

CLINICAL NOTE

## Crohn's disease and Sweet's syndrome: an uncommon association

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### ABSTRACT

Sweet's syndrome or acute febrile neutrophilic dermatosis (SS) is characterized by the sudden onset of painful erythematous lesions (papules, nodules, and plaques) together with fever and neutrophilia. The lesions are typically located on hands, arms, upper trunk, neck and face, showing an asymmetric distribution. Acute phase reactants are usually elevated and dermal infiltration of neutrophils without vasculitis is seen on skin biopsies. It is considered as a marker of systemic disease in over half of the cases, and is associated with infections, inflammatory bowel disease, autoimmune connective tissue disorders and various neoplasias.

Its association with Crohn's disease (CD) is unusual and it appears mainly in association with colonic involvement. Fewer than 50 cases have been published in the medical literature since its first description in 1964, some concurrent with the first episode of CD. We present two patients with Crohn's disease and Sweet's syndrome diagnosed in our department at the time of CD diagnosis, as well as their response to treatment, subsequent course of the disease, and a review of the scientific literature.

**Key words:** Crohn's disease. Sweet's syndrome. Neutrophilic dermatosis.

### RESUMEN

El síndrome de Sweet o dermatosis neutrofílica febril aguda (SS) se caracteriza por la aparición brusca de lesiones eritematosas, (pápulas, nódulos y placas) dolorosas, junto con fiebre y neutrofilia, siendo de presentación poco frecuente. Las lesiones se localizan preferentemente en manos, brazos, parte superior del tronco, cuello y cara, con distribución asimétrica. Suele haber elevación de reactantes de fase aguda y en las biopsias cutáneas se identifica una infiltración dérmica de neutrófilos sin vasculitis. Se considera un marcador de enfermedad sistémica en más de la mitad de los casos, asociándose a infecciones, enfermedad inflamatoria intestinal, conectivopatías autoinmunes y diversas neoplasias.

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Su asociación con la enfermedad de Crohn (EC) es poco habitual, asociado sobre todo a afectación colónica. Se han publicado menos de 50 casos en la literatura médica desde su primera descripción en 1964, algunos de ellos simultáneos con el primer brote de la EC. Presentamos dos pacientes con enfermedad de Crohn y síndrome de Sweet diagnosticados en nuestro servicio en el momento del diagnóstico de la EC, así como su respuesta al tratamiento, evolución posterior y revisión de la literatura científica.

**Palabras clave:** Enfermedad de Crohn. Síndrome de Sweet. Dermatitis neutrofílicas.

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### INTRODUCTION

*Sweet's syndrome* (SS) or acute febrile neutrophilic dermatosis was described for the first time by R.D. Sweet (1) in 1964. It is characterized by the sudden onset of painful erythematous lesions (plaques, nodules or papules), accompanied with fever, general malaise, and leukocytosis with neutrophilia. They are most frequently located on the face, neck, upper trunk, arms and hands, and are asymmetrically distributed. The characteristic histologic pattern is the presence of a dense infiltrate of neutrophils in the mid upper dermis, accompanied by intense edema, with leukocytoclasia and no vasculitis (2,3). A series of diagnostic criteria have been proposed for its diagnosis, those published by Su et al. (4) (Table I) being the ones which are used most frequently.

**Table I. Sweet's syndrome diagnostic criteria***Major criteria:*

- Sudden onset of plaques, or erythematous or violet and painful nodules
- Dermal infiltration of polymorphonuclear neutrophils without leukocytoclastic vasculitis

*Minor criteria:*

- Preceded by infections, vaccination, inflammation or associated with inflammation, hemoproliferative disorders, solid tumors or pregnancy
- Periods of fever (above 38 °C)
- Leukocytosis with neutrophilia, CRP and ESR increase
- Good response to systemic corticosteroids

A diagnosis of SS is made when two major criteria and at least two of the minor criteria are present

From Su et al. (4).

