Chapter 9

Vascular Manifestations of Behçet's Disease

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Additional information is available at the end of the chapter

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Abstract

Behçet's disease (BD), a very morphologically diverse systemic disease, may involve the vascular system. The venous system is the most frequently attacked vessel system. The arterial system, when involved, increases the severity and morbidity of Behçet's disease. Cardiac involvement, although rare, can be very subtle and in itself increases the mortality. Vasculitis is the hallmark pathology resulting in occlusion, aneurysms, or both. Vascular involvement may be very challenging in all phases of treatment beginning from diagnosis till recovery and remission.

Keywords: vascular involvement, vasculitis, arterial occlusion, venous thrombosis, arterial aneurysm

1. General cardiovascular involvement and findings associated with Behçet's disease (BD)

Behçet's disease (BD) is the only systemic vasculitis involving both arteries and veins in any sizes [1]. The most frequent vascular involvement is of the venous system. Both genders in their 20s and 30s can be affected. Prevalences differ.

BD has a decidedly increased mortality when the disease is seen in young male patients, while it is not as severe in female and aged patients. In most patients the severity of BD abates with the transition of time. The largest cause of mortality in BD is large-vessel vascular disease, especially hemorrhage because of pulmonary artery aneurysms (PAAs), which are almost always seen in men.

Etiology and pathophysiology of BD are still obscure and as of today unilluminated [2].

BD is a vasculitis which can involve all arteries and veins irrespective of diameter. The entire venous system from subcutaneous superficial veins to the vena cava and all deep lower extremity veins are under risk of thrombosis. The location of these thromboses determines the clinical picture. Cardiac involvement is one of the prognostically devastating manifestations of Behçet's disease (BD). Cardiac involvement is relatively uncommon [3]. The heart and great vessels are not primary targets of BD, but although not well recognized, arterial or cardiac involvement is life-threatening with associated strong prognostic implications in BD.

Therefore, physicians caring for BD patients should work closely with cardiologists, cardiovascular surgeons, and endovascular interventionists to increase awareness of these silent and potentially fatal vascular complications and form multidisciplinary groups to more successfully manage BD and its cardiovascular complications in the future.

2. Venous involvement and treatment modalities in Behçet's disease

2.1. Introduction

Vascular and neurological involvements make up the largest causes of mortality in BD. Men are more frequently affected than women. The entire venous system from subcutaneous superficial veins to the vena cava and all deep lower extremity veins are under risk of thrombosis. The clinical characteristics differ with regard to both clinical course and treatment in comparison to venous diseases due to other etiologies, and unfortunately, as of 2017, there is no set of algorithm for treatment.

As the world integrates and becomes a global village, our colleagues in both the traditional Silk Road countries and in countries receiving immigrants from these countries should have a practical knowledge and remember the particulars of the venous manifestations of this disease in order to differentially diagnose BD among a variety of venous diseases.

We will give clinicians information about the etiopathogenesis and clinical course of the venous manifestations of BD in light of literature and discuss related treatment options in this chapter.

2.2. Epidemiology

Although the incidence of BD does not differ according to sex, vascular involvement, the factor which determines the prognosis of the disease, is more frequently seen in men. Female to male ratio is 1 to 9 and does not change according to whether the thrombosis is venous or arterial. Vascular disease usually commences in the fourth decade within the first 5 years of the manifestation of other symptoms of BD. Although vascular involvement is seen in 15–38% of BD patients, this ratio was found 35% after 20 years of BD in a long-term prognostic study [4].

Even though the 1990 ISG criteria does not have vascular involvement as a prerequisite for diagnosis, this stems not from the fact that vascular involvement is insignificant, but because it does

not carry significance in the differential diagnosis of BD. This matter was finally resolved when the International Criteria for Behçet's Disease (ICBD) was revised in 2014 [5]. In all discussions of criteria for diagnosis of BD, venous involvement is again put on the discussion table [6].

Ten percent of patients applied to clinics with a vascular incident before being diagnosed with BD and twenty percent of them applied after BD diagnosis were made having other coincidental symptoms of BD. A new incidence of vascular involvement in the next 5 years increases by 38% after the first vascular event [7].

Venous disease comprises the largest part within the aforementioned vascular incidences. Nearly 882 BD patients had vascular incidents in a cohort of 1272 patients applying to the clinic in an investigation conducted between 1977 and 2006. Almost 67 vascular BD patients verified by retrospective radiological methods in 6 different centers in Ankara, Turkey, were studied, and in 63 patients, a venous lesion was found in 200 locations. Both arterial and venous lesions were detected in 8 of these patients [8].

2.3. Pathogenesis

The fact that BD, although seen now almost everywhere throughout the world after migrations and distribution of refugees after civil wars, is originally seen along the so-called Silk Road, makes one think that the probable factors having a role in the pathogenesis of BD and genetic tendencies like having HLA-B5(51) have also spread along the same geography.

Although genetic factors were emphasized mostly in older studies, the detection of less disease incidence in Turkish people residing in Germany in comparison to the Turkish resident population in Anatolia and Eastern Thrace (consisting of the territory of modern Turkey) and more disease than Germans living in Germany revealed that both genetic and environmental factors were individually or jointly decisive in the development of BD [9]. Clinical disease symptoms and mortality appear to vary by geography as well as ethnic group.

In the Far East, BD usually coexists with inflammatory gastrointestinal diseases, whereas this is rare in Anatolia and Eastern Thrace. While the relationship between pathergy test positivity and HLA-51 is strong in Mediterranean countries and Japan, it is not the case in North America and patients in the USA [10].

BD, whose underlying pathology is vasculitis, is encountered in patients with familial Mediterranean fever (FMF) more frequently than the normal population. The reason for this may be the gene mutation related to the HLA region involved in BD (A9 allele of MICA [class I–related chain A (MICA) antigens]) which concurrently plays a role in the FMF pathogenesis. In a gene research conducted in the Jewish population, 54 BD patients were investigated. In 24 of these patients, one or two mutations were encountered in the MEFV gene playing a key role in FMF. Also, reported in this study is that this mutation does not only lead to BD but concurrently is related to more venous occlusive course in BD [11].

According to a survey conducted by Kural-Seyahi et al., the beginning of ocular disease and its greatest destruction usually occurred within the first early years after the initial attack. This finding led to the suggestion that the "disease burden" of BD is generally confined to the early

years of the course of the disease and as the authors expressed, the disease "burns out" in time. Nonetheless, the important distinction comes from the fact that central nervous system involvement and vascular disease are exceptions to this rule. Vascular BD and central nervous BD have their beginnings later (5–10 years after onset of BD). The mortality numbers showed a less severe course in almost all disease involvement in female patients. No female patients had arterial aneurysms in the abovementioned survey [12].

No Behçet-specific factor initiating thrombosis or increasing the tendency for thrombosis could be found in studies directed at pathogenesis. BD differs from classical autoimmune diseases because of the absence of female dominance, classical pathognomonic antibodies, and being unrelated to syndromes like Sjogren's syndrome. Factors like factor V mutation, which increase the general tendency for thrombosis, may be responsible for the initial and recurrent thromboses [11]. Antithrombotic factors like protein C, S, and antithrombin III were not found deficient when all Behçet patients were examined. In the light of all these studies, it is now thought that in BD venous thrombosis develops as a result of an inflammation on the vein wall. There is a vessel wall damage and nonspecific inflammation especially in the vein adventitia [13].

T1 helper cell immune response is predominant in this inflammation, and CD4+ lymphocytes are dominant in the lesions [14]. Coagulation begins with tissue factor activation, and thrombocytes, by adhering to the present fibrin, grow ascendingly and fill the lumen.

The presence of anticardiolipin antibodies (aCL), similarly, cannot explain the increased risk of thrombosis in BD [15]. Biochemical marker negativity is not limited to anticardiolipin antibodies. RF (rheumatoid factor), ANA (antinuclear antibody), and ANCAs (antineutrophil cytoplasmic antibodies) are also negative.

Patients with BD do not have decreased protein C, protein S levels or antithrombin III activity, presence of activated protein C resistance, circulating LAC (Lupus anticoagulant) , or elevated levels of IgM aCL (anticardiolipin antibodies). A significant number of patients have elevated levels of IgG aCL, but they are not associated with venous or arterial thrombosis. No correlation was found between any variable and other clinical manifestations of the disease [15, 16].

The reason for observing so few thromboembolic events in a disease where a great number of venous thromboses are seen is the fact that thrombi have been found to be spread in an ascending and smearing fashion strongly attached to the inflammation on the vessel wall in unpublished autopsy series [17]. Histopathological specimens taken from the thromboses on the venous wall at different phases during thrombosis are needed in illuminating this specific subject.

2.4. Superficial vein thrombosis (SVT)

Superficial vein thrombosis (SVT) is a sign that can be as frequently encountered as DVT (deep vein thrombosis) with a commonly acute beginning which may be accompanied by symptoms of thrombophlebitis (an increase of skin temperature along a superficial vein, erythema, and pain).

