

Clinical presentation, radiological findings and treatment options in Hughes-Stovin syndrome

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Abstract

Hughes-Stovin syndrome is a rare disease characterized by thrombophlebitis associated with arterial or bronchial aneurysms. Even though it was described first in 1911, it is scarcely reported in the literature. Hughes-Stovin syndrome diagnosis is based on clinical manifestations as well as radiological findings. There are no validated criteria or specific laboratory findings to confirm the diagnosis. Computed tomography pulmonary angiography remains the gold standard for the diagnosis and follow-up of radiological findings, as they were recently described in a critical analysis of the largest cohort in the literature.

The aim of this review is to draw attention to this rare but potentially fatal disease and to discuss its therapeutic options.

Key words: aneurysm, thrombophlebitis, Hughes-Stovin syndrome, incomplete Behçet's disease.

Introduction

Hughes-Stovin syndrome (HSS) is characterized by thrombophlebitis associated with arterial or bronchial aneurysms. Since it was first described in the literature, it has scarcely been reported.

As radiological findings, especially computed tomography pulmonary angiography (CTPA), were recently analyzed, our aim is to depict clinical findings and highlight the contribution of radiological findings in the diagnosis and follow-up on HSS. Treatment options are also reviewed.

History of the disease

Hughes-Stovin syndrome is a rare condition, as the largest cohort of patients includes no more than 57 cases [1]. Thrombophlebitis associated with arterial and/or bronchial aneurysms is the hallmark of the disease [2].

Multiple pulmonary artery aneurysms (PAA) associated with lower limb venous thrombosis were first re-

ported in 1911 by Beattie and Hall, but “Hughes-Stovin syndrome” became a formal eponym in 1962 [3].

As the disease is rare, no validated diagnostic criteria or pathognomonic laboratory findings are described to confirm the diagnosis of HSS. Almost all the published case reports are diagnosed after ruling out differential diagnosis [2].

Hughes-Stovin syndrome is usually diagnosed in young male patients [4, 5]. No genetic background of familial predisposition has been reported and no geographic location preponderance has been described, as HSS cases have been reported from all over the world [6–9].

Disease description

Clinical manifestations of HSS result from clinical manifestations of thrombophlebitis and pulmonary or bronchial aneurysms. According to the localization of the thrombophlebitis, the patient can have seizures, diplopia, cephalalgia and papillary edema in the case of cerebral venous sinus thrombosis [3, 10, 11].

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Thrombosis is also described in the vena cava, cardiac chamber, jugular vein, iliac vein, femoral vein and dural sinuses [4, 5, 10, 12–15]. Vena cava thrombosis may be associated with abdominal superficial veins [13].

Large vessel involvement may result in pulmonary embolism [2]. Other features such as fever are described. Apart from that, patients can present with cough, hemoptysis, dyspnea and chest pain related to pulmonary aneurysms [4, 12, 16, 17].

Hemoptysis, the most severe symptom of the disease, is the hallmark of aneurysm rupture with erosion towards the bronchus. Moreover vasculitis leading to thrombosis [16] or hypertrophy in the bronchial arteries secondary to ischemic pulmonary artery occlusion may present with hemoptysis too. Nevertheless, some authors suggest that hemoptysis results more from ruptured pulmonary arteries as they reported dilated bronchial arteries [14].

Although the first descriptions as well as the definition of the disease state that aneurysms are located in the pulmonary or the bronchial arteries, aneurysms can occur anywhere in the arterial system, as they have been described in the external carotid, iliac artery, left hepatic artery and in the ascending aorta [9, 18–20].

In summary, HSS may be diagnosed in three clinical stages. The first stage is thrombophlebitis, the second stage is arterial aneurysm, and the third stage is massive hemoptysis secondary to aneurysm rupture, which may lead to a fatal outcome [21, 22].

Work-up in Hughes-Stovin syndrome

No specific biological findings exist in HSS. It is mainly diagnosed based on clinical manifestations as well as radiological findings. Patients may have biological inflammatory syndrome features. Laboratory tests usually requested are intended to rule out some differential diagnoses such as coagulation tests, antinuclear antibodies, rheumatoid factor, complement levels, antineutrophil cytoplasmic antibodies, anticardiolipin antibodies and viral serologies [23, 24].

Patients with hemoptysis may undergo bronchoscopy, showing a beating mass with fibrin and/or ectatic artery in a case of bronchial artery aneurysm [23] or bronchial obstruction related to a submucosal mass [24].

