Behçet's disease: an update on pathogenesis, diagnosis and management of vascular involvement

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Abstract

The objective of this review is to summarize reports of the prevalence, clinical presentation, diagnostic methodology and treatment of vasculitic manifestations of Behçet's disease (BD). We performed a literature search on vasculitis in BD. Articles were selected which provided insight into the pathogenesis and clinical aspects of vasculitis. Vasculitis underlies many of the clinical features of BD. Small vessel vasculitis is often found in the pathology of the mucocutaneous manifestations of BD. Large vessel vasculitis has been reported in 15-40% of BD patients. Ultrasound, angiography and tomography are applied to confirm the diagnosis when venous involvement is suspected. Endothelial dysfunction plays a role in the pathogenesis of disease. Peripheral arterial involvement in BD occurs in the form of arterial occlusion or aneurysms. Pulmonary arterial involvement is often life-threatening. The cause of cardiac vascular involvement requires an aggressive diagnostic approach. Corticosteroids and immunosuppressive agents have been used successfully in the early stage of large vessel disease and should be used as an adjunct to surgery. An increasing amount of data is available regarding the role of anti-tumor necrosis factor (TNF) agents for the treatment of BD. Anticoagulant therapy may be hazardous in patients with aneurysmal dilatation of the pulmonary vascular tree and is not effective in the treatment of venous thrombosis. Inflammation of small and large vessels is very frequent in BD. Both arteries and veins may be involved. Early recognition and appropriate management of large vessel vasculitis in BD is essential to reduce associated morbidity and mortality.

Introduction

Behçet's disease (BD) is a chronic, relapsing, multisystemic disorder characterized by urogenital ulcers and ocular inflammation with cutaneous, musculoskeletal, vascular and nervous system manifestations.[1] The etiopathogenesis of the disease remains obscure, although genetic predisposition, environmental factors and immunological abnormalities have been implicated.[2,3] It has recently been proposed that BD is an autoinflammatory disorder,[4] although there is no consensus.[5] People from the Far East, the Middle East and the Mediterranean basin are more commonly affected than those from other parts of the world.[6] In Northern Europe, Central Africa and the United States the disease is infrequent.[7] All ages may be affected, although the frequency is higher in persons in the 3rd or 4th decade. The sex predominance varies widely among the diseased population in different geographical areas.[6,7] Earlier studies suggested a male predominance in high prevalence areas, but more recent surveys indicate equal involvement of the sexes. In Western countries, females predominate.

Behçet's disease is included in the wide spectrum of vasculitides.[8] Vasculitis is a principal pathological finding in BD and vessels of all sizes are involved, both in arterial and venous systems. Large vessel vasculitis is not a rare manifestation of BD and it was proposed that this be one of the diagnostic criteria of the disease.[9] The prevalence of large vessel vasculitis varies according to the authors and the population.

Materials and Methods

Small vessel vasculitis in in Behçet's disease

In this paper, we review the prevalence, clinical manifestations, diagnostic methodology, treatment and management of vasculitis in BD. Specifically, we covered small vessel vasculitis in BD, large vessel vasculitis, venous involvement in BD, superficial thrombophlebitis, deep vein thrombosis (DVT), inferior vena cava (IVC) thrombosis, Budd-Chiari Syndrome (BCS), portal vein thrombosis, superior vena cava (SVC) thrombosis, endothelium in BD, other possible contributions to thrombosis in BD, homocysteine, coagulation factors, peripheral arterial involvement, pulmonary manifestations, cardiac manifestations, pericarditis, myocardium involvement, endocardium, coronary arteries, cerebral vasculitis, cerebral venous thrombosis, and cerebral arterial aneurysms. This is, to our knowledge, the first review which considers the wide spectrum of vascular inflammation found in patients with BD.

Results of literature review

Few studies have been published concerning the vasculitic involvement of small vessels in BD. Petechiae of the nailfolds were described in BD for the first time by Hashimoto in 1973. The first nailfold capillaroscopic study was reported in 1984 on 30 patients with BD.[10] Periungual petechiae were recognized in 50% of patients. Pallor of the background, sludge, and abnormal appearance of the venous plexus with irregularly arranged venules were also described. There was no correlation between the capillaroscopic findings and the disease duration. More severe damage was demonstrated in patients with long disease duration and these findings correlated with skin and joint manifestations. Both studies were open, without controls. Video capillaroscopy, a non-invasive, reliable procedure, may have diagnostic and prognostic value in the definition of the microvascular abnormalities in patients with BD. A recent video capillaroscopic study in 15 BD patients and 16 healthy subjects matched for age and sex was performed. Various nailfold abnormalities were found, including capillary dystrophies, numeric capillary abnormalities, sludging, petechiae and pericapillary edema in a high proportion of patients with BD. Similar findings, along with vessel microaneurysms, coiling and kinking were also found in the conjunctiva of these patients.[11] In a recent study by stereo-microscopy, qualitative capillaroscopy was performed; the reported findings were confirmed, showing high frequency of morphological abnormalities (90%) in small vessels.

In a study of the histopathology of pathergy, true vasculitis was not seen. Rather, an intraepidermal pustule and polymorphonuclear aggregates were found.[12] In an electron microscopic study, small dermal blood vessels were found to be filled by thrombus after stimulation of the skin with needle prick and in erythema nodosum-like lesions in BD patients. Excessive proliferation of endothelial cells caused vascular stenosis and the appearance of degenerated cells.[13]

On biopsy, mucous membrane and cutaneous lesions in BD patients may demonstrate small vessel inflammation, including lymphocytic and necrotizing vasculitis.[14] Vasculitis and phlebitis have been found in 48% of skin biopsies in BD patients, lymphocytic vasculitis in 31% and leukocytoclastic vasculitis in 17%.[15] A neutrophilic vascular reaction or lymphocytic infiltrates characterize the biopsy findings in other series.[16,17]

Lesions of small arteries with lymphocytic or neutrophilic cell infiltrates have been found in the subcutis in nodular cutaneous lesions. Kim noted vasculitis of small vessels in erythema nodosum-like lesions in the majority of patients with BD.[18] Biopsy specimens from nodular lesions in 24 patients with BD, 25 with nodular vasculitis and 20 with erythema nodosum (EN), were compared.[19] In 42% and 46%, (2 observers) a neutrophilic vasculitis of nodular lesions in subcutis of BD patients was noted. A neutrophil predominant inflammatory cell infiltrate was seen in BD compared with nodular vasculitis and erythema nodosum. Septal panniculitis, lymphocyte-predominating infiltrate, absence of vasculitis, and necrosis were features more likely found in biopsies from patients with EN. A spectrum of histopathological findings have been observed in erythema nodosum-like lesions of BD, similar to those found with EN associated with other disorders.[20]