It presents with symptoms like extensive body pain, chills, and tremors. There is no registered data about fever which may accompany SVT. Because the inflammation may reveal itself as

nodular lesions in the vein rather than thrombophlebitis in some patients, BD may be impossible to differentiate from erythema nodosum. Vein wall thickening and intraluminal thrombus are detected upon superficial Doppler ultrasonography.

Superficial vein thrombosis (SVT) may be simultaneously seen in BD patients with previous DVT or concomitantly with DVT [18]. SVT is more frequently observed in the presence of venous insufficiency background and appears like diffuse erythematous indurated plaques in the dermal-epidermal tissue. SVT leaves a pigmented trace or thinned but hardened vein after recovery.

2.5. Deep vein thrombosis

DVT is the initial and most frequently appearing vascular incident in BD (two-thirds of the cases). Even though it can be seen anywhere along the venous system, it is most commonly observed in the femoral and popliteal veins. There are no criteria differentiating DVT in BD from classical DVT. There is no clear data concerning the frequency or time about the development of venous insufficiency in Behçet patients with DVT. Edema due to venous insufficiency, pigmentation, and venous claudication can be observed in patients who have been followed for a long time [19]. While some studies declare the rate of postthrombotic syndrome (PTS) incidence as 20–50% in patients who have been affected by proximal DVT (DVT in iliac, common femoral veins), this rate is given as 5–10% in severe PTS patients with venous ulcers [20]. It is important to differentiate between venous insufficiency and vasculitis in patients who present with venous ulcer. Venous claudication which directly affects daily quality of life occurs in one-third of the patients [19].

Roumen-Klappe et al. in their 2009 work demonstrated that elevated IL-6, C-reactive protein (CRP), and intercellular adhesion molecule 1 (ICAM-1) levels after DVT development are directly related to PTS [21]. The increase in ICAM-1 level is also directly proportional to the severity of PTS.

Although Behçet patients who have DVT are under risk of PTS, the clinical course differs to a large extent from that in classical DVT with regard to the frequency of pulmonary thromboembolus (PTE) development. This leads to a great difference in DVT treatment protocols in BD. The chance of recanalization of the affected veins is low. Clinical relief comes more from collateral development which is copious in the venous system. DVT also can be ameliorated using thromboaspiration as an adjunct to conventional low-molecular-weight heparin treatment which is usually advised for a duration of 6 months. It has been reported that endovascular treatment with US-guided percutaneous aspiration thrombectomy can be considered as a safe and effective way to remove thrombus from the deep veins in pregnant women with acute and subacute iliofemoral deep vein thrombosis [22]. The effectiveness of this method is also corroborated in studies reporting about endovascular treatment of postpartum deep vein thrombosis [23, 24].

2.6. Vena cava thrombosis (VCT)

Vena cava thrombosis (VCT) is the second most commonly encountered venous incident after DVT. It is seen in approximately 15% of the patients, and the superior vena cava (SVC) is more commonly involved than the inferior vena cava (IVC).

Occlusion of the SVC causes the classical superior vena cava syndrome. Edema and erythema of the upper extremities and nonpulsatile congestion of the jugular veins are seen. Rarely, increased intracranial pressure and papilledema are also observed. Venous collaterals with caudal flow may be encountered upon physical examination. Pleural effusion is seen when the bronchial and pleural venous return is disrupted, and chylothorax is seen when the thoracic duct does not function properly. Contrast-enhanced computed tomography (CT) portraying the absence of venous flow is diagnostic.

IVC thrombosis shows symptoms similar to DVT. Computed tomography is again the diagnostic tool of choice. IVC thrombosis causes serious complications in the long run if intra-abdominal organs, especially the liver, are affected.

2.6.1. Budd-Chiari syndrome (BCS)

In Turkey BD is responsible for 40% of Budd-Chiari syndrome (BCS) cases [25]. The best known common characteristics of BCS cases that have been reported are the close relationship of BCS with vena cava thrombosis. Hepatic vein thrombosis coexists with IVC thrombosis in 80% or more patients with BCS [12].

Hepatic vein thrombosis should come to mind when a patient with the diagnoses of DVT or IVC thrombosis has or develops accompanying abdominal pain, ascites, and splenomegaly. High albumin gradient ascites, elevation of transaminase levels, and alkaline phosphatase may be seen in laboratory tests. In the long term, prognosis is determined by thrombosed vessels. While the prognosis is favorable in patients with solitary occurrence of the hepatic vein, the prognosis worsens when the portal vein or IVC is attacked, hitherto, the largest patient series reveals that two-thirds of 493 patients with Budd-Chiari syndrome have been lost by the end of the first year [25].

2.7. Cerebral venous thrombosis (CVT)

Cerebral venous thrombosis (CVT) as venous involvement in BD is a relatively rare vascular incident. 2.5% of Behçet patients are affected by CVT. It appears mostly in male patients over the age of 30. In a study conducted in 3908 patients, the rate of incidence was found 0.31%. This rate may differ between clinics because headache is encountered frequently in BD and diagnosis of CVT is difficult to make. The clinical course and prognosis are different from parenchymal neurological involvement [26].

CVT is the most frequent cause of intracranial hypertension [27]. Hyperhomocysteinemia as an independent factor has been held responsible for CVT [28]. In a meta-analysis it has been reported that hyperhomocysteinemia may be considered to be associated with thrombosis in BD [30]. 4.77% of CVT patients have already entered the subacute or chronic phase when diagnosis is established. The superior sagittal sinus (64%) or the transverse sinus is the most frequently involved locations. The sigmoid sinus follows in the frequency of involvement [29].

Differential diagnosis of CVTs encountered in BD can be made from other CVTs seen in different diseases or coagulation defects because of their characteristic male dominance, scarcity

of neurological signs, and unusual venous infarcts [30]. CVT should be suspected in a young male patient consulting the emergency department with headache, especially if the headache is recent and papilledema is present upon examination. Seen less is lateral rectus muscle weakness due to an increase in intracranial pressure resulting in diplopia and vomiting.

Cranial magnetic resonance imaging (MRI) and MR venography are the diagnostic golden standards. In two-thirds of the patients, the cerebrospinal fluid pressure is increased, and if no parenchymal disease accompanies CVT, the cerebrospinal fluid is normal.

Optic atrophy and resultant loss in vision are the main sequelae subsequent to long-standing papilledema in the long-term course of CVT in BD. Ventriculoperitoneal shunt may be needed in patients with elevated cerebrospinal fluid pressure. Prognosis is fair even though generally no anticoagulation is given. Early and differential diagnosis amiliorate the prognosis [31].

2.8. Treatment in venous involvement

DVT has the largest share in venous involvement. Its treatment is open to discussion. Especially for individually practicing vascular surgeons and other primary care physicians, the greater part of the treatment consists of anticoagulation. However, anticoagulation is not recommended for venous incidents in BD because the course of venous thrombosis is different in comparison to classical venous thromboses [32]. As evident from these conflicting reports, the discussion about coagulation defects is not settled yet.

It was reported in 2015 that procoagulant factors like coagulation factor V G1691A (factor V Leiden mutation) and prothrombin G20210A polymorphisms exist in BD. This led to the suggestion that these factors may be additional risk factors for thrombosis in certain people [33].

It has been reported that factor V Leiden mutation was more frequent in Turkish, but not in Italian, Spanish, and Israeli patients [34–37]. Prothrombin gene mutation was not reported to be relevant in several studies, but a meta-analysis by Ricart et al. demonstrated an interrelationship between the presence of prothrombin G20210A mutation and thrombosis in BD after excluding Turkish patients [37].

Lenk et al. reported that deficiencies of protein C, protein S, and antithrombin have not been linked to thrombosis in BD patients [15]. It has been reported that high levels of lipoprotein found in BD patients may be involved in the development of thrombosis by weakening fibrinolysis [25]. Moreover, high plasma levels of thrombin-activatable fibrinolysis inhibitor, which could lead to a substantial decrement of the clot lysis process, were documented in BD patients [38].

Although not clearly established as yet, there is conflicting data concerning the preventive potential immunosuppressive therapy on vascular diseases and complications [39]. Immunosuppressive drug therapy alone or in combination with steroids is advised during early stages of BD before the development of irreversible damage to the arterial wall [39]. Colchicine, which is a commonly used and very effective drug for mucocutaneous lesions, is not effective on vascular or ocular lesions. Colchicine may decrease nodular lesions in women, but it is not clear what percentage of these lesions is superficial thrombophlebitis.

Treatment in SVT is usually symptomatic. Nonsteroidal anti-inflammatory drugs and topical cold applications will ameliorate the local symptoms. 20–40 mg of prednisolone may be added to the treatment for patients with severe clinical course. Two weeks of steroids with mild doses may be added to the symptomatic treatment of patients with DVT.

