Published Online: 30 March 2022 *eISSN 2984-8644*

CASE REPORT

Philippine Journal of Allergy, Asthma and Immunology

The Road Less Traveled: A Case Report on Intestinal Behçet's Disease

Glaiza M. Madulara, MD and Pilar Agnes M. Gonzalez-Andaya, MD

Section of Allergy and Clinical Immunology, University of Santo Tomas Hospital, Manila, Philippines

Correspondence to:
Glaiza M. Madulara, MD
De Los Santos Medical Center
201 E. Rodriguez Sr. Avenue,
Quezon City, 1112 Metro Manila, Philippines
E-mail: glaizamadulara.md@gmail.com

ABSTRACT

Behçet's Disease (BD) is a rare, chronic, systemic vasculitis with diverse manifestations. The patient was a 29-year-old male with a 10-year history of recurrent oral ulcers and gastrointestinal symptoms, managed as different clinical scenarios prior to reaching a final diagnosis of Intestinal BD. Though BD is a diagnosis of exclusion, it should be included in the differential diagnoses of systemic disorders presenting with recurrent oral ulcers.

Keywords: case report, Behçet's Disease, oral ulcers

This case report was presented in the Philippine Society of Allergy, Asthma and Immunology (PSAAI) Inter-hospital Case Presentation, July 18, 2018, at Luxent Hotel, Quezon City, Philippines and in the Joint Congress of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology and the Asia Pacific Association of Pediatric Allergy, Respirology and Immunology Poster Presentation, October 11–14, 2018, Centara Grand and Bangkok Convention Centre at Central World, Bangkok, Thailand.

INTRODUCTION

Behçet's disease (BD) is a rare, chronic, relapsing, immune-mediated, multisystemic, variable vessel vasculitis with diverse clinical manifestations.[1,2]

To our knowledge, this is the first case report of Intestinal BD in the Philippines. This report emphasizes the importance of recognizing the evolution of the signs and symptoms of BD through time because a delay in the diagnosis can lead to serious complications.

PATIENT INFORMATION

A 29-year-old Filipino male presented with a 10-year history of recurrent painful oral ulcers responsive to steroids and gastrointestinal symptoms of abdominal pain, dysphagia, anorexia, and weight loss. Disease progression resulted in the development of joint pains and genital ulcers.

He had no exposure to tuberculosis and denied past sexually transmitted illnesses. There was no family history of recurrent oral ulcers or autoimmune or auto-inflammatory diseases. His father died of colon cancer.

CLINICAL FINDINGS

The physical examination revealed an underweight young adult with multiple round and elongated aphthous ulcers with sharp, erythematous, and elevated borders in the buccal mucosa, soft palate, and tongue, covered by a yellowish pseudomembrane (Figure 1). Genital examination revealed urethral ulcers. Physical examination of other organ systems was normal.

TIMELINE (Figure 2)

DIAGNOSTIC ASSESSMENT

Using the revised diagnostic criteria of the BD Research Committee of Japan, the patient was diagnosed with Incomplete Intestinal BD due to the presence of two main symptoms (recurrent oral ulcers and genital ulcers) plus two additional symptoms (gastrointestinal lesions represented by ileocecal ulceration and arthritis without deformity) (Table 1).[3] Recurrent oral ulcers were defined as minor/ major aphthous or herpetiform ulcerations, which recurred at least three times in one 12-month period.[2] Differential diagnoses like tuberculosis, ileocolitis, and Crohn's disease were ruled out based on clinical findings, imaging, and endoscopy.[4,5]

THERAPEUTIC INTERVENTION AND OUTCOME

The patient was referred to a rheumatologist and was treated with methylprednisolone 16 mg once daily for two weeks, followed by tapering doses of prednisone initially started at 15 mg. Colchicine 0.5 mg per day was then initiated but was discontinued after one month due to diarrhea. Termination of medications resulted in the recurrence of oral ulcers. Hence, he was immediately started on methotrexate 15 mg once weekly, with a good response.

