Thoracic Manifestations of Behçet's Disease: Reports of the Turkish Authors

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Abstract

Background: Behçet's disease (BD) is a multi systemic disease, not only confined to the Mediterranean, Middle Eastern and Asian countries as believed previously, but may also be found worldwide. Turkey is one of the countries where BD is common.

Setting: In this study, thoracic manifestations of BD were reviewed by collecting and reevaluating the case reports and case series reported by the Turkish authors. The parameters were selected as the age, gender, duration of the disease, pulmonary and extrapulmonary symptoms/findings, laboratory findings, types of the pulmonary/vascular manifestations, radiological findings, treatments and outcomes.

Results: Between 1958 and 1998, 63 cases were reported. Additionally, there were well defined case series of pulmonary manifestations of BD consisting of a total of 156 cases. Male gender and young age were the dominant demographics (among the case reports, 94% was male and the mean age was 30 years). Hemoptysis was the most common symptom in BD with thoracic involvement (64%). 54% of vascular involvement was found as pulmonary artery aneurysm.

Conclusion: Only a well-informed physician can identify BD and features of thoracic involvement. Because of the poor prognosis, massive hemoptysis in a patient with characteristics of mucosal ulceration should alert the physician to consider the development of the pulmonary artery aneurysm.

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Key words: *Behçet's Disease, thoracic involvement, massive hemoptysis, pulmonary artery aneurysm*

Introduction

Behçet's disease (BD), a syndrome of an unknown etiology described by the Turkish dermatologist Hulusi Behçet in 1937, is a multi systemic disease. It is not only confined to the Mediterranean, Middle Eastern and Asian countries as believed previously, but it is also found worldwide (1). The cardinal manifestations of this syndrome are aphthous stomatitis, genital ulceration, and ocular involvement. The involvement of the dermatological, venous or arterial, arthritic, central nervous system and gastrointestinal system are the other possible manifestations. Pulmonary

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involvement occurred in 5% of the cases with BD (2). Mainly thrombus of Superior vena cava or the other mediastinal veins, aneurysm of the pulmonary arteries, pulmonary infarct and hemorrhage, pleural effusions, cor pulmonale, and mediastinal or hilar lymphadenopathy are the thoracic manifestations of BD. Although they are not very common, physicians have to be alert to the presence of those findings because of the poor prognosis, especially for the development of the pulmonary artery aneurysm. In a patient with the characteristic mucosal ulceration, a well-informed physician would be able to identify certain conditions as Behçet's Syndrome (1).

Turkey is one of the countries where BD is common. There is a tendency to publish most of the cases and case series in Turkish literature. The authors aimed to investigate the clinical features of the thoracic involvement in this disease by collecting and reevaluating the case reports and case series reported by the Turkish authors as a large series.

Material and Method

In a three-year period, many Turkish journals in the fields of dermatology, chest medicine, internal medicine, and radiology were investigated to find the articles written by the Turkish authors on thoracic involvement of BD. Although it is hard to be sure, due to absence of a Turkish Index Medicus, the authors believe that most of the articles on this subject were obtained for the study. The data were not suitable for "meta-analyses" and also the aim of the authors was not to study only well-defined cases, therefore, the study was designed as a review of the BD cases with thoracic manifestations reported by the Turkish authors.

There were two populations investigated in this study consisting of 53 articles: previously published case reports and several case series. The entire case reports of thoracic involvement in BD reported by the Turkish authors in various medical journals, generally in the Turkish literature, were collected (in the reference list, the language of the article was noted, except the ones which took place in Index Medicus). Sixty-three cases were found between 1958 and 1998 (3-44). Additionally, there were well defined case series of pulmonary manifestations of BD consisting of a total of 156 cases between 1992-1999 (45-50). All the information given in the case reports were considered for each case and analyzed together. The number of the cases fulfilling the same parameter were considered during percentage analyses. In the case series, only the cases with pulmonary and/or thoracic vascular involvement were considered. Since the latter population could not be investigated in detail, it was demonstrated separately.