It should be born in mind that a Behçet patient with prior history of a vascular incident is under risk for a second recurrent event. All Behçet patients who have DVT are given 2.5 mg/kg/day of azathioprine. This should be continued until the fifth decade (mid-1940s) when BD activity usually decreases. Azathioprine may prevent superficial thrombophlebitis [40].

Postthrombotic syndrome (PTS) is the most serious complication in the long term. Treatment of PTS is treated classically as in PTS due to other conditions. Compression stockings, bandages, and venoactive agents can prevent venous ulcer formation, and ulcer stockings are indicated when needed.

In SVC thrombosis corticosteroids and diuretics are effective if headache and diffuse edema are present. Although prognosis is fair in the long run, azathioprine should be added to the treatment.

Endovenous interventions (IVC filter placement and thrombectomy) should be avoided in BD because they may result in pathergy like symptoms and also because PTE practically does not occur. When treatment is planned for IVC thrombosis, BCS, which is the most mortal complication of venous involvement in BD, should always be born in mind. For portal hypertension diuretics and sodium restriction and for hepatic vein thrombosis, high doses of corticosteriods and monthly pulse doses of cyclophosphamides should be considered especially if de novo thrombosis has developed in the IVC or if the anatomical level of the thrombus is near the hepatic veins. Anti-TNF treatment has been tried in some patient groups but was not successful. Azathioprine used in combination with interferon causes serious leukopenia.

Symptoms improve, and the clinical course ameliorates with corticosteroids and azathioprine in CVT. If treatment is begun early, the prognosis is fairly good. Ventriculoperitoneal shunts may be needed for stubborn diseases with increased intracranial pressure and papilledema.

3. Arterial involvement and treatment modalities in Behçet's disease

3.1. Introduction

Behçet's disease (BD) is a vasculitis which can involve all arteries and veins irrespective of diameter. Changes in endothelial function due to this involvement cause different grades of clinically observable organ lesions [41]. Vascular involvement, especially arterial involvement, is one of the major causes of morbidity and mortality [42].

BD has a high incidence along the ancient "Silk Road" stretching from the Far East to the Mediterranean. The prevalence in Turkey is 80–370/100,000, while it is only 0.12–7.5/100,000 in the United States of America and Europe [43, 44]. But recently it can be seen anywhere in the world due to immigration.

Studies performed in Turkey, Iran, Japan, and Europe report that the prevalence of vascular involvement in Behçet's disease in their respective countries is 17, 9, 9, and 10–37% [45].

Vascular involvement rarely occurs as the initial clinical appearance of BD. It was reported that in a cohort of BD patients more than 94% exibited oral and genital ulceration at the first visit, while only 20.6% displayed vascular involvement in their very first clinical examination [44].

Since the first report in Japan by Mishima et al. in 1961, written in 1973, vascular involvement in BD has been reported to be about 2–46% and seen four to five times more in men in endemic regions [46]. In a retrospective study consisting of 882 BD patients with vascular involvement, the rate of vascular recurrence 2 years after the initial episode was found to be 23% and 38% after 5 years. Only male gender was found as a potential risk factor among potential predictive factors in the same study. Arterial attack is less frequent in comparison to venous involvement. Worldwide prevalence of arterial involvement is around 1.5–3% [47]. Patients with arterial involvements tend to have multiple lesions and usually have accompanying deep vein thrombosis. Aneurysm is usually more commonly reported than occlusion [47].

Regarding the site of occurrence, there have been some geographic variations in cohorts studied so far [47, 48]. Reports from Turkey and Korea described the femoral artery and the abdominal aorta as the most common locations of aneurysm formation [49, 50]. However, a report from a Chinese registry showed the lower extremity and the abdominal aorta as the most frequently attacked sites and the femoral artery as a rarely attacked location [47]. This is a typical example of geographical difference in frequency and locations of vascular lesions.

3.2. Pathogenesis

Autoinflammatory diseases have been described as diseases characterized by increased immune response mediated by the immune system cell and molecules with a significant degree of genetic predisposition and dominant congenital characteristics. BD also falls in this group because of various clinical and inflammatory characteristics [48].

3.2.1. Genetic predisposition: HLA-B51

BD is not a Mendelian disease. However, it has an important genetic component due to its familial characteristics [48]. HLA-B51 is the strongest identified factor for genetic predisposition. The presence of this association has been proven in various ethnic groups [50].

HLA-B51 may contribute to the pathogenesis of BD by both adaptive (presentation of some pathogenic peptides to CD8 T cells) and congenital mechanisms (activation with natural killer cells and by activating intracellular inflammatory pathways) affecting the immune system [48].

The evidence obtained in the recent research established the correlation between HLA-B51 and the clinical severity of BD [51].

3.2.2. Abnormally increased inflammatory response

Increased inflammatory response against nonspecific stimuli is a known feature of BD. This particular feature forms the basis of the pathergy test which is widely used for diagnosis [6].

The distinctly marked congenital immune response in BD patients is an enhanced expression of cytokines such as IL-1, IL-6, IL-8, and tumor necrosis factor (TNF) [52]. IL-1 levels released by monocytyes, an action induced by lipopolysaccharides, can also be high in BD patients [51]. Similarly, activated neutrophils are frequently observed in pathological specimens, and BD is generally classified among neutrophilic dermatoses [53]. Systemic vasculitis and occlusive perivasculitis and thrombosis are observed [53]. The hallmark histopathologic pattern of neutrophilic vasculitides is denoted as leukocytoclastic vasculitis, which is characterized by angiocentric segmental inflammation, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls (postcapillary venules). Alavi et al. reported that the cellular infiltrate around and within dermal blood vessel walls is composed mainly of neutrophils. Direct immunofluorescence demonstrates deposition of complement C3, immunoglobulin IgM, IgA, and/or IgG in a granular pattern within the vessel walls. Circulating immune complex deposition increases adhesiveness between inflammatory cells and the endothelium and neutrophil-mediated damage to postcapillary venules. Therefore, many factors play a role in the pathogenesis of BD. Vascular damage triggered by inflammation increases the risk of thrombosis [41]. Increased plasma levels of nitric oxide (NO) and its metabolites seen in BD patients demonstrate also the presence of an endothelial dysfunction [54].

The presence of hypercoagulability also has been broadly demonstrated in BD patients. The findings supporting this observation are a decrease in physiological fibrinolysis together with high thrombin levels, low activated protein C concentrations, increase in thrombocyte activation, and the presence of lower tissue plasminogen activator levels [44, 55, 56].

The pathogenesis of aneurysms in BD is also another interesting pathological discussion. The pathogenesis of aneurysms in BD has not been clearly revealed. However, it is presumed to be caused by obliterative endarteritis of vasa vasorum concomitant with intense inflammation primarily involving the media and adventitia. Infiltration of inflammatory cells, as reported by Al-Basheer et al., causes destruction of the media and fibrous thickening of the intima and adventitia. The weakened arterial wall leads to the distension of the vessel wall which at the end causes development of a true aneurysm or perforation of the vessel wall which in turn leads to the development of a false aneurysm or arterial dissection [57].

Although the underlying causative factor is not yet well understood, BD can affect the mucocutaneous tissues, eyes, blood vessels, both arteries and vein, brain, nervous system, and gastrointestinal system with recurrent attacks. Ultimately, BD, as initially described by Hulusi Behçet, is a multifactorial disease in which many triggering factors like infections and viruses may play a role [58].

3.3. Clinical findings

Like in other vasculitides, in BD, fever, weakness, and an increase in acute-phase reactants (CRP, Erythrocyte sedimentation rate [ESR]) are the systemic findings in the acute stage of the disease [59]. The following findings can be monitored in the acute inflammatory phase and the following recovery—fibrosis phase:

1. In the vessel lumen: irregularities, narrowing, and occlusion
2. In the vessel wall: necrosis, aneurysm, rupture, and fibrosis
3. In the tissues distal to the lesion: ischemia, necrosis, and dysfunction [59]

Arterial lesions are associated with the inflammation of the adventitia and media consisting of the aseptic infiltration of tissues with neutrophils and mononuclear cells. Initially, active arteritis develops in the affected arteries. This inflammation is followed by medial destruction and fibrosis. Arterial involvements include aneurysm, stenosis, and occlusions [60]. Perforation, the most frequently seen lesion in the arterial wall, develops probably as a result of endothelial dysfunction, necrosis of elastic and smooth muscle cells. This in turn paves the way for sinister pseudoaneurysm formation or an ominous rupture.

The most frequently affected artery is the abdominal aorta. This is followed in frequency by the pulmonary, femoral, subclavian, and common carotid arteries [46]. Although rare, we may encounter visceral artery involvement such as in jejunal arteries as reported by Wu et al. [61].

3.3.1. Aneurysms

Aneurysms are encountered more frequently than arterial occlusions [47]. Aneurysms are frequent in Behçet patients whose course is severe and complicated by uveitis or deep vein thrombosis and cause high mortality rates [62]. It approximately takes 7 years for aneurysm development after the onset of BD [12].

