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Editorial

A critical analysis of 57 cases of Hughes-Stovin syndrome (HSS). A report by the HSS International Study Group (HSSISG)

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ABSTRACT

Background: Hughes-Stovin syndrome (HSS) is a systemic disease characterized by widespread vascular thrombosis and pulmonary vasculitis with serious morbidity and mortality. The HSS International Study Group is a multidisciplinary taskforce aiming to study HSS, in order to generate consensus recommendations regarding diagnosis and treatment.
Methods: We included 57 published cases of HSS (43 males) and collected data regarding: clinical presentation, associated complications, hemoptysis severity, laboratory and computed tomography pulmonary angiography (CTPA) findings, treatment modalities and cause of death.
Results: At initial presentation, DVT was observed in 29(33.3 %), thrombophlebitis in 3(5.3%), hemoptysis in 24 (42.1%), and diplopia and seizures in 1 patient each. During the course of disease, DVT occurred in 48(84.2%) patients, and superficial thrombophlebitis was observed in 29(50.9%). Hemoptysis occurred in 53(93.0%) patients and was fatal in 12(21.1%). Pulmonary artery (PA) aneurysms (PAAs) were bilateral in 53(93%) patients. PAA were located within the main PA in 11(19.3%), lobar in 50(87.7%), interlobar in 13(22.8%) and segmental in 42 (73.7%). Fatal outcomes were more common in patients with inferior vena cava thrombosis ($p = 0.039$) and ruptured PAAs ($p < 0.001$). Death was less common in patients treated with corticosteroids ($p < 0.001$), cyclophosphamide ($p < 0.008$), azathioprine ($p < 0.008$), combined immune modulators ($p < 0.001$). No patients had uveitis; 6(10.5%) had genital ulcers and 11(19.3%) had oral ulcers.
Conclusions: HSS may lead to serious morbidity and mortality if left untreated. PAAs, adherent in-situ thrombosis and aneurysmal wall enhancement are characteristic CTPA signs of HSS pulmonary vasculitis. Combined immune modulators contribute to favorable outcomes.

1. Introduction

Hughes-Stovin syndrome (HSS) was named after two British physicians (Drs. John Patterson Hughes and Peter George Ingle Stovin) in 1959. They described the clinical course of two Caucasian males with recurrent attacks of deep vein thrombosis (DVT), segmental pulmonary artery aneurysms (PAAs) with intra-aneurysmal thrombosis, cerebral venous sinus thrombosis (CVST) and right ventricle (RV) mural thrombus. Both patients died during suffocative attacks of massive hemoptysis, with autopsy proven ruptured pulmonary artery (PA) aneurysms (PAAs) into the adjacent bronchi [1]. Interestingly, this association had been described previously by Beattie and Hall in 1912 [2]. They described a 21 year old Caucasian male with a ruptured PAA and RV mural thrombus. Another report by Pirani et al. in 1949 described similar features in 14 year-old boy [3]. In both of these reports [2,3], the authors hypothesized that septic thrombophlebitis, leading to infected intracardiac thrombi and septic embolism to the pulmonary circulation was the cause for "mycotic" PAA formation. However, Kirk and Seal [4] suggested that a "mycotic" process was unlikely, given the involvement of lower extremity veins and venules, cerebral venous sinus thrombosis (CVST), systemic circulation aneurysms, as well as negative blood and bone marrow cultures. In 1961, the etiology was therefore hypothesized to relate to a systemic venous angiitis or collagen disease [5,6], which introduced corticosteroids as a potential therapeutic option [4–6].

The classic features of HSS include recurrent unexplained DVT, recurrent thrombophlebitis, venous and arterial thrombosis with or without aneurysm formation and PAAs with in-situ thrombosis [1–11]. It was not until 1962, that the eponym "Hughes-Stovin syndrome" was formally introduced in medical literature [7]. Of note, the pulmonary manifestations related to HSS were identified much earlier than Behçet's disease (BD) was described by Dr. Hulusi Behçet, who coined the classical triad of recurrent mouth, genital ulceration and iridocyclitis in three patients in 1937 [12].

The Hughes-Stovin International Study Group (HSSISG) is a multinational study group including authors from a variety of relevant specialties e.g. adult and pediatric rheumatologists, diagnostic and interventional radiologists, internists, pulmonologists, cardiologists, neurologists, vascular and cardiovascular surgeons. We included corresponding authors of previously published HSS case reports [13–45]. Each member provided detailed case data for further analysis, which was combined with other data collected by systematic literature review [46–49].

This report is the first attempt to describe a large cohort of patients with HSS, in order to analyze the variable clinical presentations, patterns of vascular involvement and associated pulmonary vasculitis, as well as to identify risk factors for significant complications and fatal outcomes. This preliminary report will provide a foundation, which can be used to determine diagnostic criteria and treatment recommendations for HSS patients in future HSSISG reports.

1.1. Patients and methods

The study included 57 published HSS patients; 43(75.4%) males and 14(24.6%) females. HSSISG members provided detailed clinical, radiological and treatment data for 41 patients [13–45]; while data from other cases were collected by systematic literature review [46–49]; including earlier case reports [1–4,7–11]. This systematic literature review was performed by searching Medline/Pubmed and EMBASE using the following keywords (Hughes-Stovin syndrome; pulmonary artery aneurysm in Hughes-Stovin syndrome; pulmonary vasculitis in Hughes-Stovin syndrome).

