Respiratory Medicine 221 (2024) 107481

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Angiographic findings of pulmonary arterial involvement in Behcet's Disease: Do they correlate with symptoms and acute phase response?

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ARTICLE INFO

Keywords:
Acute phase reactants
Behcet's disease
Pulmonary artery aneurysm
Thrombus

ABSTRACT

Introduction: Behcet's disease (BD) is a chronic inflammatory disorder with arterial vasculitis. Although, pulmonary artery aneurysm (PAA) is accepted as the prototypic arterial disorder, an increasing presence of pulmonary artery thrombosis (PAT) with or without aneurysms was also reported in recent studies. In this study, we aimed to describe computed tomography pulmonary angiography (CTPA) findings of pulmonary involvement and its correlation with symptoms and acute phase response in BD.

Method: In this retrospective study, 153 CTPA of BD patients were assessed by two radiologists. Clinical and laboratory data were collected from the patient files. Pulmonary artery involvement (PAI) was defined as thrombus or aneurysm in CT angiography.

Results: Most of (85.6 %) our patients were male and median age was 33.7 ± 10 years during angiographic assessments. Sixty-two (40.5 %) angiographies presented a thrombus: 14 subsegmental, 29 segmental, 13 lobar and 6 main branches. Among these, 82.3 % (n = 51) had bilateral involvement. Isolated PAT was present in 58 (93.5 %) angiographies with only 4 (2.6 %) angiographies displaying an aneurysm together with a thrombus. Pulmonary infarction was detected in 9 angiographies. Forty-four (29.3 %) patients, almost all of them under immunosuppressive treatments for other indications, were screened for asymptomatic pulmonary involvement (without any symptoms or increased acute-phase response (APR)), and one fourth of these were diagnosed as having a segmental or subsegmental PAT.

Conclusion: Our results show that isolated pulmonary thrombosis is the main form of PAI, and isolated pulmonary aneurysm formation is rare in our BD cases. In the presence of pulmonary symptoms with or without increased APRs, involvement of segmental or more proximal parts of pulmonary arteries is most commonly detected. We also observed that PAI may be seen in about one fourth of especially male BD patients without symptoms or increased APR. Our results suggest that BD patients with pulmonary symptoms should be screened by CTPA for PAI, however, further research is needed to clarify the role of routine CTPA screening in asymptomatic BD patients.

1. Introduction

Vascular involvement is observed in up to one third of patients with Behcet's disease (BD), a chronic, inflammatory, multi-systemic disorder with unknown etiology. Although all types and sizes of vessels can be affected, venous involvement is more common [1,2]. Despite being the most frequent form of arterial disease, pulmonary involvement is rare in BD patients with a prevalence reported in less than 5 % in different series [3,4]. In these reports, pulmonary artery aneurysm (PAA) was the prototype of pulmonary involvement in BD patients, however pulmonary artery thrombus (PAT), with or without an aneurysms, has been defined as a part of pulmonary involvement with an increasing incidence over years, possibly due to advances and increased availability of imaging techniques [5–7]. PAT is described as an 'in situ thrombi' rather than an embolic phenomenon [4,6,8–10]. Limited data is published on the typical clinical and laboratory findings of pulmonary involvement of BD

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https://doi.org/10.1016/j.rmed.2023.107481
Received 20 August 2023; Received in revised form 8 November 2023; Accepted 24 November 2023
Available online 28 November 2023

patients. Imaging features of these patients has also not been fully understood, which might affect the diagnosis and management.

In this study we aimed to describe computed tomography pulmonary angiography (CTPA) findings of pulmonary arterial involvement and the associations between the imaging and symptoms and acute phase response in BD.

2. Methods

We retrospectively collected 180 CTPA of BD patients. All available thoracic scans were re-evaluated by 2 radiologists with 10- and 25-years' experience who were blind to the clinical findings and APR of the patients. Eight of the scans were excluded from study because of the lack of imaging quality. Nineteen (10.5 %) angiographies were also excluded as there was disagreement between the radiologists on the presence of thrombi or aneurysms (Fig. 1).

