A Rare Case of Behçet Disease Presenting with Pyrexia of Unknown Origin, Pulmonary Embolism, and Right Ventricular Thrombus

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Abstract

Keywords

- Behçet disease
- right ventricular thrombus
- pulmonary embolism

Behçet disease is a systemic vasculitis characterized by recurrent oral and genital ulcers and uveitis. We describe a rare case of a 43-year-old woman with Behçet disease who was admitted for pyrexia of unknown origin, cough, dyspnea, and chest pain. Her computerized tomography scan revealed pulmonary embolism and right ventricular thrombus. She was treated with anticoagulation for pulmonary embolism and right ventricular thrombus. She was well during her last follow-up.

Background

Behçet disease (BD) is a systemic inflammatory disorder caused by underlying vasculitis, presenting with recurrent oral ulcers and any of several systemic manifestations including genital ulcers, ocular disease, skin lesions, arthritis, and gastrointestinal, neurologic, or vascular disease. It is most prevalent along the ancient Silk Road, which extends from eastern Asia to the Mediterranean area, affecting males and females equally. Most patients become symptomatic between the ages of 20s and 40s. The cause of BD is unknown, though genetic anticipation has been reported.¹

Case Report

A 43-year-old woman was admitted on October 21, 2012, with a 1-month history of recurrent fever, dry cough, chest discomfort, and shortness of breath. She had past medical history of BD diagnosed 20 years earlier, initially treated with glucocorticoids for a short period before she was lost to follow-up.

The patient had recurrent oral ulcers (at least 10 times a year) and genital ulcers (at least once a year). She also developed erythema nodosum (on and off) intermittently over the past 20 years, which increased in frequency over the last 1 year. She was noncompliant to therapy and had irregular follow-ups. There was no history of eye, joint, or

neurological involvement. She did not have any other systemic manifestations.

On taking a detailed history, she had recurrent fever for 1 month before hospitalization, with temperature spikes of around 38.5°C every day, which resolved with paracetamol. Subsequently, she developed chest discomfort, dry cough, and shortness of breath on exertion. During this period, she was treated with amoxicillin plus clavulanic acid and paracetamol by a general practitioner. The fever persisted, although less frequent over the next few days. There was no significant loss of weight or appetite. She was not on any long-term medications and had no history of tobacco or alcohol abuse. Her menstrual history and family history were unremarkable. There were no recent history of travel/exposure and she denied any high-risk behavior.

On the day of admission, she appeared well nourished but mildly pale. She was afebrile at 36.8°C; her blood pressure was 100/60 mm Hg; and heart rate was 90/minute. Her systemic examination was normal. There were no skin, oral, joint, or genital lesions.

Laboratory findings showed the following: total white blood cell count, $8.7 \times 10^9/L$ (neutrophils, 74.4%; lymphocytes, 15.5%; monocytes, 8.6%; eosinophils, 1.2%); hemoglobin, 9.3 g/dL; platelets, $306 \times 10^9/L$; albumin, 30 g/L; alanine transaminase, 32 U/L; aspartate transaminase, 47 U/L; alkaline phosphatase, 148 U/L; C-reactive protein (CRP), 185 mg/L; iron, 2 $\mu\text{mol/L}$; transferrin, 1.7 g/L; iron saturation, 5%;

Fig. 1 Computed tomographic pulmonary angiography (coronal view) showing pulmonary embolism in the left pulmonary artery.

procalcitonin, 0.05 µg/L; and blood cultures (twice) negative. Urine: WBC, 9/µL; RBC, 39/µL; no cast, crystal, bacteria, and yeast cells were seen. Urine culture was negative. Chest X-ray was relatively normal with clear lung fields. Her electrocardiogram was unremarkable.

Her temperature spiked to 39°C on the night of admission. After blood and urine cultures were taken, intravenous amoxicillin plus clavulanic acid and oral paracetamol was empirically started to treat any possible underlying infection.

The patient would need at least a week of in-hospital investigations to fulfill the criteria for pyrexia of unknown origin (PUO), and therefore we went ahead to perform further investigations to identify the cause of her unrelenting fever spells. Her erythrocyte sedimentation rate (ESR) was 105 mm/hour, antinuclear antibody was negative, malarial parasites were not seen, and acid fast bacilli smears were negative. She underwent computerized tomography (CT) scan of thorax, abdomen, and pelvis on October 22, 2012, as a workup for PUO. The scan revealed a thrombus in the right ventricle and pulmonary emboli in the left lower lobe pulmonary arteries (→Figs. 1 to 3). There was no suspicious mass/collection in the thorax, abdomen, or pelvis. There was a single hepatic lesion noted with enhancement features characteristic of a hemangioma.