Due to the lack of diagnostic criteria for HSS, diagnosis of the condition in previous reports was based on the presence of typical disease features, including; (a): widespread vasculo-occlusive disease in the form of recurrent superficial thrombophlebitis, DVT, cerebral venous sinus thrombosis (CVST), intracardiac thrombosis or arterial thrombosis; (b): normal coagulation profiles including anti-cardiolipin (aCL) antibodies, anti-β2 glycoprotein I (β2GPI) antibodies, factor V Leiden mutation, prothrombin gene mutation, antithrombin III, protein C and protein S deficiencies; (c): Computed Tomography Pulmonary Angiography (CTPA) signs of PAAs with or without adherent intra-aneurysmal in-situ thrombosis or aneurysmal wall enhancement on post contrast CTPA images. In the early reports [1–4,7–11], the diagnosis may also have been made based on autopsy findings showing lymphocytic vasculitis of the PA branches. All reports [1–4,7–11,13–49] were reviewed for patient demographics, clinical presentations at disease onset, radiological

findings, laboratory investigations, treatment modalities and cause of death. We also collected information on the presence of superficial thrombophlebitis, DVT, oral or genital ulcers, respiratory symptoms (e.g., dyspnea, chest pain, cough), hemoptysis severity (mild hemoptysis was defined as <20 mL; moderate hemoptysis was 20 to 600 mL, and severe or massive was >600 mL in 24 h) and other constitutional symptoms.

1.2. Computed tomography pulmonary angiography and 3D volume rendering technique

Computed tomography (CT) scanners from each international center [13–18,22–24,26–32,35–37,39–42,44–46] were used to acquire images of the thorax in a caudocranial direction. In all studies, the chest field of view (FOV) is considered to be the widest rib-to-rib distance acquired during breath hold after inspiration. CT images are displayed with three different gray scales with the following parameters window width/level [HU] (600/1500) and mediastinal window (40/400). Images were reconstructed with a 512 × 512 matrix with 1-mm axial and 1.5-mm coronal slice thickness and 0.8-mm slice overlap [50].

All CTPA images were reviewed and interpreted with a focus on the following radiological signs: PAA(s) presence and distribution in the main, lobar, segmental, subsegmental PA branches; PAA diameter; aneurysmal wall enhancement; adherent intra-aneurysmal thrombosis; pulmonary artery pseudoaneurysms (PAPs), which are defined as sharply-demarcated contrast-filled aneurysmal lesions with a marginal hypodense peri-aneurysmal component (marginal thrombosis); bronchial artery aneurysms (BAAs); leaking "unstable" PAAs or BAAs with loss of aneurysmal wall definition; right ventricular strain (RVS) with interventricular septum flattening.

Three-dimensional CT volume rendering technique (VRT) was performed in some patients [19,22,33,36,44,45]. The arterial paths were evaluated in axial, coronal and sagittal planes. To prevent errors during 3D reconstruction, a mediastinal view was used to visualize the vessels, and a parenchymal view was used to visualize fissures and adjacent bronchi [51].

1.3. Contrast enhanced pulmonary magnetic resonance angiography (MRA)

Magnetic resonance angiography (MRA) was performed in five patients [15,18,26,38,40]. The protocol consisted of six breath-holds, each lasting 15–19 s. The core angiographic acquisition is a rapid heavily T1-weighted 3D spoiled gradient echo (SGRE) sequence, including: three-plane single-shot fast spin-echo (SSFSE) localizers, pre-contrast T1 weighted 3D SGRE, pulmonary arterial phase T1-weighted 3D SGRE, immediate post-contrast T1-weighted 3D SGRE, low flip angle post-contrast T1-weighted 3D SGRE, T1-weighted 2D axial or 3D SGRE with fat saturation [52].

2. Multimodal endovascular management

Catheter pulmonary arteriography (CPA) is the gold standard technique for identification of feeding vessels supplying the PAA(s). Specifically, it is important to identify the location, type, and diameter of the feeding vessels. Other imaging procedures for evaluation of the pulmonary complications of HSS are detailed in previous reports [17,19,22,29,36,41,43,49].

3. Ethics

The study was approved by the applicable research ethics committee (approval number IORG 0009738 N 22^0/OMB 0990-0279).

4. Statistical analysis

Data analysis was performed using SPSS version 15.0.1. Continuous data were described using mean (±SD) and categorical data using frequencies and percentages. The non-parametric Chi-Square test of independence was used to determine if significant relationships existed between two nominal variables. The Independent Samples *t*-test was used to compare the means of continuous variables between patients with and without fatal outcomes. We evaluated for associations between other demographic, clinical and radiological signs with fatal outcomes by Chi-Square test. Regression analysis was performed to examine the relationships between fatal outcomes and other independent variables. In all tests, a p-value <0.05 was considered statistically significant.