DISCUSSION

Behçet's disease, or the "Silk Road disease", is a chronic relapsing disease with multiple organ system involvements. Onset typically occurs in the third or fourth decade of life, with male preponderance in Middle Eastern countries but more frequent in women in Japan and Korea.[6] The pooled prevalence of BD from 45 international population-based surveys (cases/100,000 inhabitants) was 10.3 for all studies and 119.8 for Turkey, 31.8 for the Middle East, 4.5 for Asia, and 3.3 for Europe.[7]

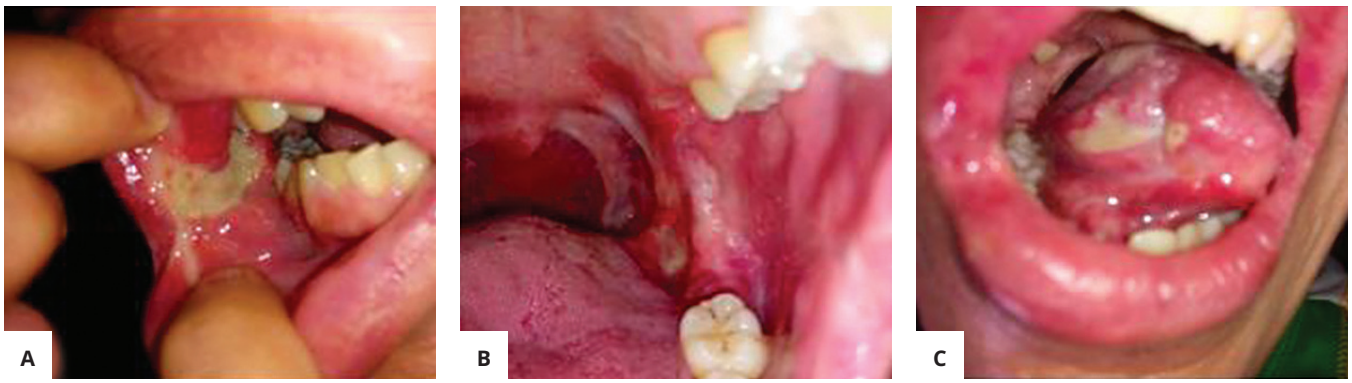

Figure 1. Oral lesions on the **(A)** buccal mucosa, **(B)** soft palate and **(C)** tongue of the patient.

