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CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Beyond the ordinary: TNF-alpha inhibitor as a rescue therapy in relapsing Hughes–Stovin syndrome with intracardiac thrombosis—a case report and literature review

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Background Hughes–Stovin syndrome (HSS) is a rare vasculitis characterized by the association of thrombophlebitis with pulmonary artery aneurysms (PAAs). Because it is rarely reported, there are currently no established diagnostic criteria or standardized treatment guidelines for HSS. While conventional immunosuppressants are generally effective as first-line treatment, relapsing and refractory cases urge the need to investigate alternative therapies, such as TNF-alpha inhibitors. However, with only five cases published in the literature, knowledge of their efficacy in HSS is very limited.

Case summary A 28-year-old man, with no past medical history, presented with haemoptysis, chest pain, and dyspnoea on exertion. Physical examination found bilateral leg swelling, with no associated lesions. CT angiography showed multiple bilateral PAA, proximal pulmonary artery thrombosis (PAT), and deep venous thrombosis (DVT) in the superior mesenteric vein and spleno-mesaraic confluence. Echocardiography was performed, identifying right intracardiac thrombosis (ICT). Initial management included high-dose corticosteroids and monthly cyclophosphamide cycles, followed by maintenance treatment with oral azathioprine. Eighteen months later, the patient presented with haemoptysis revealing a relapse of ICT and two new PAA. Infliximab was initiated, allowing complete and sustained remission after one year of follow-up.

Discussion We report the challenging case of an HSS patient presenting with multiple PAA, proximal PAT, right ICT, and extended abdominal DVT. The positive response of our patient to infliximab, following a relapse under conventional immunosuppressants, supports the efficacy of TNF-alpha inhibitors as second-line treatment in relapsing/refractory HSS.

Keywords Hughes–Stovin syndrome (HSS) • Vasculitis • Thrombosis • Pulmonary artery aneurysm • Tumour necrosis factor-alpha inhibitor • Case report

ESC curriculum 9.5 Pulmonary thromboembolism • 9.4 Thromboembolic venous disease • 9.3 Peripheral artery disease

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Learning points

- Hughes–Stovin syndrome (HSS) is a rare vasculitis characterized by the association of pulmonary artery aneurysms and thrombophlebitis, which can also involve the cardiac chambers.
- TNF-alpha inhibitors emerge as a promising second-line treatment in relapsing/refractory HSS patients.

Introduction

Hughes–Stovin syndrome (HSS) is a rare vasculitis characterized by the association of thrombophlebitis with bronchial artery aneurysm (BAA) and/or pulmonary artery aneurysm (PAA). Although some consider it an incomplete form of Behçet's syndrome (BS), its exact aetiology remains uncertain.

Currently, there are no validated criteria for the diagnosis of HSS, and standardized treatment guidelines are lacking. While conventional immunosuppressants are commonly used as first-line treatment, relapsed and refractory cases underscore the imperative to investigate alternative therapies, such as tumour necrosis factor (TNF) alpha inhibitors. However, with only five cases published in the literature,[1–5] knowledge on their efficacy in HSS is very limited.

In this report, we describe the challenging case of an HSS patient presenting with multiple PAA, proximal pulmonary artery thrombosis (PAT), intracardiac thrombosis (ICT), and extended abdominal deep venous thrombosis (DVT), who was successfully treated with a TNF-alpha inhibitor following a relapse under conventional immunosuppressants.

Summary figure

Time	Events
Day 0	Patient presented haemoptysis, chest pain, and dyspnoea on exertion.
	Cardiac TTE revealed ICT and CTA showed multiple bilateral PAA, left proximal PAT, and abdominal DVT.
Day 1–Day 3	Intravenous methylprednisolone pulse initiated.
Day 4	Switch to oral prednisone.
Day 8	1st intravenous cyclophosphamide cycle.
3rd month	Stable lesions on cardiac TTE and CTA after the 3rd cycle.
12th month	Complete resolution of ICT and DVT with stabilization of PAA after the 12th cycle.
	Switch to oral azathioprine.
30th month	Patient presented haemoptysis.
	Cardiac TTE and CTA revealed a relapse of ICT and new PAA.
	Infliximab initiated.
31th month	Partial regression of ICT and stabilization of PAA following the 3rd cycle.
36th month	Complete resolution of ICT with stable PAA.
48th month	Patient remained asymptomatic.
	Absence of new lesion on cardiac TTE and CTA.

