

Pulmonary complications of Behçet's disease

Feyza Erkan, MD^{a,*}, Esen Kıyan, MD^a, Atadan Tunacı, MD^b

^aDepartment of Pulmonary Medicine, Istanbul Medical Faculty, University of Istanbul, 34 390 Capa-Istanbul, Turkey

^bDepartment of Radiology, Istanbul Medical Faculty, University of Istanbul, 34 390 Capa-Istanbul, Turkey

Behçet's disease is a chronic, systemic, inflammatory disease of unknown origin [1–6]. A clinical triad of oral ulcers, genital ulcers, and uveitis is characteristic of the disease. This triple symptom complex was first described by Turkish dermatologist Hulusi Behçet in 1937 [7]. Behçet's disease is currently recognized as a multisystemic disease that may present with vascular, cutaneous, pulmonary, neurologic, rheumatologic, gastrointestinal, and genitourinary manifestations [8–12]. The main histologic feature is a widespread vasculitis that affects arteries and veins of all sizes [2,5,13,14]. It usually shows episodes of exacerbation and remission, and the prognosis is good unless vital organs are affected.

The real prevalence of the pulmonary involvement in Behçet's disease is unknown. In a retrospective analysis of 2179 patients with Behçet's disease, the prevalence of pulmonary involvement was 1.1%, and it was approximately 5% in other studies [2,15–17]. Pulmonary vascular involvement can lead to the formation of pulmonary artery aneurysm, thrombotic occlusion of vessels, pulmonary infarction, or pulmonary hemorrhage. It also may cause pulmonary arterial hypertension, which leads to right heart failure [9, 18,19].

Diagnosis

The variability of clinical manifestations and the absence of specific histologic or laboratory findings may cause the difficulty in diagnosis. The diagnosis is made on the basis of the criteria published in 1990

by the International Study Group for Behçet's Disease [20].

For the diagnosis, recurrent aphthous or herpetiform oral ulcerations and at least two of the following manifestations must be present:

1. Recurrent genital ulceration (aphthous ulceration or scarring)
2. Eye lesions, including anterior uveitis, posterior uveitis, or cells in vitreous on lamp examination, or retinal vasculitis
3. Skin lesions, including erythema nodosum, pseudofolliculitis, or papulopustular lesions, or acneiform nodules
4. A positive pathergy test result (read by a physician at 24 to 48 hours after oblique insertion of a 20- to 25-gauge needle)

The most common findings are oral ulcers (96–100%), genital ulcers (65–90%), eye lesions (35–70%), arthritis (30–80%), erythema nodosum (25–80%), and folliculitis (40–50%). Less common findings are caused by gastrointestinal (5–60%), neurologic (10–50%), vascular (5–30%), and pulmonary involvement (1–8%) [8,9,12,21].

In the absence of a classical presentation, Behçet's disease can be confused with other disorders such as Reiter's syndrome, inflammatory bowel disease, Stevens-Johnson syndrome, relapsing polychondritis, Takayasu's arteritis, or multiple sclerosis [6,21,22]. Hughes-Stovin syndrome, which was described in 1959, has histologic and clinical similarities with Behçet's disease [23]. It consists of multiple pulmonary artery aneurysms and peripheral venous thrombosis. On the other hand, there are no oral or genital ulcers in this syndrome. It has been suggested that this syndrome may be a variant of Behçet's disease [24,25].

* Corresponding author.

E-mail address: feyzaerkan@superonline.com
(F. Erkan).

Epidemiology

Behçet's disease is recognized worldwide but it is particularly common along the ancient Silk Road that extends from eastern Asia to the Mediterranean basin [9,11,26,27,28,29]. It is most common in Turkey (80 to 370 cases per 100,000 population). The prevalence is 7 to 8.5 per 100,000 in Japan and ranges from 2 to 30 per 100,000 in other Asian countries. By contrast, the disease is less common in North America and Northern Europe: 0.12 to 0.33 per 100,000 in the United States, 0.64 per 100,000 in the United Kingdom, 0.42 to 0.55 per 100,000 in German natives, and 21 per 100,000 among Turkish people living in Germany [11,26,30]. Although the disease may occur at any age, peak onset is seen between the second and fourth decades of life. The male:female ratio is nearly equal, but the disease has a more severe clinical course in young men with onset before 25 years of age [8,9,11].

Pathogenesis

The etiopathogenesis of Behçet's disease is unknown. Various clinical and laboratory investigations show that a genetic predisposition with a trigger, such as an environmental or infectious agent, may cause immunologic responses that result in clinical manifestations of Behçet's disease [12]. A strong association between HLA-B51 and Behçet's disease supports the genetic predisposition to the disease [12,31–33]. The role of a T-cell-mediated immune response in the pathogenesis of Behçet's disease also has been shown [34–38]. Recent studies suggest a possible pathogenic role of certain bacterial antigens that have cross-reactivity with human peptides [39–42]. The cross-reactive antigens may include the heat shock proteins. A nonspecific hyperreactivity is another important feature of Behçet's disease [12, 26,43,44]. A typical example of this hyperreactivity is the appearance of a papule or pustule after an intradermal needle prick, known as a positive skin pathergy test. Hormonal factors also may have a role in the pathogenesis [45–47].

Pathology

Histologically, the basic pulmonary lesion in Behçet's disease is a vasculitis that affects arteries and veins of all sizes and capillaries [5,14]. Because the disease is characterized by relapses and remissions, a biopsy may fail to demonstrate vasculitis [48,49]. The vasculitic process results in perivascular inflammatory

infiltrates that may be granulocytic, mononuclear, or mixed. There is a tendency to thrombus formation, and thrombi in the lumen of vessels show features of inflammation with focal areas of lymphocytes. Pathologically, the pulmonary artery aneurysms have perivascular infiltrates around the vaso vasorum, marked intimal thickening with degenerative changes in the elastic lamina, thrombotic occlusion, and recanalization and fresh thrombi [50,51]. Neutrophilic infiltrates are frequently observed in active lesions and pathergy tests [52].

