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Unusual Clinical Synergy: Crohn's Disease, Behçet's Disease, and Ankylosing Spondylodiscitis – A Comprehensive Look at Interactions

D. Rajih[1*], H. EL Marmouk[1], F. Z. Lairani[1], O. Nacir[1], A. Ait Errami[1], S. Oubaha[1, 2], Z. Samlani[1], K. Krati[1]

[1]Gastroenterology Department, Mohammed VI University Hospital, Marrakech, Morocco
[2]Physiology Department, Cadi Ayyad University, Mohammed VI University Hospital, Marrakech, Morocco

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***Corresponding author:** D. Rajih
Gastroenterology Department, Mohammed VI University Hospital, Marrakech, Morocco

Abstract **Case Report**

Crohn's disease, Behçet's disease, and ankylosing spondylodiscitis are inflammatory conditions that can pose therapeutic challenges when they occur together. Treatment decisions should be guided by the clinical presentation of each condition, its level of activity, and severity. Several points regarding this combined management need to be addressed. We report the case of a 37-year-old man diagnosed with Crohn's disease, Behçet's disease, and ankylosing spondylodiscitis, aiming to present the diagnostic approach and therapeutic specificities of this association.

Keywords: Crohn's disease - Behçet's disease - Ankylosing spondylodiscitis - Autoimmune diseases.

INTRODUCTION

Behçet's disease (BD) is an idiopathic vasculitis affecting vessels of all sizes, preferably veins over arteries. It mainly affects individuals aged 10 to 45 years, affecting both men and women. First onsets after 50 years are rare. This condition is formidable due to its complications. Diagnosis is mainly based on clinical criteria, characterized by recurrent oral and genital ulcers, associated with skin, mucous membrane, ocular, articular, vascular, and/or gastrointestinal lesions.

Crohn's disease (CD) is an inflammatory disease that can affect any segment of the digestive tract but mainly involves the terminal ileum and colon. It is usually diagnosed between 25 and 30 years of age, during the first onset or complication, but it is not uncommon in children or the elderly. Distinguishing between Behçet's disease with digestive involvement and Crohn's disease with extra-digestive involvement is not always easy. Indeed, many common extra-digestive manifestations pose unsolvable nosological problems. Treatment of BD with digestive involvement is similar to that of CD, including steroids, immunomodulators, and biological agents (anti-tumor necrosis factor α antibodies).

Here, we report the case of a man hospitalized in our department for Crohn's disease, Behçet's disease, and ankylosing spondylodiscitis, aiming to present the diagnostic approach and therapeutic specificities of this association.

CASE REPORT

The patient is a young 37-year-old man, followed for Behçet's disease since 2014, diagnosed following the recurrence of bipolar aphthosis, cutaneous pseudo-folliculitis, anterior uveitis, and a positive pathergy test. The patient was treated with colchicine, showing a favorable clinical evolution. In June 2022, the patient was admitted to our institution due to worsening abdominal pain exacerbated by eating and relieved by fasting, accompanied by asthenia and a weight loss of 12 kg in six months. Physical examination revealed no abnormalities. Laboratory tests indicated inflammatory anemia, with high levels of C-reactive protein (150 mg/l). The etiological assessment included negative tuberculin tests, positive serological markers for ASCA (anti-Saccharomyces cerevisiae antibodies), and HLA B51. A colonoscopy revealed diffuse ileitis with superficial and aphthoid ulcers, the cecal base, the right colon, and transverse colon showing erythematous colonic mucosa with an interval of healthy mucosa without ulcers or erosions (Figure 1). Esophagogastroduodenal endoscopy was normal. Histological examination of the ileocolic biopsy confirmed ulcerative ileitis and epithelioid granuloma, without caseous necrosis, consistent with Crohn's disease. No signs of vasculitis were observed, and histological examination of colonic biopsies showed vasculo-exudative inflammatory changes in the colonic

mucosa. Duodenal biopsy and celiac serology were normal. Enteric MRI revealed asymmetric circumferential thickening of the walls of the terminal ileum over a length of 8 cm, with wall thickness ranging from 5 mm to 15 mm. No fistula, collection, or peritoneal effusion was detected. Infiltration of peri-lesional fat of the right iliac fossa extending into thickening was observed, as well as adhesions to the internal wall of the sigmoid loop and to the upper wall of the bladder. Another segment of circumferential segmental thickening of a jejunal loop in the left flank was identified, measuring 17 mm in maximum thickness over a length of 20 cm, with dilation of the lumen of this affected jejunal segment (Figure 2). The diagnosis of Behçet's disease associated with Crohn's disease was made, and the patient was initially treated with intravenous corticosteroids for 7 days, then orally, along with colchicine. Subsequently, the patient was placed on azathioprine at a dose of 2.5 mg/kg/day as maintenance therapy. Clinical and biological improvement of both diseases was observed during follow-up. Nine months later, the patient presented with bilateral buttock pain and lower back pain. A frontal pelvic radiograph revealed bilateral sacroiliitis with erosions and osteosclerosis of the margins. An MRI of the hips and lumbar spine confirmed the presence of sacroiliitis without abscess formation. The diagnosis of ankylosing spondylitis associated with the two previous diagnoses was probable. The decision was made to initiate treatment with anti-TNF (Infliximab). The evolution after one year of treatment was favorable.

