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Pulmonary embolism versus pulmonary vasculitis in Hughes-Stovin syndrome: Characteristic computed tomography pulmonary angiographic findings and diagnostic and therapeutic implications. HSS International Study Group

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ABSTRACT

Background and aim: Hughes-Stovin syndrome (HSS) is a rare systemic vasculitis with widespread venous/arterial thrombosis and pulmonary vasculitis. Distinguishing between pulmonary embolism (PE) and in-situ thrombosis in the early stages of HSS is challenging. The aim of the study is to compare clinical, laboratory, and computed tomography pulmonary angiography (CTPA) characteristics in patients diagnosed with PE versus those with HSS.
Methods: This retrospective study included 40 HSS patients with complete CTPA studies available, previously published by the HSS study group, and 50 patients diagnosed with PE from a single center. Demographics, clinical and laboratory findings, vascular thrombotic events, were compared between both groups. The CTPA findings were reviewed, with emphasis on the distribution, adherence to the mural wall, pulmonary infarction, ground glass opacification, and intra-alveolar hemorrhage. Pulmonary artery aneurysms (PAAs) in HSS were assessed and classified.
Results: The mean age of HSS patients was 35 ± 12.3 years, in PE 58.4 ± 17 ($p < 0.0001$). Among PE 39(78 %) had co-morbidities, among HSS none. In contrast to PE, in HSS both major venous and arterial thrombotic events are seen.. Various patterns of PAAs were observed in the HSS group, which were entirely absent in PE. Parenchymal hemorrhage was also more frequent in HSS compared to PE ($P < 0.001$).
Conclusion: Major vascular thrombosis with arterial aneurysms formation are characteristic of HSS. PE typically appear loosely-adherent and mobile whereas "in-situ thrombosis" seen in HSS is tightly-adherent to the mural wall. Mural wall enhancement and PAAs are distinctive pulmonary findings in HSS. The latter findings have significant therapeutic ramifications.

1. Introduction

Hughes Stovin Syndrome (HSS) was named after two British physicians in 1959 [1]. They described two male patients presenting with unexplained fever, weight loss, recurrent deep vein thrombosis (DVT) despite anticoagulation, and recurrent hemoptysis. Both patients died during unpredictable massive episodes of hemoptysis [1]. Currently, HSS is regarded as a systemic vasculitis characterized by widespread venous /arterial thrombosis and serious pulmonary vasculitis leading to the formation of pulmonary artery aneurysms (PAAs). This pulmonary vasculitis can affect all pulmonary artery (PA) branches. Well-established radiological and morphological signs can be visualized with computed tomography pulmonary angiography (CTPA) [2,3].

In the most recent report, the HSS International Study Group (HSSISG) created a novel CTPA reference atlas that defines the wide spectrum of pulmonary vasculitis observed in HSS [3]. Several CTPA patterns are used to classify PAAs in HSS: true stable PAAs with adherent in-situ thrombosis, stable bronchial artery aneurysms (BAAs), stable pulmonary artery pseudo-aneurysms (PAPs) and the corresponding unstable aneurysmal patterns [4–35]. These classifications were developed according to lesion severity and to the associated morbidity [3]. Of note, all fatalities in HSS have been attributed to unpredictable massive hemoptysis explained by PAA(s) rupture into an adjacent bronchus [1,36–44].

Acute pulmonary embolism (PE) is a common and potentially fatal condition. CTPA imaging is critical in its early identification and treatment. The most prevalent cause of acute PE is lower extremity venous thromboembolism, also known as acute thrombotic PE or acute pulmonary thromboembolism. [45,46]. PE and in-situ thrombosis related to HSS are pathophysiologically separate entities. PE is caused by the embolization of a travelling thrombus from the venous periphery to the lungs, whereas in HSS, the pulmonary arterial thrombus typically evolves in-situ due to pulmonary artery mural wall vasculitis [3].In both situations, the pulmonary vascular obstruction and altered pulmonary hemodynamic will eventually lead to right ventricular strain (RVS) [2,3]. Most published HSS case reports did not include a cardiac evaluation [4–35]. However, cardiac function assessment is recommended in patients with extensive in-situ thrombosis and CTPA evidence of RVS [3]. Our aim was to compare, demographic, clinical and laboratory findings in patients diagnosed with PE versus those with HSS and especially to compare CTPA findings between PE and HSS-related pulmonary vasculitis, to identify differentiating features to facilitate diagnostic clarification and targeted treatment.

2. Methods

2.1. Study design

The current retrospective, cross-sectional study included 50 patients with established PE, enrolled from the Dr. Erfan and Bagedo General Hospital, Jeddah, KSA. These cases were compared against a retrospective cohort of 40 HSS cases, previously published by members of the HSSISG [4–35]. Only patients, in both groups, with complete clinical data and with complete CTPA studies available for review were included [4–35]. The study was conducted between 2022 and 2024. Inclusion criteria: The diagnosis of HSS cases was made based on the presence of typical features [2,3]. These features include a normal coagulation profile and widespread recurrent vasculo-occlusive disease, such as DVT, cerebral venous sinus thrombosis, pulmonary vasculitis, intracardiac or arterial thrombosis, and PAAs associated with in situ thrombosis and/or BAAs. The diagnosis of PE was made in accordance to the American College of Physicians Clinical Guidelines [47]. Only patients

fulfilling these criteria we included in the study Echo-Doppler studies were performed in all patients in both groups.

2.2. Ethics

The study was approved by the ethical committee of the medical faculty of Monastir, Tunis. The patients had provided informed consents to participate and the study was in accordance to the 1964 Helsinki declaration.

2.3. Patient and imaging characteristics

Demographics, clinical characteristics, with special emphasis on pulmonary and vascular occlusive manifestations, laboratory investigations and coagulation profile as well as CTPA findings were recorded as described in the case reports. In PE patients, D-dimer (0–0.49 mg/l), procalcitonin (0–0.07 ng/ml) and pro-brain natriuretic peptide (pro-BNP)(300 pg/ml) were also examined at the time of their initial presentation. Regarding the HSS cases, all members of the HSS working group shared their complete CTPA data, which were then uploaded to a single Siemens (Syngo.via) CT workstation. The uploaded source images were interpreted in different windows such as lung and mediastinal windows in both pre- and post-contrast phases and further analyzed. In certain cases for the purpose of illustration and demonstration, software was used to create new reconstructions from the source images, such as multi-planar reconstruction, maximum intensity projection, and three dimensional volume rendering technique in the case of unstable leaking PAAs (Figs. 1–6).