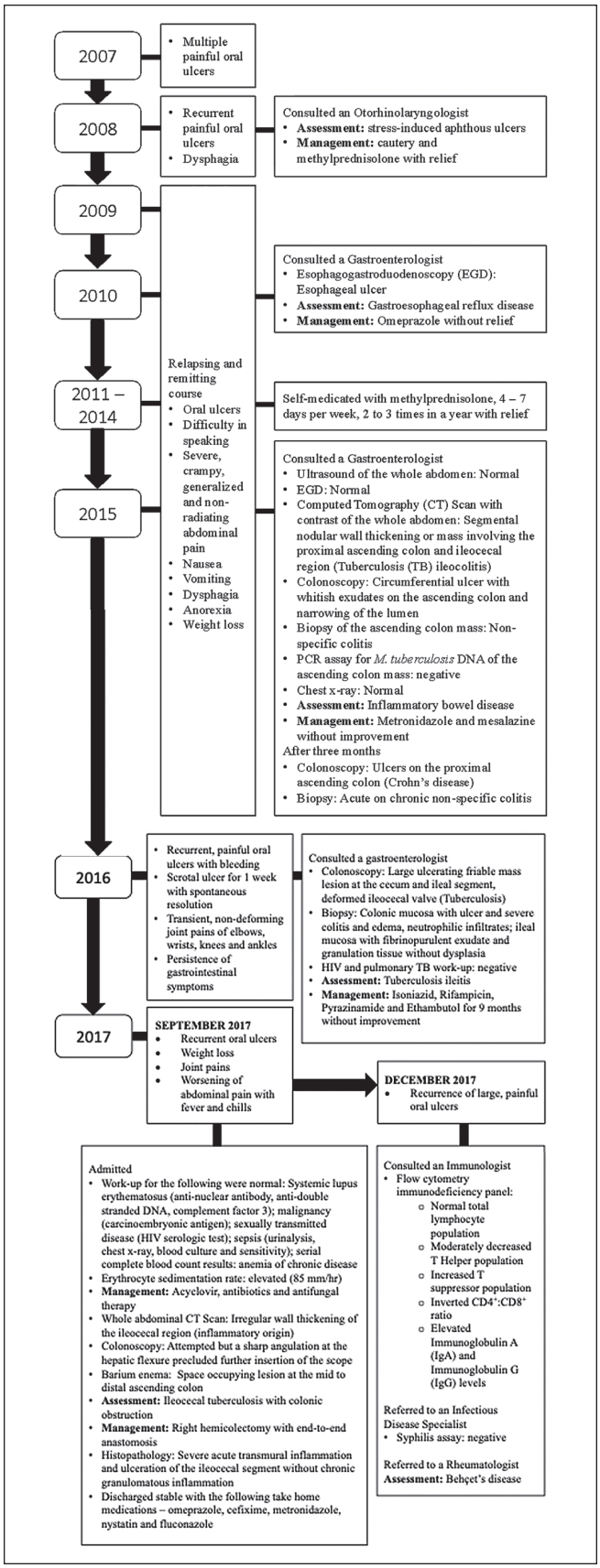

Figure 2. Timeline of Behçet's Disease of the patient.

Table 1. Revised diagnostic criteria proposed by the Behcet's Disease (BD) Research Committee of Japan in 2003[3]

Main Points
1) Main symptoms a) Recurrent oral aphthous ulcers b) Skin lesions (erythema nodosum, subcutaneous thrombophlebitis, papules, and skin hypersensitivity) c) Ocular lesions (iridocyclitis, posterior-uveitis) d) Genital ulcers
2) Additional symptoms a) Arthritis without deformity or sclerosis b) Epididymitis c) Gastrointestinal lesion with ileocecal ulceration d) Vascular lesions e) Central nervous system lesions
3) Criteria for diagnosis of disease types a) Complete type: i) 4 main symptoms appeared during the clinical course b) Incomplete types: The following appeared during the clinical course: i) 3 main symptoms, or 2 main symptoms and 2 additional symptoms ii) Typical ocular lesion and another main symptom, or 2 additional symptoms c) BD suspected i) Although some main symptoms appear, the case does not meet the criteria for the incomplete type ii) Typical additional symptom is recurrent or becomes more severe d) Special lesions i) Gastrointestinal lesions ii) Vascular lesions iii) Neuronal lesions
Clinical Laboratory Data
1) Clinical laboratory data contributing to the diagnosis (not essential) a) Negative or positive pathergy test b) Negative or positive prick test for vaccine for streptococci c) Inflammatory responses i) Increase of ESR, CRP positive, neutrophilia in peripheral blood, increase of complement activity d) Positive for HLA-B51 e) Other pathological findings

Its exact prevalence in the Philippines is unknown. In a local descriptive study done in a tertiary hospital, there were 31 patients with BD, of which 77% were females. The average delay in diagnosis was three years, which hindered early treatment since symptoms may emerge at different points in time.[8] In this case report, the patient was a 29-year-old male whose symptoms started ten years prior to the diagnosis of BD.

The heterogeneous clinical presentation differs among geographies, wherein gastrointestinal disease was reported to be common among Asians.[9] Among Filipinos, the most common features were oral ulcers (94%), followed by ocular manifestations (68%), cutaneous disease (65%), genital ulcers (58%), and vascular involvement (10%).[8] There were no recorded patients who presented with gastrointestinal symptoms.

The diagnosis remains on clinical grounds.[2] The International Study Group for BD defined a set of classification criteria, which included recurrent oral ulceration plus 2 of the following: recurrent genital ulceration, eye lesion, skin lesions, and/or a positive pathergy test (≥2 mm sterile pustule 24 to 48 hours after an intradermal injection on the forearm.[2,10] Pathergy test is a non-specific, type IVd skin hyperreactivity.[2,11] Among Filipinos with BD, it was positive in only 17%.[8] Pathergy-like inflammatory reactions can also be triggered by skin trauma or needle injury.[12] In this patient, the pathergy test was presumed to be negative since he did not have a history of skin hyperreactivity induced by needle prick.