Large vessel vasculitis

In Behcet's disease, vessels of all sizes are involved. Arteries, veins and capillaries are affected. Aortic and peripheral artery aneurysms, pulmonary artery occlusion and aneurysms, coronary artery aneurysms, deep vein thrombosis, and cerebral venous thrombosis have been described. The pathogenesis of the aneurysms and thrombosis is unclear. It is suggested that an interaction of an exogenous agent with the mononuclear cells from a genetically predisposed patient may result in damage and functional impairment. Inflammatory obliterative endarteritis of the vasa vasorum, endothelial cell swelling and mononuclear perivascular infiltration cause destruction of media, arterial wall weakening and aneurysm formation.[21] Immunohistology of skin pathergy reaction demonstrated a variable dense focal mononuclear cell infiltrate

around vessels and skin appendages. The majority of the T lymphocytes were CD4^{+} and almost all expressed CD45RO. Neutrophils constituted less than 5% of the infiltrating cells.[22]

In Takayasu's disease, large arteries, including the aorta and its branches, and pulmonary arteries are affected. Transmural granulomatous inflammation and chronic intimal fibrosis with luminal obstruction is found. Granuloma formation and giant cells are predominantly found in the media and adventia of the large elastic arteries.

In Giant Cell arteritis large arteries are also involved, with mononuclear cells, macrophages and multinuclear giant cells. Giant cells are typically found at the junction between the intima and media.

Immunopathogenesis

Multiple cell types contribute to the tissue damage in Behcet's disease. Neutrophils have enhanced chemotaxis and phagocytosis, induce superoxide generation and myeloperoxidase expression and also expression of CD11[a], CD10 and CD14 on the cell surface.[23] The mechanism underlying the hyperfunction of neutrophils in BD is not known but it has been shown that heightened neutrophil chemotaxis is related to the presence of HLA-B51 in patients with BD. Neutrophil function is also regulated and maintained by cytokines IL-1, IL-2, IL-6, IL-8 and TNF-α and others. It has been suggested that Th1 type cytokines and chemokines including IL-17, largely produced by activated CD4^{+} and CD8^{+} T cells, are involved in the recruitment of neutrophils to the site of inflammation.[24] Activated neutrophils in BD patients produce significant quantities of IL-12 and IL-18. Enhanced chemotactic activity may be important in pathergy hyperactivity in the skin and mucus membranes. Neutrophils accumulate in inflammatory lesions where they induce neutrophilic vasculitis. Neutrophil function and cell surface markers were evaluated with flow cytometry in patients with BD compared to healthy and diseased controls.[25] Most phenotypical and functional analyses show findings compatible with *in vivo* activation of neutrophils.

It has been observed that epidermal Langerhans cells were found to be significantly increased at the site of pathergy reaction. Interleukin 18, produced by antigen presenting cells, (APCs) contributes to Th1 polarization, particularly in association with IL-12. Genetically determined hyperactivity of APCs might play a role in the pathogenesis of BD. APCs, either primary or secondary to their stimulation with Th1 cytokines, cause enhanced production of IL-12 and IL-18. Thus, interaction of APCs, Th1 lymphocytes and neutrophils form the basis of the immune

aberrations observed in patients with BD.[25]

T cells play a pivotal role in the pathogenesis of BD. Several investigators have observed that T cells dominate in the involved tissues and their phenotypic characteristics have been studied. In BD uveitis, CD8^{+} CD56^{+} T cells were found.[26] In the histopathology of the pathergy reaction mononuclear cells predominate composed of T lymphocytes and mononuclear macrophages. The majority of the T lymphocytes were CD4^{+} and almost all cells expressed CD45RO. In a recent study, the histology of central nervous system lesions in BD was studied. In histological studies of acute neuro Behcet's disease, the infiltration of mononuclear cells around small vessels consisted of CD45RO^{+} T lymphocytes and CD68^{+} monocytes, and few CD20^{+} B lymphocytes. Phenotypical and functional abnormalities of ab^{+} and $\gamma\delta$ T-cell subsets were found in BD.[24] A reduced CD4^{+}/CD8^{+} T-cell ratio is found in BD patients. A lower frequency of CD4^{+}CD45RA^{+} T cells were found in the peripheral blood lymphocytes in active BD compared to controls, while CD4^{+}CD29^{+} T cells were similar in frequency.[27] The proportion of CD45RA^{+} CD45RO^{−} V9vδ2 cells in peripheral blood $\gamma\delta$ T cells increased in BD patients which may not depend on the disease activity.[28] In normal subsets, $\gamma\delta$ T cells usually had a phenotype of CD45RA^{−} CD45RO^{+} Vγ9+Vδ2^{+}. It has been demonstrated that CD45RA^{+}$\gamma\delta$ T cells produce more TNF-α and β than did CD45RO. During the active disease, a subpopulation of $\gamma\delta$ T cells in BD express activation markers including IL-2 receptors and HLA-DR. A phenotypically distinct subset of $\gamma\delta$ T cells CD45RA^{+} CD45RO^{−}Vγ9+Vδ2^{+} may contribute to immunological abnormalities which play an important role in the pathogenesis of the disease.[28]

Strong polarization of the immune response toward the Th1 pathway correlates with BD progression, as increased percentages of CD3^{+}/IFN γ^{+} and CD3^{+}/IL-2^{+} cells were observed in patients with active disease compared those with complete remission and with healthy controls.[29] Plasma levels of IFN-α and IL-12 have been found to be elevated in parallel with increased Th1 cells. These findings suggest a pathogenetic role of a Th1 immune response in active disease.

In a recent review, Zierhut discussed the role of genetics, microbial infectious, T and other cells and also the role of endothelium and coagulation abnormalities in BD.[24] It has been shown that Vγ9/Vδ2 T lymphocytes from patients with BD are activated and may play a role in the pathogenesis of the disease.[30] In unstimulated 5^{−} day cultures, $\gamma\delta$[+] T cells CD8^{+}ab^{+}, CD4^{+} CD56^{+} and CD8^{+} CD-11β^{+} T lymphocyte subsets were found to be up-regulated significantly in BD compared to healthy controls.[31] This study confirms that these cells may contribute to Th1 polarization of BD. CD8^{+}

CD56^{+} T cells in active BD uveitis are polarized to produce large amounts of INF-γ upon stimulation compared with the inactive BD and normal subjects.

Increased serum levels of Th2 type cytokines including IL-4, IL-10 and IL-12 have also been found in patients with BD.[32] This finding can be explained by compensatory mechanisms in opposition to a strong Th1 type immune response. The increase in IL-12 and IFN-γ expression within the mucocutaneous BD lesions associated with the absence of typical Th2 cytokines supports a strong polarized Th1 immune response.[33]

The role of NK cells is controversial in BD, with normal, decreased or elevated levels reported in the peripheral blood. Increased levels of NK cells after bacterial stimulation have been reported.[31] NK and NK-T cells kill target cells and may represent cells involved in crosstalking between innate and aquired immunity by the production of IFN-γ and IL-4. Thus, it seems that NK and NK-T cells may play a role in induction and/or regulation of various types of immune response, including several autoimmune diseases and in ocular inflammation in BD. NK cells can kill target cells within minutes of the first stimulation of activating receptors and respond rapidly to challenge limiting capacity to an antigen load.