Case presentation

A 28-year-old man, with no past medical history, presented to the emergency department with haemoptysis, chest pain, and dyspnoea on exertion (NYHA III). On admission, cardiac and pulmonary auscultations were normal. The patient exhibited bilateral leg swelling, without jugular venous distention, hepatojugular reflux, enlarged liver, or ascites. Mucocutaneous examination did not find oral or genital ulcers, pseudofolliculitis, erythema nodosum, or other lesions. The pathergy test was negative. The remainder of the physical examination, including ocular evaluation, was unremarkable.

The electrocardiogram showed right axis deviation and right bundle branch block, with an S1Q3 pattern. Chest CT angiography (CTA) revealed multiple bilateral proximal and distal PAA, all partially thrombosed, with left proximal PAT (*Figures 1* and *2*). Cardiac transthoracic echography (TTE) identified a right intraventricular floating mass of 18 × 16 mm, with dilated right cavities compressing the left ones, in association with a paradoxical septal motion and an estimated mean pulmonary arterial pressure of 33 mmHg. The left ventricle was normal-sized with no hypertrophy or systolic dysfunction. Mild tricuspid regurgitation was detected, with no vegetation found on the heart valves (*Figure 3*). To identify additional vascular lesions, abdominopelvic CTA was performed, showing thrombosis in the superior mesenteric vein and spleno-mesaraic confluence.

Complete blood count showed hyperleukocytosis (12 180/mm^3) with elevated neutrophils (9330/mm^3), normal haemoglobin level (13 g/dL), and platelet count (450 000/mm^3). Inflammatory markers were raised, with an erythrocyte sedimentation rate (ESR) of 75 mm/h, and C-reactive protein of 66 mg/L. Repeated bacterial cultures (blood, urine, sputum) and serological investigations (HIV, HVB, HVC, Syphilis) did not provide evidence of infection. Tuberculosis work-up (tuberculin skin test, interferon-gamma assay, sputum microscopy, specific culture, and PCR) yielded negative results. Coagulation parameters, including prothrombin time (PT: 100%), activated thromboplastin time (aPTT: 30 s), and fibrinogen level (4 g/L), were within the normal ranges. Screening for acquired and inherited thrombophilia (lupus anticoagulant, anticardiolipin, anti-beta-2-glycoprotein I, hyperhomocysteinaemia, protein C and S deficiency, antithrombin deficiency, factor V Leiden mutation, and prothrombin gene mutation) was negative. Brain natriuretic peptide (BNP)

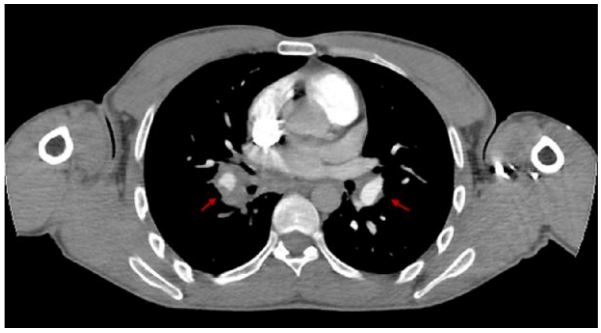

Figure 1 CTA, computed tomography angiography; PAA, pulmonary artery aneurysm.

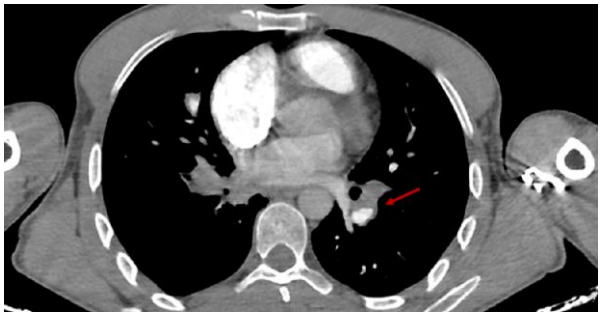

Figure 2 CTA, computed tomography angiography; PAT, pulmonary artery thrombosis.

