Regression of Sweet's syndrome associated with Crohn's disease after anti-Tumour Necrosis Factor therapy

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Abstract

The association of inflammatory bowel disease and acute febrile neutrophilic dermatitis (Sweet's syndrome) has infrequently been reported in the literature.

We describe the case of a 41-year-old Caucasian woman with ileo- anal Crohn's disease who presented simultaneously an erythema nodosum and a Sweet's syndrome.

A dramatic regression of the cutaneous lesions was observed after infliximab treatment, indicating that this therapy might be useful for both Crohn's disease and Sweet's syndrome. (Acta gastroenterol. belg., **2005**, 68, **376-379**).

Key words : Sweet's syndrome, Crohn's disease, anti-TNF therapy.

Introduction

Systemic complications of inflammatory bowel diseases (IBD) are well known.

Skin manifestations are observed less frequently than rheumatologic symptoms but are more prevalent than ophthalmic and hepato-biliary complications.

Among muco-cutaneous lesions, aphtous ulcers are common (10%), followed by erythema nodosum (5-10%) and neutrophilic dermatitis which includes pyoderma gangrenosum, Sweet's syndrome and less common disorders (1).

We report the infrequent association of Sweet's syndrome and Crohn's disease, and the improvement of skin lesions after anti-TNF alpha treatment.

Case report

A 41-year-old Caucasian woman with a history of ileal Crohn's disease since 1970 was admitted to the hospital in October 2002 because of vesiculo-bullous lesions on the upper limbs and the back.

An appendectomy and a cure of anal fistula had been performed in 1982.There was no familial history of IBD and the patient was a non smoker. The current treatment included mesalazin (Colitofalk®) 500 mg four times daily and budesonide (Budenofalk®) 3 mg four times daily but she had received several courses of oral corticosteroid between January and May 2002 because of flare-up of the disease (methylprednisolone 32 mg daily for 3 weeks with progressive reduction until March 2002 when the dose had to be increased from 8 mg to 16 mg daily which was maintained until June) ? In July 2002, she developed typical lesions of erythema nodosum on both legs, which disappeared spontaneously.

In September, she had three to four soft stools daily, without diarrhoea, rectal bleeding or maelena. Simultaneously, she noticed a stinky vaginal discharge, independent of her periods.

The week prior to admission, numerous oral aphtae appeared as well as skin lesions characterized by infiltrated erythematous plaques on the upper limbs and the back. She also complained of pain at the lumbar column, left shoulder and right elbow. There was no fever.

There was no loss of appetite and the weight was stable.

On admission, her weight was 74 kg and her height 174 cm (BMI : 24,4 kg/m^2). Body temperature was 36.3°C, pulse rate 80 bpm and blood pressure 130/90 mm Hg.

Clinical examination revealed numerous oral aphtae (more than five) measuring each about five mm in diameter. The abdomen was normal and peristaltism was present. Two cutaneous ulcerations were observed in the perianal area. Ophthalmologic examination revealed a bilateral and ulcerated conjunctivitis. Skin lesions were of two types. Tender, erythematous and violaceous nodules were seen on both legs corresponding to typical erythema nodosum.

Moreover, a bullar and vesicular eruption stand on both upper limbs, posterior aspects of the arms and the top of the back (Fig. 1).

Pertinent laboratories findings were : serum C- reactive protein 17 mg/dl (Nl < 0.8) and fibrinogen 800 mg/dl (Nl : 150-400). Hemoglobin level was 9.5 g/dl with a mean corpuscular volume of 70 m^3. Leucocytosis was 9200 /ml with 7500 neutrophils.

The abdominal CT scan and ultrasound examinations showed a thickening of the ileocaecal and rectal wall and an infiltration of the perirectal fat with satellite lymphadenopathy, without ascite or abscess. Bubbles of air were seen in the uterus. A barium follow-through revealed a sub-stenosis with no prestenotic dilatation just above the Bauhin's valvule.

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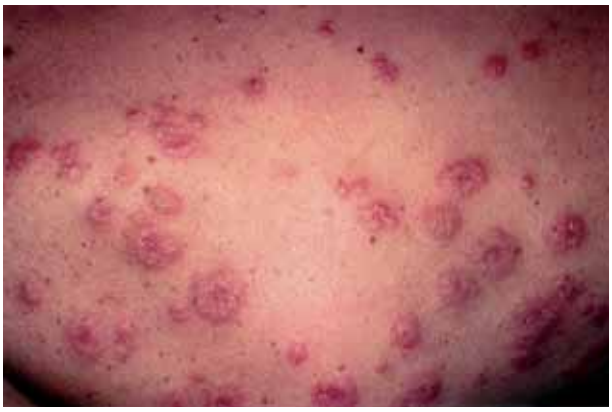

Fig. 1. — Bullo-vesicular lesions of the back corresponding to neutrophilicdermatosis (Sweet's syndrome).

