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Other Systemic Involvement of Behçet's Disease

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Behçet's disease is a chronic, systemic disease, the cause of which is not clear. The disease was defined by Hulusi Behçet in 1937 as a condition characterized by oral ulcer, genital ulcer and uveitis [1]. It may involve many organs and systems like skin, joints, vessels, the central nervous system and the gastrointestinal system and present with various clinical signs [2].

Involvement of the gastrointestinal system is called intestinal Behçet's disease or entero-Bahçet's disease. This involvement varies with countries. It more frequently appears in the Far East than in Mediterranean countries [3]. The prevalence of gastrointestinal involvement is 50% in Japan [4], but 0-5% in Mediterranean countries [5,6].

CLINICAL MANIFESTATIONS OF INVOLVEMENT OF THE GASTROINTESTINAL SYSTEM

Gastrointestinal involvement is clinically important since it is a cause of considerable morbidity and mortality. The most frequent symptoms are abdominal pain, nausea, vomiting, diarrhea, gastrointestinal bleeding and weight loss [4,7-9]. Although the most frequently involved gastrointestinal segments are the ileum and the cecum, Behçet's disease can involve all the segments from the mouth to the anus and other gastrointestinal organs [10,11]. Gastrointestinal involvement occurs due to vasculitis in small vessels of the intestinal wall and frequently in the veins [12]. It has two forms in general. The first one presents with mucosal inflammation and ulcer due to phlebitis and the other presents with intestinal ischemia and infarct due to involvement

of large vessels [13]. There are two types of ulcer; i.e. localized and diffuse. Localized ulcers frequently appear in the ileocecal region and are located in deep tissues. They can penetrate in the serosal surface and can be complicated by perforation. However, diffuse ulcers more frequently occur in the colon, appear like holes created by a staple on endoscopy, are located in different parts and are high in number. On endoscopy, they look like ulcers in Chron's disease [12,14].

Esophageal involvement is rare and frequently appears in males [15]. It presents with substernal pain, dysphagia and hematemesis. The disease involves the mid segment of the esophagus and this involvement is nonspecific. Esophageal lesions have variations including erosions, linear or perforating ulcers, aphthous, widespread esophagitis, esophageal varices and severe stenosis [16-18]. Some patients may have dyspeptic complaints due to disrupted motor activity [19,20]. Differentiation of esophageal involvement from infection and malignity requires biopsy and culture [16]. Esophageal lesions in Behçet's disease usually respond to corticosteroid treatment [19,20].

The least frequently affected organ in Behçet's disease is the stomach and the most frequent sign is aphthous ulcers [21,22]. Dyspeptic symptoms and epigastric pain are frequent complaints and the most frequent endoscopic finding was ulcers located in the gastroduodenal region [23].

Any part of the colon including the rectum can be affected. The ileocecal region was the region most frequently affected by the disease. Rectal involvement rarely occurs [24]. Intestinal involvement can have two forms; i.e. ulcer due to small vessel involvement and mucosal inflammation and intestinal infarct due to large vessel involvement [25]. When ulcers penetrate all colon walls, perforation, fistulae or bleeding may develop [26].

There is not a specific serum marker for intestinal involvement in Behçet's disease. In a patient fulfilling diagnostic criteria for Behçet's disease, the diagnosis of intestinal involvement is based on oval ulcers in the terminal ileum or ulcerations and inflammation in the small and large bowels. Before its diagnosis, Chron's disease, tuberculosis, enterocolitis due to non-steroidal anti-inflammatory drugs and malignities should be excluded. Behçet's disease and Chron's disease are similar especially in terms of clinical picture. In both diseases, endoscopy shows discontinuous mucosal ulcers with normal intestinal mucosa between ulcer areas [14,27,28]. Presence of large and deep ulcers, less frequent granuloma formation and more frequent intestinal perforation are in favor of Behçet's disease [28]. Table 1 shows radiological and clinical features of Behçet's disease and Chron's disease [28].

Table 1: A Comparison of Radiological and Clinical Features in Patients with Behçet's Disease and Patients with Chron's Disease.

