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ASSOCIATION OF SWEET'S SYNDROME AND BEHÇET'S DISEASE: IS IT POSSIBLE? A CASE REPORT

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ABSTRACT

Introduction: Behçet's disease is a systemic vasculitis characterized by a large clinical polymorphism with a particular frequency of cutaneous signs. Sweet's syndrome is a neutrophilic dermatosis marked by the sudden appearance of painful skin lesions in the form of erythematous papules, nodules or plaques. This syndrome is associated with high fever, neutrophilia and histologically a diffuse infiltrate of neutrophils in the dermis.

Observation: We report the case of a 43-year-old patient followed for Behçet's disease, who developed cutaneous plaques of neutrophilic dermatosis of both upper limbs. The clinical and biological picture was in favor of Sweet's syndrome.

Conclusion: The coexistence of Sweet's syndrome and Behçet's disease is already reported in the literature. The association is however very rare given the differences in the clinical and pathogenic features between the two conditions.

KEYWORDS

Behçet's disease, Sweet's syndrome, pathogenesis, association

LEARNING POINTS

- The appearance of neutrophilic dermatosis during a skin flare-up of Behçet's disease alerted us to a possible link between Sweet's syndrome and Behçet's disease.
- The morphology of the skin lesions associated with these pathologies is heterogeneous, making diagnosis sometimes difficult.
- Cases reported in the literature concerning the association between Sweet's syndrome and Behçet's disease are rare.

INTRODUCTION

Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, was originally described by Robert Douglas Sweet in 1964[1]. It is one of the neutrophilic dermatoses and frequently affects young women. Sweet's syndrome is characterized by clinical polymorphism, mainly at the cutaneous level. Although the association between Sweet's syndrome and Behçet's disease has been reported in a few cases, reports remain rare. This paper reports on the association of these two pathologies in a patient.

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We describe the physiopathology, the different clinico-biological aspects that were observed and the therapeutic choices that were made.

CASE REPORT

This is the case of a 43-year-old woman followed since 2005 for Behçet's disease, with bipolar aphtosis and pseudofolliculitis on the thighs and back. The patient initially received a treatment based on colchicine 1 mg/day with a good clinical outcome (a few episodes of mouth sores and total disappearance of skin flare-ups and genital lesions). For one year, the patient stopped colchicine without medical advice. Afterwards, she developed lesions on both forearms and hands with outbreaks of mouth ulcers. This outbreak of skin lesions appeared suddenly seven days before admission, evolving in a context of fatigue and fever.

On clinical examination, the patient had a temperature of 38.7 °C. The skin lesions observed were in the form of circinate patches on the forearm, more marked on the periphery *(Fig. 1 and 2)*, two recent mouth sores and scars of genital sores. There were also erythema nodosum lesions on both legs. The pleuro-pulmonary, cardiovascular and neurological examinations were without abnormality. The pathergy test was positive.

Biological assessment revealed a high sedimentation rate of 86 mm in the first hour, hyperleukocytosis of 13,300/mm^3 (neutrophils at 80%), with no other abnormalities. Renal assessment was normal (creatinine and proteinuria). Syphilitic and HIV serologies were negative. Chest X-ray and abdominopelvic ultrasound were unremarkable. Digestive fibroscopy showed pangastritis and histology revealed the presence of *Helicobacter pylori*.

The skin biopsy performed on a lesion of the forearm revealed edema of the superficial dermis, with diffuse dermal infiltrate formed by mature neutrophils, without leukocytoclastic vasculitis *(Fig. 3)*, characteristic of Sweet's syndrome. A diagnosis of Sweet's syndrome associated with Behçet's disease was made.

The patient received treatment for *Helicobacter pylori*-mediated gastritis (HP gastritis), with reintroduction of colchicine at a dose of 1 mg/day. The initial treatment was corticosteroid therapy at a dose of 40 mg/d for 15 days, then the dose was reduced. The evolution was favorable, marked by the disappearance of the fever after a few hours and the whitening of the lesions after 20 days.

DISCUSSION

The diagnosis of Sweet's syndrome is established in the presence of painful erythematous plaques of sudden onset with, in histology, a dermal infiltrate of polymorphonuclear neutrophils (PMN). In our patient, other diagnostic criteria were observed such as a fever above 38 °C, an inflammatory syndrome and hyperleukocytosis with a proportion of polymorphonuclear neutrophils above 70%. The diagnostic criteria are presented in *Table 1*.