5. Results

The study included a total of 57 HSS cases (43 males), mean age 33.8 years and mean disease duration 54.2 months. Presenting clinical features varied widely among patients: with DVT in 19(33.3%), superficial thrombophlebitis in 3(5.3%), hemoptysis in 24(42.1%), neurological symptoms due to underlying CVST (headache and diplopia) and seizures each in 1 patient (1.8%), respectively. During the entire course of disease, superficial thrombophlebitis occurred in 29 (50.9%) patients, while DVT occurred in 48 (84.2%) patients, and was bilateral in 13 (22.8%) patients. Recurrent hemoptysis occurred in 53(93.0%) patients. Death due to massive suffocative hemoptysis occurred in 12(21.1%) patients. Other detailed demographic, initial disease presentations, other clinical manifestations, distribution of vascular thrombosis and fatal outcome are summarized in Table 1. We present the geographical distribution of cases by patient nationality in Fig. 1.

An abnormal coagulation profile was found in 3(5.3%) patients. Two patients had positive aCL antibodies in two patients 2(3.5%), although both were negative for antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), and anti-β2GPI antibodies. One patient had a Factor V Leiden mutation.

Regarding treatment, 32 patients (56.1%) received initial pulse methylprednisolone and 47(82.5%) received oral corticosteroids (CS) as maintenance therapy. Ten (17.5%) patients received oral CS as a single agent, while 39 (68.4%) patients used steroids in combination with other immunosuppressant medications. Eight (14%) patients did not receive any immunosuppression. Twenty-four (42.1%) patients received IV pulse cyclophosphamide (CP). Azathioprine (AZA) maintenance therapy was received in 18(31.6%). Anti-TNF therapy was received by 4 (7%) patients. We present additional data on laboratory results and treatment in Table 2.

Plain film chest x-ray showed pulmonary opacification in 48(84.2%) patients (Fig. 2a). Direct pulmonary angiography was performed in 20 (35.1%), pulmonary MRA in five (8.8%) patients, CTPA in 47(82.5%) patients (Figs. 2 and 3) and 3D VRT in 4(7%) patients (Fig. 2b and c). CTPA showed unilateral PAAs with in-situ thrombosis in 4(7%) patients and bilateral PAAs in 53(93%) patients (Fig. 2d–i).

CTPA also identified aneurysmal wall enhancement with adherent in-situ thrombosis in 44(77.2%) patients (Fig. 2d), bronchial artery aneurysms (BAAs) in 8(14%) (Fig. 2c), pulmonary artery pseudoaneurysms (PAPs) in 6(10.5%) (Fig. 3a–e), pulmonary infarction in 7 (12.3%), and ruptured PAA in 19(33.3%) (Fig. 2 e, f, h). Surgical lobectomy was performed for 14(24.6%) patients, while endovascular coiling and/or embolization of either PAAs or BAAs (Fig. 4) were performed in 11(19.3%) patients [19].

We found significant associations between patients that experienced fatal outcomes and the presence of IVC thrombosis ($p = 0.039$) and ruptured PAAs ($p < 0.001$) (Fig. 3b and c). Death was less common in patients that were treated with oral corticosteroids ($p < 0.001$), pulse cyclophosphamide ($p < 0.008$), azathioprine ($p < 0.008$), or combined immunosuppression ($p < 0.001$). Those that underwent PAA

Table 1
Detailed demographic, clinical presentations, major arterial and/or venous thrombotic events among the studied group of HSS patients.

HSS patients (n = 57)			
Variables	Values	Variables	Values
Age (Years)	33.84 ± 12.05	Age at onset (Years)	31.44 ± 10.58
Median (IQR)	35(16.50)	Median (IQR)	33(14)
Male	43(75.4%)	Disease duration (Months)	54.18 ± 61.45
Female	14(24.6%)	Median (IQR)	36(52.50)
Fever	40(70.2%)	Total DVT	48(84.2%)
Weight loss	27(47.4%)	Common femoral vein	20(35.1%)
Cough	54(94.7%)	Iliofemoral vein	2(3.5%)
Dyspnea	49(86.0%)	Common iliac vein	16(28.1%)
Pleuritic chest pain	5(8.8%)	Popliteal vein	20(35.1%)
Total hemoptysis (mL/24 h)	53(93.0%)	Anterior tibial vein	3(5.3%)
None	4(7%)	Posterior tibial vein	4(7%)
Mild (<20 mL/24 h)	16(28.1%)	IVC	19(33.3)
Moderate (20 to 600 mL/24 h)	17(29.8%)	Basilic vein	1(1.8%)
Massive (>600 mL/24 h)	20(35.1%)	Internal jugular vein	4(7%)
Fatal suffocative hemoptysis	12(21.1%)	Brachial vein	1(1.8%)
Genital ulcers	6(10.5%)	Pelvic veins	1(1.8%)
Mouth ulcers	11(19.3%)	Renal vein	1(1.8%)
Superficial thrombophlebitis (Total)	29(50.9%)	Hepatic veins	1(1.8%)
First presentation at disease onset		Budd-Chiari syndrome	1(1.8%)
DVT	19(33.3%)	Brachial vein	1(1.8%)
Superficial thrombophlebitis	3(5.3%)	Portal vein	1(1.8%)
Hemoptysis	24(42.1%)	CNS involvement	
DVT and hemoptysis	10(17.5%)	Transverse myelitis	1(1.8%)
Headache and diplopia	1(1.8%)	Papilledema	1(1.8%)
Seizures	1(1.8%)	Retinal occlusive vasculitis	1(1.8%)
Arterial thrombosis		CNS vasculitis	1(1.8%)
Aorta	2(3.5%)	Intracardiac thrombosis	
Common iliac	2(3.5%)	Right atrium	5(8.8%)
Thrombosed arterial aneurysms		Right ventricle	6(10.5%)
Superior mesenteric artery	1(1.8%)	Right atrium and right ventricle	1(1.8%)
Celiac artery	1(1.8%)	Cerebral venous sinus thrombosis	
Hepatic artery	1(1.8%)	Superior sagittal sinus	4(7%)
Splenic artery	1(1.8%)	Superior sagittal and Lateral sinus	1(1.8%)
External carotid artery	2(3.5%)	Sigmoid sinus	2(3.5%)
Superior mesenteric artery	1(1.8%)	Transverse sinus	2(3.5%)
Basilic artery	1(1.8%)	Follow up in months	28.30 ± 29.42
Brachial artery	1(1.8%)	Fatal outcome	12(21.1%)