Radiological and Clinical Features	Behçet's Disease	Crohn's Disease
Location of lesions	Proximal jejunum and ileum	Proximal jejunum and ileum
Small and large bowels	Frequently involved section: right colon	More frequently extending to the left colon
Features of ulcers	Deep, penetrating	Longitudinal or linear ulcer
Features of the mucosa neighboring with the ulcer	Severe swelling Minimal or no inflammatory response	Less swelling Marked inflammatory response
Cobblestone appearance	Less frequent	More frequent
Fistulae formation	Less frequent	Very frequent
Stricture	Less frequent	Very frequent
Intestinal perforation	Very frequent	Less frequent

In Behçet's disease with abdominal vascular involvement, vasculitis signs are more frequently seen in arteries and arterioles [29]. Ulcers and infarcts caused by involvement of small and large vessels develop and lead to acute or chronic symptoms. The most frequently involved veins are the hepatic vein and the vena cava inferior. One of the most frequent causes of Budd-Chiari Syndrome is Behçet's disease. Other forms of vascular involvement are thrombosis in the portal vein and the vena cava superior [30].

Other intraabdominal involvements are acute pancreatitis due to pancreatic involvement, chronic hepatitis, hepatosteatosis and primary biliary cirrhosis due to hepatic involvement and splenic involvement [11,30-32].

LABORATORY FINDINGS AND DISEASE ACTIVITY INDEX

Although several clinical scoring systems like Disease Activity Index for Intestinal Behçet's Disease (**DAIBD**) are used to determine disease activity, they have low clinical efficacy [23,33].

There is a weak relation between disease activity and C-reactive protein (**CRP**) and erythrocyte-sedimentation rate [34]. CRP does not usually increase in Behçet's disease [35]. Therefore, very high CRP levels in a patient with gastrointestinal Behçet's disease should suggest complications such as stricture, fistulae and abscess. No specific laboratory marker for gastrointestinal Behçet's disease has been found yet. Anti-Saccharomyces Cerevisiae Antibodies, used to diagnose Chron's disease, have been shown to be high in patients with gastrointestinal Behçet's disease [36-39].

ENDOSCOPIC AND RADIOLOGIC FINDINGS

Radiologic and endoscopic findings in patients with gastrointestinal Behçet's disease are quite similar to those in patients with Chron's disease. When intestinal involvement is suspected, colonoscopy must be performed. Although colonoscopy is sufficient to detect lesions of the small intestine close to the terminal ileum, capsule endoscopy or double balloon endoscopy is necessary to diagnose other pathologies of the small intestine [40].

Well-demarcated punched-out ulcers or aphthous ulcers are the most frequently encountered gastrointestinal Behçet's disease [41]. Especially small ulcers may resemble oral aphthous ulcers [42]. Larger ulcers are usually oval or have an irregular configuration. The depth of ulcer penetration varies. Superficial ulcers and deep ulcers which sometimes depict disintegration usually extend along the intestinal wall [43,44]. On endoscopy, typical gastrointestinal Behçet's disease is seen in the form of singe or a few deep round ulcers in the ileocecal region or anastomosis sites [41,45].

On radiological imaging, these lesions appear to be separate collar studs or round penetrating lesions. Failure to detect these lesions result in a high rate of perforation, fistulae development and bleeding. Sometimes, gastrointestinal Behçet's disease may appear to be a mass and can be mistaken for neoplasm [28].

Computed tomography is useful in revealing spread of the lesions and identifying the cases likely to have complications. On computed tomography, the segment affected by gastrointestinal Behçet's disease may appear to be a polypoid mass or a thickened intestinal wall [46]. In most of the cases, the thickening in the intestinal wall is irregular.

The imaging techniques like computed tomography and magnetic resonance imaging/ enterocolysiscan be used to diagnosis the disease.

DIAGNOSIS

The diagnosis of gastrointestinal Behçet's disease is based on presence of diagnosed Behçet's disease and intestinal lesions without causes other than Behçet's disease. The procedures necessary to be performed in patients with gastrointestinal symptoms are upper gastrointestinal endoscopy and colonoscopy depending on symptoms. The most frequent finding likely to be seen on colonoscopy is single or multiple lesions located in the ileocecal region. In a patient fulfilling the criteria for Behçet's disease, ileocecal or colonic ulcers are sufficient to diagnose gastrointestinal Behçet's disease. Capsule endoscopy and contrast imaging can be used to make the diagnosis and to follow development of complications [19,20,47].

