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Pulmonary vasculitis in Behçet's disease: Reference atlas computed tomography pulmonary angiography (CTPA) findings and risk assessment-management proposal

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Abstract. *Background and aim*: Pulmonary artery aneurysms (PAAs) are the most well-defined type of pulmonary vascular complication in Behçet's disease (BD). The aim of this study is to analyze which CT pulmonary angiography (CTPA) signs are associated with serious morbidity and mortality. *Methods*: The study included 42 BD patients with pulmonary vascular complications. All patients' medical records were reviewed retrospectively in terms of demographics, disease characteristics, laboratory investigations, pulmonary manifestations, arterial and/or venous thrombosis and CTPA vascular and parenchymal findings. *Results*: Deep venous thrombosis was observed in 31 (73.8%) patients, arterial thrombosis in 13 (31%), peripheral arterial aneurysms in 12 (28.5%), haemoptysis in 38 (90.5%), and fatal haemoptysis in 8 (19 %) patients. CTPA revealed: in situ thrombosis in 14(33.3%) patients, true stable PAAs in 13 (31), true unstable PAAs in 11 (26.2%), stable pulmonary artery pseudoaneurysms (PAPs) in 7 (16.7%), unstable PAPs in 17 (40.5%), perianeurysmal leaking in 26 (61.9%) and bronchial indentation in 19(45.2%). In regression analysis, fatal outcomes were associated with age in years (p=0.035), arterial thrombosis (p=0.025), peripheral arterial aneurysms (p=0.010), intracardiac thrombosis (p=0.026) and positively associated with haemoptysis severity (p<0.001). The severity of hemoptysis affects the likelihood of death over time (p=0.0057), whereas combined immunomodulator therapy reduces the risk of death over time (P= 0.0680). *Conclusion*: Peripheral arterial thrombosis and/or aneurysms, intracardiac thrombosis and haemoptysis severity are predictors of fatal outcomes in BD pulmonary vasculitis. PAPs with perianeurysmal alveolar haemorrhage and/or bronchial indentation are serious CTPA signs that require prompt

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identification and aggressive treatment. PAPs are a more serious aneurysmal pattern than true PAAs because they are a contained rupture of a PA branch in the context of pulmonary vasculitis.

Key words: Behçet's disease, pulmonary vasculitis, pulmonary artery pseudoaneurysms, true pulmonary artery aneurysms, vasculitis management

Introduction

Behçet's disease (BD) is a systemic disorder characterized by the triple-symptom complex: recurrent oral aphthous ulcers, genital ulcers, and uveitis. The disease was first described by Dr. Hulusi Behçet in 1937, coining the disease with the classical triad (1). BD is currently classified as a multi-system vasculitis with variable arterial and/or venous vasculo-occlusive manifestations exhibiting significant heterogeneity among patients regarding demographics, organ manifestations, frequency and severity of relapses, disease course, response to treatment, and prognosis. Because of this heterogeneity, it has been difficult to interpret and compare study results, standardize disease assessment, and develop management strategies in different disease domains (2). BD-related pulmonary vasculitis is one of the most serious disease complications, and pulmonary artery aneurysms (PAAs), associated with in-situ thrombosis, are the most well-defined type of pulmonary disease in BD, with significant morbidity and mortality (3).

The most common and prominent symptom is haemoptysis of varying degrees (up to 500 ml). In an early report, the rupture of pulmonary artery aneurysm (PAA) with erosion into a bronchus was proposed as explanation for the haemoptysis. (4). In a recent case report, a catastrophic unpredictable massive haemoptysis was the leading cause of death in a young male patient, after PAA ruptured into an adjacent bronchus, which was aided by anticoagulation therapy during the fatal event. (5).

On the other hand, the Hughes-Stovin syndrome (HSS) is a type of systemic vasculitis that closely resembles the vasculo-occlusive manifestations as seen in BD (6, 7). The syndrome was first described by Hughes and Stovin in 1959 (8). The authors described the clinical disease course of two male patients with undefined systemic illness, presenting with constitutional manifestations, recurrent deep venous thrombosis (DVT) despite anti-coagulation, and both patients died from unpredictable massive suffocative haemoptysis. The autopsy findings are quite compelling; the authors described widespread vasculo-occlusive disease e.g. inferior vena cava (IVC) thrombosis, intracardiac thrombosis, cerebral venous sinus thrombosis (CVST), and bronchial artery involvement, as well as a ruptured PAA into an adjacent bronchus, as the leading cause of death in their patients (8). The latter vascular manifestations have been reported sporadically in the literature in both BD (2) and HSS (6, 7), leading to the conclusion that HSS is an incomplete form of BD (8) and raising debates about whether HSS is an outcome of BD or a different clinical disease entity, or a specific expression of BD that lacks the classic triad complex that tends to dominate the early disease presentations of BD (9).

Computed tomography pulmonary angiography (CTPA) is considered the gold standard non-invasive tool for examining the pulmonary artery vascular bed in relation to intraluminal changes such as in-situ thrombosis as well as extraluminal changes such as leaking aneurysm and other parenchymal lesions as seen in both BD (3-5, 11-23) and HSS related pulmonary vasculitis (6, 7).

Recently the HSS international study group (HSSISG), created a reference atlas and CTPA guide, defining the wide spectrum of pulmonary vasculitis as observed in HSS. The atlas classifies HSS-related pulmonary vasculitis with aneurysm formation into the following categories: true PAA at different stages of development with in-situ thrombosis, bronchial artery aneurysm (BAA), pulmonary artery pseudoaneurysms (PAPs), and the corresponding unstable morphological and CTPA radiological patterns at impending risk of rupture (7). According to our observations, pulmonary vasculitis in BD and HSS are identical, and the same CTPA radiological definitions used to classify pulmonary aneurysms in HSS (7) are applicable in BD.

The main aim of the current study is to critically analyse retrospectively the most serious CTPA radiological signs that may be associated with serious morbidity or mortality in BD-related pulmonary vasculitis, and to investigate the relationships between fatal outcomes and other important clinical and CTPA radiological findings. Importantly, the

available literature in this domain will be thoroughly discussed and critically analyzed.

Patients and methods

A total of 42 BD patients with known pulmonary vascular complications, notably PAAs as shown by CTPA, were included and re-evaluated retrospectively. Included were only patients meeting the international Study Group for BD diagnostic criteria (24).The cases were recruited from various international university hospitals (Careggi University Hospital, Florence, Italy; Faculty of Medicine ,Cairo University, Cairo Egypt; Hospital Britanico de Buenos Aires, , Buenos Aires, Argentina; Faculty of Medicine, Assuit University, Assuit, Egypt; Faculty of Medicine, Mansoura University, Mansoura, Dakahlia, Egypt; Faculty of Medicine, Suez Canal University, Ismailia, Egypt; Fattouma Bourguiba University Hospital, University of Monastir, Monastir, Tunisia; Hedi Chaker Hospital, Sfax, Tunisia; North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences , Meghalaya, India).

A detailed history, demographics, disease characteristics, laboratory findings, medical lines of treatment and/or surgical and/or interventional procedures such as pulmonary artery coil embolization (PACE) were reviewed and recorded retrospectively from the patients' medical files for further statistical analysis. All patients (n=42) underwent initial CTPA studies following the onset of chest manifestations, most notably hemoptysis, and the initial CTPA findings were used to perform further statistics. Follow-up CTPA studies (n=20) were performed on patients who had recurrent bouts of hemoptysis, but the findings were not included. To reach a final consensus on which images to include, all CTPA studies from various academic affiliations were shared with all authors, and four experienced radiologists (Ragab.Y, Ibrahim.O, Abdelali.M, and Hassanein.S) reviewed the images to select the most relevant CTPA images covering various patterns of pulmonary vascular as well as any associated lung parenchymal lesions.

Statistical analysis

The data was coded and analysed using the Statistical Package for Social Sciences (SPSS) version 12.0 for Windows. Continuous data was described using the mean (SD), while categorical data was described using frequencies and percentages. The relationships between fatal outcomes due to massive haemoptysis as the dependent variable and other relevant independent variables were investigated using linear regression analysis. Cox regression for survival analysis (MedCalc® Statistical Software version 20.305) was used to investigate the effect of several covariables on the time it takes for a fatal outcome to occur. The latter assumes that the predictor variables' effects on survival are constant over time and additive on one scale. Additionally, five models were performed to identify association between fatal outcomes due to massive hemoptysis and different risk factors, the latter were identified as associated with outcome measurement, when P value was < 0.05.

Results

The retrospective, cross sectional study included a total of 42 BD patients; they were 39(92.9 %) male patients and 3(7.1%) female patients. The mean age (±SD) of the studied group of patients was 32.52(±7.23) years, the mean age at onset (±SD) was 29.12 (±7.42) years and the mean disease duration (±SD) was 52.52(±50.47) months. Other detailed disease characteristics, and various clinical manifestations, deep venous thrombosis (DVT), arterial thrombosis and/or arterial aneurysms formation and lines of treatment received are summarized in Table 1.

CTPA findings

All patients' source CTPA images were thoroughly reviewed, with special emphasis placed on the CTPA radiological categories I-VI [7] as listed below (Figure 1-8). Furthermore, volume rendering software was used to create a three-dimensional 3-D representation and maximum intensity projection (MIP) of data for illustration purposes (Figure 1 a-i).

Aneurysmal wall enhancement on post-contrast CTPA

Arterial mural wall enhancement is defined radiologically as an 'enhancing aneurysmal wall,' which is typically seen in the mediastinal window during sequential arterial and venous post-contrast phases (Figure 2, a, b, c, e).

True "stable" PAA

This is defined radiologically as a 'contrast-filled aneurysmal lesion of the affected PA branch with a

Table 1. Demographics, clinical manifestations, laboratory investigations, vasculocculsive arterial and venous complications, and treatment options among the studied group of patients.

