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Case report

Clinical course of Behcet's disease in a patient with delayed diagnosis and radiological follow-up of the thrombi with computed tomography angiography: a five-year follow-up under immunosuppressive treatment

Evolução clínica da doença de Behçet em paciente com atraso do diagnóstico e seguimento radiológico dos trombos com angiotomografia computadorizada: seguimento por 5 anos durante tratamento imunossupressor

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Introduction

Behçet's disease (BD) is a chronic inflammatory disease of unknown etiology.[1] The diagnosis is made on the basis of the combination of clinical findings; therefore delay in the diagnosis is not rare. Sometimes, cardiovascular and pulmonary involvement is seen before making diagnosis of BD. Such manifestations can be life-threatening and failure to diagnose BD in such a patient may be very serious.[2–4] In this paper, we describe a BD patient diagnosed late with intracardiac, superior vena cava, and bilateral pulmonary artery thrombi. We used computed tomography angiography (CTA) to study the time course of thrombus development from the time of initial diagnosis throughout treatment. In this aspect, this is the first report to use CTA to explore the long-term course of intracardiac, superior vena cava, and bilateral pulmonary artery thrombi.

Case report

Our patient is a woman who was 27 years at the time of diagnosis, and her first complaint was fever, which commenced in January 2005. Prior to that time, she had suffered from aphthous lesions, but did not seek medical attention. In April

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2005, investigations revealed elevated levels of acute phase reactants including the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level; these were 38 mm/h and 149 mg/L, respectively. She was admitted to hospital at that time. On physical examination, multiple oral aphthous ulcers were detected. Although BD was considered in differential diagnosis, she was not diagnosed with the disease because other signs of BD were absent. In fact, she did have a genital ulcer but, unfortunately, it was not mentioned to the physician, and the genitalia were not examined. Exhaustive tests seeking the etiology of the fever were conducted; all of infectious, autoimmune, and malign etiologies were considered. Echocardiography revealed a cardiac mass 24 mm × 13 mm in dimensions on the lateral wall of the right ventricular cavity. This was confirmed by cardiac magnetic resonance imaging (MRI); a soft tissue mass 25 mm × 40 mm × 40 mm was evident in the right ventricular cavity. The main features of this soft tissue mass were its partially moving character during systole and diastole, iso-hypointense according to the myocardial tissue and without contrast enhancement. A cardiac thrombus was initially suspected. A biopsy was performed, but it was non-diagnostic. Subsequently, the patient experienced her first episodes of pleuritic chest pain and hemoptysis. Lung ventilation/perfusion scintigraphy was performed; perfusion loss in multiple segments of both lungs was evident. Possible foci of thrombosis and causes of thrombophilia were sought. She was heterozygous for the prothrombin G-A20210 mutation, but neither the V Leiden nor the MTHFR gene was mutated. The activated partial thromboplastin time, and the levels of lupus anticoagulant, protein C, protein S, anti-thrombin III, anticardiolipin antibodies, anti-beta 2-glycoprotein 1 antibodies, and homocysteine were all normal.

One month later, the right ventricular mass was biopsied once more and found to contain only normal heart muscle fibers and adipose tissue. Hemoptysis re-occurred after biopsy and persisted for about 1 week. Pulmonary CTA was then performed, and a hypodense filling defect was evident in the right ventricle and right pulmonary artery (Fig. 1A1 and B1). Therefore, anticoagulant therapy (low-molecular weight heparin followed by warfarin) was commenced.

In September 2005, while still on anticoagulant therapy, the patient was hospitalized with fever, cough, neck and facial swelling, dyspnea, and palpitations. On physical examination, she had fever (38.5 °C), bilateral jugular venous distention, face and neck edema, osteofolliculitis, and erythema nodosum on the right pretibial region. In addition, two genital ulcer scars and oral aphthae were observed. Human leukocyte antigen B51 test was positive and pathergy test was negative, so the diagnosis of BD was made. Pulmonary CTA was performed again. The intracardiac thrombus (ICT) noted earlier remained, but now, dilatations of 2 cm of the ascending and 2.5 cm of the descending branches of the right pulmonary artery were evident, together with a dilatation of 3 cm of the descending branch of the left pulmonary artery. All dilatations were associated with the presence of mural thrombi. Also, neither the right brachiocephalic vein nor the superior vena cava could be visualized because of thrombosis. The clinical findings that developed over the 9-month period prior to subsequent treatment are shown in chronological order (Table 1).

