Ann Vasc Dis Vol. 11, No. 1; 2018; pp 52–56

Online March 2, 2018
doi: 10.3400/avd.ra.18-00002

Review Article

What Is Vascular Behçet's Disease?

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Vascular Behçet's disease (BD) would keep risk of anastomotic pseudoaneurysm due to deterioration of the disease even after vascular surgery was successfully done. Therefore, it is one of the least-welcome diseases for vascular surgeons. There still exist several points on a concept and criteria of the vascular BD which not only general practitioners but also the vascular surgeons do not understand. Clinical findings strongly suspecting vascular BD are follows; saccular aneurysms without atherosclerosis developed in younger than 50-year-old patients, superior vena cava syndrome or deep vein thrombosis in bilateral legs without apparent causes, and multiple superficial thrombophlebitis, etc. It is very difficult to make a diagnosis of BD in the patients whose onset of the disease is a vascular lesion, because vascular BD combines few ocular lesions. In such case, it is very important to find out not only oral and genital ulceration, but also past history of arthritis. To establish the vascular BD, we vascular surgeons have to collect cases of the vascular BD and to revise criteria of the disease. (This is a translation of Jpn J Vasc Surg 2017; 26: 19–23.)

Keywords: Behçet's disease, vascular Behçet's disease, criteria

Introduction

Behçet's disease (BD), an intractable recurrent chronic systemic inflammatory disease, was first described by a Turkish, Hulusi Behçet, in 1937 and is characterized by oral aphthae, genital ulcers, skin and eye lesions, and repeated bouts of acute inflammation.[1–4] However, the disease has existed since ancient times, with similar symptoms described by Hippocrates.

Along with prosthetic graft infections, vascular BD is a disease that vascular surgeons prefer not to encounter because it poses a permanent risk of postoperative anastomotic aneurysms due to the recurrence of primary disease, regardless of prior successful surgery. The concept of vascular BD and its current diagnostic criteria are still not well understood not only by general clinicians but also by vascular surgeons.

Epidemiology

Also known as the "silk road disease," BD is highly prevalent on the belt across from the Mediterranean to East Asia. It has a particularly high prevalence in Turkey, occurring in 80–370 per 100,000 population. Moderate prevalence is reported in other regions such as Japan, Korea, China, and the Middle East (13.5–35 per 100,000 population).[5] In contrast, BD is very rare in North America and Northern Europe, with a reported prevalence of 0.2 per 100,000 population.[6] Onset of the disease is usually in their late 20s–40s, but pediatric case reports exist rarely. There are no sex distribution differences in high prevalence area, but in North America and Northern Europe, it is more common in females than in males. BD has medical and societal problems because the disease frequently occurs during patients' productive working age. In addition, ocular lesions often cause vision loss, and special type BD, such as vascular, gastrointestinal, and neural-type BD can be directly related to death.

The prevalence of BD in Japan has been steadily increasing, with the number of affected patients increasing from 8,000 in 1972 to 12,700 in 1984 and 18,300 in 1991, according to the Ministry of Health, Labour and Welfare's (MHLW) "Number of Recipient Certificates Issued for Specific Disease Treatment." However, the number of patients has recently become steady with 19,147 in 2013.[1] Recent changes in epidemiological characteristics include an increase in the mean onset age, a decrease of complete-type BD (29%), an increase of incomplete-types BD (55%), and an increase of female patients with mild symptoms.

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Received: January 4, 2018; Accepted: January 6, 2018
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This is a translation of Jpn J Vasc Surg 2017; 26: 19–23.

Etiology

BD is considered as one type of vasculitis. In general, vasculitis is divided into three types based on the size of the affected vessel: large vessel (Takayasu arteritis and giant cell arteritis), medium vessel (polyarteritis nodosa and Kawasaki disease, etc.), and small vessel vasculitis (Goodpasture syndrome and Wegener's granulomatosis, etc.). However, BD is characterized by its potential to affect veins, as well as large, medium, and small arteries.[7,8]

The etiology of BD remains unknown. Genetic factors, infection, and immunological factors are thought to be involved in disease development.[1] In Turkey, familial accumulation is reported; however, in Japan, familial incidence is not high.[9] The association of BD and the HLA-B51 gene variant is well-known. HLA-B51 is positive in approximately 10% of the general population, whereas 50%–60% in BD patients. HLA-B51-positive individuals have a 7.9-fold relative risk of developing BD. HLA-A26 and other linked predisposing factors may also play an important role in disease development. A decreased ability to control inflammation due to decreased production of IL-10 has also been reported as a potentially increased inflammation in BD patients. External factors may also play an important role. Interactions between genetic predispositions and pathogenic microorganisms may trigger abnormalities in the immune system, including autoimmune abnormalities or neutrophilic hyperfunction, ultimately leading to the onset of the disease.

