Behcêt’s disease depart the ‘Silk Road’: a case report and brief review of literature with geographical comparison

Zohair Ahmed, MD¹*, Maria L. Rossi, MD¹, Sherri Yong, MD², Daniel K. Martin, MD³, Saqib Walayat, MD³, Michael Cashman, MD³, Steven Tsonaides, MD⁴ and Sonu Dhillon, MD³

¹Department of Medicine, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL, USA; ²Department of Pathology, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL, USA; ³Department of Gastroenterology and Hepatology, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL, USA; ⁴Department of Surgery, Division of Colorectal Surgery, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL, USA

Behcêt’s disease (BD) is a chronic multisystem inflammatory disease most prevalent in Eastern Asia and along the Mediterranean basin, an area referred to as the ‘Silk Road’. The diagnosis of BD is largely based on the International Study Group (ISG) criteria, which are more specific than sensitive. ISG criteria do not include intestinal manifestations, a feature more commonly seen in the West. Intestinal BD is one of several findings that are not typically seen along the ‘Silk Road’. Herein we report a rare case of intestinal BD and compare Western versus traditional BD. A 25-year-old male with a history of painful oral aphthous ulcers, pericarditis, and diffuse papulopustular rash presented to the emergency department with two terminal ileal perforations. Pathology demonstrated mucosal necrosis with active inflammation and no chronic inflammatory changes. Post-surgical laboratory studies showed an elevated c-reactive protein of 35.57 mg/dL, erythrocyte sedimentation rate of 82 mm/h, and a positive anti-Saccharomyces cerevisiae antibody. Rheumatological workup including ANA, RF, PR3 antibody, MPO antibody, ANCA, SSA and SSB, Smith antibody, SCL-70, and anti-Jo-1 antibodies were all negative. His pericarditis symptoms improved with colchicine and prednisone prior to discharge. Our patient did not meet the current ISG criteria for traditional BD; however, he clearly showed findings typically seen in Western patients with BD, which include intestinal manifestations, cardiac involvement, and lack of pathergy reaction and ocular changes. Our investigation demonstrates that the clinical manifestations common to this disorder vary among geographic and ethnic populations. Commonly used criteria for the diagnosis of BD may not be sensitive for some populations, such as Western BD, potentially leading to underdiagnoses and mismanagement. Recognition and select inclusion of these differences may be one way to assist with diagnosing Western BD in the future. As our knowledge of BD continues to evolve, so must the population-specific criteria used to define BD.

Keywords: Behcêt’s disease; Crohn’s disease; inflammatory bowel disease; intestinal; perforation

*Correspondence to: Zohair Ahmed, Department of Internal Medicine, University of Illinois, Peoria Campus, OSF Saint Francis Medical Center, 530 NE Glen Oak Avenue, Peoria, IL 61603, USA, Email: zahmed23@uic.edu

Received: 10 November 2015; Revised: 16 December 2015; Accepted: 21 December 2015; Published: 17 February 2016

Behcêt’s disease (BD) is an uncommon chronic multisystem inflammatory disease with an unknown etiology that is associated with significant morbidity. In 1937, Dr. Hulusi Behcêt, a dermatologist from Turkey, first described it as a ‘triple symptom complex’: aphthous stomatitis, genital ulcers, and relapsing uveitis (1). BD is most prevalent in regions of Eastern Asia extending to the Mediterranean basin in an area primarily referred to as the ‘Silk Road’ and has even been referred to as ‘Silk Road Disease’. Prevalence in those regions reaches 420 per 100,000 compared to 2 per 100,000 in Western countries (2–5). Based on molecular research, there is likely an environmental trigger that causes immune dysregulation in genetically susceptible hosts leading to a variety of inflammatory changes and clinical manifestations (6–8).

There is no pathognomonic finding or laboratory test that is diagnostic of BD, but rather the diagnosis of BD is based on select diagnostic criteria. No disease has ever prompted so many different diagnostic criteria as BD.
However, the most widely accepted are the International Study Group (ISG) criteria. The ISG criteria include recurrent oral aphthae \((\geq 3/\text{year})\) plus 2 of the following: genital aphthae, eye lesions, skin lesions, and/or positive pathergy ‘skin prick’ test (9). Due to the importance of early recognition of BD, the criteria continue to evolve, which allows improvement of the sensitivity and specificity of the diagnosis.

Intestinal BD is a rare subset of BD, which was recognized by the Japanese in 1964. Intestinal BD may be seen in 10% of patients at the time of presentation. Intestinal BD is characterized by gastrointestinal manifestations, which include, but are not limited to, chronic abdominal pain, diarrhea, gastrointestinal bleeding, mucosal ulceration, and bowel perforation (10). Intestinal BD carries a higher morbidity and mortality when compared to BD alone. In one study, up to 50% of intestinal BD patients required surgical intervention due to intestinal perforations, gastrointestinal bleeding, and fistulae formation (11).