First, warfarin therapy was discontinued because it was possible that both a pulmonary arterial aneurysm and arteritis were present. Methylprednisolone (1 g/day for 3 days) was administered, followed by 1 mg/kg/day of oral prednisolone. A cyclophosphamide (CYC) pulse of 1 g was started and continued monthly thereafter. Prednisolone was tapered 4 weeks later. Symptoms were relieved, and both the CRP level and the ESR fell to normal ranges. Hemoptysis gradually decreased and then disappeared.

In November 2005, the patient was re-evaluated by pulmonary CTA. Thrombi persisted in the intracardiac region, the superior vena cava (Fig. 1D2) and both pulmonary arteries. Multiple collateral intercostal veins, which drain the azygos vein, were serving to drain the upper extremities. A filling defect was observed in the descending branch of the left pulmonary artery (Fig. 1C2). This created a dilatation in the vessel wall, which was associated with minimal intraluminal contrast enhancement. However, this was not considered to be an aneurysm. In September 2005, the report of a pulmonary artery aneurysm was reviewed and re-classified as wall dilatation caused by an intraluminal thrombus.

Eleven months later, while still undergoing monthly CYC treatment, fever with chills re-occurred associated with an elevated ESR and CRP level (37 mm/h and 51 mg/L, respectively). Therefore, interferon-alpha (5 MU three times per week) was added to therapy and the dose of prednisolone was increased to 1 mg/kg/day. The patient received a total of 15 g of CYC over an 18-month period. Interferon therapy was continued for approximately 11 months. Next, azathioprine 150 mg/day and acetylsalicylic acid 100 mg/day were commenced. At the time of writing, the patient remains on this treatment, and the signs and symptoms previously reported have not re-appeared.

Pulmonary CTA was used to follow-up the thrombi in the intracardiac region, the pulmonary arteries, and the superior vena cava. The thrombus in the right ventricle had decreased in size by 2008 (Fig. 1A2). In 2010, thus 5 years after initial CTA, the size of the right ventricular thrombus (and the calcific part thereof) had become further reduced (Fig. 1A3). The thrombus in the pulmonary artery remained visible on the CTA images in 2008 and 2010. In comparison with the scan performed in 2005, CTA revealed that the thrombi in the right intermediate lobar pulmonary artery (Fig. 1B1–B3) and in the left inferior lobar pulmonary artery (Fig. 1C1–C3) decreased in size over time. In the CTA scans carried out in 2008 and 2010, thrombosis in the superior vena cava persisted unchanged in the cranial section of the azygos drainage (Fig. 1D2–D4). No new thrombi were noted on follow-up pulmonary CTA. Currently, no clinical or laboratory evidence indicates the presence of active disease.

Discussion

We report a BD patient with serious complications including cardiac and vascular involvement. We describe clinical findings prior to clinical diagnosis (thus before treatment) and use of CTA to follow-up thrombi over 5 years of treatment.

The clinical course of BD is notably more severe in males. Severe complications such as vascular, neurological and pulmonary involvement as well as mortality are mostly related to the male gender.[5] Here, life-threatening complications