Symptoms

Main symptoms of BD are oral aphthae, ocular lesions, genital ulcers, and skin lesions. Neural, vascular, and gastrointestinal types exist as special type of BD.[10]

Ocular lesions contain anterior chamber empyema, iridocyclitis, and uveoretinitis (retinochoroiditis). Ocular lesions often cause blindness. BD was previously the leading cause of uveitis; however, it is currently the third-leading cause after sarcoidosis and Harada's syndrome.[1]

Oral aphthae of BD are characterized by its recurrence three or more times a year. However, they are indistinguishable from simple oral ulcers, both macroscopically and histopathologically. Similarly, the intestinal ulcers seen in gastrointestinal-type BD are also difficult to differentiate from non-BD simple ulcers.[11]

Genital ulcers also recur but occur less frequently than oral aphthae. They are similar in shape to oral aphthae and develop in the scrotum in males and in the vulva in females.

Skin lesions include erythema nodosum, folliculitis-like eruptions, and acne-like eruptions. In Western countries, pathergy testing is emphasized (needle reaction testing: a 20-G needle is inserted into the skin to 5 mm deep. The presence of a papule measuring ≥2 mm after 24–48 h indicates a positive result).[12,13] It is important to note that superficial venous thrombophlebitis is classified as a skin lesion, not a vascular lesion in Japanese criteria.[1] This may be why the lower incidence of vascular BD in Japan than in other countries.[8]

Articular lesions are often manifested in the major joints of the limbs, exhibiting swelling, pain, and redness.[14] Lesions in small joints resembling rheumatic arthritis are rare, and deformations or rigidity is not observed. The lesions may be nonerosive, asymmetrical, or non-deforming and can occur in single or multiple large and medium-sized joints, such as the knees, ankles, and wrists. Articular lesions occur in approximately 50% of BD patients during disease progression. Synovial fluid and biopsy tissues also reveal inflammation.[15]

Vascular Lesions

Vascular lesions of BD can occur in large, medium, or small arteries or veins.[8] Venous lesions cause occlusion, whereas arterial lesions cause both occlusion and aneurysm; aorta typically develops aneurysms. Majority of these aneurysms are saccular, and very few are spindle-shaped. Vascular lesions occurred in 14% of 2,319 Turkish BD patients, most of whom were males,[16] including superficial venous thrombosis (53%), deep vein thrombosis (30%), and arterial lesions (4%). On the other hand, vascular lesions occurred in 13% of 796 Chinese BD patients, including arterial lesions (55%), venous lesions (71%), and both arterial and venous lesions (26%). Male to female ratio was 4:1, with a mean age at onset of 29.5 years.[17] Large vessel lesions occur in approximately one-third of BD patients. Perivascular or endovascular inflammation is thought to cause constriction, aneurysms, and thrombus formation in arteries and veins. They are often found in the aorta, iliac, femoral, popliteal, and carotid arteries but rarely develop in the cerebral, renal, or coronary arteries. There are numerous reports of pulmonary artery aneurysms in the Western countries, but rare in Japan.[18] As mentioned before, superficial thrombophlebitis is classified as a skin lesion, not a vascular lesion in Japan.[1]

In clinical practice, patients with suspected vascular BD are typically characterized by the following findings: aneurysms in young patients (≤50 years old), saccular aneurysms without arteriosclerotic degeneration, arterial occlusion or pseudoaneurysm after puncture, superior vena cava syndrome or bilateral deep vein thrombosis of unknown cause, recurrent superficial thrombophlebitis, or skin ulcers of the lower leg with unknown cause.

Table 1 Criteria for BD

A: Japan (Minister of Health, Labour and Welfare)[1]	
Major symptoms	
1. Recurrent oral aphthoid ulcer	
2. Skin lesions	
3. Ocular symptoms	
4. Genital ulcer	
Minor symptoms	
1. Arthritis without deformity and ankylosis	
2. Epididymitis	
3. Gastrointestinal lesions such as ileocecal ulcers	
4. Vascular lesions	
5. Central nervous system lesion	
Complete type: 4 major symptoms during the course	
Incomplete type: 3 major symptoms, 2 major+2 minor symptoms, or typical ocular symptoms+1 major symptom or 2 minor symptoms	
B: International Study Group[12]	
Major criteria	
Recurrent oral ulceration	
Minor criteria	
1. Recurrent genital ulceration	
2. Eye lesions	
3. Skin lesions	
4. Pathergy test	
Major+2 minor criteria indicate BD	
C: International Criteria for BD[13]	
Ocular lesions	2 points
Oral aphthosis	2 points
Genital aphthosis	2 points
Skin lesions	1 point
Central nervous system involvement	1 point
Vascular manifestations	1 point
Positive pathergy test	1 point