Laboratory findings

Behçet's disease has no pathognomonic laboratory findings [9]. The erythrocyte sedimentation rate, C-reactive protein, and other acute phase reactants may be raised in Behçet's disease. There may be mild anemia, mild leukocytosis, and thrombocytopenia. These findings have been found to be significantly higher in the active disease. Anticardiolipin antibodies are found in plasma but are not unique to the condition. Lupus anticoagulants and antiphospholipid antibodies are usually absent. Increased levels of factor VIII-related antigen are found in some patients in whom large vessels are involved.

Pulmonary artery aneurysm

The pulmonary artery is the second most common site of arterial involvement, preceded by the aorta. Aneurysms of the pulmonary artery are more common than thrombosis. Pulmonary artery aneurysm is one of the characteristic lesions of Behçet's disease and is mostly seen in young men [9,16,17, 53–55].

Venous thrombosis of the lower extremities and superior or inferior vena cava occlusion frequently occur in patients with pulmonary artery aneurysms [4,19,21,53]. Hemoptysis is the most common clinical manifestation of pulmonary artery aneurysm [1,15, 17,50]. It may be caused by the rupture of aneurysm with erosion into a bronchus [35,48,56,57]. It also may be the result of the development of in situ thrombosis related to the active vasculitis [4]. Sometimes hemoptysis may be massive, life threatening, or fatal. Because it is usual to see associated peripheral deep venous thrombosis along with abnormal ventilation-perfusion scans, hemoptysis can lead to misdiagnosis of pulmonary thromboembolism. Other manifestations of pulmonary artery aneurysm include cough, dyspnea, and chest pain [25,50].

Pulmonary artery aneurysms appear as a hilar enlargement or round, lobulated opacities on chest radiographs (Fig. 1) [26,56,58,59]. During acute episodes of hemoptysis, aneurysms appear poorly defined; otherwise, they have a distinct outline [54,58,60,61]. Aneurysms may be single or multiple, unilateral or bilateral [53,57,62,63]. They may be located in the main pulmonary artery (Fig. 2) or they may be either lobar (Fig. 3) or segmental (Fig. 4) and be located proximal to an occluded artery. They are located most frequently in the right lower lobar arteries, followed by the right and left main pulmonary arteries [56,57]. Pulmonary artery aneurysms also may be occluded totally or partially by a thrombus (Fig. 2, 4, 5). Thrombosed aneurysms cause ischemia and infarction in pulmonary parenchyma.

Contrast studies of the arteries and veins carry certain high risks in patients with Behçet's disease. There is a propensity for aneurysms to develop after trauma to arteries as produced by diagnostic angiography [13,22,56]. Various studies also have shown an exacerbation of hemoptysis and disease activity after this procedure [16,50]. On the other hand, venipuncture, intravenous infusion, rapid injection of large quantities of contrast material, or insertion

of venous catheters may initiate or aggravate an already developed thrombosis in the peripheral veins [2,4]. For this reason pulmonary angiography is no longer recommended for the diagnosis of pulmonary artery aneurysms.

Helical CT has been suggested as a safe method of investigation of vascular changes. Because helical CT reveals excellent vascular images with only a small amount of contrast material, it is currently the method of choice for the diagnosis of aneurysms [17,19,60]. With this method, saccular or fusiform dilatations that show homogeneous contrast filling simultaneously with the pulmonary artery are considered suggestive of aneurysm. Aneurysms of the more peripheral branches of the pulmonary artery may be demonstrated on CT scans as enlargements of the vessels in comparison with the caliber of the corresponding bronchi.

Magnetic resonance imaging is also a noninvasive method for diagnosing aneurysms [64,65]. Although there are no comparative studies, MRI is considered to be less sensitive than helical CT in demonstrating small aneurysms. Digital subtraction angiography also has been used to demonstrate aneurysms. It carries a lower complication rate, but it may be inadequate to



Fig. 1. Chest radiograph of a patient with Behçet's disease shows right pulmonary artery aneurysm as a hilar enlargement.

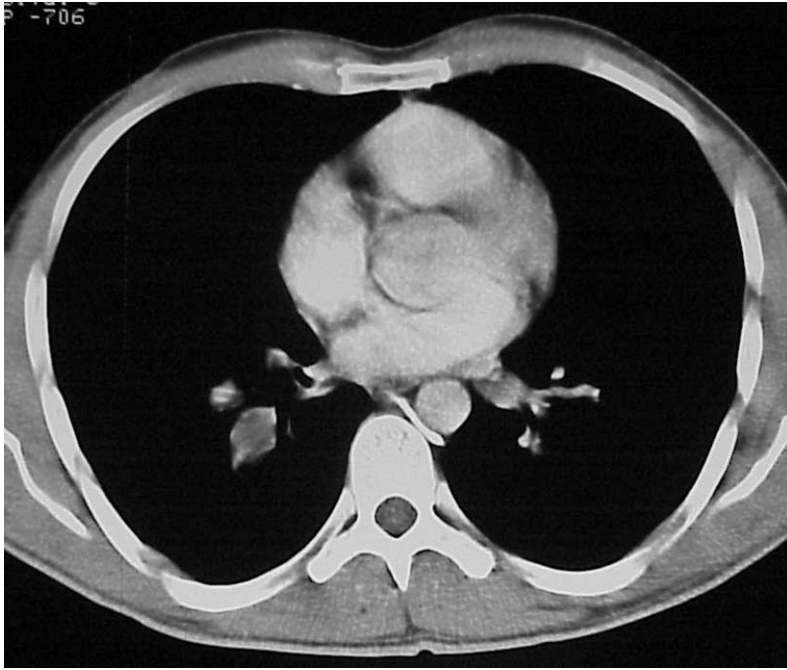


Fig. 2. Contrast-enhanced chest CT scan demonstrates right and left main pulmonary artery aneurysms that are thrombosed at the distal part.