Sweet's syndrome is often associated with other diseases: infections, inflammatory diseases, connective tissue disorders and various neoplasias, especially of hematologic origin (5). The association with Crohn's disease (CD) is uncommon, appearing in most cases in patients with colonic involvement of the disease, and predominantly in females (6). Cases have been described in long-term evolution CD patients, and, less frequently, in patients at the onset of the disease (7-9). Some authors consider that it must be taken into account, in spite of its low incidence, as one of the extraintestinal skin manifestations of CD (6,10).

We present two cases, diagnosed in our department, in which the presence of SS coincided with the first episode of CD, as well as the treatments used and the course of their disease.

## CASE REPORTS

### Case 1

Fifty six year old male with a history of duodenal ulcer at the age of 18, COPD (non-smoker for the past three years, previously two packs of cigarettes/day). Operated of hypertrophic anal papilla in 2007 with perianal fistula and early recurrence.

Admitted for presenting diarrhea with 8-10 daily soft-liquid stools, some bloody, diurnal and nocturnal, ongoing for two months, that partially remitted following treatment with oral Ciprofloxacin. On the days prior to admission, there is a clinical worsening with bloody mucorrhea (6-8 stools/day), hypogastric pain and intense proctalgia. Over the last month he suffers from increasing asthenia and febrile episodes, mainly in the evenings, of up to 38.5 °C over the last week. Active perianal fistulas or suppuration were not present.

Following admission, there is evidence of sudden onset of pustule-like erythematous inflammatory lesions on plaques, on the arms and dorsum of both hands, with an umbilicated centre, painful, and asymmetrically distributed (Fig. 1). Upon rectal examination the presence of complicated perianal disease with two inactive fistulous orifices, hemorrhoidal skin tags and acute midline fissure stand out.



Fig. 1. Subcutaneous erythematous nodules on palms.

Laboratory results show iron-deficiency hypochromic microcytic anemia, without leukocytosis, and with normal coagulation, with GGT of 203 mU/ml, CRP: 248 mg/l and ESR: 120 mm/h of note. Blood and stool cultures were negative.

Abdominal ultrasound describes thickening of the walls of the sigma, confirmed by abdominal CT scan which also reveals thickening of the transverse colon and cecum, with multiple adenopathies in iliac vessels, with no free fluid. In the colonoscopy, the rectal mucosa appears to be edematous and erythematous, with pseudopolypoid formations extending through most of the colon, with interspersed areas of preserved mucosa. The ileum is macroscopically normal. Colonic biopsies confirm the presence of ulceration and chronic inflammation, with no evidences of granulomas.

The patient is assessed by the Dermatology Department. A skin biopsy of the hypothenar eminence of the hand evidences the presence of neutrophilic infiltrate with dermal edema, with no evidence of vasculitis, confirming the diagnosis of neutrophilic dermatosis (ND) (Fig. 2).

Therefore, the patient is diagnosed of: a) colonic Crohn's disease with an episode of moderate activity with CDAI: 345 (disease onset), and perianal disease (PAD), Montreal classification: A3 L2 B1p; and b) Sweet's syndrome, meeting the accepted criteria.

Treatment was initiated with fluid therapy, methylprednisolone (60 mg/i.v./24 h), antibiotic therapy (ciprofloxacin

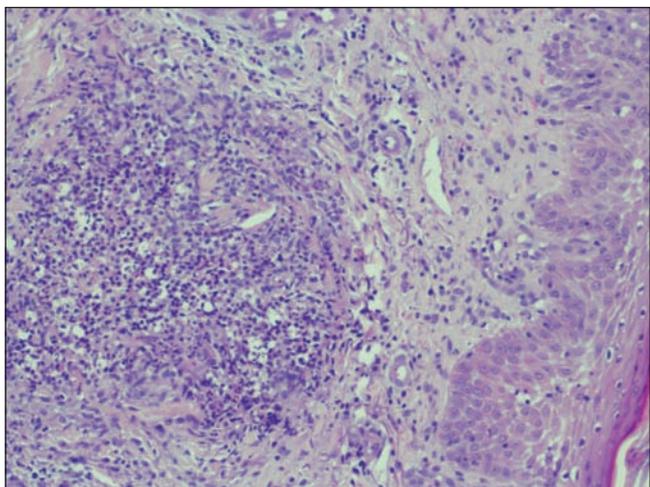


Fig. 2. Skin biopsy (X100). Epidermis with spongiosis and predominantly perivascular inflammatory infiltrate in which neutrophils stand out.

