

Pulmonary manifestations in a group of patients with Behçet's disease

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Background and aim

Behçet's disease (BD) is a multisystem vasculitis and pulmonary involvement in BD is reported to indicate a poor prognosis and high mortality. We aimed to study the manifestations of pulmonary involvement in a group of patients with BD and to study the correlation of pulmonary involvement with other clinical manifestations.

Patients and methods

Our study included 15 patients with BD admitted to Cairo University Hospital, 14 men (93.3%) and one woman (6.7%), mean age 30.06 ± 9.8 years. All patients fulfilled the diagnostic criteria published by the International Study Group for Behçet's Disease in 1990. All patients were subjected to both plain chest radiography and a helical computed tomography study of the chest.

Results

Pulmonary manifestations were present in 11 patients, 10 men (90.9%) and one woman (9.1%). The main pulmonary and constitutional symptoms were as follows: dyspnea (81.8%), cough (63.6%), expectoration (36.4%), chest pain (54.5%), hemoptysis (36.4%), massive hemoptysis (9.1%), fever (36.4%), and weight loss (63.6%). In the 11 patients with pulmonary manifestations, analyses of both vascular and parenchymal lung lesions in helical computed tomography scan indicated the following: pulmonary artery aneurysm occurred in five patients (45.4%), pulmonary nodules in three patients (27.2%), pleural effusion in three patients (27.2%), pulmonary infarction in one patient (9.1%), and pneumonitis in one patient (9.1%). Pulmonary involvement was associated significantly with a positive pathergy test, erythema nodosum, and gastrointestinal manifestations.

Conclusion

A high frequency of pulmonary artery aneurysm was observed in our patients with pulmonary BD. Patients with pulmonary BD have higher frequencies of skin and gastrointestinal manifestations.

Keywords:

behçet's disease; pulmonary manifestations; pulmonary artery aneurysm

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Introduction

Behçet's disease (BD) is a multisystem and chronic inflammatory disease with unknown cause. The disease was first described by the Turkish dermatologist Hulusi Behçet in 1937 and consists of a triad of recurrent ulcers of the oral and genital mucosa with relapsing uveitis. Since its first description, additional clinical manifestations in other locations (skin, joints, gastrointestinal tract, genitourinary tract, central nervous system, cardiovascular system, and lung) were later described [1].

The diagnosis is made on the basis of the criteria proposed by the International Study Group for Behçet's Disease in 1990 [2]. According to the criteria, recurrent oral ulcerations must be present and at least two of the following:

- (a) Recurrent genital ulcerations,
- (b) Eye lesions, including uveitis, and retinal vasculitis,

- (c) Skin lesions (papulopustular lesions, pseudofolliculitis, acneiform nodules, and erythema nodosum), and
- (d) Positive skin pathergy test.

The actual prevalence of the pulmonary manifestations in BD is unknown as no prospective study has evaluated all pulmonary symptoms in an unselected group of patients. The reported prevalence has ranged from 1 to 7.7% [3,4].

BD involving the chest can manifest as a wide spectrum of abnormalities. Pulmonary vascular problems such as pulmonary artery aneurysms (PAAs), pulmonary emboli/infarction, and the involvement of small-sized vessels are the most common pulmonary disorders in BD [5].

Aneurysms of the pulmonary arteries, with or without thrombosis, are typical manifestations of BD. Inflammatory obliterative endarteritis of the vasa

vasorum causes destruction of media, arterial wall weakening, and aneurysm formation [5].

Hemoptysis of varying degrees is the most common and predominant symptom. The rupture of an aneurysm with erosion into a bronchus and the development of in-situ thrombosis from active vasculitis have been suggested as explanations for the hemoptysis [6].

Helical computed tomography (CT) as a noninvasive technique is the most appropriate diagnostic method because it provides excellent vascular images with the contrast material applied in small doses over a very short time. Helical CT can be used for the diagnosis and follow-up of the pulmonary aneurysms in BD [7].