The diagnosis of Behçet's disease is also established

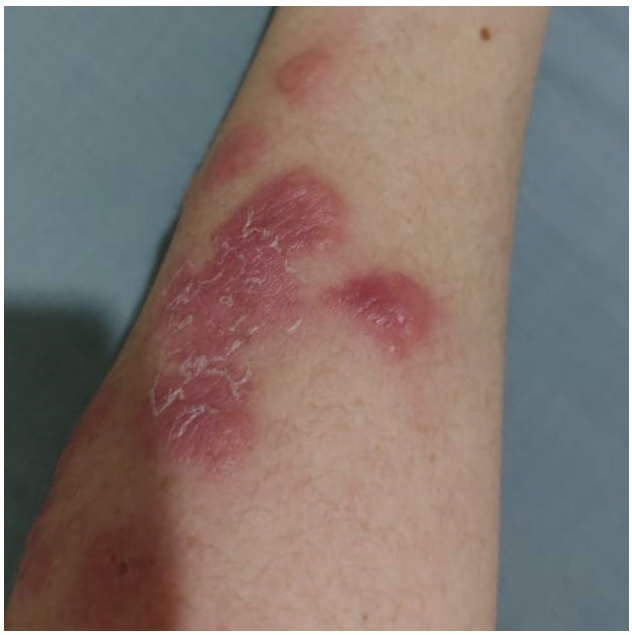

Figure 1. Forearm image showing a 3 to 4 cm plus patch with 3 other circinate lesions

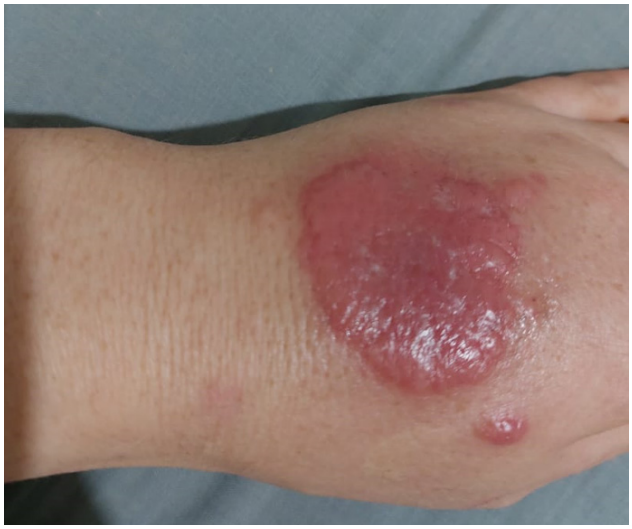

Figure 2. Circinate lesion on the dorsal surface of the left hand

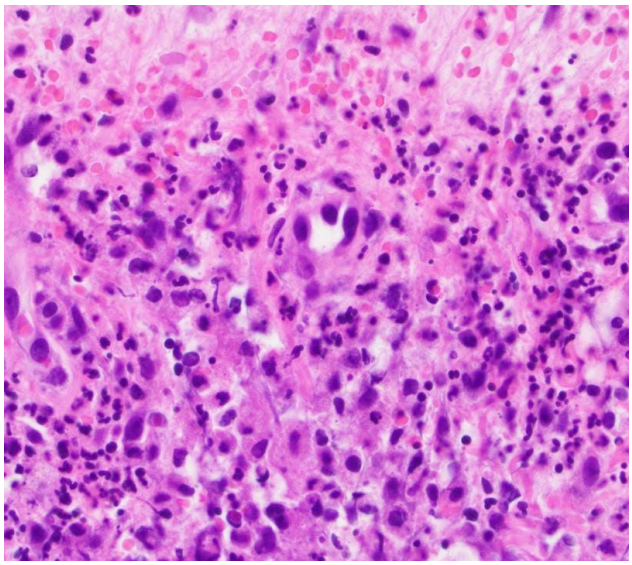

Figure 3. Histological section showing a dermal infiltrate rich in neutrophils, without vasculitis (x200)

Classic form:	Medication-induced form:
Two major and two minor criteria are required for the diagnosis of the disease	
Major criteria 1. Sudden onset of painful erythematous or violaceous plaques or nodules 2. Neutrophilic infiltration in dermis without leukocytoclastic vasculitis **Minor criteria** 3. Fever (>38 °C) 4. History of non-specific gastrointestinal or respiratory infection, vaccination, or the association of autoimmune disease, hemoproliferative diseases, malignancy, or pregnancy 5. Good response to systemic corticosteroids or potassium iodide 6. Leukocytosis >8000/^{mm3}, elevated erythrocyte sedimentation rate >20 mm/h, C-reactive protein positive, neutrophilia >70%.	A. Sudden onset of painful erythematous or violaceous plaques or nodules B. Neutrophilic infiltration in dermis without leukocytoclastic vasculitis C. Fever (>38 °C) D. Temporal link between drug administration and clinical presentation or recurrence upon reintroduction of the drug. E. Disappearance of lesions after drug discontinuation or treatment with systemic corticosteroids.