2.4. Interpretation of CTPA findings

Full CTPA studies in both groups were reviewed and interpreted. The shape, distribution and laterality of the PE, adherence to the mural wall of the pulmonary artery (PA) branch and the in-situ thrombosis in the HSS were recorded. Pulmonary infarction, lung infection, pulmonary consolidation, ground glass opacification, parenchymal and/or intra-alveolar hemorrhages were noted. In HSS patients, the pattern, distribution of PAAs, loss of aneurysmal wall definition, perianeurysmal leaking with adjacent ground glass opacification, and bronchial indentation by the aneurysm were recorded. CTPA images were analyzed and classified according to the recently published CTPA Reference Atlas by the HSSISG [3]. We evaluated for the following CTPA signs in HSS patients: mural wall enhancement on post-contrast CTPA and PAAs. PAAs were classified into distinctive CTPA patterns including true stable PAAs with adherent in-situ thrombosis, BAAs, PAPs and corresponding unstable aneurysmal patterns. Radiological evaluation of the proximity and structural associations of PAAs and PAPs with adjacent bronchi is critical in determining the risk of subsequent rupture and fatal outcomes [3]. Table 1 depicts detailed CTPA definitions of each lesion.

2.5. Statistical analysis

Data were collected on a standardized data collection forms and stored in an electronic database.. Statistical Package for Social Sciences (SPSS) version 25 was used. Variables were presented using descriptive statistics, including frequencies and percentages for categorical variables or mean and standard deviation for continuous variables. Bivariate comparison was done using Chi-square test (categorical data) or Mann Whitney *U* tests (continuous data). *P* value 0.05 was considered statistically significant for all analyses.

3. Results

This study included 40 patients diagnosed with HSS, with a male to female ratio of 3:1, and 50 patients with established PE with a male to female ratio of 1.2:1 ($p = 0.04$). The mean age at diagnoses was 35 ± 12.3 years among patients with HSS compared to 58.4 ± 17 years in patients with PE ($p < 0.0001$). In HSS cases, mean disease duration was 55.1 ± 67.6 months prior to diagnosis and the mean age at onset was 32.2 ± 10.2 years. Presenting clinical features in the HSS group were DVT in 18 (45 %) patients, hemoptysis in 23 (57.5 %), thrombophlebitis in three (7.5 %), fever in five (12.5 %) and diplopia due to cerebral venous sinus thrombosis in two (5 %). Other detailed comparisons are presented in Table 2. Among the PE patients 39(78 %) had co-morbidities, among HSS none. For details see Table 2.

The mean D-dimer (12.4 ± 9.6 mg/l), procalcitonin (5.6 ± 11.2 ng/ml), and pro-BNP (1824 ± 3252.5 pg/ml) were elevated. Positive anti-cardiolipin (ACL) and β2-glycoprotein (anti-β2-GPI) antibodies were found in 4 (8 %) PE patients; three were in their thirties and one was 16 years old. Two (5 %) HSS patients had positive ACL.

Detailed peripheral vascular complications, distribution of thrombotic events (venous and arterial) and arterial aneurysms are detailed in Table 3.

Regarding CTPA findings, PAAs were only seen in HSS patients.

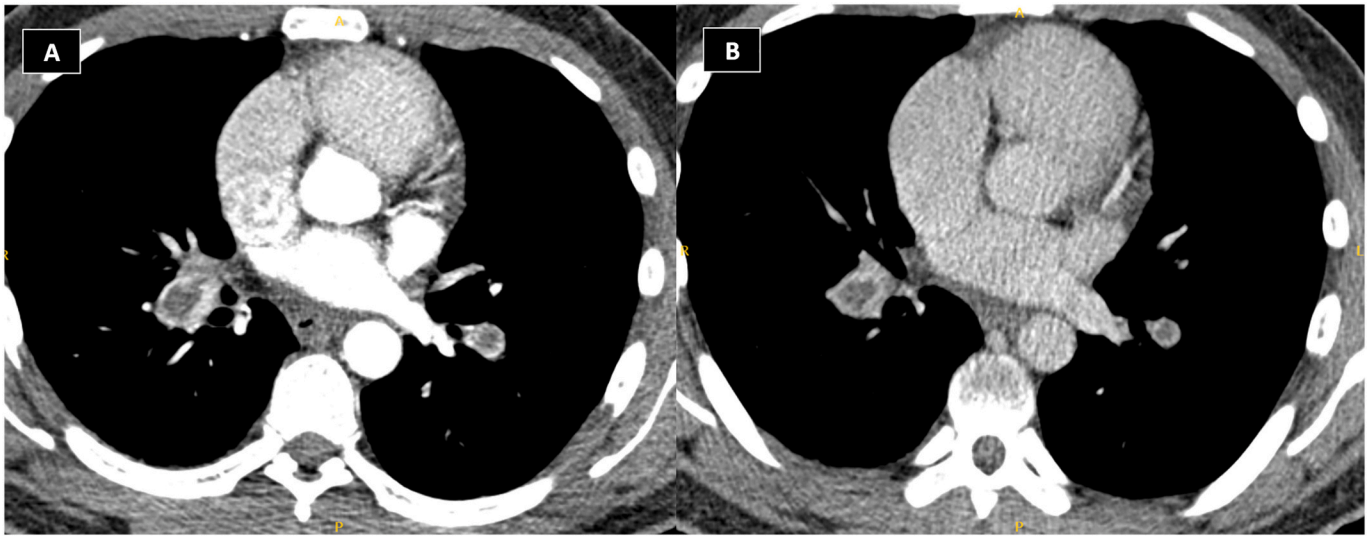

Fig. 1. CTPA of patient with HSS showing bilateral lower lung lobar arterial filling defects with aneurysmal dilatation and marginal enhancement in sequential late arterial (a) and venous (b) phases.

