Clinical Case Report

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Multiple aneurysms and gastrointestinal involvement in Behcet's disease

A case report

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Abstract

Rationale: Behcet's disease (BD) is a rare systemic vasculitis disorder that can involve vessels of any size.

Patient Concerns: A 60-year-old female had recurrent painful mouth ulcers about 30 years ago and recently presented with abdominal distension, conjunctival congestion, and chest pain in sequence.

Diagnoses: The patient was diagnosed with BD according to the International Criteria for Behcet's Disease (ICBD).

Interventions: A therapy of glucocorticoids and cyclophosphamide was administered.

Outcomes: After a 3-month treatment, follow-up examination showed a depression of the inflammation and a slight decrease of the arterial aneurysms.

Lessons: BD patients may get a delayed diagnosis because of the long duration between the first and subsequent manifestations. Suspect patients should be followed-up and the diagnosis of BD should be considered when multiple tissues or organs are involved.

Abbreviations: ACA = anticentromere antibodies, ANA = antinuclear antibodies, BD = Behcet's disease, BDCAF = Behcet's Disease Current Activity Form, CRP = C-reactive protein, CT = computed tomography, CTA = computed tomography angiography, ESR = erythrocyte sedimentation rate, GWAS = genome-wide association studies, ICBD = International Criteria for Behcet's Disease, ISG = International Study Group, LAD = left anterior descending branch, LCA = left coronary artery, MPO-ANCA = antibodies to myeloperoxidase, PR3-ANCA = antibodies to proteinase-3, RAU = recurrent aphthous ulceration, UC = ulcerative colitis, UCG = ultrasound cardiogram.

Keywords: Behcet's disease, gastrointestinal involvement, multiple aneurysms

1. Introduction

Behcet's disease (BD) is a multisystem disease that has been classified among vasculitides since the 2012 International Chapel Hill Consensus Conference.[1] It typically starts around the third or fourth decade and infrequently develops before puberty or after one's 50s.[2] The typical triad of BD is recurrent oral aphthous ulceration associated with genital ulceration and ocular lesions. Involvement of the cardiovascular, pulmonary, neurological, or gastrointestinal systems is rare, though they may cause serious disability or be life threatening.[3] The symptoms of BD exhibit a pattern of exacerbation and remission, and they can occur either simultaneously or in sequence, sometimes the interval duration between 2 symptoms can be as long as 30 years, especially when oral aphthous lesions occur first.[4] As a disease with no specific laboratory markers, judgment of the disease is based mostly on clinical features and the physician's experience. As a result, when only one or few uncommon manifestations present first, it is usually difficult to make a definite diagnosis.

In this paper, we report a BD patient with multiple aneurysms and gastrointestinal involvement. Old age, atypical symptoms, and long intervals between the manifestations made it difficult to diagnose. The case subject was carrying the HLA-B13/40 phenotype, which was seldom reported in the past. She was given a therapy of glucocorticoids and cyclophosphamide. Three months later, the patient showed a depression of inflammation with a decrease of the arterial aneurysms.

Approval for the study by the local institutional review board was not required because it was a case report. Informed consent has been given by the patient.

2. Case report

A 60-year-old woman was admitted to our department on 11 April 2016 with complaints of intermittent abdominal distension for the past 3 years which aggravated 6 months earlier. The abdominal distension would be triggered by cold or hot diet, but was not accompanied by abdominal pain, vomiting,

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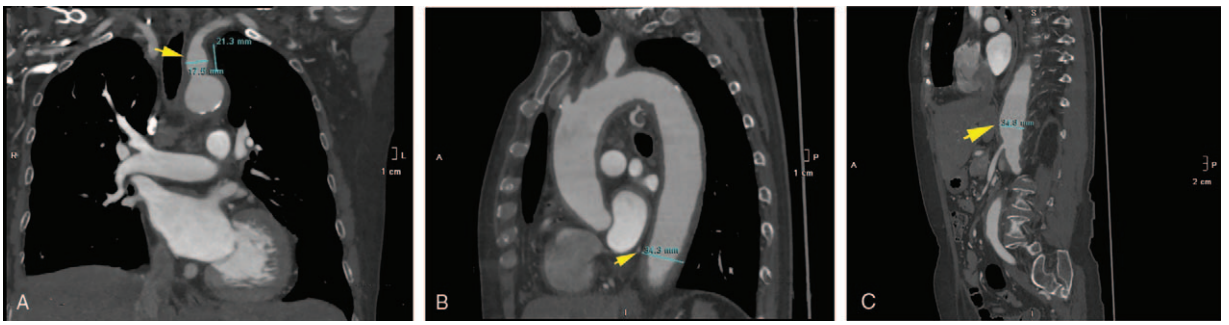

