Case Report

Association of crohn's disease and behcet's disease: a case report

Reda Berraida, Hanane Basr, Brahim Aitbihi, Sara Jamal, Fouad Nejjari, Mouna Tamzaourt, Fatiha Benhamou, Sara Mourabit, Sanae Berrag, Fedoua Rouiba, Aziz Aourarh

INTRODUCTION

Behçet's disease (BD) is a chronic, multisystemic and relapsing inflammatory vasculitis, characterized by recurrent oral ulcers, genital ulcers, uveitis, and skin lesions. It can also affect other visceral organs, the musculoskeletal system and nervous system, blood vessels, and gastrointestinal tract. Crohn disease (CD) is a complex relapsing and transmural inflammatory disorder which primarily affects the small bowel and the colon, but can involve the entire gastrointestinal tract. We report a case of woman hospitalized in our department for Behçet’s and Crohn’s diseases in order to showcase the diagnosis process and therapeutical specifics of this association.

CASE REPORT:

41 year-old woman with a family history of colon adenocarcinoma in a father. The patient has been under treatment and medical monitoring for Behçet’s disease since 2015, its diagnosis was retained by the recurrence of bipolar aphtosis and ocular involvement. Granulomatous anterior uveitis (Fig. 1). The patient was initially treated with oral corticosteroids, then switched to colchicine with a good evolution. The patient was admitted for chronic diarrhea, arthralgia (affecting the lower limbs), asthenia and a 17 kg weight loss in a 6 months lapse. Physical examination was normal. Laboratory tests underline anemia, iron-deficiency and elevated C-reactive protein levels (37 mg/l). The patient was also tested for tuberculosis infection: both sputum tests and quantiferon were negative. However, a colonoscopy revealed an ulcerative ileitis. Histological examination of ileal biopsy found a subacute ulcerative ileitis related to an inflammatory bowel disease; there is no sign of vasculitis. Magnetic Resonance Enterography (MR enterography) reveals an inflamed terminal ileum and ileocecal valve (Fig. 2). The diagnosis of associated Behçet and Crohn’s disease was retained and the patient was treated with oral corticosteroids (Budesonide) and Colchicine. A positive evolution of the clinical and biological course of both diseases was observed during follow up.

DISCUSSION

Behçet’s disease (BD) is a chronic, multisystemic, relapsing inflammatory disorder, characterized by recurrent oral ulcers, genital ulcers, uveitis, and skin lesions. It also attacks other systems involving the musculoskeletal system, blood vessels, nervous system, and gastrointestinal tract. BD is predominantly found in eastern Mediterranean countries and the eastern rim of Asia, including China.1,2 When BD patients have predominantly gastrointestinal symptoms and show gastrointestinal lesions with certain objective measures, the disease is defined as intestinal BD.3 The prevalence of intestinal BD varies from 0% to 60% of all BD patients with geographic and ethnic differences. The ileocecal region is the most commonly

ABSTRACT

Crohn’s disease and Behçet’s diseases are two multifactorial autoinflammatory diseases that share many clinical similarities. Their association is exceptional and poses a nosological problem. We report a case of 41 year-old woman monitored for Behçet’s disease since 2015 hospitalized in our department for management for chronic diarrhea revealing Crohn’s disease. We focused on association of crohn’s and Behçet’s disease in order to showcase the diagnosis process and therapeutical specifics of this association.

Key words: Behçet, crohn, disease, intestinal, corticosteroids
Intestinal BD often mimics Crohn’s disease (CD). Both diseases commonly have an early age of onset, nonspecific gastrointestinal symptoms, similar extra intestinal manifestations, and chronic, waxing, and waning course. Distinguishing between them is clinically challenging. There are only a few comparative studies regarding the differential diagnosis, which were conducted in Korean patients.

CD is a complex disorder, which primarily involves the small intestine and the colon, is a relapsing and transmural inflammatory disease which can affect the entire gastrointestinal tract. Typical presentations include the presence of longitudinal ulcers with a cobblestone appearance, skip lesions, and the development of complications such as strictures and fistulas. However, various extra-intestinal manifestations of the disease including oral and genital ulcers, erythema nodosum, uveitis, and arthritis may also be observed. Skin changes may be seen in 5%-10% of patients. Erythema nodosum (5.6%-13.5%), pyoderma gangrenosum (0.75%-0.15%), and acute neutrophilic dermatoses, also termed Sweet’s disease, are among the main skin lesions. Other skin conditions include oral aphthous lesions, perianal lesions, large ulcers, fissures, fistulas, and aseptic abscesses. Pathergy positivity is extremely low in patients with CD, compared to those with BD. The most common ocular conditions are uveitis, episcleritis, conjunctivitis, and blepharitis. Non-granulomatous anterior uveitis may develop and recurrent episodes may result in permanent vision loss. Ocular complications are not associated with disease severity. Additionally, retinal vasculitis, which is extremely rare, has been reported in the literature as case studies.