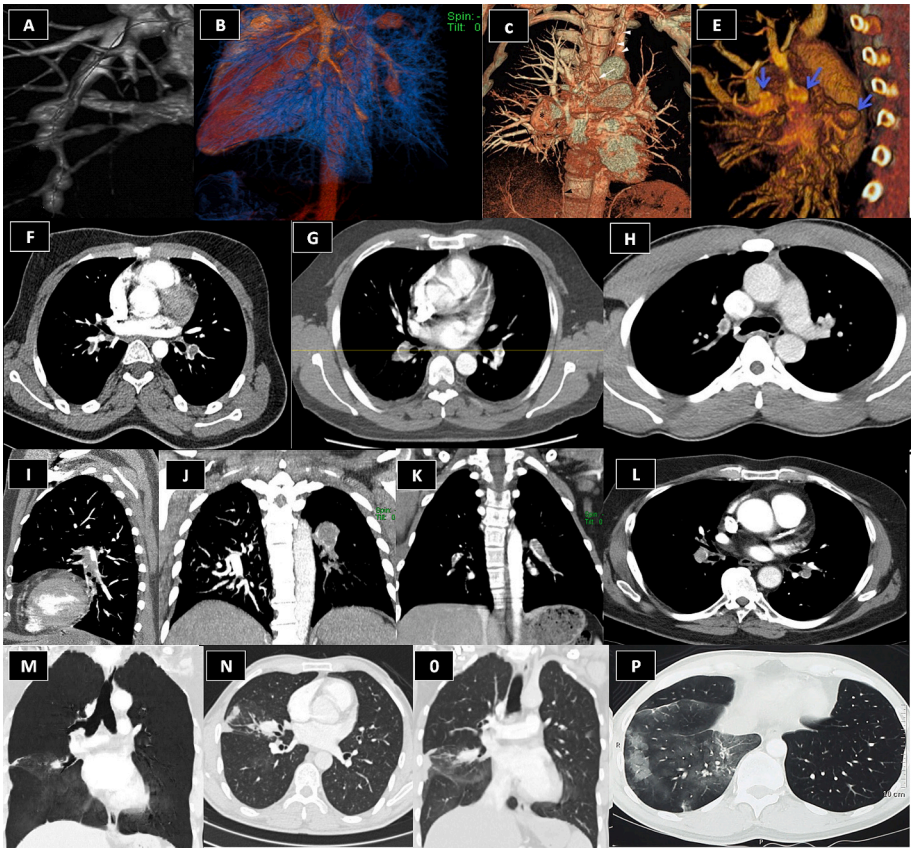

Fig. 2. (A) Magnified 3-D reconstruction of right lower lobe pulmonary artery true saccular aneurysms; (B–C), and (E) Volume render oblique magnified views showing right lower lobe pulmonary artery aneurysms (PAAs); (F): Axial image of CTPA mid thoracic level, demonstrating stable bilateral lower lobe PAAs with in-situ thrombosis; (G) Axial CTPA obtained in delayed phase to demonstrate the circumferential arterial mural enhancement of the affected lower lobe arteries bilaterally; (H): Axial CTPA obtained in delayed phase demonstrating right upper lobe pulmonary artery mural enhancement in a stable PAA with in-situ thrombus; (I): Sagittal CTPA (late phase) showing stable PAA of the lobar and segmental arteries with in-situ thrombosis in the lower lobe branches with mural enhancement; (I–L): Sagittal, coronal and axial CTPA images for patients with true bilateral pulmonary artery aneurysms with floating thrombi/emboli; (M-P): Coronal and axial CTPA images showing pulmonary hemorrhage as right lower lobe ground glass opacities around pulmonary artery aneurysms.

Table 4 compares CTPA findings between patients with PE vs. HSS, including the pattern of PAAs, PA branches involved, bronchial indentation, pulmonary infarction, and parenchymal hemorrhage.

4. Discussion

Our study has an atypical design. We use retrospective data of patients diagnosed with PE from a single center and then compare that data with those of HSS patients seen by members of the HSS study group. We only included HSS cases when complete clinical and radiological data were available. To make clear, our study is not a comparison with data from a literature review. As our HSSIgroup includes the authors of most HSS cases published world-wide during the last decade, one may consider the HSS cases included in this study as a worldwide retrospective series of HSS patients.

Distinguishing PE from in-situ thrombosis in HSS-related pulmonary vasculitis is a key diagnostic challenge, particularly in the early stages of both conditions. Accurate early diagnosis has significant therapeutic and prognostic implications. In the case of PE, anticoagulation is mandatory, whereas immunosuppressive drugs are the mainstay line of treatment in HSS-related pulmonary vasculitis and associated in-situ thrombosis to prevent pulmonary disease progression. Thus, misdiagnosis can have life-threatening consequences. Untreated in-situ thrombosis will progress to the formation of PAAs. If inflammation extends extra-luminally, PAAs can become unstable and cause unpredictable, life-threatening haemoptysis. Individuals with HSS that are inappropriately treated with anticoagulation without immunomodulatory therapy are therefore at risk of severe haemoptysis.

The HSSISG recommended that the decision to initiate anticoagulation for major vascular venous/arterial thrombotic events in HSS should be made after careful interpretation of CTPA findings and the exclusion of unstable aneurysm patterns, such as unstable true or false aneurysms [2,3]. HSS and Behçet disease (BD)-related pulmonary vasculitis share identical characteristic CTPA signs [2–5,11,19,22,52]. Although, BD patients typically present with the classic triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis. When pulmonary manifestations develop after a DVT or PAAs are visible on CTPA, then discriminating BD-related pulmonary vasculitis from PE can be straightforward [48,49]. Patients with BD that have vascular thrombotic events or iridocyclitis should receive immunosuppressants based on the 2018 update of the EULAR recommendations [50]. This immunosuppression should simultaneously improve the associated pulmonary vasculitis, except in aggressive cases with a rapidly progressive disease course [2,3]. We recommend that the radiological term “in-situ thrombosis” should be used in a standardized manner to describe the early stages of either HSS or BD-related pulmonary vasculitis, in order to distinguish it from PE.