Due to unusual presentations and incomplete disease types, the BD Research Committee of Japan revised the criteria to emphasize a broader disease spectrum, including gastrointestinal lesions (Table 1).[3,13]

There are no diagnostic laboratory tests for BD (Table 1).[3] However, affected individuals may present with anemia of chronic disease, elevated ESR, and elevated IgG and IgA levels – all of which were manifested by the patient.[14,15] IgA level was elevated secondary to oral and gastrointestinal mucosal injury and inflammation, while high IgG level reflected its role in chronic, active inflammation.[14]

Understanding the pathophysiology is challenging because it is "at the crossroad between an autoimmune and an autoinflammatory syndrome."[16]

BD may be initiated by environmental factors—such as infectious agents—in genetically susceptible patients (Figure 3).[6] An association with human leukocyte antigen (HLA)-B*51 is the strongest genetic risk factor.[17] Other disease susceptibility genes include other non-HLA polymorphisms.

Infectious agents—such as *Streptococcus sanguinis* in the oral flora—are possible triggers. Immune response commences in the oral mucosa by recognition of bacterial heat shock protein (HSP), homologous to human HSP, which leads to molecular mimicry.[18] HSP is recognized by pattern recognition receptors as a danger signal, which leads to uncontrolled activation of innate and adaptive systems, resembling an autoinflammatory reaction. Proinflammatory cytokines activate autoantibody production, such as anti-endothelial cell autoantibodies,

