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BRIEF REPORT

Pattern of pulmonary vasculitis and major vascular involvement in Hughes-Stovin syndrome (HSS): brief report of eight cases

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Abstract

To describe the pattern of pulmonary artery vasculitis and the characteristic computed tomographic pulmonary angiography (CTPA) signs in patients with Hughes-Stovin syndrome (HSS). In a retrospective study, the medical records of eight HSS patients (six men), seen between February 2008 and January 2018, were reviewed regarding history, disease characteristics, laboratory investigations, imaging, and treatments. The mean (SD) age was 37.375 ± 8.65 years (range 30–55) and mean (SD) follow-up 30 ± 41.60 months (range 9–132). In all patients, routine laboratory investigations and complete coagulation profile were done. In all, CTPA studies were performed as well as and Doppler ultrasound for suspected deep vein thrombosis (DVT). Four patients had a history of thrombophlebitis, and DVT was observed in all, in two cases bilateral. Arterial thromboses involving popliteal, tibial, common iliac, and femoral arteries were observed in one patient. All patients had mild to moderate hemoptysis, and one had massive hemoptysis. None of the patients had a history of recurrent mouth and/or genital ulcers, uveitis, or arthritis. In all patients, CTPA identified bilateral pulmonary artery aneurysms (PAAs) with adherent in situ thrombosis and mural enhancement in all patients. Lobar PA branches were involved in all patients, segmental in six and main PA in five patients. Proper immunomodulators were initiated early, with favorable outcome; none was treated with TNF-α antagonists. HSS is a systemic vasculitis that may affect virtually all major veins and arteries in patients with normal coagulation profile. PAAs, adherent in situ thrombosis, and mural wall enhancement are characteristic CTPA signs. Early treatment with immunomodulators is essential.

Key Points

- *Hughes Stevin syndrome (HSS) is a systemic vasculitis that may affect virtually all major veins and arteries in patients. It has a normal coagulation profile.*
- *Computed tomography (CT) pulmonary angiography is considered to be the most important diagnostic tool to assess the degree and the extent of the characteristic pulmonary artery aneurysms, and in situ thrombosis, and mural wall enhancement.*
- *It is likely that HSS syndrome is often not recognized and misdiagnosed as deep venous thrombosis (DVT) with pulmonary thromboembolism.*
- *Early treatment with combined immunomodulators is essential to ensure favorable outcome.*

Keywords Hughes-Stovin syndrome (HSS) · Pulmonary artery aneurysms · Pulmonary artery in situ thrombosis · Pulmonary vasculitis · Pulmonary vasculitis in Behçet's disease

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Introduction

Hughes-Stovin syndrome (HSS) was first described in 1959 by two British physicians, Drs. John Patterson Hughes and Peter George Ingle Stovin, in two white male patients, presenting with deep venous thrombosis (DVT) and segmental pulmonary artery aneurysms (PAAs) [1]. At first, septic thrombophlebitis was postulated as the underlying etiology, leading to intracardiac infected thrombus that shifted into the pulmonary artery (PA) branches, leading to "mycotic" pulmonary artery aneurysms (PAAs) [2, 3]. In 1964, Kirk and Seal [4] concluded that the involvement of leg veins, venules, and cerebral venous sinus thrombosis (CVST) combined with repeatedly negative blood and bone marrow cultures made a "mycotic" process unlikely. In the following years, the etiology of HSS was ascribed to systemic venous angiitis or collagen disease [5, 6]. Since then, corticosteroids were generally used as first-line treatment in HSS to control the widespread vascular affection [4–6]. Generally, HSS is considered to result from a vasculitis similar to that seen in Behçet's disease (BD). Some investigators suggest that HSS is actually a subtype of BD, but we can only speculate about that, as the etiology of both diseases is still uncertain. Such a link seems likely as occasionally HSS has been described as a feature in BD and even as its presenting manifestation [7–9]. BD is a systemic vasculitis which can affect venous and arterial vessels of any size. Fei et al. [10] evaluated the prevalence and characteristics of vascular involvement in BD. In a total of 796 BD patients, vascular involvement was observed in 12.8% of the patients and more frequently in male patients. Vascular involvement was the initial presentation of the disease in 28 patients with a male to female ratio 3.86:1; venous lesions were more frequently observed than arterial lesions. The authors mentioned that vascular lesions correlated with a high frequency of cardiac involvement and a low incidence of ocular lesions, genital ulcers, and arthritis.