In our study, there were significant differences between the PE and HSS patients that could help differentiate between these clinical entities at an early disease stage. The presence of PAAs are pathognomonic of HSS. We also observed that PE occurred more frequently in elderly patients with other co-morbidities. However, those with systemic lupus erythematosus, antiphospholipid syndrome, and other coagulopathies are at risk for developing PE at a younger age. Positive ACL and β2-GP-I

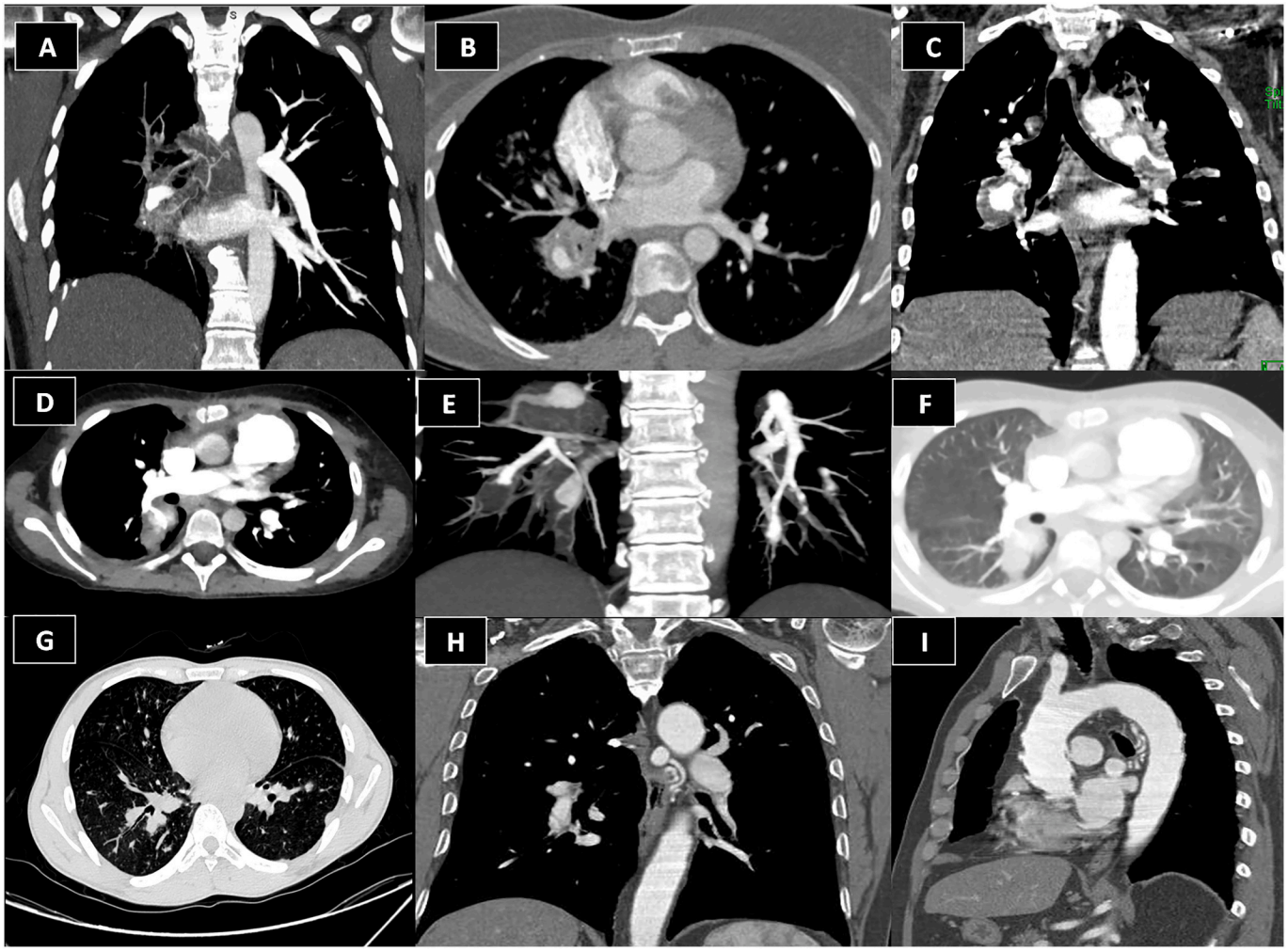

Fig. 3. (A–D): Coronal and axial CTPA images demonstrating a right lower lobe pulmonary artery pseudoaneurysm (PAP) with eccentric thrombus. (E) Coronal reformatted CTPA image for the same patient showing bilateral true and pseudoaneurysms. (F) Axial lung window for the same patient with a right lower lobe pulmonary pseudoaneurysm and left lower lobe true aneurysm. (G) Axial lung window CT image showing bilateral lower lobe pulmonary aneurysms. (H) and (I): Coronal and Sagittal reformatted images showing true bronchial artery aneurysms.

antibodies were found in 8 % of PE patients; three in their thirties and one was 16 years old. ACL was also present in 5 % of HSS patients. DVT was the most common cause of PE (up to 85 % of cases), followed by thrombosis of the iliac, renal, and inferior vena cava. The upper limbs are rarely identified as a source of significant PE [51].

Risk factors for PE are age, a history of venous thromboembolism DVT, active malignancy, heart or respiratory failure, congenital or acquired coagulation disorders, hormone replacement therapy, and oral contraception [53]. In our study, most PE patients had co-morbidities such as hypertension, diabetes, dyslipidaemia, ischemic heart disease, with heart failure, malignancy, stroke, or liver cirrhosis. Death occurred in 28 % of PE patients. Co-morbidities were uncommon in HSS patients but death due to massive haemoptysis occurred in 15 %. Alveolar hemorrhage was more frequently observed among HSS cases when compared to those with PE ($p < 0.001$). In HSS, alveolar hemorrhage may occur due to leakage through the inflamed aneurysmal wall, which is exacerbated by anticoagulation. Pulmonary hemorrhage in PE has been attributed solely to anticoagulation therapy.

In both PE and HSS patients, DVT typically occurred in lower limb veins. Both PE and HSS patients experienced widespread vascular venous thrombotic events. However, superficial thrombophlebitis was significantly more common among HSS patients. Major thrombotic events, such as inferior vena cava thrombosis, were also more common in HSS compared to PE patients. Peripheral arterial thrombosis and aneurysms were also more common among HSS patients than after PE, including aneurysms of the femoral, brachial, splenic and superior mesenteric arteries. Peripheral arterial aneurysms in HSS are indicative of the underlying systemic vasculitis, which also explains the involvement of both the pulmonary and bronchial circulations [2,3].

The most important finding of this study was that the CTPA findings in PE patients differ significantly from those with HSS-related pulmonary vasculitis. In younger patients with major venous/arterial thrombotic events and/or peripheral arterial aneurysms, without evidence of a prothrombotic disorder or significant co-morbidities, HSS-related pulmonary vasculitis should be considered.

Although CTPA findings between acute PE and HSS are overlapping in the early stages of disease, there are characteristic findings which can differentiate the two conditions and accurately identify those with HSS. Approximately one-third of the HSS patients show arterial wall enhancement on CTPA (Fig. 1), which does not occur in typical PE. arterial wall enhancement may be an early sign of pulmonary vasculitis in HSS, indicating true mural wall inflammation related to the underlying vasculitic process. Furthermore, the in-situ thrombosis that evolves locally is due to the activation of coagulation cascade and is adherent to the mural wall. This is distinct from typical PE, where the embolus appears loose in the lumen and is serpiginous.