400 mg/i.v./12 h and metronidazole 1,500 mg/i.v./24 h), enteral nutrition and mesalazine (3 g/per os/24 h), with a very good clinical response. The fever disappeared in 48 h, and the abdominal discomfort and diarrhea disappeared over a few days.

Topical beclometasone was associated as treatment of the skin lesions. The size of the lesions decreased, with the local discomfort diminishing after three days of treatment. The patient was discharged with tapering doses of oral prednisone, and disappearance of the papules was verified after 6 weeks, with no evidence of scarring or cutaneous sequelae.

## Case 2

Thirty four year old female, smoking 10 cigarettes/day, tonsillectomized. Previous admission to Internal Medicine as a result of weight loss, general malaise and fever, with normocytic anemia, acute phase reactants and alkaline phosphatase increase, and hypoalbuminemia, which was labeled as fever of unknown origin.

Previously asymptomatic, is admitted into the Digestive Department in April 2009 as a result of abdominal pain lasting for one month with 4-6 daily semi-fluid stools, without blood or mucous, occasionally at night. Weight loss of 6 kg during that month, and fever up to 39 °C with breakdown of the general health status.

During the 10 days prior to admission, erythematous, pruriginous lesions of up to 2 cm in diameter appear, evolving into umbilicated pustules on upper extremities and trunk (Figs. 3 and 4). There are no articular or ocular manifestations. Laboratory results point out normocytic-normochromic anemia, leukocytosis with neutrophilia, and ESR (84 mm/h) and CRP (168 mg/l). Stool cultures and test for parasites were negative.

Colonoscopy revealed patchy erythematous areas 35 cm from the anal margin up to the right colon, with mucus bridges and serpiginous ulcers, the mucus between these being healthy. The abdominal CT scan confirmed the inflammation of the colon wall, and a circumferential thickening of the terminal ileum with reactive adenopathies. Histopathology showed an intense chronic inflammatory activity, with no granulomas.

Skin biopsies evidenced intense edema of the papillary dermis, spongiotic changes in the epidermis, and a dense inflammatory infiltrate in the reticular dermis with a predominance of leukocytes, all of which compatible with neutrophilic dermatosis (Fig. 5).

The patient was therefore diagnosed of ileocolic Crohn's disease with an inflammatory pattern (Montreal classification: A2L3B1) and moderate activity (CDAI:310), and of Sweet's syndrome.

Following initiation of corticosteroids (methylprednisolone 60 mg/i.v./24 h), antibiotic therapy (ciprofloxacin 400 mg/i.v./24 h and metronidazole 1,500 mg/i.v./24 h),



Fig. 3. Extensive bullae filled with clear fluid surrounded by inflammatory halo.



Fig. 4. Erythematous papules and bullae on upper chest.

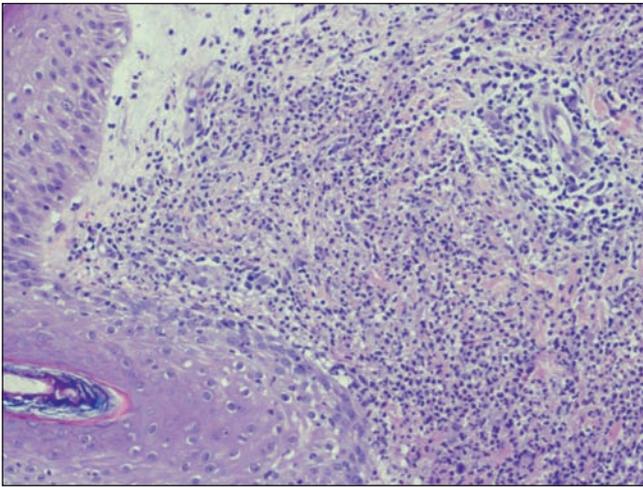


Fig. 5. Skin biopsy x100: dermal spongiosis, edema in dermis and intense neutrophilic infiltrate.

mesalazine (3 g/per os/day) and the usual measures, the patient's symptoms improved significantly during admission, the skin lesions becoming more isochromic, painless and smaller after 7 days of treatment. During follow-up in the Outpatient Clinic, their disappearance was evidenced after 2 months of treatment with tapering doses of corticosteroids, and the patient showed complete clinical remission.