Variables	BD patients (n=42) Mean ±SD and/or *n* (%)	Variables	BD patients (n=42) Mean ±SD and/or *n* (%)
Age (Years)	32.52±7.23	Peripheral arterial thrombosis	13(31)
Gender (M/F)	39 (92.9) / 3 (7.1)	Abdominal aorta thrombosis	1(2.4)
Age at onset (Years)	29.12±7.42	Peripheral arterial aneurysms	12(28.6)
Disease duration (Months)	52.52±50.47	Common femoral artery aneurysms	5(11.9)
Recurrent Aphthous ulcers	14(97.6)	External iliac artery aneurysms	3(7.1)
Recurrent genital ulcers	39(92.9)	Popliteal artery aneurysm	1(2.4)
Skin lesions	18(42.9)	Thoracic aortic aneurysm	2(4.8)
Anterior uveitis	27(64.3)	Celiac artery aneurysm	1(2.4)
Posterior uveitis	21(50)	Subrenal aortic aneurysm	1(2.4)
Vitritis	5(11.9)	CVST	1(2.4)
Retinal vasculitis	3(7.1)	Neuro-Behçet Behçet's	3(7.1)
Arthritis	5(11.9)	Gastrointestinal Behçet's	1(2.4)
Fever	30(71.4)	Intracardiac thrombosis	9(21.4)
Weight loss	6(14.3)	Right atrium	6(14.3)
Cough	37(88.1)	Right ventricle	1(2.4)
Dyspnea	38(90.5)	Left ventricle	1(2.4)
Chest pain	30(71.4)	Right atrium & Right ventricle	1(2.4)
Hemoptysis	38(90.5)	ESR 1st hour (mm/h)	58.095±23.279
Mild hemoptysis	16(38.1)	CRP (mg/dl)	14.67±12.86
Moderate hemoptysis	17(40.5)	Hemoglobin	10.48±1.457
Massive hemoptysis	5(11.9)	WBC	11.241±4.8254
Superficial thrombophlebitis	30(71.4)	Platelets	343.428±96.237
DVT	31(73.8)	Oral Colchicine	36(85.7)
Unilateral DVT	31(71.4)	IV pulse methylprednisolone	40(95.2)
Bilateral DVT	6(14.3)	Oral CS therapy	41(97.6)
Anterior tibial vein	19(45.2)	Oral AZA	30(71.4)
Posterior tibial vein	25(59.5)	Monthly IV pulse CP	32(76.2)
Great saphenous vein	7(16.7)	Anti-TNF inhibitors	2(4.8)
Femoral vein	15(35.7)	MTX	2(4.8)
Profunda femoris vein	8(19)	Anticoagulant	32(76.2)
IVC thrombosis	5(11.9)	Combined Immunosuppressive therapy	22(52.4)
SVC thrombosis	6(14.3)	Fatal outcome	8(19)

Abbreviations: BD: Behçet disease; DVT: deep vein thrombosis: IVC: inferior vena cava; SVC: superior vena cava; CVST: Cerebral venous sinus thrombosis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood cells; CS: corticosteroids; AZA: Azathioprine; CP: Cyclophosphamide; TNF: Tumor necrosis factor; MTX: Methotrexate.

well-defined aneurysmal wall and associated with intra-aneurysmal adherent in-situ thrombosis (filling defects) without any perianeurysmal parenchymal ground-glass opacification (GGO), implying that there is no "extra-luminal leaking process" (best visualized in the lung window) (Figure 3 a-f).

Unstable leaking true PAA ("acute phase")

Unstable PAA is defined as: 'aneurysm formation (contrast-filled) of the affected PA branch with loss of aneurysmal wall definition and perianeurysmal alveolar hemorrhage (ground-glass opacification

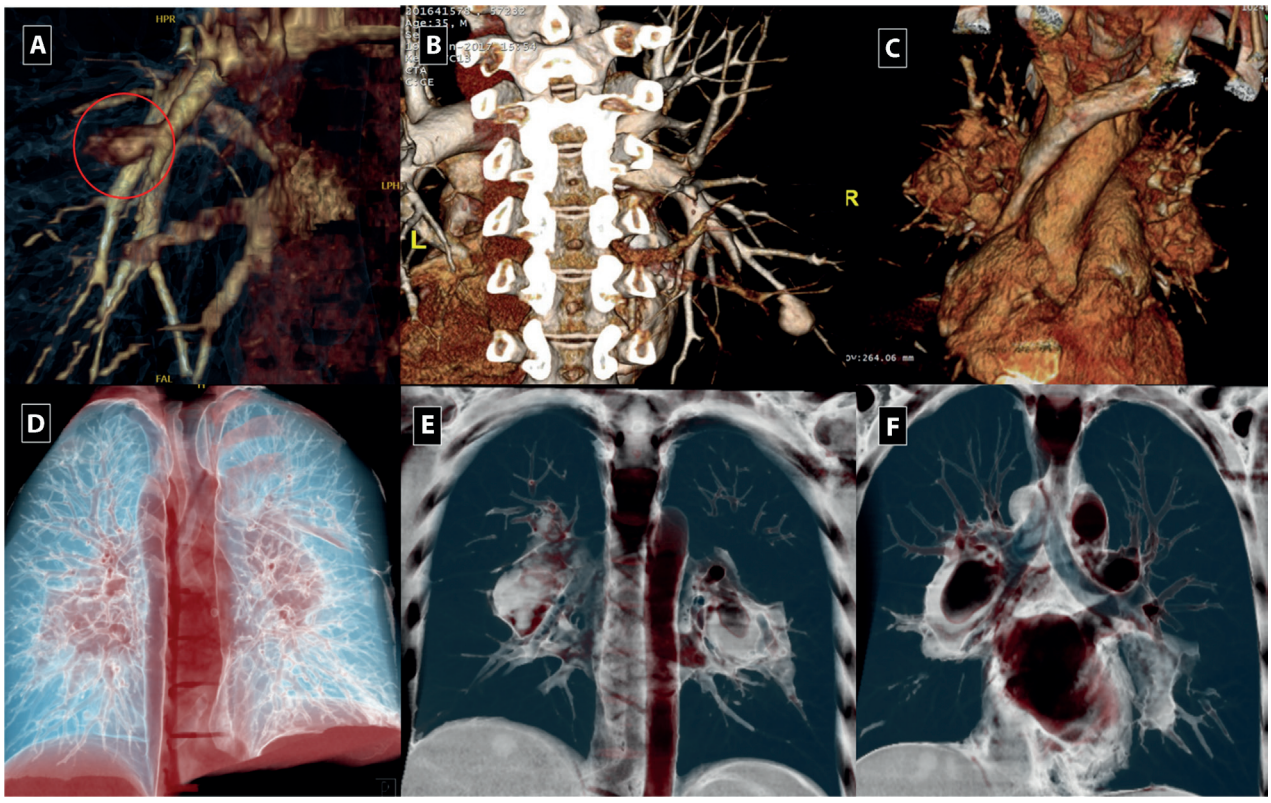

Figure 1. Examples of 3D, Maximum Intensity Projection (MIP) of pulmonary artery aneurysms (PAAs) in Behçet disease (BD); (A): Example of PAA, Coronal 3D CTPA showing a segmental PAA of the right lower lobe branch (red circle); (B): Coronal reformatted MIP CTPA image, illustrating a segmental left lower lobe PAA; (C): Extensive bilateral PAAs in 3D, MIP CTPA; (D): 3D CTPA showing extensive bilateral central pulmonary artery aneurysms (PAAs); (E&F): Bilateral central PAAs in coronal reformatted MIP CTPA.

and/or consolidation) with or without "air-bronchograms". Air-bronchograms refers to air-filled bronchi (dark) being made visible by the opacification of surrounding alveoli (grey/white). This finding is almost always caused by a pathologic airspace/alveolar process in the adjacent surrounding lung parenchyma in the context of BD pulmonary vasculitis, resulting from blood leaking through the inflamed mural wall into the adjacent lung parenchyma. The latter findings are best visualized in the lung window (Figure 4).

Pulmonary artery pseudoaneurysm (PAP) ("chronic phase")

A PAP is defined as "sharply demarcated contrast-filled aneurysmal lesions with a variably sized marginal hypodense perianeurysmal component ("marginal thrombosis") entangling a contrast-filled ectatic lumen." The absence of adjacent ground glass opacification or frank consolidation distinguishes the lesion from leaking unstable PAP. Within the hypodense component, air bronchograms (air-filled bronchi/bronchiole) can be seen (Figure 5).

Unstable PAP

This is defined radiologically as: Sharply demarcated contrast-filled aneurysmal lesions with a variably sized marginal hypodense perianeurysmal component (i.e. "marginal thrombosis") entangling the sharply demarcated contrast-filled ectatic lumen and adjacent GGO or frank consolidation due to active hemorrhage from the leaking ectatic lumen. Air bronchogram (air-filled bronchi/bronchiole) can be associated within the hypodense component (Figure 6).

Bronchial indentation by the aneurysm as well as air loculi within the extraluminal marginal thrombosis were also noted and presented (Figure 7).