In this brief report, we describe eight cases with HSS and detail their clinical presentations at disease onset, disease characteristics, and CTPA radiological findings with special attention for pulmonary vasculitis patterns. The treatments applied are described.

Patients and methods

Clinical assessment

Eight patients with HSS (six men) were retrospectively recruited from Dr. Erfan General Hospital, Jeddah, Saudi Arabia, and from the Rheumatology Department, Faculty of Medicine, Cairo University, between February 2008 and January 2018. Patients' hospital medical records were reviewed regarding past or present history of DVT, recurrent abortions, painful recurrent mouth and/or genital ulcers, or eye involvement. Other data about chest symptoms like dyspnea, chest pain, cough, and hemoptysis severity (mild hemoptysis is < 20 mL, moderate hemoptysis is 20 to 600 mL, and severe or massive >600 mL in 24 h) as well as constitutional manifestations like fever, anorexia, and weight loss were noted and recorded. Clinical assessment included any symptoms or signs suggestive of systemic lupus or antiphospholipid syndrome like malar rash, alopecia, livedo reticularis, Raynaud's phenomenon, and any skin lesions suggestive of leukocytoclastic vasculitis.

Laboratory investigations

In all patients, routine laboratory investigations and complete coagulation profile were done including anticardiolipin antibodies, factor V Leiden mutation, β2-glycoprotein I, prothrombin gene mutation, and protein C and protein S assays to exclude any predisposing factors for venous and/or arterial thrombosis.

Radiological investigations

Plain chest X-rays were made, and computed tomography (CT) pulmonary angiography (CTPA) was performed in all patients according to the standardized CTPA protocols as detailed in a previous report [11]. CTPA images were reviewed and interpreted in each lung filed with special emphasis on PAA distributions along the PA branches including the main, lobar, interlobar, and segmental, and subsegmental branches intra-aneurysmal in situ thrombosis, adherence of the thrombus to the pulmonary artery aneurysm (PAA) arterial wall, PAA mural wall enhancement on post-contrast CTPA images, largest diameter of PAA in millimeters, and its distribution were also noted and recorded, and the same was applied for bronchial arteries.

Ethics

The local ethical committee approved the study design. All patients gave informed written consent to be enrolled into the study according to the Declaration of Helsinki.

Results

Eight patients with HSS (six men) were retrospectively included in this report. Their mean (SD) age in years was 37.375 ± 8.65 ranging between 30 and 55 years. Their mean (SD) disease duration in months was 45.38 ± 41.15 and ranged between 15 and 132 months. Their mean duration of follow-up (SD) was 30 ± 41.60 ranging between 9 and 132 months. None of the patients had a present or past history

of recurrent painful mouth and/or genital ulcers, and none had recent or previous attacks of uveitis or arthritis. Four patients had thrombophlebitis, and deep vein thrombosis (DVT) was observed in all patients with bilateral involvement in only two cases, proven by Doppler ultrasound. Iliac veins were affected in two cases, common femoral veins and popliteal veins, each in six patients. Unilateral arterial thrombosis affecting the popliteal, tibial, femoral, and common iliac arteries without aneurysm formation was observed in one patient. All patients had mild to moderate hemoptysis, and one had massive hemoptysis.

Their mean (SD) ESR 1st hour was 45.50 ± 19.86 and ranged between 22 and 77 mm/h, mean CRP was 13.33 ± 14.64 and ranged between 2 and 46 mg/dL, and mean (SD) hemoglobin level was 10.45 ± 1.703 and ranged between 8.3–13.1 g/dL. Four patients had anemia, two had mild leukocytosis, and two patients had thrombocytosis.

All patients showed normal coagulation profile with normal values of anti-cardiolipin antibodies, no factor V Leiden mutation, β2-glycoprotein I, prothrombin gene mutation, and protein C and protein S assays.

Detailed demographic, clinical disease characteristics, laboratory findings, and CTPA findings are summarized in Table 1.