Venous involvement in Behçet's disease

Superficial thrombophlebitis (SVT), deep vein thrombosis, vena cava thrombosis, Budd-Chiari syndrome, portal vein thrombosis, and cerebral venous thrombosis are the principal manifestations of vasculitic involvement of the large veins. Thrombophlebitis of the lower extremities and of the retina in a BD patient was first recognized and described by Adamantiades 16 years after his first report of the disease in 1930.[34] Adamantiades emphasized the frequent occurrence of thrombophlebitis in this disorder and suggested that thrombophlebitis should be included as the fourth cardinal sign of the disease.

Superficial thrombophlebitis

Subcutaneous thrombophlebitis was the most frequent type of vascular involvement, found in as many as 47.3% of patients with BD.[8] The prevalence of SVT was reported as 26.7%,[35] and a frequency of 23% in males and 8% in females has also been reported from Turkey.[36] A prevalence of 2.2-20%, has been noted by other investigators.[37-39]

SVT or erythema nodosum-like lesions may predict visceral involvement in BD. The risk of venous occlusion in the lower extremity and/or inferior vena cava was found to be 22.8% in patients with subcutaneous thrombophlebitis, while the risk was 5% in patients without sub-

cutaneous thrombophlebitis.[8] Factor analysis clustering also reveals an association between superficial and deep venous thrombosis[36] and both conditions may be connected with thrombosis at any other site.

The main symptom of SVT is localized extremity pain, with swelling and erythema. Thrombosis of superficial veins can occur after venipuncture and has been reported at sites of heparin infusion. The diagnosis of superficial thrombophlebitis can be confirmed by Doppler ultrasound, which can distinguish this problem from erythema nodosum-like lesions.

Deep vein thrombosis

The incidence of DVT in BD was found to be 24.9% in Tunisia.[40] Higher figures (38.9%) were reported by other researchers [41] from the same country. In a more recent study (2006),[40] 519 patients were studied, while in the 2001 series 113 cases from different areas of the country were reported. Like all large vessel lesions, males are affected more frequently than females and the problem is found more commonly in patients with a younger age at onset of BD.[42] The highest risk of venous occlusion was in the lower extremities and/or inferior vena cava in the report of Koç.[8]

There is little consistency in reports of the timing of DVT in respect to the onset of BD. The complication can occur in the first years of the disease. DVT is thought to be an infrequent presenting sign of BD but has been reported as the initial symptom of the disease in 23 of 84 patients.[43] The most critical period for the development of DVT was found to range from 2 to 3.2 years following the diagnosis of BD.[8,41] DVT tends to occur earlier than arterial involvement.

Associations with DVT include ocular involvement,[44] erythema nodosum-like lesions, and pathergy.[8,41]

Venography, venous ultrasonography, MRI, MRI venography, or CT may be sufficient diagnostic methods for the diagnosis of DVT. Anticoagulants with anti-inflammatory drugs are indicated for the treatment of venous thrombosis.[45] However, anticoagulants for thrombosis as monotherapy may not be sufficient, since thrombosis can occur despite anticoagulant therapy.[38,46] The treatment of superior vena cava syndrome and extracranial arterial occlusion includes a combination of immunosuppressants, glucocorticosteroids, and anticoagulants.[45] In acute thrombosis of the large veins, heparin infusion and corticosteroids and, possibly, fibrinolysis are employed, and for maintenance treatment warfarin, corticosteroids and immunosuppressant drugs are also recommended.[38]

Inferior vena cava thrombosis

Inferior vena cava (IVC) thrombosis in patients with BD with large vessel involvement

was found in 15.8% of patients.[8] This complication should be suspected in patients with alternating venous thrombosis of the lower limbs or recurrent venous thrombosis in one limb.[45] Series of IVC thrombosis have been reported by several investigators.[8,38,41,47]

Budd-Chiari syndrome

The obstruction of Budd-Chiari syndrome (BCS) can be due to acute or chronic thrombosis,[47] but clot may be associated with vessel stenosis. BCS is an uncommon but serious manifestation of BD. Hepatic vein thrombosis was reported in 26.4% of 53 patients in a series of BD patients with large vessel thrombosis.[47] Series of BCS cases have been reported by other investigators.[40,48-50] This complication is characterized by hepatome-galy, right upper quadrant abdominal pain, ascites, and edema of the lower extremities.[47] The diagnosis of BCS can be established by ultrasonography, angiography, vena cavography or computed tomography, and typical findings may be found on liver biopsy.

Twenty-one cases (4 reported and 17 from the literature) of hepatic vein thrombosis caused by BD were compared to 24 cases of hepatic vein thrombosis caused by primary myeloproliferative disorders. Five out of 20 patients with BD had acute liver failure and died within the first month of the clinical onset, while patients with myeloproliferative diseases had a progressive course.[51] Rarely, spontaneous improvement may occur but most patients remain at risk for slowly progressive liver failure, elevated portal pressure and esophageal varices. We recommend treatment with heparin, pulse methylprednisolone and cyclophosphamide in the acute stage of the disease.

BCS without involvement of the vena cava has been successfully treated with early surgical decompression of the portal system.[52] However, portocaval shunt is not possible in the setting of inferior vena cava thrombosis due to an unsuitable pressure gradient between the portal vein and the inferior vena cava. The successful use of a transjugular intrahepatic portosystemic shunt in BD has not yet been reported. Percutaneous transluminal angioplasty (PTA) was performed in a 45-year old BD patient and a dramatic reduction of portal venous pressure (from 24 mm Hg to 15 mm Hg) resulted. This procedure may be safe and effective for BCS when caused by segmental obstruction of the IVC whether complicated or not by middle and left hepatic venous occlusion.[53] The very limited experience with anti-TNF agents in the treatment of this syndrome has not been favorable.[54]

Portal vein thrombosis

Portal vein thrombosis is another infrequent complication in BD.[47] Patients with BD

and portal vein thrombosis clinically have or develop splenomegaly, but the clinical presentation may be clouded if thrombosis is present in other large veins.