Scoring ≥4 indicates BD. BD: Behçet's disease

Issues on Diagnosis of Vascular BD

Because there are no disease-specific examinations for BD, its diagnosis is determined by clinical symptoms. In Japan, the MHLW issued the BD Diagnostic Criteria in 1987, which are commonly used for differential diagnosis[1] (**Table 1**). Based on these diagnostic criteria, BD is classified into complete, incomplete, or suspected types by the presence or absence and combinations of four major and five minor symptoms. The symptoms may be present at the time of diagnosis but can include past symptoms. Complete-type BD is characterized by the presence of all four major symptoms. Incomplete-type BD is characterized by the presence of either three major symptoms, two major symptoms with two minor symptoms, or typical ocular lesion with one other major or two other minor symptoms. The Japanese diagnostic criteria weight ocular lesions. Patients with recurrent oral aphthae and typical ocular lesions can be diagnosed with incomplete-type BD. However, patients with vascular BD rarely combine ocular lesions.[10] None of my patients experienced ocular lesions. Vascular lesions are minor symptoms of BD, and ocular lesions combine rarely, so, it is impossible to diagnose as complete-type in patients with vascular BD. This is not a problem when a patient with diagnosis of BD develops new vascular lesions, but it can be challenging to diagnose incomplete-type BD in a patient without previous diagnosis of BD. Patient with both oral aphthae and a genital ulcer cannot be diagnosed even as incomplete-type BD, if he/she has no typical skin symptoms. HLA-B51 or HLA-A26 positivity is considered useful in clinical practice, but is no use for meeting the criteria. Therefore, the patient must be examined for the four minor symptoms of arthritis, epididymitis, gastrointestinal lesions, and central nervous system lesions. Among these, arthritis is the only one symptom that can be diagnosed by a vascular surgeon. Arthritis in BD is defined as nonerosive, asymmetrical, and nondegenerative lesions occurring in medium and large joints and can include previous arthritis as well. Therefore, a diagnosis of incomplete-type BD can be made, if the patient states any current or previous symptoms of arthralgia (arthritis).

Interestingly, there are currently no internationally standardized diagnostic criteria for BD, so the criteria differ between countries and researchers. The International Study Group for BD (ISG) analyzed sensitivity and specificity of five diagnostic criteria and proposed a list of simplified ISG criteria[12] (**Table 1**). According to these criteria, BD can be diagnosed if a patient presents with recurrent oral ulcers and two of the followings: recurrent genital ulcers, typical ocular lesions, typical skin lesions, or positive skin pathergy testing. Sensitivity, specificity, and accuracy are all similar to the Japanese diagnostic criteria and seem to be superior to the Japanese criteria for the diagnosis of vascular BD because of rare ocular lesions of vascular BD in Japan. The International Criteria for BD (ICBD) is another set of diagnostic criteria, in which a total score of ≥4 points defines a BD diagnosis based on the following point system: ocular lesions (2 points), oral aphthae (2 points), genital aphthae (2 points), skin lesions (1 point), central nervous system lesions (1 point), vascular lesions (1 point), and skin pathergy testing (1 point)[13] (**Table 1**). The sensitivity, specificity, and accuracy of ICBD are 87%–97%, 89%–97%, and 74%–86%, respectively; however, this system is not as widely used as the ISG criteria.

Vascular lesions are not even included in the ISG diagnostic criteria, and these weight half of those in ICBD criteria and only a quarter of those in the Japan's MHLW diagnostic criteria. This is probably because diagnosis of BD has been made mainly by ophthalmologists in Japan.

Treatment

There are no established safe surgical treatments for vascular BD. Considering vascular BD has a high risk of postoperative anastomotic aneurysms, thrombotic occlusions, and other postoperative complications, immunosuppressant therapy should be advanced before surgery in the acute inflammatory phase if possible.[19] However, rupture or impending rupture of the aneurysm is an indication for emergency life-saving surgery. Stent graft surgery is less invasive than conventional prosthetic graft placement and has been reported to have equal or lower rates of complications and deaths.[20–23] However, there exist anatomic limitations for stent graft surgeries, such as difficulty of application to aneurysms involving important tributaries, as well as pseudoaneurysms formation at an edge of the stent graft. In addition, it is a newly developed operative method, so long-term outcomes are not certain. Operative method should be appropriately considered based on patient background and experience of the surgeon and the institution.

Arterial occlusion develops with a completely different mechanism from ordinary atherosclerotic occlusions; thus, endovascular treatment (balloon dilatation or stent placement) should be selected with caution.

Deep vein thrombosis should be treated with ordinal thrombolytic therapy following anticoagulant therapy.[24,25] Placement of an inferior vena cava filter should not be performed to avoid venous wall injury.

Conclusion

Recently, anti-human TNF-α monoclonal antibodies (infliximab) has been approved to use for vascular BD.[26] However, this approval is based on data on inflammatory symptoms diminished only four patients, and additional clinical data on vascular BD are required. Use of infliximab is limited only for complete- and incomplete-type BD and it cannot be used on suspect-type BD. Under the current diagnostic criteria, it is difficult to diagnose vascular BD whose initial onset was vascular lesions. Data of the vascular BD should be collected on a national scale to revise the diagnostic criteria for BD in Japan.

Disclosure Statement

The author has no conflicts of interest to declare.

Additional Remarks

The content of this study was presented at the 16th Post-Graduate Educational Seminar of the Japanese Society for Vascular Surgery held in Nara City on October 15, 2016.

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