Plain chest X-rays were abnormal in seven cases; CTPA showed abnormal findings in all cases (Figs. 1 and 2). All patients showed PAAs and intra-aneurysmal in situ thrombosis (Fig. 1b–d and Fig. 2d) with bilateral lung field involvement in all patients. Lobar PA branches were involved in all patients, segmental in 6 cases, and main PA in five cases (Fig. 2 a, b), while none of the patients showed bronchial artery involvement. The CTPA findings are detailed in Figs. 1 and 2.

The treatment of all patients included pulse IV methylprednisolone therapy in a dose of 1000 mg/day for five

Table 1 Demographic and disease characteristics, laboratory radiological findings, and lines of treatment used in the studied group of patients

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)	30	35	32	55	40	44	30	33
Gender	Male	Male	Male	Male	Female	Female	Male	Male
Nationality	Egyptian	Egyptian	Egyptian	Egyptian	Egyptian	Egyptian	Arabian	Egyptian
Disease duration (months)	24	36	24	132	84	27	21	15
First presentation	DVT	DVT	Phlebitis	DVT	DVT	DVT	DVT	Hemoptysis
Weight loss	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Positive
Dyspnea	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Cough	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Fever	Negative	Positive	Positive	Negative	Negative	Positive	Positive	Positive
Pleuritic chest pain	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative
ESR 1st hour (mm/h)	66	30	22	34	44	31	77	60
CRP (mg/dL)	23	8.5	9.4	2.1	5.3	8.2	4.2	46
HB (gm/dL)	8.3	13.1	12	11.3	10.1	9.3	11	8.5
WBCs (10^{10}/L)	9	11.7	7.4	6.2	7.1	8.2	11.5	8
Platelet count (10^3/μL)	370	184	230	220	204	350	550	624
DVT	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Thrombophlebitis	Positive	Positive	Positive	Negative	Positive	Negative	Negative	Negative
Hemoptysis	Moderate	Mild	Mild	Mild	Moderate	Mild	Moderate	Massive
PAAs and in situ thrombosis	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Main PA	Positive	Negative	Negative	Positive	Positive	Negative	Positive	Positive
Lobar	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Interlobar	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive
Segmental	Negative	Negative	Positive	Positive	Positive	Positive	Positive	Positive
Size of largest PAA (mm)	25	14	12	20	24	22	22	30
Bilateral affection	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Major vein thrombosis	Positive	Negative	Negative	Negative	Positive	Negative	Negative	Negative
Major arterial thrombosis	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative
Intra-cardiac thrombus	Negative	Negative	Negative	Negative	Negative	Negative	Right atrium	Negative
Pulse methylprednisolone	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Oral CS dose (mg/day)	40	30	40	20	30	30	30	40
Duration of oral CS (months)	12	12	12	132	24	15	12	12
Dose of pulse CP (mg/iv/month)	NR	NR	NR	NR	NR	750	1000	1000
Duration of CP (months)	NR	NR	NR	NR	NR	15	12	12
Azathioprine dose	150	150	150	150	150	NR	NR	NR
Duration of azathioprine (months)	12	12	12	132	24	NR	NR	NR
Combination therapy	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Anticoagulation	Received	Received	Received	Received	Received	Received	Received	NR
Follow-up (months)	12	12	24	132	24	15	9	12

CP cyclophosphamide, *AZA* azathioprine, *CS* corticosteroids, *NR* not received; Combination therapy means: maintenance oral CS combined with either AZA or CP