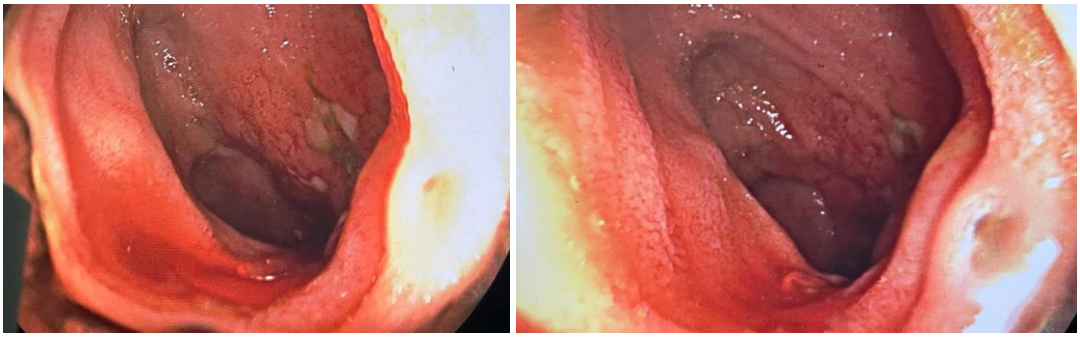

Figure 1: Ileal mucosa with erythema and superficial aphthoid ulcers

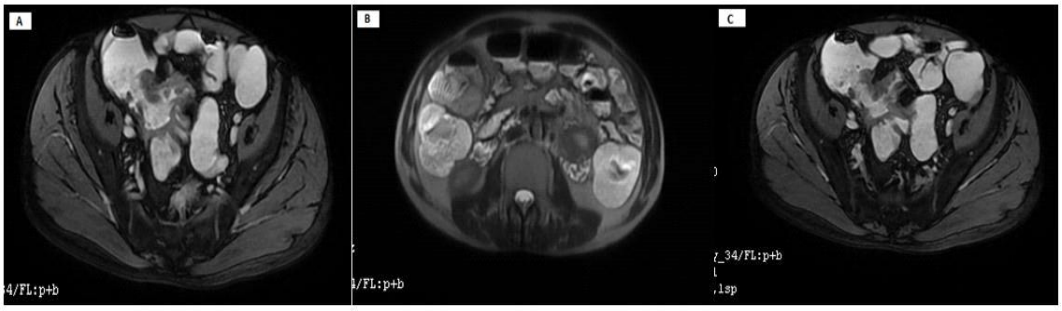

Figure 2: The enteric MRI reveals thickening of the jejunum (B) and the terminal ileum (A), with the latter infiltrating the surrounding fat and adjacent structures (sigmoid (C) and bladder) and showing fissures and deep ulcers

DISCUSSION

Behçet's disease (BD) is an idiopathic vasculitis of unknown etiology, particularly prevalent in young individuals, with a higher frequency observed in Mediterranean countries and Japan. Clinical manifestations are diverse, including cutaneous, ocular, articular, neurological, and vascular involvement. Intestinal involvement, termed enteric Behçet, is rare and accounts for approximately 2-6% of cases, although this proportion is higher in Japan, reaching 30-50%. Ulcerations can affect all segments of the digestive tract but preferably the ileum and cecum (76%), presenting with nonspecific clinical symptoms such as abdominal pain and diarrhea. Although the endoscopic and histological appearance is not specific, the depth of the lesions suggests BD. Vasculitis lesions, although characteristic, are rarely seen on simple biopsies due to their depth. The diagnosis can be complicated by similarities with chronic inflammatory bowel diseases, notably Crohn's disease, with frequent complications (50%), often in the form of perforations.

Crohn's disease (CD), a transmural inflammatory disease, can affect any segment of the digestive tract but mainly involves the terminal ileum and colon. It is usually diagnosed between 25 and 30 years of age, often during the first onset or complication. Its clinical presentation is polymorphic, and it can also manifest with skin, joint, and ocular involvement.