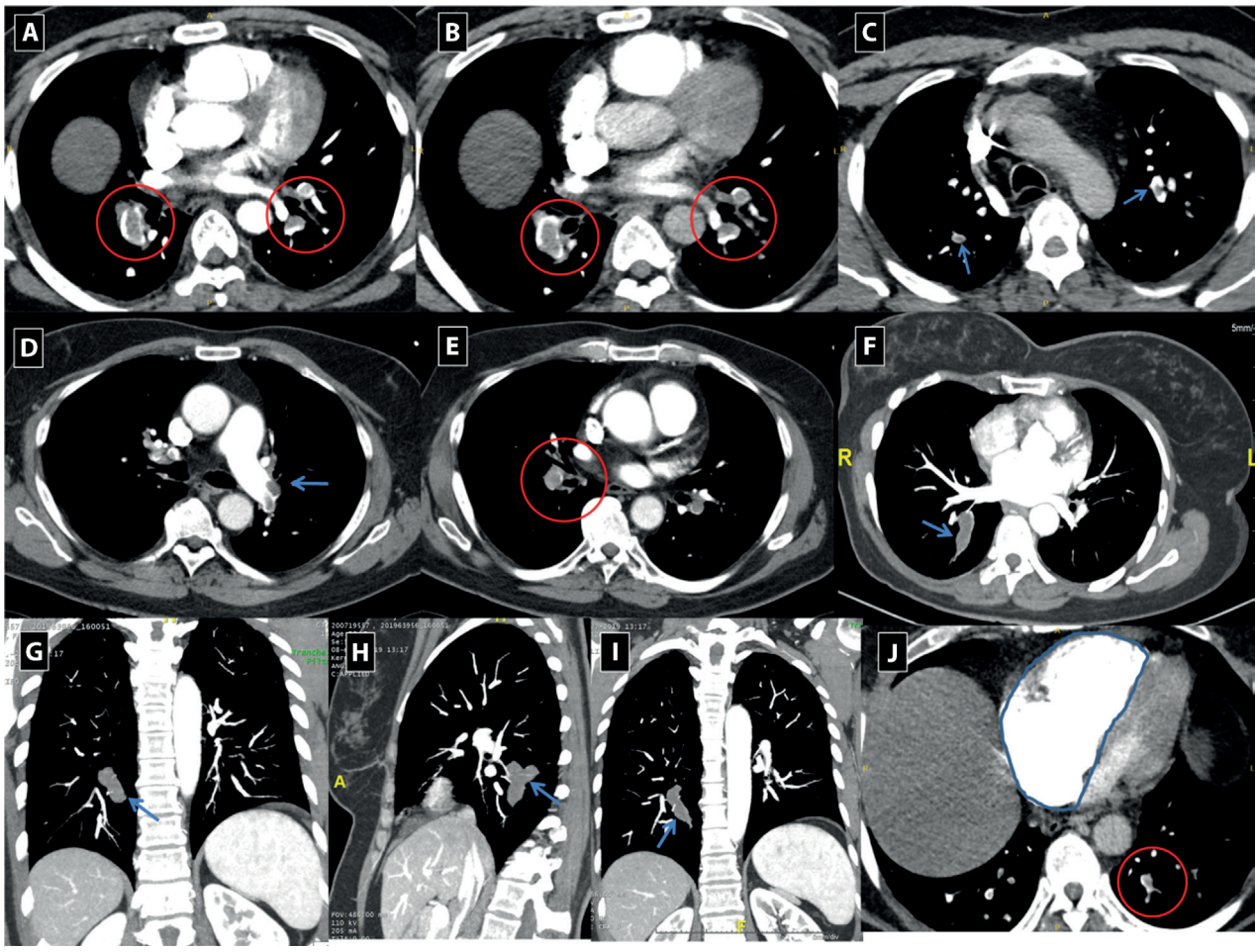

Figure 2. (A) and (B): Axial CTPA images of the same patient showing a central and bilateral lower lobar pulmonary in-situ thrombosis seen as filling defects with circumferential higher attenuation of surrounding arterial wall "arterial mural wall enhancement" (Red circles); (C): Axial CTPA in a different patient, demonstrating bilateral upper lobe segmental pulmonary in-situ thrombosis with circumferential higher attenuation (Blue arrows); (D): Axial CTPA, showing in-situ thrombosis of the left main pulmonary artery (Blue arrow); (E) and (F): Axial CTPA, demonstrating a right lower lobe pulmonary artery in-situ thrombosis in (E) and completely thrombosed true PAA in (F) (E~ RED CIRCLE & F~ BLUE ARROW); (G), (H) and (I): Coronal and sagittal reformatted CTPA images, demonstrating a true stable right lower lobe posterior segmental PAA with occlusive thrombosis; (J): Axial CTPA, demonstrating a small left lower lobe posterior segmental pulmonary artery aneurysm with an occlusive embolus (red circle)and evident subsequent right ventricular strain (blue line).

The radiological and morphological differences between the true PAA and the false "PAP" with colored effects for illustration purposes are depicted in Figure 8.

Right ventricular strain (RVS) with or without intracardiac thrombosis

RVS is defined by the CTPA as "interventricular septal flattening or paradoxical interventricular septal bowing towards the left ventricle caused by altered pulmonary hemodynamics in the context of pulmonary hypertension". Furthermore, RVS is distinguished by a right ventricle that is larger than the left ventricle. CTPA defines intracardiac thrombosis as a low attenuation, non-enhancing filling defect in the involved cardiac chamber (s) (Figure 2J).

Additional findings such as autoimmune pneumonitis, gastrointestinal BD and other peripheral vascular arterial lesions are depicted in (Figure 9).

Pulmonary vascular complications diagnosed with CTPA

In-situ thrombosis was observed in 14(33.3%) patients, true stable PAAs in 13(31%), true unstable

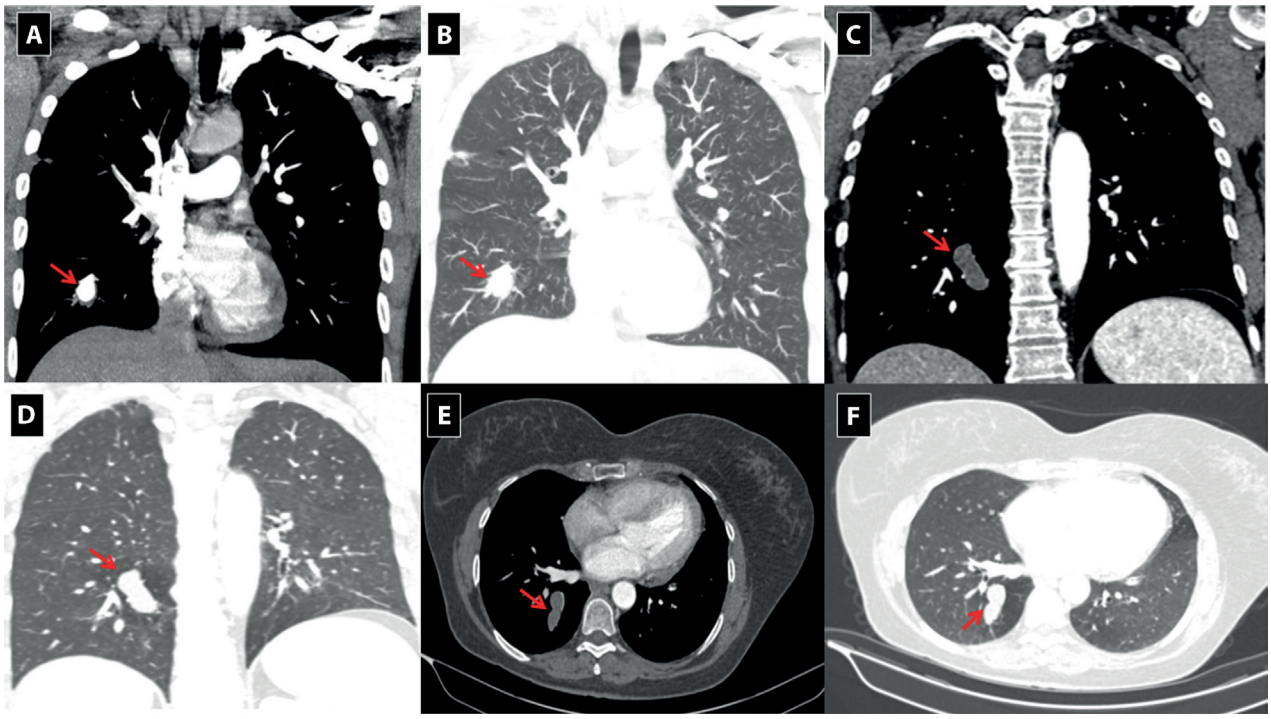

Figure 3. Examples of true stable PAAs: (A) and (B): Coronal reformatted CTPA images for the same patient and same anatomical level in mediastinal and lung windows, demonstrating a stable right lower lobe segmental true PAA, with no peri-aneurysmal leaking process noted; (C) and (D): Coronal reformatted CTPA (E) and (F): axial images of the same patient, demonstrating a true, stable right lower posterior segment PAA with an occlusive thrombus (Red arrows).

PAAs in 11(26.2%), stable PAPs in 7(16.7%) and unstable PAPs in 17(40.5%) patients and bilateral vascular involvement in 38(90.5%). Other detailed pulmonary vascular and parenchymal lesions are detailed in Table 2.

In a logistic regression analysis, the relationships between fatal outcomes due to massive suffocative haemoptysis as a dependent variable and other important independent variables were estimated. Among the demographic features, only age in years was significantly associated with fatal outcomes (P=0.035). Fatal outcomes were examined against variable describing vascular complications, pulmonary symptoms, CTPA findings and lines of treatment using separate models. We found that fatal outcomes were positively associated with peripheral arterial thrombosis (P=0.025), peripheral arterial aneurysms (P=0.010) and intracardiac thrombosis (P=0.026). In another module fatal outcomes were highly and positively associated with haemoptysis severity (P<0.001), while no significant associations were found between fatal outcomes and other CTPA findings. Regarding different lines of immunosuppressive lines of treatment, a significant negative association was found between fatal outcomes and the use of oral corticosteroids as one of the most important lines for induction and maintenance of remission (p=0.035); other detailed regression analysis results are presented in Table 3.