Although aneurysms can occur in almost all arteries, the abdominal aorta is the most frequently involved artery. Rupture is the most commonly seen complication of aneurysms and the most frequently encountered cause of vascular death [63]. Multiple aneurysms are also relatively common in comparison to the normal population [47].

3.3.2. Systemic arterial aneurysms

Aneurysms in BD differ from degenerative aneurysms in many ways. They diverge from degenerative aneurysms because they are observed in young patients, suprarenal location is more frequent in aneurysms detected in Behçet patients, and the shape of these aneurysms is more often saccular rather than fusiform. Often multiple aneurysms coexist, and patient symptoms more frequently appear under emergency conditions [47]. Aneurysms are the most complex vascular lesions encountered in BD. They are among the most challenging pathologies for vascular surgeons because of technical difficulties they present and their association with high recurrence rates [64]. It is a unique fact that BD is the only vasculitis known to lead to pulmonary artery aneurysms [57]. Also, it is a unique fact for BD that there is no correlation between the diameter of an aneurysm and the risk of rupture [65].

Pseudoaneurysms develop as a result of frequent rupture of saccular aneurysms. Defects are usually located on the posterior walls of arteries. There is a thick fibrous tissue containing reactional lymph nodes in the retroperitoneum in abdominal aortic aneurysms. It may be surgically difficult to expose the aorta because of this reason.

Peripheral artery aneurysms may present as painful swellings. Following the aorta and the pulmonary arteries, the carotid, femoral, popliteal, and subclavian arteries are the most frequently affected sites. Apart from these usual locations, all visceral arteries may be attacked [64, 66, 67]. Involvement of cerebral and renal arteries is rare. Abdominal aortic aneurysms are often discovered in the chronic stage, with vague symptoms like back pain or abdominal discomfort [51].

3.3.3. Pulmonary artery aneurysms

BD may attack any pulmonary artery in the pulmonary arterial tree regardless of diameter causing aneurysm or occlusion in a similar fashion akin to what it does in the arterial system [60]. Pulmonary artery aneurysms (PAAs) usually involve large- or medium-sized arteries. Hemoptysis is the most frequent and generally the initial symptom [68]. Fatal hemorrhages can occur when aneurysmatic arteries rupture into the bronchi [68, 69]. PAAs tend to occur more in men and appear in younger patients in comparison to arterial involvement in other areas. PAA can be multiple and bilateral. These patients generally also have DVT, caval or intracardiac thrombi, and systemic arterial aneurysms [45, 70, 71].

The inflammatory process in PAA occurs in the vasa vasorum of the artery. Consequent ischemia occuring in the artery wall causes weakening in the vessel wall and causes rupture [55]. It is rather rare to have concomitant true and false PAA side by side. These lesions frequently erode bronchi and cause massive and potentially mortal hemoptyses [72].

3.3.4. Occlusive lesions

Arterial lesions are usually solitary, but they may sometimes be multiple. They are generally accompanied by venous thromboses [73]. Arterial lesions may be asymptomatic depending on the sufficiency of the collateral circulation or may present with ischemic symptoms. Thrombi may develop within the aneurysmal sac, and very rarely distal embolization may occur leading to threatening limb ischemia [74]. The femoral artery is frequently affected. But an extremity artery or coronary and splenic or visceral arteries like the mesenteric artery can be occluded [60].

3.4. Diagnosis

The revised International Criteria for Behçet's Disease (ICBD) published in 2014 is the latest diagnosis/classification criteria. The diagnosis is made clinically. Although the classical triad includes urogenital ulcer, chronic ocular inflammation (uveitis), and mucocutaneous lesions, BD is a multisystemic disease [74]. The new criteria include oral aphthosis, genital aphthosis, ocular lesions, neurological manifestations, skin lesions, vascular manifestations, and positive pathergy test. Oral aphthosis, genital aphthosis, and ocular lesions each get two points, whereas skin lesions, vascular manifestations, neurological manifestations, and positive pathergy test each get one point. A patient scoring four points or above is classified/diagnosed as BD [5].

As reported by Wu et al., various symptoms in BD do not necessarily manifest themselves at the same time. Sarica-Kuçukoğlu report that in 6.8% of their cases, vascular involvement preceded or occurred during the diagnosis of BD, and 33.7% of the patients developed vascular disease within 5 years of diagnosis [75].

Early diagnosis of BD in young males with aneurysms is critical to avoid any ruptured aneurysms. Early diagnosis may be based on radiographic imaging such as ultrasound angiography, CT, and magnetic resonance angiography. CT has become the procedure of choice in evaluating patients with aneurysm. Selective angiography has proven useful for both the diagnosis and treatment of intestinal bleeding.

Patients with diagnosis of BD must be investigated with regard to multiple silent aneurysms; close follow-up should be conducted and must especially be reinvestigated after major activation phases of BD [74].

Noninvasive methods such as Doppler ultrasonography, CT, MRI, or PET/CT should be preferred in evaluation and follow-up of arterial lesions. Arterial punctures made in classical angiography may cause pseudoaneurysm development, a process similar to the reaction produced by the pathergy test in the skin [76, 77].

3.5. Treatment modalities

The treatment strategy for a peripheral artery aneurysm associated with BD is determined by the anatomical location and clinical presentation, including rupture or impending rupture and the active or remission stage of disease.

The presence of arterial involvement changes the course of BD dramatically and is associated with bad prognosis [74]. Surgery or endovascular treatment used without immunosuppressive medical therapy increases the risk of development of complications and pseudoaneurysm after the operation or intervention [61]. Because of this important fact, endovascular or surgical treatment must be combined with medical therapy.

3.5.1. Medical treatment

Steroids are the mainstay of treatment. They may be used systemically or topically. It is critically important to begin cyclophosphamide or prednisolone with aggressive immunosuppressive therapy in a combined fashion for the inhibition of progression of vascular lesions and causes good prognosis [78]. Medical therapy should be the first choice for the treatment of asymptomatic occlusive or stenotic lesions [60].

Anticoagulant, fibrinolytic, or antiplatelet agent use increases the risk of aneurysm rupture. Serious hemorrhages can lead to death. There is no proof supporting the use of anticoagulants in the treatment of arterial lesions. Anticoagulant use is not advised [61]. Nevertheless, the use of anticoagulants or antiaggregants in combination with immunosuppressive and anti-inflammatory agents in order to prevent graft occlusions in the postoperative period may be useful [60].

3.5.2. Surgical treatment

Surgical treatment is indicated generally for the treatment of systemic arterial aneurysms because of increased risk of rupture. Since the risk of rupture of arterial aneurysms in BD is not directly proportional to their diameter, they should be treated even if they are less than 5 cm in the abdominal aorta [47, 74]. Nevertheless, arterial repair under emergency conditions can be complicated because of recurrent disease, graft occlusion, or development of anastomotic pseudoaneurysm [57, 79]. Due to these difficulties, strenghthening of the anastomotic sites with prosthetic material thus decreases the dead space, and omental wrapping for fistula prevention can be protective [47, 62].

Because the inflammatory process in BD may involve the autologuous venous material, sythetic material (Dacron or polytetrafluoroethylene [PTFE]) should be used instead of the saphenous vein for graft material. Anastomoses should be performed at healthy-looking zones [60].

Reconstruction should always be performed in a disease-free–looking segment of the artery. To avoid suture line problems of development of pseudoaneurysms, the suture lines can be reinforced with plagets made of Teflon, and the graft can be wrapped with omentum. The choice of graft material is significant in decreasing long-term complications. Vasculitis may be present in the veins of the patient, and because of this factor, the use of autologous grafts should be avoided, and synthetic grafts should be preferred. The graft of choice in the abdominal area should be Dacron, whereas it should be polytetrafluoroethylene (PTFE) in the extremities [74].

Especially if collateral circulation is deemed adequate, ligation of the aneurysmatic artery is an alternative surgical treatment in distal aneurysms like popliteal artery aneurysm and for unstable patients with ruptured aneurysms [80, 81].

Mortality of emergency surgery for ruptured pulmonary artery aneurysms is very high. Therefore, it is advisable to avoid surgery as much as possible if there is no life-threatening hemorrhage [82].

Recurrent false aneurysms at anastomotic sites may result in as high as 30–50% of cases. Therefore, anastomoses should be done in macroscopically disease-free segments [83].

3.5.3. Endovascular treatment

Endovascular methods are increasingly widely used treatment modalities for patients with BD. Endovascular treatment became popular because of being less invasive. They are more preferred in BD because in BD the length of aneurysmatic segments is shorter, and these aneurysms are in relatively younger group of patients in comparison to the older patients with atherosclerotic aneurysms [65].