Superior vena cava thrombosis

Superior vena cava (SVC) thrombosis is yet another vascular manifestation found in patients with BD. The reported frequency of the SVC obstruction was 1.4-9.8% of cases with venous involvement.[35, 55] Other series of SVC thrombosis were published recently.[50,56]

In unusual cases, SVC thrombosis has resulted in blockage of the lymphatic circulation and chylothorax.[57,58] The chylous effusion contains triglycerides, cholesterol, increased protein and white blood cells.[57]

Doppler ultrasound often reveals occlusion of the SVC in affected patients. Upper extremity venography with or without digital substraction angiography demonstrates the obstruction of the SVC.[57]

The suggested treatment includes corticosteroids, azathioprine, anticoagulants and/or intervention with stent placement.[55,56]

Cerebral venous thrombosis

The main symptoms of cerebral venous thrombosis (CVT) are a persistent headache and papilledema due to intracranial hypertension with elevated pressure of the cerebrospinal fluid. The cerebrospinal fluid in cases without parenchymal involvement was usually not accompanied by elevation of proteins or pleocytosis.[59] Symptoms of elevated intracranial pressure may be the presenting manifestation of BD. Multiple cases and series of patients with CVT have been reported.[59-63] The first case of CVT in BD during pregnancy was published in 1995.[64] The presence of major vessel disease was studied in 88 patients with CNS disease.[61] Coexisting vascular problems were identified in 15 of 77 patients with parenchymal CNS disease. Eleven of these patients also had venous involvement, one had both arterial disease and venous thrombosis, and 3 patients had coexisting arterial disease. The majority of patients with CVT, 7 of 11 patients, had coexisting vascular problems. Five CVT patients had venous thrombosis and 2 patients had both arterial and venous thrombosis. In 80 controls with BD who did not have CNS disease, 18 had major vessel involvement. The age of onset of CVT in men was significantly lower than the age of onset of parenchymal disease, 23.1(8.8) vs. 32.0 (7.5) years, respectively. Among the 3 women studied no such trend could be recognized.

The diagnosis of CVT is established by MRI and magnetic resonance venography of the brain. Medical management of BD-associated CVT includes corticosteroids and anticoagulants. Combination therapy with these agents has been associated with satisfactory immediate and long-term prognosis.[60]

Cerebral venous thrombosis is not rare in BD patients; it was present in 7.8% of 820 patients with BD in a recent study.[65] Patients with cerebral venous thrombosis (CVT) had less parenchymal central nervous system involvement compared to those without. In this report, anticoagulation was applied which was safe and effective. In previous studies, the prevalence of CVT was 10-12% among patients with neuroBD.[59,62] BD patients with CVT who experience a relapse may have an associated prothrombotic factor.[65]

The endothelium in Behçet's disease

Disordered function of endothelial cells may play a pivotal role in the development of venous and other vascular manifestations in BD. Measurement of vessel characteristics may help to understand structural and functional changes in the vessel wall and possibly provide information for the diagnosis and treatment in patients of BD with high cardiovascular risk.[66]

Flow mediated dilatation was significantly higher in patients with BD compared to control subjects, indicating abnormal endothelial function[67] in active and inactive stages of the disease. In a subsequent study, aortic elastic properties were found to be impaired.[68] A significant higher pulse wave velocity has been demonstrated in BD patients and compared with matched healthy controls indicating aortic stiffness. Increased arterial stiffness may relate to endothelium dysfunction and acute or chronic inflammation.[69,70] Significant carotid artery intima-media thickness in patients with BD compared to control subjects has been found by ultrasonography.[71] Increased intima-media thickness and arterial distensibility are related in BD patients.[66]

Brachial artery flow mediated dilatation was reduced in BD patients compared to normal controls.[72] However, in a more recent study there was no significant difference in endothelial dependent and independent vasodilatation in patients with and without vascular involvement.[73] These differences may be due to the effect of immunosuppressive drugs in patients with vasculitis, the small sample size, or the exclusion of patients with active disease.

Endothelial dysfunction was shown to be associated with plasma homocysteine levels in BD,[74] but the nature of this association is unclear. In one study, homocysteine levels were higher in BD patients with vascular involvement than in those without, but there was no correlation of homocysteine levels and endothelial dependent vasodilatation.

The etiology of endothelial dysfunction in BD is probably multifactorial and includes high homocysteine levels as well as oxidative stress, although all of the mechanisms that underlie this dysfunction are not clearly known. The

recognition of endothelial dysfunction in BD should lead to aggressive management of other risk factors for atherosclerosis in BD patients.[73]

Multiple other factors may lead to endothelial dysfunction and vascular disease in BD. Significantly higher serum levels of vascular endothelial growth factor (VEGF) were found in patients with BD compared to normal controls, particularly at the active stage of the disease[75,76] and in patients with vascular manifestations and ocular involvement.[76] VEGF, therefore, could be a risk factor for the development of ocular disease, contributing to poor visual prognosis.[76] Elevated levels of endothelin-1, homocysteine, and nitric oxide (NO) were found in BD patients as compared to controls. These factors represent other substances which may contribute to the ocular manifestations, promoting ischemia and retinal capillary closure.[77]

The production of VEGF may be subject to genetic control. The association of *VEGF* gene polymorphism with BD was studied in patients and controls.[78] Carriers of –634C and allele 1 are associated with susceptibility to developing BD. VEGF may also play a contributing role in the development of venous thrombosis in BD. Levels of VEGF were significantly increased in patients with acute thrombosis compared to those with chronic thrombosis.[79] VEGF activates endothelial cells and causes the release of vasoactive substances inducing vascular thrombosis and inflammation. VEGF also up-regulates NO synthase which may induce damage to host cells and tissue.[76]

Asymmetric dimethylarginine (ADMA) and NO levels may reflect signs of endothelial dysfunction in BD.[80] The endothelial NO synthase gene polymorphism Glu – 298 Asp of exon 7 is associated with BD when compared to controls.[81] Other investigators have found that increased plasma ADMA levels and decreased plasma NO levels are risk factors for cardiovascular events in patients with BD.[80]

Activation of endothelial cells has been found in a high proportion of patients with BD (42%) irrespectively of current ocular disease. The thrombotic tendency in BD patients may relate to enhanced endothelial cell activation.[82]

Anti-endothelial cell antibodies have been found in the serum of BD patients, particularly during the active stage of the disease. However, the exact role of these antibodies in the disease has not been clarified.[83-85] Endothelial cell antibodies were detected in 18-37% of patients with BD.[86,87] However, others have not found any statistically significant difference between patients and controls.[88] This discrepancy likely reflects methodological differences in ELISA assays for anti-endothelial antibodies.[88] The serum levels of several cytokines were determined in 94 BD patients, 74 with active disease, and 75 healthy individ-

uals matched for age and sex who served as controls. Increased levels in the serum of IL-8 were found in patients with active disease with oral ulcers and neurological manifestations compared to the patients with inactive disease and controls. IL-8 secretion by dermal microvascular endothelial cells is stimulated in the presence of Behçet serum.[89] It is postulated that circulating anti-endothelial cell antibodies may be responsible for this effect.[89]

Dyslipidemia, particularly hypertriglyceridemia, might be expected to be a risk factor for thrombosis in BD. However, patients with and without thrombosis have similar triglyceride profiles and there were no differences in any of the lipid parameters that were analyzed.[90] Leiba,[91] however, reported that patients with thrombosis had significantly higher mean levels of factor VIII, total cholesterol, triglycerides, VDRL cholesterol and apolipoprotein B-100, C-11 and C-14 than those without thrombosis. There were a large percentage of patients with arterial events (10%) in the latter series, possibly accounting for the discrepancy.[90]

Other possible contributions to thrombosis in Behçet's disease

Several coagulability factors have been suspected to play a role in the thrombotic events in BD. Hyperhomocysteinemia and decreased levels of antithrombin III, protein C, protein S, and the factor V Leiden mutation have been investigated, with no consistency in the findings and little relationship with thrombotic episodes in the disease.