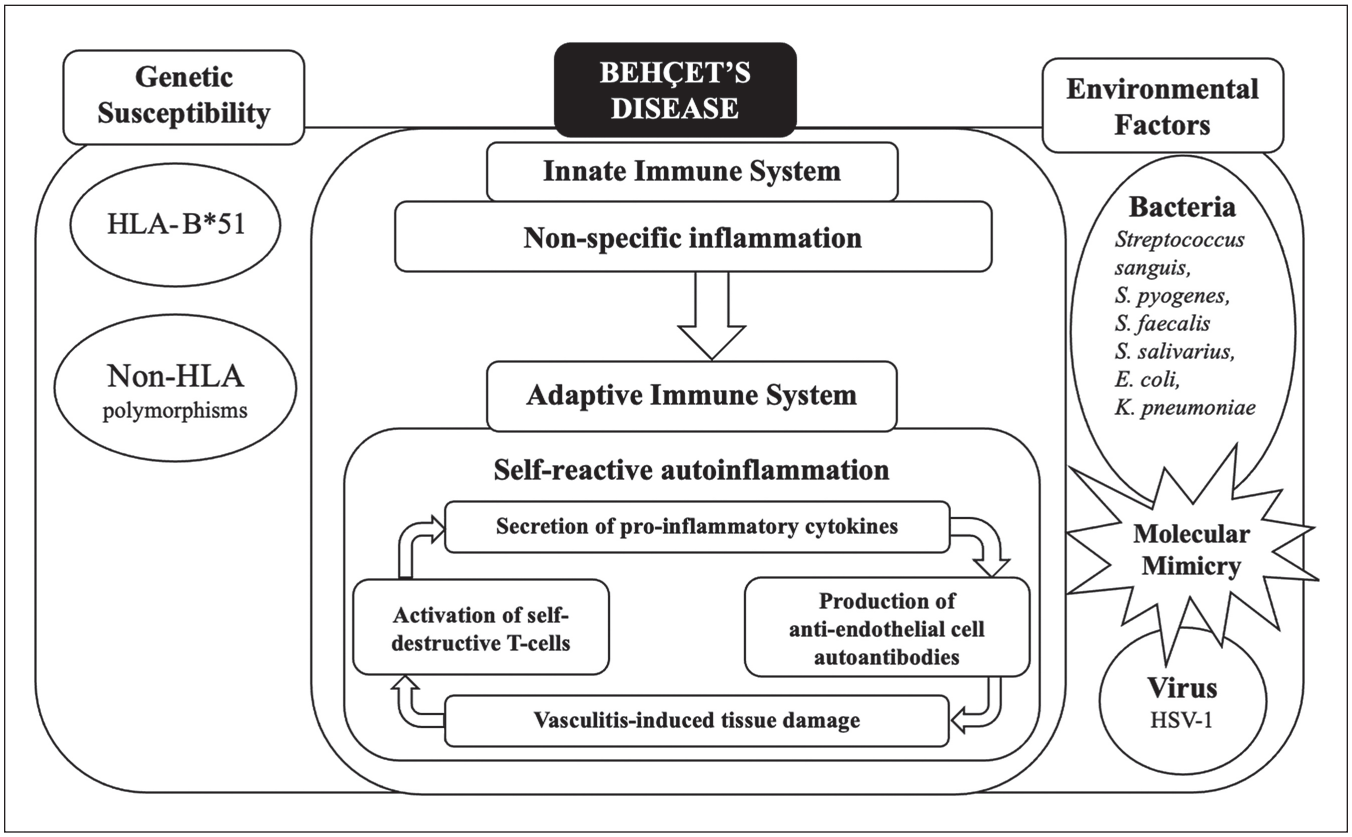

Figure 3. Etiopathogenesis of Behçet's disease.

Modified from Cho SB, et al. New Insights in the Clinical Understanding of Behçet's Disease.[6]

which activate self-destructive T-cells, as with an autoimmune response.[6] This leads to a continuous cycle of tissue injury via delayed-type hypersensitivity reaction, macrophage activation, and activation of neutrophils, γδ T cells, and natural killer cells.[19,20]

In BD, antigen presentation by antigen-presenting cells to naïve $CD4^+$ T cells leads to activation of Th1 cells, which stimulates macrophage activation; activation of Th17 cytokines, which induces neutrophil-induced tissue injury; and suppression of T regulatory cells, which leads to immune dysregulation and loss of immune tolerance.[20] Th17 cells are abundant in the gastrointestinal tract, suggesting their importance in the development of pathologic intestinal inflammation in BD. The patient's flow cytometry results show decreased $CD4^+$ T helper population and an increased $CD8^+$ T suppressor population. $CD4^+$ T cells orchestrate and regulate immune responses against pathogens. Hence, diminished $CD4^+$ numbers lead to susceptibility to infection and autoimmunity.[21] Elevated $CD8^+$ T cells are responsible for the cytotoxic tissue destruction.[22]

Classified as a type IVd hypersensitivity reaction, BD corresponds to a delayed hypersensitivity, T-cell-dependent, sterile neutrophilic inflammation. The patient's ileocecal biopsy revealed neutrophilic infiltrates with inflammation. The release of CXCL8 and GM-CSF activates sterile neutrophils, the main agents responsible for endothelial dysfunction and tissue damage.[19,20,23]

Approximately 3–16 % of patients with BD have gastrointestinal involvement.[1] Symptoms appear 4.5–6 years after the onset of oral ulcers.[24] There are no specific symptoms for Intestinal BD. However, Watanabe et al., recommended that Intestinal BD should be considered when abdominal pain, bloody stool, abdominal mass, diarrhea, and weight loss are present.[15]

Since it is challenging to make a diagnosis when gastroenteropathy is the predominant manifestation, consensus statements for the diagnosis and management of Intestinal BD were developed (Table 2).[4]

Gastrointestinal involvement of BD should be confirmed by endoscopy and/or imaging.[5] In BD, colono-scopies reveal oval punched-out ulcers or multiple ulcers with well-defined margins.[15] The ileocecal region is most commonly affected, but the transverse colon and ascending colon are sometimes involved.[25] The patient's colonoscopy displayed an ulcerating mass at the ileocecal segment and a circumferential ulcer on the ascending colon. Barium studies demonstrate discreet ulcer/s with thickened mucosal folds and ileocecal mass with ulceration in BD patients.[26] The patient's barium enema showed a space-occupying lesion at the ascending colon. CT scans of BD patients reveal uneven bowel wall thickening with enhancement, which suggests blood stasis due to vasculitis. This is supported by histopathological findings of leukocytoclastic vasculitis, chronically active non-specific inflammation, neutrophilic infiltration, and fibrinoid necrosis.[15,26] The patient's CT scan exhibited irregular wall thickening. His histopathology revealed fibrinopurulent exudate and severe acute inflammation and ulceration of the ileocecal segment.