In patients with HSS where the diagnosis is initially missed, there are characteristics features of disease progression. Persistent arterial wall

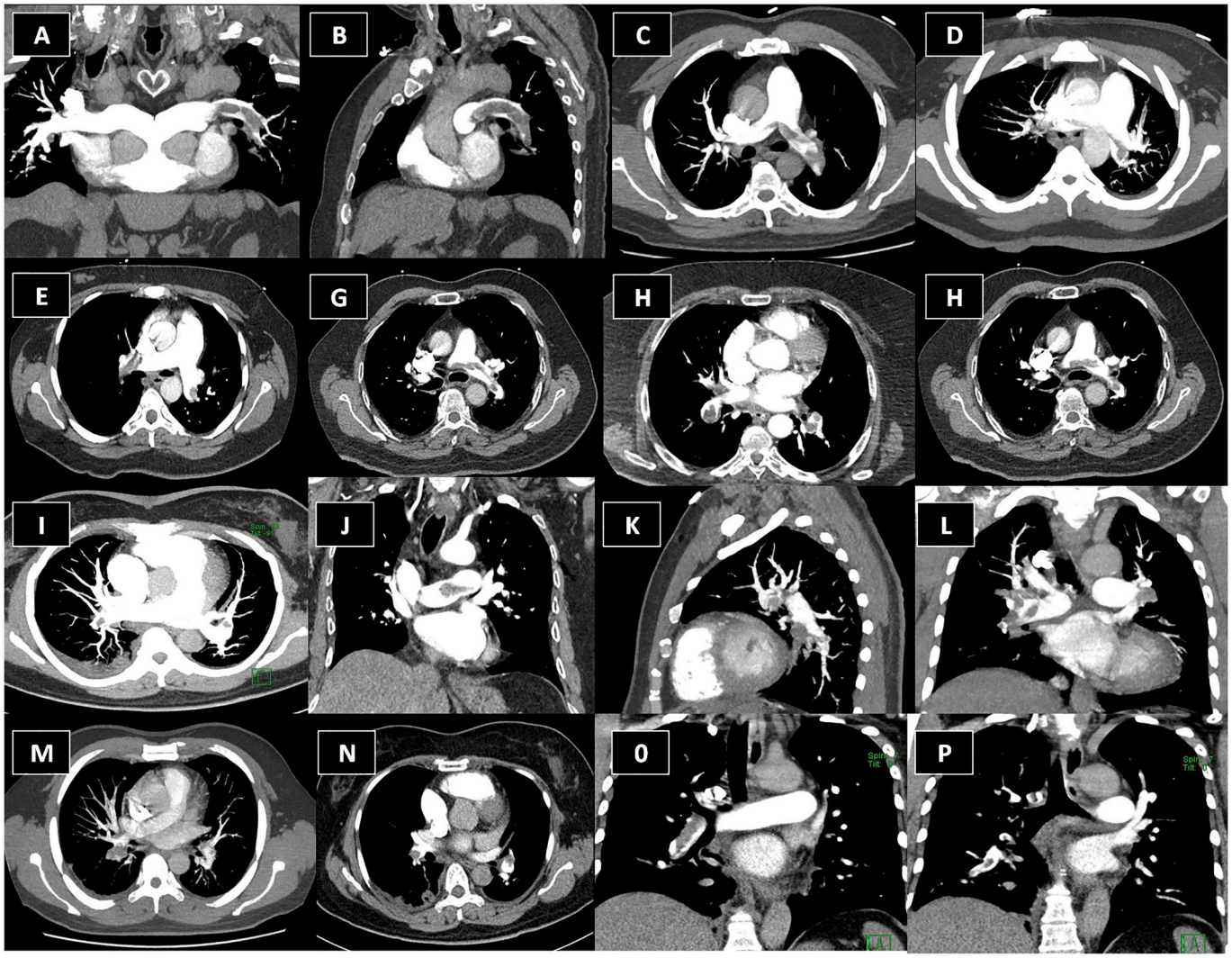

Fig. 4. (A) Maximum intensity projection coronal CTPA image showing a floating thrombus within the main left pulmonary artery. (B) Sagittal reformatted CTPA image showing a pulmonary artery embolism as a floating thrombus/embolus. (C) Axial CTPA images for the same patient showing a saddle thrombus surrounded with contrast. (D–I) Axial CTPA images for the same patient showing a saddle thrombus surrounded with contrast in a case of acute pulmonary embolism. (J–L) Coronal and sagittal reformatted CTPA images for a case of acute bilateral pulmonary embolism demonstrated as bilateral pulmonary artery filling defects surrounded with contrast. (M–P) Axial and coronal reformatted CTPA images for the same patient with acute bilateral pulmonary embolism with non-adherent PE.

inflammation of PA branches results in progressive mural wall injury. Over time, with exposure to the shear forces of the pulmonary circulation pressure, this can lead to outpouching of the wall, which is identified by CTPA as a stable "true PAA" (Fig. 2F–L). "True PAAs" are histologically defined as: 'focal dilatation of PA branch involving all three layers of the arterial wall' [2,3]. True PAAs may progress to become unstable; loss of arterial wall definition and peri-aneurysmal parenchymal hemorrhage can occur due to acute rupture (Fig. 2M–P). Aneurysm rupture typically occurs due to missed or delayed diagnosis and suboptimal immunosuppressive treatment, but can occur earlier in rapidly progressive cases. Other patients with HSS may experience chronic extravasation of blood through an inflamed aneurysmal wall. This gradually accumulates and coalesces around the dilated arterial lumen, resulting in a pulmonary artery pseudo-aneurysm ("PAP"). PAPs are defined as a sharply demarcated contrast filled aneurysmal lesion with a variably sized marginal hypodense perianeurysmal component. This represents 'marginal thrombosis' entangling the sharply demarcated contrast filled ectatic lumen with adjacent ground glass opacification or frank consolidation in the case of active hemorrhage (best visualized in a lung window; Fig. 3). This stage represents a contained rupture of the aneurysm [2,3]. Careful assessment should be made for the presence of an "air bronchogram" and its relationship to the false aneurysmal wall. Subsequent formation of a broncho-vascular fistula can lead to sudden death from massive haemoptysis. We found that air bronchograms were seen adjacent to the false wall of PAPs in 62.5 % of patients.

