptoms.

Postal Address : Jan Tack, M.D., Ph.D., Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.



a b

Fig. 1. — A. Histology shows a dense infiltrate that fills up the entire papillary dermis and that focally invades the epidermis. B. On high power magnification, this infiltrate consists of a mixture of neutrophilic polymorphs and mononuclear histiocytes. Haematoxylin and eosin, original magnification × 125 (a) and × 219 (b).

Discussion

We have described a female patient presenting with diarrhea, high fever and an acute dermatosis, diagnosed as Crohn's disease and Sweet's syndrome. Sweet's syndrome is clinically characterized by the presence of tender red papules, nodules or plaques on the upper extremities, the trunk, the lower extremities, the hands and the face. The skin rash is often associated with fever, increased erythrocyte sedimentation rate, leukocytosis and sometimes arthralgia and arthritis (3). When present, the evolution of joint manifestations parallels that of the skin lesions (3). More rarely, pulmonary involvement, conjunctivitis and episcleritis may also be present (3).

Biopsies of skin lesions in Sweet's syndrome typically show edema and a dense infiltrate of polymorphonuclear leukocytes in the dermis. The epidermis is usually intact, and there are no signs of leukocytoclastic vasculitis. Siu and Liu have proposed criteria to diagnose Sweet's syndrome (9). These are summarized in table 1. One major and two minor criteria are needed for a definite diagnosis of Sweet's syndrome. Our patient furfilled six of the seven proposed criteria.

About 50% of the patients with Sweet's syndrome have an underlying systemic disorder. Ten to 15% of known cases of Sweet's syndrome occur in patients with an underlying malignancy, very oßen acute myelogenous leukemia (3,7,10). Sweet's syndrome has also been reported in association with chronic non-malignant diseases such as Sjogren's syndrome, Behcet's disease, rheumatoid arthritis, ulcerative colitis, subacute lupus erythematosus, subacute thyroid gland pathology and various infectious diseases (2,3,7,10). Some cases of Sweet's syndrome appear to be drug-related (3).

More recently, the association of Sweet's syndrome and Crohn's disease has also been reported (8). The fact that Sweet's syndrome is most often a cutaneous manifestation of underlying disease makes a chance association less likely. Moreover, Sweet's syndrome is related to other neutrophilic dermatoses which have been associated with Crohn's disease, such as pyostomatitis vegetans, subcorneal pustular dermatosis and vesiculo-pustular eruption. From the reported cases, a predilection for female patients and colonic involvement of Crohn's disease seems apparent (8). The relationship to Crohn's disease activity is still unclear. In some cases, the clinical course of the cutaneous manifestations parallels intestinal disease activity (3,6). Although it is generally assumed that chronic inflammatory bowel disease is the triggering factor and that the skin lesions occur secondarily, the possibility that both the cutaneous and the intestinal inflammation are two expressions of the same reaction pattern to an unknown stimulus cannot be discarded.

The pathogenesis of Sweet's syndrome is unknown. Sweet's syndrome is frequently associated with HLA type Bw54, which suggests some immunogenetic predisposition. However, involvement of non-immunological pathways, such as toxins originating from the intestinal tract, cannot be excluded. Neutrophils represent about 90% of the cellular infiltrate in the early lesions of Sweet's syndrome. Hence, the pathogenesis of Sweet's syndrome may parallel the pathophysiological mechanisms of the remote inflammatory reaction, e.g. the gastrointestinal tract in inflammatory bowel disease. During inflammation, mature polymorphonuclear cells adhere to the vascular endothelium, and then migrate into the inflamed tissue.

Unfortunately, factors that influence migration of neutrophils into the skin are poorly understood, and there are conflicting data on neutrophil function and cytokine or complement levels in Sweet's syndrome (6,10-13). It has been suggested that anti-neutrophil cytoplasmic antibodies could be a marker for Sweet's syndrome, but others could not confirm this (6,8,12). Activation, recruitment and proliferation