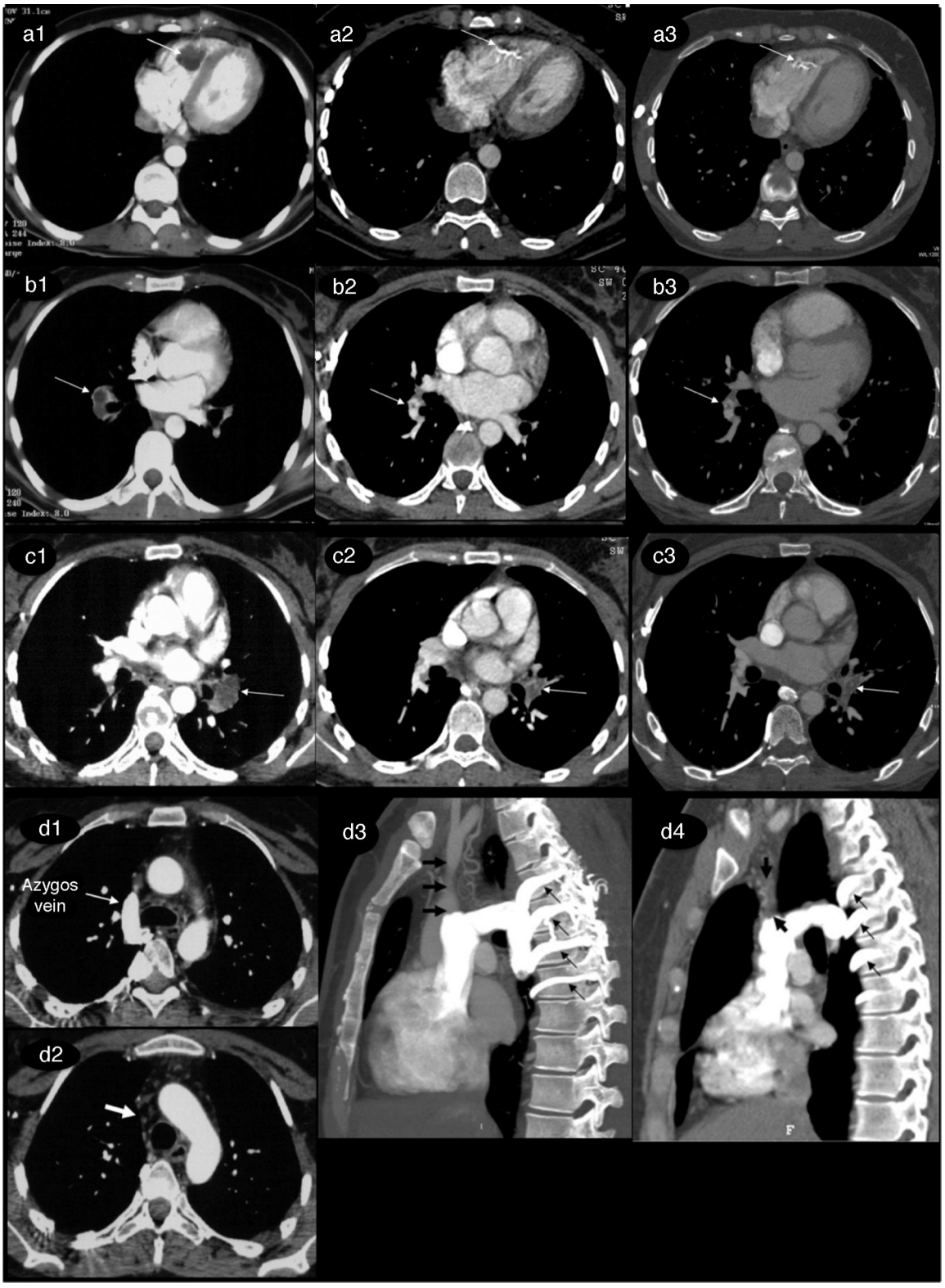

Fig. 1 – Five-year computed tomography angiography (CTA) follow-up of thrombi in the intracardiac region, the superior vena cava, and both pulmonary arteries.
In 2005 (A1), a CTA scan revealed a large hypodense thrombus in the right ventricle (arrow). In 2008 (A2), the thrombus decreased in size and was partly calcified, and such shrinkage continued to 2010 (A3).
In 2005 (B1), intraluminal filling defects were evident in the right intermediate lobar pulmonary artery (arrow). In 2008 (b2) and 2010 (b3), a thrombus was evident in this region but became progressively smaller in size.