The effect of time on survival rate was investigated by using time series analysis Cox regression. The duration of follow-up was in months as the survival time and the fatal outcome as the endpoint. DVT, major venous thrombotic events, peripheral arterial thrombosis, hemoptysis severity (quantitative), and combined immunomodulators therapy were included in the analysis as important covariables. examining the effect of the time until the event occurs (fatal outcome), we found no difference between groups, 1: Fatal outcome and 0: assumed Survived. The severity of hemoptysis has a significant effect on death over time (p=0.0057), indicating that hemoptysis severity increases the likelihood of death over time (Exp (b) = 1.0056). Furthermore, the effect of combined immunomodulators therapy was found to have borderline significance (P=0.0680), indicating

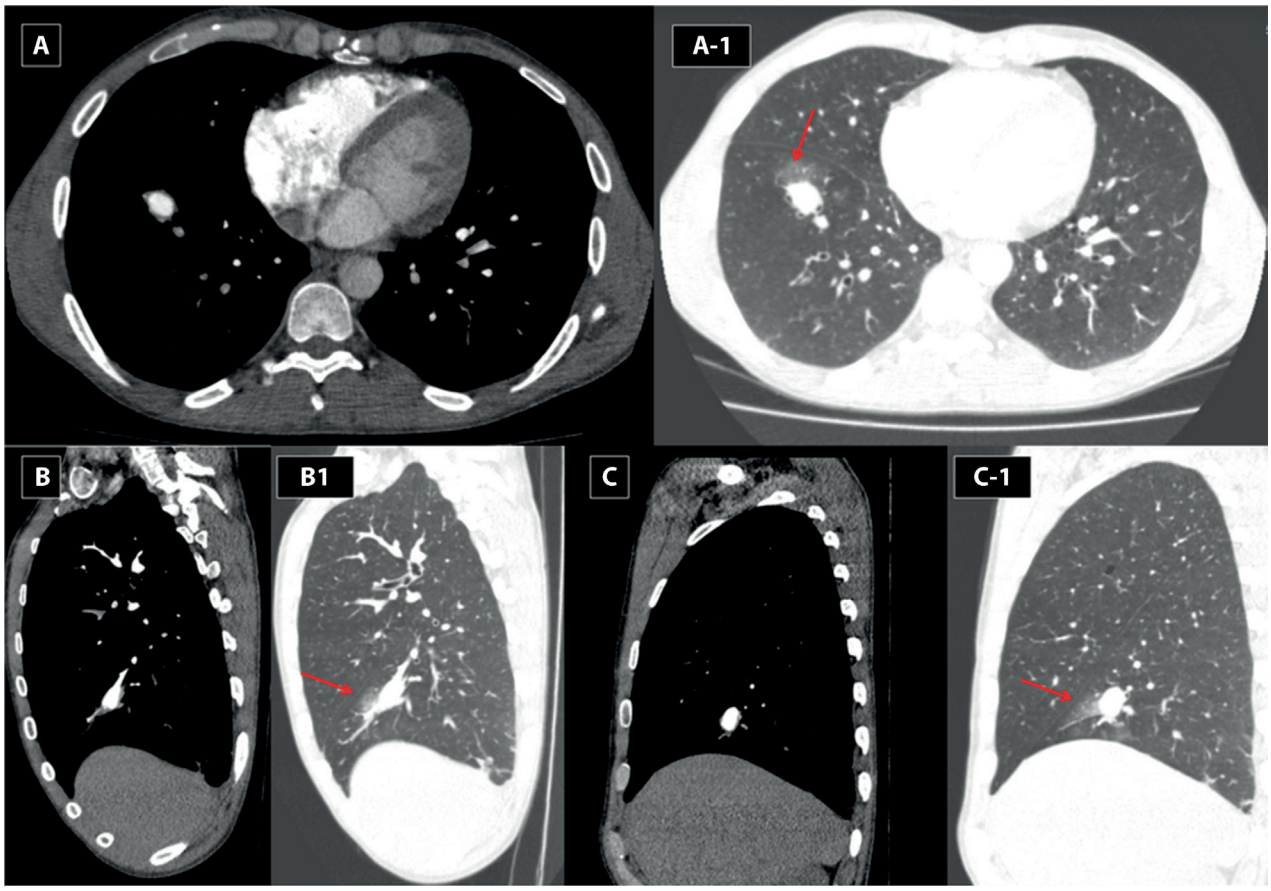

Figure 4. Examples for perianeurysmal leaking from unstable true PAA: The top images (A) and (A1) are axial CTPA images in mediastinal and lung windows. The bottom images (B) and (B1) + (C) and (C1) are sequential sagittal images for the same patient in mediastinal and lung windows. All images demonstrate a right lower lobe anterior segment leaking true PAAs with perianeurysmal air-space veiling and ground-glass opacities.

that starting combined immunomodulators therapy resulted in a lower risk of death over time (Exp (b) = 0.0193). While other covariables had no effect on mortality over time; more details are presented in (Table.4).

Discussion

In a group of BD patients with known pulmonary vascular and parenchymal lesions, we looked at the CTPA findings, specifically at PAAs, known to be associated with serious morbidity and mortality. One of the most important CTPA signs explored in the current study is arterial wall enhancement (AWE), which was observed, in 9(21.4%) of the BD patients. We had described this sign early in HSS related pulmonary vasculitis. (6, 7, 25). We believe that AWE could be the earliest CTPA sign reflecting true mural wall inflammation caused by an underlying vasculitic process in BD. The latter causes contrast uptake with the typical CTPA sign of circumferential enhancement of the aneurysmal wall, in sequential arterial and venous post-contrast phases (Figure 2). Such pulmonary artery (PA) mural wall inflammation will eventually activate the coagulation cascade, resulting in the formation of thrombus that is adherent to the inflamed mural wall. Given that, "in-situ thrombosis "should be the official radiological term to use in BD and HSS-related pulmonary vasculitis (6, 7).

The other most significant CTPA findings in this study in BD patients is the identification of two distinct CTPA radiological patterns of pulmonary aneurysms, one for true PAAs and the other for PAPs type of lesion, as well as the corresponding unstable patterns. The latter findings were typical and identical to those seen in HSS pulmonary

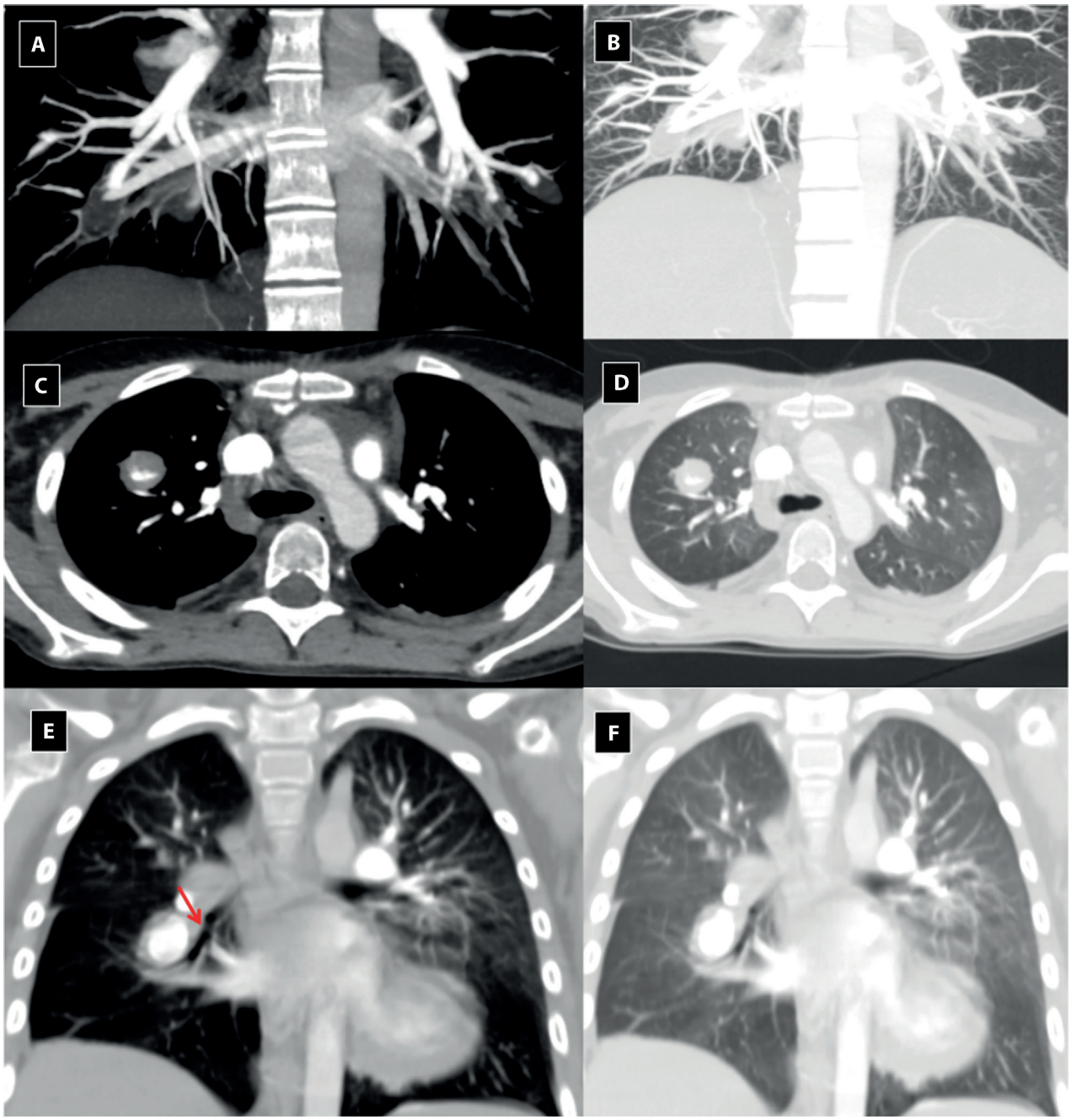

Figure 5. Examples of stable PAPs: (A) and (B) Coronal reformatted magnified images at the basal lung zones in mediastinal and lung windows, demonstrating bilateral lower lobe segmental stable pulmonary artery pseudoaneurysms (PAPs) without leakage; (C) and (D): Same level axial images CTPA images in mediastinal and lung windows showing right upper lobe segmental pulmonary artery pseudoaneurysms without leakage; (E) and (F): Coronal reformatted CTPA in mediastinal and lung windows, demonstrating right lower lobe PAP indenting the lower lobe bronchus (Red arrow), with no peri-aneurysmal leakage demonstrated.

vasculitis (6, 7). The application of such new terminology and precise radiological definitions to pulmonary aneurysms in both BD and HSS will change the way we assess the degree, severity and the extent of pulmonary vasculitis in both domains; it also will change the risk-assessment comprehensive approach for optimum management based on proper CTPA assessment of each individualized lesion(s). Such