Table 2. Consensus statements for the diagnosis and management of Intestinal Behçet's Disease[4]

Diagnosis and Management
1) Diagnosis of intestinal Behçet's disease can be made if there is/are: a) a typical oval-shaped large ulcer in the terminal ileum, OR b) ulcerations or inflammation in the small or large intestine, and clinical findings meet the diagnostic criteria of BD.
2) Acute appendicitis, infectious enteritis, tuberculosis, Crohn's disease, non-specific colitis, drug-associated colitis, and other diseases that mimic intestinal Behçet's disease should be excluded by clinical findings, radiology, and endoscopy before diagnosis of intestinal Behçet's disease is made.

The patient's clinical, radiologic, and endoscopic findings were compatible with BD. Tuberculosis (TB) ileocolitis was considered since TB is common in the Philippines. Both TB ileocolitis and Intestinal BD manifest ulcerations in the ileocecal region. But unlike BD, intestinal tuberculosis is characterized by granuloma with positive acid-fast bacilli stain, which was not present in the patient.[26] Crohn's disease (CD) was also considered due to the similarity in symptoms. Like CD, intestinal BD manifests with ulcers, discontinuous bowel involvement, and rectal sparing.[26] Histologically, both have chronic non-specific inflammation with normal intervening mucosa. However, unlike CD, Intestinal BD is characterized by vasculitis of the small veins and venules with deep ulcerations, without a cobblestone appearance, granulomas, and skip lesions.[26] Poor response to TB and CD treatments and recurrence of oral ulcers with improvement during steroid therapy prompted the physicians to entertain the diagnosis of Intestinal BD.

Since no curative solution is currently available, treatment aims to suppress exacerbations to prevent irreversible organ damage.[5] For oral and genital ulcers, topical steroids are recommended.[5] For prevention of recurrent mucocutaneous lesions and patients with acute arthritis, colchicine is usually tried first.[5] Several open studies on methotrexate (7.5–20 mg once a week over four weeks) reported improved mucocutaneous, neurological, ocular, and gastrointestinal involvement.[4,27] For Intestinal BD, some of the therapeutic strategies and

Table 3. Excerpt of consensus statements for the standard treatment of intestinal BD (second edition) by Research Committee for small bowel inflammation of unknown etiology and BD Research Committee, Japan[4]

Standard Treatment	
Patients with severe symptoms (i.e., abdominal pain, diarrhea, gastrointestinal bleeding) and complications with deep ulcers	
Corticosteroids	• Initial dose = 0.5–1 mg/kg per day of prednisolone for 1–2 weeks • When clinical improvement is observed, prednisolone should be tapered by 5 mg every week and finally stopped.
Adalimumab	• Induction therapy (subcutaneously; 160 mg at 0 week, 80 mg at 2nd week, 40 mg at 4th week) • Maintenance therapy should be considered among responders (40 mg subcutaneously every other week)
Infliximab	• Induction therapy (5 mg/kg at week 0, 2, and 6) • Maintenance therapy should be considered among responders every 8 weeks.
Patients with mild to moderate activity	
Mesalazine (5-ASA)	• Effective for induction therapy
Patients in clinical remission	
5-ASA and colchicine	• Effective for maintenance therapy • Optimal dose of 5-ASA = 2.25–3 g/day
Sulfasalazine	• Optimal dose = 3–4 g/day
Corticosteroid-dependent, corticosteroid-resistant, or anti-TNFmAb-resistant patients	
Azathioprine (AZA)	• Initial dose = 25–50 mg/day
6-mercaptopurine, cyclosporine, tacrolimus and methotrexate	• Use of these immunomodulators require consultations with specialists who have sufficient experience.

standard doses were summarized in Table 3 based on the recommendations of the Research Committee in Japan.[4] Other organ-specific management of BD is beyond the scope of this report but can be found in the "2018 Update of the EULAR Recommendations for the Management of Behçet's Syndrome".[5]