Figure 1. (A) A 17.5 × 21.3 mm-diameter arterial aneurysm in the left subclavian artery. (B) A 34.3 mm-diameter arterial aneurysm in the descending aorta. (C) A 34.8 mm-diameter arterial aneurysm in the proximal abdominal aorta.

hematochezia, or diarrhea. A colonoscopy 3 years ago showed multiple, small ulcers in the ascending colon, leading to a diagnosis of ulcerative colitis (UC) and subsequent treatment with *mesalazine* for 6 months. Her symptoms persisted and a repeat colonoscopy revealed that the ulcers were still present. The patient took herbal decoctions occasionally. A detailed history revealed that in her 30s, the patient had recurrent painful aphthous ulcers almost once a month. She also had a 10-year history of anemia, a 6-year of asthma and recurrent conjunctival congestion in her left eye for 1 year. Two months before admission, she began experiencing chest pains with increasing frequency. The patient had no personal or family history of hypertension, diabetes mellitus or coronary heart disease. On admission, her physical examination revealed a blood pressure of 160/90 mm Hg and conjunctival congestion in the left eye. Laboratory analysis revealed that her hemoglobin was 8.5 g/L, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated at 75.8 mg/L and 102 mm/h, respectively. Stool routine and occult blood test were negative. During her stay, colonoscopy was not recommended because of her frequent chest pains, while an EKG showed a ST-T segment depression in a VL, V4, V5, and V6. Ultrasound cardiogram (UCG) showed an enlarged left ventricle with widened ascending aorta and moderate aortic insufficiency. Coronary artery CT revealed a slight calcification with calcium score 12.5 and mild stenosis of her left coronary artery (LCA) and left anterior descending branch (LAD). Further immunologic test revealed positive for antinuclear antibodies (ANA) and anticentromere antibodies (ACA)1:1000 (using indirect immunofluorescence assay), but negative for antibodies to proteinase-3(PR3-ANCA), antibodies to myeloperoxidase(MPO-ANCA), anticardiolipin antibodies, anti-β2GP1 antibodies, TB test, and PPD (diameter of the nodule is 2 mm). Gene testing was positive for HLA-B13:02 and HLA-B 40:01 phenotypes. Ophthalmic consultation showed retina vasculitis in her left eye. Bone marrow biopsy showed no pathologic change that could accounted for her anemia. An expansion in the thoracic and abdominal aorta was revealed by an abdominal computed tomography (CT). A computed tomography angiography (CTA) on May 3, 2016 showed a 17.5 × 21.3 mm-diameter aneurysm in the left subclavian artery (Fig. 1A), a 34.3 mm-diameter aneurysm in the descending aorta (Fig. 1B) and a 34.8 mm-diameter aneurysm in the proximal abdominal aorta (Fig. 1C).

Taking the history of recurrent aphthous ulcers, ulcers in the ascending colon, and the CTA results into consideration, she was diagnosed with BD according to International Criteria for Behcet's Disease (ICBD) (Table 1). The patient's activity index score was 3 according to the Behcet's Disease Current Activity Form (BDCAF).[5] She was then treated with methylprednisolone 32 mg daily combined with cyclophosphamide 50 mg twice a day orally starting on June 8, 2016. However, the patient had difficulty falling asleep after taking the medicine. So methylprednisolone was replaced with prednisolone 40 mg daily after a week. After 2 months, her abdominal distension was relieved and the chest pains less frequent, leading to a reduction in cyclophosphamide to 50 mg once a day starting on August 2, 2016. Three months later after she was first treated, her activity index score reduced from 3 to 1, CRP and ESR levels declined to 18 mm/h and 10 mg/L, respectively. The colonoscopy found no ulcers in the colon. CTA was repeated and showed an 18.6 mm-diameter aneurysm in the left subclavian artery and a 31.6 mm-diameter aneurysm in the descending aorta and (Fig. 2B), and a 34.1 mm-diameter aneurysm in the proximal abdominal aorta (Fig. 2C). Timeline of patient presentation, intervention, and follow-up was shown in Table 2.

