CASE REPORT

Behçet's disease with major vascular involvement

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SUMMARY

A 40-year-old Chinese man was admitted for haemoptysis and progressive deep vein thrombosis involving the inferior vena cava (IVC) despite anticoagulation. An IVC filter had been placed earlier at an outside hospital. CT angiography revealed two pulmonary artery aneurysms. The patient was found to have a history of oral and genital ulcers, uveitis and erythema nodosum, thus meeting criteria for Behçet's disease. Other causes of the haemoptysis and thrombophilia were excluded. He underwent successful coil embolisation of the pulmonary artery aneurysms and responded well to immunosuppressive therapy with cyclophosphamide and steroids. Anticoagulation was cautiously continued to limit the long-term risk of secondary thrombosis from his IVC filter. The patient remains well 5 months after initiation of immunosuppressive therapy. Making a diagnosis of Behçet's disease in the setting of thrombosis is crucial, as treatment must include immunosuppression, and, thus, fundamentally differs from the management of most other thrombotic disorders.

BACKGROUND

Behçet's disease (BD), a multisystem autoinflammatory condition, is relatively common in regions along the 'Old Silk Road' and is associated with the classic triad of recurrent oral ulcers, genital ulcers and uveitis.¹ Pulmonary aneurysms and deep venous thrombosis (DVT) are typical albeit relatively rare features of the disease (4–5% of all cases) and often co-occur. This co-occurrence has also been described as a distinct entity named Hughes-Stovin syndrome, an extremely rare condition in which patients generally present with cough, haemoptysis, dyspnoea and chest pain following a history of venous thrombosis. The aetiology is unknown, but it is considered as an incomplete form of or undiagnosed 'true' BD by many authors and managed similarly.^{2–5} Thrombosis in BD differs from other forms of thrombosis insofar as thrombi stick firmly to the vessel wall, do not tend to embolise and are 'inflammatory', thought to be primarily due to disease processes located in the vessel wall, rather than secondary to true hypercoagulability.⁶ Consequently, treatment for thrombosis in BD must target the underlying vasculitis. In fact, the European League Against Rheumatism recommends immunosuppression as the sole form of treatment.⁷

Anticoagulation is associated with a high risk of bleeding from concomitant aneurysms,⁸ and the observation of thrombosis progression despite its use points to a limited role.⁶ Regardless, anticoagulation therapy remains controversial as there are no

data from randomised controlled trials. In addition, many physicians face diagnostic uncertainty given the rarity of BD in the West and fear the detrimental consequences of withholding anticoagulation should they misdiagnose the condition.⁹ This report describes the case of a Behçet's patient with the rare but characteristic phenotype of major vascular disease and depicts the diagnostic challenges as well as the evolution of his management going from a peripheral medical facility, through a tertiary referral centre and, finally, to a Behçet's specialty clinic in the USA.

CASE PRESENTATION

A 40-year-old Chinese man was transferred from a peripheral outside hospital for acute haemoptysis and progressive bilateral DVT to a tertiary referral centre. Five months prior to admission to the tertiary hospital, he had been diagnosed with idiopathic right lower extremity DVT and was started on warfarin. Three months later, he experienced a massive gastrointestinal bleed from multiple colonic ulcers of 'unknown etiology'. Spiral CT showed a presumed pulmonary embolus. An inferior vena cava (IVC) filter was placed and anticoagulation was stopped for a week. A month later the colonic ulcers healed, but his DVT progressed to involve bilateral lower extremities, despite the use of warfarin which was subsequently increased from 3 to 4 mg/day. Two days prior to admission, the patient presented to the outside hospital with an isolated episode of haemoptysis and an international normalised ratio (INR) of 7.5. On transfer to the tertiary hospital, the patient's history and review of systems revealed occasional oral ulcers on initial questioning, but was otherwise unremarkable. His vital signs were normal and the physical examination was notable for prominent superficial abdominal veins (figure 1) and swollen, tender calves. CT of the chest showed possible pulmonary artery aneurysms. The patient was admitted under a working diagnosis of Hughes-Stovin syndrome versus BD. Subsequently during the hospitalisation, he developed oral and scrotal ulcers similar to past eruptions that he now admitted had recurred intermittently for a number of years. He then reported a several-year history of recurrent skin lesions characteristic of erythema nodosum. These longer-standing symptoms were either missed or possibly dismissed as irrelevant on initial evaluation of his DVT at the outside hospital. Given the high index of suspicion for BD at this point, ophthalmological evaluation was conducted at the tertiary care centre and revealed bilateral intermediate uveitis. Thus, a final diagnosis of BD was made. The patient met International Study Group criteria for BD with his