Intestinal lesions in BD are associated with poor prognosis, resulting in emergency abdominal surgery and bowel resection.[1] The deep ulcers are responsible for intestinal complications, such as obstruction, as seen in the patient. Other complications include bleeding, fistula, and perforation.[1]

The impact of BD on psychosocial well-being is significant. While there is no direct effect on fertility, the influence of genital ulcerations and psychological stress is immense.[28]

The strength of this case report was its detailed history of the evolution of Intestinal BD. Complete BD is easy to identify, but incomplete forms require high clinical suspicion. Its limitation was the lack of long-term follow-up. Regular follow-up is vital because post-operative recurrence can occur within two years, with a recurrence rate as high as 30% to 75%.[15]

CONCLUSION

Patients with recurrent oral ulcers may represent a *forme fruste* of BD. Diagnosis of Intestinal BD is clinical, with no specific laboratory, radiologic, or histologic findings. Timely diagnosis is ideal for providing early intervention and avoiding its complications.

REFERENCES

1. Hisamatsu T, Naganuma M, Matsuoka K, Kanai T. Diagnosis and management of intestinal Behçet's disease. Clin J Gastroenterol. 2014;7(3):205-12. PMID: 24883128 PMCID: PMC4037558 DOI: 10.1007/s12328-014-0488-0
2. Leonardo NM, McNeil J. Behcet's Disease: is there geographical variation? a review far from the silk road. Int J Rheumatol. 2015;2015:945262. PMID: 26798344 PMCID: PMC4698787 DOI: 10.1155/2015/945262
3. Kurokawa M, Suzuki N. Behcet's disease. Clin Exp Med. 2004;4(1):10-20. PMID: 15598081 DOI: 10.1007/s10238-004-0033-4
4. Hisamatsu T, Ueno F, Matsumoto T, et al. The 2nd edition of consensus statements for the diagnosis and management of intestinal Behçet's disease: indication of anti-TNFα monoclonal antibodies. J Gastroenterol. 2014;49(1):156-62. PMID: 23955155 PMCID: PMC3895195 DOI: 10.1007/s00535-013-0872-4
5. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018;77(6):808-18. PMID: 29625968 DOI: 10.1136/annrheumdis-2018-213225
6. Cho SB, Cho S, Bang D. New insights in the clinical understanding of Behçet's disease. Yonsei Med J. 2012;53(1):35-42. PMID: 22187230 PMCID: PMC3250322 DOI: 10.3349/ymj.2012.53.1.35
7. Maldini C, Druce K, Basu N, LaValley MP, Mahr A. Exploring the variability in Behçet's disease prevalence: a meta-analytical approach. Rheumatology (Oxford). 2018;57(1):185-95. PMID: 28339670 DOI: 10.1093/rheumatology/kew486
8. Limgenco-Hipe JR, Salido E, Penserga E. Disease characteristics of Behcet's disease among Filipino patients seen in rheumatology clinics. Philipp J Intern Med. 2017; 55(4):1-5. https://pcp.org.ph/images/PJIM/PJIM_2017_Vol55_no4/FINAL-2015-027_Disease_Characteristics_of_Behcet_s_Disease_among_Filipino_Patients_Seen_in_Rheumatology_Clinics.pdf