Due to the rarity of this disease, there is limited research guiding therapy and follow-up in these patients. Unfortunately, there are no pathognomonic characteristics, laboratory tests, or imaging studies to identify affected individuals. Clinicians are left with a variety of clinical criteria and classifications, which may not be applicable or sensitive enough for populations outside of the ‘Silk Road’ (12). Herein we report a case of intestinal perforation in a 25-year-old male, which most likely represents manifestations of BD in the Western population.

**Case report**

A 25-year-old male presented to the emergency department with a 48-hour history of progressively worsening epigastric and left upper quadrant pain. He was febrile with an elevated white blood cell count of \(18.23 \times 10^3/\text{L}\). Computed tomography (CT) of the abdomen and pelvis with contrast demonstrated a bowel perforation (Fig. 1). He underwent an emergent surgical laparotomy with repair of two terminal ileal perforations located on the anti-mesenteric border that were not associated with any chronic inflammatory changes or creeping fat. Biopsy of the perforations demonstrated acute transmural inflammation and necrosis with adjacent mucosal ulceration and active inflammation (Fig. 2). No chronic inflammatory changes or evidence of Crohn’s disease was seen. Immunohistochemical staining for cytomegalovirus was negative. The patient was in good health until 5 months prior to admission when he sought medical attention for painful aphthous oral ulcers producing bilateral mandibular tooth pain. Four months later, he returned complaining of a diffuse papulopustular rash and chest pain. An electrocardiogram showed changes consistent with pericarditis, and an echocardiogram showed no pericardial fluid. He was treated with indomethacin for 10 days before presenting with two ileal perforations. Post-surgical laboratory studies showed an elevated c-reactive protein (CRP) of 35.57 mg/dL and erythrocyte sedimentation rate (ESR) of 82 mm/h. Antinuclear antibody, rheumatoid factor, proteinase 3 antibody, myeloperoxidase antibody, antineutrophilic cytoplasmic antibody, and urinalysis were all negative. A serum protein electrophoresis showed inflammatory pattern with low albumin of 2.9 g/dL, and an IgA lambda small monoclonal antibody was noted. Both C3 and C4 complement levels were normal. Sjogren’s syndrome antibody-A (SSA) and -B (SSB), Smith antibody (SM), scleroderma-70 (SCL-70), and anti-Jo-1 antibodies were all negative. Pathergy test was also negative. Anti-*Saccharomyces cerevisiae* antibodies (ASCA) were positive. CT-angiogram of abdomen and pelvis with and without contrast revealed no evidence of vasculitis. Five days prior to discharge from his 27-day hospital course, his bilateral tooth pain and pericarditis symptoms recurred. Repeat ESR was elevated at 87 mm/h, and repeat CRP was

![Fig. 1. CT abdomen pelvis with contrast. Findings consistent with an abdominal viscus perforation with extravasated bowel contents in the right lower quadrant.](image1)

![Fig. 2. Intraoperative biopsy of the perforation site demonstrating necrosis and acute transmural inflammation with adjacent mucosal ulceration and active inflammation (H&E 200x).](image2)
elevated at 14.82 mg/dL. He was discharged on colchicine and prednisone. He reported relief from his pericarditis symptoms and denied any gastrointestinal complaints at his first follow-up outpatient visit.

Discussion

Due to the lack of laboratory or imaging findings for Behçet’s disease, the diagnosis rests on the application of specific clinical criteria. There are 17 different sets of diagnostic criteria for the diagnosis of BD. The most commonly used is the ISG criteria. A recent article by Davatchi et al. found that the sensitivity of the ISG criteria varies in patients from different parts of the world. For the United States, these authors cite a sensitivity of 76% using the ISG criteria (12). Another recent article was also published by Davatchi et al. on behalf of the International Team for the Revision of the International Criteria for Behçet’s Disease (ITR-ICBD). Their revised criteria was superior in sensitivity but was inferior in specificity when compared to the ISG criteria. The ICBD criteria are still not widely accepted, but this may change in the future.

Our patient met the first ISG criteria with more than three recurrent oral aphthae in a year. He met only one of the second defining criteria with skin lesions. While he did not completely fulfill the current ISG criteria for BD, he presented with (1) pericarditis, a known cardiac manifestation of BD, although not included in the ISG criteria (13, 14) and (2) discrete ileocecal perforations, which are findings strongly associated with intestinal BD (11). Some experts have recommended ileocecal perforations to be included in the ISG criteria and/or replace pathergy. Also per the ICBD criteria, our patient scored 3 points (2 points for apthous ulcers and 1 point for skin lesions); 4 points are required to make the diagnosis.

Review of the literature clearly demonstrates a distinct difference in the prevalence of intestinal BD and other criteria in patients along the ‘Silk Road’ and in patients not directly associated with the ‘Silk Road’. We defined Western BD as cases from North America and Northern Europe and compared important criteria to traditional BD (Table 1). Intestinal BD has a prevalence of 50% in Western populations and is considered rare in traditional BD (15). The prevalence of oral apthous ulcers and genital ulcers is similar in Western and traditional BD (16). Likewise, skin manifestations characterized by papulopustular lesions are similar in the two populations (17). These clinical manifestations are part of the ISG criteria. The remaining two other ISG criteria, eye lesions and pathergy phenomenon, are much less common in Western BD. Only 10–20% of patients in North America and Northern Europe demonstrate the pathergy phenomenon compared to 50–75% of patients in more endemic areas (18). Ocular disease occurs less frequently and is less severe in North American and Northern European populations (19). Intestinal Behçet’s disease, while not on the ISG criteria, is significantly more common in Western BD (15). Thus, the ISG criteria may not be sensitive enough for Western patients with BD.