Fig. 2 Computed tomographic pulmonary angiography (axial view) showing pulmonary embolism in the left pulmonary artery.

Fig. 3 Computed tomographic pulmonary angiography showing right ventricular thrombus.

A transthoracic echocardiography (TTE) was performed to rule out predisposing cardiac conditions. The TTE results are as follows: a left ventricular ejection fraction of 60%; normal left ventricular systolic function; no right ventricular systolic impairment; mass in right ventricle (RV) 18 × 13 × 18 mm; knobbly, not tubular, unlike venous thrombus; sits on surface of septum but appears separate from endocardium; not typical for invasive tumor; and no atrioventricular septal defect was seen.

As per the recommendations of the cardiologists, a cardiac magnetic resonance imaging (MRI) was performed to further evaluate the nature of the intrathoracic mass. The MRI revealed a right ventricular lesion suggestive of a thrombus (→Fig. 4). She was started on anticoagulation subsequently (day 2 of admission) and remained relatively afebrile for the next few days.

Further investigations were done to ascertain the source/etiology of her thromboembolic phenomenon. Bilateral lower limb Doppler ultrasonography did not reveal deep vein thromboses (DVT). Her thrombophilia workup showed the following results: protein C activity, 88% (normal range, 70 to 150%); protein S activity, 65% (normal range, 55 to 130%); antithrombin III, 76% (normal range, 80 to 130%); lupus anticoagulant weakly present; anticardiolipin IgM, 1 U/mL.

Fig. 4 Chest magnetic resonance imaging showing right ventricular thrombus and liver hemangioma.

(normal range, < 10 U/mL); IgG, 3 U/mL (normal range, < 10 U/mL); and factor V Leiden was normal.

She underwent esophagogastroduodenoscopy and colonoscopy in view of the iron-deficiency anemia. Anticoagulation was stopped briefly for a few days before her scopes. The scope findings were normal.

Further Progress of Patient

Complete blood cell count, ESR, and CRP trendings are given in ► **Table 1**. Blood and urine culture results twice reported no growth. She had been afebrile on treatment with anticoagulation. We went on to complete the empiric amoxicillin plus clavulanic acid for 1 week. By then, her blood cultures and urine cultures were negative.

Interestingly, she developed intermittent episodes of low-grade fever during the period in which anticoagulation was withheld. Upon resuming anticoagulation after her endoscopic procedures, there were no fevers noted.

An infectious diseases consult promptly ruled out infective endocarditis. In keeping with her stable fever-free clinical state, improving inflammatory markers, and the possibility of sepsis out of the way, we attributed her PUO to the underlying BD manifesting with pulmonary embolism and RV thrombus. Therefore, a rheumatology consult was performed, and a decision to commence immunosuppression therapy was made. However, the patient refused immunosuppression therapy. She was discharged well, having been afebrile for 1 week in the ward. And outpatient follow-up revealed a reduction in the size of the RV thrombus from 18 × 13 mm to 17 × 9 mm.

Discussion

The International Study Group (ISG) criteria published in 1990 remains the most widely used in the diagnosis of BD. The criteria for diagnosis entails the presence of recurrent

oral aphthae (at least three times in 1 year) plus two of the following in the absence of other systemic diseases: recurrent genital aphthae (aphthous ulceration or scarring), eye lesions, skin lesions (including erythema nodosum, pseudo-vasculitis, etc.), and a positive pathergy test.² The International Criteria for Behçet disease (ICBD) was developed in 2006 in an effort to improve sensitivity compared with the ISG criteria. The ICBD criteria requires a total of at least three points for the diagnosis of BD: genital aphthosis (two points), ocular lesions (two points), oral aphthosis (one point), skin lesions as pseudofolliculitis or erythema nodosum (one point), vascular lesions (superficial phlebitis, DVT, large vein thrombosis, arterial thrombosis, or aneurysm) (1 point), and pathergy (1 point). According to history, this patient fits both the diagnostic criteria of BD.^{3,4}

Both veins and arteries of all sizes can be involved in BD.⁵ Vascular involvement has been considered to result from systemic vasculitis, and it occurs in 5 to 10% of these patients.⁶ Although rare, BD complicated by right ventricular thrombosis and/or pulmonary embolism has been reported.^{7,8} And the right heart is the most common site of involvement.^{9,10} Patients commonly present to the hospital with fever, rash, cough, dyspnea, chest pain, weight loss, and hemoptysis. Fever is more common when the pulmonary artery is involved.^{6,11–18} Thus, gathering a thorough history, especially with patients who have not been diagnosed with BD, is important for further workup and management.