Table 1 – Clinical course of Behcet's disease in a patient with delayed diagnosis and treatment.

Clinical findings	Dec. 2004	Jan. 2005	March 2005	April 2005	May 2005	June 2005	Sep. 2005
Genital ulcer	+	–	–	–	–	–	–
Oral aphthous lesion[a]		+	+	+	+	+	+
Fever		+	+	+	+	+	+
Palpitation			+	+	+	+	+
Intracardiac thrombus				+	+	+	+
Pleuritic chest pain					+	+	+
Hemoptysis					+	+	+
Cough					+	+	+
Pulmonary artery thrombus						+	+
Genital ulcer scars[b]							+
Erythema nodosum							+
Acneiform and pseudofollicular skin lesions							+
Uveitis			–				–
Face and neck edema							+
Jugular venous distention							+
Pathergy test			–				–
HLA B51							+
Superior vena cava thrombus							+
Treatment	–						
– Oral empirical antibiotics		+					
– IV antibiotics			+				
– LMWH, followed by warfarine						+	–
– Cyclophosphamide and corticosteroid							+

LMWH, low molecular weight heparin.
[a] She was suffering from these lesions previously, but those were rare.
[b] Not examined by the physician previously.

developed during diagnostic evaluation were not fatal. It remains poorly known why females with severe complications suffer less mortality than males. As a mechanism, estrogens may suppress pro-inflammatory activities of the vascular endothelium and neutrophils.[6] Alternatively, testosterone may augment neutrophil functionality, especially in males.[7]

Thrombophlebitis and major vessel thrombosis are common manifestations of vascular involvement in BD patients, whereas ICT is extremely rare.[1] As in our case, pulmonary and cardiac complications frequently co-exist.[1,8] Fever, hemoptysis, dyspnea and cough are common presenting symptoms.[8] The frequencies of such complications may be underestimated because the clinical presentation of ICT is nonspecific in most patients.

In differential diagnosis of BD with venous thrombosis and pulmonary involvement, Hughes–Stovin Syndrome (HSS) should be considered. The clinical, radiological, and histopathological findings of HSS and BD overlap significantly. HSS is a very rare disorder characterized by thrombophlebitis and by the presence of multiple pulmonary and/or bronchial aneurysms. HSS patients usually present with cough, dyspnea, fever, chest pain and hemoptysis; these symptoms are also evident in BD patients. Specifically, the extent of pulmonary involvement is often identical in patients with these diseases. Indeed, HSS has been considered to be a variant of BD or an incomplete form of the disease. However, findings associated specifically with BD include recurrent genital ulceration, eye lesions, skin lesions, iritis, arthralgia and a positive pathergy test; these help to distinguish BD from HSS.[9]

Thrombophilic factors are expressed in some BD patients and may contribute to thrombus formation. In our patient, heterozygous mutation of prothrombin G-A 20210 gene was detected. Importantly, ICT has been reported to be associated with deep vein thrombosis and thrombosis of the vena cava in 50% and 22% of BD cases, respectively.[10] We found no evidence of deep vein thrombosis on Doppler ultrasonography. In patients with ICT associated with BD, the presence of a pulmonary embolism and/or thrombus should be investigated even if venous thrombosis cannot be detected.

In 2005 (C1), hypodense filling defects were evident in the left inferior lobar pulmonary artery. In 2008 (C2) and 2010 (C3), a thrombus was evident in this region but became progressively smaller in size.
In 2005 (D1, D2), thrombosis was evident in the superior vena cava (thick white arrow), and the upper extremities drained to the VCS *via* azygos vein (thin white arrow). In 2008 (D3), coronal CTA imaging revealed thrombosis in the superior vena cava (thick black arrow). The upper extremities drained to the VCS *via* the collateral circulation and the intercostal veins (thin black arrows). In 2010 (D4), sagittal MIP CTA imaging conducted at the same level as the 2008 CTA scan revealed that little change had occurred. It was very apparent that multiple collateral intercostal veins (thin black arrows) draining the azygos vein also served to drain the upper extremities.