detect thrombosed aneurysms [21,56,65]. In such cases, MRI has been suggested. Ventilation-perfusion

lung scans show bilateral, well-defined, mismatched areas with normal ventilation [15,66]. Although deep

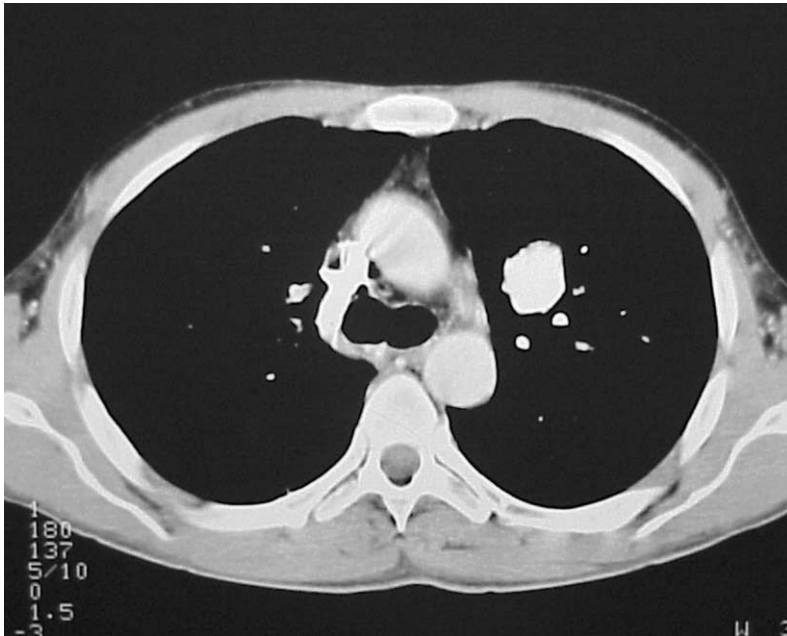


Fig. 3. Contrast-enhanced chest CT scan shows lobar pulmonary artery aneurysm in the left upper lobe.

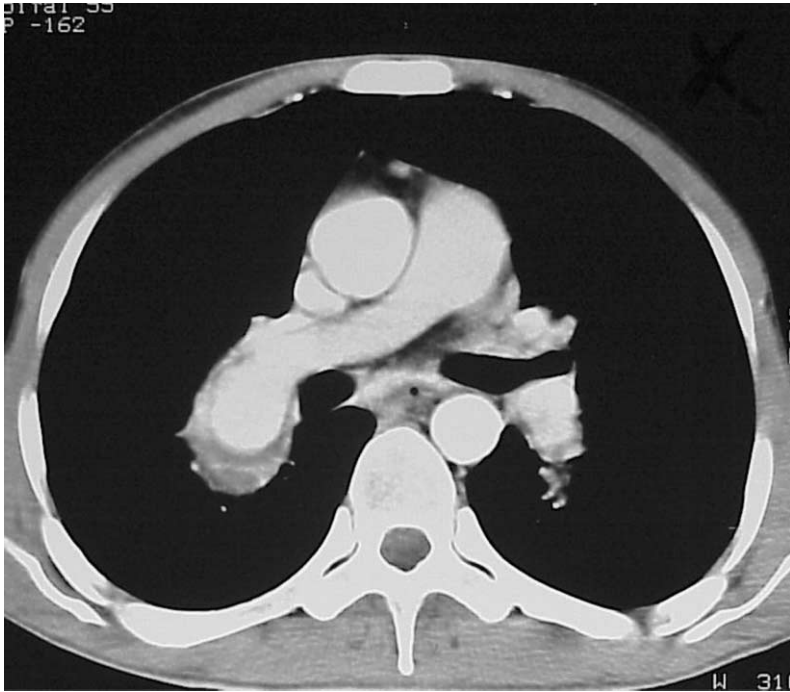


Fig. 4. Contrast-enhanced chest CT scan shows completely thrombosed segmented pulmonary artery aneurysm in the right lower lobe.

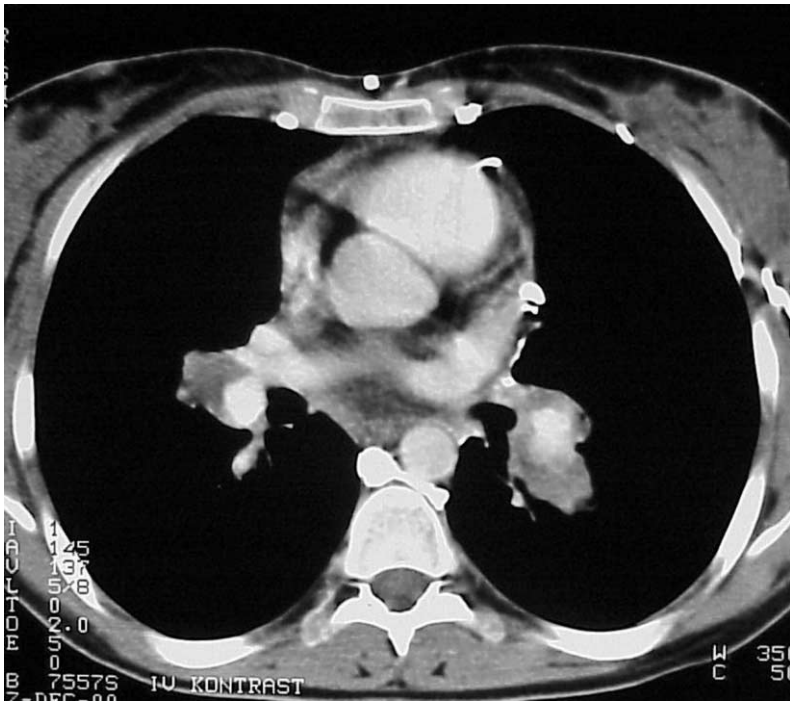


Fig. 5. Contrast-enhanced chest CT scan shows bilateral partially thrombosed lobar pulmonary artery aneurysms.

venous thrombosis of the lower extremities is common in Behçet's disease, pulmonary thromboembolism is rare in this disease because the thrombi in inflamed veins are strongly adherent [17].