We aimed to study the manifestations of pulmonary involvement and the association of other clinical manifestations with pulmonary involvement in a group of patients with BD who were admitted to Cairo University Hospital.

Patients and methods

Fifteen patients diagnosed with BD, admitted to Cairo University Hospital, were studied for further evaluation of their symptoms. All patients fulfilled the new set of diagnostic criteria published by the International Study Group for Behcet's Disease in 1990 [2].

All patients were subjected to a full assessment of history and a thorough clinical examination. Demographic features such as age, sex, age at disease onset, duration of disease, and different clinical manifestations were recorded. The pathergy test was performed; 0.2 ml of normal saline was injected intradermally into the flexor aspect of the forearm. An erythematous papule or pustule greater than 2 mm at the prick site at 48 h was considered a positive pathergy test. All patients were examined by an ophthalmologist for evidence of eye lesions in the form of anterior or posterior uveitis or retinal vasculitis. Laboratory parameters such as complete blood count, erythrocyte sedimentation rate, kidney and liver function tests, and coagulation profile were determined for all patients.

All patients were subjected to both plain chest radiography and a helical CT study of the chest to assess the pulmonary vasculature and lung parenchyma. CT scans were obtained using a Somatom Plus-S scanner (Siemens, Erlangen, Germany). Unenhanced contiguous sequential sections with 10-mm collimation were obtained from the lung apex to the diaphragm. After these images were reviewed, a helical scan was obtained after the contrast material was administered at a rate

of 2–3 Mi/s. Delay times ranged from 20 to 30 s. The parameters used were 5-mm section thickness, 5 mm/s table feed (pitch of 1), and a 24-s scanning time. The images were reconstructed at 5-mm intervals. All images were viewed at standard mediastinal and lung window settings. High-resolution CT scans were obtained at the levels where parenchymal abnormalities were observed. Saccular or fusiform dilatations that showed homogeneous enhancement simultaneously with enhancement of the pulmonary arteries were considered suggestive of aneurysms. The location, number, and size of aneurysms, presence or absence of intra-arterial thrombosis, and perianeurysmal pulmonary parenchyma changes were noted for each patient.

According to the declaration of Helsinki, an informed consent was obtained from all patients and the study was approved by the institution review board.

Statistical analysis

All data were collected, tabulated, and statistically analyzed. Numerical variables were presented as mean and SD and analyzed using the Student *t*-test. Categorical variables were presented as number of cases and percent; they were analyzed using the χ^2 -test. Any difference with a *P*-value less than 0.05 was considered statistically significant.

Results

Fifteen patients were included in our study, 14 men (93.3%) and one woman (6.7%). Their mean age was 30.06 ± 9.80 years and the mean age at onset of BD was 23.70 ± 5.54 years.

Clinical characteristics of 15 patients with Behcet's disease

Oral ulcers and genital ulcers occurred in 100% of cases, eye lesion in 40%, erythema nodosum in 13.3%, other skin lesions in the form of papulopustular and acneiform lesions in 20%, a positive pathergy test in 26.6%, musculoskeletal symptoms in 60%, neurological manifestations in 20%, gastrointestinal manifestations in 13.3%, vascular involvement in 80%, and pulmonary involvement (vasculature or parenchyma) in 73.3% of cases.

Vascular involvement in Behcet's disease patients

Deep venous thrombosis (DVT) was the most frequent vascular involvement (53.3%), followed by PAA (33.3%), inferior vena cava (IVC) thrombosis (13.2%), aortic artery aneurysm (6.6%), femoral artery aneurysm (6.6%), and pulmonary thromboembolism (6.6%) (Table 1).