A close and intimate relationship has been explained in an autopsy report by Kirk and Seal in 1964. [38].The authors described the histopathological findings of ruptured PAP in one HSS patient, which revealed a segmental disruption of the elastica of the pulmonary artery 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. The organizing thrombus was separated from the bronchial lumen by a thin layer of respiratory epithelium, and squamous metaplasia had occurred in places. Given that, in-situ thrombosis which is intra-luminal and adherent to the aneurysmal wall in true PAAs is quite different from extra luminal marginal thrombosis as seen in PAP which indicates chronic leaking through the inflamed aneurysmal wall (contained rupture). Such unmistakable pattern in HSS was first described in the literature by the HSSISG and was considered the most serious pattern because it can result in unpredictable fatal hemoptysis and should be considered for immediate stabilization by pulmonary artery coil

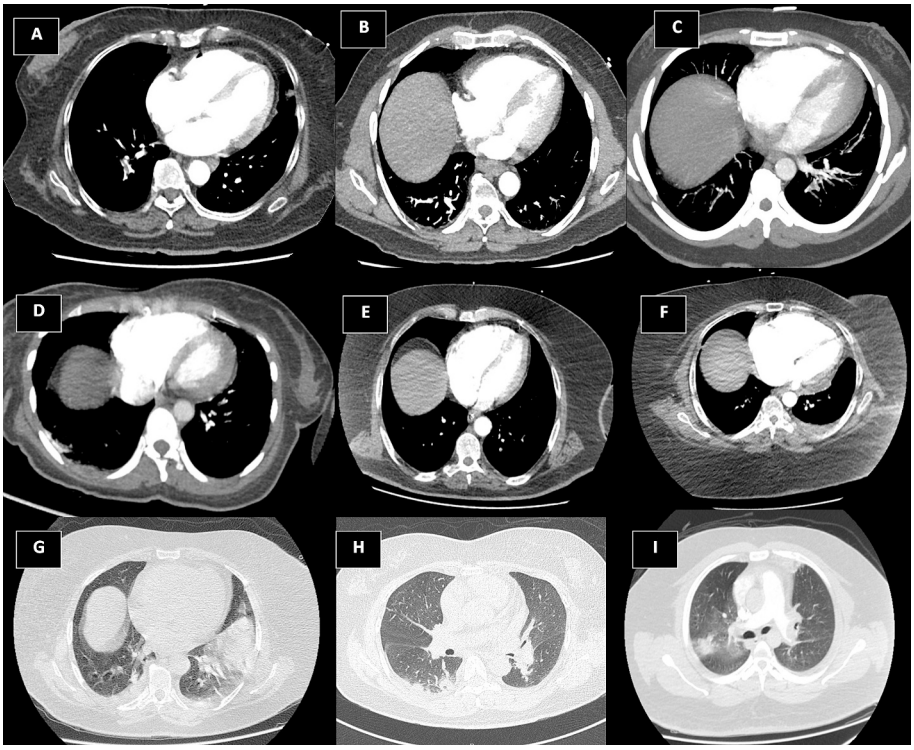

Fig. 5. (A): Axial CTPA image with acute pulmonary embolism appeared as non-adherent filling defects in the right lower lobe segmental branches with evidence of acute right ventricular strain (RVS). (B–E): Axial CTPA images with acute RVS in a case of acute PE. (H) Axial lung window image with left basal triangular opacity, in keeping with pulmonary infarction secondary to acute PE. (I): Axial lung window image with right basal pleural based opacities, in keeping with small pulmonary infarction secondary to acute PE. (J): Axial lung window image with right lung middle lobe ground glass opacity, in keeping with pulmonary hemorrhage secondary to acute bilateral PE.

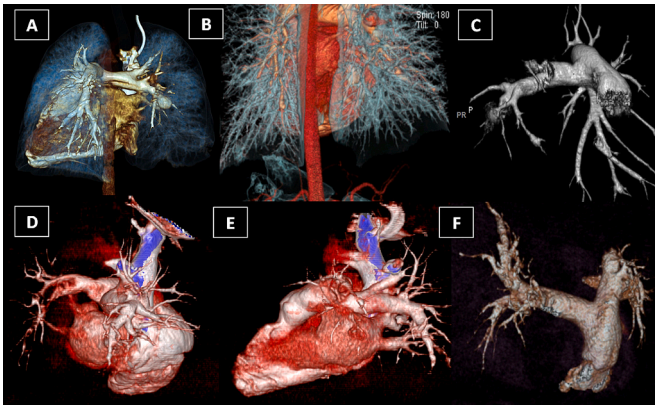

Fig. 6. 3D reconstructed images of CTPA in different known patients with PE. (A–C) are known cases of HSS with PAAs appearing as multiple mural nubs seen at the external arterial walls. While in images (D–F) patients with acute PE showing diffuse distension of the arteries due to the presence of PE, but without external mural nubs.

embolization (PACE). [1–3]

Another significant finding of the present study was that RVS was observed on CTPA in 30 % of HSS and 25 % PE patients. Both conditions can rapidly increase pulmonary vascular resistance, resulting in hemodynamic consequences. Increased pulmonary vascular resistance in HSS due to widespread in-situ thrombosis also predisposes to PAA formation. Thus, the presence of RVS on CTPA may be an indicator of disease progression. Due to the lack of vascular wall inflammation, patients with PE do not develop knobby arterial wall as seen in HSS (Fig. 6). Vascular wall inflammation also results in BAAs in 7.5 % of HSS patients but not in PE. Because of their smaller diameter, bronchial arteries can develop high resistance, low capacitance, and less distensible circulation. When pulmonary blood flow is reduced, the bronchial circulation and other collateral vessels can hypertrophy to maintain blood flow to ischemic lung areas and engage in gas exchange via systemic-pulmonary arterial anastomoses. [54]. Additionally, with reduced pulmonary blood flow, the total systemic cardiac output to the bronchial arteries may increase from 1 to 18–30 % [55]. Although the latter hemodynamic changes occur in both domains, vascular wall inflammation in HSS combined with increased bronchial artery pressures increase the risk of BAA formation in HSS.

The study has some limitations. Ideally would have been a prospective series of PE and HSS patients from one or several centers. As that is not feasible, HSS being an extremely rare disease, our study has an atypical design. We use retrospective data of patients diagnosed with PE from a single center; the findings in our PE series appear to be comparable with those in the world literature. We compare the data of the PE series with those of all HSS patients seen by members of the HSSISG who had complete clinical and CTPA data available. Thus we consider our cases as a world-wide retrospective series of HSS patients.