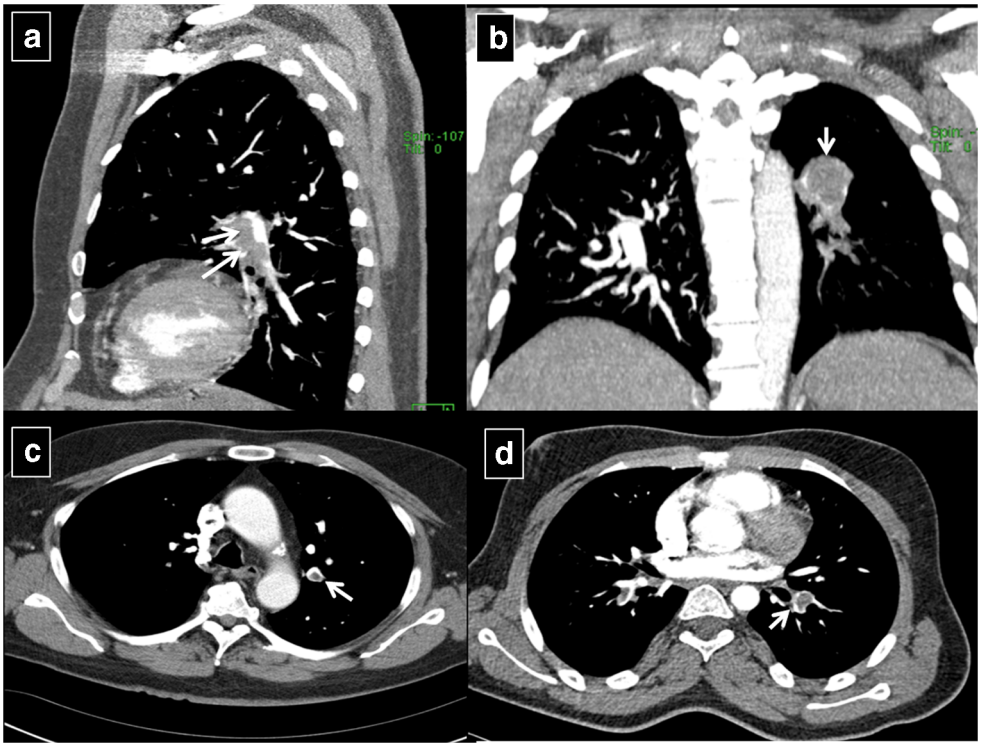

Fig. 1 **a** Sagittal reconstruction computed tomography pulmonary angiography (CTPA) showing large defect of the left main pulmonary artery (PA) (white arrows) adherent to the ventral wall of the artery. **b** Coronal reconstruction CTPA image showing pulmonary artery aneurysm of the left main PA and intra-luminal in situ thrombosis (white arrow). **c** Axial CTPA image showing left upper lobar PA branch adherent in situ thrombosis (white arrow). **d** Axial CTPA image showing in situ thrombosis of the left lower lobar PA branch and notice arterial wall mural enhancement (white arrow)

consecutive days as induction therapy; other lines of treatment applied are summarized in Table 1. None of our patients was treated with TNF-α antagonists or other biologicals. Seven patients had been treated with (short acting) anticoagulants; in one case, this was not feasible with massive hemoptysis. All patients improved regarding hemoptysis frequency and severity, and DVT without any recorded new events compared to the baseline at disease onset and no fatal outcomes were recorded during the duration of their follow-up.

Discussion

In this report, we describe the pattern of pulmonary vasculitis in a series of patients with HSS. To date, no criteria have been proposed to diagnose HSS; however, it is now established that recurrent thrombophlebitis and/or DVT, PAAs, and intra-aneurysmal in situ thrombosis with variable degree of hemoptysis are the constant and key features in patients with HSS otherwise normal coagulation profile [9]. In our report, all patients presented with DVT and other major vein thrombosis. Widespread vascular thrombotic events are dominant features in HSS, e.g., vena cava, intra-cardiac, jugular vein, iliac vein, femoral vein, and portal veins [9], and cerebral venous sinus thrombosis (CVST) [7]. Moreover, extensive arterial thrombosis reaching up to the level of the aorta and common iliac and celiac artery aneurysm was recently reported [9]. In this series, none had ocular lesions, genital ulcers, or arthritis. This is compatible with the findings of Fei et al. who found lower incidence of ocular involvement, genital ulcers, and arthritis in BD patients with vascular lesion than in those without [10].