Regarding radiological findings, chest radiography can reveal hilar enlargement or round lobulated opacities related to PAA [25]. Pulmonary angiography is the means to assess the diagnosis of PAA and also contributes to the assessment of angiodysplastic bronchial arteries.

However, this technique can be hazardous in selective pulmonary angiography as it can lead to aneurysm rupture [14] and it is even impossible in patients with

vena cava thrombosis [7]. Therefore, helical CT can be effective for the diagnosis [7, 16]. Magnetic resonance angiography can be an alternative for the diagnosis but is less sensitive than helical CT for small aneurysms [11, 14, 26–28].

Computed tomography pulmonary angiography is considered the gold standard imaging technique for the pulmonary involvement in HSS. To best describe radiological findings in CTPA, the HSS International Study Group (HSSISG) published a comprehensive reference atlas of CTPA images to illustrate the broad range of CTPA manifestations described in HSS [28].

According to this atlas, PAA are classified as true PAA, bronchial artery aneurysms (BAA), pulmonary artery pseudoaneurysms (PAP) and unstable PAA/PAP based on signs of extraluminal hemorrhage and signs of right ventricular strain [28].

Vasculitis presents initially as aneurysmal wall enhancement. In fact, some PAA present with adherent thrombus to the aneurysmal wall, which may have aneurysmal enhancement, suggesting then an inflamed arterial wall and thus vasculitis [29].

Stable aneurysm presents as a contrast-filled expansion in the pulmonary artery as well as the lobar segmental bronchial branches. Unstable aneurysms are characterized by extraluminal leakage with possible signs of air bronchograms [28].

Chronic leakage is considered as severe disease aggravation resulting in PAP [29]. The latter will appear on CTPA as an ectatic vascular lumen with sharp and demarcated contrast filling with a perianeurysmal component having a marginal hypodensity [1].

Fluorodeoxyglucose-positron emission tomography (PET)/CT could be an appropriate tool to estimate how important the vessel inflammation is. To our knowledge, there are no published data on this tool yet.

Histological features

According to reports of autopsy cases, the main histologic findings are destruction of the arterial wall with disruption of the muscular layers and perivascular lymphomonocytic infiltration of capillaries and venules [23, 30, 31].

Aneurysms in HSS are categorized as true PAA described as a focal expansion of all the arterial wall, and PAP involving only the outer layers of the vessel wall. The latter may result from a progressing non-treated true PAA as described in necropsy reports [31].

Differential diagnosis

A differential diagnosis of HSS is Behçet's disease (BD), as both of them can present with thrombosis and pulmonary aneurysms. In many published reports we

believe that HSS is an incomplete form of BD or a cardiovascular manifestation of BD as there is an overlap between clinical, radiological and histological findings between BD and HSS [20, 22, 32, 33].

In fact, HSS and BD mostly affect young male adults even if in some populations BD is characterized by a female preponderance [34, 35]. However, finding some clinical signs such as recurrent bipolar ulcerations, uveitis, cutaneous lesions as well as a positive pathology test is specific to BD [36].

Other differential diagnoses are mycotic or bacterial aneurysms reported in tuberculosis or syphilis for example, associated with antiphospholipid syndrome leading to thrombosis. Other inherited diseases of connective tissue such as Marfan's disease may present with aneurysms.

Anti-inflammatory drugs and anticoagulation

As there is a limited number of patients with identified HSS and there are no controlled trials, treatment of HSS still is not consensual as there are no guidelines. It can either be medical or surgical. Medical management of HSS can be tailored according to BD treatment since they share many common clinical features.

Vascular involvement, whether arterial, venous thrombosis or aneurysms, occurs in 7–38% of patients with BD. The European League Against Rheumatism (EULAR) recommendation established strategies for the treatment of BD disease, especially with regards to vascular involvement [37].

Vessel inflammation is the leading cause of thrombosis and thus glucocorticosteroids (GCs) and immunosuppressors are the cornerstone of the treatment [38]. Similarly, HSS treatment is based on GCs and immunosuppressors to stabilize and even reduce aneurysms.

As the histological findings are based on lymphocytic infiltration, some treatments such as anakinra (anti-IL1 monoclonal antibody), colchicine, anti-tumor necrosis factor α monoclonal antibodies (anti-TNF- α), rituximab (anti-CD20 monoclonal antibody) and tocilizumab (anti-IL-6 antibody) could be discussed [1]. Anticoagulant therapy is still debated due to a high risk of fatal hemorrhage.

Immunosuppressive therapy

The first line treatment, based on several clinical case reports, consists in the combination of GCs at high doses and monthly intravenous cyclophosphamide. This is thought to be the most effective treatment for the thrombo-inflammatory process [4].