Pleural and pulmonary parenchymal findings

Pulmonary parenchymal changes in Behçet's disease are nonspecific. The most commonly described parenchymal findings are transient focal or diffuse alveolar infiltrates, wedge-shaped opacities, linear shadows, atelectasis, subpleural nodules, excavated nodules, rounded opacities, ill-defined or reticular infiltrates, and areas of parenchymal hypovascularization [1,18,48,56,67]. In some cases, chest CT scans can show a mosaic pattern of variable attenuation that reflects nonhomogeneous perfusion. The infiltrates are generally attributed to pulmonary hemorrhage or infarct areas. The pathologic diagnosis of the parenchymal lesions has been documented only in a few cases, however [56,68,69].

Primary pleuritic disease is less common in Behçet's disease, and there is no sufficient documentation about pleural histology [5]. Three patients have been reported with pleural effusion and vasculitis of pleura proved by pleural biopsy [56]. Pleural effusions may result from superior vena cava thrombosis, pulmonary infarction, or pleural vasculitis. Peripheral subpleural opacities may excavate or even rupture into the pleural space, which can lead to a hydropneumo-

thorax [56]. Pulmonary infarctions appear as atelectasis, wedge-shaped opacities, linear shadows, or pleural effusions. They are most probably the result of thrombi within the pulmonary arteries, but emboli from peripheral veins, vena cava, or intraatrial thrombus cannot be excluded. Reticular or ill-defined infiltrates may represent small-vessel vasculitis [15]. A recent case report described organizing pneumonia with pulmonary artery aneurysms in a patient with Behçet's disease [68]. Eosinophilic pneumonia, which was presented with nonsegmental pulmonary infiltrates and diagnosed by transbronchial biopsy, has been reported in another patient [56]. Recurrent pneumonitis, pulmonary fibrosis, and obstructive airway disease also have been described in association with Behçet's disease [1,4,18,70,71].

Other intrathoracic complications

Superior vena cava occlusion

Venous occlusions are more common than arterial lesions in Behçet's disease [6,21,25]. Recurrent superficial thrombophlebitis and deep thrombophlebitis of the lower extremities are the most common abnormalities, followed by superior and inferior vena cava thrombosis. As many as one third of patients with pulmonary complications of Behçet's disease may have accompanying inferior or superior vena cava thrombosis (Fig. 6) [1,4,67,72,73]. The pathogenesis



Fig. 6. Contrast-enhanced chest CT scan shows superior vena cava occlusion and numerous collaterals.

of superior vena cava occlusion is either in situ thrombus formation or propagation of a thrombus from a distal vessel. It may cause facial and upper limb swelling, headache, and shortness of breath. Thrombosis of the innominate and subclavian veins may accompany superior vena cava occlusion. Chest radiography may reveal mediastinal widening. For the diagnosis, MRI is preferred.

Intracardiac thrombus formation

Intracardiac thrombosis is a rare but serious complication of Behçet's disease and often occurs in association with pulmonary artery aneurysm. Young men seem to be most at risk, and the right heart is the most frequent site of involvement [74,75]. Patients with intracardiac thrombosis have a poor prognosis. Because intracardiac thrombus is tightly attached to the endocardium or myocardium, thromboembolism from the cardiac cavity seems to be relatively uncommon. Because of the nonspecific clinical symptoms, which can be attributed to endocarditis, the diagnosis of intracardiac thrombus in Behçet's disease is not easy. Even echocardiography is not always helpful because its findings are easily confused with those of vegetations or an intracardiac tumor. The differentiation between the intracardiac thrombus and atrial myxoma is also difficult.

Involvement of aortic arch and other arteries

Aneurysms of the aortic arch and occlusion of the brachiocephalic arteries can occur in patients with Behçet's disease [76,77]. Because radiographic features of aortic involvement in Behçet's disease are similar to those of Takayasu's arteritis, the two diseases must be clinically differentiated [6,21]. A false aneurysm of the coronary artery that presented as a large mediastinal mass has been reported [78].

Treatment

The main goal of treatment in Behçet's disease is suppression of inflammation, thereby preventing irreversible damage. Although there is no consensus on the treatment of Behçet's disease, current treatment is based on the site and severity of manifestations. Antiinflammatory drugs, such as colchicine, thalidomide, dapsone, and levamisole, have been shown to be effective on mucocutaneous lesions [79–81]. Because of the possible role of streptococci in the pathogenesis of Behçet's disease, the effectiveness of penicillin therapy also has been evaluated. Two

prospective studies with penicillin reported favorable results in mucocutaneous lesions and arthritis [82,83]. New alternatives, such as interferon- α in the treatment of eye involvement, have shown encouraging results [12]. Corticosteroids also suppress inflammation, especially in acute phases, but they are not sufficient for long-term suppression. For this reason, other immunosuppressive therapies have been studied. Therapies with azathioprine, methotrexate, chlorambucil, cyclophosphamide, and penicillamine reported favorable results, especially for uveitis [12, 79,81,84–86]. Some of these drugs have restricted usage because of their major acute and long-term side effects, however.

Treatment of pulmonary complications

The mainstay of treatment is immunosuppressant therapy [79,85]. Other treatment modalities should be used only in combination with this therapy and as palliative measures in special complications. Because the disease has a more severe course in young male patients, these patients must be treated more aggressively.