Table 1. — **Diagnostic criteria for Sweet's syndrome**

Major criteria :
- Abrupt onset of tender or painful erythematous plaques and nodules.
- Predominantly neutrophilic infiltration in the dermis without leucocytoclastic vasculitis.
Minor criteria :
- Symptoms preceded by fever or infection.
- Symptoms are associated with fever, arthralgia, conjunctivitis or underlying malignancy.
- Leukocytosis > 10*10 9/l
- ESR > 50 mm/h
- Good clinical response to systemically administered steroids, and not to antibiotics.

of neutrophils can be triggered by cytokines like IL-1 and IL-6. The associated systemic manifestations (fever, arthralgia, leukocytosis,...) could also be induced by these and other cytokines. It has been suggested that the production of IL-1 by neoplastic mononuclear cells might play a role in the induction of leukemia-associated Sweet's syndrome (14). The effects of IL-1 are partially mediated by granulocyte-colony stimulating factor (G-CSF), another candidate cytokine involved in the pathogenesis of Sweets' syndrome. This is supported by the observation that Sweet's syndrome has been described as a complication of G-CSF therapy and by the frequent association between Sweet's syndrome and hematological malignancies. G-CSF may in turn promote the secretion of the pro-inflammatory cytokine IL-6.

In our patients, as in literature, we observed a good response to corticosteroids. The cutaneous lesions became inactive in the first week of steroid therapy, and no new lesions appeared. The manifestations of Crohn's disease also responded favorably to this treatment.

In conclusion, Crohn's disease is one of the underlying disorders present in patients diagnosed with Sweet's syndrome. Inflammatory bowel disease should be excluded in patients presenting with Sweet's syndrome and diarrhea. Alternatively, Sweet's syndrome should be considered as a diagnosis when a patient with Crohn's disease develops skin lesions.

References

1. LY S., BEYLOT-BARRY M., BEYSSAC R. Syndrome de Sweet associé à une maladie de Crohn. *Med. Interne*, 1995, **16** : 931.
2. KEMMET D., GAWKRODGER D., WILSON G. Sweet's syndrome in Crohn's disease. *BMJ*, 1988, **297** : 1513.
3. BECUWE C., DELAPORTE E., COLOMBEL J. Sweet's syndrome associated with Crohn's disease. *Acta. Derm. Venereol.*, 1989, **69** : 444.
4. SITJAS D., PUIG L. Acute febrile neutrophilic dermatosis (Sweet's syndrome). *Int. J. Dermatol.*, 1993, **32** : 261.
5. BEITNER H., NAKATANI T., HAMMAR H. A case report of acute neutrophilic dermatosis (Sweet's syndrome) and Crohn's disease. *Acta. Dermatol. Venereol.*, 1991, **71** : 360.
6. ACTIS G., LOGGET M., CIANCIO A. Recurrent Sweet's syndrome in reactivated Crohn's disease. *J. Clin. Gastroenterol.*, 1995, **21** (4) : 317.
7. VON DEN DRIESCH P., SCHLEGEL R., KIESEWETTER F. Sweet's syndrome : clinical spectrum and associated conditions. *Cutis*, 1989, **44** : 193.
8. TRAVIS S., INNES N., DAVIES M. Sweet's syndrome : an unusual cutaneous feature of Crohn's disease or ulcerative colitis. *Eur. J. Gastroenterol. Hepatol.*, 1997, **9** : 715.
9. SU W.P.D., LIU N.H.N. Diagnostic criteria for Sweet's syndrome. *Cutis*, 1986, **37** : 1670-174.
10. VON DEN DRIESCH P. Sweet's syndrome. *J. Am. Acad. Dermatol.*, 1994, **31** : 535-556.
11. SITJAS, D., PUIG L., CHATRECASAS M. *et al.* Acute febrile neutrophilic dermatosis (Sweet's syndrome). *Int. J. Dermatol.*, 1993, **32** : 261-268.
12. NUNZI E., CROVATO F., DALEGRI F. *et al.* Immunopathological studies on a case of Sweet's syndrome. *Dermatologia*, 1981, **163** : 393-400.
13. OSEROFF A.R., ADLER L., MALLOY M., *et al.* Neutrophil abnormalities in a patient with Sweet's syndrome. *J. Invest. Dermatol.*, 1981, **76** : 331.
14. GOING J.J. Is the pathogenesis of Sweet's syndrome mediated by Interleukin-1 ? *Br. J. Dermatol.*, 1987, **116** : 282-286.