Homocysteine

Increased levels of homocysteine were found in 27.6% of BD patients, compared to 6.9% in healthy controls.[92] Aksu[93] found mean plasma concentration of homocysteine to be higher in BD patients than in healthy controls (11.5±5.3 vs. 8.8±3.1 μmol/L). Hyper-homocysteinemia was reported to be significantly higher in patients with active disease than in patients with inactive disease and in control subjects.[94] Moreover, high levels of homocysteine were reported in 64% of patients with BD with thrombosis as compared to 9% in those without thrombosis.[93] However, in a study from Tunis,[95] hyperhomocysteinemia was more frequent in patients than in controls, but there was no difference in those with or without thrombosis. Increased levels of homocysteine were also found in patients with ocular involvement compared to those with non-ocular disease and healthy control subjects.[77] In another recent study, hyperhomocysteinemia was confirmed as a definite finding in BD patients compared to controls.[96] Other researchers have found no association between venous involvement and hyperhomo-

cysteinemia, thought not to be an independent factor for vascular involvement.[97]

Aksu[93] hypothesized that homocysteine had a deleterious effect on endothelial cells, causing endothelial cell damage, smooth muscle cell proliferation, and increased oxidative stress. An alternate mechanism for induction of vascular disease and thrombosis could be the interference with coagulation mechanisms. Other researchers blame the generation of superoxide and hydrogen peroxide by homocysteine for this effect, both of which may induce endothelial damage.[77] According to this hypothesis, homocysteine changes coagulation factor levels so as to encourage blood clot formation with aggregated platelets. Other investigators suggest that homocysteine may contribute to a decrease in serum paraoxonase (PON 1) activity, particularly in patients with active disease.[94] A current hypothesis suggests that homocysteine may have a deleterious effect in BD by decreasing NO levels and also through immune system effects. Homocysteine activates T cells and increases the interaction of monocytes and T cells with endothelial cells.[96] From these studies it is obvious that the exact mechanism by which hyperhomocysteinemia is related to vascular disease and venous thrombosis remains to be clarified by further investigation.

Coagulation factors

The prevalence of antithrombin III, protein C, protein S deficiencies, the factor V Leiden and prothrombin G→A[20210] mutations, the methylenetetrahydrofolate reductase C677T polymorphism, and acquired thrombophilic risk factors including anticardiolipin antibodies (ACL-Ab), lupus anticoagulant, and serum homocysteine levels have all been the subject of recent investigations. Overall comparison of the reported findings in patients with BD in Spain with healthy controls showed no significant differences.[98] Nonetheless, deficiencies of the anticoagulant proteins antithrombin III, protein C and protein S have been implicated for the thrombotic events in certain patients with BD.

Antiphospholipid antibodies may be a marker for a risk of development of thrombosis. However, several reports failed to demonstrate a correlation between ACL-Ab or lupus anticoagulant in patients with BD, but a prevalence of 0-8% has been reported.[99-102] Although found in patients with BD, there has been no correlation with any vascular complications of the disease. Circulating lupus anticoagulant or elevated levels of IgG ACL-Ab were detected in a significant number of patients with BD without any demonstration of a relationship to arterial or venous thrombosis.[103] In another study of 64 patients with BD, 23.4% with vascular involvement, only 2 patients (13.3%) had lupus anticoagulant and

one (6.6%) had both lupus anticoagulant and acl β2-GP1 antibodies.[104]

High von Willebrand factor antigen (vWF:Ag) levels may be found in BD patients, but are possibly secondary to vascular damage due to endothelial cell injury.[105] More recently, significantly higher vWF: Ag levels were reported in BD patients compared to a control group.[106] There was no statistically significant difference between vWF: Ag levels in patients with and those without organ involvement. A significant linear correlation between high vWF: Ag and serum ferritin levels was observed, suggesting that vWF: Ag was related to disease activity.[106]

BD with deep vein thrombosis and the factor V Leiden mutation has been reported.[107] However, others authors have not found any association between three thrombogenic mutations (factor V gene G169IA, methylenetetrahydrofolate reductase gene C677T, and prothrombin G→A[20210] mutation) and BD patients with thrombosis.[108] Heterogeneity for factor V gene mutation was considered to be a risk factor for venous thrombosis by others.[109,110] In a study from Italy, there was no association between deep venous thrombosis and the factor V Leiden mutation.[111] Factor V Leiden did not correlate with retinal vascular occlusion in 53 patients from the United Kingdom.[112] However, an association was found between the factor V Leiden mutation and ocular BD, particularly for the development of vascular occlusion.[113] The prevalence of factor V Leiden in these Turkish patients with retinal occlusion was 53.3%, compared to 26.7% in those without vascular occlusion. The prothrombin G→A[20210] mutation was not detected in any of the BD patients in that study. The variable results reported from the studies could be related to the methodology and/or to the different populations studied.

In a recent study from Spain, the prevalence of inherited and acquired thrombophilic risk factors in 79 patients with BD and in 84 healthy control individuals was studied. Three of 23 patients with thrombosis were carriers of the prothrombin G→A[20210] mutation, compared with none of 56 patients without thrombosis (P = 0.022).[98] In a meta-analysis, these authors found an association with the factor V Leiden as well as the prothrombin G→A[20210] mutation with thrombosis in BD. A study from Italy found no association with deep venous thrombosis, but a high frequency of the prothrombin G→A[20210] mutation was found in a subgroup of patients with posterior uveitis and retinal vasculitis, supporting the possibility that this factor may influence the development and also the severity of eye involvement in BD patients.[111]

Among 20 BD patients with vascular involvement, 55% had Mediterranean fever gene mutations compared to 11% in the non-vascu-

lar group, a statistically significant difference.[114] Plasma E, L, and P selectin concentrations were significantly higher in patients with severe BD.[115]

Peripheral arterial involvement

Several large series and case reports of patients with BD and peripheral artery abnormalities have been reported.[8,39,40,42,116-118] The frequency of arterial involvement in BD ranges from 2.2-18%, with marked male predominance.[39,42,45,119] The reason for the sex difference in the prevalence of BD remains uncertain, but sex hormones and/or genetic factors have been implicated.[118]

Arterial involvement can be found in any peripheral artery, particularly in femoral artery, popliteal artery, iliac artery and abdominal aorta, while it is infrequent in carotid artery. Venous involvement is found in most patients with arterial disease. Peripheral arterial occlusions are more frequent than arterial aneurysms, but the concurrent appearance of occlusions and aneurysms is not an unusual finding.[120] Pseudoaneurysms of large or median sized arteries with occlusion or stenosis of distal run off arteries in Korean patients have been reported.[121] A case of pseudoaneurysm of renal interlobar artery has also been reported.[122]