Pulmonary manifestations in Behçet's disease patients

Pulmonary involvement was present in 11 patients with BD, 10 men (90.9%) and one woman (9.1%). Their mean age of the patients was 28.80 ± 8.07 , the mean age at onset of BD was 23.20 ± 5.59 years, and the mean disease duration until lung manifestations appeared was 3.70 ± 4.80 years. The main pulmonary and constitutional symptoms were as follows: dyspnea in nine patients (81.8%), cough in seven (63.6%), expectoration in four (36.4%), chest pain in six (54.5%), hemoptysis in four (36.4%), massive hemoptysis (500 ml of expectorated blood over a 24-h period) in one (9.1%), fever in four (36.4%), weight loss in seven (63.6%), and malaise in three (27.2%) patients (Table 2).

Results of helical computed tomography scan of the chest

Analysis of both vascular and parenchymal lung lesions in the helical CT scan of the 15 patients with BD showed that 11 patients had pulmonary involvement [PAA occurred in five patients (45.4%), pulmonary nodules in three patients (27.2%), pleural effusion in three patients (27.2%), pulmonary thromboembolism and infarction in one patient (9.1%), and pneumonitis in one patient (9.1%)]. Saccular aortic arch aneurysm was present in one patient and no abnormalities were detected in the remaining three patients (Table 3).

Details of helical chest computed tomography and computed tomography pulmonary angiography

Among the 11 patients with pulmonary involvement documented by helical CT chest, five patients (45.4%) had PAAs. The first patient had multiple PAAs in the lower lobar pulmonary artery associated with intracardiac thrombosis in the right ventricle (Fig. 1), the second patient showed multiple bilateral PAAs

being larger on the left side associated with a right basal pulmonary nodule (Fig. 2), the third patient showed a partially thrombosed aneurysm of the inferior lobar pulmonary artery as well as the right lower lobar lateral segmental branch (Fig. 3), the fourth patient had a right inferior PAA with distal thrombosis, and the fifth patient had a small rounded pulmonary lesion seen at the superior lingular segment that was proved

Table 1 Vascular involvement in 15 patients with Behçet's disease

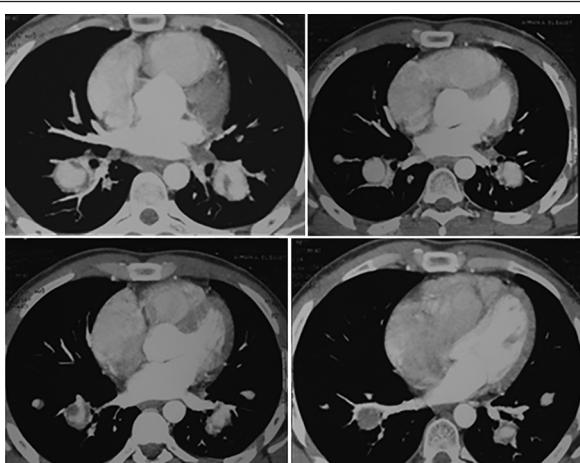
Vascular involvement	N (%)
DVT	8 (53.3)
PAA	5 (33.3)
IVC thrombosis	2 (13.2)
Aortic aneurysm	1 (6.6)
Femoral artery aneurysm	1 (6.6)
Pulmonary thromboembolism	1 (6.6)

DVT, deep venous thromboses; IVC, inferior vena cava; PAA, pulmonary artery aneurysm.

Table 2 Demographic and clinical symptoms of patients with pulmonary Behçet's disease

Features	Mean \pm SD or N (%)
Age (years)	28.80 ± 8.07
Age at disease onset (years)	23.20 ± 5.59
Disease duration until lung manifestations appeared (years)	3.70 ± 4.80
Dyspnea	9 (81.8)
Cough	7 (63.6)
Expectoration	4 (36.4)
Chest pain	6 (54.5)
Hemoptysis	4 (36.4)
Massive hemoptysis	1 (9.1)
Fever	4 (36.4)
Weight loss	7 (63.6)
Malaise	3 (27.2)

Figure 1



Multiple pulmonary artery aneurysms and intracardiac right ventricular thrombus.