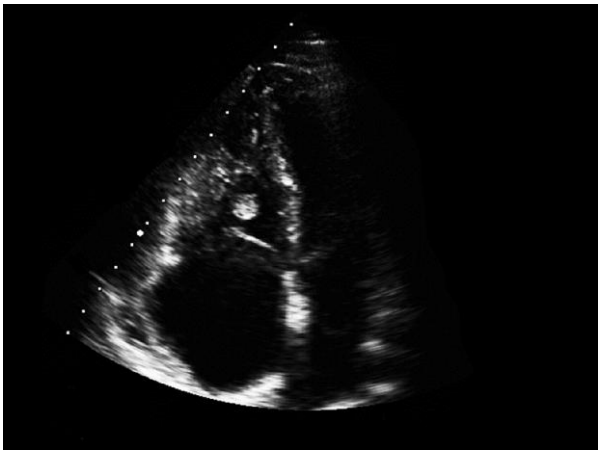

Figure 3 TTE, transthoracic echography.

was elevated (325 pg/mL), and high-sensitivity troponin (hs-Tn: 12 ng/L) was negative.

As the patient exhibited vascular lesions, without skin, ocular, or neurological manifestations, the criteria for BS were not met (see Supplementary file), leading to the diagnosis of HSS. Given the major cardiovascular involvement, an intravenous pulse of methylprednisolone (15 mg/kg/day) was administered for 3 days, transitioned to oral prednisone (1 mg/kg/day), and progressively tapered. Additionally, intravenous cyclophosphamide (1 g/month) was initiated. After the 12th cycle, complete resolution of ICT and vascular thrombosis was achieved, with stabilization of the size and number of PAA, and the patient was switched to oral azathioprine (150 mg/day).

Table 1 **Evolution of the main laboratory results of our patient**

Main laboratory results	At presentation	After 1st line treatment	At relapse	After 2nd line treatment
Blood count				
Haemoglobin (g/dL)	13	13.5	13.3	14
Haematocrit (%)	39	41.5	39	42
Leucocytes (/mm^3)	12 180	5900	14 560	5500
Neutrophils (/mm^3)	9 330	3600	11 320	3100
Lymphocytes (/mm^3)	1 700	1300	1500	1600
Platelets (/mm^3)	450 000	320 000	420 000	370 000
Clotting				
PT (%)	100	100	100	100
aPTT (s)	30	25	28	32
Fibrinogen (g/L)	4	3.2	3.7	3.1
Inflammatory markers				
ESR (mm/h)	75	10	62	12
CRP (mg/L)	66	5	55	3
Cardiac markers				
BNP (pg/mL)	325	85	420	55
hs-Tn (ng/mL)	12	10	18	15

PT, prothrombin time; aPTT, activated thromboplastin time; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BNP, brain natriuretic peptide; hs-Tn, high-sensitivity troponin.

Table 2 **Summary of our case and five reports from the literature illustrating the successful use of TNFa inhibitors in relapsing/refractory Hughes–Stovin syndrome patients**