Documentation of the cases were made in the light of information obtained from the original case reports. The parameters were selected as age, gender, duration of the disease, pulmonary and extrapulmonary symptoms-findings, erythrocyte sedimentation rate (ESR), previous diagnosis, type of the pulmonary-vascular manifestations, radiological findings, treatments and outcomes.

Results

1. Case Reports

1. a. General features

Of the 63 cases which have been reported between 1958 and 1998, 24 were known as having BD. 11 of the 42 cases have presented to the hospital with the pulmonary complaints and were diagnosed as BD. Mean age of the cases was 30±8 years (mean±SD) (range 17-50 years). Of the 63 cases, 59 were males (%94), four were females (%6). There was only one case with a family history of BD (in his daughter). Although there was no information about cardinal manifestations and examination findings of BD in some cases (marked consequently), oral and genital ulcerations were seen in all of the cases. The other ratios are as shown in Table 1.

Table 1. Cardinal manifestation rate and ratio according to the analyses of the case reports

Manifestation	Rate (%)	Ratio
Oral aphtous ulceration	100	51/51
Genital ulceration	100	51/51
Ocular involvement*	51	24/47
Dermatological manifestations#	28	11/40
Positive Pathergy test	88	28/32
Arthritic manifestations	30	13/43
Fever	33	15/46
Peripheral lympadenopathy	28	10/36

* i.e. uveitis, iridocyclitis, enucleation, optic atrophy
\# i.e. erythema nodosum, folliculitis, pyodermie, ulceration)

Hemoptysis was the most common symptom in BD with thoracic involvement (64%). The symptoms for 59 of the 63 case reports are detailed in Table 2.

There were 82 vascular manifestations in 56 cases. Superior vena cava syndrome and arterial occlusion-pulmonary embolus were the most frequently observed manifestations (Table 3).

Table 2. Complaints at presentation

Complaints	Rate (%)	Ratio
Hemoptysis *	64	38/59
Dyspnea†	54	32/59
Cough&	34	20/59
Chest pain	20	12/59
Pleuritic pain	12	7/59
Fever	15	9/59
Sputum production	7	4/59
Wheezing	2	1/59
Weight loss	10	6/59

*8 of them were massive hemoptysis. In 11 of 38 cases, hemoptysis was the single complaint.
†8 of them exertion dyspnea, 2 of them paroxysmal nocturnal dyspnea
&22 cases with hemoptysis did not complain of cough

Table 3. Vascular involvement

Type	Rate (%)	Ratio
Pulmonary artery aneurysm	54	30/56
Superior vena cava syndrome	30	17/56
Arterial occlusion-pulmonary embolus	20	11/56
Trombophylebitis	20	11/56
Deep Venous Thrombosis	16	9/56
Venous occlusion	4	2/56
Right ventricular thrombosis	2	1/56
Pseudoaneurysm	2	1/56
Right ventricular thrombosis	2	1/56

Pulmonary manifestations, except pulmonary artery aneurysm, were observed in 28 cases. There were 11 types of pulmonary manifestations (Table 4).

1. b. Laboratory findings

The number of cases for which laboratory tests were

Table 4. Pulmonary involvement except pulmonary artery aneurysm

Type	Rate (%)	Ratio
Pleural effusion*	36	10/28
Pulmonary embolus	29	8/28
Pulmonary infiltration in alveolar type	7	2/28
Recurrent pneumonia	3.5	1/28
Pleural thickness	3.5	1/28
Bronchospasm	3.5	1/28
Ampyema	3.5	1/28
Pulmonary mass	3.5	1/28
Multiple pulmonary nodules	3.5	1/28
Honey comb finding	3.5	1/28
Subacute vasculitis	3.5	1/28

* 4 bilateral, 5 right side, 1 left side

Table 5. Laboratory findings

Finding	Rate (%)	Ratio
Increased ESR (mm1hr)	73	35/48
Anemia	64	25/39
Pulmonary function abnormality*	59	10/17

* 7 obstructive, 2 restrictive, 1 mixed pattern

reported was different for each test. The ESR, red blood cell count and pulmonary function test were the tests generally took place in the case reports (Table 5).