After 6 weeks of being asymptomatic, she noticed a progressive worsening of her general health status, with high fever, abdominal pain, asthenia, 5 kg weight loss, and diarrhea with no pathological signs. Skin lesions of similar characteristics appeared again, with raised papules on well delimited, erythematous, painful, asymmetrically distributed plaques on the neck, chest and arms, with a noticeable, well delimited, 2 cm papule-pustule with a slight central excavation on the left cheek. She reported generalized arthralgias over the past week, with redness, edema, increase of local heat and functional impotence of the right elbow. She was assessed by Rheumatology and monoarthritis of the elbow was confirmed, and local measures and symptomatic treatment were prescribed.

Normocytic anemia (Hb: 10.3 g/dl), leukocytosis with left deviation and thrombocytosis, ESR of 40 mm/h and CRP of 194 mg/l were evidenced, with a negative rheumatoid factor. Abdominal ultrasound confirmed an increase in the colonic parietal thickness, predominantly in the right colon and cecum, and an important increase in vascularization. Stool cultures and *Clostridium difficile* toxin were negative, and the skin biopsy showed an important leukocytic infiltrate with dermal edema, compatible with neutrophilic dermatosis.

As an episode of Crohn's disease with monoarthritis, and a new episode of Sweet's syndrome were suspected, corticosteroid parenteral therapy (methylprednisolone 60 mg/i.v./24 h) and ciprofloxacin plus metronidazole i.v.

were initiated, obtaining a symptomatic response within 48 hours. Articular manifestations and skin lesions improved progressively although total disappearance of the skin lesions was evidence at 4 weeks, with only a slight desquamatory redness remaining at the base of the lesion which subsequently disappeared completely.

## DISCUSSION

Sweet's syndrome (SS), also known as acute febrile neutrophilic dermatitis, is an uncommon disease of unknown origin that was described in 1964 (1). Its importance resides in its marked clinical expressiveness and its frequent association with other systemic diseases. Its pathogenesis is unknown although certain mechanisms of the disease have been put forward: a) type III hypersensitivity reaction; b) T lymphocyte dysfunction; c) alteration of the neutrophil function in the immune response; or d) associations with determined histocompatibility antigens such as Bw54 (2,11,20). Regulatory alterations of certain proinflammatory cytokines (IFN gamma, IL1, IL3, IL6 or IL8) have been shown (3). The onset of cases of SS following the administration of the granulocyte colony stimulating factor (G-CSF), and the presence of elevated serum levels of this cytokine in some SS patients have emphasized its potential role in the development of SS (12).

Clinically, it is characterized by the sudden onset of multiple tender or painful erythematous lesions (plaques, nodules or papules) accompanied by fever and breakdown of the general health status with neutrophilic leukocytosis. Occasionally, these lesions may present a pale appearance in the center as a result of the intense edema, or they may evolve into pseudovesicles or real pustules. They are most frequently found on the face, neck, upper trunk, arms and hands, and are asymmetrically distributed (5). Its characteristic histologic pattern is the presence of a dense infiltrate of neutrophils located in the upper half of the dermis, accompanied by an important edema, with leukocytoclastia, without vasculitis (3). The description of skin alterations in both patients coincides with this spectrum of lesions, both cases being of sudden onset, with multiple and asymmetrical lesions predominantly on the upper half of the body. Articular involvement is common (37-51% of cases) in the form of arthralgia or, more uncommonly, arthritis. There may be ocular involvement in the form of conjunctivitis or episcleritis, and pathergy similar to what happens in 8% of the cases of pyoderma gangrenosum has been described (2). In addition to leukocytosis with neutrophilia, there is an increase of the acute phase reactants (ESR and CRP), more notable when it is associated with CD, together with a potential relative increase in CRP in these cases.