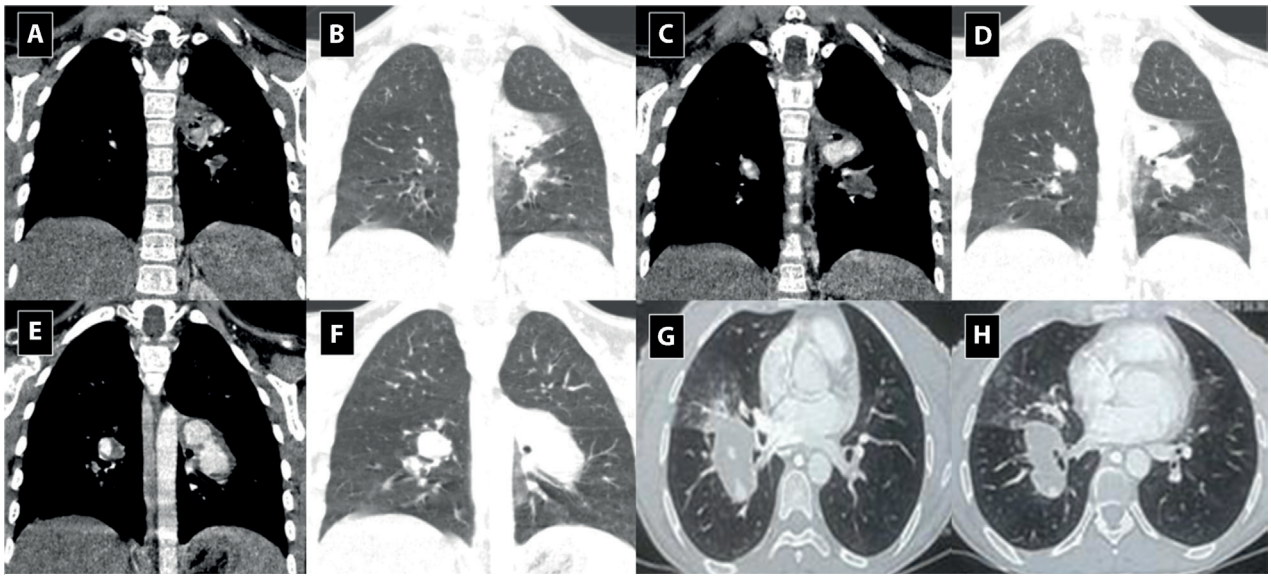

Figure 6. Examples of unstable pulmonary artery pseudoaneurysms (PAPs) lesions with peri-aneurysmal leakage; (A) and (B): Coronal reformatted CTPA images at the same anatomical level for the same patient in mediastinal and lung windows, demonstrating central left pulmonary artery pseudoaneurysm (PAP) with peri-aneurysmal ground glass veiling, consistent with active leaking process; (C), (D), (E), (F): Sequential coronal reformatted CTPA images, in mediastinal and lung windows, showing leaking bilateral central PAPs; (G) and (H): Axial CTPA images in mediastinal and lung windows, showing a large right PAP with leaking process demonstrated as ground glass opacity in the right middle lung lobe.

concept will enable to select which patients are at high risk of major bleeding, as previously stated in the 2018 update of the EULAR recommendations for the management of BD in relation to PAAs (26).

On the histopathological level, PAAs have perivascular infiltrates around the vasa vasorum, significant intimal thickening with degenerative changes in the elastic lamina, thrombotic occlusion with recanalization, and fresh thrombus which is currently known as "in-situ thrombosis" in the context of BD or HSS related pulmonary vasculitis (6, 7, 27). In a previous report (16), a patient with BD underwent right lower lobectomy after a ruptured PAA, and the histopathological examination revealed intimal thickening and destruction of elastic fibers in the media. The aneurysm wall was heavily infiltrated by polymorphonuclear and mononuclear cells, and adherent thrombus had penetrated into the adjacent bronchus. The report provides clues to many important facts: first the nature of the underlying vasculitic process, second the thrombus being adherent to the mural wall because it evolved "in-situ", and third, and most importantly, the extraluminal extension of the thrombus that eventually invaded the adjacent bronchus, causing massive hemoptysis and necessitating surgical intervention as a life-saving line of treatment. In a similar report (28), a patient with BD presented with massive fatal hemoptysis, and autopsy revealed a necrotizing vasculitis involving pulmonary arteries, muscular arteries, and bronchial erosions leading to the formation of a large "arterio-bronchial fistula", which explained the cause of death.

Given that, persistent mural wall inflammation of the pulmonary arterial vascular bed can lead to other serious complications seen in BD- especially if not recognized early and thus eventually inadequately treated. In addition to in-situ thrombosis, as the first event, persistently inflamed PA branches will eventually yield despite low pressure pulmonary circulation, leading to focal dilatation involving all layers that can affect the main PA and/or any of its peripheral branches, which appear as variable sized knobs along the exterior wall upon volume rendering 3D reconstruction (Figure1). All of these sequential events will result in the formation of "true stable PAAs," which are defined by CTPA as aneurysmal lesion (contrast filled), with a well-defined aneurysmal wall and associated with adherent intra-aneurysmal

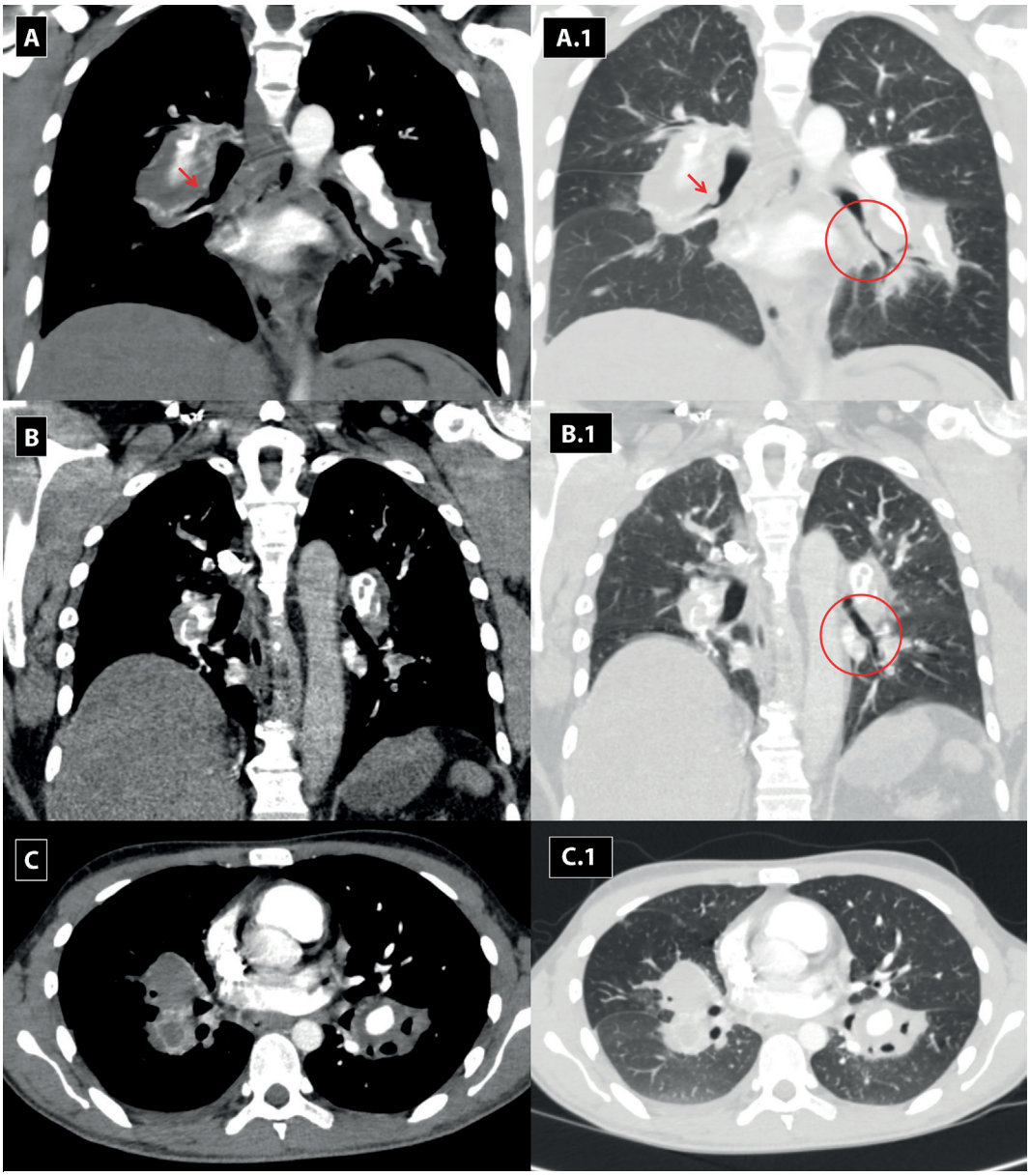

Figure 7. Examples of bronchial indentation by PAPs: (A-A1), (B-B1) are sequential coronal reformatted CTPA in mediastinal and lung windows with massive bilateral lower lobar PAPs and gross indentation of the adjacent bronchioles (Red arrow in image (A-A1) and red circles in images (A1-B1); (C- C1): axial CTPA images in mediastinal and lung windows with large bilateral lower lobar PAPs. There are few air-filled cavities within the PAPs bilaterally, more obviously demonstrated in the left as two air-filled cavities seen at the left lower lung lobe within the posterior and lateral aspects of the PAP indicating bronchial communication with the PAP.

"in-situ thrombosis," which can be seen as intra-luminal filling defects (Figure 2 A-E), or completely thrombosed true PAA (Figure 2 F-I).