In our report, all patients showed PAAs in different PA branches and ranging from main PA up to other peripheral branches, e.g. lobar, inter-lobar, and segmental, and distributed in both lung fields, and all PAAs are seats of intra-aneurysmal in situ thrombosis and mural wall enhancement on post-contrast CTPA images. An important detail that merits consideration in HSS is that the clots in the PA branches in HSS are mostly due to underlying arterial vasculitis rather than venous thromboembolism; the latter fact was explained recently in one patient with superficial thrombophlebitis without actual DVT who developed PAAs and intra-aneurysmal adherent in situ thrombosis [9]. Moreover, the thrombi in the lower extremities in BD and HSS are tightly adherent to the inflamed veins with no tendency for propagation [11]. Nevertheless, in HSS-related pulmonary vasculitis, intra-luminal thrombus evolve in situ due to underlying arterial wall vasculitis, which was documented by Hughes and Stovin themselves on pulmonary autopsy findings in two patients with ruptured PAAs [1]. Important to note in our report is that we showed that intra-aneurysmal in situ thrombosis which is adherent to arterial wall and mural wall enhancement seen on post-CTPA are characteristic and important radiological signs, which are reflecting true arterial wall inflammation due to the underlying vasculitic process; the latter is important to examine in future research involving larger number of patients in this domain. Taken together, pulmonary vasculitis in HSS can activate the coagulation cascade and initiate in situ thrombosis