In BD, neutrophilic infiltration, lymphocyte aggregation of the surrounding vessels, and vascular proliferation have been observed in biopsy specimens of oral aphthae and genital ulcers. Neutrophil-predominating infiltration, abscess formation and vasculitis-related changes may be present in skin lesions. Aggregation of lymphocytes, neutrophils, and eosinophils as well as edema and leukocytoclasis occur in the pathology test site within the first 12 h. In the presence of large vessel involvement such as aortic involvement, medial elastic fiber ruptures or loss may be seen, while proliferation of the vaso vasorum and lymphocytic infiltration of the surrounding tissue may develop. Lymphocytic and necrotizing vasculitides are other conditions involving pulmonary arteries, veins, and septal capillaries. In addition, transmural necrosis and aneurysms of great vessels and pulmonary arteries may arise. Despite the non-specific nature, perivascular lymphocyte/plasma cell infiltration and myelin loss of parenchymal CNS lesions may develop.

Furthermore, inflamed intestinal BD may lead to mesenteric vasculitis with ischemia or necrosis of the intestines. Ulcer specimens often show non-specific patterns, including fibrinopurulent exudates and necrotic debris in active ulcers and transmural fibrosis in chronic ulcers. Inflammation from the lumen to the serosa is present in the perforated site with mural necrosis. Vasculitic changes secondary to the inflamed surrounding tissue and thrombus formation in the small vessels including both arteries and veins are other critical manifestations. Lymphoid follicles may be seen due to mucosal erosion in some cases. The differential diagnosis of these lesions, which are histopathologically suggestive of CD is highly challenging.

Histopathological characteristics of CD are discontinuous cryptic architectural abnormalities, mucin preservation at active sites, discontinuous inflammation, focal cryptitis, and epithelioid granulomas. Granulomas in histological sections are key features of CD, but are not necessary for diagnosis. In the submucosa, fibromuscular obliteration, nerve fiber hyperplasia and transmural lymphoid aggregates are found. Transmucosal increases in lamina propria cellularity and neutrophils are an indicator of disease activity.

Both BD and CD may present with transmural enteritis and colitis. Longitudinal ulcers, cobblestone appearance, and anorectal fistula are usual findings in Crohn’s colitis. The presence of granulomas in biopsy specimens indicates CD, while vasculitides are suggestive of BD.

Although there is no specific diagnostic test for BD, diagnostic criteria sets described at different time points are available. The International Study Group (ISG) criteria, which were defined in 1990, are the most commonly used criteria for the diagnosis of BD (Table 1). These criteria are based on the most frequent clinical signs of BD. In addition, some cases of CD meet these criteria.

In this case, our patient is suffering from Behçet disease according to criteria of international classification of Behçet disease with associated Crohn disease according to endoscopic and histological data.

Several diagnostic and classification criteria for CD have been proposed (Table 1). The location and appearance of lesions are important for the diagnosis of CD. According to the Vienna and Montreal classifications, the diagnosis of CD is established by three variables: (1) age at diagnosis; (2) disease location; and (3) behavior of the disease. The Lennard-Jones criteria based on endoscopic, surgical/histopathological, radiological and clinical findings. The Copenhagen criteria include histopathological confirmation of CD. A diagnostic criteria set for CD based on alterations of gastrointestinal morphology was published in 2011. However, no validated and widely adopted criteria set is currently available for the diagnosis of CD in clinical practice. The diagnosis usually relies on the patient history, physical examination, laboratory results, imaging studies, and endoscopic findings in combination with histopathological examination. Patients with BD, particularly with intestinal involvement, may be misdiagnosed and mismanaged as CD by clinicians with insufficient experience and knowledge on BD.

As BD is a multisystem condition, effective management of the disease requires a multidisciplinary approach. Although the disease should be primarily managed by a rheumatologist,
consultation is provided by a dermatologist, neurologist, gastroenterologist and cardiovascular surgeon, if necessary. The disease is inflammatory; therefore, immunosuppressive and immunomodulatory agents are first-line therapies. Due to the limited number of randomized-controlled clinical trials, management usually depends on the clinical experience of the treating physician. In 2008, the European League Against Rheumatism (EULAR) published a recommendation guideline for the management of BD.26