The endovascular approach is an alternative for treating arterial lesions. According to a report by Kim et al., which stresses the importance of induction of remission of active disease by preoperative immunosuppression, successful results have been achieved with an acceptable complication rate [65]. Endovascular treatment looks like a safe and less invasive modality for arterial pathologies linked with BD. In cases in which ligation cannot be performed because

of the risk of peripheral ischemia, the endovascular approach may be a treatment option for arterial involvement associated with BD.

Surgical and endovascular surgery, whichever is suitable for the patient, must be combined with preoperative, perioperative, and postoperative medical therapy in order to increse the chance of success.

3.6. Prognosis

The presence of BD increases morbidity and mortality significantly. This is even higher in patients with vascular involvement. The highest morbidity and mortality rates in BD are seen in patients who have pulmonary artery aneurysm. One-year survival is 50% in these patients [84].

The most important reason of mortality is aneurysm rupture. One- and five-year mortalities are 1.2 and 3.3 %, respectively [42]. Mortality rates, which are higher between ages 15 and 34, decrease after age 35 [42].

In a multivariate analysis conducted by Sadooun et al., male gender, arterial involvement, and multiple disease exacerbations were found independent factors of mortality [85].

3.7. Future and recommendations

Predicting which patients will have cardiovascular complications is the major concern of recent investigations. Early diagnosis of vascular involvement is helpful for planning effective management and improving the prognosis. Long-term follow-up is also essential in patients with BD because of the relapsing nature of the disease [86]. The cornerstone in the treatment of Behçet patients is the avoidance of surgical intervention during the active stage of the disease. But this is not possible in many cases [87]. Kasirajan suggests that all patients after the age of 55 with aneurysms involving large- and medium-sized vessels should have an ESR and a CRP evaluation [76].

The infrequent nature of aneurysms in patients with BD precludes a large prospective study evaluating open surgery versus endovascular technique. Nevertheless, the data at the present time compels one to take the endovascular route if feasible. An increased awareness of BD and its vascular complications is essential.

Management for arterial involvements associated with BD requires perioperative and postoperative comprehensive medical therapy to control the inflammation [88]. Consensus regarding the graft of choice for arterial vasculature in BD is debatable. For example, successful treatment of celiac artery aneurysm with extra-anatomical aorta-common hepatic artery bypass using e-PTFE graft has been reported by Maeda et al. [89]. Koksoy et al. declared that the choice of graft material did not affect the outcomes [90].

After surgical management, a high incidence of anastomotic dehiscence is one of the major problems in the treatment of vasculo-BD (VBD) [65]. There is no universally accepted method for assessing disease activity in these patients, and no standard immunosuppressive protocol exists for pre-/postendograft treatment. Nevertheless, the results of a small pilot study supported the

usefulness of immunosuppressive treatment combined with endovascular pseudoaneurysm repair (exclusion) in BD when the immunosuppressive agent kept the serum ESR level within the normal range [90].

There are no data or evidence of benefit from anticoagulant, antiplatelet, or antifibrinolytic agents in the management of DVT or for the use of anticoagulation for arterial lesions of BD.

The thrombus in BD adheres to the vessel wall and does not result in emboli, so pulmonary embolism is rare. Another reason to avoid these agents is the possibility of a coexisting pulmonary arterial aneurysm, which might result in fatal bleeding.

In the EULAR (European League Against Rheumatism) recommendation, immunosuppressive agents, such as corticosteroids, azathioprine, and cyclophosphamide, are suggested to reduce this inflammation because the primary pathology leading to DVT in BD is inflammation of the vessel wall [90]. Several case reports showed the efficacy of antitumor necrosis factor-alpha (TNF-α) agents for BD patients with complications of vascular involvement, such as PAA, aortitis, and deep vein thrombosis. But only a limited number of studies about these agents have been published [91–94]. In contrast, several studies have raised caution regarding the possibility of development of thrombophlebitis as a side effect of infliximab in BD patients [95, 96]. Further research is needed to clarify the efficacy and safety of anti-TNF-α agents in the treatment of vascular involvement in BD.

4. Cardiac involvement and treatment modalities in Behçet's disease

4.1. Introduction

Cardiac involvement is one of the prognostically devastating manifestations of Behçet's disease (BD). Cardiac involvement is relatively uncommon [97]. The heart and great vessels are not primary targets of BD, but although not well recognized, arterial or cardiac involvement are life-threatening with associated strong prognostic implications in BD [3]. Cardiac involvement is one of the most severe complications in patients with BD despite its sporadic occurrence, being greatly correlated with mortality [98]. The incidence and nature of cardiac involvement in Behçet's disease are not yet clearly documented [99].

Cardiac involvement includes pericarditis, coronary artery aneurysms, or stenoses independent of atherosclerosis because of BD per se. Spontaneous coronary artery dissection, myocarditis, cardiomyopathy, congestive cardiac failure, valvular diseases due to endomyocardial fibrosis called Behçet's valvulitis, intracardiac thrombosis (ICT), sinus of Valsalva aneurysms, ventricular aneurysms, aneurysms of the ascending aorta or branches of the aorta such as the carotid arteries, and aneurysms of the thoracic aorta are the other phenomena associated with BD that will be discussed in this section.

BD may attack the myoendothelial damaging valves leading to conduction disturbances. Endomyocardial fibrosis or valve dysfunction usually in the form of insufficiencies rather than stenoses occur. Coronary arteritis may induce thrombi within ventricles, most commonly the right ventricle [100]. Several cardiac manifestations may occur in the same patient [2].

4.2. Epidemiology

BD is common in countries along the ancient Silk Road (from the Far East to the Mediterranean region). The highest prevalence is in Turkey 40–370/100,000 [2]. In the Eastern Mediterranean and the Middle East, middle-aged men suffer a more aggressive course especially when the vascular system is affected. But nowadays, due to immigrations, BD is seen in almost everywhere throughout the world [101].

4.3. Pathogenesis

Over the past few years, pathophysiology of cardiovascular disease has been substantially revised, and new facts have been discovered. Mechanisms of atherothrombogenesis have been associated with inflammation and immune disorders [2]. In the recent past, many authors began to classify BD as an autoinflammatory disease rather than an autoimmune disease [3].

The pathogenic mechanism underlying thrombotic propensity in patients with BD is not however yet completely understood. It is believed that endothelial cell ischemia or disruption leads to enhancement of platelet aggregation. It is important to consider BD as a prototypic example of thrombotic diseases associated with T-cell–mediated neutrophilic inflammation. In various studies it was shown that TNF-α-103 C allele and polymorphism in IL-21, IL-10, and IL-8 genes are related to the pathogenesis if BD [1]. In addition, similar to the other disorders with increased risk of thrombosis formation, there is endothelial cell injury and a hypercoagulable state in BD. Furthermore, selectins, a group of adhesion molecules consisting of P- and E-selectins mediating leukocyte adhesion to platelets and endothelium, have a role in thrombogenesis. Increased E- and P-selectin levels were reported in BD in some studies [102].

Prothrombin gene mutation was identified in some BD patients. Increased plasma homocysteine levels are also a risk factor for thrombosis in BD. It was shown that mean plasma homocysteine levels in BD patients were substantially higher in comparison to that in healthy subjects, which led to the suggestion that another conceivable pathogenic mechanism of thrombosis in BD may be related to the presence of antiphospholipid antibodies, which have been reported in 18% of cases in a study [103].

The vessel wall attracts cytokinergic and neutrophilic reactions causing damage by excessive production of superoxide anion radicals and lysosomal enzymes leading to vascular wall destruction with aneurysm formation [3]. Endothelial dysfunction, release of von Willebrand factor, activation of platelets, enhanced thrombin and fibrin generation coupled with antithrombin deficiency, and impaired fibrinolysis lead to increased thrombocoagulation associated with perivasculitis [104, 105]. In a case series, histological samples of right-sided intracardiac masses secondary to BD were studied which demonstrated dense inflammatory infiltration, neovascularization, endocardial fibrin deposition, and fibrosis [106].

The pathogenesis of valvular regurgitation in BD was suggested as resulting from dilatation of the aortic or mitral annulus caused by a typical inflammation [107]. Diffuse aortitis leads to proximal aortic dilatation and aortic regurgitation requiring aortic valve replacement. Histopathology of the aorta reveals features similar to those observed in other systemic diseases with aortic involvement, destruction of the valve tissue itself, diffuse aortitis of the ascending aorta, and

aneurysm of the sinus of Valsalva. Several specific echocardiographic discoveries have been made like redundant aortic valve cusps with prolapse, vegetation-like masses, and echolucencies in Behçet's valvulitis [108].

There is uncertainty about whether the coronary lesions are caused by atherosclerosis or vasculitis in these patients. Many studies investigated the possibility of increased atherosclerosis in BD. Most findings refute this hypothesis. Atherosclerosis by itself does not seem to be enhanced by BD [109].