Data are mean ± (SD), and others are number (%); IQR: InterQuartile Range HSS: Hughes-Stovin syndrome; DVT: Deep vein thrombosis; Inferior vena cava (IVC), SVC: superior vena cava central nervous system (CNS).

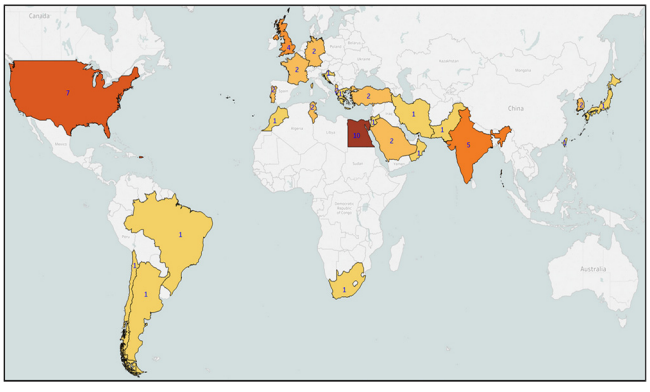

Fig. 1. Map graph showing the geographic distribution of the studied patients according to their country of origin.

embolization and/or coiling were also less likely to have fatal outcomes, although this was not statistically significant ($p = 0.057$). There was no significant association observed between fatal outcomes and gender ($p = 0.475$), recurrent thrombophlebitis ($p = 0.473$), DVT ($p = 0.425$), anemia ($p = 0.656$), dyspnea ($p = 0.115$), cough ($p = 0.592$), fever ($p = 0.262$), pleuritic chest pain ($p = 0.227$), intra-cardiac thrombosis ($p = 0.706$), CVST ($p = 0.131$), bronchial artery aneurysm ($p = 0.768$) or arterial thrombosis ($p = 0.425$). However, severe hemoptysis was more frequently associated with dyspnea ($p = 0.043$), IVC thrombosis ($p = 0.043$), ruptured PAAs ($p < 0.001$), DVT ($p = 0.015$), lobar PAAs ($p = 0.053$), arterial thrombosis ($p = 0.008$). Severe hemoptysis was less common in patients treated with corticosteroids ($p = 0.037$), combined immunosuppression ($p < 0.001$), as well as those with lobar PAAs ($p = 0.053$), DVT ($p = 0.015$) or arterial thrombosis ($p = 0.008$).

In further regression analysis, ruptured PAA was strongly associated with mortality ($p < 0.001$). Combined immunosuppression was strongly associated with lower mortality ($p < 0.001$). We describe this regression analysis in detail in Table 3.

Table 2
Laboratory findings and treating plans among the study group.

HSS patients (n = 57)	
Variables	Values
Laboratory findings	
ESR 1st hour (mm/h)	51.25 ± 26.06
Median (IQR)	45(37)
CRP (mg/dl)	15.37 ± 14.470
Median (IQR)	11(14.75)
HB (gm/dl)	11.06 ± 1.790
Median (IQR)	11.1(2.6)
Anemia	30(52.6%)
WBCs (10^{10}/L)	8.86 ± 3.819
Median (IQR)	8.2(3)
Platelet count (10^3/μL)	332.33 ± 86.47
Median (IQR)	340(60)
Abnormal coagulation panel	3(5.3%)
aCL autoantibodies	2(3.5%)
Factor V Leiden mutation	1(1.8%)
anti β_2GPI antibodies	0(0.0%)
Protein C and protein S assay	0(0.0%)
Prothrombin gene mutation	0(0.0%)
Medical lines of treatment	
Patients received Pulse Methylprednisolone	32(56.1%)
Dose of Pulse Methylprednisolone (mg/day)	535.09 ± 489.71
Median (IQR)	750(1000)
Duration of pulse Methylprednisolone (days)	2.28 ± 2.17
Patients received Oral steroid maintenance (mg/day)	47(82.5%)
Dose of Oral steroid maintenance (mg/day)	31.67 ± 18.59
Median (IQR)	30(15)
Duration of oral steroid therapy (Months)	31.67 ± 18.59
Median (IQR)	12(6)
Patients received Pulse Cyclophosphamide IV (mg/month)	24(42.1%)
Dose of Pulse Cyclophosphamide IV (mg/month)	429.825 ± 469.504
Median (IQR)	0.0(1000)
Duration of pulse Cyclophosphamide (Months)	5.04 ± 6.24
Patients received azathioprine maintenance	18(31.6%)
Dose azathioprinemaintenance (mg/day)	41.23 ± 65.55
Median (IQR)	0.0(125)
Duration of azathioprine therapy (Months)	6.49 ± 18.84
Patients received Anti-TNF blockers	4(7.0%)
Duration of Anti-TNF blockers(Months)	1.912 ± 6.10
Patients received single immunomodulator (Oral Steroids)	10(17.5%)
Patients received combined immunomodulators	39(68.4%)
No immune modulators received	8(14%)
Patients received anticoagulation therapy	34(59.6%)