Immunosuppressant treatment

Pulmonary artery aneurysm has a poor prognosis and is one of the leading causes of death in patients with Behçet's disease [17,57]. Patients with pulmonary artery aneurysms and superior vena cava occlusion are usually treated with a combination of cyclophosphamide and methylprednisolone, although there is no convincing evidence about the efficacy of this combination [8,12,79]. In the authors' clinical practice, cyclophosphamide in combination with oral methylprednisolone, 1 mg/kg, is the treatment of choice. Cyclophosphamide is given either orally, 2 mg/kg/d, or in the form of monthly 1-g intravenous boluses. In the case of severe hemoptysis, treatment starts with intravenous pulses of methylprednisolone (0.5–1 g for 3 days) combined with pulsed cyclophosphamide [8,12,57,72]. The prednisolone dose is then tapered depending on the clinical response, whereas the cyclophosphamide regimen is continued for at least 1 year after complete remission. In the follow-up, cyclophosphamide is frequently changed with azathioprine [15,17,58].

Anticoagulant and thrombolytic treatment

Because of the lack of controlled trials of anticoagulants and thrombolytic agents in Behçet's disease, there is no consensus on the usage of these drugs. Administration of heparin or oral anticoagulation with the false diagnosis of thromboembolism may

cause fatal bleeding from pulmonary artery aneurysms. For this reason, these medications must be used cautiously and only after systemic immunosuppressant treatment [4,17,58]. If thrombi are not extensive, low-dose antiplatelet treatment may be sufficient [15,58]. There are no sufficient data about thrombolytic treatment in Behçet's disease. Urokinase was tried in one patient with a thrombosed pulmonary artery aneurysm, and streptokinase was tried in a patient with superior vena cava syndrome [87,88]. There was no evidence of thrombotic episodes during the follow-up period of 2 years in these patients. In these two reports, it is difficult to assess the efficacy and risks of thrombolytic therapy because both patients also received immunosuppressive treatment at the same time.

Surgery

The surgical treatment of aneurysms in Behçet's disease should be considered cautiously because the operative morbidity and mortality rates are high. The reported incidence of recurrent, usually anastomotic, aneurysm after graft repair and patching is 25%. [89–92]. Postoperatively, there has been a tendency for aneurysm, arteriovenous fistulas, and thrombus formation. Aortobronchial fistula from the thoracic aorta also has been reported. Perioperative medical treatment with steroids and immunosuppressive drugs can reduce the risk of recurrence. Lobectomy and pneumonectomy have been performed in urgent cases with massive hemoptysis only.

Embolization

The use of transcatheter arterial embolization in patients with Behçet's disease complicated by pulmonary artery aneurysms has been reported [93,94]. Because complications of pulmonary aneurysm may be self-limited and benign, it may be difficult to assess the value of this therapeutic modality. At the same time, the size and number of aneurysms, the presence of superior or inferior vena cava occlusion, and the potential complication of severe bleeding are the main limitations of this procedure.

Prognosis

Behçet's disease has episodes of exacerbation and remission. The disease runs a severe course in young men. Pulmonary artery aneurysm has a poor prognosis: 30% of patients with pulmonary artery aneurysms die within 2 years [50]. In another study, mean survival after the onset of hemoptysis was reported to be approximately 10 months in patients with pulmon-

ary artery aneurysms [17]. A recent follow-up study of 13 patients who received immunosuppressant treatment therapy showed the complete disappearance or regression of pulmonary artery aneurysms during 3 to 42 months (mean, 21) of treatment [57]. Before the treatment, aneurysms were preceded by thrombus formation. Some studies reported massive bleeding in patients who received immunosuppressive therapy, although a partial remission of aneurysms was achieved [17,57].

Summary

Our knowledge about pulmonary complications of Behçet's disease continues to evolve, but we need controlled trials for the management of the disease. The main goal should be to elucidate the pathogenesis and standardize the management according to the underlying pathologic process.

References

- [1] Cadman EC, Lundberg WB, Mitchell MS. Pulmonary manifestations in Behçet syndrome. *Arch Intern Med* 1976;136:944–7.
- [2] Chajek T, Fainaru M. Behçet's disease: report of 41 cases and a review of the literature. *Medicine (Baltimore)* 1975;54:179–96.
- [3] Chamberlain MA. Behçet syndrome in 32 patients in Yorkshire. *Ann Rheum Dis* 1977;36:491–9.
- [4] Efthimiou J, Johnston C, Spiro SG, Turner-Warwick M. Pulmonary disease in Behçet's syndrome. *QJM* 1986; 227:259–80.
- [5] Matsumoto T, Uekusa T, Fukuda Y. Vasculo-Behçet's disease: a pathological study of eight cases. *Hum Pathol* 1991;22:45–51.
- [6] Shimizu T, Ehrlich GE, Inaba G, Hayashi K. Behçet's disease. *Semin Arthritis Rheum* 1979;8:223–60.
- [7] Behçet H. Über rezidivierende, aphtöse, durch ein virus verursachte geschwüre am mund, am auge und an den genitalien. *Dermatol Wochenschr* 1937;105:1152–7.
- [8] Hamuryudan V, Yurdakul S, Yazıcı H. Behçet's syndrome. *Rheumatol Eur* 1997;26:31–3.
- [9] Kaklamani VG, Vaiopoulos G, Kaklamani PG. Behçet's disease. *Semin Arthritis Rheum* 1998;27:197–217.
- [10] O'Duffy JD, Carney JA, Deodhar S. Behçet's disease: report of 10 cases, 3 with new manifestations. *Ann Intern Med* 1971;75:561–70.
- [11] Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med* 1999;314:1284–91.
- [12] Yazıcı H, Yurdakul S, Hamuryudan V. Behçet's syndrome. *Curr Opin Rheumatol* 1999;11:53–7.
- [13] Koc Y, Gullu I, Akpek G, Akpolat T, Kansu E, Kiraz S, et al. Vascular involvement in Behçet's disease. *J Rheumatol* 1992;19:402–10.