Case no.	Authors	Age (yrs)/sex	Symptoms	Cardiovascular lesions	1st line treatment	Evolution	2nd line treatment	Evolution
	Our case	28/M	Haemoptysis Chest pain Dyspnoea	PAA PAT ICT Abdominal DVT	Glucocorticoids Cyclophosphamide Azathioprine	ICT recurrence New PAA	Infliximab	Remission (12 months)
1	Cruz *et al.* (2009)[1]	37/M	Fever Haemoptysis Chest pain Leg pain Weight-loss	PAA PAT Lower-extremity DVT Abdominal DVT	Glucocorticoids Cyclophosphamide	PAA rupture	Pneumectomy Infliximab Adalimumab	Remission
2	Groga-bada *et al.* (2017)[2]	19/M	Fever Leg swelling Dyspnoea Chest pain	PAA PAT ICT Lower-extremity DVT	Glucocorticoids Cyclophosphamide Anticoagulant	Inflammatory markers elevation	Infliximab	Remission (3months)
3	Farber *et al.* (2018)[3]	48/F	Cough Dyspnoea Weight-loss	PAA PAT Lower-extremity DVT	Glucocorticoids Cyclophosphamide Anticoagulant Thromboendarterectomy	New PAT Increase PAA size	Infliximab	Remission
4	Ghirardo *et al.* (2019)[4]	17/M	Fever Diplopia Vomiting Abdominal pain Leg pain	PAA Peripheral aneurysms ICT Lower-extremity DVT Cerebral DVT	Glucocorticoids Cyclophosphamide Peripheral aneurysm repair	Inflammatory markers elevation	Infliximab	Remission
5	Villacis-Nunez *et al.* (2023)[5]	15/M	Fever Vomiting Abdominal pain Weight-loss	ICT PAT Cerebral DVT	Glucocorticoids Anticoagulant ICT surgical removal (partial)	Stable ICT New PAT Upper-extremity DVT PAP	Lobectomy Cyclophosphamide Infliximab Methotrexate	Remission (11 months)

M, male; F, female; PAA, pulmonary artery aneurysm; PAT, pulmonary artery thrombosis; ICT, intracardiac thrombosis; DVT, deep vein thrombosis; PAP, pseudoaneurysm.

Eighteen months later, the patient presented haemoptysis with increased inflammatory markers (ESR: 62 mm/h, C-reactive protein: 55 mg/L) and BNP levels (420 pg/mL), revealing two new PAA and a recurrence of ICT. Following methylprednisolone pulse, treatment with infliximab was initiated (3 mg/kg) at S0, S2, and S6, then every 8 weeks. After 6 months, complete resolution of ICT was observed on echocardiography, with a stable aspect of PAA on chest CTA, and normalization of the inflammatory and cardiac markers. At the 1-year follow-up visit, the patient remained asymptomatic under infliximab, and the laboratory work-up was unremarkable (*Table 1*). Control cardiac TTE confirmed the disappearance of ICT, alongside the absence of new vascular lesions on thoracic and abdominopelvic CTA.

Discussion

We report the case of a young man who presented with ICT, multiple PAA, proximal PAT, and abdominal DVT. In the absence of sufficient criteria for BS, the patient was diagnosed with HSS and initially treated with high-dose corticosteroids and cyclophosphamide. After a relapse of ICT and new PAA under azathioprine, infliximab was initiated, and the patient achieved complete remission, sustained after 1 year of follow-up.

Hughes–Stovin syndrome is a rare condition first described in 1911, and later named after two British physicians, J. Hughes and P. Stovin, who reported in 1959 four male patients having DVT and segmental PAA.[6] Since then, it has been rarely reported, with the largest artificial cohort from the HSS international study group including merely 57 patients.[7] To date, there are no established criteria or laboratory findings to confirm the diagnosis of HSS. The association of BAA and/or PAA with thrombophlebitis in a young male patient, in the absence of other aetiological factors and normal coagulation profile, is considered the main feature of the syndrome.

The exact pathogenesis of HSS remains unclear. Several theories were suggested to explain the manifestations of this syndrome, including infection-septic embolisms and angiodysplasia of bronchial arteries. Nevertheless, the consensus is that vasculitis is the primary pathological process in HSS, given the clinical, radiological, and histological evidence of inflammation.[8] Furthermore, some authors consider HSS to be an incomplete form or a cardiovascular manifestation of BS, due to similar findings of vascular thrombosis and PAA.[9,10]

