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EDITORIAL

Hughes-Stovin syndrome (HSS): current status and future perspectives

Sebastian Sanduleanu[1,2] · **Tim L. T. A. Jansen**[1]

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In 1959, John Patterson Hughes and Peter George Ingle Stovin, two British physicians, described two male patients presenting with an undefined systemic illness characterized by severe recurrent hemoptysis due to deep venous thrombosis (DVT) and segmental pulmonary artery aneurysms (PAA) [1]. At autopsy a rupture of the arterial aneurysms into the adjacent bronchi had occurred in both patients who died suffocating by massive hemoptysis [1]. A similar description was given as early as 1912 by Beattie and Hall [2]. In 1962, the first paper using the eponym "Hughes-Stovin syndrome" (HSS) was published [3]. But what exactly is HSS?

HSS is considered a syndrome with a sporadic occurrence and with only 90 cases described in PubMed. Most of these are single case reports. All of the fatalities reported in HSS were related to unpredictable massive hemoptysis due to rupture of pulmonary artery aneurysms with suffocation as was originally described by Hughes and Stovin [1]. Due to a lack of diagnostic criteria, the diagnosis is mainly based on classical clinical features of a syndrome with vascular occlusive disease (venous and/or arterial), with a normal coagulation profile. A crucial element to establish the diagnosis of HSS appears to be the characteristic computed tomography pulmonary angiography (CTPA) revealing images with pulmonary artery aneurysm (PAA) associated with adherent intra-aneurysmal in situ thrombosis. Pulmonary artery aneurysm (PAA) is a rare abnormality of the diseased pulmonary vasculature and represents one of the hallmark findings in HSS. The incidence of PAA is estimated to be 1 in 14,000 based on a landmark study conducted on 19,571 autopsies at the Mayo Clinic by Deterling and Clagett in 1947 [4]. The mortality rate associated with the rupture of a pulmonary artery aneurysm (PAA) has been reported from 50 to 100%: death ensuing secondarily to aspiration and asphyxia after intrapulmonary hemorrhage. Recently, the HSS International Study Group (HSSISG) published the radiological features in their initial report following a critical overview of 57 HSS cases [5]

For the first time since its original description in 1959 by Hughes and Stovin, the international study group HSSISG created a comprehensive reference atlas of computed tomography pulmonary angiography (CTPA) images, a guide that defines the wide spectrum of CTPA findings as have been observed in HSS. The atlas may best serve categorizing clinical pictures during the course of HSS-related pulmonary vasculitis and possibly to find appropriate therapeutic decisions based on the CTPA features of each individualized pulmonary lesions; see Fig. 1.

Individual pulmonary artery aneurysms were categorized into different radiographic and morphological patterns ranging from "true" PAA, to bronchial artery aneurysm (BAA), to "false" pulmonary artery pseudoaneurysm (PAP), to unstable PAA/PAP aneurysms based on signs of extraluminal hemorrhage and signs of right ventricular strain in the context of altered pulmonary hemodynamics and pulmonary hypertension. The CTPA images give the clinician encountering HSS a base understanding of the radiological signs of PAA/PAP lesions, albeit not setting clear radiological thresholds for PAA/ BAA/PAP lesions that warrant therapeutic intervention. Furthermore, the underlying pathophysiological/immunological changes in the disease are only briefly touched upon, expectedly due to the sporadic occurrence of extensive autopsy reports.

Early signs of vasculitis in HSS present themselves as aneurysmal wall enhancement on post-contrast phase CTPA-acquired images [10]. Stable aneurysmal disease is characterized by a contrast-filled dilation in the pulmonary artery (or a variably sized marginal hypodense peri-aneurysmal component in pseudo-aneurysmal disease) as well as the lobar/segmental bronchial branches [10]. Unstable

