# Is Hughes-Stovin syndrome Behçet's disease?

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# ABSTRACT

Hughes-Stovin syndrome (HSS) is a rare clinical disorder, which has been described as the presence of pulmonary artery aneurysm in the setting of sys temic thrombosis. The term "Incom plete Behcet's Disease" has also been used to describe this syndrome due to the clinical and histopathological simi larities between Behçet's disease and HSS. Indeed, pulmonary involvement can be indistinguishable between these two conditions of unknown pathophysi ology. We describe an HSS patient who presented with a recurrent pulmonary artery aneurysm, review the clinical and pathological manifestations of HSS, discuss its similarities to Behcet's disease, and finally make the argument that HSS is in fact Behçet's disease.

# Introduction

The coexistence of pulmonary artery aneurysm (PAA) and systemic thrombosis is an unusual but serious clinical presentation associated with a very high mortality rate. This aneurysmthrombosis combination can be seen in patients with Behçet's disease (BD); however a distinct clinical syndrome, namely Hughes-Stovin syndrome (HSS), was also described in 1959 (1). Since then, the nature and the etiopathogenesis of this syndrome have been debated and there have been a limited number of reports and histopathological analyses of reported patients.

Although patients with HSS lack clinical manifestations suggestive of BD or other autoimmune disorders, in the presence of the clinical, radiological, and histopathological similarities between HSS and BD, it has been suggested by several authors that HSS could be a variant or a particular expression of BD (2-4). We report a patient with the diagnosis of HSS who presented with a recurrent PAA, review the clinical and histopathological manifestations of HSS, discuss its similarities to BD, and finally make the argument that HSS is in fact Behcet's disease.

# **Case presentation**

A 26-year-old Iranian male presented with sudden onset dry cough followed by hemoptysis. The patient's past medical history was significant for Hodgkin's Disease (HD) and HSS, which were diagnosed 10 and 6 years prior, respectively. Hodgkin's disease had been in remission following chemotherapy with doxorubicin, bleomycin, and vinblastine; the patient had received no radiation therapy. Hughes-Stovin syndrome was originally diagnosed based on thromboses of the inferior vena cava (IVC) and portal vein in the presence of a right pulmonary artery aneurysm. The patient was initially treated with high-dose corticosteroids (CS) for 6 months, anticoagulation, and colchicine. He had a normal chest computerized tomography (CT) 9 months after the diagnosis of HSS and was stable since then except for two episodes of transient, mild hemoptysis.

On admission the patient had no complaints except a one-day history of dry cough, exertional dyspnea, and only one episode of a small amount of hemoptysis. He denied fever, weight loss, genital and oral ulcers, rash, alopecia, Raynaud's phenomenon, arthralgia, arthritis, chest pain, abdominal pain, or urinary symptoms. His medications were colchicine 0.6 mg oral (PO) daily which he stopped taking 6 months earlier, furosemide 20 mg PO daily, and warfarin. He had no known drug allergies and was not a smoker. His family history was non-significant for any autoimmune disease including BD. On physical examination, he was afebrile and vital signs were stable. Pulse oximetry was 98% on room air. The examination was unremarkable except for abdominal and chest wall varicose veins and mild splenomegaly. No lymphadenopathy or oral-genital ulcers were noted. Complete blood count, serum creatinine, erythrocyte sedimentation rate, urine analysis, and serum complement levels (C3, C4) were within normal limits; antinuclear antibody, double-

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stranded-DNA, anticardiolipin antibodies, and anti-neutrophile cytoplasmic antibodies (c-ANCA, p-ANCA) were negative. Human leukocyte antigen (HLA) typing was not performed. Chest X-ray demonstrated left hilar mass and left upper lobe infiltrates (Fig. 1).