Table 1

The New ICBD[6].

Sign/symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin manifestations	1
Neurological manifestations	1
Vascular lesions	1
Pathergy phenomenon (test)	1*

* Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted 1 extra point may be assigned for a positive result.

3. Discussion

Recurrent oral and genital aphthosis, ocular lesions, skin manifestations, and pathergy phenomenon are the most common characteristics of BD. International Study Group (ISG) criteria requires the presentation of oral aphthosis and 2 other manifestations to establish the diagnosis of BD. However, the ISG criteria, though being widely used, have a relatively low sensitivity, especially for atypical BD. On one hand, the abovementioned symptoms may not be the obligatory symptoms of BD. Gharibdoost et al[6] reported that 27% out of 2,176 Behcet's cases presented without oral lesions as the initial manifestation and 5% of patients did not exhibit any oral lesions at all. On the other hand, the manifestations of cardiovascular,

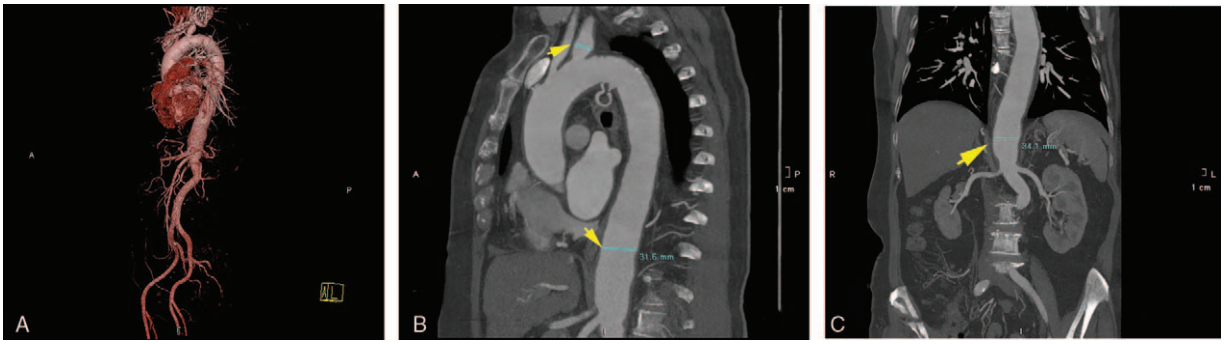

Figure 2. (A) A three-dimensional imaging of the arteries after 3 months. (B) An 18.6 mm-diameter arterial aneurysm in the left subclavian artery and a 31.6 mm-diameter arterial aneurysm in the descending aorta. (C) A 34.1 mm-diameter arterial aneurysm in the proximal abdominal aorta.

nervous, and gastrointestinal systems, which are more closely related to the prognosis, only serve as additional items in ISG criteria. A new criteria created by International Team for the Revision of ICBD in 2014 is based on a large cohort of patients from 27 countries (Table 1). It includes both typical and atypical symptoms of the disease and BD can be diagnosed when the 4 or more points can be fulfilled. The sensitivity of ICBD criteria was much higher than ISG (94.8% vs 85%), and the specificity was lower but still acceptable high (90.5% vs 96%).[7] The case we report had recurrent oral aphthosis, ocular lesions, and vascular lesions. Scoring 5 points on the ICBD and having symptoms that no other disease can explain satisfactory, it makes a definite diagnosis of BD.

Vascular involvement is one of the most important features of BD, which can be seen in about 2.2 to 50% of BD patients, depending on the country. In China, the percentage is about 7.7%, and it happens more frequently in males.[2] Vessels of any size, from capillaries to large vessels can be involved. The most common manifestation is vein thrombosis. When it involves arteries, the manifestations are usually thrombosis and aneurysms. Aneurysms of major arteries commonly lead to bleeding infarction, organ failure, or potentially fatal ruptures.