✉ Tim L. T. A. Jansen
tjansen@VieCuri.nl

Sebastian Sanduleanu
ssanduleanu@VieCuri.nl

[1] Department of Rheumatology, VieCuri Medical Center, Venlo, Netherlands

[2] Maastricht University Medical Center, Maastricht, Netherlands

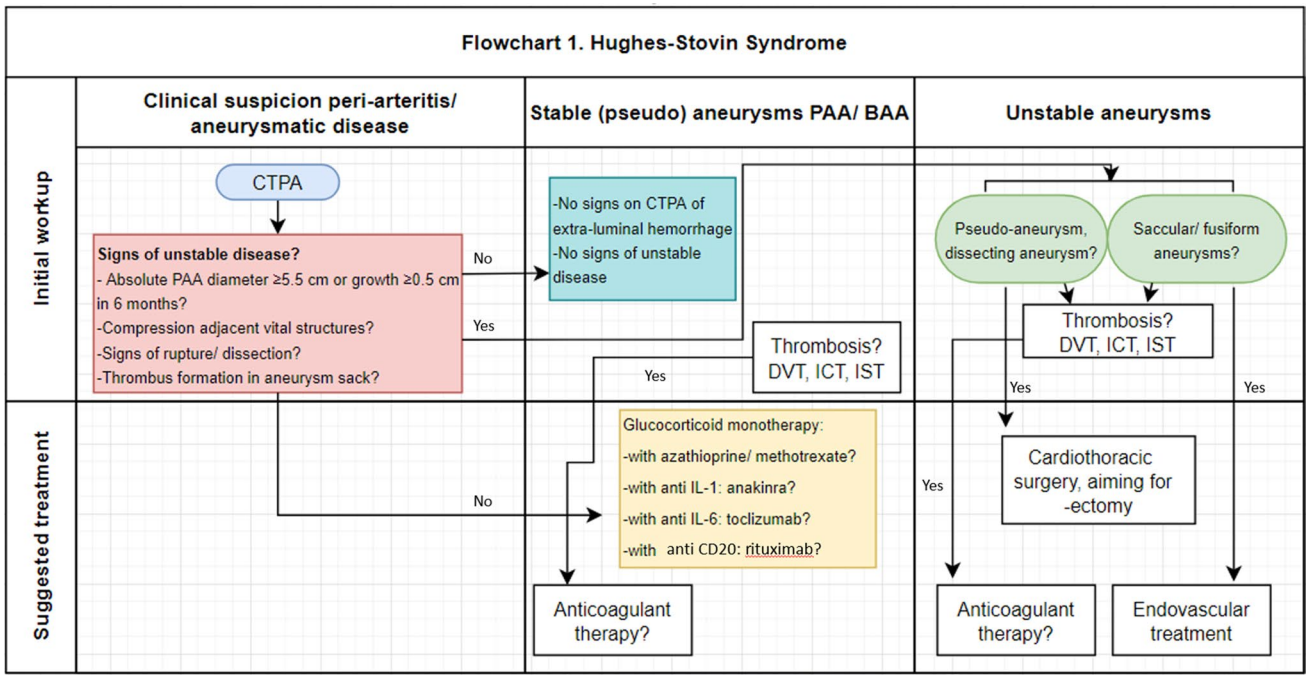

Fig. 1 Flowchart suggested initial workup/treatment of patients with HSS. Abbreviations: CTPA, computed tomography pulmonary angiography; DVT, deep venous thrombosis; ICT, intracardiac thrombosis; IST, in situ thrombosis PAA/BAA/PAP

aneurysmal disease is characterized by signs of extra-luminal leakage, such as loss of aneurysmal wall definition and peri-aneurysmal ground-glass opacification/consolidation with possible signs of air bronchograms (dark air–filled bronchi being made visible by the opacification of surrounding alveoli) [10].

The research agenda is formulated by the international study group HSSISG to compare CTPA findings such as HSS-related in situ PAA/BAA/PAP thrombosis (IST) as sign of a vasculitic process versus pulmonary thromboembolism (PTE). The pulmonary artery thrombosis is thought to develop in situ due to the inflammation of the arterial wall and not as thromboembolism developing from peripheral vein thrombosis. Intracardiac thrombi appear to be a result of endomyocardial fibrosis, a sequela of vasculitis involving the endocardium, myocardium, or both. Deep venous thrombosis, a highly common phenomenon in HSS, is also thought to be a sequela of vasculitis, thrombophlebitis, and subsequent thrombus formation [6].

The CTPA findings are different and combined with clinical conditions may well impose important therapeutic implications. In both clinical conditions, thrombosis dominates the clinical presentation, and thus anticoagulation is an essential line of treatment. Likewise according to the HSSISG, conditions such as IST and PTE appear to be pathophysiologically distinct entities; PTE is caused by a propagating thrombus from the venous periphery to the lungs, whereas in HSS, the thrombus typically evolves in situ due to the underlying pulmonary arterial wall hiding a vasculitic process being adherent as previously demonstrated in autopsy reports [1]. PTE, on the other hand, are serpiginous and extremely mobile, traveling through the bloodstream from the deep venous system to lodge in the pulmonary artery branches. Taken together, in situ thrombosis should be the official radiological term to use in order to define the adherent intraluminal thrombosis seen in HSS-related pulmonary vasculitis [5, 7, 8].