Three additional mechanisms have been proposed for development of coronary artery disease (CAD) in BD in the past decade:

1. Subclinical atherosclerosis
2. Silent ischemia
3. Spontaneous coronary artery dissection

A Spanish group reported about spontaneous coronary artery dissection of the LAD in a Behçet patient. They proposed that spontaneous coronary artery dissection could possibly be a cause of coronary ischemia in BD [110]. A recent meta-analysis pointed to the fact that subclinical atherosclerosis, not clinically apparent atherosclerosis, is increased in BD as depicted by impaired flow-mediated dilatation and increased intima-media thickness but whether this translates into coronary artery disease in time is controversial [111].

4.4. Clinical findings

Estimated incidence of cardiac involvement is reported 1–5% in a case series. Mortality is rather high (around 20%). Cardiac involvement in BD could be asymptomatic [112]. Cardiac involvement, when occurs, coexists with mucocutaneous manifestations.

Pericarditis is the most common cardiac complication in BD. Acute pericarditis, tamponade, and constrictive pericarditis have been reported. Myocarditis, cardiomyopathy causing diastolic and systolic dysfunction, valvular pathology coronary thromboses, coronary aneurysms, coronary rupture, predominantly right-sided intracardiac thrombus, aneurysm of the aorta, and its branches including the arch of aorta are other important cardiac complications of BD [112]. Several cardiac manifestations may occur in one patient [2]. This manifests itself such as ICT accompanied by peripheral arterial or venous involvement. Pulmonary, venous, and arterial involvements are more common in patients with ICT than in patients without ICT. Recurrent ICT formation, especially right ventricular or atrial thrombosis due to BD, is therefore another important problem.

ICT was noted in 1.9% of 626 BD patients in a 2016 study. ICT typically involves the ventricles rather than the atria and usually the right ventricle. The ICT is usually multiple, hyperechoic, and homogenous with well-demarcated margins and mostly immobile with a broad-based attachment to the ventricle or atrium [108].

Coronary artery disease (CAD) is rare in BD. It is more common in males younger than 40 years of age. CAD can lead to clinical manifestations such as stable or unstable angina which

usually leads to myocardial infarction (MI). Sometimes silent ischemia occurs which may later cause problems. Aneurysms readily occur in coronary arteries, sometimes multiple and accompanied by stenoses. Coronary lesions tend to be proximal and easily cause MI leading to development of ventricular aneurysm formation or cardiomyopathy [113]. Aneurysm formation and occlusion of coronary arteries are the most common etiologies for CAD in BD.

Coronary aneurysms are more frequent than stenoses and can present as acute coronary syndrome and MI but sometimes are symptomatic [112]. In young adults with myocardial infarction, BD should be considered as a nonatherosclerotic cause of CAD. Silent myocardial infarction and subclinical disease may also be present in cardiac involvement of BD [114]. Therefore, understanding the etiology of acute myocardial infarction in BD is important for determination of treatment strategy.

Although coronary arteritis may cause MI (myocardial infarction), in some of the patients with MI, the coronary arteries are normal. Severe cases of BD look more prone to AMI (acute myocardial infarction), and it was also demonstrated that occlusion of coronary arteries usually developed because of thrombus formation in CAD (coronary artery disease) leading to AMI.

Intracardiac thrombus that often precedes other manifestations of BD has been reported. These thrombi are found mainly in the right ventricle and are often associated with pulmonary artery aneurysm. Endomyocardial fibrosis plays a role in the intracardiac thrombus development in some patients. Due to high specificity of the right heart thrombus in BD, in any patient with this finding, diagnosis of BD should be considered. Intracardiac thrombus is the major differential diagnosis when a young patient presents with an intracardiac mass. It is especially common in young adult BD patients from the Middle East or the Mediterranean basin.

The right and left ventricular function may also be subtly impaired in patients with BD. There is a relationship between the duration of BD and cardiac involvement. As the duration of BD lengthens, the development of left ventricular diastolic dysfunction increases [115, 116].

Interatrial septal aneurysm, atrial septal defect, mitral valve prolapse, and mitral failure are also seen, albeit rarely [113]. It was reported that valvular prolapse including mitral valve prolapse can be related to vasculitis and tissue derangement [112].

Most of the aneurysms of the sinus of Valsalva observed in BD have been seen in the right coronary sinus, which may protrude into the right atrium or ventricle [112]. Most unfortunately this pathology is discovered after rupture. A few cases of the sinus of Valsalva aneurysm, which usually developed in the active phase of BD, have been reported. Heart failure may occur because of the ruptured aneurysm necessitating urgent surgical intervention [112].

Conduction abnormalities that could directly be ascribed to BD and those that could not be ascribed directly to BD were reported in the past [112].

Aortic valve involvement occurs late in the course of the disease as in the case of arterial lesions. They usually occur 3.2–7.9 years after diagnosis [107]. Aortitis by itself or seen with valvulitis in BD is very rare and frequently causes clinically important aortic regurgitation leading eventually to hemodynamic decompensation for which surgical treatment is generally needed. Surgical

treatment is demanding because of the presence of inflamed, fragile aortic tissue. The most dangerous complications seen postoperatively are prosthetic valve detachment, bypass graft occlusion, and pseudoaneurysm development leading to more morbid and sometimes mortal second operations. A high rate of prosthetic valve detachment rate of 40% and a low rate of 5-year freedom from reoperation (64%) in patients with BD were reported [117]. In a study, the reoperation rate was 7.4% per patient-year, and the mortality rate was 3.7% per patient-year [118].

Radiographic evidence of ascending aortic dilatation has been reported in 48% of BD patients in a series [99]. Other cross-sectional studies have reported various prevalences of thoracic aortic aneurysm: 5% in a Turkish cohort and 5.4% in a French cohort of BD patients in similar-sized BD cohorts [119, 120]. In a longitudinal study, eight patients diagnosed with thoracic aortic aneurysm were followed up for a median of 7.6 years. During this follow-up period, three deaths occurred, and the cause of death was recorded as due to thoracic aortic aneurysm [120]. However, despite many advances over recent years in imaging techniques for thoracic aortic aneurysm, international recommendations, such as those currently provided by the European League Against Rheumatism (EULAR), do not provide any guidance about screening and monitoring thoracic aortic aneurysm [121]. Aortic root inflammation can cause mural thickening, dilatation, valvulitis, and aortic valve insufficiency in a variety of infectious and noninfectious aortitides. Specific echocardiographic findings have been described as redundant aortic valve cusps with prolapse, vegetation-like masses, and echolucencies with Behçet's valvulitis [122].

As early as 1997, Morelli et al. reported mitral valve prolapse which was observed in 50% and proximal aorta dilatation in 30% of their patients. There was a significant difference in the rate of these abnormalities in comparison to their control group. The positivity rate of antinuclear and anticardiolipin autoantibodies was found to be very low (7%), with no difference between the study and control groups. HLA-B51 was detected in 82.7% of the patients in comparison to 21.7% in the control group ($p < 0.00001$). As a result, this study showed a high rate of cardiac abnormalities in patients with BD [123].

4.5. Diagnosis

Because BD lacks proper, clear-cut pathognomonic clinical and especially laboratory findings, the diagnosis may be difficult to reach. Also, it is important to bear in mind the fact that autoinflammatory diseases such as BD are heterogeneous diseases showing heterogeneous symptoms and clinical courses. Diagnosis is, therefore, clinically made [101]. Cardiac BD affects males more than females and is prone to delayed diagnosis because some patients do not have typical clinical manifestations at cardiac onset [124].

Cardiac valve involvement is a rare entity in BD, but when it occurs, it presents as a critical problem that necessitates urgent and correct diagnosis and treatment. Echocardiography is very useful for the necessary timely diagnosis. Diagnosis of FDG-PET scans may have a clinical value as a workup study for patients with BD who have cardiovascular presentations [125].

The right and left ventricular function is impaired in patients with BD. Novel methods such as tissue Doppler echocardiography (TDE) or Doppler-derived myocardial performance index (MPI) allow more objective estimation of cardiac functions [126].

4.6. Treatment

Treatment of BD is still unfortunately based on the low level of evidence (experts' opinion) [127]. Treatment of Behçet's disease is symptomatic and empirical but remains unsatisfactory because of variable, heterogeneous manifestations with uncertain etiology and pathogenesis. In addition, clinical disease manifestations and mortality appear to vary by ethnic group [128].

4.6.1. Medical treatment

Corticosteroids, cyclophosphamide, methotrexate, azathioprine, cyclosporine, and colchicine provide remissions of variable remissions in most patients. Experience with the use of anti-TNF agents in BD has advanced in recent years. Colchicine is shown to be effective in cases of pericarditis.

Corticosteroids plus immunosuppressants reduce the thrombus formation and improve aortic regurgitation and heart failure in cardiac BD, whereas surgery alone does not lead to complete resolution of thrombus [129].

In cases of ICT, the current therapy is built according to the severity of the disease and the location of the lesion. Since BD usually has an ever-changing fiery and silent-phase variations, it is generally difficult to monitor the effectivity of treatment. Like in other serious vasculitides, the mainstay of treatment in BD is immunosuppressive therapy.

