A Rare but Fatal Behçet Variant: The Hughes–Stovin Syndrome—Successful Case Report and New Evidence from Literature Review

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Abstract

Hughes–Stovin syndrome (HSS) is a rare potentially fatal vasculitis supposedly belonging to the spectrum of Behçet disease without ocular involvement. HSS tends to play by a temporal pattern, starting with thrombosis and followed by formation of pulmonary aneurysms. Since its mortality can reach 25% of cases, early recognition and appropriate therapy represent the major clinical challenges. We describe a rare case of HSS successfully treated via multidisciplinary management by an endovascular approach and immunosuppressive therapy.
**Introduction**

Hughes–Stovin syndrome (HSS) is a rare disorder characterized by multiple pulmonary aneurysms and thrombophlebitis: it is a life-threatening disease believed to be a cardiovascular clinical variant of Behçet disease (BD). It prefers the population between the second and fifth decades and the male sex. The evolution of the clinical course is characterized by the appearance of symptoms related to thrombophlebitis, the formation of aneurysms in pulmonary or bronchial arteries, and eventual hemoptysis, often fatal. In our case, the treatment of thrombophlebitis revealed the presence of hemoptysis. Endovascular therapy and successful pulmonary aneurysm exclusion was combined with immunosuppressive therapy.

**Case Presentation**

A 33-year-old male patient presented to our emergency room after an episode of hemoptysis the same morning, associated with shortness of breath and 5 days of pain in the left lower limb. Three days previously, he went to his general physician, who made diagnosis of deep venous thrombosis (DVT) and prescribed low-molecular-weight heparin (LMWH) 10,000 IU per day, which the patient took for 3 days until the hospitalization. In the emergency room, the left lower limb was edematous, and dorsalis pedis and popliteal arteries pulsation on the left side, although present, were thready. Homan’s sign, dorsiflexion of the foot, and Bauer’s sign, palpation of the calf following compression of the sural muscles against the interosseous membrane, were negative.

Arterial blood gases showed pH 7.45 (normal range [nr]: 7.35–7.45), $P_{O_2}$ 66 mm Hg (nr: 80–100 mm Hg), $P_{CO_2}$ 38 mm Hg (nr: 35–45 mm Hg), $SO_2$ 94.7% (normal value [nv]: >97%), lactate 0.9 mmol/L (nr: 0.5–1.6 mmol/L), partial pressure of oxygen in arterial blood ($P_{O_2}$)/inspired fraction of oxygen ($P/F$) ratio 314 mm Hg (>350), $FiO_2$ 21%.

He also had an history of recurrent oral ulcers, present at evaluation, and a lesion suggestive for a genital ulcer in the left scrotal region.

Initial laboratory investigation showed hemoglobin 9.5 g/dL (nv: 13–18 g/dL), white blood cell count 11.3 million/µL (nr: 4.300–10.000 million/µL), lactate dehydrogenase 507 U/L (nv: 80–300 U/L), C-reactive protein 29.9 mg/dL (nr: 0–5 mg/dL), D-dimer 2,740 ng/mL (nv: <500 ng/mL).

An urgent chest X-ray detected three oval radiopacities with irregular margins, one in middle left length (40 × 25 mm), one in the inferior left lung (27 × 27 mm), and the largest one at the base of the right lung (82 × 81 mm). A computer tomography of the chest (Fig. 1A) revealed multiple, irregular-shaped arterial aneurysms, pulmonary embolism, and pulmonary consolidation at both lung bases, as well as, ground-glass opacities in the middle and lower lobes of the right lung. The computed tomography (CT) also showed partial inferior vena cava thrombosis and left external iliac and femoral vein thrombosis. Doppler study of the lower limbs vein confirmed DVT, demonstrating filling defects in the left common femoral vein and in the left popliteal vein. CT angiography revealed an ecstatic venous vessel with drainage to the right transverse sinus, and Fluorescein angiography detected a delayed filling of the inferior nasal vascular arch and dilation of the venous capillary plexuses in the left optical disc.

During hospitalization, the patient underwent urgent embolization of the largest pulmonary arterial aneurysm (Fig. 1B) and implantation of a vena cava filter.

After the aneurysmal embolization and a careful risk–benefit analysis, the patient was initiated on anticoagulation therapy with LMWH in a preventive dose, 2,000 IU 1 vial subcutaneously (fl sc) in the morning and 4,000 IU 1 fl sc in the evening.

Further laboratories exams showed a heterozygous mutation in the methylene tetrahydrofolate reductase (MTHFR) C677T gene increased Factors IX (144%) and VIII (176%) and a Factor VII less than 50% (nv: 50–200%). In addition to this, protein electrophoresis showed mildly increased beta1 and beta2 fractions complement component 3: 185 mg/dL (nr: 80–185 mg/dL) and 4: 36.8 mg/dL (15–53 mg/dL), homocysteine: 15.91 µmol/L (nv: <15 µmol/L), anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, and anti β2-glycoprotein antibodies were all normal. Moreover, genetic evaluation revealed HLA-B51:01:01 and HLA-B18:01:01 haplotype, which are...
associated with BD in 50 to 70% of cases, mainly the B51:01:01 subtype.

