Vascular Involvement in Behçet’s Disease

Key words: vasculitis, thrombosis, endothelial cell

It is becoming clear that Behçet’s disease (BD) has a nature of systemic vasculitis accompanied by thrombotic tendency (1–3). Superficial thrombophlebitis, which is included in skin lesions according to the 1987 Revised Clinical Diagnostic Criteria of Behçet’s Disease by the Behçet’s Disease Research Committee of Japan, is the most common vascular symptom in BD. Furthermore, a subtype of BD patients who develop serious symptoms due to large vascular involvement are categorized into vasculo-Behçet’s disease in the Japanese Criteria (1). The latest epidemiological study revealed that in Japan 9% of all BD patients belong to this category (1).

Thromboses in large veins impair venous return, leading to superior vena cava syndrome and Budd-Chiari syndrome. Dural venous sinus thrombosis is a major cause of intracranial hypertension in BD patients of Middle East Asian countries, though such patients are rare in Japan (4). In the arterial system, aneurysmal dilatation and stenosis or thrombotic occlusion of the aorta and its branches can develop and cause serious symptoms such as rupture of aneurysm, aortic arch syndrome, cerebral stroke and renovascular hypertension. There are sporadic reports that BD patients present cardiac manifestations which arise from ventricular or atrial thrombosis, valvular regurgitation and coronary lesions (2, 5).

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Pulmonary vascular lesions can lead to fatal hemoptysis (6). Thus, because cardiovascular involvement has serious consequences, therapy for vascular lesions is given prior to any other symptoms observed in patients with vasculo-BD.

Vasculitis is an essential pathological component in all subtypes of BD (1–3). Indeed, histological studies demonstrate vasculitis in most of the active lesions including oral aphthoid ulcers, erythema nodosum, epididymitis, posterior uveitis, and central nervous system lesions.

Various immune abnormalities may be implicated in the vasculitis of BD, though the precise mechanism remains obscure. Sera from BD patients upregulate expression of lymphocyte function-associated antigen (LFA)-1 on neutrophils, and expression of intercellular adhesion molecule (ICAM)-1 on endothelial cells, resulting in the increased adherence of neutrophils to endothelial cells in vitro (7). Presumably, elevated circulating proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL) -1, and IL-8 are responsible for the augmented interaction between neutrophils and endothelial cells through the upregulated adhesion molecules, leading to vasculitis and subsequent tissue damage in vivo (2, 7). The findings that deposition of immune complexes to endothelial cells and circulating anti-endothelial antibodies are detected in some patients with BD suggest possible roles of the autoantibodies in the development of BD vasculitis (2). However, because anti-neutrophil cytoplasmic antibody (ANCA) is rarely found in BD patients, BD should be considered distinct from the series of ANCA positive vasculitis syndromes such as Wegener’s granulomatosis and microscopic polyangiitis (1, 2, 8).

Thrombotic tendency is another important hallmark of BD (1–3). It is a rule that hypercoagulable states arise from an imbalance between procoagulant and anticoagulant forces (9). Reduced anticoagulants can cause deep vein thrombosis as shown in congenital deficiencies of antithrombin III, protein C, and protein S (9). On the other hand, there is no evidence that quantitative and qualitative abnormalities in these anticoagulants are associated with BD. Genetic studies have revealed that some genetic polymorphisms of coagulants such as a Factor V Leiden mutation (506Arg/Gln) and a polymorphism of prothrombin G20210A in the 3’-untranslated region are closely related to the susceptibility of idiopathic deep vein thrombosis in Caucasians (9). Recently, association of Factor V Leiden mutation with BD patients having thrombosis and ocular involvement has been reported from Saudi Arabia and UK (10, 11). It has been also reported from Turkey that some BD patients with thrombotic lesions have a prothrombin G20210A mutation (12). Paradoxically, there is no individual with the gene polymorphisms of these coagulants in East Asian countries including Japan, where BD is the most prevalent. The thrombosis-related genetic polymorphisms are potential, but not major contributors to the development of thrombosis in patients with BD.

Blood-coagulation cascade is offset by natural anticoagulants, most of which reside in normal endothelial cells (9). Accumulating data suggest that endothelial cell injury is responsible for the thrombotic tendency in BD. Circulating von Willebrand factor antigen, endotherlin-I, and thrombomodulin, which are released from damaged endothelial cells, are consistently elevated in BD patients, irrespective of their disease activity (2, 3). Impaired arachidonic acid metabolism in endothelial cells is also implicated in the development of thrombosis through increased platelet adhesion and aggregation in BD patients (5). However, no specific finding has been confirmed in BD.

Because vasculitis underlies most of the lesions, it may be a useful therapeutic strategy to suppress the development of vas-
cular injuries in BD. We need to determine which pathological events are critical for the development of vasculitis and thrombosis in BD.

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References