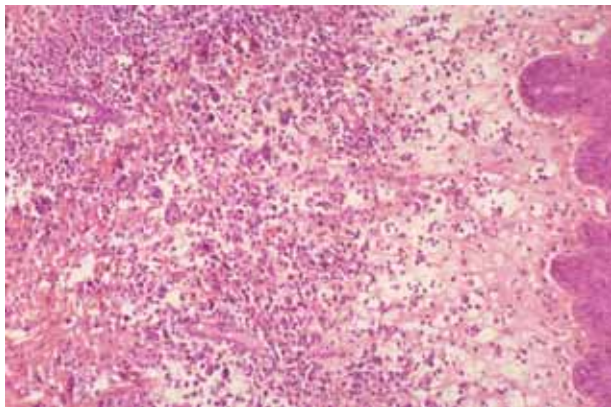

Fig. 2. — Diffuse neutrophilic infiltration of the superficial dermis.

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A rectosigmoidoscopy showed an inflammatory zone in the anterior rectal face with two fistula openings and a sigmoid ulcerated mucosa.

Histology of the vesicular lesions confirmed the clinical diagnosis of Sweet's syndrome (Fig. 2).

We concluded to ileocolic Crohn's disease, complicated by a rectovaginal fistula and associated with several systemic manifestations including Sweet's syndrome.

A course of antibiotics was initiated (ciprofloxacine 500 mg twice a day and metronidazole 1.5 g per day). The fistula and the recurrence of the illness despite corticosteroid treatment led us to initiate an anti-TNF alpha therapy (Remicade® 375 mg/ cure) associated with azathioprine (100mg per day). Skin lesions resolved in two days .Three courses of Remicade® were administred over a six- week period. One year later, she remained in remission on azathioprine 100 mg/day. Symptoms due to the rectovaginal fistula had largely improved and she had gained three kilos. No surgery was performed.

Discussion

The association of Sweet's syndrome and IBD is rare. Up to 1997, about 30 cases had been reported in the literature, mainly associated with Crohn's disease (ratio Crohn's disease /ulcerative colitis 3:2) (2).

Acute febrile neutrophilic dermatitis, first described in 1964 by Robert Douglas Sweet, is characterized by raised erythematous plaques with pseudoblistering ; occasionally pustules occur on the face, neck, chest and extremities, accompanied by fever and general discomfort.

Involvement of eyes, joints, and oral mucosa as well as visceral manifestations (lung, liver, kidneys, and central nervous system) have been described. Arthralgias or arthritis occur in 33% to 62% of patients, affecting mainly hands, wrists, ankles, knees, and shoulders.

Conjunctivitis and episcleritis are reported in approximately one third of patient but other ocular disorder have been observed (uveitis, limbal nodules, inflammatory glaucoma).

Lung involvement has often been reported in patients with an underlying haematologic disorder (3).

Interestingly, Fain et al described a colic involvement distinct from IBD (4). Marie *et al* reported a focal aseptic osteitis underlying neutrophilic dermatosis in a patient with Crohn's disease (5).Finally aseptic skin abscesses may result from a deep localization of neutrophilic disease and have been associated to Crohn's disease (6).

Sweet's syndrome is associated with inflammatory (Behcet's disease, Sjögren's syndrome, systemic lupus erythematosus, thyroiditis, rheumatoid arthritis,) and neoplastic haematological disorders (myelodysplasia, myelofibrosis, acute leukaemia, multiple myeloma) in approximately 25% of cases, and 2% occur in pregnancy (3).

Some medications (celecoxib, granulocyte colony-stimulating factor, nitrofurantoine, furosemide) are also held responsible of the syndrome (7).

On physical examination, the plaques are erythematous, non pruritic and painful. Their size can vary from few to ten centimeters and are located as mentioned above. The surface of these plaques may exhibit a mamillated appearance with pseudovesiculation, pseudopustulation, and pustules. They are red to blue-red, with a faint central white-yellow discoloration leading to the impression of a target lesion similar to erythema multiforme. On the lower legs, lesions resembling erythema nodosum are common and almost indistinguishable (3). However, patients presenting simultaneously Sweet's syndrome and erythema nodosum have been reported (8,9,10). Moreover, the histology of those two lesions may be very similar.