Figure 2



Multiple bilateral pulmonary arterial aneurysms were larger on the left basal region.

by CT angiography to be a PAA along the descending branch of the right pulmonary artery. Thromboembolic changes in the segmental branches of inferior lobar pulmonary arteries and right basal pulmonary infarcts

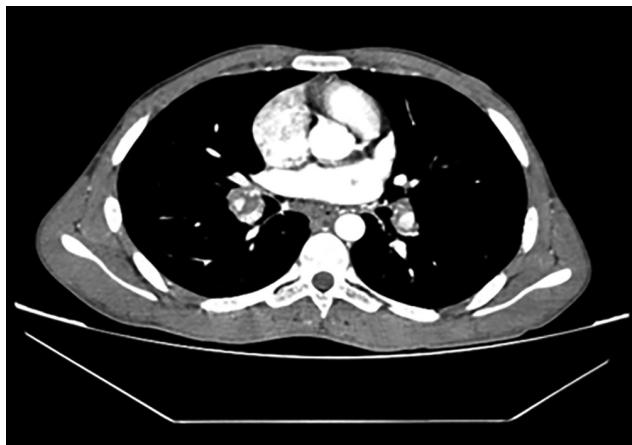
were documented in one patient (9.1%) (Fig. 4). Pleural effusion was detected in three patients (27.2%). Also, helical CT indicated pulmonary nodules in three patients (27.2%). One of these patients had a nodule

Table 3 Pulmonary symptoms and radiological findings in 15 patients with Behçet's disease

Patient number	Age	Sex	Pulmonary and constitutional symptoms	Chest radiography	CT scan
1	22	M	Dyspnea, weight loss	Mild bilateral pleural effusion	Thrombosed IVC, mild bilateral pleural effusion
2	35	M	–	NAD	NAD
3	23	M	Massive hemoptysis, dyspnea, cough, expectoration, chest pain, malaise, weight loss, syncope	Mildly prominent hilar vascular shadow	Multiple PAA, intracardiac thrombosis in the right ventricle
4	34	M	Dyspnea, cough, expectoration, chest pain, weight loss, syncope	Left moderate pleural effusion	Bilateral PA thromboembolism, bilateral pleural effusion, pulmonary infarcts
5	43	M	Hemoptysis, dyspnea, cough, chest pain	Increased pulmonary vasculature	PAA with distal thrombosis
6	30	M	–	NAD	NAD
7	34	M	Weight loss	Emphysematous chest with hyperinflated lungs, widened retrosternal space, and flat diaphragm	Small well-defined nodule seen in the left upper lung lobe
8	18	F	Dyspnea, chest pain, fever	NAD	Subpleural pulmonary nodules
9	17	M	–	NAD	NAD
10	22	M	Hemoptysis, dyspnea, cough, chest pain, weight loss	Obliterated cardiac waist	Thrombosed aneurysm of inferior lobar PA
11	38	M	Fever, cough, weight loss	NAD	Left lower lobe pneumonitis
12	52	M	Chest pain	Widening of the mediastinal silhouette	Saccular aortic arch aneurysm
13	26	M	Hemoptysis, dyspnea, cough, fever, malaise, weight loss	Multiple coin shaped shadows	Multiple bilateral PAA, right basal pulmonary nodule
14	23	M	Hemoptysis, dyspnea, cough, expectoration, malaise, weight loss	Enlarged right hilar, well-defined, rounded, opaque shadow	PAA along the descending branch of the right pulmonary artery
15	29	M	Dyspnea, chest tightness	NAD	Mild bilateral pleural effusion

CT, computed tomography; IVC, inferior vena cava; NAD, no abnormality detected; PA, pulmonary artery; PAA, pulmonary artery aneurysm.

Figure 3



Partially thrombosed aneurysm of inferior lobar pulmonary arteries as well as the right lower lobar lateral segmental branch.