As HSS is a very rare disease and <100 HSS patients (in total 88 in PubMed) have been described world-wide, and complete CTPA studies are only available during last decennium, in our opinion this is the best and only feasible way to collect these data. We realise that our study design may still raise questions about appropriateness of the statistical comparisons between the two cohorts, given the inherent differences in study populations and methodologies.

The strength of our study is that it is the first attempt to compare manifestations and outcomes of a large series of HSS cases with those of a representative series of PE patients, showing clear differences that have clinical consequences.

Table 1
Computed tomography pulmonary angiography (CTPA) definitions of arterial wall enhancement, pattern of pulmonary artery aneurysms, right ventricular strain (RVS) and intracardiac thrombosis in Hughes-Stovin syndrome (HSS) patients.

Variable	CTPA definition
AWE	Arterial wall enhancement is the earliest CTPA sign in HSS-related pulmonary vasculitis. It is frequently observed during early stages of the disease process. Arterial wall enhancement is radiologically defined as an "enhancing aneurysmal wall," which is typically visualized in the mediastinal window in sequential arterial and venous post-contrast phases
True stable PAA	True stable PAA is defined as an "aneurysmal lesion (contrast filled) of the affected PA branch with a well-defined aneurysmal wall and associated with intra-aneurysmal adherent in-situ thrombosis (filling defects) without any perianeurysmal parenchymal GGO, which would be suggestive of an extra-luminal acute leak (best visualized in the lung window)"
Unstable leaking true PAA	Unstable PAA is defined as "aneurysmal lesion" (contrast filled) of the affected PA branch with loss of aneurysmal wall definition and perianeurysmal alveolar hemorrhage (ground-glass opacification and/or consolidation) with 'air-bronchograms'.The latter refers to air-filled bronchi (dark) being made visible by the opacification of surrounding alveoli (gray/white).
Pulmonary artery pseudoaneurysm (PAP)	A PAP is defined radiologically as "sharply demarcated contrast-filled aneurysmal lesions with a variably Sized marginal hypodense perianeurysmal component (marginal thrombosis) entangling a contrast-filled ectatic lumen." The lesion is not associated with adjacent ground glass opacification or frank consolidation, distinguishing it from leaking PAA or PAP. Air bronchograms (air-filled bronchi/bronchiole) can be associated within the hypodense component (marginal thrombosis).
Unstable Pulmonary artery pseudoaneurysm (PAP)	Unstable PAP is defined radiologically as "sharply demarcated contrast-filled aneurysmal lesions with a variably sized marginal hypodense perianeurysmal component (marginal thrombosis), entangling the sharply demarcated contrast-filled ectatic lumen plus adjacent GGO or frank consolidation due to active hemorrhage from the leaking ectatic lumen." The air bronchogram (air-filled bronchi/bronchiole) can be associated within the hypodense component.
RVS	RVS is defined radiologically by CTPA as "interventricular septal flattening or paradoxical interventricular septal bowing towards the left ventricle, which occurs secondary to the altered pulmonary hemodynamic in the context of pulmonary hypertension." In addition, RVS is characterized by a right ventricle size that exceeds that of the left ventricle.
Intracardiac thrombosis	Intracardiac thrombosis is defined by CTPA as a low attenuation non-enhancing filling defect in the involved cardiac chamber(s).

PAA; Pulmonary artery aneurysm; PAP; Pulmonary artery pseudoaneurysm; CTPA: Computed tomography pulmonary angiography; GGO: ground-glass opacification; RVS: right ventricular strain.

5. Conclusions

Differentiating acute PE from in-situ thrombosis seen in HSS-related pulmonary vasculitis represents a challenging diagnostic dilemma, given the overlap in clinical CTPA features in the early stages of HSS. However, there are characteristic CTPA findings, related to the underlying pathophysiology of HSS, which can differentiate the two conditions and facilitate early diagnosis and treatment of HSS-related pulmonary vasculitis.

Table 2
Demographic, disease manifestations, laboratory findings and co-morbidities in the pulmonary thromboembolism (PE) and Hughes-Stovin syndrome (HSS) patients.

Variables	HSS (n = 40)	PE (n = 50)	p
Age (years)	35 ± 12.3	58.4 ± 17	<0.0001
Gender (M/F)	30:10 (3:1)	27:23 (1.2:1)	**0.037**
Disease duration (months)	55.1 ± 67.6	27.9 ± 24	0.0096
Age at onset (years)	32.2 ± 10.2	56.3 ± 16.8	<0.0001
Smoking	0(0)	16(32)	NA
Fever	26(65)	14(28)	0.000072
Cough	37(92.5)	20(40)	<0.0001
Dyspnea	34(85)	16(32)	<0.0001
Chest pain	6(15)	14(28)	0.13
Hemoptysis (ml/24 h)	36(90)	13(26)	<0.0001
Mild (< 20 ml/24 h)	12(30)	13(26)	0.67
Moderate (20–600 ml/24 h)	14(35)	0(0)	NA
Massive (> 600 ml/24 h)	10 (25)	0(0)	NA
Superficial thrombophlebitis	21(52.5)	5(10)	<0.0001
DVT	34(85)	42(84)	0.89
Intra cardiac thrombosis	8(20)	1(2)	0.004
ESR (mm/1st h)	52.8 ± 25.8	48.5 ± 24.4	0.43
CRP (mg/dl)	18.9 ± 19.6	9.3 ± 9	0.006
HB (gm/dl)	11.1 ± 1.8	11 ± 1.9	0.81
WBCs (10^{10}/L)	8.7 ± 4.2	8.8 ± 4	0.88
Platelet count (103/μL)	333.5 ± 105.6	263.1 ± 106.7	
Abnormal coagulation panel	3(6)	5(10)	0.67
aCL autoantibodies	2(5)	4(8)	0.57
Factor V Leiden mutation	1(2.5)	1(2)	0.87
Beta-2 glycoprotein	0(0)	4(8)	NA
Comorbidities	0(0)	39(78)	NA
Hypertension	0(0)	38(76)	NA
Diabetes	0(0)	21(42)	NA
IHD with heart failure	0(0)	17(34)	NA
SLE/APS	2(5)	4(8)	0.57
Cardiac anomalies	0(0)	1(2)	NA
Pulmonary metastasis	0(0)	6(12)	NA
CVA	0(0)	7(14)	NA
Dyslipidemia	0(0)	26(54)	NA
Liver cirrhosis	0(0)	2(4)	NA
Fatal outcome	6(15)	14(28)	0.14

Data are either Mean ± SD or n (%);HSS: Hughes-Stovin syndrome; aCL: anti-cardiolipin antibodies; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; HB: Hemoglobin; WBCs: White Blood Cells; CVA: cerebral vascular accident; SLE/APS: Systemic Lupus Erythematosus/Antiphospholipid Syndrome; IHD: Ischemic heart disease; Anti-TNF: Anti-tumor necrosis factor; IQR: Inter Quartile Range; NA = Not Applicable.