With persistent arterial vascular bed inflammation, a "true stable PAA" may progress over time and become disrupted, resulting in the formation of an unstable yet true PAA with loss of aneurysmal wall definition and perianeurysmal GGO, indicating an extra-luminal acute leaking process (Figure 4). At this stage, the patient is expected to have pulmonary manifestations such as dyspnoea, cough, and haemoptysis, the severity of which will depend on the size

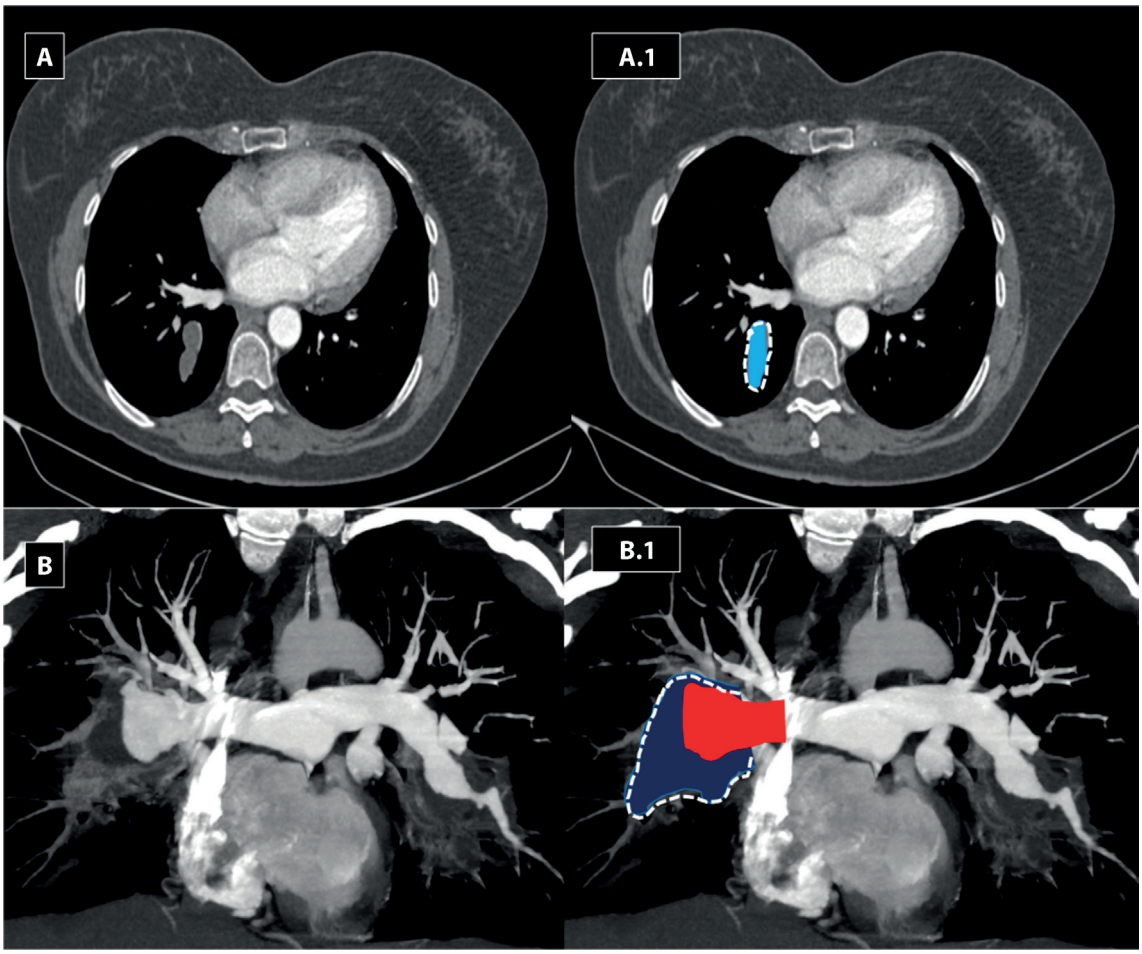

Figure 8. True stable PAA versus unstable PAP: (A and A1): Axial CTPA images demonstrating a true right lower lobe PAA with large occlusive thrombus. The thrombus in a true PAA is illustrated in "blue colour" and the white dotted line represents the wall of the true PAA; (B and B1): Coronal reformatted CTPA images, demonstrating a leaking central pulmonary artery pseudoaneurysm with rupture and a contained pei-aneurysmal leaking. "The red colour" represents the well-delineated contrast filled right main pulmonary artery lumen without intra-luminal filling defect. "The blue colour" represents the extra-luminal hypodense component due to a contained rupture typically seen in PAPs. "The dotted white line" represents the false wall of PAP lesion.

of the perianeurysmal parenchymal bleeding. If the leaking process is mild and occurs toward the lung parenchyma, the patient will be fortunate; however, if extensive perianeurysmal parenchymal bleeding occurs as a result of a ruptured aneurysm, massive alveolar hemorrhage may occur, potentially leading to a fatal disease course, especially if the patient is on anti-coagulation therapy at the time of the event. An autopsy finding in a young female patient after aneurysm rupture and massive fatal haemoptysis revealed diffuse alveolar hemorrhage in a previous report (19). Another potentially fatal scenario would be if the PAA ruptured into an adjacent bronchus, resulting in the formation of an "arterio-bronchial fistula" and severe, massive haemoptysis as previously reported (28).

In our study we identified by CTPA in addition to true PAAs, also stable PAPs in 7(16.7%) patients and unstable PAPs in another 17(40.5%) patients, which are considered by far the most ominous pattern of aneurysms, with quite unpredictable behavior. In our study, stable PAPs were defined as "sharply demarcated contrast-filled ectatic lumen with a variably sized hypodense perianeurysmal component representing marginal thrombosis (organizing blood clot) without intra-luminal filling defects" (Figure5). This

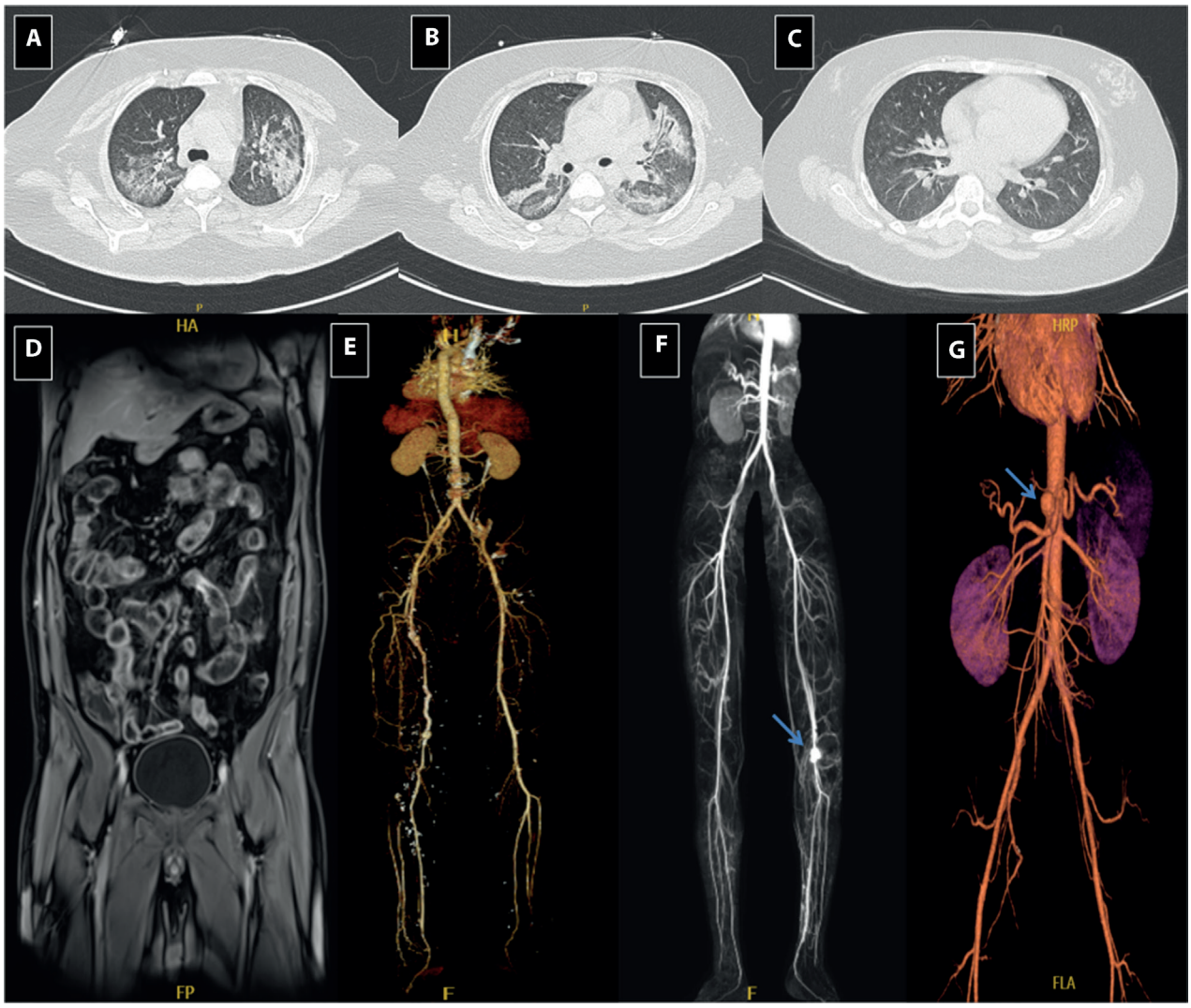

Figure 9. Miscellaneous findings: (A), (B) and (C): Axial lung window CT sequential images of the same patient, showing bilateral patchy autoimmune pneumonitis of different ages and (C): showing radiological improvement after initiation of immunosuppressive treatment; (D): Coronal reformatted CE CT of the abdomen and pelvis, showing a small intestinal BD enteritis; (E): 3D, MIP CTA of the abdominal aorta and lower limb arteries, demonstrating a beaded appearance of the LL arteries secondary to peripheral arterial vasculitis. (F): 3D, MIP CTA of the abdominal aorta and lower limb arteries, demonstrating a left popliteal artery aneurysm (Blue arrow); (G): 3D, MIP CTA of the abdominal aorta and lower limb arteries, demonstrating a celiac artery aneurysm (Blue arrow).

type of lesion is not associated with adjacent GGO or frank consolidation, distinguishing it from unstable PAPs (Figure 6). Most importantly, air bronchogram, which is air-filled bronchi/bronchioles, can be associated with the extra-luminal hypodense component (Figure 7). Such an unmistakable CTPA pattern for PAPs could only be explained by a leaking process through the inflamed aneurysmal wall, where the leaked blood organizes and forms a clot that surrounds the ectatic lumen and slowly expands in the adjacent lung parenchyma, acquiring a false wall and giving that distinctive unmistakable CTPA pattern of a hypodense component encasing a well delineated contrast filled lumen, the latter represents a contained lumen rupture. (Figure 8B).