Standard anticoagulation with heparin or oral anticoagulants is not recommended in all BD cases. However, anticoagulation with immunosuppression is the recommended treatment in BD cases with ICT. Aneurysms may reduce in size or may even disappear with medical treatment (combination of cyclophosphamide and methylprednisolone) [127].

It was reported that recurrent right atrial thrombus due to BD is commonly observed despite continued anticoagulation therapy. It is important to know that thrombus disappears after the initiation of immunosuppressive therapy [129]. Medical treatment with immunosuppressants may be the first choice for patients with BD who have ICT [111]. To avoid a progression to thrombus or cardiac dysfunction in recurrent cases, the early identification of cardiac involvement of BD using echocardiography and/or cardiac magnetic resonance imaging is of great importance. Combined immunosuppressive therapy with prednisolone and cyclophosphamide are usually needed to treat recurrent thrombosis due to BD [111, 129].

4.6.2. Surgical and endovascular treatment

There is surprisingly limited evidence of quality in planning a consistent treatment strategy for cardiovascular involvement of BS, especially in the potential role for surgery [130].

In patients with BD, aortitis or other cardiovascular complications should be evaluated carefully in those with chest discomfort. Steroid administration is important, especially preoperatively, which not only decreases inflammatory reactions but also reduces the postoperative steroid dosage and diminishes the associated side effects.

Coronary arterial disease is generally treated with either conservative or invasive procedures and by surgery when indicated. Less invasive therapies are the first choice because many

perioperative complications may await the patient. Graft failure due to thrombosis and development of aneurysms at anastomotic sites are such complications. Moreover, complications such as disseminated venous thrombosis leading to pleural effusion, Budd-Chiari syndrome, and central nervous system involvement following coronary artery bypass grafting (CABG) surgery treated with anticoagulant and anti-inflammatory therapy have been reported [131].

In the course of CABG, the use of arterial grafts and avoidance of aortic manipulation, in order to decrease the risk of pseudoaneurysmal formation, are strongly recommended [132]. The use of free arterial grafts is advised because of the risk of possible left subclavian arterial occlusion after CABG which may cause a devastating MI [133].

Behçet's disease involves all types of vessels, but coronary arterial involvement is extremely rare. The patients are generally young, and they are frequently treated medically. CABG is performed with care on these patients, and off-pump techniques are generally preferred. Surgical treatment of Behçet patients is itself challenging because the tissues are fragile and the coronary arteries are inflamed [132]. Therefore, some surgeons prefer not to perform CABG because the tissues are fragile, the grafts are affected by inflammation, and hypercoagulopathy may be a problem perioperatively [134]. Others recommend percutaneous interventions (PCI) or minimally invasive procedures such as off-pump no-touch aorta techniques [135].

Major problems after CABG surgery are also bleeding and anastomotic pseudoaneurysm. Minimal manipulation of the tissues, meticulous hemostasis, and concomitant use of corticosteroids and immunosuppressants are important to circumvent these devastating complications [131, 132, 134].

Hematoma and/or pseudoaneurysm, especially of the femoral artery after coronary angiography, may be encountered. Multiple punctures must be avoided, and catheters should be removed as early as the patient's condition allows to prevent such complications [134].

Advances in noninvasive imaging modalities such as CT coronary angiography increased our noninvasive capability of evaluating coronary artery disease. When control imaging like angiography is needed, this ever-developing cost-effective method should be utilized [136].

There are no comprehensive studies on the long-term patency of the grafts used for coronary bypass because the grafts may be affected by the disease. Therefore, patients must be informed about possible reoperations and reinterventions.

Surgery alone in treating ICT leads to recurrences. ICT has risk of recurrence [129]. Combined immunosuppressive therapy with steroids (prednisolone) and cyclophosphamide is needed to treat ICT and prevent recurrences. Immunosuppressive therapy reduces ICT relapse [137]. EULAR does not recommend anticoagulants in the treatment of thrombosis [121]. Unfortunately, as of now, there are no controlled studies or evidence of benefit from experience with anticoagulants, antiplatelet, or antifibrinolytics in vascular BD [129].

Rates of prosthetic valve detachment in BD of the aortic valve are significantly higher than in other valvular diseases such as rheumatic valve disease. Performing prosthetic aortic valve replacements for a Behçet-related valvulopathy carries an increased risk of dehiscence if no

preoperative immunosuppression is administered; on the other hand, total aortic root replacement may allow more durable results.

The surgical implications and management of Behçet's aortitis with associated severe aortic insufficiency remain a serious challenge, because the aortic tissue involved not only is inflamed but also may be irrevocably fragile. The postoperative period may be affected by complications that may be both costly and life-threatening. Reoccurrence and reoperation rates in BS are high contributing to higher morbidity and mortality. Modified surgical techniques like valved conduit procedures and perioperative and postoperative continuous immunosuppression are advised.

There is a high recurrence rate of complications in PAA stemming from inadequate medical therapy and the inherent disadvantages of surgical treatment. This fact makes PAA candidates for endovascular management. Successful treatment of PAA with endovascular embolization using n-butyl cyanoacrylate (NBCA) has been reported [138–140].

Percutaneous NBCA embolization of PAAs is also reported as a safe and effective front-line treatment in BD patients presenting with life-threatening massive hemoptysis [139].

Emergency surgery after the diagnosis of PAA has a high potential of complications like perivascular leaks, graft thrombosis, and anastomotic leaks due to the very nature of PAA. Anastomotic leaks causing recurrence of hemoptysis have also been reported. Surgical treatment may have the disadvantage of the potential need for repeated thoracotomy because of recurrence of aneurysm. Postoperative healing has been shown to be compromised because of long-term corticosteroid usage. The risk of infection is high. PAAs commonly occur bilaterally. Increased pulmonary artery pressure after lobectomy on one hemithorax may cause increased size of other PAAs with eventual rupture and mortality. Due to these setbacks and the possible high mortality rate associated with surgical treatment, endovascular treatment looks like a reliable alternative instead of surgery when life-threatening hemoptysis and a narrow window of opportunity to save patients' lives are present [139]. PAA patients treated by embolization with or without immunosuppressive therapy were reported to have a better prognosis than patients who underwent surgery with or without immunosuppressive therapy [139].

Delaying surgery in cases with active-phase inflammation and initiating immunosuppressive therapy before and after surgery is recommended when the patients' lives are not immediately threatened. Moreover, because of high reoperation and mortality rates, long-term follow-up is mandatory after surgery.

4.7. Prognosis

BD significantly increases mortality especially in young male patients, while it is less severe among females and the aged with regard to cardiac and vascular involvement. In many patients, the disease tends to abate with the passage of time. The main cause of mortality is large-vessel disease, especially bleeding PAA, almost exclusively among male patients [84]. BD is a chronic inflammatory disease which shows exacerbations and remissions. Especially,

young male patients have severe prognoses. With advancing age remission periods lengthen and the severity of exacerbations decrease. A five-year survival rate of BD was 95.8% without cardiac complications. But this rate drops to 83.6% if cardiac BD is present [113]. Annual BD mortality varies between 2 and 4% [3]. Prognosis of coronary artery involvement is poor. MI accounted for 25% of deaths in a cohort published in 2012 [113].

Poor prognostic factors in BD include vascular and cardiac involvement per se, male gender, and early age of onset. Involvement of the aortic valve is also a bad prognostic factor with a given 44% mortality rate in a study [141].

Follow-up is also problematic. In a study conducted in Korea about long-term mortality after treatment for aortic involvement revealed 47% mortality of which none occurred at the operating room but all in the postoperative period. Also, in this study event-free survival at 13 years in patients who were administered immunosuppressive therapies versus no immunosuppression was 34% to zero (0%), respectively, underlining the importance of continuation of immunosuppressive therapy perioperatively. It was also reported that aortic root replacement in comparison to solitary aortic valve replacement had much better prognosis, namely, 39% versus 4%, respectively [142].

4.8. Suggestions and future

In young male patients with intracavitary thrombus, BD must come to mind as a probable diagnosis.

Arterial, venous, and pulmonary involvements are generally more frequently seen in BD patients in whom ICT occurs in comparison to the general BD population As DVT has been documented in almost half of the BD patients with ICT, we recommend that all BD patients with ICT should be examined for venous disease using duplex ultrasonography. Because pulmonary involvement (PAA and PTE) and ICT are oftentimes encountered concomitantly, we suggest that pulmonary involvement should be investigated by thoracic CT in all BD patients with ICT.

In patients with BD who are in the active inflammatory stage of the disease, periodic echocardiography examination for early detection of an aneurysm or valvular involvement should be made even if there are no symptoms. We recommend for all BD patients a systematic echocardiographic examination not only when clinically indicated but also routinely once every year [130].