Figure 4



Thromboembolic changes in the segmental branches of inferior lobar pulmonary arteries on both sides with secondary pleural effusion and right basal pulmonary infarcts.

Table 4 Comparison of the frequency of other clinical manifestations among patients with and without pulmonary involvement

Clinical manifestations	Pulmonary involvement (n = 11) [N (%)]	No pulmonary involvement (n = 4) [N (%)]	Total (n = 15) [N (%)]	P-value
Oral ulcers	11 (100)	4 (100)	15 (100)	0.71
Genital ulcers	11 (100)	4 (100)	15 (100)	0.71
Eye lesions	5 (45.4)	1 (25)	6 (40)	0.43
Erythema nodosum	2 (18.2)	0 (0)	2 (13.3)	0.005*
Papulopustules	2 (18.2)	1 (25)	3 (20)	0.02*
Pathergy test	4 (36.3)	0 (0)	4 (26.6)	0.001*
Articular manifestations	7 (63.6)	2 (50)	9 (60)	0.439
DVT	7 (63.6)	1 (25)	8 (53.3)	0.76
Neurological manifestations	2 (18.2)	1 (25)	3 (20)	0.02*
Gastrointestinal manifestations	2 (18.2)	0 (0)	2 (13.3)	0.005*

DVT, deep venous thrombosis; *Statistically significant.

in the left upper lung lobe and the other one had right anterior middle lobar nodules. In the third patient, the nodules were encountered in the base of the right lung.

Comparison of the demographic data and clinical manifestations between Behçet's disease patients with and without pulmonary involvement

There was no significant difference in the mean age or disease duration between patients with or without pulmonary involvement ($P = 0.6$ and 0.2 , respectively). Oral and genital ulcers were present in all cases (100%). Positive pathergy test, erythema nodosum, and gastrointestinal involvement were associated significantly with pulmonary BD ($P = 0.001$, 0.005 , and 0.005 , respectively). Eye lesions, articular manifestations, and DVT were more common in patients with pulmonary BD, but there was no statistically significant difference. Neurological manifestations and papulopustules were less common in patients with pulmonary involvement (18.2 vs. 25%, $P = 0.02$ for neurological manifestations and 18.2 vs. 25%, $P = 0.02$ for papulopustules) (Table 4).

Discussion

BD is a chronic, systemic, inflammatory disease of unknown origin. The main histological feature is a widespread vasculitis that affects vessels of all sizes. Pulmonary involvement in BD is reported to indicate a poor prognosis and high mortality [8].

To our knowledge, this is the second study to analyze the characteristics of pulmonary involvement in a group of Egyptian patients with BD.

The pulmonary manifestations in patients with BD were evaluated using CT by Celenk *et al.* [9]. They detected eight patients (16%) with pulmonary involvement among 50 patients with BD.

Ahn *et al.* [10], studied nine patients with BD. Radiographs showed mediastinal widening in five patients (56%), lung mass in three patients (33%), air space consolidation in five patients (56%), and lung mass because of aneurysm of the right and left pulmonary artery in three patients (33%). These results were comparable with our study, where 33.3% of our patients had PAA. Thrombosis of the IVC was not detected in their patients whereas in our study, 2/15 (13.2%) had IVC thrombosis. Four of their patients had superior vena cava thrombosis (44.4%), whereas none was identified in our study.

DVT was detected in eight of our patients (53.5%) whereas pulmonary thromboembolic disease was detected only in one patient (6.6%). This is in agreement with the previous observation that although DVT is common in BD, pulmonary embolism is rare because the thrombi in the inflamed veins of the lower extremities are strongly adherent to the vessel wall. Intraluminal clot in the pulmonary arteries might evolve *in situ* secondary to pulmonary artery wall inflammation rather than venous thromboembolism, notably in cases without DVT [11].