The patient was admitted for further observation. On the first day of the admission, he had severe hemoptysis (150 cc). An emergency bronchoscopy showed left upper lobe bronchial obstruction by a submucosal lesion. Chest-abdomen CT demonstrated left upper lobe ground glass opacities which were consistent with blood, a single 3 cm left main PAAencroaching on the left upper lobe bronchus (Fig. 2A), diffuse venous collateral vessels (Fig. 2B, constructed CT images with contrast), IVC thrombosis and hyperdense nodular lesions in the liver (Fig. 2C). Figure 2D demonstrates a constructed CT image of the PAA. Transesophagial echocardiography was normal. A ventilation-perfusion scan demonstrated absent perfusion in the middle and lower right lung posteriorly and laterally, decreased perfusion within the left upper lung, and multiple perfusion defects at the right lung base posteriorly and laterally.

He was initially treated with pulse CS (1000 mg for 3 days) followed by prednisone 60 mg PO daily. Warfarin was held. His condition stabilized after pulse CS without further hemoptysis. He persistently refused an immunosoppressive agent (cyclophosphamide or azathioprine). He was discharged 9 days after the admission in a stable condition. Prednisone was continued and a follow-up chest CT in 3 months demonstrated significant decrease in the size of the aneurysm with partial thrombosis.

One month after the follow-up CT, the patient died due to massive hemoptysis. No further information was obtained as the family declined an autopsy.

## Discussion

The combination of systemic venous thrombosis and PAA has been referred to as "Hughes-Stovin Syndrome" since a 1959 British report by Drs John Pat-

terson Hughes and Peter George Ingle Stovin, who discussed two patients with this unusual combination of clinical findings (1). Since then, approximately thirty papers were published in the English literature (5). Hughes-Stovin syndrome commonly occurs in young males and is frequently fatal due to the rupture of the PAA into a bronchus resulting in massive hemoptysis. Pulmonary artery aneurysms are generally multiple, and bilateral in 50% of the patients. No other parts of the lungs are involved (5). Bronchial, hepatic, and iliac artery aneurysms have also been reported (6-8). The majority of patients develop peripheral venous thrombosis; however intracardiac, dural sinus, inferior and superior vena cava, jugular, iliac, and femoral vein thromboses have also been reported (1, 5, 9-11). Fever and hemoptysis are the most common initial presentations; elevated intracranial pressure secondary to dural sinus thrombosis can also occur (1, 10).

We believe that our patient, with a known diagnosis of HSS, in fact had BD based on the following: a) a pulmonary artery aneurysm in the presence of systemic thrombosis is an almost



Fig. 1. Chest x-ray demonstrating left hilar mass and left upper lobe infiltrates.

unique manifestation of BD; b) atypical BD patients exist and pulmonary system involvement in BD can be identical to HSS; c) the histopathologic findings of reported HSS patients show similarities to those seen in BD patients; and d) HSS patients may continue to develop thrombosis despite anticoagulation, demonstrating that anticoagulation alone is not only dangerous but often inadequate for HSS patients.

Pulmonary artery aneurysm in the presence of systemic thrombosis is an almost unique manifestation of BD. The differential diagnosis of PAA includes infectious (tuberculosis, mycotic infections which are mostly associ-



**Fig. 2.** Chest-abdomen computerized tomography (CT) demonstrating a single 3 cm left main pulmonary artery aneurysm (PAA) encroaching on the left upper lobe bronchus ( $\mathbf{a}$ ), diffuse venous collaberal vessels in a constructed CT image with contrast ( $\mathbf{b}$ ), and inferior vena cava (IVC) thrombosis and hyperdense nodular lesions in the liver ( $\mathbf{c}$ ). Aconstructed CT image of the PAAis shown in ( $\mathbf{d}$ ).