The clinical presentation of aneurysms varies widely from the asymptomatic to pulsatile mass, back pain, painful mass, hematoma, intermittent claudication, abdominal pain, gangrene of the forefoot, and less frequently hemoperitoneum, anuria, or fever. Multiple aneurysms can be seen in peripheral arteries.[123]

Relapses of arterial involvement are very frequent and sudden death from aneurysm rupture has been reported. The rate of death in patients with aneurysm rupture was found to be as high as 60%.[124] The mortality rate in BD has been studied by several authors.[42,118]

Computed tomography, ultrasonography and MRI angiography can all be helpful for the diagnosis of arterial aneurysms. Intravenous digital substraction angiography should be considered in order to minimize the occurrence of aneurysm formation at the site of arterial puncture. Recently ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) was used in BD with impressive results for the diagnosis of arterial involvement in a woman with BD.[125] Histological examination of the aortic wall involvement shows a thinned media and fragmentation of elastic fibers. Mononuclear cells and lymphocytes were demonstrated, particularly in the adventitia where fibrosis prevailed. Thrombosis of the vasa vasorum has also been described.[120]

Combination treatment with corticosteroids and immunosuppressive drugs (azathioprine, cyclophosphamide) and, rarely, anticoagulants have been used in the treatment of large vessel vasculitis in BD.[45,116] Because rupture of these aneurysms with fatal outcome is not rare, physicians usually elect for urgent surgical intervention. Surgery should be performed in a patient with a large or growing aneurysm, acute bleeding of the aneurysm or acute ischemia.[126] Various surgical procedures have been employed in the treatment of aneurysms including bypass, ligation and tube graft insertion, and aneurysmectomy but should always include simultaneous medical management.[127,128] Combined morbidity (anastomotic pseudoaneurysms) and mortality of BD patients after endovascular repair is considerably lower than open surgery.[129] Endovascular repair is a less invasive procedure and is more often successfully accomplished in BD patients compared to those with atherosclerosis because patients are younger and the aneurysm typically involves a shorter vessel segment.[126] However, the long-term results of endovascular procedures remain uncertain and further studies with long-term follow-up are needed to determine the optimal surgical strategy.[126] In a study by Hosaka,[118] the postoperative course in 10 patients (9 males), many requiring multiple procedures, was complicated by graft occlusion in 5 patients, anastomotic false aneurysm in 5 patients, and new aneurysms in different sites in 7 patients. Five patients were alive, one patient died and 2 were lost to follow-up. The overall cumulative incidence of formation of anastomotic pseudoaneurysm was 12.9% (5 of 49 anastomoses) at five and ten years.[118]

Immunosuppressive treatment could be needed together with any surgical repair method including endovascular repair.[119]

Pulmonary manifestations

Pulmonary artery aneurysms (PAA), pulmonary arterial and venous thrombosis, pulmonary infarction, recurrent pneumonia, bronchiolitis obliterans, organizing pneumonia and pleurisy are the major pulmonary complications in BD.[130,131] Thee are no prospective studies examining the true prevalence of lung involvement in BD, but the reported prevalence ranged from 1-7.7%.[132]

The most severe complication of pulmonary vasculitis is PAA. While uncommon, these have a poor prognosis and are a leading cause of death in patients with BD.[42,133,134] Pulmonary arterial vasculitis almost exclusively affects males and has a strong association with a systemic pattern of vessel involvement at other sites.[119,134]

The most frequent symptoms of PAA are chest pain and hemoptysis in 80% of patients.[133] Massive hemoptysis can occur. The cause of bleeding is rupture of the aneurysm with erosion into a bronchus or massive hemoptysis[135] or *in situ* thrombosis from active vasculitis.[130] Pathologically, acute inflammatory destruction of elastic and muscular pulmonary arteries or extensive inflammatory disruption of alveolar capillaries is seen. It should be recognized that anticoagulant therapy, usually given for coexisting DVT or because of the clinical suspicion of a pulmonary embolus, is extremely hazardous and may increase the risk of extensive, fatal pulmonary hemorrhage.[131,136,137] Confirmation of the cause of hemoptysis in any BD patient is essential to the choice of appropriate treatment.

Associations with PAA included deep vein thrombosis of the lower extremities in 81%, vena cava thrombosis in 15%, intracardiac thrombus in 12% and arterial aneurysm at other sites in 15%.[133] Pulmonary artery aneurysms are typically confined to main pulmonary arteries and their lobar branches.[119] Theses aneurysms can be unilateral or bilateral, single or multiple,[138] true aneurysms.[131] The occurrence of pulmonary artery aneurysms and deep vein thrombosis is referred to as Hughes-Stovin syndrome.[139,140]

The diagnosis of pulmonary aneurysm is suspected by clinical findings and confirmed by chest X-ray, Doppler ultrasonography, helical computed tomography, pulmonary angiography, scintigraphy, MRI angiography, and thoracic computed tomography.[131] FDG-PET has been used successfully for the visualization of pulmonary artery aneurysms in one case.[141] On chest X-ray peripheral or central pulmonary nodular opacities occur and are frequently multiple.[142]

Histological findings in PAA reveal a pulmonary vasculitis affecting arteries, veins, venules and capillaries.[143] The inflammatory process may be initiated in the vasa vasorum.[119] Pathological findings can include inflammatory infiltrates with alterations of the intima and elastic lamina, necrosis of the vessel wall, fresh thrombi and thrombotic occlusions, and true and false aneurysms.[144]

The prognosis of PAA is extremely poor and requires prompt diagnosis and treatment to improve survival. In an earlier cohort of Turkish patients, half of the PAA patients were reported to have died within ten months after the onset of hemoptysis.[134] In a more recent report of patients with PAA, the same researchers found an overall 5-year survival rate of 63%; patients diagnosed since 1992 had a 5-year survival rate of 80%.[133] The improved prognosis was believed to be due to earlier diagnosis and rational use of immunosuppressive agents. In another recent study, the cumulative survival of patients with PAA was 57% at one year and 39% at five years.[131]

There are no randomized controlled studies regarding the optimal treatment of PAA and the recommendations are based on consensus or observational studies.[131] Spontaneous remission of PAA has only rarely been reported.

Current recommendations include corticosteroids and immunosuppressive drugs. Corticosteroids and immunosuppressive drugs may be particularly beneficial especially when introduced in the early stages of the development of this complication, before irreversible damage to the arterial wall develops. Pulse methylprednisolone and pulse cyclophosphamide have been administered for two years, and then they are continued or replaced by azathioprine.[132,133,143] Recently the anti-TNF agent infliximab was administered to a patient with life-threatening hemoptysis from pulmonary aneurysm with complete remission.[145] These results should be confirmed by other studies.