The diagnosis of Behçet's disease with digestive involvement presents a challenge as no single clinical,

biological, or histological characteristic has been identified. Moreover, some manifestations, such as oral ulcers, are common in the general population, making the distinction between gastrointestinal involvement of BD and CD difficult. Although several sets of classification criteria have been developed, they all have limitations when applied individually. For example, when developing the criteria of the International Study Group for Behçet's Disease, one of the most widely accepted sets, the control group did not include patients with CD. It is important to note that CD shares many characteristics with BD, such as extra-intestinal manifestations, including oral aphthous ulcers, arthritis, uveitis, erythema nodosum, and pyoderma gangrenosum, as well as thromboembolic events. However, these characteristics have distinct specificities when they occur in BD, thus facilitating differentiation between the two diseases. For example, uveitis in BD is often more severe and recurrent, leading to blindness without adequate treatment. Joint manifestations also differ, with arthralgia, oligoarthritis, and polyarthritis predominating in BD compared to spondyloarthritis more frequently observed in CD. Genital, neurological, and vascular involvement is more common in BD. At the intestinal level, although both diseases have a predilection for the ileocecal region, anal complications such as stenoses, fistulas, and abscesses, common in CD, are rare in BD.

Symptom/Feature	Behcet's Syndrome	Crohn's Disease
Oral Aphthous Ulcers	Almost universal	Rare
Genital Ulcers	Frequent	Very rare
Uveitis	Frequent	Rare
Dermatological Manifestations	Frequent	Rare
Musculoskeletal Manifestations	≈50%	≈20%
Cardiac Involvement	Rare	Rare
Neurological Disease	Rare	Very rare
Vascular Disease	10 to 40% of all sizes of vessels (arterial and venous)	Rare
Main Gastrointestinal Involvement	Ileo-cecal region mainly	Entire gastrointestinal tract
Fistulas, strictures, and abscesses	Rarely causes, but when present, they are less frequent	More frequent
Endoscopic Appearance	Single or rare, large, round or oval ulcers	Longitudinal ulcers with patchy distribution, cobblestone appearance
Histology	Vasculitis, neutrophil infiltration	Focal cryptitis and epithelioid granulomas

Figure 3: Here is a comparative table of the main differences between Behçet's syndrome and Crohn's disease

The endoscopic findings in Behçet's disease (BD) typically show round/oval ulcers, perforated lesions with discrete margins (>1 cm), and a focal distribution (<5 ulcers), in contrast to Crohn's disease (CD), where ulcers are more longitudinal with a cobblestone appearance. A Korean study suggested a classification score to help differentiate BD from CD, where irregular/geographic ulcers and focal distributions suggest Behçet's enteritis, while segmental/diffuse lesions suggest CD. Pathological characteristics also differ, with BD showing vasculitis of small veins and venules accompanied by deep ulcers, without granulomas or cobblestones, ischemic perforation, and thrombosis. In CD, transmural inflammation of the mucosa is noted with an infiltrate of inflammatory cells (lymphocytes, plasma cells), focal crypt irregularity, and granulomas.

Chronic intestinal and articular inflammation are closely related. Spondyloarthritis (SpA) and inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are well-known for their association. Behçet's disease also represents a chronic condition involving both digestive and articular

inflammation.

The coexistence of chronic digestive, vascular, and articular inflammation, especially in the Behçet/IBD/SpA association, requires tailored management, considering the activity and severity of each condition. Commonly used treatments include steroids, aminosalicylates, immunomodulators, and biological agents, such as anti-tumor necrosis factor α (anti-TNF) antibodies.

Treatment of BD is largely dictated by the type and severity of organ involvement. There is controversy regarding the effectiveness of 5-aminosalicylates (5-ASA) in CD, but they may be used to treat mild clinical and endoscopic activity in gastrointestinal BD. Other options for treating gastrointestinal BD, in addition to steroids, include thalidomide, thiopurines, and tumor necrosis factor α (anti-TNF), largely overlapping with CD treatment, although anti-TNF therapy appears to be more effective in CD. As with all systemic diseases, treatment should be guided by the overall clinical picture, aiming to be effective in each manifestation and not deleterious.

CONCLUSION

Crohn's disease (CD) primarily affects the gastrointestinal system and can present with various extraintestinal signs and symptoms. On the other hand, Behçet's disease (BD) is a condition or syndrome that presents in a multisystemic manner, also including the gastrointestinal tract among its main sites of involvement. These two diseases have significant overlap, affecting the gastrointestinal system, and share common features such as age of onset, sex, and inflammatory biomarkers such as erythrocyte sedimentation rate and C-reactive protein. Despite these similarities, notable differences exist in immunopathogenesis, genetic factors, and regional distribution. While both diseases involve similar systems, they have distinct histopathological characteristics.

The management of these complex conditions requires an individualized approach, considering the specific manifestations of each patient. Common treatments such as steroids, immunomodulators, and biological agents, including anti-tumor necrosis factor α antibodies, are often used to control inflammation and improve the quality of life of patients. However, ongoing research is needed to deepen our understanding of these diseases, particularly their underlying mechanisms, in order to develop more targeted and effective therapeutic approaches.

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