A total of 153 CTPA were included to the study and in case of disagreement about the details of involvement (when two radiologists agreed on the presence of thrombi but did not have the same opinion about the level or extent of the involvement), the decision of the senior radiologist (NCC) was accepted.

We collected clinical and laboratory data from the patient files. Patients were classified as BD according to international study group (ISG) criteria. Recurrent oral aphthous lesions is mandatory and two out of other four criteria: genital aphthous lesions, papulonodular skin lesions, uveitis, pathergy positivity are necessary to classify BD. All patients except 4 completed the ISG criteria for BD diagnosis. These 4 patients had a history of recurrent oral aphthous ulcers and pulmonary disease without any thrombophilia risk factors, and were diagnosed as BD with expert opinion [11].

We described pulmonary artery involvement (PAI) if angiographies displayed any thrombus or aneurysm in patients with BD diagnosis. Constitutional symptoms were defined as fever (with or without night sweats) and weight loss, pulmonary symptoms as bloody sputum, chest pain and dyspnea; and chronic pulmonary symptoms as lasting more than one month.

We described increased acute phase reactants if C reactive protein (CRP) and/or erythrocyte sedimentation rate was more than twice the upper limit of normal within one week of angiography without a possible other explanation such as infection.

The Local Ethics Committee of the Marmara University School of Medicine approved the protocol for this study. The study was performed according to the Declaration of Helsinki.

2.1. Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were tested for normality assumption with histogram, normal quantile plot, Kolmogorov Smirnov, and skewness kurtosis tests. Continuous variables without normal distribution were presented with median, 25%–75 % values. Continuous variables were compared between the groups by using Mann Whitney U and Kruskal Wallis tests. p value of less than 0.05 was considered significant. All statistics and visualization steps were performed with SPSS Version 21.0. (IBM Corp, Armonk, NY).

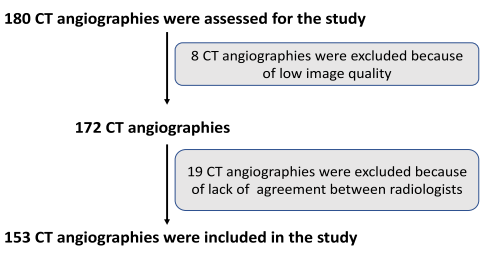

Fig. 1. Flowchart demonstrating the exclusion of CT angiographies from the study.

3. Results

3.1. Study population

The study population consisted of 153 patients, 85.6 % male and median age was 33.7 ± 10 years. Table 1 displays demographic and clinical characteristics of our study group.

CT angiographies of 153 BD patients were included in the study. Patients were grouped according to their symptoms and APRs levels. Increased APR were present in 82/129 (63.6 %) of the patients (at least once). CT angiographies were performed because of increased APR together with a symptom for 24 (16 %) patients, increased APR without a symptom for 59 (39.3 %) patients and a symptom without increased APR for 13 (8.7 %) patients.

Forty-four (29 %) patients with a mean age 32.3 ± 7.9 years, underwent pulmonary angiography for screening (they were free of symptoms and had normal acute phase reactants). Thirty-five (79.5 %) patients were male and 32 (72.7 %) patients had major organ involvement during angiography in this group.

3.2. CT angiography findings

Sixty-two out of 153 angiographies (40.5 %) presented a thrombus: 14 subsegmental, 29 segmental, 13 lobar and 6 main branches. Among them 82.3 % (n = 51) with thrombi presented bilateral involvement. Only 4 (2.6 %) angiographies displayed an aneurysm together with a thrombus. Six angiographies with isolated PAT and 3 angiographies with PAT together with aneurysm presented with an infarct. Mean pulmonary artery diameter was 24.5 ± 3.4 cm. A few CT angiography findings of our patients are presented in Fig. 2.