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Figure 1 Prominent collateral superficial abdominal veins in this patient with extensive deep venous thrombosis involving the inferior vena cava. R, rostral.

recurrent oral ulcers, genital ulcers, uveitis and skin lesions in the absence of another disease explaining his presentation.¹⁰

INVESTIGATIONS

CT pulmonary angiography revealed two pulmonary artery aneurysms in the right lower lobe (figure 2A). Venous duplex ultrasound showed thrombus extending from posterior tibial veins into the IVC and the left main renal vein. CT of chest, abdomen and pelvis did not indicate lesions suspicious for any malignant processes. Homocysteine level and factor V assay were within normal limits. IgG and IgM anti- β_2 glycoprotein

Figure 2 Pulmonary artery aneurysms in this patient with Behçet's disease. (A) Contrast-enhanced CT scan of the chest (soft tissue window) showing pulmonary artery aneurysms in the right lower lobe of the lung (arrows), a characteristic location for Behçet's disease. (B) Pulmonary angiogram status post coil embolisation of two pulmonary artery aneurysms in the right lung vasculature, approximately 16 and 6 mm in diameter, respectively.

antibodies (both <9), IgG and IgM anticardiolipin antibodies (<9 and 10, respectively) were within normal limits, and lupus anticoagulant was weakly positive after emergency reversal of his anticoagulation with allogeneic fresh frozen plasma was necessary to control his acute haemoptysis shortly before transfer from the peripheral outside hospital. QuantiFERON-TB Gold assay, antiglomerular basement membrane (anti-GBM), antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) panel all tested negative. Human leucocyte antigen-B51, which is associated with BD in some ethnic groups though neither sensitive nor specific for the disease, was negative.

DIFFERENTIAL DIAGNOSIS

The diagnostic challenge in this case is synthesising the constellation of signs and symptoms into the simplest diagnostic explanation while not ignoring the possibility that multiple conditions could be independently contributing to the clinical picture. In a patient presenting with haemoptysis and DVT, it is crucial to first exclude life-threatening conditions such as pulmonary embolism. The differential diagnosis for haemoptysis is broad and includes infections, cancer, and inflammatory, immune and vascular disorders. For example, systemic lupus erythematosus can also present with oral ulcers and haemoptysis, but his lack of other classic lupus symptoms (eg, rash) and negative ANA panel made this unlikely. Other autoimmune diseases including Goodpasture's syndrome and ANCA-associated vasculitides such as granulomatosis with polyangiitis and microscopic polyangiitis, must be considered in the differential diagnosis of haemoptysis but were unlikely here, given the lack of renal involvement, the absence of relevant antibodies (ie, anti-GBM and ANCA panel), and the involvement of the pulmonary arteries which is not usually seen in ANCA-associated vasculitides. Colonic ulcers, erythema nodosum, oral ulcers and uveitis can be associated with inflammatory bowel disease, which, at times, is hard to differentiate from BD (those patients may even formally fulfil diagnostic criteria for BD), but his lack of chronic gastrointestinal symptoms, non-specific colonic biopsies and the presence of pulmonary artery aneurysms made this diagnosis unlikely. While all of these inflammatory disorders may be associated with an increased risk of venous thrombosis, they all typically lack pulmonary artery aneurysms which are so characteristic of major vascular BD.