Table 1. Diagnostic criteria for Sweet's syndrome[2]

according to the 2013 international criteria[3]. The clinical diagnosis is made in the presence of bipolar aphtosis and cutaneous involvement characteristic of Behçet (pseudofolliculitis and erythema nodosum).

Sweet's syndrome is most often observed during a flare-up of Behçet's disease. Hassikou et al.[4] described a case of Sweet's syndrome revealing Behçet's disease with cutaneous and joint manifestations. In another study, Miura et al.[5] also found that Sweet's syndrome is one of the cutaneous manifestations of Behçet's disease, occurring during a cutaneous flare of vasculitis. In the case of our patient, the neutrophilic dermatosis lesions appeared at the time of a cutaneous outbreak of Behçet's disease after the treatment was discontinued by the patient. This suggests a link between these two pathologies.

Studies have shown that the two diseases are genetically distinct. Mizoguchi[6] observed an elevated frequency of HLA B51 and HLA-DQw3 in patients with Behçet's disease, while HLA-Bw54 was significantly higher in patients with Sweet's syndrome.

The pathogeneses of Sweet's syndrome and Behçet's disease are not fully understood. However, several hypotheses have been made. For Sweet's syndrome, the association with autoimmune diseases, infections, neoplasia and medications suggests hyperresponsiveness of the immune system. The pathogenesis of Sweet's syndrome is closely linked to a cytokine-mediated inflammatory response. Cytokines involved include IL-1, IL-6, IL-8, interferon gamma, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). The role of the innate immune system is well established, in particular, the activation of helper T lymphocytes responsible for the activation of neutrophils. In addition, the involvement of the adaptive immune system has recently been demonstrated[7].

In Behçet's disease, the cytokine cascade is thought to be triggered by a combination of genetic and environmental factors. The main cytokines involved in Behçet's disease are IL-1, IL-6, IL-8, IL-18 and TNF-α. These cytokines lead to the recruitment and activation of neutrophils as well as other immune cells, which cause the characteristic lesions of Behçet's disease.

Recent studies have also demonstrated the involvement of helper T lymphocytes in the pathophysiology of Sweet's syndrome and Behçet's disease. According to Dalghous, the proportion of Th1 lymphocytes in peripheral blood and the levels of Th1-type cytokines in biopsies of mouth ulcers are significantly elevated in patients with Behçet's disease[8]. We propose the probable involvement of the HSV-1 and HSV-2 viruses as triggering factors in the occurrence of skin lesions in Behçet's disease and Sweet's syndrome[9].

From a histological point of view, during a pathergy test, skin lesions are initially characterized by acute inflammation at the point of needle puncture, mainly consisting of an infiltration of polymorphonuclear neutrophils. After 48 hours, the cellular infiltration becomes mainly composed of mononuclear cells (macrophages, monocytes and T lymphocytes), thus marking the transition from acute inflammation to chronic inflammation[10]. The histological appearance of skin lesions in Behçet's disease differs from that of Sweet's syndrome, due to the presence of lymphocytic vasculitis and polymorphic dermal infiltrate[11]. In Sweet's syndrome, the histological appearance corresponds to edema with polymorphonuclear infiltrates localized in the superficial dermis. Deep localizations of Sweet's syndrome are also possible, producing inflammatory nodules close to the erythema nodosum[4]. Another characteristic differentiating the two entities is the absence of fibrinoid necrosis on the walls of the vessels in Sweet's syndrome[12]. The histology in our patient - the presence of a polymorphonuclear infiltrate and the absence of vasculitic lesion - is in favor of lesions of neutrophilic dermatosis.

For the treatment regimen, the lesions are generally sensitive to corticosteroid therapy. The dose and duration depend on the severity of the clinical presentation. Colchicine is strongly indicated to manage the activity of both diseases and to prevent relapses. Dapsone, cyclosporine and anti-TNFα are recommended in case of failure of first-line treatment[7].

Current studies suggest that both pathologies involve a cascade of cytokine activation leading to an influx of neutrophils and other immune cells. The activation of neutrophils leads to tissue infiltration, thus causing characteristic lesions of the affected organs and cutaneous manifestations specific to each pathology. Thus, the association between the two disorders is not fortuitous. The cutaneous manifestations of Behçet's disease may present with signs similar to those of Sweet's syndrome ("sweet-like"), and sometimes the dermatological symptoms of Behçet's disease may reveal an associated Sweet's syndrome[4,5]. In addition, several studies have reported the coexistence of these two entities[6]. However, further clinical and biological studies are needed to confirm this theory.

CONCLUSION

The association between Sweet's syndrome and Behçet's disease is uncommon. The occurrence of Sweet's syndrome during a flare-up of Behçet's disease suggests a very probable pathogenic link between these two entities and stresses the need for further pathophysiology research.

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