Multiple studies have demonstrated that susceptibility to BD is strongly associated with the presence of the HLA-B151 allele. Of note, up to 81% of Asian patients with BD who live along the ‘Silk Road’ express this allele. Conversely, only 13% of patients with BD in Western countries express HLA-B151 (23–25). Environmental factors such as ubiquitous antigens and infectious pathogens, including herpes simplex virus, hepatitis C, parvovirus B19, and Streptococcus sanguis, have also been implicated as factors in the diverse clinical manifestations of patients with BD (26). Scientists have hypothesized these antigens may trigger a cross-reactive autoimmune response in patients with BD.

Of all the clinical manifestations of BD, reports have indicated vascular pathology and bowel perforation as the most significant cause of morbidity and mortality (20, 27, 28). Patients with vascular manifestations of BD are more likely to have cardiac involvement (20). Early recognition and diagnosis is crucial for improved outcomes in these patients. The differential diagnosis for BD varies based on each patient’s clinical presentation. Our patient presented with intestinal signs and symptoms characteristic of both

### Table 1. Prevalence of clinical features in Western and traditional Behçet’s disease

| Clinical manifestation          | Western BD (%) | Traditional BD (%) | Source                |
|--------------------------------|----------------|--------------------|-----------------------|
| Recurrent apthous stomatitis   | 97–100         | 97–100             | Gurler et al. (16)    |
| Genital Ulcers                 | 50–85          | 50–85              | Gurler et al. (16)    |
| Papulopustular lesions         | 30–96          | 30–96              | Ergun et al. (17)     |
| Pathergy phenomenon            | 10–20          | 50–75              | Dinc et al. (18)      |
| Ocular involvement             | 25             | 75                 | Nussenblatt (19)      |
| Joint involvement              | 50             | 50                 | Yurdakul et al. (21)  |
| Vascular involvement           | 6              | 40                 | Indeguchi et al. (20) |
| Gastrointestinal involvement   | 50             | Rare               | Cheon et al. (15)     |
| Neurologic involvement         | 23             | 3–10               | Joseph and Scolding (22) |
| Cardiac involvement            | 6              | Uncommon           | Goldeli et al. (14)   |

Citation: Journal of Community Hospital Internal Medicine Perspectives 2016, 6: 30362 - http://dx.doi.org/10.3402/jchimp.v6.30362
Crohn’s disease (CD) and BD, which included painful, oral aphthous ulcers, ulceration and perforation of the terminal ileum, and elevated CRP, ESR, and ASCA (seen in 45% of patients with intestinal BD). Inconsistent with CD, our patient presented with a multisystem disease and did not have a history of recurrent intestinal discomfort, diarrhea, perianal disease, nor was creeping fat or other chronic inflammatory changes seen at the time of surgery.

The biopsy of the perforated ileum taken at the time of surgery showed necrosis and transmural inflammation with active inflammation. No granulomas or chronic inflammatory changes typically associated with CD were identified. Multiple studies have reported inflamed intestinal BD may lead to mesenteric vasculitis with ischemia or necrosis of the intestines. Descriptions of ulcers in the literature reported from BD patients are similar to the specimen from our patient and include antimesenteric oval-shaped ulcers with discrete margins, associated with transmural inflammation (29). According to the scientific literature, patients with intestinal BD may be misdiagnosed and mismanaged as CD by clinicians with limited experience and knowledge of BD. Modifying the current ISG criteria may be one way to clarify the differences between these two diseases in the future.

The variation in sensitivity and specificity described for the diagnosis of this disease most likely reflects the different environmental triggers thought to play a role in the clinical manifestations of the disease. Our study supports this finding and shows that gastrointestinal involvement is more significantly seen in Western BD. Our study also demonstrates that Western BD is less likely to have ocular involvement and a positive pathergy reaction. While our patient did not meet the ISG criteria, he did exhibit the clinical findings typically seen in Western BD (oral aphthous ulcers, skin lesions, gastrointestinal involvement, and cardiac findings). His lack of a pathergy reaction is also in accordance with Western BD. As our knowledge of BD both clinically and molecularly continues to evolve, so must the criteria that are used to define BD.

Authors’ contributions
ZA, MLR, SW, and DKM reviewed the literature, collected the patient data, and drafted the manuscript. ST and MC reviewed and edited the article to be published. SY and SD reviewed the article, made critical revisions related to the content of the article, and approved the final version of the article to be published.

Conflict of interest and funding
All authors declare no conflicting interest related to the manuscript submitted for publication.

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