The prevalence of SMI is high in patients with BD. Therefore, myocardial perfusion scintigraphy should be recommended for patients with duration of BD greater than 10 years.

Physicians caring for BD patients, internists, rheumatologists, and dermatologists should work closely with cardiologists and cardiovascular surgeons to increase awareness of these silent and potentially fatal vascular complications and form multidisciplinary groups to address this problem not only for individual cases as they arise but also in order to generate the future evidence bases to more successfully manage BD and its cardiovascular complications in the future.

5. Behçet's disease and vascular involvement in the pediatric age group

BD occasionally involves children before the age of 16 in 4–26% of BD cases [143]. Large-vessel vasculitis is the leading cause of vascular mortality seen in the pediatric age group. In children with vascular involvement, male patients are predominantly affected with a ratio of 6 to 1.

BD manifests itself differently in children. Ocular disease is usually absent, and establishment of diagnosis is usually late. The diagnosis of BD is difficult to establish in itself, and because of the insidious onset in children it is more subtle and challenging [144]. Because of this difficulty, several new pediatric BD classifications were proposed [145].

In a study conducted in children, vascular involvement was observed in 25% of the children affected by BD, and all of them had venous thrombi [146]. Half of these were cerebral thrombi and the other half was peripheral thrombi. These rates were also found in similar percentages in another study conducted in children [147]. The main locations of thrombosis were the cerebral sinuses in 11 patients (52.4%) and lower limbs in 9 patients (40.9%)

Although very rare, Budd-Chiari syndrome and rupture of pulmonary artery aneurysms have all been reported in children [144].

In a comprehensive study comprising four countries, the mortality rate in pediatric BD (3%) was generally related to large-vessel involvement [148]. In this study, 18 episodes of venous thrombosis were observed in 10 (15%) patients: 7 boys and 3 girls. They occurred six times in the lower extremities (both legs in two cases). It was reported that one patient experienced eight episodes of IVC thrombosis and died eventually of multiple deep vein thromboses. Arterial involvement including arterial aneurysms (four) and arterial thrombosis (five) occurred in six patients (four boys, two girls). Pulmonary arteries were the most frequently attacked (three), causing life-threatening hemoptyses. Geographic differences among patients with vascular complications were reported as not statistically significant [148].

In a study conducted on vascular BD patients in the pediatric age group, out of seven patients two had superficial vein thrombosis, two patients exhibited atrial or ventricular thrombosis, and one showed arterial involvement with PAA. Two of the patients had thrombosis of the venous sinuses in the central nervous system. The average apperance of vascular involvement was reported 4 months after the diagnosis of BD. All of these patients were administered with colchicine and steroids. The ones with thrombosis in the venous system received additional azathioprine, whereas those with pulmonary arterial or cardiac involvement initially received cyclophosphamide and then were changed to azathioprine for 6 more months. All patients other than the PAA patient were administered with a course of anticoagulation treatment as well. These patients were then followed up for at least 18 months and were free of vascular relapses as of reporting [149].

The abovementioned study had some recommendations for both physicians and families. They suggested that pediatricians should follow and monitor their patients with BD for arterial and venous vascular disease. All families should be informed about the possible characteristics and appearances of peripheral venous involvement, signs of sinus thrombi, and be warned

and informed about chest pain. When pertinent symptoms arise, urgent medical care and diagnostic techniques should be used. They reported that effective management and the judicious use of immunosuppressives are successful in disease control and recommended avoidance of biological agents [149].

6. Behçet's disease and vascular involvement in pregnancy

6.1. Introduction

Because BD occurs more prevalently during fertile years and is multisystemic in its involvements, disease activity in pregnancy and its obstetric and neonatal outcomes deserve special attention.

BD is often diagnosed in women in the childbearing age [150]. The rate of de novo occurrence of BD in pregnancy is rare [151]. BD presents itself with similar symptoms observed in nonpregnant patients. Patients with BD do not have a higher rate of vascular complications during pregnancy. Similarly, the obstetric complication rate is not increased.

6.2. Clinical course

Symptoms are inclined to improve in pregnancy, and most patients have a symptom-free pregnancy. Remission of disease activity is seen in a minority of pregnant BD patients [152]. Because of this reason, vascular complications are very rare in pregnant patients with BD.

Regression of disease activity during pregnancy is attributed to the inhibition of T cell, macrophage, and natural killer cell activity [153]. Interleukin 10 (IL-10) levels have been found elevated during pregnancy, but those levels were decreased at the end of pregnancy. The anti-inflammatory properties of IL-10 may have reduced the occurrence of BD exacerbations during the obstetric period, but decreased levels of IL-10 may explain some of the symptoms occurring in the postpartum period [154]. Estrogen also has anti-inflammatory actions like suppression of IL12 production and suppression of antigen-presenting capacity and stimulation of anti-inflammatory IL-10 production [155].

6.2.1. The neonatal outcome

The neonatal outcome is debatable. In a study presented in 2014, a series of 298 pregnancies of which 94 had BD were compared with 95 healthy controls, and it was reported that BD patients delivered smaller babies and miscarriages were more numerous in the BD group that could be attributed to vasculitis of the placenta [156]. However, in a study conducted in Turkey, among 342 deliveries 41 deliveries occurred in patients with BD. The rates of stillbirth, preeclampsia, preterm delivery, and intrauterine growth retardation did not differ in pregnant patients with BD. Perinatal mortality, neonatal intensive care unit admissions, and low birth weight incidences were similar to those without BD [152].

6.2.2. Vascular complications

The overall incidence of vascular complications in pregnant patients with BD was 5%, which was significantly higher than the normal pregnant patients [152]. Various types of thrombotic attacks have been reported during pregnancy and in the postpartum period. The postpartum period may be complicated by thromboses refractory to anticoagulation.

It was reported that complications during pregnancy in Behçet patients who had prior vascular involvement were higher in comparison to the normal population [154]. The annual rate of BD flare was threefold lower during pregnancy. The rate of obstetric complications was 16% and was increased in BD patients with a history of venous thrombosis [154]. In a study the presence of venous involvement increased the odds of obstetric complications by sevenfold [157]. All of such patients in a French cohort who had venous BD exacerbations had experienced prior DVT, and two had associated cerebral venous thrombosis [154].

The risk of fetal loss in BD is, however, lower than the risk of fetal loss observed in antiphospholipid syndrome [158].

Most BD flares during pregnancy are mucocutaneous or ocular in character [159]. Vascular involvement usually includes the venous system similar to the nonpregnant population. Heart failure due to tricuspid regurgitation and related right ventricular dysfunction resulting from ventricular endomyocardial fibrosis has been reported [151]. BD exacerbation developed in 29.7% of the pregnancies in a series [154]. This rate ranges from 8% to 60% in the literature [150, 160]. In the above-mentioned series, the main symptoms during BD activity were oral ulceration (58.3% [range 50–66.7%]) and genital ulceration (44.4% [range 25–55.6%]), followed by skin lesions (25% [range 8.3–33.3%]) and ocular inflammation (5.6% [0–25%]) [150, 160].

Vascular manifestations were reported in two series: one patient experienced Budd-Chiari syndrome, and one patient had DVT [150, 157]. Apart from these series, some case reports have been published and described exceptionally severe disease exacerbations such as DVT with nephrotic syndrome, SVC thrombosis, dural sinus thrombosis, or intracardiac thrombosis [161–164].

6.3. Treatment

Surgical thrombectomy has been used for DVT [12]. Thrombolytic therapy is effective for DVT and intracardiac thrombus and may be safer and more effective than surgery [164]. Thrombolysis and stent placement are viable options in SVC thrombosis [165].

Medical treatments, especially acetylsalicylic acid and low-molecular heparin, are safe in pregnancy and are widely used. The use of colchicine is reported to reduce the risk of severe BD exacerbations, because the proportion of disease exacerbations was twofold lower in BD patients treated with colchicine [154]. Because colchicine crosses the human placenta, the safety of colchicine treatment in pregnant BD patients is an important point. Although colchicine has antimitotic effects, the safety of this drug during pregnancy was recently assessed in a prospective comparative cohort study in which 238 colchicine-exposed pregnancies were

followed up [166]. No increase in teratogenicity or congenital abnormalities was observed. Therefore, colchicine treatment is safe in pregnant women with BD and could even reduce the risk of disease exacerbations. Other medications such as azathioprine, glucocorticoids, and biological agents like infliximab can also be used during pregnancy, apparently without an increased risk of complications [167].

7. Conclusion

Since the first description by Hulusi Behçet in 1937, BD has been one of the most thoroughly researched diseases. But the enigma continues. The mechanisms of vascular involvement are still very obscure. Cardiac Behçet, since continuous perioperative immunosuppression administration became the rule, and thrombolysis became available, began to have fair results after intervention or surgery. Moreover, in the last two decades, vascular manifestation of BD has at least begun to be amenable to vascular and endovascular surgery increasing hopes for better quality of life for BD patients.

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