CARDIOVASCULAR INVOLVEMENT

The rate of cardiac involvement is high in Behçet's disease. This involvement presents with subclinical signs and symptoms. It may be sometimes life-threatening. All cardiac structures ranging from the endocardium to the pericardium and all vascular structures can be affected.

The incidence of cardiac involvement in Behçet's disease is unclear. However, it has been reported to vary from 7% to 46% in previous studies [48]. Cardiac structures involved are the coronary artery system, conduction system and endocardium and myocardium [49].

Etiology of Behçet's disease has not been elucidated yet [50]. Genetic factors clearly play a role in the disease. Although human leukocyte antigen (**HLA**) is not associated with the disease, HLA

types can vary with countries and involvements of different organs [51]. HLA-B51has been found to be associated with the disease, but not with cardiac involvement [52]. Biopsies of the arteries affected by Behçet's disease have shown vasculitis and thrombosis [50].

ENDOMYOCARDIAL INVOLVEMENT

Although this type of involvement presents with endomyocardial fibrosis in the right or left side of the heart, it may create a tendency to develop bacterial endocarditis, valve involvement and intracardial thrombosis [48,53]. On echocardiography, it appears to be diffuse, bright, thickened endocardial mass. This can be confused with tumor, cardiac thrombosis and bacterial endocarditis [54-56]. It can only be diagnosed in postmortem examinations in some cases. Myocardial involvement is frequently related to endomyocarditis [54,55,57].

INTRACARDIAC THROMBOSIS

Intra cardiac thrombosis is the most frequently reported serious complication of Behçet's disease. It is especially common in the patients living in Mediterranean countries [58]. Although more frequently encountered in young people, it can be the first manifestation of the disease [58]. It can be misdiagnosed as intra cardiac tumor or pulmonary embolus [57-59]. Involvement of the right ventricle is frequent; however, involvement of the right ventricle can be observed [60,61]. Thrombosis may recur despite treatment. It may be iatrogenic [62].

Management of thrombus varies with mobility of thrombus and extra cardiac involvement. If it is immobile, it can be treated with anticoagulant or immunosuppressive drugs. However, if thrombus is mobile, thrombolytic treatment can be utilized. In patients resistant to medical treatment, thrombus may have to be rejected [57-59].

PERICARDIAL INVOLVEMENT

Pericardial involvement has been reported to be the common manifestation of cardiac involvement [48]. It may present with acute pericarditis, pericardial tamponade, recurrent pericarditis, and asymptomatic pericardial effusion [63,64]. It can usually be accompanied by cardiovascular involvement or occur alone [65]. Colchicum and immunosuppressive agents can be used for its treatment. In refractory cases, pericardiectomy can be useful [63,64]. When tamponade develops, pericardiocentesis can be required [63].

INVOLVEMENT OF THE CARDIAC CONDUCTION SYSTEM

Behçet's disease can affect the cardiac conduction system. Cardiac rhythm disorders such as first-degree atrioventricular block, complete heart block, right bundle branch block, ventricular premature beats and ventricular tachycardiamay appear [66,67].

CORONARY INVOLVEMENT AND CARDIOMYOPATHY

Coronary artery abnormalities and pathologies are other frequent causes of cardiac involvement. Coronary involvement may occur at any time of the disease course. It may present as silent ischemia, stabile angina pectoris or myocardial infarction [68-70]. Although myocardial infarction may result from inflammatory coronary disease triggered by Behçet's disease, it may appear in patients with Behçet's disease having normal coronary arteries [70]. Myocardial infarction in Behçet's disease can be caused by thrombosis, coronary arteritis and prolonged vasoconstriction [71].

Underlying the pathogenesis of coronary artery disease due to Behçet's disease is leukocytoclastic vasculitis, arteritis and aneurism formation [69]. Angiography is used for the diagnosis of the disease. Coronary arteritis due to Behçet's disease is treated with supportive medications, percutaneous interventions and coronary bypass surgery [68-71].