3.3. Clinical characteristics and laboratory findings of patients

During angiography, 48 patients had a symptom: 3 patients had constitutional symptoms (1 had a PAI) and 6 patients had pulmonary symptoms together with constitutional (5 had a PAI), 31 had acute/subacute pulmonary symptoms (19 had PAI) and remaining 8 patients had either chronic pulmonary symptoms or other symptoms (7 had PAI). Fig. 3 presented pulmonary angiographic findings in BD patients according to the presence of symptoms and increased acute phase

Table 1
Clinical and demographic characteristics of study population.

	Number of patients, %
Sex (male)	131, 85.6 %
Family history* (n = 149)	39, 26.2 %
Major organ involvement	107, 71.3 %
Oral aphthous ulcers	153, 100 %
Genital ulcer	119, 77.8 %
Papulopustuler lesions (n = 136)	82, 60.3 %
Erythema nodosum (n = 150)	80, 53.3 %
Vascular involvement	51, 33 %
Eye	51, 33 %
Neurologic	11, 7.2 %
Gastrointestinal	4, 2.6 %
Pathergy positivity (n = 124)	74, 59.7 %
Smoking (n = 53)	32, 60.4 %
Age at angiography (years)	33.7 ± 10
Time duration between angiography and diagnosis (months, median (25/75 %))	48.5 (10.5–103.75)
IS usage during angiography (n = 146)	75, 51.4 %
AC usage during angiography (n = 146)	19, 13 %

AC: anticoagulation treatment, IS: immunosuppressant.
*First- and second-degree relatives were accepted as family history.