Gastrointestinal involvement is more frequently seen in the Far East region such as Japan. Though ileocecal involvement is most commonly described, mucosal inflammation and ulceration can occur at any segment of the alimentary tract from the esophagus to the anus. Abdominal distension is one of most common manifestations other than abdominal pain.[8] When it occurs in colon, just as the case we report, it should be differentiated from UC. Although oral ulcer, ocular involvement and vascular lesions can also be seen in UC, the patient was ruled out for several reasons. Firstly, UC patients always present with abdominal pain and bloody diarrhea, while our patient did not exhibit these symptoms and her occult blood test was negative. Secondly, the patient was treated with *mesalazine* for 6 months when she was first diagnosed with UC, but her symptoms showed no improvement and a repeat colonoscopy showed the ulcers still existed as before. However, after treatment with methylprednisolone combined with cyclophosphamide for 3 months, the colon ulcers resolved. UC can be complicated with vascular injuries such as Takayasu Arteritis (TA) but the occurrence of TA in patients with UC has rarely been reported in the world and develops mostly in young women.[9] The abnormality of TA is often the thickening of the vessel wall by inflammation that further leads to the stenosis of the artery.[10]

Ocular manifestations are the most disabling injuries of BD. All internal components of the eye can be involved. Destructive and recurrent attacks will cause loss of vision that may progress to blindness if left untreated. Uveitis is most frequently seen and other manifestations also include iridocyclitis, keratitis, episcleritis, scleritis, vitritis, vitreous hemorrhage, retinal vasculitis, retinal vein occlusion, retinal neovascularization, and optic neuritis.[11] The patient we reported had a recurrent and relapsing conjunctival congestion for about 1 year and at last was diagnosed with retina vasculitis.

Currently, with no laboratory markers that directly correlate with clinical activity in BD, judgment of disease activity is usually based on the clinical manifestations and the physician's

Table 2

Timeline of patient presentation, intervention and follow-up.

Date/Time	Action
30 years ago before admission	The patient had recurrent painful oral ulcers almost once a month in her thirties and then got spontaneous remission
3 years ago before admission, about in 2013	Colonoscopy revealed multiple, small ulcers in the ascending colon
February, 2016	The patient began experiencing chest pains with increasing frequency
March, 2016	The patient began to present with recurrent conjunctival congestion in her left eye
May 3, 2016	CTA showed arterial aneurysms in the left subclavian artery, the descending aorta and the proximal abdominal aorta
June 8, 2016	The patient was treated with methylprednisolone 32 mg daily combined with cyclophosphamide 50 mg twice a day orally
June 15, 2016	Methylprednisolone was replaced with prednisolone 40 mg daily because the patient had difficulty falling asleep after taking the medicine
August 2, 2016	Cyclophosphamide was reduced to 50 mg once a day
September, 2016	The activity index score reduced from 3 to 1. CRP and ESR levels have declined. The colonoscopy found no ulcers in the colon. And CTA showed a decrease of the arterial aneurysms.

experience. BDCAF is one of the most common instruments used to access the activity of BD based on clinical features.[12] Though there is debate on the relationship between ESR and CRP to BD activity,[13] these 2 laboratory parameters remain the most widely used in clinical practice. In our case, we used CRP, ESR combined with BDCAF scores to evaluate the activity of the disease, and our results showed the BDCAF score index was closely correlated with the level of ESR and CRP.

Although the etiology of BD remains unclear, it is thought that genetic factors play a significant role on BD's onset and development. HLA-B51 has been recognized as the gene most associated with BD. Recent studies further discovered other related genes such as HLA-B27, HLA -B57, and HLA-A26, especially in HLA-B51 negative patients.[14,15] Moreover, recent genome-wide association studies (GWAS) have identified some BD susceptibility locus outside the MHC, such as IL23R, IL-12Rβ2, STAT4 and TNFAIP3.[16] The case we report carried HLA-B13/40 *phenotype* which has hitherto not been widely recognized.[17] HLA-B13 has been reported more frequently in recurrent aphthous ulceration (RAU) in the Turkish population.[18] Evidently, there is still more to be studied, especially in the Chinese-majority population.

4. Conclusion

BD usually starts with one manifestation and most often, it is oral aphthosis. The diagnosis of BD may be delayed due to the long duration between the first and subsequent manifestations. BD patients may be treated as RAU or UC for years because it is a practical challenge to differentiate one from the other. In patients who have been diagnosed with BD, systemic evaluation is necessary to rule out involvement of vital organs, especially those concerning the cardiovascular, pulmonary and neurological systems, which can trigger complications such as bleeding, shock, or even death.

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