The management of patients with BD is based on the presence of organ involvement and disease severity. Colchicine is a widely used treatment for BD. Corticosteroids and azathioprine can be prescribed if colchicine monotherapy is inadequate. Colchicine is used for the management of mucocutaneous and musculoskeletal findings. Corticosteroids and azathioprine can be combined in patients who does not are respond to colchicine treatment and who have ocular, vascular, neurological, or intestinal involvement. Cyclosporine and interferon-alpha are immunosuppressive agents used in the management of refractory uveitis and retinal vasculitis. A small number or patients with inadequate response may require mycophenolate mofetil and infliximab. Currently, these agents are used experimentally in the management of vascular involvement. In addition, cyclophosphamide is an effective immunosuppressive agent with increased side effects in patients with arterial, venous and neurological involvement who are refractory to other agents. Other agents that are preferred in unresponsive arthritis with a chronicity tendency include methotrexate and sulfasalazine. The latter is the most widely preferred agent in patients with intestinal BD, after corticosteroids and azathioprine. On the other hand, there are no randomized-controlled clinical trials in BD patients. Observational studies and case series have revealed that steroids, mesalazine, azathioprine, and sulfasalazine are likely to be used in the management of inflammatory bowel diseases. Recently, experience related to the use of anti-TNF agents have increased and some patients respond well to treatment. In addition to immunosuppressive agents, antiaggregants, and anti-coagulants can be initiated in patients with venous and neurological involvement. However, no consensus on the use of antiaggregants and anti-coagulants has been reached yet, due to the low embolization tendency of BD-associated thrombosis and high bleeding risk secondary to arterial aneurysms. In clinical practice, these agents are prescribed in patients with low bleeding risk.26-29

Corticosteroids have been used in the management of CD for over five decades. Corticosteroids are the most effective therapeutic agents in relieving disease exacerbations. They exert remarkable effects in suppressing pro-inflammatory cytokines and active lymphocytes and inhibiting inflammatory processes of the intestinal lamina propria. Although corticosteroids are more effective in higher concentrations, treatment-related side effects are likely to increase. Prednisolone treatment is usually initiated at 40-60 mg/d and reduced on a gradual basis. Nearly 48%-58% of the patients achieve complete remission, while 26%-32% achieve partial remission following 30 d of treatment. Approximately 16%-20% of patients are unresponsive. Six-mercaptopurine and its pro-drug azathioprine are the most commonly used agents in patients unresponsive to corticosteroids and maintenance therapy. Methotrexate is an alternative agent in patients who are intolerant or unresponsive to these agents. On the other hand, controversial data are available on the efficacy of 5-aminosalicylic acid (5-ASA) preparations. In several meta-analyses, mesalazine 4 g/d significantly reduced disease activity in patients with mild to moderate activity. All these agents are frequently prescribed due to their low side-effect potential.30,31 Anti-TNF agents including infliximab, adalimumab, and certolizumab pegol can be used in refractory patients with relapsing disease. Meta-analyses have demonstrated that anti-TNF agents are effective as both induction and maintenance therapy in CD patients with fistulizing disease.32 Surgery is indicated in patients with perianal involvement, fistulas, fissures, and intra-abdominal abscesses.

Medical and surgical management approaches for CD and intestinal BD are similar. Recently, a retrospective case series with long-term outcomes for both diseases was reported.33 Ten year-follow-up data after diagnosis showed no significant difference in the need for surgery between the study groups with CD and intestinal BD. However, CD patients required a higher dose of corticosteroids and immunosuppressive agents. The doses of biological agents were also higher in CD patients compared to patients with intestinal BD (14.2% vs 1.4%). Based on these results, long-term prognosis appears to be similar in patients with CD and intestinal BD.

**CONCLUSION**

CD primarily involves the gastrointestinal system and can present with various extra-intestinal signs and symptoms. However, BD is a condition or syndrome that presents with multisystem involvement. The gastrointestinal tract is also one of the main sites of involvement in these patients. Both diseases have a true overlap, affecting the gastrointestinal tract. Furthermore, both conditions share similar characteristics with respect to age of onset, gender, and inflammation biomarkers such as erythrocyte sedimentation rate and C-reactive protein. Despite these similarities, the immunopathogenesis, genetic factors, and regional distribution are quite different. Although both diseases involve similar systems, they have distinct histopathological characteristics. For instance, uveitis is more common in BD, and CD patients are more likely to suffer from episcleritis or conjunctivitis.
<table>
<thead>
<tr>
<th>International Study Group Diagnostic Criteria for Behçet’s disease</th>
<th>Proposed diagnostic criteria for Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major findings</td>
<td>Recurrent oral ulcerations</td>
</tr>
<tr>
<td>Minor findings</td>
<td>Recurrent genital ulcerations Eye lesions Skin lesions Positive pathergy test</td>
</tr>
<tr>
<td>Definite</td>
<td>Major finding plus two minor findings</td>
</tr>
</tbody>
</table>
Figure 1: Granulomatous anterior uveitis

Figure 2: Magnetic Resonance Enterography reveals an inflamed terminal ileum and Ileocecal valve

REFERENCES