9. Yazici H, Ugurlu S, Seyahi E. Behçet syndrome: is it one condition? Clin Rev Allergy Immunol. 2012 Dec;43(3):275-80. PMID: 22674015 DOI: 10.1007/s12016-012-8319-x
10. Davatchi F, Chams-Davatchi C, Shams H, et al. Behcet's disease: epidemiology, clinical manifestations, and diagnosis.Expert Rev Clin Immunol.2017;13(1):57-65.PMID: 27351485 DOI: 10.1080/1744666X.2016.1205486
11. Burks AW, Holgate ST, O'hehir RE, et al (eds). Middleton's allergy: principles and practice, 9th ed. Philadelphia: Elsevier Inc; 2020.
12. Johnson TL, McCleskey PE, Rathkopf M, Meffert JJ, Hagan LL. Pathergy response to skin prick testing. J Allergy Clin Immunol. 2007;119(5):1270-2. PMID: 17353037 DOI: 10.1016/j.jaci.2007.01.033
13. Kirino Y, Nakajima H. Clinical and genetic aspects of Behçet's disease in Japan. 2019;58(9):1199-207. PMID: 30626832 PMCID: PMC6543215 DOI: 10.2169/internalmedicine.2035-18
14. Polat M, Parlak AH, Serin E, et al. Humoral immune response in Behçet's disease: cross-sectional study. J Turk Acad Dermatol. 2010;4(4):04401a. https://cms.jtad.org/Uploads/Article_32367/jtad-4-0-En.pdf
15. Watanabe K, Tanida S, Inoue N, et al. Evidence-based diagnosis and clinical practice guidelines for intestinal Behçet's disease 2020 edited by intractable diseases, the health and labour sciences research grants. J Gastroenterol. 2020;55(7):679–700. PMID: 32377946 PMCID: PMC7297851 DOI: 10.1007/s00535-020-01690-y
16. Hedayatfar A. Behçet's disease: Autoimmune or autoinflammatory? J Ophthalmic Vis Res. 2013;8(3):291-3. PMID: 24349676 PMCID: PMC3853784
17. Marshall SE. Behçet's disease. Best Pract Res Clin Rheumatol. 2004;18(3):291-311. PMID: 15158742 DOI: 10.1016/j.berh.2004.02.008
18. Mumcu G, Fortune F. Oral health and its aetiological role in Behçet's disease. Front Med (Lausanne). 2021;8:613419. PMID: 34095159 PMCID: PMC8172597 DOI: 10.3389/fmed.2021.613419
19. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med. 2003;139(8):683-93. PMID: 14568857 DOI: 10.7326/0003-4819-139-8-200310210-00012
20. Emmi G, Silvestri E, Squatrito D, et al. Behçet's syndrome pathophysiology and potential therapeutic targets. Intern Emerg Med. 2014;9(3):257-65. PMID: 24415351 DOI: 10.1007/s11739-013-1036-5
21. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol. 2010;28:445-89. PMID: 20192806 PMCID: PMC3502616 DOI: 10.1146/annurev-immunol-030409-101212
22. Al-Dalaan A, Bahabri S, Al-Balla SR, et al. Abnormalities of T cell subsets in Behcet disease. Ann Saudi Med. 1993;13(3):275-9. PMID: 17590677 DOI: 10.5144/0256-4947.1993.275
23. Kovacs DB, Ray DK, Dasgupta K, Borowski DW. Intestinal complications of Behçet's disease. BMJ Case Rep. 2013;2013:bcr2013200253. PMID: 23917369 PMCID: PMC3762539 DOI: 10.1136/bcr-2013-200253
24. Valenti S, Gallizzi R, De Vivo D, Romano C. Intestinal Behçet and Crohn's disease: two sides of the same coin. Pediatr Rheumatol Online J. 2017;15(1):33. PMID: 28427473 PMCID: PMC5397832 DOI: 10.1186/s12969-017-0162-4
25. Saadoun D, Wechsler B. Behçet's disease. Orphanet J Rare Dis. 2012;7:20. PMID: 22497990 PMCID: PMC3472229 DOI: 10.1186/1750-1172-7-20
26. Wu QJ, Zhang FC, Zhang X. Adamantiades-Behcet's disease-complicated gastroenteropathy. World J Gastroenterol. 2012;18(7):609-15. PMID: 22363131 PMCID: PMC3281217 DOI: 10.3748/wjg.v18.i7.609
27. Alpsoy E. New evidence-based treatment approach in Behçet's disease. Patholog Res Int. 2012;2012:871019. PMID: 22007346 PMCID: PMC3189606 DOI: 10.1155/2012/871019
28. Nair JR, Moots RJ. Behcet's disease. Clin Med (Lond). 2017;17(1):71-7. PMID: 28148585 PMCID: PMC6297594 DOI: 10.7861/clinmedicine.17-1-71