Data are mean ± (SD), and others are number (%); IQR:InterQuartile Range; HSS: Hughes-Stovin syndrome; aCL: anticardiolipin antibodies; (β2GPI) β2 glycoprotein I; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; WBCs: White Blood Cells; Anti-TNF: Anti-tumor necrosis factor.

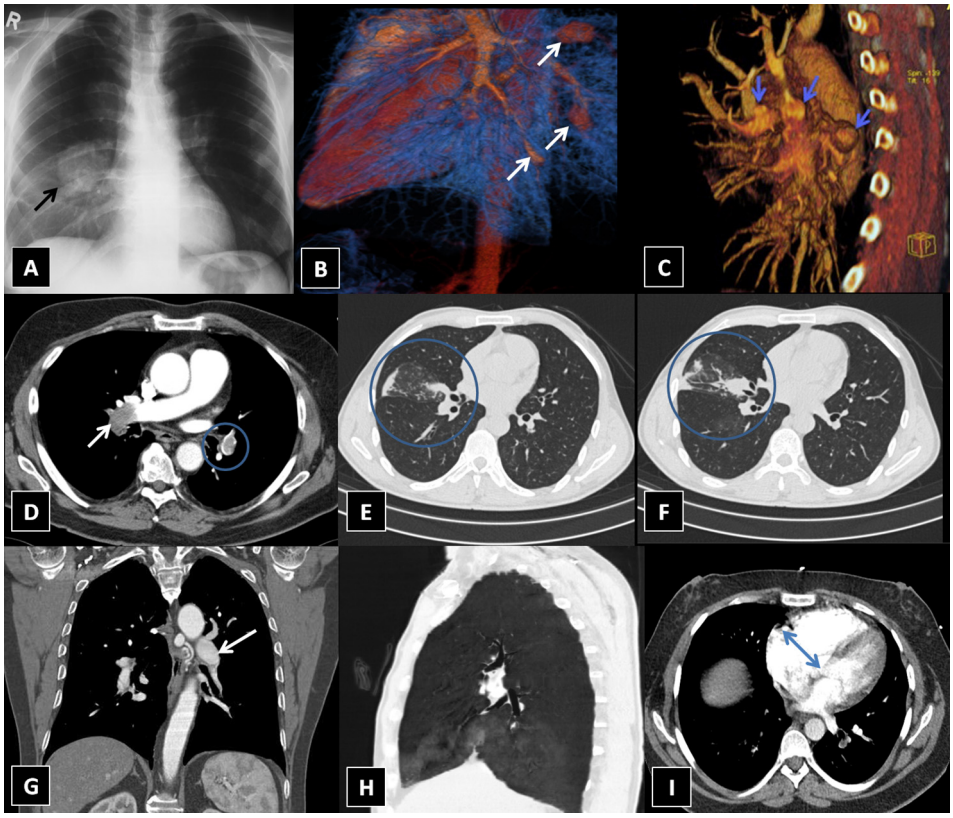

Fig. 2. (a): plain chest X-ray anteroposterior (AP) showing right perihilar lobulated opacity with veiling lower lobar lung fields (black arrow). (b): 3D volume rendering technique (VRT), showing pulmonary artery aneurysms (PAAs) at different stages of development (white arrows). (c): 3D-VRT showing multiple bronchial arterial aneurysms (blue arrows) (Courtesy of Natalia Jaramillo; International Journal of Cardiology 178 (2015) e5-e7). (d): right main pulmonary artery thrombosis (white arrow) demonstrating typical arterial wall enhancement (blue circle); the thrombosis in HSS is adherent because it evolves in-situ as a result of underlying wall inflammation. (e and f): CTPA axial lung window showing leaking PAA involving the right main pulmonary artery (PA) with pulmonary opacity in the lateral segment of the middle lung lobe indicating disturbed true PAA with loss of arterial wall definition and parenchymal hemorrhage (blue circles). (g): CTPA (mediastinal window) with coronal 2D reconstruction showing PAA (white arrow) involving small right lower lung lobar PA branch. (h): Minimum-intensity projection (MIP), sagittal 2D reconstruction showing veiling opacities in the lower lung lobes basal segments due to alveolar hemorrhage from leaking PAA. (i): CTPA showing inter ventricular septum flattening and right ventricular enlargement (double blue arrow) when compared to left ventricle indicating right heart strain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