Table 6. Chest x-ray findings of 60 cases

Finding	Rate (%)	Ratio
Normal*	8	5/60
Hilar enlargement†	33	20/60
Mediastinal enlargement&	8	5/60
Nodule and mass#	23	14/60
Cardiomegaly	7	4/60
Pleural effusion°	20	12/60
Pleural thickening	5	3/60
Chronic obstructive pulmonary disease	3.5	2/60
Pulmonary infiltrates	15	9/60

* 3 VCSS, 1 subacute vasculitis, 1 pulmonary artery aneurysm and right ventricular thrombus
† 11 bilateral, 5 right sided, 5 left sided
&3 superior mediasten, 1 right sided, 1 undefined
3 multiple nodules, 8 right sided, 3 undefined
° 6 right sided, 4 bilateral, 2 left sided (1 ampyema in right pleura, 1 chylous pleurisy in left)

1. c. Radiographical findings

Chest x-ray

Chest x-ray was a common investigation performed in 60 of the cases, 8% of x-rays were normal and most common finding was hilar enlargement (33%) (Table 6).

Table 7. Thoracic CT findings: 35 in 28 cases

Finding	Rate (%)	Ratio
Normal	6	2/35
Pulmonary artery aneurysm*	48.5	17/35
Nodule and Mass	11	4/35
SVCS	8.5	3/35
Parenchymal infiltration	8.5	3/35
Pleural thickening	8.5	3/35
Mediastinal shift	3	1/35
Pericardial effusion	3	1/36
Inactive tuberculosis	3	1/36

* 4 right sided, 10 bilateral, 3 left sided

Thorax Computerized Tomography (CT)
Before 1989, there was only one case's thorax CT result as normal parenchymal findings in the case of SVCS and pleurisy. CT was diagnostic in 22 of the 28 cases for whom CT scans were performed (Table 7).

Ventilation/Perfusion Scan
Perfusion defects found in all of the cases were detected scintigraphically (23 cases) and one was accompanied with ventilation defect.

1. d. Therapy regimen and outcomes
The treatment options included steroids, antineoplastic drugs, anticoagulants, colchicine, diuretics alone or in combination.

11 of the 17 deaths (65%) were due to hemoptysis. All except one had pulmonary artery aneurysm, while the outcomes of 7 cases with pulmonary artery aneurysm were unknown. Only 4 cases with pulmonary artery aneurysm showed improvement.

2. Case Series
The analysis of the case series published by Turkish authors is summarized in Table 8. Six series consisting of a total of 125 cases, reported between 1992 and 1998 were evaluated. Two of them have been published in English. The authors included only the number of the cases with thoracic involvement. Male/female ratio could not be determined. Hemoptysis was a common symptom and pulmonary artery aneurysm was a frequently observed finding. In the series of Numan et al., there were 15 cases with pulmonary artery aneurysm and 5 of them had died (Table 8).

Discussion
As a result of the frequency of pulmonary involvement in randomly selected 54 cases, BD was found to be 46% in one of the studies (47), and further investigations are required in this field in order to prevent the underestimation of the number of findings.

Generally, those results were not different from the criteria of International Study Group for BD (51). However, in detail, the positive Pathergy test and typically defined eye lesions were the most common findings of the recent study (88% and 51% respectively), following the oral and genital ulceration in BD cases with thoracic manifestations. Since the rates of genital ulceration mentioned in the case reports of thoracic involvement are very high, it is necessary to investigate the prevalence of this sign in such cases by more sensitive methods.

Hemoptysis is the worst prognostic sign in BD, leading to death in 30% of the cases, 80% within 2 years (2). According to the results of the recent analysis, the superiority of hemoptysis as a complaint for the BD on admission (64%), sometimes as a single complaint but in massive nature, it is very important that BD should be considered in the differential diagnosis for hemoptysis.

The main pathology in BD is vasculitis, which may be associated with arterial, venous or capillary vessels. The most common venous occlusion is superior vena cava syndrome. For the artery, the development of occlusion and aneurysm have been reported (52). While the thrombus has been addressed to occlusion, the development of aneurysm has been explained pathologically by the rupture of internal and external elastic laminae with thickening of the intima, degeneration of the media, and vasculitis of the vasa vasorum, with perivascular infiltration predominantly of lymphocytes (1,52).