When considered separately, the differential diagnosis for pulmonary artery aneurysms and recurrent DVT is still fairly broad (see table 1). After pulmonary artery aneurysms were detected on imaging,

Table 1 Differential diagnosis of pulmonary artery aneurysm and recurrent venous thrombosis

Pulmonary artery aneurysm ^{11 12}	Recurrent venous thrombosis ¹³
<i>Infections</i>	<i>Inherited thrombophilia</i>
Tuberculosis	Factor V Leiden mutation
Syphilis	Prothrombin gene mutation
Septic emboli (mycotic aneurysm)	Protein S deficiency
<i>Vasculitis</i>	Protein C deficiency
Behçet's disease	Antithrombin deficiency
Hughes-Stovin syndrome	Dysfibrinogenemia
Takayasu arteritis	<i>Acquired thrombophilia</i>
<i>Other</i>	Malignancy
Neoplasms	Antiphospholipid syndrome
Trauma (iatrogenic)	<i>Vasculitis</i>
Chronic pulmonary hypertension	Behçet's disease
Congenital heart defects	Hughes-Stovin syndrome
Marfan syndrome	

they were recognised as the most likely source of the patient's haemoptysis, and their presence—in conjunction with DVT—narrowed the differential diagnosis to principally two disorders: BD and Hughes-Stovin syndrome. Given his ethnic background and the history of recurrent oral ulcers, the patient's presentation was now consistent with BD, not Hughes-Stovin syndrome and the subsequent evaluation which turned out to be positive for uveitis, genital ulcers and a history of erythema nodosum confirmed this diagnosis.

TREATMENT

At the tertiary care facility, the patient underwent successful coil embolisation of the pulmonary aneurysms (figure 2B), and heparin drip was started. Once major infectious aetiologies were excluded, an immunosuppressive regimen of prednisone 60 mg daily was begun. He responded well, with reduced swelling in his legs and lack of recurrence of his pulmonary aneurysms on follow-up imaging. The patient also received hydroxychloroquine 200 mg twice daily. He was bridged to warfarin and discharged to the Behçet's speciality clinic where hydroxychloroquine was stopped, oral cyclophosphamide was started, and prednisone was tapered slowly. Target INR was lowered to 2–2.5, but anticoagulation was continued out of concern for the possibility of secondary thromboembolism from the patient's IVC filter.

OUTCOME AND FOLLOW-UP

At 5 months after discharge from the hospital, the patient is in a stable condition. Additional testing for lupus anticoagulant after 3 months was negative, and he had a positive pathergy test. He is undergoing cyclophosphamide induction therapy at a dosage of 2 mg/kg/day for the minimum length of 6–12 months. There was no evidence of pulmonary artery aneurysm recurrence, and his IVC thrombosis has resolved completely on repeat imaging at 4 months after the initiation of cyclophosphamide. Oral cyclophosphamide was chosen over monthly intravenous cyclophosphamide bolus (the more widely accepted regimen in BD) for feasibility considerations. Rituximab was considered briefly by some team members, extrapolating from its beneficial role in ANCA-associated vasculitis¹⁴ as well as some recent reports supporting its possible efficacy in BD uveitis^{15 16}; however, there is insufficient evidence to justify its use as a first-line agent in life-threatening BD with major vascular involvement. Similar concerns were raised regarding the potential use of antitumour necrosis factor agents, especially infliximab, for which several case reports have been published suggesting possible efficacy in vascular BD, including in cases that were non-responsive to cyclophosphamide and steroids.¹⁷

Currently, his prednisone is being tapered. Removal of his IVC filter was determined to have an unacceptably high risk of complications, so he remains on warfarin with a target INR of 2–2.5 to reduce the risk of filter-related thromboembolism, not for BD-related therapeutic considerations. The patient is monitored for possible recurrence of his pulmonary aneurysms through regular imaging.