Aneurysms in HSS are usually observed in the bronchial and/or pulmonary arteries, however, they can also be found in the systemic circulation.[8] Pseudoaneurysms (PAPs), which involve only the external layers of the arterial wall, are also frequent and at greater risk of rupture and fatal haemorrhage.[11–13] Intraluminal thrombosis is often seen in these aneurysms and increases the risk of pulmonary hypertension.[14] Venous thrombosis commonly affects the superficial and deep veins, with reports of DVT in the vena cava, dural sinuses, and jugular veins.[9] It is primarily argued that thrombosis in HSS is due to an inflammatory process secondary to vasculitis rather than hypercoagulability. In fact, PAT is thought to develop *in situ* due to the inflammation of the arterial wall and not as thromboembolism from peripheral vein thrombosis. Intracardiac thrombosis, observed in ∼20% of the patients, could be a result of endomyocardial fibrosis, a sequela of vasculitis affecting the endocardium and/or myocardium.[14]

The management of HSS is challenging, and the absence of treatment guidelines adds an additional layer of complexity. Nonetheless, given the inflammatory origin of the vascular lesions, a combination of glucocorticoids and cyclophosphamide is widely considered as the cornerstone of the treatment, and is usually sufficient for achieving remission.

Anticoagulants and thrombolytic agents in HSS are still a matter of debate. Although some authors consider them acceptable after bleeding-risk stratification, there are generally contraindicated due to the increased risk of fatal haemorrhage from PAA rupture.[8,9] In the present case, anticoagulation was not prescribed for our patient given the presence of multiple PAA at-risk of rupture, and the expected favourable response of the vascular lesions to anti-inflammatory and immunosuppressive therapy. Indeed, mirroring the vascular involvement of BS, in which meta-analyses have shown no added benefit from anticoagulants adjunction, experts also question the need of this therapy in HSS, given the strong adherence of the thrombi to the inflamed wall, which minimize the risk of emboli.[15–17]

In cases of large or rapidly increasing PAA size, leaking unstable PAA, and PAP, procedural management, typically by pulmonary artery coil embolization (or surgical resection in high-risk lesions), should be considered. In patients with multiple and/or bilateral PAA, such as in our patient's case, embolization or surgical resection may not be technically feasible and even warranted, given the regression of the lesions under immunosuppressants.[13]

Although long-term outcomes of HSS remain unclear, it is likely that similar to BS, HSS exhibits a relapsing course.[18,19] Because of the shared pathological mechanisms of HSS with the vascular phenotype of BS, in which TNF-alpha inhibitors were proved to be effective,[17] they may be considered as potential second-line treatment in relapsing and refractory HSS cases. However, with only five reports published in the literature (*Table 2*),[1–5] little data are available on this issue. In the present case, the use of infliximab, following a relapse of ICT and PAA under conventional immunosuppressants, led to complete remission, sustained over 1 year of follow-up. To our knowledge, this case represents the longest documented remission to date of an HSS patient under a TNFa inhibitor. Other biological agents need to be further investigated, as only one report described the limited efficacy of tocilizumab (anti-IL-6) in HSS.[4]

Conclusion

We present a rare case of an HSS patient presenting with ICT, multiple PAA, proximal PAT, and abdominal DVT, highlighting the complexity of this condition. Similarly to BS management, TNF-alpha inhibitors emerge as a promising second-line treatment. Our patient favourable response to infliximab, following a relapse under conventional immunosuppressants, supports this consideration and adds valuable insights to the limited knowledge on the efficacy of TNF-alpha inhibitors in HSS.

Lead author biography

Sarra Chadli (MD, PhD candidate) is a resident physician in the Internal Medicine Department at Ibn Sina University Hospital in Rabat, Morocco.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Data availability

All data generated during this study are included in this published article.