- [14] Lakhanpal S, Tani K, Lie JT, Katoh K, Ishigatsubo Y, Ohokubo T. Pathologic features of Behçet's syndrome. *Hum Pathol* 1985;16:790–5.
- [15] Erkan F, Çavdar T. Pulmonary vasculitis in Behçet's disease. *Am Rev Respir Dis* 1992;146:232–9.
- [16] Grenier P, Bletry O, Cornud F, Godeau P, Nahum H. Pulmonary involvement in Behçet disease. *AJR Am J Roentgenol* 1981;137:565–9.
- [17] Hamuryudan V, Yurdakul S, Moral F, Numan F, Tuzun H, Tuzuner N, et al. Pulmonary artery aneurysms in Behçet's syndrome: a report of 24 cases. *Br J Rheumatol* 1994;33:48–51.
- [18] Decroix AG. Thoracic manifestations in Behçet's syndrome. *Thorax* 1969;24:380.
- [19] Gunen H, Evereklioglu C, Kosar F, Er H, Kizkin O. Thoracic involvement in Behçet's disease and its correlation with multiple parameters. *Lung* 2000;178:161–70.
- [20] International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990;335:1078–80.
- [21] Sullivan EJ, Hoffman GS. Pulmonary vasculitis. *Clin Chest Med* 1998;19:759–76.
- [22] Hamza M. Large arterial involvement in Behçet's disease. *J Rheumatol* 1987;14:554–9.
- [23] Hughes JP, Stovin PGI. Segmental pulmonary artery aneurysms with peripheral venous thrombosis. *Br J Dis Chest* 1959;53:19–27.
- [24] Durieux P, Bletry O, Huchon G, Wechsler B, Chretien J, Godeau P. Multiple pulmonary arterial aneurysms in Behçet's disease and Hughes-Stovin syndrome. *Am J Med* 1981;71:736–41.
- [25] Plotkin GR. Miscellaneous clinical manifestations, part I: cardiac, vascular, renal, and pulmonary features. In: Plotkin GR, Calabro JJ, O'Duffy JD, editors. *Behçet's disease: a contemporary synopsis*. New York: Futura Publishing Co.; 1988. p. 203–38.
- [26] Erkan F, Gül A, Tasali E. Pulmonary manifestations of Behçet's disease. *Thorax* 2001;56:572–8.
- [27] O'Duffy JD. Summary of International Symposium on Behçet's disease. *J Rheumatol* 1978;5:229–33.
- [28] Yurdakul S, Günaydin I, Tüzün Y, Tankurt N, Pazarli H, Ozyazgan Y. The prevalence of Behçet's syndrome in a rural area in Northern Turkey. *J Rheumatol* 1988;15:820–2.
- [29] Zouboulis CC. Epidemiology of Adamantiades Behçet's disease. *Ann Med Interne (Paris)* 1999;150:488–99.
- [30] Zouboulis BP, Kotter I, Djawari D, Kirch W, Kohl PK, Ochsendorf FR, et al. Epidemiological features of Adamantiades Behçet's disease in Germany and in Europe. *Yonsei Med J* 1997;38:411–22.
- [31] Mizuki N, Inoko H, Ohno S. Pathogenic gene responsible for the predisposition to Behçet's disease. *Intern Rev Immunol* 1997;14:33–48.
- [32] Ohno S, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Aizama M. Close association of HLA-Bw51 with Behçet's disease. *Arch Ophthalmol* 1982;100:1445–58.
- [33] Zouboulis CC, Büttner P, Djawari D, Kirch W, Keitel W, Garbe C, et al. HLA-class I antigens in German patients with Adamantiades-Behçet's disease and correlation with clinical manifestations. In: Wechsler B, Godeau P, editors. *Behçet's disease*. Amsterdam: Excerpta Medica; 1993. p. 175–180.
- [34] Esin S, Gül ES, Hodara V, Jeddı-Tehrani M, Dilsen N, Konice M, et al. Peripheral blood T cell expansions in patients with Behçet's disease. *Clin Exp Immunol* 1997;107:520–7.
- [35] Freysdottir J, Lau S-H, Fortune F. T cells in Behçet's disease (BD) and recurrent aphthous stomatitis (RAS). *Clin Exp Immunol* 1998;118:451–7.
- [36] Hasan A, Fortune F, Wilson A, Warr K, Shinnick T, Mizushima Y, et al. Role of T cells in the pathogenesis and diagnosis of Behçet's disease. *Lancet* 1996;347:789–94.
- [37] Hirohota S, Hashimoto T. Abnormal T cell responses to bacterial superantigens in Behçet's disease. *Clin Exp Immunol* 1998;112:317–24.
- [38] Yamashita N, Kaneoka H, Kaneko S, Takeno M, Oneda K, Koizumi H, et al. Role of T lymphocytes in the development of Behçet's disease. *Clin Exp Immunol* 1997;107:241–7.
- [39] Direskeneli H, Eksioğlu-Demiralp E, Yavuz S, Ergun T, Shinnick T, Lehner T, et al. T cell responses to 60/65 kDa heat shock protein derived peptides in Turkish patients with Behçet's disease. *J Rheumatol* 2000;27:708–13.
- [40] Kaneko S, Suzuki N, Yamashita N, Nagafuchi H, Nakajima J, Wakisaka S, et al. Characterization of T cells specific for an epitope of human 60-kd heat shock protein (hsp) in patients with Behçet's disease (BD) in Japan. *Clin Exp Immunol* 1997;108:204–12.
- [41] Pervin K, Childerstone A, Shinnick T, Mizushima Y, van der Zee R, Hasan A, et al. T-cell epitope expression of mycobacterial and homologous human 65-kilodalton heat shock protein peptides in short term cell lines from patients with Behçet's disease. *J Immunol* 1993;151:2273–82.
- [42] Stanford MR, Kasp E, Whiston R, Hasan A, Todryk S, Shinnick T, et al. Heat shock protein peptides reactive in patients with Behçet's disease are uveitogenic in Lewis rats. *Clin Exp Immunol* 1994;97:226–31.
- [43] Gül A, Esin S, Dilsen N, Konice M, Wigzell H, Bieberfeld P. Immunohistology of skin pathergy reaction in Behçet's disease. *Br J Dermatol* 1995;132:901–7.
- [44] Sensi A, Gavioli R, Spisani S, Balboni A, Melchiorri L, Menicucci A. HLA B51 antigen associated with neutrophil hyperreactivity. *Dis Markers* 1991;9:327–31.
- [45] Dilsen N, Konice M, Aral O, Ocal L, Inanc M, Gul A. Risk factors for vital organ involvement in Behçet's disease. In: Wechsler B, Godeau P, editors. *Behçet's disease*. Amsterdam: Excerpta Medica; 1993. p. 165–9.
- [46] Ergun T, Gürbüz O, Dogusoy G, Mat C, Yazici H. Histopathologic features of the spontaneous pustular lesions of Behçet's disease. *Int J Dermatol* 1998;37:194–6.
- [47] Yazıcı H, Tuzun Y, Pazarli H, Yurdakul S, Ozyazgan Y, Ozdogan H, et al. Influence of age of onset and pa-