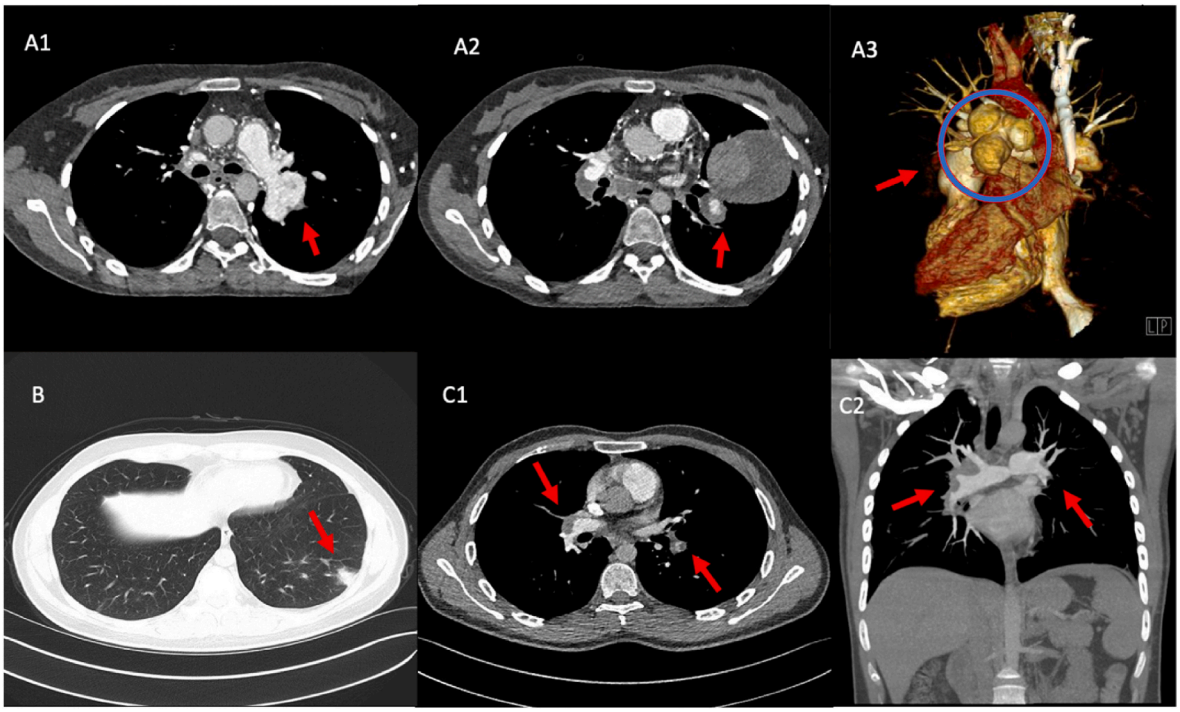

Fig. 2. Radiological examples of pulmonary involvement
A1. Aneurysmatic dilatation in the left main pulmonary artery. A2. Thrombus surrounding the aneurysmatic wall. A3. 3D configuration of the pulmonary aneurysm. B. Pulmonary infarct in the left lower lobe. C1 and C2. Coronal and axial images of pulmonary thrombi in right main and left lower lobar pulmonary arteries.

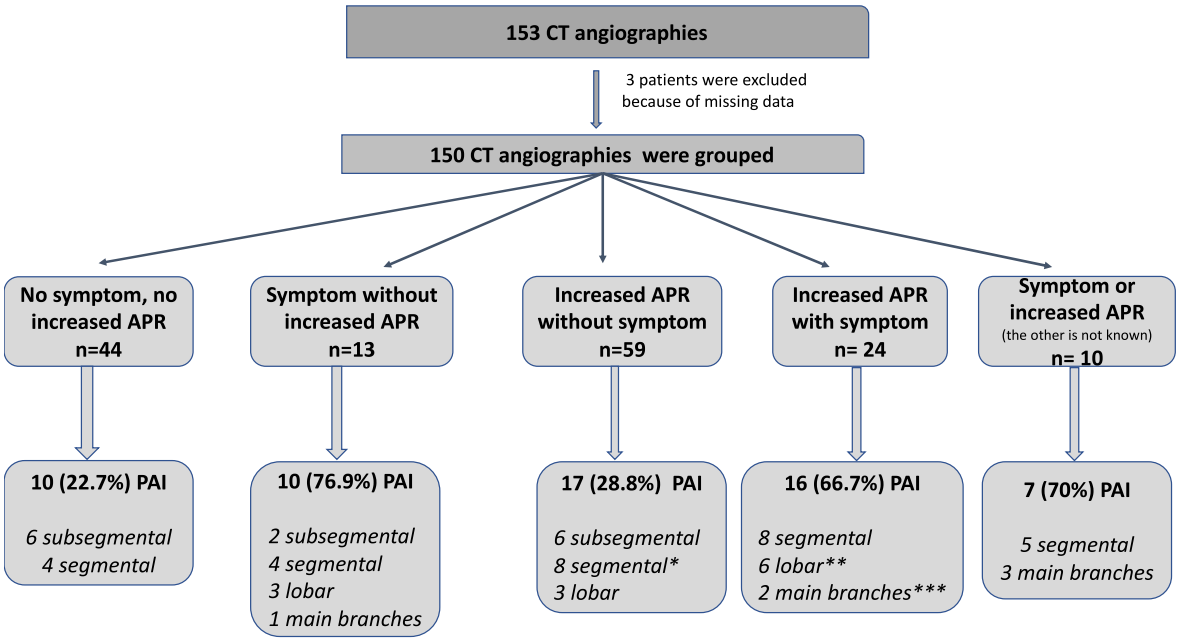

Fig. 3. Pulmonary angiographic findings according to the presence of symptoms and/or increased acute phase response.

response.

APR: acute phase response, CT: computed tomography, PAI: pulmonary artery involvement.

All PAI include pulmonary artery thrombus.

*: 1 angiography with aneurysm accompanied to thrombus.

**: 2 angiographies with aneurysm accompanied to thrombus.

***: 1 angiography with aneurysm accompanied to thrombus.

Table 2 represents general clinical and laboratory characteristics of patients with different segments of pulmonary artery involvement. All patients with main pulmonary artery involvement were male and had respiratory symptoms (chest pain, hemoptysis, and dyspnea) with or without constitutional symptoms during angiography.