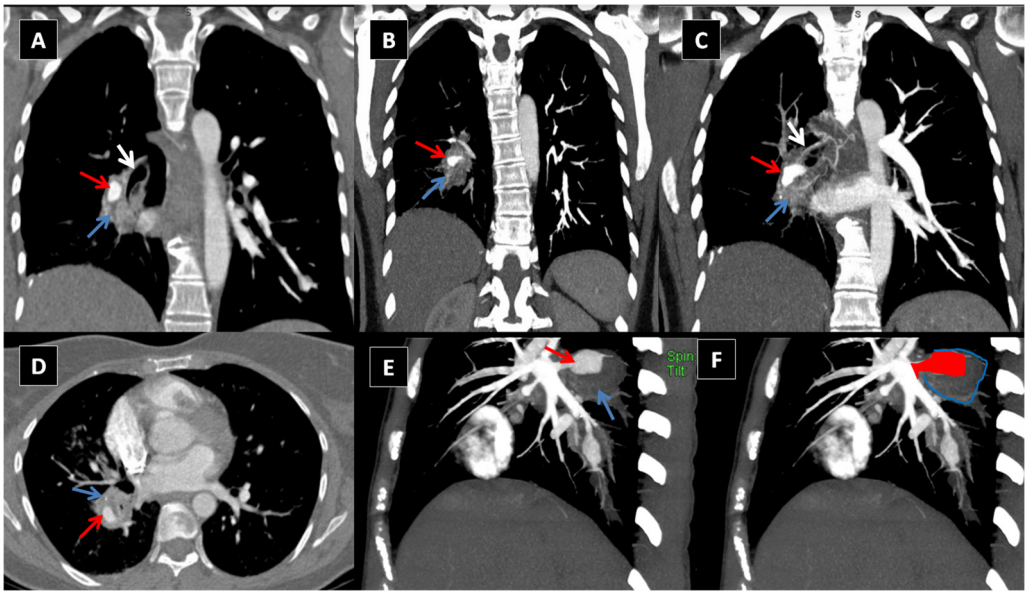

Fig. 3. (a, b and c) CTPA coronal 2D mediastinal window showing different patterns of pulmonary artery pseudoaneurysms (PAPs) involving right lower lobar PA branch. (d) axial and (e) sagittal oblique CTPA; notice the sharply demarcated contrast filled aneurysmal lesion (red arrows) with variably sized marginal hypodense component "marginal thrombosis" (blue arrows) entangling the sharply-demarcated contrast-filled ectatic lumen. An air bronchogram is also seen in close relation to the marginal thrombosis (a, c) (white arrows). (f) well-demarcated contrast-filled lumen (red color) entangled with hypodense component (marginal thrombosis) (marked with blue line).

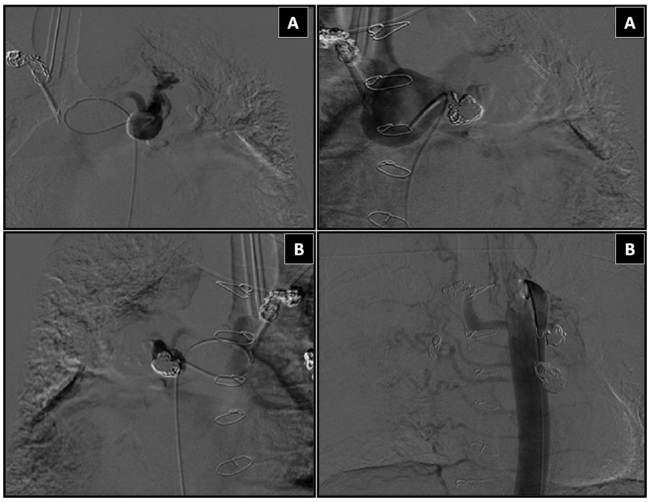

Fig. 4. Digital subtraction *bronchial* angiography showing bronchial *artery aneurysm* before and after coiling with remarkable with complete regression. (Courtesy of Natalia Jaramillo; International Journal of Cardiology 178 (2015) e5-e7).

Table 3
Regression analysis module showing the relationship between fatal outcomes as dependent variable and other selected demographic, clinical, CTPA findings and different lines of treatment as independent variables.

Regression analysis module	t	Sig.	95% Confidence Interval for B	
			Lower Bound	Upper Bound
(Constant)	2.901	0.006	0.176	0.973
Age (Years)	−1.483	0.145	−0.011	0.002
Disease duration(Months)	−0.134	0.894	−0.001	0.001
Hemoptysis severity	0.105	0.917	−0.080	0.089
DVT	0.392	0.697	−0.142	0.210
IVC thrombosis	0.212	0.833	−0.126	0.156
Intra-cardiac thrombosis	0.047	0.962	−0.088	0.092
Ruptured PAA	5.020	0.000**	0.242	0.566
PA coil embolization	−0.705	0.484	−0.273	0.131
Combination therapy	−4.189	0.000**	−0.354	−0.124

Dependent variable (Constant) fatal outcome; DVT: Deep vein thrombosis; IVC: Inferior vena cava, CTPA: computed tomography pulmonary angiography; TNF: Anti-tumor necrosis Factor; PAAs: pulmonary artery aneurysms; PAA: pulmonary artery aneurysm; PA: pulmonary artery.