Five subgroups of SS have been described: a) idiopathic (70% of cases); b) parainflammatory (16%); c) paraneoplastic (especially in acute myeloid leukemias or other malignant hematologic neoplasias); d) drug-induced (the drug

most frequently involved is the G-CSF); and d) SS associated with pregnancy (3). The criteria proposed by Su et al. (4) are used (Table I) to make the definite diagnosis of SS.

Sweet's syndrome is rarely associated with inflammatory bowel disease (IBD). Benton et al. described its association with ulcerative colitis (UC) for the first time in 1985 (15). Since then, several authors have reproduced this association through the publication of isolated cases (16-18). The association with Crohn's disease is less common, with fewer than 40 cases described in the literature. Kemmet et al. described, for the first time, two women with SS and granulomatous colitis.

There is a predominance of females in the cases described which, in some series, have reached up to 87%, with an age ranging from 25 to 63 years old (7). Colonic involvement is practically constant, occasionally with perianal involvement, with no involvement of the small intestine alone having been described to date. This observation coincided with the works of Greenstein et al. (19), who indicated a greater incidence of extraintestinal manifestations when there was colonic involvement of the disease. The two patients described showed lesions in the colon, one of them with, in addition, perianal involvement, and the other one with ileocecal location.

Frequently, this type of SS is associated with other extraintestinal manifestations. Articular involvement has been described in more than half of the patients with CD and SS, with the presence of clear arthritis such as the one described in our patient being uncommon (25% of cases approximately) (2,13,14). One quarter of the patients have associations with ocular alterations (mainly conjunctivitis, episcleritis and iritis), or other skin manifestations, erythema nodosum (EN) being the most common one (2,6,9,10). This association is of clinical importance as we must think that, in a patient presenting with an episode of CD and skin lesions, various neutrophilic dermatoses may coexist (e.g. pyoderma gangrenosum and SS) or they may appear together with other more common lesions such as erythema nodosum. The absence of dermal necrosis may distinguish between PG and SS, as well as the appearance of lesions on the upper half of the body in a multiple and asymmetrical manner, may point to SS in patients with concurrent EN (20,28).

Sweet's syndrome appears concurrently with the episode of CD (75% of the cases) although in 20% of the cases, SS may precede the digestive symptoms (10), or it may occur up to 30 years after the diagnosis of CD (20). Our patients presented SS concurrent with a first episode of CD, which occurs in one third of the patients described in the literature.

After the diagnosis of CD and SS, our patients were treated with high doses of endovenous corticosteroids, and antibiotic therapy with ciprofloxacin and metronidazole, obtaining a good response. Steroids at a dose equivalent to prednisone 1 mg/kg/day, and subsequent tapering doses have shown to be very effective in the treatment of skin lesions which disappear after a few weeks without

scarring in practically all the cases described (2,3,5). The association with metronidazole may have an additional effect in the treatment of SS, its usefulness per os having also been described (14). Our patient had a recurrence of SS concurrent with a new episode of CD. This uncommon possibility is remarked upon in other published cases (21,22). Re-treatment with both drugs over a few weeks was very effective.

Other treatments for SS such as dapsone, potassium iodide, doxycycline or pentoxifiline have been described, obtaining worse results, especially in recurring cases (2,9). Good results have been published with some immunosuppressants such as tacrolimus in cases of corticosteroid refractory ulcerative colitis, or more recently, with anti-TNF agents such as infliximab, with a good clinical response (23-25). It is useful to remind the fact that some drugs used for the maintenance of remission in CD patients such as azathioprine, may cause drug-induced SS, and therefore this possibility must be investigated in patients with compatible dermal lesions following initiation of these treatments (26,27).

We can conclude that SS is an uncommon disease that may be associated with CD, and must be part of the differential diagnosis of associated skin lesions. When associated with CD, it is more common in women, there is usually colonic involvement, and the coincidence with an episode of the disease is frequent. The presence of typical SS lesions in a patient with no prior history of digestive diseases may justify the conduct of studies (especially colonoscopy given the frequent colonic involvement) to rule out the presence of inflammatory bowel disease. Treatment with steroids, associating metronidazole in certain patients, obtains a rapid clinical response, healing dermal lesions within a few weeks without leaving sequelae.

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