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ated with right-sided endocarditis, or syphilis), congenital (such as Marfan's syndrome), traumatic (endovascular such as damage from a balloon-tipped Swan-Ganz catheter or extravascular such as Rasmussen's aneurysm, created by the erosion of a vessel by a disease process involving the lung parenchyma), and vasculitic disorders (1,2). Furthermore, dissecting aneurysms can occur in the presence of pulmonary hypertension. All but vasculitic disorders generally cause a single PAA and occur in the absence of systemic thrombosis. Multiple PAA, especially in the presence of systemic thrombosis, generally occur in BD patients (12). However, HSS and BD patients with single PAA have been reported (10, 13). To our knowledge, PAA are not associated with other vasculitic disorders including Takayasu arteritis (personal communication with Gary Hofman, MD) and polyarteritis nodosa (personal communication with Loïc Guillevin, MD). Our patient had no proven infectious etiology, nor congenital or traumatic cardiopulmonary defects. Although he had been diagnosed with HD, his disease was under remission, he had no signs of active malignancy, and there have been no reported associations between lymphomas and BD or HSS.

Atypical BD patients exist and pulmonary system involvement in BD can be identical to HSS. Although the diagnostic criteria for BD include oral and genital ulcers, typical eye and skin lesions, and a pathergy test (14), atypi**Table I.** Similarities between the pulmonary involvement of Behcet's disease (BD) and Hughes-Stovin syndrome (HSS).

Gender	Mostly young males		
Common clinical manifestations	Fever – Arthralgia – Thrombosis		
Pulmonary artery aneurysm (PAA)	Association with thrombosis - HSS: 100% - BD: 80%		
Common histopathologic findings of PAA	Perivascular inflammation Arterial wall destruction		
Treatment of choice	Cyclophosphomide or azathiprine and corticosteroids		
Prognosis of HSS and BD (in the presence of PAA)	Usually fatal due to the rupture of PAA		

cal presentations can occur involving the cardiopulmonary, gastrointestinal, vascular, neurological, and musculoskeletal systems. Behçet's disease patients with atypical manifestations do not necessarily have a milder course and should be evaluated and managed similar to patients fulfilling the International Classification Criteria (15).

One to two percent of BD patients develop pulmonary involvement and the most typical pulmonary manifestation is PAA (16). Pulmonary artery occlusions due to thrombosis, pulmonary hemorrhage, and rarely pleurisy with caval obstruction can be also seen. Pulmonary artery aneurysms are common in young male BD patients; they are usually multiple (although one-fifth can be single), occur during the third decade of life, and often develop approximately four to five years after the disease onset. The most common location (35%) for the PAA in BD patients is the lower right lobar artery (16). Eighty percent of patients with PAA have also deep vein thrombosis, mostly in the lower extremities. The most common clinical manifestation of the pulmonary involvement in BD is hemoptysis, which is due to a bronchoarterial fistula and may occur with or without an aneurysm. Pulmonary artery aneurysm is the most common cause of mortality in BD (17), as well as in HSS (2). In the presence of pulmonary system involvement and systemic thrombosis alone, HSS can be indistinguishable from BD. Furthermore, patients with BD and HSS share other clinical manifestations such as prolonged fever, erythema, and arthralgia (2). Thus, the term "Incomplete Behçet's Disease" has also been used for HSS patients due to the similarities between these two disorders of unknown etiology (11) (Table I). Our patient did not fulfill the International Classification Criteria for

Table II. Selected Hughes-Stovin syndrome patients with histopathological analysis of the pulmonary artery aneurysm (PAA).

Pt # (ref)	Age	Sex	Selected clinical findings	Treatment	Outcome	Pathology – Aneurysm wall
1 (1)	35	М	VT, CVST, PAA	Anticoagulation Lobectomy	Death	Destroyed elastic and muscle fibers Infiltration with foam and plasma cells, lymphocytes
2(1)	12	М	VT, AT, CVST, PAA	CS	Death	Similar to case 1 as stated by the authors
3 (18)	25	W	VT, PAA	NR	Death	Aneurysm rupture into a bronchus Destruction of the intima, elastic, and outer layers
4 (19)	19	М	VT, PAA	Lobectomy, CS	Death	Atheroscleotic changes Little inflammatory cell infiltration
5 (20)	33	М	VT, CVST, PAA	NR	Death	Eosinophilic angiitis
6 (21)	12	М	VT, PAA	Lobectomy	Death	Aneurysm eroded the wall of the adjacent bronchus Destruction of intima, elastic fibers, and adventitia

Pt: patient; ref: reference number; VT: venous thrombosis; AT: arterial thrombus; CVST: cerebral venous sinus thrombosis; PAA: pulmonary artery aneurysm; CS: corticosteorids; NR: not reported.