6. Discussion

To our knowledge, this report represents the largest cohort of patients with HSS ever collected and provides additional information on the variable clinical manifestations of HSS. The main aim of this preliminary report was to critically analyze the clinical presentations of HSS and to determine factors associated with mortality. This understanding can promote earlier disease recognition, improved understanding of complications associated with the condition and provide information of the efficacy of various treatment modalities.

Earlier case reports [1–4,7–11] have involved male patients between 14 and 37 years of age, with survival times ranging from several months to eight years after disease onset. All reported fatalities have been caused by suffocating massive hemoptysis. None of those patients received corticosteroid therapy or other immunomodulators, given the uncertain nature of the disease and lack of established treatment options. [1–4,7–11].

In our report, 11(19.3%) patients had mouth ulcers and 6(10.5%) had genital ulcers, but no patients had iridocyclitis. The predominant clinical manifestations were widespread vasculo-occlusive disease occurring as minor or major thrombotic events in both venous and arterial systems with or without aneurysmal formation (Table 1). In our study, IVC thrombosis was associated with a higher mortality rate. Pirani et al. [3] documented a case in 1912 where IVC thrombosis was obliterated with connective tissue and heavily infiltrated with lymphocytes. These findings suggest that thrombosis of the major veins in HSS is due to an underlying venular wall inflammation, leading to activation of the coagulation cascade and subsequent widespread vascular thrombosis. This highlights the potential therapeutic role of immunosuppression, in order to dampen widespread arterial and venular wall inflammation and pulmonary vasculitis.

We hypothesize that fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT may be a useful tool to assess the degree of vascular bed inflammation, but to our knowledge there is currently no data available in HSS patients. Compared with FDG-PET, CTPA still is considered the gold standard imaging technique for the pulmonary manifestations of HSS. CTPA can provide accurate information regarding the morphological patterns of pulmonary artery aneurysms at various stages of development in HSS. Unfortunately, there is no specific test or biomarker currently available to diagnose HSS, which remains a diagnosis based on typical clinical and radiological features.

A great of information regarding HSS came from the early report published by Hughes and Stovin, [1] including detailed autopsy findings of the major veins, arteries, heart, CNS and lungs. Hughes and Stovin [1] highlighted that in addition to PAAs, bronchial arteries can become involved by the same process. Currently, typical pulmonary findings are confirmed by CTPA, which has been supplemented with multiplanar reconstruction (MPR) [13–18,22–24,26–32,35–37,39–42,44–46], 3D VRT software [19,22,33,36,44,45], and pulmonary MRA [15,18,26,38,40] in recent reports. Hughes and Stovin [1] also documented that the primary features seen in their two cases were consistent with those reported earlier by Beattie and Hall in 1912 [2] and Pirani et al. in 1949 [3]. Beattie and Hall described as early as 1912 [2] and long before the description of BD associated pulmonary vasculitis [53-55].

Based on our current understanding of HSS and the additional information available with modern imaging techniques, we know that pulmonary vasculitis in HSS could affect almost every pulmonary arterial branch. In our case series, the main PA was involved in 18 cases, the lobar branches in 50(87.7%), interlobar branches 13(22.8%) and segmental branches in 42(73.7%). Bilateral involvement occurred in 53 (93%) patients. Any involved arterial branches can become the site of aneurysmal formation and in-situ thrombosis. Using CTPA images, we documented intra-luminal “in-situ” thrombus, which was adherent to the aneurysmal wall and occurred together with aneurysmal wall enhancement in 44(77.2%) patients (Fig. 2d). Aneurysmal wall enhancement documented by CTPA is suggestive of arterial wall inflammation due to an underlying vasculitic process. This is consistent with prior histopathological reports on autopsy specimens [1,2,4,7–11]. Importantly, Pirani et al. [3] in 1949 reported histopathological sections through the wall of a ruptured PAA and showed extensive lymphocytic infiltrations and disruption of the muscular layers. Similar findings were also reported by Kirk and Seal in 1964 [4], Kinjo et al. in 1978 [9], and Kopp and Green in 1962 [7]. Acute leaking from “true PAA” are usually symptomatic, with CTPA imaging demonstrating loss of aneurysmal wall definition and perianeurysmal alveolar hemorrhage (i.e., ground-glass opacification and consolidation), with air-bronchograms in the hemorrhagic process within in the adjacent lung parenchyma (Fig. 2 e, f, h). Chronic leaking through an inflamed aneurysmal wall and subsequent extra-luminal extension of the inflammatory process is the most serious disease complication. This can result in the formation of pulmonary artery pseudoaneurysm (PAP), which differs morphologically and radiologically from “true PAA”. PAP are radiologically defined in our report as a sharply-demarcated contrast-filled ectatic lumen, with a marginal hypodense perianeurysmal component representing thrombosis (Fig. 3a–f) and associated air bronchograms (Fig. 3a and c). This radiologic pattern can progress to fatal suffocative hemoptysis