Cardiomyopathy, a rare component of Behçet's disease, is due to ischemic, non-ischemic or inflammatory causes [72,73]. Although it may present as systolic or diastolic heart failure, it can be asymptomatic. It is frequently diagnosed with echocardiography, radionuclide ventriculography, and electrocardiography. Its treatment is achieved with prednisolone and azathioprine in addition toroutine treatment for heart failure [73].

CORONARY ANEURISM AND OTHER ABNORMALITIES

Angiographies performed to detect Behçet's disease can show coronary aneurisms. Their sizes are variable. While some aneurisms are asymptomatic, most of the patients present with the clinical picture of coronary syndrome [74,75]. Aneurisms can be calcific and saccular [75]. Ventricular pseudoaneurisms can be rarely seen. Mural thrombus can also be encountered [76].

INVOLVEMENT OF MAJOR VESSELS OF THE HEART

Sinus Valsalva aneurisms and aortitis are cardiac complications involving especially the root of the aorta [77-79]. The patients often present with myocardial infarction, syncope and tiredness. The patients developing aortic failure can have diastolic murmur. ST-T changes and rhythm disorders can be seen on electrocardiography [77,80]. Sinus Valsalva aneurisms can occur alone or in combination with other sinus aneurisms. The diagnosis is made with echocardiography, aortography and ventriculography. It is frequently treated with aortic root replacement [79,81].

Behçet's disease lead to pulmonary arterial aneurismal dilatation. It can be accompanied by pulmonary embolism or cardiac thrombosis. The patients may present with respiratory distress, cough and hemoptysis. The diagnosis can be made with pulmonary angiography and computed tomography. Treatment can be achieved with transcatheter embolectomy [82-85].

RENAL INVOLVEMENT

Renal Involvement and Amyloidosis

Unlike antineutrophil cytoplasmic antibody associated vasculitis and other systemic vasculitis, Behçet's disease affects medium-sized vessels [86,87]. It presents with proteinuria and asymptomatic hematuria most of the time. Nephrotic syndrome, edema, hypertension and renal failure can also appear [88]. The main causes of Behçet's disease related renal involvement are amyloidosis, glomerulonephritis, renal vascular disease and interstitial involvement [89]. Renal involvement is more frequent in males than in females. Thrombosis of the major vessels is the primary underlying risk factor [90]. Time elapsing from the first symptom to complications is about ten years [88].

The most frequent clinical presentation of amyloidosis (type AA) is nephrotic syndrome with or without renal failure [89,91]. It is thought that amyloidosis develops due to chronic inflammation and predisposing factors [92]. Proteinuria may or may not be present.

Although colchicumis useful in treatment of amyloidosis secondary to familial Mediterranean fever, its role in treatment of amyloidosis due to Behçet's disease is not known well. While some studies have shown that it reduces proteinuria and improves renal functions, other studies have revealed that it is ineffective [90].

GLOMERULONEPHRITIS

The incidence of glomerulonephritis has been reported to be <1%. It may present with asymptomatic hematuria, proteinuria and rapidly progressive renal disease [93]. It is frequently accompanied by hypertension.

On histological examinations, the disease has a wide variation ranging from minor glomerular changes to crescentic glomerulonephritis. Focal proliferative, mesangial proliferative, membraneous, minimal changes and glomerulosclerosis have also been reported. On immunofluorescence examination, Ig G, Ig A, Ig M andC3are accumulated in the mesangium [94,95].

The disease can be treated with corticosteroids, azathioprine, cyclophosphamide, cyclosporine and plasmapheresis.

RENAL VASCULAR DISEASE

Renal vascular pathologies have been found in <1% of the patients with Behçet's disease having vascular involvement [96]. The most frequent renal vascular disease is renal artery aneurisms [97,98]. It is usually accompanied by hypertension. Another vascular involvement in Behçet's disease's is renal vein thrombosis. It can be accompanied by nephrotic syndrome or another major vascular pathology [99]. Perivascular fibrosis and fibrinoid deposits around

arteries and arterioles are another type of vascular involvement. It may cause hematuria and proteinuria [100].

The diagnosis of renal vascular disease is made by ultrasonography, computed tomography, magnetic resonance imaging and conventional angiography.

Intravascular stents can be used in addition to corticosteroids and cyclophosphamide for the treatment of the disease.