References

1. Cruz VA, Muniz YA, Torres PPTES, Teixeira KISS, Rego J, da Silva NA. Hughes–Stovin syndrome. *Rev Bras Reumatol* 2009;**49**:747–752.
2. Groga-Bada P, Klumpp B, Fougère CL, Nikolaou K, Eick C, Gawaz M, et al. Severe cardiovascular involvement in Hughes–Stovin syndrome. *Case Rep Intern Med* 2017; **4**:52.
3. Farber Harrison W, McDermott S, Witkin Alison S, Kelly Noreen P, Miloslavsky Eli M, Stone James R. Case 11–2018: a 48-year-old woman with recurrent venous thromboembolism and pulmonary artery aneurysm. *N Engl J Med* 2018;**378**:1430–1438.
4. Ghirardo S, Pastore S, Gortani G, Tommasini A, Taddio A. Hughes Stovin: sustained remission and regression of pulmonary aneurysms with anti-tumor necrosis factor treatment. *Pediatr Pulmonol* 2019;**54**:E13–E15.
5. Villacis-Nunez DS, West Z, Khan AY, Rodriguez F, Shane AL, Rytting H, et al. Successful medical–surgical management of intracardiac thrombosis and pulmonary pseudoaneurysms in an adolescent with Hughes–Stovin syndrome. *J Investig Med High Impact Case Rep* 2023;**11**:23247096231166672.
6. Hughes JP, Stovin PGI. Segmental pulmonary artery aneurysms with peripheral venous thrombosis. *Br J Dis Chest* 1959;**53**:19–27.
7. Emad Y, Ragab Y, Kechida M, Guffroy A, Kindermann M, Robinson C, et al. A critical analysis of 57 cases of Hughes–Stovin syndrome (HSS). A report by the HSS International Study Group (HSSISG). *Int J Cardiol* 2021;**331**:221–229.
8. Kechida M, Daadaa S, Jomaa W. Clinical presentation, radiological findings and treatment options in Hughes–Stovin syndrome. *Reumatologia/Rheumatology* 2022;**60**:148–152.
9. Khalid U, Saleem T. Hughes–Stovin syndrome. *Orphanet J Rare Dis* 2011;**6**:15.
10. Emad Y, Ragab Y, Shawki AEH, Gheita T, El-Marakbi A, Salama MH. Hughes–Stovin syndrome: is it incomplete Behçet's? Report of two cases and review of the literature. *Clin Rheumatol* 2007;**26**:1993–1996.
11. Ribeiro BN de F, Ribeiro RN, Zanetti G, Marchiori E. Hughes–Stovin syndrome: an unusual cause of pulmonary artery aneurysms. *Radiol Bras* 2016;**49**:202–203.
12. Park HS, Chamarthy MR, Lamus D, Saboo SS, Sutphin PD, Kalva SP. Pulmonary artery aneurysms: diagnosis & endovascular therapy. *Cardiovasc Diagn Ther* 2018;**8**: 350–361.
13. Emad Y, Ragab Y, Robinson C, Pankl S, Young P, Fabi M, et al. 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* 2021;**40**:4993–5008.
14. Sanduleanu S, Jansen TLTA. Hughes–Stovin syndrome (HSS): current status and future perspectives. *Clin Rheumatol* 2021;**40**:4787–4789.
15. Seyahi E, Yazici H. To anticoagulate or not to anticoagulate vascular thrombosis in Behçet's syndrome: an enduring question. *Clin Exp Rheumatol* 2016;**34**:S3–S4.
16. Ozguler Y, Leccese P, Christensen R, Esatoglu SN, Bang D, Bodaghi B, et al. Management of major organ involvement of Behçet's syndrome: a systematic review for update of the EULAR recommendations. *Rheumatology (Oxford)* 2018;**57**:2200–2212.
17. Tazi Mezalek Z, Khibri H, Chadli S, El Fari S, Ammouri W, Harmouche H, et al. Vascular complications of Behçet disease. *Minerva Med* 2021;**112**:767–778.
18. Sachdev G, Yadav S, Balakrishnan C, Nanavati R. Hughes–Stovin syndrome: an experience of management of 3 cases from a tertiary health care centre. *Clin Med Insights Arthritis Musculoskelet Disord* 2023;**16**:11795441231168648.
19. Bennji SM, du Preez L, Griffith-Richards S, Smit DP, Rigby J, Koegelenberg CFN, et al. Recurrent pulmonary aneurysms: Hughes–Stovin syndrome on the spectrum of Behçet disease. *Chest* 2017;**152**:e99–e103.