In the present study, we identified five patients with PAA, with concomitant DVT in three of them; one of these patients had bilateral large PAAs and presented with severe hemoptysis on initiation of anticoagulation therapy for concomitant DVT.

Hemoptysis that could be massive is a common symptom among BD patients with pulmonary involvement. Rupture of an aneurysm with erosion into a bronchus and the development of *in-situ* thrombosis from active vasculitis have been suggested as an explanation for the hemoptysis [6]. Hemoptysis occurred in four (36.4%) and massive hemoptysis in one (9.1%) of our patients with pulmonary involvement. All of these patients had PAA. Hilar and peripheral opacities, frequently multiple and bilateral on the chest radiograph, can

represent PAAs [12]. PAAs are located most frequently in the right lower lobar arteries, followed by the right and left main pulmonary arteries [13].

Nodular and reticular opacities have been described in BD with or without PAAs [14]. These findings are generally accepted as foci of pulmonary hemorrhage and/or infarcts. However, the pathological correlation of the parenchymal opacities has only been documented in a few cases [15].

Emad *et al.* [16], studied 16 Egyptian patients with BD, where a plain chest radiograph and CT pulmonary angiography were performed for all patients in an attempt to assess the pulmonary vasculature and lung parenchyma. The demographic features of the group of patients studied were comparable with those of our patients. A high frequency of pulmonary involvement was observed in their study. PAAs of varying sizes were detected in nine patients (56.3%) versus five patients (33.3%) in our study, main pulmonary artery ectasia in two patients (12.5%), pulmonary artery embolism in two patients (12.5%) versus one patient (6.6%) in our study, venacaval thrombosis in seven patients (43.8%) versus IVC thrombosis in two patients (13.2%) in our study, and pulmonary venous varices in four patients (25%). Pulmonary parenchymal abnormalities, in the study by Emad and colleagues, were as follows: three patients (19.8%) with mild central bronchiectasis, one patient (6.3%) with atelectasis, one patient (6.3%) with a subpleural nodule versus three patients (20%) in our study, and four patients (25%) with interstitial lung disease versus one patient with pneumonitis (6.3%) in our study.

Vascular involvement in BD is an important major cause of morbidity and mortality. Overall, 25–50% of BD patients are likely to develop this complication [17]. Ethnic origin is one of the main factors that may modulate the prevalence and expression of BD. Our study showed vascular involvement in 12/15 patients (80%). In a previous study from Egypt, vascular lesions were reported in 57.1% of patients [18], which was higher than that in other Arabic countries (in Kuwait, 34% [19], in Saudi Arabia, 40% [20], in Iraq, 17% [21], and in Lebanon, 36.8% [22]). In Asian non-Arabic populations, the expression of vascular BD is less than that in the Arab populations. The prevalence was 8% in Iran, [23], 5.4% in Singapore [24], 11% in Hong Kong [25], and 1.8% in Korea [26]. In Turkey, vascular involvement was detected in 39.4% of patients [27].

Our study showed that a positive pathergy test and erythema nodosum were more frequent in BD patients with pulmonary involvement. A higher prevalence of erythema nodosum in patients with vascular BD

has been reported previously by Koç *et al.* [17]. Also, a significantly higher frequency of gastrointestinal manifestations was observed in BD patients with pulmonary involvement in our study.

PAAs carry a poor prognosis in patients with BD, with a 50% mortality rate [28]. A variety of treatment modalities, such as surgery, anticoagulation, embolization, and most effectively, immunosuppression, especially with cyclophosphamide and high-dose steroids, have been used in the management of PAA with limited success [29]. However, a more recent study showed an improved survival rate of 62%, secondary to a prompt diagnosis of PAA and early commencement of long-term immunosuppression with cyclophosphamide and steroids [30]. In two previous case reports of BD patients with PAAs, a course of cyclophosphamide and corticosteroid therapy resulted in complete resolution of their radiologic findings [31,32].

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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