DISCUSSION

The rarity of BD in the West leaves many physicians unfamiliar and relatively inexperienced with BD and some of its rarer manifestations. In young patients with South European, North African, Middle Eastern or Far Eastern ethnic backgrounds, it is important to consider BD in the differential diagnosis of seemingly 'idiopathic' DVT, particularly if recurrent oral ulcers are present. This should trigger an aggressive search for the presence or history of other BD-related manifestations, such as

uveitis, erythema nodosum, pustulosis and genital ulcers. Imaging of the pulmonary arteries should be obtained to screen for aneurysms in these cases. Although the constellation of DVT with pulmonary artery aneurysms has been described as Hughes-Stovin syndrome, significant doubt has emerged as to its existence as an independent entity rather than undiagnosed BD.^{18 19} A 'Hughes-Stovin' presentation in a young Middle or Far Eastern (mostly male) patient with a history of recurrent oral ulcers is highly suggestive—and virtually diagnostic—of BD, even at a point when other diagnostic criteria for BD are either not present or cannot be elicited from the patient.

In patients with BD, pulmonary haemorrhage is one of the leading causes of mortality and prognosis is poor if pulmonary aneurysms are left untreated.⁸ However, in those with coexisting venous thrombosis, physicians are often pressed to start anticoagulation. There are no controlled trials to guide optimal therapy for these patients, but expert consensus supports a regimen consisting of cyclophosphamide and steroids while abstaining from anticoagulation, especially if pulmonary aneurysms are present.^{7 20 21} These and other therapies for BD are comprehensively reviewed elsewhere.²²

Our case illustrates all of the aforementioned issues, beginning with the initial delay of diagnosis in a peripheral setting where BD and relevant immigrant populations may be rare. This triggered a chain of complications related to the initiation of anticoagulation without immunosuppression, including the insertion of an IVC filter after finding 'pulmonary embolus' on spiral CT (a finding much more likely to be due to in situ thrombus formation than embolism from DVT in Behçet's)²³ and bleeding colonic ulcers (a typical feature of BD). Later, the patient was correctly diagnosed and treated with immunosuppressive therapy at the tertiary referral centre, but uncertainty regarding the role of anticoagulation persisted. At the Behçet's specialty clinic, anticoagulation was finally deemed not to be indicated

Learning points

- ▶ The combined findings of deep venous thrombosis and pulmonary artery aneurysms in a young, most often male, patient marks a life-threatening condition with a very narrow differential diagnosis, consisting primarily of Behçet's disease and Hughes-Stovin syndrome.
- ▶ Before accepting a diagnosis of Hughes-Stovin syndrome, it is reasonable to assume that the patient has Behçet's disease, and to search aggressively for additional signs and symptoms to confirm this diagnosis.
- ▶ Steroids and immunosuppressive agents (ie, cyclophosphamide) comprise the principal therapy in Behçet's patients with major vascular disease, aimed at controlling the vasculitis and associated thrombosis. Tumour necrosis factor inhibitors may be an alternative, especially in cases of treatment failure with cyclophosphamide and steroids or in the presence of absolute contraindications to cyclophosphamide, but their routine use as first-line agents in these patients requires further study and is not advisable at present.
- ▶ Anticoagulation in this setting remains controversial as its risk is high while efficacy is questionable. If a patient requires anticoagulation for other reasons, it should be used cautiously and preferably after pulmonary (and other) aneurysms have either been ruled out or shown to have resolved, while continuously monitoring for their recurrence.

for the treatment of this patient's BD per se, but cautiously continued in order to reduce the risk of thromboembolism related to the IVC filter.

In conclusion, diagnosing patients with vascular BD requires a high index of suspicion and familiarity with the disease in order to be able to follow relevant clinical clues leading to a correct diagnosis. Once diagnosed, immunosuppression is essential, while anticoagulation is not generally recommended and should be tailored based on individual circumstances.

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