Nine (75 %) of patients with lobar thrombi had symptoms with or without high acute phase reactants during angiography. CT angiography was performed because of increased acute phase reactants without symptoms for the remaining 3 patients.

There was no difference between patients with or without thrombi in terms of acute phase reactants. Although, the level of thrombi had no

correlation with acute phase reactants, increased presence of having a symptom was observed with more proximal parts of pulmonary artery involvement (Table 2).

There were 17 patients diagnosed as having a thrombosis in any other vascular system during the last month before angiography and screened for pulmonary involvement, 5 (29.4 %) of them had an associated pulmonary symptom and 4 out of these 5 patients were diagnosed as having a PAT. Also, 2 patients without a symptom were diagnosed with PAT and 1 patient with multiple thromboses (deep vein thrombose and sinus vein thrombi) was diagnosed with PAA + PAT even though he did not have any pulmonary or constitutional symptoms.

Thrombophilia factors were evaluated in only 13 patients and 9 them were positive for Factor V Leiden, prothrombin gene mutation or MTHFR mutations.

4. Discussion

Pulmonary artery is the most commonly involved artery in vascular BD and is the main cause of mortality for BD patients [1,2,12,13]. Although pulmonary artery involvement was only attributed to PAA in early reports, following studies defined that not only PAA with a thrombus but also isolated pulmonary artery thrombi can be seen in about one third of BD patients with pulmonary involvement [3–5]. This difference may be explained with the increased availability of imaging modalities and early detection and treatment of pulmonary involvement before the transition from PAT to PAA [5]. Also, some authors described parenchymal pulmonary involvement as microscopic pulmonary vascular disease and tried to define the differences/similarities between macroscopic and microscopic pulmonary involvements [6].

In our study, PAI was detected in 62 (40.5 %) angiographies and 82.3 % of these were bilateral. All angiographies with PAI showed a thrombus formation and aneurysm accompanied to a thrombus in only 4 angiographies. Main or lobar, segmental pulmonary arteries were involved in 19 (30 %) and 29 (46.8 %) angiographies respectively. Similar to our results, previous BD cohorts also reported that pulmonary involvement was usually bilateral and mostly segmental, lobar and main arteries were involved [3,5]. Isolated PAT was present in 58 (93.5 %) of angiographies with PAI in our study, which is higher than the previous series [3,5]. A recent comparative study from our center showed that PAT was more common than PAA not only in Turkish, but also in French patients [14]. The trend of describing almost all PAI in BD patients as PAA in previous papers has changed through years and in recent studies isolated PAA was less than one third of all PAI in BD patients [15,16]. This change may be explained by widened use of CTPAs and early detection of PAI.

More than half of patients with a pulmonary symptom had PAI and almost all patients with pulmonary symptoms together with constitutional symptoms had been diagnosed with PAI in our study. Fever was previously defined as the preceding symptom for pulmonary artery vasculitis [5,17]. Hemoptysis was also found as the most common (66–79 %) pulmonary symptom in BD patients with PAI, especially for PAA (91–100 %) [5,6]. However only 6 patients in our study presented with hemoptysis, and chest pain, dyspnea were more common pulmonary symptoms. Lower hemoptysis rate can be associated with fewer aneurysm presences in our study.

Seyahi et al. showed that patients with PAI had increased CRP and erythrocyte sedimentation rates [5]. Although patients with main pulmonary artery involvement had increased CRP level compared to other groups in our study, it did not reach statistical significance. In 59 patients, increased APRs were the only reason to perform a CTPA and a thrombus was found in almost one third of them. Our findings show that, increased APRs without pulmonary symptom may be an alarming symptom for PAI in BD if there is no other cause to explain.

In the present study, about one fourth of patients without a symptom or increased APR had bilateral segmental and sub-segmental thrombus (only one unilateral sub-segmental) in CTPAs. Most of these patients (8 out of 10) was under immunosuppressive (IS) treatments for other disease manifestations and subsegmental/segmental thrombus were detected more commonly in patients under IS treatments compared to patients without ISs. As ISs are the mainstay of vascular inflammation treatment in BD, our results suggest that ISs may prevent more severe PAI such as lobar involvement, leading only to asymptomatic subsegmental and segmental thrombus - as a limited form of PAI [18–20].