Intravenous methylprednisolone is first prescribed for three days (15 mg/kg daily), then oral prednisone will be progressively tapered [39]. It is associated with

cyclophosphamide, which is maintained for 1 year after complete remission [25].

The analysis of 57 patients diagnosed with HSS showed that early initiation of immunomodulatory drugs is significantly associated with favorable outcomes and lower rates of mortality; 17.5% received a single immunomodulator (oral steroid) and 68.4% received combined immunomodulators [29].

The European League Against Rheumatism recommends a combination of GCs and immunosuppressors such as azathioprine, cyclophosphamide, or cyclosporine A for the treatment of deep venous thrombosis in BD.

For pulmonary aneurysms a treatment based on high-dose GCs and cyclophosphamide is endorsed and thought to be sufficient. Monoclonal anti-TNF- α antibodies are a second line treatment in some cases [37].

Indeed, Ghirardo et al. [40] reported a complete remission of pulmonary aneurysms in a HSS patient treated with anti-TNF- α antibody as he was refractory to cyclophosphamide and prednisone.

Anticoagulants and thrombolytic agents

Anticoagulation in patients with HSS may be complicated. On one hand HSS patients have a high likelihood of thrombotic events, while on the other hand these patients may be at higher risk of catastrophic hemorrhage from pulmonary aneurysms [2].

The optimal management of the patient is therefore challenging. The European League Against Rheumatism does not recommend the use of anticoagulants and antifibrinolytic agents for the treatment of thrombotic events in BD [37]. Glucocorticosteroids, immunosuppressants as well as anti-TNF- α antibodies can be the treatment of thrombosis in HSS, as well as BD, instead of anticoagulants.

Anticoagulation can be used with high caution in particular situations attentively evaluated and when benefits are expected to largely exceed risks, especially when deep vein thrombosis is associated with an intracardiac thrombus and pulmonary embolism. Intracardiac thrombosis was found in a total of 12 patients (21.1%) in a study of 57 patients with HSS [29].

Anticoagulation is meant to prevent extension of thrombosis and the formation of deep venous thrombi in aneurysms [19].

Kim et al. [22] and Kechida et al. [18] successfully used oral anticoagulation after starting with intravenous heparin, in a patient with HSS with intracardiac thrombus in one case, and deep vein thrombosis in another. Anticoagulation should be halted if PAA leakage is noted, as it is considered dangerous in unstable true PAA or unstable PAP lesions [2].

Surgical treatment

There are no clear recommendations for surgical management of HSS. Surgery can be performed if there is a ruptured aneurysm in one lobe or lung resulting in heavy bleeding [32].

Other indications of surgery would be recurrent cardiac thromboses, thromboses refractory to medical treatment, or massive thrombosis associated with heart congestion [41]. Robinson et al. [42] recommend a surgical treatment in solitary aneurysms that are large (≥ 30 mm) or expanding (≥ 3 mm in 6 months).

Because of the inflammatory nature of the condition, aneurysms can recur at the anastomotic site in 25% of cases after surgery [2]. For BD, EULAR recommends not performing surgery on a pulmonary aneurysm unless life-threatening. Choosing the surgical technique depends on the surgeon's experience as well as the size and the location of the aneurysm [37].

Endovascular treatment (embolization)

As surgery was associated with high morbidity, transcatheter embolization would be an alternative to surgery in most cases of artery aneurysms. Arterial embolization is proposed as a treatment option in the patients who should not be operated on (bilateral multifocal aneurysms and/or severe or recurrent hemoptysis) [19].

Transcatheter embolization may be indicated in a case of an emergency, to stop progressive pulmonary artery aneurysm considered highly likely to rupture without waiting for a response to immunomodulators [1]. There are several agents used in embolization such as steel coils, Ethibloc and an epoxy, isobutyl cyanoacrylate.

Tzilalis et al. [43] successfully used Amplatzer vascular plug-in embolization of a PAA with use of multiple agents. Contrary to surgical treatment, the patients rarely require repeated embolizations.

Conclusions

Hughes-Stovin syndrome is a rare disease whose diagnosis remains clinical as there are no pathognomonic laboratory findings. Although rare, HSS remains a fatal disease when it is complicated with aneurysm rupture.

Computed tomography pulmonary angiography is considered the gold standard imaging technique for its pulmonary involvement, allowing positive diagnosis and follow-up. Treatment options are tailored to BD treatment based mainly on medical options and on endovascular procedures for specific cases.

The authors declare no conflict of interest.

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