We found that PE was more common in older individuals with significant co-morbidities that predispose to venous thromboembolism, whereas HSS-related pulmonary vasculitis is more common in previously healthy younger individuals, with a male predominance. The presence of major venous and/or arterial thrombotic events or peripheral arterial aneurysms with normal coagulation profiles and no associated co-morbidities should raise suspicion for HSS.

On CTPA imaging, PE typically appear to be more mobile and non-adherent to the pulmonary artery mural wall, whereas in-situ thrombosis in HSS exhibits characteristic features, including adherent thrombi and arterial wall enhancement. These CTPA features can be used to guide diagnosis and therapeutic decision-making in this patient population.

6. In summary

If we see in our clinics a (young, male) patient with unexplained DVT, recurrent thrombophlebitis, with no co-morbidities and/or risk factors, and normal coagulation profile, presenting with major arterial or venous thrombotic events or peripheral arterial aneurysms, one should raise the clinical suspicion of HSS and not PE. This diagnosis HSS is confirmed when on CTPA adherent thrombus to the pulmonary mural wall is seen with mural wall enhancement in post arterial phase

Table 3
Vasculoocculisve findings and peripheral arterial aneurysms in pulmonary thromboembolism (PE) and Hughes-Stovin syndrome (HSS) patients.

Variables	HSS (n = 40)	PE (n = 50)	p
CVST	3(7.5)	0(0)	NA
Intra-cardiac Thrombosis	8(20)	1(2)	0.004
Right ventricle	4(10)	1(2)	0.09
Right atrium	4(10)	0(0)	NA
Venous thrombosis			
DVT (unilateral vs. bilateral)	26:8 (3.3:1)	40:2 (20:1)	0.72
Inferior vena cava	10 (25)	2 (4)	0.003
Internal jugular vein	2 (5)	0 (0)	NA
Common femoral vein	14(35)	25(50)	0.15
Iliac vein	13 (32.5)	8 (16)	0.065
Popliteal vein	17 (42.5)	34 (68)	<0.001
Superficial femoral vein	2 (5)	30 (60)	
Anterior tibial veins	6 (15)	24 (48)	0.0009
Posterior tibial veins	7 (17.5)	32 (64)	<0.001
Peroneal vein	0 (0)	9 (18)	NA
Soleal vein	0 (0)	3 (6)	NA
Saphenous vein	0 (0)	7 (14)	NA
Arterial thrombosis			
Aortic artery	2 (5)	1 (2)	0.43
Common iliac artery	2 (5)	1 (2)	0.43
Anterior tibial artery	1 (2.5)	1 (2)	0.87
Posterior tibial artery	1 (2.5)	1 (2)	0.87
Superior mesenteric artery	1 (2.5)	0 (0)	NA
Femoral artery	1(2.5)	1 (2)	0.87
Brachial artery	2 (5)	0 (0)	NA
Splenic artery	1 (2.5)	0 (0)	NA
Popliteal artery	1 (2.5)	1 (2)	0.87
Peripheral arterial aneurysms			
Celiac artery	1 (2.5)	0 (0)	NA
Femoral artery	1 (2.5)	0 (0)	NA
Brachial artery	1 (2.5)	0 (0)	NA
Splenic artery	1 (2.5)	0 (0)	NA
Aortic artery	1 (2.5)	1 (2)	0.87
Superior mesenteric artery	1 (2.5)	0 (0)	NA

CVST: cerebral venous sinus thrombosis; DVT: deep vein thrombosis; NA = Not Applicable.

Table 4
Computed tomography pulmonary angiography (CTPA) findings in pulmonary thromboenbolism (PE) and Hughes-Stovin syndrome (HSS) patients.

Variables	HSS (n = 40)	PE (n = 50)	p
AWE	13(32.5)	0(0)	NA
Pulmonary artery aneurysms	40(100)	0(0)	NA
Stable true PAAs	15(37.5)	0(0)	NA
Unstable true PAAs	9(22.5)	0(0)	NA
BAAs	3(7.5)	0(0)	NA
Unilateral vs. Bilateral	4/36	10/40	0.19
PA branches involved			
Main	19(47.5)	30(60)	0.24
Lobar	34(85)	49(98)	
Segmental	27 (67.5)	39(78)	0.28
Subsegmental	10 (25)	13(26)	0.92
Air bronchogram in the vicinity of PAAs	25(62.5)	0(0)	NA
Pulmonary infarction	13(32.5)	14(28)	0.64
Pleural effusion	3(32.5 %)	14(28)	0.01
Parenchymal hemorrhage	25(62.5)	3(6 %)	<0.001
Main PA diameter (mm)	2.91 ± 0.56	2.47 ± 0.7	0.002
CTPA /RVS	15(30)	10(25)	0.6
PACE	6(15)	0(0)	NA

PA: Pulmonary artery;PAAs: pulmonary artery aneurysms; BAAs: bronchial artery aneurysm; PA: pulmonary artery; CTPA: computed tomography pulmonary angiography; RVS: right ventricular strain; PACE: pulmonary artery coil embolization.

persisting in the venous phase,

Abbreviations

ACL anticardiolipin
BAAs bronchial artery aneurysms,
CTPA computed tomography pulmonary angiography
DVT deep vein thrombosis
EULAR European Alliance of Associations for Rheumatology
Hughes-Stovin syndrome (HSS)
HSSISG HSS International Study Group
PA pulmonary artery
PAAs Pulmonary artery aneurysms
PAPs pulmonary artery pseudo-aneurysms
PE pulmonary embolism
RVS right ventricular strain
SPSS Statistical Package for Social Sciences

Ethics

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate.

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Declaration of competing interest

The authors declare no conflict of interest regarding this study.

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