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BD; however, in the presence of recurrent PAA and systemic thrombosis, we propose the diagnosis of atypical BD. *Histopathologic findings reported for HSS patients show similarities to those seen in BD patients*. Although we do not have biopsy or autopsy findings for our patient, several groups have reported that the histopathologic findings of HSS and BD can be indistinguishable, with arterial wall destruction and perivascular inflammatory cell infiltration (2, 4).

Drs Hughes and Stovin suggested that in the absence of any other definitive pathology, pulmonary artery aneurysms might be related to a qualitative defect, possibly congenital degenerative changes in the bronchial arteries (1). However, it was later realized that the histopathologic examination of the PAA in HSS patients is characterized by vessel wall destruction and perivascular infiltration (2, 18), identical to that seen in BD patients, even though some reports were not able to identify the vasculitic nature of HSS patients (19). Durieux et al. reported that the pathologic nature of the aneurysm in HSS includes very intense neutrophilic inflammation of the vessel wall, which erodes into the surrounding structures (2). Meireles et al. observed widespread eosinophilic angiitis in a patient with HSS (20) and Francois suggested microangiitis of the vaso vasorum in the pathogenesis of the syndrome (4). Selected HSS patients with histopathological analysis of the PAAare summarized in Table II.

Similar to HSS, arterial aneurysms in BD occur secondary to obliterative endarteritis of the vasa vasorum (thromboangiitis of arteries of all sizes, veins, and venules). The aneurysm in BD is a pseudo-aneurysm; the vessel wall is very edematous due to the intense inflammation, the integrity of the vessel wall is destroyed, and erosion into the surrounding structures and bronchus occurs eventually.

Hughes Stovin syndrome patients may continue to develop thrombosis despite anticoagulation (21), demonstrating that anticoagulation alone is inadequate for HSS patients. Anticoagulation alone is not sufficient in the management of HSS and it should be used cautiously in the presence of PAA and systemic thrombosis; preferably after the immunosuppressive treatment. The three main treatment options for both BD and HSS patients are immunosuppressive treatment, surgical resection, or embolization; none of them alone or in combination provide a favorable outcome. Colchicine was reported to be successful in a single HSS patient (22).

Behçet's disease patients with pulmonary involvement are managed by following the general principles of systemic vasculitis treatment. Cyclophosphamide or azathioprine in addition to corticosteorids are the first-line treatment of choice for BD and HSS patients, although no controlled trials exist (5,15,23). In 13 BD patients receiving immunosuppressive therapy for PAA, 35/46 (75%) of the aneurysms disappeared over a mean follow-up period of 21 months and 9/46 aneurysms decreased in size. In this study, both the disappearance and regression of the aneurysms were preceded by thrombus formation (24), as was seen in our patient.

Surgery (total pneumectomy or lobectomy) is indicated in the presence of massive bleeding due to a ruptured aneurysm. However, in the absence of rupture, it is associated with significant mortality. Surgery is not feasible in the presence of multiple bilateral aneurysms. Furthermore, in BD patients there is a 25% risk of recurrent aneurysms, usually at the anastomosis site (25).

Transcatheter embolization (TE) of PAA has been used in both BD and HSS patients (7, 8, 16); however, no long-term follow-up data exist. We believe that TE is not the best management option in BD and HSS patients as the main pathological involvement is in the surrounding invasive structures of the aneurysm, not the aneurysm itself. Furthermore, massive bleeding is a major complication of TE.

In conclusion, PAA and systemic thrombosis can occur with (commonly) or without (uncommonly) the usual features of BD. The prognosis of PAA is guarded despite medical or surgical treatment. When this combination occurs, patients should be carefully evaluated for the other features of BD and, even in the absence of other BD features, they should be managed as aggressively as BD patients.

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