[1–4,7–11,27,33,34,39,47]. As such, we consider pulmonary artery pseudoaneurysms (PAPs) to be the most common cause of fatal hemoptysis in HSS. Histologically, a true PAA is a focal dilatation of all three layers of the vessel wall, whereas PAP involve only the external layers of the arterial wall (i.e., medial and adventitial layers). Therefore, PAPs are associated with a higher risk of rupture compared with "true PAA", in part due to the relatively low resistance of the surrounding tissues [56]. We believe that PAP may develop as a progression of untreated "true PAA", as described in older autopsy reports [4,7,9].

CTPA also plays an important role in the follow-up HSS patients, to evaluate for PAA regression and to exclude additional sequelae along the pulmonary arterial branches that may necessitate augmentation of immunomodulators and/or PAA coil embolization (such as leaking PAA or the presence of a PAP). Coil embolization may be indicated on an urgent basis without waiting for the effect of immunomodulators to control a rapidly progressive PAA with high risk of rupture. Moreover, PAA coil embolization may be life-saving option in certain critical situations (e.g., leaking PAA and/or bronchial artery aneurysms (BAAs) with loss of aneurysmal wall definition, unstable PAP or in PAA associated with intracardiac thrombus). When intracardiac thrombus exists and anticoagulation is required, securing potentially serious PAA and/or BAA is a priority and one should not wait for immunomodulation to become effective over a period of months. In our study, intracardiac thrombosis was observed in a total of 12(21.1) patients, with right atrial location in 5(8.8%), right ventricular location in 6(10.5%) and combined right atrium and RV location in another one patient 1(1.8%). Interestingly in the most recent report biventricular intracardiac thrombus formation and pericardiac effusion was recently reported in one patient [57].

In our report massive hemoptysis was the cause of death [1,2,7–9,27,33,34,39,47] in 12(21.1%) patients. Early initiation of immunomodulatory drugs, either as single agents or in combination were significantly associated with favorable outcomes and a lower rates of mortality. Hence, early diagnosis and immunosuppression initiation has been associated with improved patient survival in HSS. We stress the importance of careful consideration of CTPA radiological signs while treating HSS patients presenting with hemoptysis. Anticoagulation therapy should be stopped in case of leaking PAA with loss of aneurysmal wall definition associated with parenchymal hemorrhage (Fig. 2 e,f,h) and/or PAP lesion (Fig. 3a–f). In this clinical setting, endovascular coiling is advisable on urgent basis to avoid unpredictable massive hemoptysis.

In our report, positive aCL antibodies were observed in two patients (3.5%), with negative ANA, negative anti-DNA and negative anti β_2GPI. Interestingly this finding has also been previously reported in BD patients [58–60]. Although the levels of aCL antibodies are typically higher in BD, no significant differences were observed in systemic clinical manifestations between aCL positive and negative patients with BD [58]. However, it is not believed that aCL plays a primary role in the pathogenesis of BD, and no positive associations were observed between aCL and thrombotic events in BD as might be expected [59]. The reported frequency of aCL was found to be 9.5% in studies from Turkey, compared with 25.5% in other series ($p < 0.0001$). The significantly lower frequency of aCL autoantibodies in Turkish BD patients compared with other series may indicate that environmental and/or genetic factors may play a role in production of aCL antibodies in BD [59]. In our study and other studies in BD patients, aCL antibody positivity has not associated with positive anti-β_2GPI antibodies, differentiating these disorders from systemic lupus erythematosus [60].

The strength of our report is that it is the first attempt to critically analyze HSS manifestations and outcomes in a large number of patients using an international study group. It provides a foundation for the development of diagnostic criteria and treatment recommendations for this rare disorder. Our future directions include providing detailed descriptions of the CTPA findings in HSS and differentiating radiological features from pulmonary thromboembolism and other similar disorders.

7. Conclusions and recommendations

HSS remains an under-recognized clinical entity and the diagnosis is based on a high degree of clinical suspicion and careful interpretation of clinical and radiologic features.

I. Diagnosis: widespread vascular thrombosis involving either the minor or major venous and/or arterial vascular bed or features of PAAs associated with adherent in-situ thrombosis and arterial wall enhancement on CTPA, in patients with normal coagulation profile, should raise the possibility of HSS.
II. Management: combined immunosuppression contributed significantly to favorable outcomes in our series. Decisions regarding medical treatment should be guided by follow-up CTPA to ensure pulmonary disease remission. Endovascular PAA coil embolization may be a life-saving option in certain critical scenarios such as leaking PAAs with loss of aneurysmal wall definition or PAPs
III. Prognosis: if left untreated, "true" PAAs in HSS can progress to PAPs. This can lead to aneurysmal wall disruption and potential communication with adjacent bronchus, producing sudden fatal suffocative hemoptysis.

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Declaration of Competing Interest

None of the authors has any conflicts of interest to declare.

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