In the past, hemoptysis has been attributed to vasculitis of small lung vessels and to the rupture of bronchial veins when intraluminal pressure is increased by thrombosis of superior vena cava. However, hemoptysis may also result by the rupture of large pulmonary artery aneurysms and arterio-venous fistulas (53).

Table 8. Documentation of the case series of the Turkish authors (46-51)

Author	Case	Hemoptysis	SVCS	Death	Abnormal Rx	Aneurysm CT*	Perfusion defect *
Acican	26	15	3	1	24	7/10	7/9
Cobanli	53	23	14	1	48	1	9/11
Azizlerli	25	-	-	5	0	-	18/25
Numan	15	15	-	5	15	15/15	-
Elbeyli	4	-	1	2	-	2/3	-
Erkan	12	11	-	1	11	5/9	12/12

* except these two columns where the values were given as the number of cases in total number of whom the test performed; all values were given as number of cases
(-) no data reported

Pulmonary artery aneurysms are the most common thoracic manifestation. The hilar enlargement on the chest x-ray is suggestive of pulmonary artery aneurysm in a patient with BD. Although Kalyoncu F et al., has suggested the opposite (54), chest x-ray has been presented as the best imaging technique for evaluating pulmonary signs and symptoms (45,52). However, the CT imaging of thorax, especially with spiral CT, has been considered diagnostic and less invasive than angiography and as the gold standard method for arterial aneurysm (52,55).

Although it has not been included in this study because of the incomplete clinical data, the most recent case reported by the Turkish authors has been examined in detail with magnetic resonance imaging and digital subtraction angiography findings (56). The case was a 16-year-old girl and she died because of massive hemoptysis after a three-month period of recurrent hemoptysis.

The pleural effusion also attracted attention with its frequency. Although it is usually attributed to pulmonary infarction or an infectious process, Tunacı A et al., demonstrated vasculitis of pleura by biopsy in their three cases of BD (52).

There was no consensus on the treatment options. Steroids have been used commonly for therapy alone or in combination. In more recent case reports, the treatment regime consisted of corticosteroid plus one of the antineoplastic agents, cyclophosfomide or azothioprine. The outcomes of the treatment, even surgery, were not good in the patients with pulmonary artery aneurysms. Raz I et al., suggested that immunomodulation therapy (corticosteroids, cytotoxic and potentially cyclosporin A) might be beneficial, especially when initiated in early stages, before irreversible damage due to the arterial wall develops (2). Although they agreed to surgical excision to prevent fatal pulmonary hemorrhage when the disease was localized to one area of the lung, the recent studies investigated did not report if the surgical excision performed was successful or not. However, the authors have followed a male case with pulmonary vascular involvement of BD for three years after unilateral pneumonectomy (unreported data), life-threatening hemoptysis was solved. According to the knowledge of the authors, surgical treatment for massive hemoptysis, especially for the pulmonary artery aneurysm should be considered.

One of the important points of treatment is the potential hazards of anticoagulant therapy for patients suffering from aneurysmatic dilatation of the pulmonary blood vessels (2), somehow is not supported by the recent results.

Tunacı M et al., reported the results of cyclophosphamide and prednisolone regime in 13 patients with BD as a CT imaging results before and after treatment. The percentage of aneurysms which had completely disappeared was 76%, while which became smaller was 24% (55). In addition, Erkan F. has emphasized aneurysmal healing process followed by CT with immunosuppressive treatment (57).

Summary

Since the frequency of pulmonary involvement of the cases with BD is known as 5%, it is necessary to design studies in some areas like Turkey. Mainly, aneurysm of the pulmonary arteries, thrombus of superior vena cava or the other mediastinal veins, pulmonary infarct and hemorrhage, pleural effusions, cor pulmonale, and mediastinal or hilar lymphadenopathy are the thoracic manifestations of BD. Although they are not very common, physicians have to be alert to the presence of those findings because of the poor prognosis, especially for the development of the pulmonary artery aneurysm. In a patient with hemoptysis, if the characteristic mucosal (oral and/or genital) ulceration has also occurred, a physician should remember Behçet's syndrome. The treatment options for this condition is controversial and needs further investigation.

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