Su and Liu proposed clinical and biological diagnostic criteria of Sweet's syndrome.

Later, minor criteria were reviewed by von den Driesh (3) (Table 1). In our case, the two major criteria and 2 minor criteria were met, allowing the diagnosis.

Table 1. — **Diagnostic criteria initiated by Su and Liu for the diagnosis of Sweet's syndrome (3)**

Major criteria
1. abrupt onset of tender or painful erythematous plaques or nodules occasionally with vesicles, pustules or bullae.
2. Predominantly neutrophilic infiltration in the dermis without leukocytoclastic vasculitis.

Minor criteria
1. Preceded by a nonspecific respiratory or gastrointestinal tract infection or vaccination or associated with :
   – Inflammatory diseases such as chronic autoimmune disorders, infections
   – Hemoproliferative disorders or solid malignant tumors
   – Pregnancy
2. Accompanied by periods of general malaise and fever (> 38°C).
3. Laboratory values during onset : ESR > 20 ; C-reactive protein positive ; segmented-nuclear neutrophils and stabs > 70% in peripheral blood smear ; leukocytosis > 8000 (three or four of these values necessary)
4. Excellent response to treatment with systemic corticosteroids or potassium iodide.

The two major criteria and two minor criteria are needed to establish the diagnosis.

Multiple diagnosis should be evoked by the clinician in the face of vesicular and pustular lesions in a patient with Crohn's disease. The erythema elevatum diutinum associate signs of vasculitis to papulopustular lesions. A cutaneous metastasis will be easily diagnosed by histology (11). Classic pyoderma gangrenosum is clinically easy to distinguish but simultaneous occurrence of Sweet's syndrome and pyoderma gangrenosum may be confusing (3). Crickx *et al.* reported a patient with Crohn's disease associated to multiform erythema mimicking a Sweet's syndrome (12). Finally the bowel bypass syndrome presents clinical and histological similarities with the Sweet's syndrome (13).

Although both genders are equally affected by IBD, 90 percent of the reported cases who suffered from both Sweet's syndrome and Crohn's disease were young females (14). On the other hand, regardless of the etiology, females are more often affected than men by Sweet's syndrome (sex ratio of 3,7/1) (3). Colonic and perianal area are most often affected (14) but ileocolic involvement has been described (2,11,15-18). Travis et al reported 20 cases of Crohn's disease associated with Sweet's syndrome of whom 40% presented fistula (2). The appearance of Sweet's syndrome usually follows the onset of Crohn's disease but may precede the intestinal symptoms, even by several years (14). The relationship between the appearance of Sweet's syndrome and the activity of Crohn's disease has been largely debated. However, 80 percent of the patients identified by Travis *et al.* (2) had a recurrence of the intestinal illness as in our case.

Sweet's syndrome responds rapidly to systemic therapy with corticosteroids but recurs in about 25% of the cases. Alternative treatments (e.g. potassium chloride, colchicine, dapsone, ciclosporine) have also been used (3). Most cases of Sweet's syndrome associated to Crohn's disease reported in the literature responded favourably to corticosteroid treatment. Metronidazole, known to be effective for the treatment of perianal Crohn's disease, has been used successfully once to treat a patient with Sweet's syndrome and Crohn's disease not controlled by dapsone, colchicine and systemic corticosteroid (19).

The anti-TNF alpha agent (infliximab) is a chimeric monoclonal antibody, composed of a complement-fixing human IgG constant region and a murine-derived antigen-binding variable region (20). Unless important questions remain to be addressed to define the most appropriate use of infliximab, the efficacy of the drug is largely proved in patients with perianal and cutaneous fistulas (21). Recently, the efficacy of infliximab to treat cutaneous manifestations of Crohn's disease has been observed. Vanbiervliet *et al*. (10) reported the improvement of cutaneous (Sweet's syndrome) and intestinal lesions on a corticoresistant Crohn's disease rapidly after the initiation of anti-TNF alpha therapy. To our knowledge, this is the second report of complete resolution of a Sweet's syndrome associated to Crohn's disease with infliximab. Among patients with Crohn's disease, 8 cases of pyoderma gangrenosum have also been treated successfully with infliximab (22-26). Lastly, Konrad *et al.* (27) reported the significant improvement of cutaneous and metastatic lesions in a corticoresistant Crohn's disease under infliximab. In conclusion, Crohn's disease is rarely associated with Sweet's syndrome and anti-TNF alpha therapy may be useful to treat both the cutaneous and intestinal lesions.

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