- tient's sex on the prevalence and severity of manifestations of Behçet's syndrome. *Ann Rheum Dis* 1984; 43:783–9.
- [48] Davies JD. Behçet's syndrome with haemoptysis and pulmonary lesions. *J Pathol* 1973;109:351–6.
- [49] Ehrlich GE. Vasculitis in Behçet's disease. *Int Rev Immunol* 1997;14:81–8.
- [50] Raz I, Okon E, Chajek-Shoul T. Pulmonary manifestations in Behçet's syndrome. *Chest* 1989;95:585–9.
- [51] Slavin RE, de Groot WJ. Pathology of the lung in Behçet's disease: case report and review of the literature. *Am J Surg Pathol* 1981;5:779–88.
- [52] Sakane T. New perspectives on Behçet's disease. *Int Rev Immunol* 1997;14:89–96.
- [53] Gibson RN, Morgan SH, Krausz T, Hughes GR. Pulmonary artery aneurysms in Behçet's disease. *Br J Radiol* 1985;58:79–82.
- [54] Numan F, Islak C, Bermen T, Tuzun H, Cokyüksek O. Behçet's disease: Pulmonary arterial involvement in 15 cases. *Radiology* 1994;192:465–8.
- [55] Park JH, Han MC, Bettman MA. Arterial manifestations of Behçet disease. *AJR Am J Roentgenol* 1984; 143:821–5.
- [56] Tunacı A, Berkmen YM, Gökmen E. Thoracic involvement in Behçet's disease: pathological, clinical and imaging features. *AJR Am J Roentgenol* 1995;76: 155–7.
- [57] Tunacı M, Özkokmaz B, Tunacı A, Gül A, Engin G, Acunas B. CT findings of pulmonary artery aneurysms during treatment for Behçet's disease. *AJR Am J Roentgenol* 1999;172:729–33.
- [58] Erkan F. Pulmonary involvement in Behçet disease. *Curr Opin Pulm Med* 1999;5:314–8.
- [59] Muftuoglu AU, Yurdakul S, Yazıcı H, et al. Vascular involvement in Behçet's disease: a review of 129 cases. In: Lehner T, Barnes CG, editors. *Recent advances in Behçet's disease*. London: Royal Society of Medicine Services Limited; 1986. p. 255–60.
- [60] Greene RME, Saleh A, Taylor AKM, Callaghan M, Addis BJ, Nzewi DC, et al. Non-invasive assessment of bleeding pulmonary artery aneurysms due to Behçet disease. *Eur Radiol* 1998;8:359–63.
- [61] Stricker H, Malinverni R. Multiple, large aneurysms of pulmonary arteries in Behçet's disease. *Arch Intern Med* 1989;149:925–7.
- [62] Almog Y, Polliack G, Elhalel M, Shalit M, Rosenmann E. Bilateral pulmonary artery aneurysms in Behçet's disease. *Eur Respir J* 1993;6:1067–9.
- [63] Winer-Muram HT, Gavant ML. Pulmonary CT findings in Behçet disease. *J Comput Assist Tomogr* 1989;13: 346–7.
- [64] Berkmen T. MR angiography of aneurysms in Behçet disease: a report of four cases. *J Comput Assist Tomogr* 1998;22:202–6.
- [65] Celenk C, Celenk P, Akan H, Basoglu A. Pulmonary artery aneurysms due to Behçet's disease: MR imaging and digital subtraction angiography findings. *AJR Am J Roentgenol* 1999;172:844–5.
- [66] Basoglu T, Canbaz F, Bernay I, Danaci M. Bilateral pulmonary artery aneurysms in a patient with Behçet syndrome. *Clin Nucl Med* 1998;23:735–8.
- [67] Ahn JM, Im JG, Ryoo JW. Thoracic manifestations of Behçet syndrome: radiographic and CT findings in nine patients. *Radiology* 1995;194:199–203.
- [68] Gül A, Yilmazbayhan D, Büyükyabani N, Lie JT, Tunacı M, Tunacı A, et al. Organizing pneumonia associated with pulmonary artery aneurysms in Behçet's disease. *Rheumatology* 1999;38:1285–9.
- [69] Petty TL, Scoggin CH, Good JD. Recurrent pneumonia in Behçet's syndrome. *JAMA* 1977;238:2529–30.
- [70] Ahonen AV, Steinus-Aarniala BS, Viljanen BDC, Halttunen PE, Oksa P, Mattson KV. Obstructive lung disease in Behçet's syndrome. *Scand J Respir Dis* 1978; 59:44–50.
- [71] Gibson JM, O'Hara MD, Beare JM, Stanford CF. Bronchial obstruction in a patient with Behçet's disease. *Eur J Respir Dis* 1982;63:356–60.
- [72] Abadoğlu O, Osmalı E, Uçan ES, Akkoc N, Kupelioglu A, Akbaylar H. Behçet's disease with pulmonary involvement, superior vena cava syndrome, chyloptysis, and chylous ascites. *Respir Med* 1996;90:429–31.
- [73] Terzioğlu E, Kırmaz C, Uslu R, Sin A, Kokuludag A, Sağduyu A, et al. Superior vena cava syndrome together with multiple venous thrombosis. *Clin Rheumatol* 1998;17:176–7.
- [74] Mogulkoc N, Burgess MI, Bishop PW. Intracardiac thrombus in Behçet's disease: a systematic review. *Chest* 2000;118:479–87.
- [75] Vanhaleweyk G, El Rahami KM, Hazmi M, Sieck JO, Zaman L, Fawzy M. Right atrial, right ventricular and left ventricular thrombi in (incomplete) Behçet's disease. *Eur Heart J* 1990;11:957–9.
- [76] Nonaka K, Makuuchi H, Naruse J, Kobayashi T, Goto M, Yamamoto T. Pseudoaneurysm of aortic arch and rupture into pericardium, a case report of successful surgical management. *Jpn J Thorac Cardiovasc Surg* 1998;46:772–6.
- [77] Okita Y, Ando M, Minatoya K, Kitamura S, Matsuo H. Multiple pseudoaneurysms of the aortic arch, right subclavian artery and abdominal aorta in a patient with Behçet's disease. *J Vasc Surg* 1998;28:723–6.
- [78] Kaseda S, Koiwaya Y, Tajimi T, Mitsutake A, Kanaide H, Takeshita A, et al. Huge false aneurysm due to rupture of the right coronary artery in Behçet's syndrome. *Am Heart J* 1982;103:569–71.
- [79] Fresko I, Yurdakul S, Hamuryudan V, Ozyazgan Y, Mat C, Tanverdi MM, et al. The management of Behçet's syndrome. *Ann Med Interne (Paris)* 1999;150: 576–81.
- [80] Hamuryudan V, Mat C, Saip S, Ozyazgan Y, Siva A, Yurdakul S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet's syndrome: a randomized, double-blind, placebo controlled trial. *Ann Intern Med* 1998;128:443–50.
- [81] O'Duffy JD. Treatment and prognosis. In: Plotkin GR, Calabro JJ, O'Duffy JD, editors. *Behçet's disease: a contemporary synopsis*. New York: Futura Publishing Co.; 1988. p. 295–304.