END-STAGE RENAL FAILURE

Uremia is a rare complication of renal involvement in Behçet's disease. Amyloidosis and glomerulonephritis are the most frequent two causes of end stage renal failure. The activity of Behçet's disease has been observed to decrease after hemodialysis [89]. Dialysis and renal transplantation are treatment options in patients with end stage renal failure.

PULMONARY INVOLVEMENT

The prevalence of pulmonary involvement varies between 1% and 5%. It frequently presents in the form of vascular lesions. Other presentations of the disease are pulmonary infarct and hemorrhage and parenchymal involvement and pericardial effusion [101-103]. Clinical signs of pulmonary involvement in Behçet's disease are recurring dyspnea attacks, cough, chest pain and hemoptysis. Hemoptysis is a life-threatening symptom most frequently seen in the patients with thoracic involvement. It is frequently due to pulmonary artery aneurism and pulmonary infarct and rarely due to diffuse alveolar hemorrhage depending on capillarity.

PULMONARY PARENCHYMAL INVOLVEMENT

Pulmonary parenchymal involvement is indicative of the disease activation. Pulmonary vasculitis and pulmonary vascular thrombosis cause infarcts, focal and diffuse hemorrhage and focal atelectasis. Recurrences of parenchymal damage may result in bronchial stenosis, fibrosis, decreased pulmonary volume and emphysema [101,103,104].

PLEURAL INVOLVEMENT

Pleural effusion occurs frequently due to pulmonary infarct or an infectious pathology. It can be serious or hemorrhagic. It has been reported in the literature that pleural biopsy shows vasculitis.

The first examination used to evaluate pulmonary signs and symptoms is posteroanterior pulmonary X-ray. Pulmonary parenchymal changes are nonspecific and may present as focal or diffuse opacities. Computed tomography can be utilized to show parenchymal and vascular lesions [101,103,104].

AUDITORY AND VESTIBULAR DYSFUNCTION

It has been reported that hearing loss is variable in patients with Behçet's disease. It may be that different hearing tests and frequencies are used in the studies. Although reported audiometric findings vary, the most common finding is bilateral high frequency sensorineural hearing loss showing a down slope tendency [105-107]. Sensorineural hearing loss is frequently encountered in 23%-32% of the patients with Behçet's disease [108]. Hearing loss is unilateral or bilateral. Most of the hearing losses are at their initial stage; however, they display a progression over the years [109-111]. Sudden hearing loss can be the indicator of ear involvement [107]. Although hearing loss can be a central nervous system pathology, it may be harbinger for neural Behçet's disease. There is not a relation between hearing loss and age; however, several studies have suggested that old age and a longer duration of the disease can be the risk factors of neural Behçet's disease [109]. The HLA-B51 frequency has been found to be higher in the patients with hearing loss than those without hearing loss [107].

There is limited information about treatment of hearing loss due to Behçet's disease. Corticosteroids, cyclophosphamides and cyclosporine can be used for its treatment [112]. In cases refractory to this treatment, cochlear implantation can be a treatment alternative [113].

The most frequent vestibular dysfunction symptoms are dizziness and imbalance. They can appear in 20%-40% of the patients with Behçet's disease [114]. It has been reported that the patients with isolated central vestibular involvement do not have signs indicating neural Behçet's disease [107].

In a retrospective study Morales-Angula et al. on manifestations of ear, nose and throat in 33 patients with Behçet's disease, six patients were found to have audiovestibular manifestations. Out of six patients, three had hypoacusis and three had vertigo [115].

OTHER INVOLVEMENTS

Patients with Behçet's disease can have such constitutional symptoms as fever and weakness. It was shown in a study by Seyahi E. et al. that 22% of the patients had a history of fever and that fever attacks had a strong relationship with vascular, neurological and articular involvements [116].

Fibromyalgia accompanies Behçet's disease in many patients. It was shown in a study by Lee SS. et al. that 37% of 70 patients with Behçet's disease had fibromyalgia. It was associated with anxiety and depression but not with the disease activity [117]. In another study Melileoglu M. et al. 18 out of 104 patients with Behçet's disease were found to have fibromyalgia. It was not associated with the disease activity, but it was reported to have a relation with fatigue, headache and arthralgia [118].

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