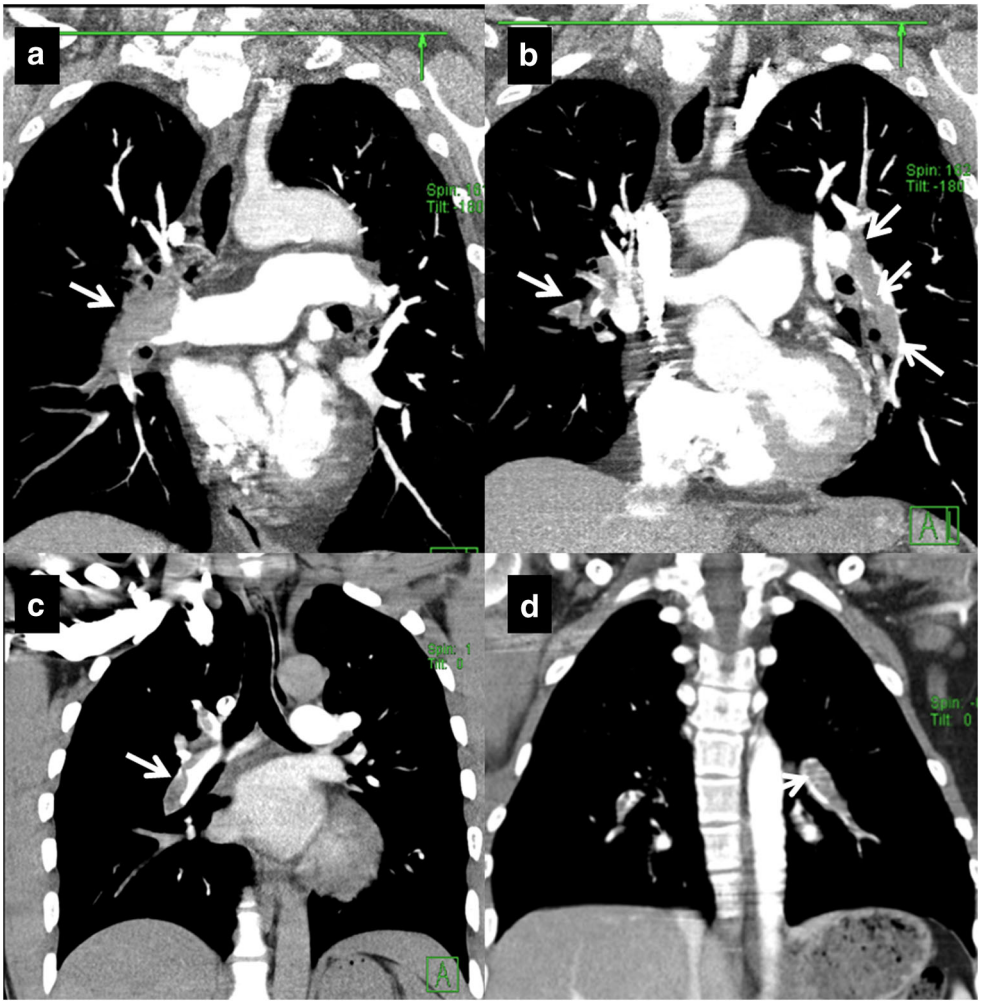

Fig. 2 **a** Coronal reconstruction CTPA image illustrating in situ thrombosis of the right main PA adherent to the mural wall and dilated right main PA. **b** Coronal reconstruction CTPA image showing bilateral main pulmonary arteries and lower lobar in situ thrombosis (white arrow). **c** Coronal reconstruction CTPA image showing eccentric in situ arterial thrombosis adherent to the mural arterial wall of the right main PA and lower lobar PA branch (white arrow). **d** Coronal reconstruction CTPA image showing eccentric in situ thrombosis and mural wall enhancement (white arrow) of the left lower lobar PA branch

and if left untreated may lead to rupture of PAA, with potential communication to an adjacent bronchus and eventually massive and fatal suffocative hemoptysis, which was recorded as the cause of death and in the autopsy findings in the early report by Hughes and Stovin [1].

In our case series in all patients, we used pulse methylprednisolone as the initial line of treatment in a dose of 1000 mg for five consecutive days as induction therapy; thereafter, oral corticosteroid therapy was prescribed in all patients as illustrated in Table 1. For maintenance of remission, we used, besides oral corticosteroids, either azathioprine in a dose of 150 mg/day (in five patients) or pulse cyclophosphamide for at least 1 year duration (in the other three patients). The treatment of pulmonary vasculitis in HSS and BD generally follows the same lines, as these are the only two conditions known to predispose to PAAs [7, 9, 11].

For the management of BD-related pulmonary vasculitis, the updated EULAR recommendations [12] advise, for treating PAAs, the use of high-dose glucocorticoids and cyclophosphamide and in refractory cases monoclonal anti-TNF antibodies should be considered. If there is a high risk of major bleeding, generally, PA embolization should be preferred to open surgery. Acute DVT in BD patients, and thus also in HSS cases, should be treated with glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide, or cyclosporine-A. In case of aneurysms of the aorta or in peripheral arteries, medical treatment with cyclophosphamide and corticosteroids is recommended as first choice, before considering operative repair [12]. The recurrence rate of DVT is significantly decreased when these patients are treated with immunosuppressives while anticoagulants did not reduce recurrence of DVT as shown in a meta-analysis of case-control studies [13]. If a patient also has extensive acute thrombosis, starting anticoagulation may be considered like in seven of our cases. When there is massive hemoptysis, due to leaking PAA, this is contraindicated, like in one of our patients. The decision to start with anticoagulants should be decided for each case individually, considering the patient presentation and the extent and severity of pulmonary vasculitis. The issue of anticoagulation in patients with HSS (and BD) remains complex, and further studies are needed before definite recommendations can be made. The use of anticoagulants and anti-

fibrinolytic agents in BD is not currently recommended by EULAR [12]. As biologic treatments, mostly TNF-inhibitors have become more important in the treatment of patients with BD, and further studies are needed to determine the place of biologics in HSS [13].

The strength of our report is that we presented detailed CTPA findings in eight patients with HSS simultaneously and illustrated a comprehensive approach to reach the correct diagnosis at an early stage and to avoid misdiagnosis with pulmonary thromboembolism. Moreover, the CTPA images presented can be used as reference images for the pattern of pulmonary vasculitis in HSS and as a diagnostic tool of assessment in this domain.

Conclusions

HSS is a systemic vasculitis that can virtually affect all minor or major venous and/or arterial vessels, intracardiac thrombosis, and CVST. In patients presenting with widespread vascular thrombosis, where HSS is clinically suspected, screening of coagulation profile seems mandatory. PAAs and adherent intra-aneurysmal in situ thrombosis and mural wall enhancement on post-contrast images are the main CTPA findings characteristic of pulmonary vasculitis in HSS, the latter can affect all PA branches ranging from the main PA to other peripheral branches, e.g., lobar, interlobar, and segmental. In this clinical setting, CTPA is considered to be the most important diagnostic tool to assess the degree and the extent of PA branches involved first, to establish the diagnosis and to start effective lines of treatment in order to avoid serious and potentially fatal consequences. Further studies are needed to determine the role of biologics in the treatment of HSS syndrome.

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Compliance with ethical standards

Disclosures None.

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