After rheumatological consultation, the patient was treated with initial regimen consisted of prednisone (1 mg/kg/d) in combination with oral cyclophosphamide (2 mg/kg/d–100 mg/d). The patient remained in a stable condition with tapering doses of prednisone in a month and daily oral cyclophosphamide. At the follow-up (1 and 3 months later), no genital and oral ulcers nor vascular thrombosis occurred, and acute phase reactants were in normal range.

Follow-up
The patient remains in good general condition at 30-month follow-up, with the vascular filter in place. Follow-up CT scan (Fig. 1C) shows persistent exclusion of right pulmonary artery aneurysm and stable diameter of the contralateral pulmonary artery aneurysm.

Discussion
BD is a relapsing multisystemic inflammatory disease characterized by oral and genital aphthae, uveitis, thrombophlebitis, and which frequently involves the joints, skin, central nervous system, cardiovascular system gastrointestinal tract. Its etiology is unknown, although some scientific studies have hypothesized a genetic association with the HLA-B51 antigen.

HSS can be evoked before any deep vein thrombosis arising in a young man with BD and a fortiori when repeated hemoptysis occurs. In these conditions, chest CT scans must be performed systematically looking for aneurysmal imagings.

Behçet Disease and Genetic Pathogenesis
The epidemiology of BD is uniquely distributed along the ancient Silk Road from Mediterranean countries to Middle Eastern and East Asian countries. BD is rarely seen in Northern Europe (0.64 cases per 100,000 population), North America (0.12–0.33 cases per 100,000 population), Australia, and Africa.

The pathogenic mechanism of BD is not completely clear. It is known that genetic susceptibility together with trigger factors and immunological abnormalities are the influence manifestation of the disease.

An important role is played by the presence of the HLA-B_51 allele of the major histocompatibility complex, through the combination of different HLA class I-associated functions and/or structural characteristics of the HLA-B_51 heavy chain. These data have been confirmed by several independent studies on 4,800 BD patients and 16,289 controls from different geographical regions. This evidence could be correlated with genetic analyzes that hypothesize the presence of the alteration of the HLA-B51 antigen in BD. In fact, familiarity and the contemporary geographical area of belonging could correspond to a single belonging phenotype. Although there is no consensus on the etiology, HSS should be included among the pathologies in which genetics play a potential role and may provide opportunities for prevention. In our analysis, despite the rarity of occurrence, the geographic distribution...
of the disease suggests the need for genetic evaluations for better definition and prevention, to develop future genetic treatment models. However, it is important to identify the disease early and allow prompt treatment of any complications with accurate follow-up.

**New Clinical Findings**

There is no unanimous consensus on the therapy of patients diagnosed with HSS. The review of therapies and the duration of follow-up did not show a superiority of medical therapy compared with medical and surgical therapy. Our data were collected from literature review between 1911 (this year is report in the first publication in 1959, from Hughes and Stovin) and 2020, combined and 57 papers since 1959 were selected with one or more cases of HSS. Two cases were added from the Hughes–Stovin study published in 1959, which cited the earlier cases of Beattie and Pirani. Seven papers were excluded because no data are available on follow-up. Repeated papers are excluded. A total of 40 patients were analyzed. The comparison of surgical/medical or medical alone therapy on length of follow-up is reported in Fig. 3. No differences in survival rate were observed between the two groups.

**Therapeutically Options**

The advent of endovascular procedures has expanded the possibilities for treatment. At the beginning, therapeutically options

![Fig. 2 Number of confirmed cases of Hughes–Stovin syndrome reported by geographic area.](image)

![Fig. 3 Literature review of follow-up length of patients after Hughes–Stovin syndrome diagnosis: surgical versus medical/surgical therapy.](image)
were represented by pneumonectomy, lobectomy, and segmentectomy. Aneurysm resection with saphenous vein replacement or lung transplantation were also proposed. More recently, embolization, even with repeated procedures, have been performed, with good immediate and mid-term results (See Supplementary Materials 1–3).

The simultaneous presence of phlebitis and aneurysms makes the subsequent therapeutic path difficult because of the hemorrhagic risk associated with oral anticoagulation. In our case, the association between deep vein thrombosis and the simultaneous presence of a contralateral pulmonary aneurysm was addressed using a cava filter, which thus reduces the risk of DVT embolism and at the same time protects the patient from complications of anticoagulant therapy and aneurysm bleeding.

HSS syndrome is rare, but its consequences can be fatal. Since its mortality can reach 25% of cases, the early recognition with an appropriate therapy represents the major challenges. Verifying a genetic correlation, also linked to BD, may be represent the challenge of the future. New therapeutic options make treatment less invasive. The association with immunosuppressant has immediate and mid-term good results.

Note
This study was presented at the 70th International Congress of the European Society for Cardiovascular and Endovascular Surgery and 7th International Meeting on Aortic Diseases, Liege, Belgium, between June 20–23, 2022.

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Conflict of Interest
The authors declare no conflict of interest related to this article.

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