Association of a thrombotic superior vena cava syndrome with ICT is not common in BD patients. However, the incidence of pulmonary embolism and/or thrombus is high in BD patients with ICT.[1,8] The presence of all of ICT, thrombotic superior vena cava syndrome, and a pulmonary artery thrombus/embolism, is extremely rare in BD patients; only five cases (including the present case) have been described in the literature. It is sometimes hard to echocardiographically distinguish between ICT, vegetations and tumors. However, such distinctions are important, because the treatments and prognoses differ. Computed tomography and MRI might be better methods for investigating the extension of the involvements, as in our case.[1,8] Also, although biopsies of the mass in the right ventricular cavity were not diagnostic for our patient, these did allow us to exclude myxoma, endomyocardial fibrosis, and endocarditis.[11]

Hemoptysis and fever are the most common symptoms of pulmonary artery involvement in BD.[12] Hemoptysis can be caused by pulmonary aneurysms and/or pulmonary arteritis. In our case, no aneurysm was detected, and we thus consider that the hemoptysis was caused by pulmonary arteritis. Confirmation of the cause of hemoptysis in a BD patient is essential to guide the choice of appropriate treatment.[11] Hemoptysis caused us to discontinue anticoagulant therapy.

Regardless of the site of organ involvement in BD, the aim of treatment is to prevent irreversible damage that occurs principally at early stages of the disease. Thus, early diagnosis is important.[11] In our case, diagnosis was made approximately 9 months after symptom onset; this delayed initiation of immunosuppressive therapy. No consensus has yet emerged on the management of major vessel disease (with thrombi) and ICT in BD patients.[13] Various treatment modalities including surgery, immunosuppressive and anticoagulation medications, antiplatelet treatments, and thrombolytic therapy have been used.[10] However, no randomized controlled study has assessed the efficacy of the various therapeutic regimens, and current recommendations are based on only partial consensus or observational studies.

Intravenous thrombolytic therapy might be considered for BD patients with ICT and widespread thrombi but without pulmonary artery aneurysms.[8] It is important to emphasize that if a pulmonary embolism in suspected in a BD patient, neither anticoagulant nor thrombolytic treatment should commence before CTA scanning confirms that aneurysms are absent; such treatment would be associated with a high risk of hemorrhage if aneurysms were present. The form of pulmonary artery occlusion seen in BD patients differs from classic pulmonary embolisms because the BD occlusions represent principally *in situ* thrombi complicating underlying vasculitis, which may also result in infarction, hemorrhage, hemoptysis, and formation of pulmonary artery aneurysms.[8,14] As hemoptysis was evident, and as it was possible that *in situ* thrombosis was present in the pulmonary arteries, we eschewed use of thrombolytic therapy.

After surgical removal of ICT, thrombus recurs in some BD patients despite prescription of heparin therapy. This emphasizes the risk that BD can be worsened by surgery. Therefore, to avoid surgery, immunosuppressive agents should be given.[10,13,15,16] High-dose methylprednisolone and CYC should be the treatment of choice. Interferon alpha should be given if symptoms do not resolve quickly.[11,15,17]

We initially used pulse methylprednisolone and continued with monthly CYC (15 g in all), and 1 mg/kg/day prednisolone. Eleven months later, interferon alpha was added because of recurrence of fever and hemoptysis; this was given for 11 months. We then continued with azathioprine.

A notable feature of this case report is that complications did not completely disappear despite immunosuppressive therapy (Fig. 1A–D). Corticosteroids and immunosuppressive drugs may nonetheless be very beneficial, particularly if given at an early stage of development of complications, thus before irreversible damage develops.[10,13]

In conclusion, use of the non-invasive CTA technique is valuable in diagnosis and follow-up of BD patients with intracardiac and major vascular thrombi. We suggest that BD should be kept in mind upon differential diagnosis of patients with ICT and fever. Familiarity with the radiological and clinical characteristics of BD is essential to ensure accurate early diagnosis and prompt treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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