Nonetheless, the therapeutic approaches are quite different, as in the case of *pulmonary thromboembolism*, anticoagulation is mandatory, but in the case of HSS with *active pulmonary vasculitis plus pulmonary aneurysm(s)* associated with in situ thrombosis, anticoagulation may have to fatal consequences, in case of unstable true PAA with parenchymal hemorrhage or unstable PAP lesion [5]. Pathologically, at biopsy a necrotizing lymphocytic vasculitis has been found [9], leading to questions on efficacy of early glucocorticoids and/or anakinra (interleukin 1 blockade to inhibit neutrophilic invasion) or colchicine (a selective nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 [NLRP3] inhibitor with some effect in Behcet's disease) or TNF inhibitor (though not effective in vasculitic disorders in general), rituximab (B cell inhibition with proven efficacy in systemic granulomatosis and polyangiitis) or tocilizumab (interleukin 6 inhibition as is corticoid sparing in giant cell arteritis). And a predominant if not exclusive position of vasculitic/aneurysmatic lesions in

the pulmonary arterial branch poses questions on a potential role for pulmonary hypertension and/or pulmonary arterial rigidity by endothelial/smooth muscle cell dysfunction. NT-proBNP concentrations nor arterial pulmonary pressures are done in the cases described so far. Pathobiological pathways are unknown so far, but clearly anticoagulation in the later stages may be fatal, whereas urgent surgical interventions may be needed. Physicians will have to make a choice between the following palettes [10]: urgent vascular intervention (aneurysmorrhaphy/aneurysmectomy, segmentectomy/lobectomy, in cases of distal PAA) when potentially instable (pseudo)aneurysms are found, anticoagulation when thromboembolism is found versus anti-inflammatory regimens when vasculitic lesions are found, and possibly arterial dilatators when pulmonary arterial hypertension is detected. Our pathogenetic understanding often starts with description and imaging, so for the sporadic HSS a promising start now has been made by the international task force.

Declarations

Disclosures None.

References

1. Hughes JP, Stovin PG (1959) Segmental pulmonary artery aneurysms with peripheral venous thrombosis. Br J Dis Chest 53:19–27. https://doi.org/10.1016/s0007-0971(59)80106-6
2. Beattie JM, Hall AJ (1912) Multiple embolic aneurysms of pulmonary arteries following thrombosis of veins of leg; death from rupture of aneurysm into lung. Proc R Soc Med 5((Pathol Sect)):147–55
3. Kopp WL, Green RA (1962) Pulmonary artery aneurysms with recurrent thrombophlebitis. The "Hughes-Stovin syndrome." Ann Intern Med 56:105–114
4. Deterling RA Jr, Clagett OT (1947) Aneurysm of the pulmonary artery; review of the literature and report of a case. Am Heart J 34:471–499
5. Emad Y, Ragab Y, Kechida M, Guffroy A, Kindermann M, Robinson C et al (2021) A critical analysis of 57 cases of Hughes-Stovin syndrome (HSS). A report by the HSS International Study Group (HSSISG). Int J Cardiol 331:221–229. https://doi.org/10.1016/j.ijcard.2021.01.056
6. Anupama BK, Tymko C, Subedi R, Virk J et al (2020) Hughes Stovin syndrome, a rare form of Behcet's disease presenting as recurrent intracardiac thrombus. Cureus 12(5):e7907. https://doi.org/10.7759/cureus.7907
7. Emad Y, Ragab Y, Ael-H S et al (2007) Hughes-Stovin syndrome: is it incomplete Behçet's? Report of two cases and review of the literature. Clin Rheumatol 26:1993–1996. https://doi.org/10.1007/s10067-007-0609-y
8. Emad Y, Ragab Y, Ibrahim O et al (2020) Pattern of pulmonary vasculitis and major vascular involvement in Hughes-Stovin syndrome (HSS): brief report of eight cases. Clin Rheumatol 39:1223–1228. https://doi.org/10.1007/s10067-019-04872-z
9. Robinson C, Miller D, Will M et al (2018) Hughes-Stovin syndrome: the diagnostic and therapeutic challenges of peripheral pulmonary artery aneurysms. QJM 1(111):729–730. https://doi.org/10.1093/qjmed/hcy110
10. Emad Y, Ragab Y, Robinson C et al (2021) Pulmonary vasculitis in Hughes-Stovin syndrome (HSS): a reference atlas and computed tomography pulmonary angiography guide – a report by the HSS international study group. Clin Rheumatol. https://doi.org/10.1007/s10067-021-05912-3