Surprisingly, PAPs lesions in BD were mentioned once in the literature by Cengiz Seyhan et al (23); the authors presented the CTPA description of two PAPs originating from the upper and lower branches of the left PA, their central zones filled with contrast material, and the periphery of the lower lesion was less opaque, matching with the hypodense

Table 2. Radiographic and CTPA findings among the studied group of patients.

Variables	BD patients (n=42) *n* (%)
Positive X-ray findings	30(71.4)
Pulmonary vascular parenchymal lesions (CTPA findings)	
Arterial wall enhancement	9(21.4)
In-situ thrombosis	26(61.9)
True stable PAAs	13(31)
True unstable PAAs	11(26.2)
Stable PAPs	7(16.7)
Unstable PAPs	17(40.5)
Main pulmonary artery aneurysm	19(45.2)
Lobar PAAs	30(71.4)
Segmental PAAs	31(73.8)
Bilateral PAAs	38(90.5)
Perianeurysmal alveolar haemorrhage	26(61.9)
Bronchial indentation	19(45.2)
Autoimmune pneumonitis	6(14.3)
Pleural effusion	13(31)
Pulmonary infarction	12(28.6)
Surgical lobectomy or segmentectomy	1(2.4)
PACE	1(2.4)

Abbreviations: BD: Behçet disease; CTPA: CT pulmonary angiography; PAAs: Pulmonary artery aneurysms; PAPs: Pulmonary artery pseudoaneurysms; PACE: Pulmonary artery coil embolization.

component as we early explained, which is totally extraluminal and encasing the contrast filled lumen as seen by CTPA in their report. It is worth noting that the typical CTPA radiological pattern of PAPs lesions described in the radiology literature (29, 30) corresponds with the current study's CTPA findings (Figure 5-7) as well as previous findings in HSS (6, 7).

PAPs can form due to a variety of causes, including idiopathic, post-traumatic injury to a pulmonary artery (e.g. stab wound to the chest, placement of PA Cather and lobectomy), infection, primary or metastatic lung neoplasm, pulmonary hypertension, BD and HSS pulmonary vasculitis (6,7,29). However, in the current study, we explained the CTPA signs of PAPs in the context of pulmonary vasculitis in BD, with the proposed mechanism being contained rupture leading to extravasations of blood forming an organizing clot that entangles the ecstatic lumen and extravasated blood is held back by compressed pulmonary tissue. Importantly, the extraluminal marginal thrombosis can become unstable at any time, especially if anticoagulation therapy is used. Furthermore, with air bronchogram (air-filled bronchus/bronchiole) in the vicinity of the marginal thrombosis may lead to massive life-threatening hemoptysis which is unpredictable and can occur at any point during this stage. More seriously, in aggressive cases, bronchial indentation (Figure 7) and/or bronchial erosions may be seen, and the appearance of air loculi within the hypodense component of PAPs lesions is considered a very serious sign. The latter represents trapped air and indicates direct communication with a neighboring bronchus and/or bronchiole (Figure7C1). This trapped air within the hypodense component was linked to fatal hemoptysis in one of our patients with unstable PAPs, lending support to the idea that direct communication with neighboring bronchus or bronchiole is the underlying cause of this entrapped air as seen in the lung window. It should be noted that this trapped air within the hypodense component has been appeared numerous times in previous case reports, with no comprehensive interpretation of its gravity (5, 11, 13, 17, 23).

Generally, PAPs have been found to have a strong preference for peripheral PA branches, and a plethora of PAPs can be found specifically in endocarditis, and pulmonary metastasis. Most importantly, PAPs can be fatal, but they are frequently missed clinically and underreported by radiologists. According to the radiology literature, the most precise mechanism for PAPs is a contained rupture of a PA branch, and the extravasated blood is contained by compressed extravascular pulmonary tissue forming a marginal clot around the lumen, which forms the false wall of the aneurysm (29). In the context of pulmonary vasculitis in BD, CTPA PAPs pattern appeared frequently in BD reports after a thorough review of the available literature (3-5, 13, 12, 16, 18, 20, 23). However; they were never explained or radiologically identified and addressed as PAPs, instead being referred to as pulmonary aneurysms.

Reviewing the evidence from previous reports in this domain would greatly improve our practice, and involving the radiologist in the assessment is an essential part of developing a precise comprehensive approach to selecting the best medical, interventional, or surgical therapeutic decisions in this domain,

Table 3. Logistic regression analysis modules for estimating the relationships between fatal outcome and demographics, vascular manifestations, CTPA findings, and treatment lines among the patients studied.

Model 1 **Fatal outcome versus demographic**	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	
	B	**Std. Error**	**Beta**		**P-value**
(Constant) Fatal outcomes	0.894	0.359	-	2.489	0.017
Age (years)	-0.064	0.029	-1.165	-2.194	0.035*
Gender	-0.160	0.236	-0.105	-0.679	0.502
Disease duration (months)	0.004	0.003	0.535	1.567	0.126
Age at onset (years)	0.046	0.024	0.852	1.878	0.068
Model 2 **Fatal outcome versus vascular complications**	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	
	B	**Std. Error**	**Beta**		**P-value**
(Constant) Fatal outcomes	0.120	0.151	-	0.798	0.430
DVT	-0.113	0.150	-0.127	-0.753	0.457
Thrombophlebitis	0.161	0.138	0.185	1.164	0.253
IVC thrombosis	0.050	0.210	0.041	0.237	0.814
SVC thrombosis	-0.131	0.183	-0.117	-0.718	0.478
Peripheral arterial thrombosis	0.600	0.256	0.706	2.344	0.025*
Peripheral arterial aneurysms	-0.712	0.261	-0.819	-2.730	0.010*
Intracardiac thrombosis	0.324	0.139	0.339	2.332	0.026*
Model 3 **Fatal outcome versus pulmonary symptoms**	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	
	B	**Std. Error**	**Beta**		**P-value**
(Constant)	-0.078	0.186	-	-0.417	0.679
Chest pain	-0.009	0.109	-0.010	-0.081	0.936
Dyspnea	-0.178	0.183	-0.133	-0.973	0.337
Cough	-0.133	0.127	-0.147	-1.043	0.304
Hemoptysis severity	0.363	0.073	0.761	4.983	<0.001**
Model 4 **Fatal outcome versus CTPA findings**	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	
	B	**Std. Error**	**Beta**		**P-value**
(Constant) Fatal outcomes	-0.126	0.143	-	-0.879	0.385
Unstable true PAAs	0.315	0.309	0.352	1.020	0.315
Unstable PAPs	0.107	0.355	0.134	0.303	0.764
Perianeurysmal alveolar hemorrhage	-0.195	0.288	-0.241	-0.675	0.504
Bronchial indentation	0.031	0.223	0.040	0.140	0.889
Size of the largest aneurysm in millimeters	0.011	0.006	0.392	1.884	0.068
Model 5 **Fatal outcome versus lines of treatment**	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	
	B	**Std. Error**	**Beta**		**P-value**
(Constant) Fatal outcomes	1.173	0.416	-	2.823	0.008
Oral CS	-0.963	0.440	-0.374	-2.187	0.035*
Azathioprine	0.016	0.146	0.019	0.110	0.913
Pulse Cyclophosphamide	0.112	0.157	0.121	0.711	0.482

Table 3 (*Continued*)

Model 5 Fatal outcome versus lines of treatment	Unstandardized Coefficients		Standardized Coefficients	t	P-value
	B	Std. Error	Beta		
Anti-TNF	-0.157	0.288	-0.085	-0.545	0.589
Anti-coagulation therapy	-0.173	0.144	-0.188	-1.202	0.237

Abbreviations: BD: Behçet disease; DVT: deep vein thrombosis: IVC: inferior vena cava; SVC: superior vena cava; CVST: CS: corticosteroids; AZA: Azathioprine; CP: Cyclophosphamide; TNF: Tumor necrosis factor; CTPA: CT pulmonary angiography; PAAs: Pulmonary artery aneurysms; PAPs: Pulmonary artery pseudoaneurysms.

Table 4. Summary of Cox proportional-hazards regression survival analysis.

Survival time			Duration of follow-up in months
End point			Fatal outcome
Cases summary			
Number of events a			8(19.048)
Number censored b			34(80.952)
Total number of cases			42(100)
Overall Model Fit			
Null model -2 Log Likelihood			50.141
Full model -2 Log Likelihood			28.485
Chi-squared			21.656
DF			7
Significance level			P = 0.0029
Coefficients and Standard Errors			
Covariate	**P**	**EXP(b)**	**95% CI of Exp(b)**
DVT	0.6199	0.5742	0.0641 to 5.1433
Hemoptysis severity	**0.0057**	1.0056	1.0016 to 1.0097
Combined immunomodulators	**0.0680**	0.0193	0.0003 to 1.3398
Peripheral arterial thrombosis	0.7763	1.4495	0.1120 to 18.7645
Cardiac thrombosis	0.6052	1.6564	0.2444 to 11.2261
IVC thrombosis	0.2464	19.7251	0.1274 to 3053.5256
SVC thrombosis	0.2701	5.6380	0.2608 to 121.8781

Abbreviations: DVT: deep vein thrombosis; IVC: Inferior vena cava; SVC: Superior vena cava.

ensuring favorable outcomes. Furthermore, from a management standpoint, discussing various case reports with successful outcomes of management of ruptured PAAs in BD is critical, as it provides overall cumulative experience for definitive management of BD patients with pulmonary vasculitis, particularly those presenting with life-threatening hemoptysis.