Among 17 patients with non-pulmonary arterial thrombosis who were screened for PAI, 7 (41 %) patients were diagnosed with PAI in CTPA. One out of seventeen (5.9 %) was diagnosed as having an aneurysm together with PAT while others had isolated PAT. Of these 7 patients, one patient with PAA together with PAT and 2 patients with isolated PAT did not have any symptom. Association of venous thrombus with pulmonary vasculitis (especially deep vein thromboses) was similarly reported by Tascılar et al. previously [2]. Therefore, screening pulmonary involvement for BD patients during another vascular event may show a larger extent of vascular disease and lead to better optimization of management.

CT angiographies have recently been more available (replacing regular X-rays) which may have increased the tendency for overuse. The European Society of Cardiology guidelines described the clinical relevance of ‘subsegmental emboli’ diagnosis with CTPA as ‘unknown’ with also decreased interobserver reliability for small arteries. A discordance of 10 % among experienced radiologists for angiographic findings were present in our study, mostly in subsegmental and segmental involvement. Clinical symptoms or increased acute phase reactants were also less present with subsegmental PAI (85.7 % with segmental PAI vs 61.5 % with sub-segmental PAI). Our results, therefore, suggest that additional diagnostic methods may be helpful in especially patients with no symptom and subsegmental thrombosis before a change in management decisions.

Retrospective data collection was the main limitation of our study. Also, lack of the assessment of thrombophilia factors in most patients is another limitation.

In conclusion, our results show that isolated pulmonary thrombosis is the main form of PAI, and the presence of aneurysms is a rare type of PAI in our BD cases. We also observed that PAI may be seen in about one fourth of especially male BD patients without symptoms and increased APR. In the presence of pulmonary symptoms with or without increased acute phase reactants, involvement of segmental or more proximal part of pulmonary artery is mostly detected by CTPA in BD patients. Asymptomatic subsegmental and segmental thrombus, which is a limited form of PAI, were also detected more frequently under IS treatments in our study. This result may suggest that IS treatment may

Table 2
Characteristics of patients with pulmonary involvement according to the involved arterial segment.

Segment of pulmonary involvement	Sex (male, %)	Increased acute phase reactants	Presence of a symptom	Median (25/75 %) CRP level	History of a vascular event	IS usage during angiography
No involvement	81, 89 %	50, 66.7 %	17,18.9 %	8 (3–28)	30, 33 %	45, 51.1 %
Subsegmental	11, 78.6 %	6, 42.9 %	2, 14.3 %	3.5 (3–19.5)	5, 35.7 %	12, 85.7 %
Segmental	24, 82.8 %	16, 64 %	16, 57.1 %	13 (3–30)	15, 51.7 %	14,56 %
Lobar	9, 69.2 %	7, 63.6 %	9, 75 %	10 (3–28)	5, 38.5 %	3,23.1 %
Main pulmonary artery	6, 100 %	3, 75 %	5, 100 %	41 (5.75–70.25)	4, 66.7 %	1, 16.7 %

limit the extension of PAI in BD.

Our results suggest that BD patients with pulmonary or constitutional symptoms should be screened by CTPA for PAI. However, further research is needed for screening of patients with asymptomatic course or only increased APRs with CTPA.

CRediT authorship contribution statement

Aysun Aksoy: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Derya Kocakaya:** Methodology, Software, Resources, Visualization. **Ozlem Demircioglu:** Software, Resources. **Nuri Cagatay Cimsit:** Software, Supervision. **Bedrettin Yildizeli:** Supervision, Validation. **Sait Karakurt:** Supervision, Validation. **Haner Direskeneli:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Fatma Alibaz-Oner:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement/Disclaimers/Conflict of interest

No specific funding was received from any bodies in the public, commercial, or not-for-profit sectors to carry out the work described in this article.

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