In these cases, initial symptoms such as fever, cough, dyspnea, chest discomfort, and hemoptysis are mostly non-specific; therefore, an early diagnosis can be challenging.¹⁹ However, diagnosis of BD might still be considered if a patient presents with a mass in the right-sided cardiac chambers, even in the absence of the characteristic clinical features of the condition.²⁰ This is particularly applicable if the patient is a young male from the Eastern Asia, Mediterranean basin, or the Middle East,^{9,21} though such conditions can also occur in patients without predisposing ethnic or geographic factor.²²

Table 1 Trending of CBC, CRP, and ESR during hospitalization

Test name	Reference range	Units	20/11/2012	23/10/2012	25/10/2012	30/10/2012	05/11/12	09/11/2012
Hemoglobin	11.0–15.0	g/dL	8.7	8.6	9.4	9.6	10.5	10.3
Hematocrit	35.0–45.0	%	28.2	25.9	28.2	28.8	32.2	31.3
White blood cell	3.6–9.3	×10 ⁹ /L	8.7	7.3	6.6	6.1	5.4	6.6
Neutrophils		%	74.4	76.8	66.1	61.4	53.9	63.4
Lymphocyte		%	15.5	14.9	23.7	25.8	32.5	26.3
Monocytes		%	8.6	6.2	6.7	10.2	7.9	5.8
Eosinophils		%	1.3	1.8	2.9	2.2	5.2	3.9
Basophils		%	0.2	0.3	0.6	0.4	0.5	0.6
Platelets	170–420	×10 ⁹ /L	306	307	425	343	257	232
CRP	0.0–5.0	mg/L	185			20.2	11.2	12.4
ESR	3–15	mm/h	105			80	55	35

Abbreviations: CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

For this patient, chest CT scan was done for the evaluation of PUO, and pulmonary embolism and right ventricular thrombus were incidentally found. Infective endocarditis was ruled out according to the Duke criteria.²³ After the review of the patient's past medical history and a complete screening to rule out other possible infections, her clinical manifestations were decisively attributed to the underlying BD.

An early diagnosis and treatment are essential for the management of BD especially with large-vessel manifestations.¹⁵ Chest CT or MRI is commonly used to detect pulmonary and intracardiac thromboembolism.^{7,8} And echocardiography is most widely used for the assessment of progress and efficacy of treatment and follow-up.^{12,14,24,25}

The possible cause of fever in this patient was suspected to be pulmonary embolism. The patient was treated with oral amoxicillin plus clavulanic acid before hospitalization, but her fever and other symptoms prevailed. During hospitalization, her fever subsided after commencing anticoagulant therapy above the empirical antibiotic therapy (amoxicillin and clavulanic acid). It has been reported, though not common, that pulmonary embolism with thrombosis can cause high fever. And fever of this cause responds to anticoagulant therapy.^{26–29} Moreover, fever is also a common presentation in BD.^{14,30,31}

With regard to the management, medical treatment is the mainstay.³² Anticoagulation (warfarin) with/without immunosuppression therapy (cyclophosphamide and corticosteroid are reported to be effective^{5,16,33}) is the most preferred approach and has been proven to be very effective.^{7,33} But occasionally due to hemodynamic compromise, surgery has been done to remove intracardiac thrombus.^{12,14,34} Before the start of immunosuppression therapy, a thorough workup to rule out any possible infection should be performed. Patients should be well informed to identify signs of infection especially those treated as outpatients. Occasionally, patients will decline immunosuppression therapy largely due to concerns with adverse effects of these drugs. In this patient, immunosuppression therapy was offered by the rheumatologist, but the patient had clearly declined it. In such situations, to commence anticoagulation and closely monitor the size of the thrombus may be the optimal approach. Because of lack of data, the comparison of efficacy between anticoagulant therapy alone and anticoagulant therapy together with immunosuppression therapy is not well known.

Conclusion

Patients with BD may develop pulmonary embolism and right ventricular thrombus as part of systemic vascular complication. Such a manifestation may infrequently present as PUO. Early diagnosis may be difficult due to nonspecific clinical manifestations. Thus, a thorough history, physical examination, and appropriate imaging studies are essential for diagnosis. The mode of management includes anticoagulation with or without immunosuppression therapy, with close follow-up on the size of thrombus by echocardiography. These patients will ultimately benefit from a collaborative management approach involving the vascular physician, rheumatologist, and cardiologist.

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