Embolization with n-butyl-cyanoacrylate (NBCA) has been successfully used in patients with PAA presenting with life-threatening hemoptysis.[146] Aneurysm size or vena cava thrombosis may limit the use of endovascular embolization in some patients.[119] Patients treated with embolization, with or without immunosuppression, have a better prognosis than patients who underwent surgery without immunosuppressive therapy who had the highest mortality rate.[131] Anticoagulant therapy may be hazardous in patients with aneurysmal dilatation of the pulmonary vascular tree, and the beneficial effect of corticosteroid therapy has been discussed.[142]

Urgent surgery was performed in 3 patients with pulmonary artery aneurysm due to life-threatening massive hemoptysis, and these patients died in the post-operative period.[147] Surgical therapy should be reserved for those patients with life-threatening disease. The presence of pulmonary artery aneurysms in general confers a poor prognosis with many fatalities in these young patients. Multiple other vascular complications may contribute to the prognosis.

Pulmonary embolization is rare in BD. This is thought to be because thrombi are adherent to the vessel wall as a result of the inflammation present and do not detach easily from the endothelium.[136,148]

Pleural effusion is not rare in BD patients. It may result from vasculitis of the pleura, which has been demonstrated by biopsy, pulmonary infarction, thrombosis of the superior vena cava[149] or of the innominate and subclavian veins, and may be chylous due to lymphatic obstruction (*see above*). Treatment of pleural effusion in BD is directed to the underlying cause of the fluid and may include corticosteroids, immunosuppressive drugs and surgical drainage. Pleurodesis with tetracycline has been employed.[57]

Cardiac manifestations

Cardiac abnormalities in BD include pericarditis, myocarditis with conduction system findings, endocarditis with valvular regurgitation, intracardiac thrombosis, endomyocardial fibrosis, coronary arteritis with or without infarction, and aneurysms of the coronary arteries or sinus of Valsalva. Clinical cardiac involvement in BD has been found in as many as 16.5% of cases in a postmortem series[150] and may be demonstrated in more patients if sensitive techniques are employed.

Pericarditis

Pericarditis may be symptomatic with chest pain and fever, although it can also be asymptomatic.[151] Pericarditis may be associated with coronary infarction, myocarditis, pleural effusion and/or obstruction of the veins of the extremities. Constrictive pericarditis is a very rare complication.[152,153]

The pericardial fluid in BD patients is usually inflammatory, although it can rarely be chylous.[57] The histology of the pericardium has been found to show vasculitic lesions with perivascular infiltration of lymphocytes and plasma cells or fibrosis,[57] or reactive mesothelial proliferation and fibrin exudation.[152]

Pericarditis may subside with non-steroidal anti-inflammatory drugs, but corticosteroids and immunosuppressive drugs may be required for treatment of associated lesions.[153,154] Pericardial drainage may be necessary in cases of large effusions with compressive symptoms.[57,153]

Myocardium involvement

Myocardial manifestations in BD include cardiac arrhythmias[155] and, rarely, myocarditis.[156] In the first study to use pulsed wave Doppler tissue echocardiography, ventricular diastolic function was found to be abnormal in BD patients as compared to control subjects.[157] Diastolic dysfunction was reported in 37% of patients using transthoracic and multiplane transesophageal echocardiography.[158] Potential explanations for this dysfunction include the possibility of primary myocardial disease, disturbance of the coronary microcirculation, or the presence of silent ischemia.[157] In one recent study, no differences were found in left ventricular function in systole and diastole at rest and with exercise in patients as compared to healthy control subjects.[159] This discrepancy of the reported studies may be due to the patient selection or to the sensitivity of the assessment methods.

Endocardium

Mitral and aortic valvular insufficiency has been observed in patients with BD.[160,161] Mitral regurgitation is the most frequent valvular disorder, reported in as many as 40% of patients of BD and in 6% in healthy controls.[158] Valvulitis of mitral and aortic valves has been reported and the histological findings have been described. Mitral valve leaflets covered by fib-

rin with necrosis and massive growth of granulation tissue have been reported.[162] Dilatation of the aortic and mitral valve with or without endocardiac thrombus has been demonstrated.[163,164] A case reported with aortitis had vegetations of aortic and mitral valves resembling aortic valve endocarditis with subaortic complications.[163] Anterior prolapse of the mitral valve was found in 6% of BD patients and in 3% of healthy subjects.[165] A more recent study found a prevalence of mitral valve prolapse of 25% in patients with BD, while in control subjects it was the same (3%) as in the previous study.[158] Dilatation of the ascending aorta was found in 48% of BD cases and 3% in normal subjects.[165] Differences between studies may be due to different diagnostic criteria, technical differences, and heterogeneity of the study population.

In patients with BD, it may be appropriate to perform both transthoracic and transesophageal endocardiograms these being the most sensitive tools to detect endocardiac and myocardial abnormalities.

A serious complication in BD is the formation of an endocardial thrombus or endocardiac mass.[166-169] Males are affected much more frequently than females and more than half of the cases were found to have intracardiac thrombus at the time BD was first recognized.[170] The principal clinical findings at the time of detection of intracardiac thrombus were fever in 52% of patients, hemoptysis in 48%, dyspnea in 44%, and cough in 20%. An accelerated erythrocyte sedimentation rate was frequently found, although it was a poor indicator of disease activity.[170] Cardiac thrombi in BD are located in the right atrium, left atrium, right ventricle and rarely in other sites of the endocardium.[170,171] The reason for the propensity to right-sided intracardiac thrombus in BD is unclear. BCS, PAA, and IVC thrombosis are often associated with clots of the endocardium.[172]

Transesophageal echocardiogram, enhanced helical CT, and indium 111 platelet scintigraphy have been used for the diagnosis of endocardiac thrombosis. Scintigraphy can distinguish between whether the thrombus is acute or chronic. Blood fibrinolysis was impaired in a 34-year old male with myocardial infarction and BD.[91]

In some individual cases, thrombophilic factors have been present and may contribute to intracardiac thrombosis. Heterozygous prothrombin G →A[20210] mutation has been recognized in 2 patients.[166,167] In most cases, prothrombotic factors are not found and the cause of thrombus formation is not well understood.[91,173]

Anticoagulants, colchicine, thrombolytic agents, corticosteroids, and immunosuppressants have been employed in the treatment of intracardiac thrombus in BD patients with

some success.[167,168,171] The surgical removal of thrombus was successful in a 16-year old male, followed by anticoagulant and corticosteroid treatment.[169] Recurrence of the intracardiac thrombus after surgical removal occurred and azathioprine was added. In another patient, recurrence of the intracardiac thrombus after surgical removal was observed and treated with prednisone and cyclophosphamide.[167,168,171] We believe that this complication should be treated with immunosuppressive agents which are often indicated in any case because of comorbid complications.