- [82] Calguneri M, Ertenli I, Kiraz S, Erman M, Celik I. Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behçet's disease. *Dermatology* 1996;192:125–8.
- [83] Calguneri M, Kiraz S, Ertenli I, Benekli M, Karaarslan Y, Celik I. The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behçet's disease: a randomized clinical trial. *Arthritis Rheum* 1996;39:2062–5.
- [84] Hamuryudan V, Ozyazgan Y, Hizli N, Mat C, Yurdakul S, Tuzun Y, et al. Azathioprine in Behçet's syndrome: effects on long term prognosis. *Arthritis Rheum* 1997;40:769–74.
- [85] Singer NG, Cune WJ. Update on immunosuppressive therapy. *Curr Opin Rheumatol* 1998;10:169–73.
- [86] Yazıcı H, Pazarlı H, Barnes CG, Tuzun Y, Ozyazgan Y, Silman A, et al. A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990;322:281–5.
- [87] Kroger K, Ansasy M, Rudofsky G. Postoperative thrombosis of the superior caval vein in a patient with primary asymptomatic Behçet's disease. *Angiology* 1997;48:649–53.
- [88] Sanchez-Burson J, Corzo JE, Marengo JL, Rejon-Gieb E. Thrombolytic therapy in pulmonary embolism of Behçet's disease. *Acta Haematol* 1996;96:181–3.
- [89] Bradbury AW, Milne AA, Murie JA: Surgical aspects of Behçet's disease. *Br J Surg* 1994;81:1712–21.
- [90] de Montpreville VT, Macchiarini P, Darteville PG, Dulmet EM. Large bilateral pulmonary artery aneurysms in Behçet's disease: rupture of the contralateral lesion after aneurysmorrhaphy. *Respiration* 1996;63:49–51.
- [91] Tuzun H, Hamuryudan V, Yıldırım S, Besirli K, Yoruk Y, Yurdakul S, et al. Surgical therapy of pulmonary arterial aneurysms in Behçet's syndrome. *Ann Thorac Surg* 1996;61:733–5.
- [92] Tuzun H, Besirli K, Sayin A, Vural FS, Hamuryudan V, Hizli N, et al. Management of aneurysms in Behçet's syndrome: an analysis of 24 patients. *Surgery* 1997;121:150–6.
- [93] Lacombe P, Frijia G, Parlier H, Lang F, Hamza M, Hamza R, et al. Transcatheter embolization of multiple pulmonary artery aneurysms in Behçet's syndrome: report of a case. *Acta Radiol Diagn (Stockh)* 1985;26:251–3.
- [94] Mouas H, Lortholary O, Lacombe P, Cohen P, Bourezak SG, Dolche A, et al. Embolization of multiple pulmonary arterial aneurysms in Behçet's disease. *Scand J Rheumatol* 1996;25:58–60.