From a therapeutic standpoint, medical treatment with immunosuppressive agents remains the mainstay line of treatment for various patterns of PAAs in BD, with favorable outcomes as described in various reports (3, 12, 15, 18, 31, 32) and also contributed to a successful post-operative outcome following an emergency surgical intervention for life-threatening hemoptysis in order to induce and maintain remission to prevent further PAAs formation (16). In the current study, COX regression analysis was used to simultaneously evaluate the effect of several factors on survival, and it was found that the severity of hemoptysis has a significant effect on death over time (p=0.0057), indicating that hemoptysis severity increases the likelihood of death over time (Exp (b) = 1.0056).

In a previous report, Kage et al. (18) used immunosuppressive therapy to treat what we believe were unstable PAPs lesions in a 42-year-old man

with BD. The patient developed massive hemoptysis five months after beginning anticoagulation for DVT and CTPA revealed GGO predominantly located in the right middle lobe, findings that were all suggestive of "perianeurysmal alveolar hemorrhage". Apart from supportive measures and discontinuation of anticoagulation, intravenous methylprednisolone (1g/day) was started for three consecutive days, followed by oral prednisone 50 mg/day, and intravenous cyclophosphamide (750 mg) was also administered every 3 weeks for a total of six cycles, followed by oral azathioprine as maintenance therapy. The authors reported that hemoptysis resolved within two weeks of initiating the aforementioned lines of treatment, with no need for PACE or surgical intervention (18).

First and foremost, the lessons from this perfectly presented case report (18) are critical: PAPs lesions are the most serious type of pulmonary lesions, presenting initially with severe massive hemoptysis. Second, adequate immunomodulation treatment lines may take a few weeks to achieve their desired effects of inducing pulmonary disease remission and may take a few months to achieve a reasonable and safe disease remission. Third, the follow-up CTPA revealed a reduction in the size of the hypodense component encasing the contrast-filled ectatic lumen in one of the PAP lesions, indicating tight control of the active vasculitic process of the inflamed aneurysmal wall with no active extra-luminal leaking episodes through it after five months of treatment. Agha et al. (12) reported a similar case in which an 18-year-old male patient with BD presented with life-threatening massive hemoptysis and initially CTPA revealed typical bilateral sizable PAPs lesions on both sides. After nearly a year of oral corticosteroids and azathioprine therapy, the false aneurysms on both sides had completely resolved in a follow-up CTPA study after one year of immunosuppressive therapy. In another report, Yadav et al (32) demonstrated complete resolution of what we believe to be PAPs lesions after immunosuppressive therapy, with a decrease in the size of both the ectatic lumen as well as the extra-luminal hypodense component, indicating tight control of the vasculitic process. Nonetheless, anti-TNF inhibitors demonstrated comparable radiological improvements as well as very promising therapeutic efficacy in inducing and maintaining pulmonary vasculitis disease remission, as evidenced by improved symptoms and significant reductions in the size of PAAs (33-38). In our study, we observed that combined immunomodulator therapy has borderline significance (P= 0.0680) in terms of reducing the risk of death over time (Exp (b) = 0.0193).

The HSSISG task force was the first to identify the specific CTPA radiological signs associated with PAPs lesions in HSS in the context of pulmonary vasculitis. (6, 7). Kirk and Seal (39) reported the histopathological examination of a ruptured false aneurysm, now known as "PAP" in relation to HSS. There was a segmental disruption of the elastica of the PA at its origin. The clot was mostly extra-luminal, with a large portion of its wall formed by an expanded "false wall" of the adjacent bronchus. A thin layer of respiratory epithelium separated the organizing thrombus from the bronchial lumen, and squamous metaplasia had occurred in places. The edge of the false aneurysm was encroaching on a bronchial lumen and a branch of the PA showed disruption of the tunica elastica and separated from the bronchial lumen by a thin layer of respiratory epithelium, and squamous metaplasia had occurred in places. Such a thorough histopathological examination provided a wealth of information, and the correlation between histopathological findings and CTPA symptoms is critical. The extra-luminal clot as identified by Kirk and Seal (39) corresponds to extra-luminal marginal thrombosis (hypodense component) that encase the ectatic lumen as seen by CTPA in PAPs, which we believe is identical in BD and HSS (figure.8 B&B1). Paying close attention to the CTPA radiological definitions mentioned is critical in determining the degree, extent, severity, and, most importantly, seriousness of each individual lesion in order to make timely appropriate therapeutic decisions.

Although pulmonary vasculitis in BD is indistinguishable from that seen in HSS, there are some clinical differences that should be considered. In the former, if pulmonary complications manifest with haemoptysis, the treating physician and radiologist will point to the high possibility of pulmonary vasculitis complicating the course of BD, because the disease is tagged by the classic triad. Furthermore, if the patient is already receiving aggressive immunomodulatory medications, such as high-dose steroids or anti-TNF inhibitors, to treat underlying refractory uveitis or peripheral arterial vascular disease, these medications are already known to treat even aggressive forms of pulmonary vasculitis and will likely ameliorate the pulmonary vascular complications to a large extent.

Importantly, endovascular management with PACE as minimally invasive procedure continues to play important therapeutic roles in the management of BD pulmonary vascular complications, most notably caused by ruptured unstable PAAs or PAPs that usually associated with serious life-threatening haemoptysis. When performed by an experienced interventionist, these well-established techniques that avoid open surgery are safe and effective (40). In the context of BD-pulmonary vasculitis, in a previous report, a 45-year-old man with known BD presented with recurrent attacks of hemoptysis. The patient underwent PACE to control a leaking PAA, and two months later, he suffered from massive hemoptysis, necessitating immediate intubation and mechanical ventilation (41). An emergency bronchoscopy was performed, which revealed fresh blood coming from the left main stem bronchus as well as multiple clots. The patient's left lung was isolated using "endobronchial balloon occlusion", which was followed by successful definitive surgical intervention. Endobronchial balloon occlusion appears to be a very promising technique for controlling active bleeding and providing ample space for elective well-planned surgical intervention. Endovascular therapy may be most effective in treating saccular PAAs or PAPs in both the central and peripheral PA branches. Fusiform aneurysms of the peripheral pulmonary arteries, on the other hand, can be treated endovascularly if there is adequate pulmonary function and reserve. However, central fusiform aneurysms, on the other hand, necessitate surgical intervention (41). Recently, endovascular treatment with a stent graft has been considered a safe alternative to PACE in the management of disturbed PAPs. By implanting coated stent graft into the injured PA excludes the false aneurysm, which stops bleeding while maintaining antegrade blood flow (42). The latter procedure is still waiting evaluation in the context of endovascular management of unstable PAPs in both BD and HSS and seems very effective procedure from the theoretical point of view.

Surgical procedures like lobectomy with PA plasty have been shown to be effective in treating life-threatening haemoptysis caused by ruptured pulmonary aneurysms into adjacent bronchus (16, 17). On the contrary, other surgical procedures, on, such as aneurysmorrhaphy, appear to have a very high risk of fatal hemoptysis in the very early post-operative period, particularly if insufficient time was given to induce pulmonary disease remission by immunosuppressive lines of treatment (22, 23).

In our study peripheral arterial aneurysms were observed in 12(28.6%) and arterial thrombosis in 13(31%). In vasculo-BD, the large arterial lesion represents inflammation in the media and adventitia, where active arteritis develops first in the affected arteries, followed by media destruction and fibrosis. Severe media destruction caused by active inflammation is the most common cause of saccular aneurysms (43). Importantly, the thrombotic events in BD raise the question of whether immunosuppressives, anticoagulants, or a combination of the two should be used to treat the disease. Anticoagulants have not been shown to reduce the risk of recurrence, but they have been shown to reduce the risk of post-thrombotic syndrome (44), and appear to be required in cases of vascular surgery or intervention to repair peripheral arterial aneurysms.

In the current study, we presented the most serious CTPA signs that could be associated with serious morbidity or mortality in BD-related pulmonary vascular complications, which was supported by high quality and very illustrative CTPA. Taking all of these evidence-based facts into account would aid in reaching an international consensus on the specific serious CTPA radiological signs that could be associated with serious consequences as detailed in our report, such as an unstable leaking true PAAs or PAPs on the verge of rupture into adjacent bronchus, which can result in an unpredictable massive life-threatening hemoptysis

Limitations of the study: It is a retrospective; cross sectional study so no follow up data are available. The strengths of our study are that it focuses on a critical and potentially fatal complication of BD, as well as the need of recognizing CTPA findings, particularly the differences between true and false pulmonary aneurysms, for optimum management and eventually a favorable prognosis.

Conclusions and recommendations

The current report sheds light on the most serious CTPA signs, such as unstable leaking true PAAs and unstable PAPs on the verge of rupture, both of which can put BD patients at risk of life-threatening hemoptysis. PAPs patterns are the most serious pulmonary vascular complications, and currently regarded to be a contained rupture of the involved

pulmonary arterial branches. PAPs can be asymptomatic until they break into a neighboring bronchus, causing an arterio-bronchial fistula and potentially fatal massive hemoptysis. (27, 28). Bronchial indentation and/or trapped air within the hypodense component of PAPs are extremely concerning CTPA signs that necessitate immediate attention because they indicate direct communication with a neighbouring bronchus.

From therapeutic standpoint. Immunosuppressive therapy, with oral corticosteroids and pulse cyclophosphamide for induction of remission, followed by azathioprine for maintenance of remission, are still the mainstay lines of treatment, with the latter lines being the best studied in this domain (3, 12, 13, 15, 18, 21, 34). Anti-TNF therapy has been shown to be effective in a variety of reports, particularly in refractory cases (36-41). A definitive, well-planned surgical intervention, such as lobectomy, may be lifesaving, whereas aneurysmorrhaphy may carry a very high risk of fatal haemoptysis in the very early postoperative period (22, 23). Endovascular intervention with PACE, offers less invasive line of intervention in case of ruptured pulmonary aneurysm, whereas stent graft has recently been considered a safe alternative to PACE in the management of unstable PAPs. Patients with BD who have started anticoagulation for major arterial and/or venous thrombosis or intra-cardiac thrombosis should have CTPA to rule out leaking unstable PAAs.

Conflict of Interest: Each author in this work declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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