Endomyocardial fibrosis is a rare complication of BD, but reported by several investigators.[174,175] It has been suspected that endomyocardial fibrosis could be the result of treatment with corticosteroids, anticoagulants, or antiaggregants.[175] More likely, this problem may be the sequela of vasculitis involving the endocardium, myocardium or both, complicated by mural thrombus.[175] Endomyocardial fibrosis is located in the right and left ventricles and only rarely in the atrium. Histologically, dense fibrous tissue with neovessels, mononuclear and polymorphonuclear infiltrates and calcified areas have been found. If endomyocardial fibrosis is complicated by cardiac failure, surgical excision has been a successful treatment in the short term.[174,175]

Coronary arteries

Coronary artery aneurysms in BD are rare and few reports have been published. In one recent case,[21] the aneurysm was associated with an inflammatory obliterative endarteritis of the vasa vasorum with endothelial cell swelling. The infiltration consisted of mononuclear perivascular infiltration which caused destruction of media, arterial weakening and aneurysm formation. The aneurysm developed in the patient during a period of apparent clinical remission of 13 years. Conservative management with aspirin, metoprolol and atorvastatin was elected and the patient had no chest pain over follow-up of one year. Coronary angiography in another patient showed complete proximal occlusion of the circumflex artery and an aneurysmal fistula between the left main branch and the pulmonary artery.[176]

Rarely, myocardial infarction has been the presenting symptom of BD.[173] Myocardial infarction with normal coronary arteries in young patients has been observed, presumed to be due to coronary arteritis.[161,177] Myocardial infarction may be accompanied by other manifestations, such as pericarditis, recurrent venous thrombosis.[161] In all young adults with BD and myocardial infarction, non-atherosclerotic etiologies such as emboli, dissection, trauma, spasm or arteritis should be investigated.

The treatment of myocardial infarction in BD is unclear. Coronary stent placement in one young BD patient was followed by proximal

in-stent restenosis and aneurysm formation.[178] The long-term results of stent placement in BD patients are unknown, considering the possibility of pathergy in these patients and an underlying vasculitis. Immunosuppressive therapy should be considered in these patients when progressive complications are recognized. Aneurysmal dilatation of sinus of Valsalva was detected by transesophageal echocardiography in 28% of BD patients and in 3% of controls.[158] These aneurysms may be asymptomatic, but ruptures of these aneurysms have been reported.[179]

Cerebral vasculitis

Cerebral vasculitis in BD can result in cerebral venous thrombosis or, less commonly, in intracranial aneurysms. The role of true vasculitis in the pathogenesis of parenchymal CNS disease in BD is not well documented.

Cerebral arterial aneurysms

Cerebral aneurysms are rather infrequent in BD but multiple case reports and case series have been published.[180-182] A rare case of brain abscess of the parietooccipital lobe with associated brainstem encephalitis in a female with BD and another patient with subarachnoid hemorrhage due to a ruptured aneurysm of the superior cerebellar artery were reported.[181] Rupture of a superior cerebellar artery aneurysm after five months of disease has also been reported,[182] but this is a very rare early manifestation of the disease. The clinician should be alerted to the possibility of rupture and treatment initiated before catastrophic neurological damage results. Neurological symptoms proceeded the diagnosis of BD in only a very few cases.[59] The main presenting symptom of a cerebral arterial aneurysm is headache, resulting from the rupture and hemorrhage.[180,183] Digital substraction angiography or MR angiography can be used for the detection of arterial aneurysms.[184]

Treatment of cerebral aneurysms in BD is generally surgical clipping, as it is for aneurysms in the absence of the disease.[180,183] If an unruptured aneurysm is recognized, high-dose corticosteroids have been recommended.[184] Aneurysm occlusion by an endovascular approach can provide an equivalent therapeutic result without the need for a craniotomy.[183,185] This procedure can be performed in the early stage of subarachnoid hemorrhage, particularly in those patients with poor neurological status.[182,183]

Discussion

We performed an extensive literature review on the participation of vascular inflam-

mation in multiple clinical manifestations of BD. The disorder is classified among the systemic vasculitides. Vasculitis is believed to be involved in the pathogenesis of most of the problems seen in patients with the disease and it is important for the clinician to understand the process of vascular inflammation in order to best treat these patients.

Vasculitis may be recognized in multiple tissues examined by biopsy or during the course of surgery, but there are no specific diagnostic findings to support the diagnosis of BD. Rather, it is the expanded spectrum of blood vessels involved, from the smallest vessels to the great vessels, and the involvement of both arteries and veins, both in the systemic circulation as well as in the pulmonary circulation, that is characteristic of BD. The term "vasculo-Behçet" has been used to identify that subgroup of BD patients who have a particular predilection for large vessel involvement, often with an additive, progressive course that concludes with pulmonary artery aneurysm, the complication most associated with mortality in this disorder.

The pathogenesis of the vasculitis in BD continues to be studied in many centers around the world and a clearer picture of the multiple contributing factors is slowly emerging. There has been little support for circulating factors in the pathogenesis of the venous thrombosis associated with the disease, but inherited coagulation abnormalities may compound the problem of vascular inflammation leading to adherent clot.

We reviewed the clinical presentation of patients with vasculitis in various organ systems and the diagnostic approach to confirm the presence of disease. A discussion of the treatment of the vasculitis in BD would include a review of the treatment of the whole disease, as vasculitis is usually responsible. We have focused our comments on treatment to large vessel manifestations. While recommendations for treatment are limited by the lack of randomized controlled trials, a recent publication by a European League Against Rheumatism subcommittee has provided guidelines based on available data as well as on expert opinion.[186] In the area of large vessel involvement, the guidance statements by this group include the following: i) there is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis in BD, immunosuppressive agents like corticosteroids, azathioprine, cyclophosphamide or cyclosporine A are recommended. For the management of both pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended; ii) there are no controlled data on, or evidence of benefit from uncontrolled experience with: anticoagulants, anti-platelet or fibrinolytic agents in the man-

agement of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD. We believe that these statements accurately describe the current status of our beliefs in the treatment of large vessel inflammation or thrombosis. Aggressive treatment of the inflammation in large vessel arterial and venous disease with immunosuppressive agents is recommended. The lack of benefit from use of anticoagulants in the treatment of these disorders should discourage the use of these agents as sole treatment of any of these vascular complications.

Conclusions

In conclusion, we reviewed the wide variety of vasculitis and vascular manifestations that can be seen in patients with BD. The vasculitis of BD can affect vessels of all sizes, both in the arterial and venous circulations, including the specialized vessels of the pulmonary circulation. The occurrence of multiple involvements in BD is distinctive, if not unique, among the vasculitides, and can certainly support the diagnosis of the disease when present, although vascular involvement is not included in the criteria of the International Study Group. Studies of the vasculitis in BD continue, especially with regards to the endothelial dysfunction and thrombosis which occurs in these patients. Careful observation of BD patients can lead to early diagnosis of vascular involvement. While randomized controlled studies of the treatment of large vessel complications of the disease have not been carried out, experience with multiple reported cases and the improved prognosis of affected patients with aggressive treatment can guide the clinician in treatment efforts.

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