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CASE REPORT

Recurrent symptomatic ischemic stroke in a 46-year-old African male revealing Angio-Behçet with severe cardiovascular involvement

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KEYWORDS

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Abstract Behçet'sdisease (BD) is a chronic, multisystem vasculitis. It is categorized under variable vessel vasculitis in the new Chapel Hill nomenclature as it involves blood vessels of any type and size. It is characterized by relapsing aphthous ulcers commonly occurring in the oral mucosa and genitalia with ocular involvement. Other organ systems may be involved any time throughout the course of the disease. The exact cause is unknown. However, combination of genetic and environmental factors is likely to play a role.

Cardiac involvement may occur in the form of intracardiac thrombus, endocarditis, myocarditis, pericarditis, endomyocardial fibrosis, coronary arteritis, myocardial infarction, and valvular disease.

We present a case of Angio-Behçet in a 46-year-old African male with severe cardiovascular involvement including pulmonary artery hypertension (PAH), right ventricular failure and left ventricular diastolic dysfunction diagnosed after 2 episodes of symptomatic ischemic stroke resulting from complete occlusion of the right internal carotid artery (ICA) up to its intracranial portion.

Immunosuppressive and anticoagulant therapies have induced improvement in cardiac manifestations. Nevertheless, prompt recognition of the primarily vascular manifestation of BD without mucocutaneous manifestations was responsible for considerable delay that did not afford surgical therapy for the carotid occlusion.

1. Introduction

Behçet's disease (BD) is a chronic, multisystem vasculitis. It is categorized under variable vessel vasculitis in the new Chapel Hill nomenclature as it involves blood vessels of any type and size.[1] It is characterized by relapsing aphthous ulcers

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commonly occurring in the oral mucosa and genitalia with ocular involvement.[2–4] Other organ systems may be involved any time throughout the course of the disease.

The exact cause is unknown. However, combination of genetic and environmental factors is likely to play a role. Some researchers believe that an environmental factor or infection, such as a virus, bacterium, or pollution, may trigger an autoinflammatory reaction within people who have certain disease susceptibility genes.[5–7]

Behçet's disease has a worldwide distribution. However, it is observed commonly among populations living along the historic Silk Road (Japan, China, Turkey and Iran). That is also why it was given the name "Silk Road Disease".[8] It is most common in Turkey with estimated prevalence of 421 per 100,000 population.[9] It remains rare in other countries such as the Americas and African countries.[8]

To date, Behçet's Disease remains a clinical diagnosis based on its disease manifestations. There is no relevant biological test for diagnosis.

Vasculo-Behçet disease (vasculo-BD) is one of the most severe and life-threatening facets of BD which predominantly appears in large blood vessels.[10]

Cardiac involvement may occur in the form of intracardiac thrombus, endocarditis, myocarditis, pericarditis, endomyocardial fibrosis, coronary arteritis, myocardial infarction, and valvular disease.[4]

We herein report a case of Angio-Behçet with severe cardiovascular involvement discovered after 2 episodes of symptomatic ischemic stroke.

2. Case report

A 46-year-old previously healthy male was admitted in 2015 for evaluation of recurrent ischemic strokes happened in 2009 and 2010, fatigue and lack of energy since 2013.

Further detailed medical history revealed that the patient had a history of traffic Road accident in 2008 with multiple rib fractures and hemothorax. Recurrent oral aphthae started 1 year later after the accident and a history of fertility abnormalities.

Physical examination on admission determined Dyspnea on exertion (NYHA III), murmur of tricuspid regurgitation, accentuated pulmonic component of the second heart sound, also referred to as P2, and external signs of right heart failure (peripheral edema, elevated jugular venous pulsations and hepatomegaly).

It was noted also a small right pleural effusion and ataxia.

Oral aphthae, scrotal scar and erythema nodosum in the lower extremities were present.

Laboratory test showed an increased level of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

On ECG, there was a complete right bundle branch block.

The transthoracic echocardiography performed showed that the right-sided cardiac structures were larger than normal with severe tricuspid regurgitation and pulmonary artery pressure was 70 mmHg (Fig. 1). It was also noted, signs of left ventricular diastolic dysfunction with preserved systolic function.

Spiral CT scanner performed in emergency excluded acute or chronic pulmonary embolism, but showed multiple consolidated rib fractures (Fig. 2).

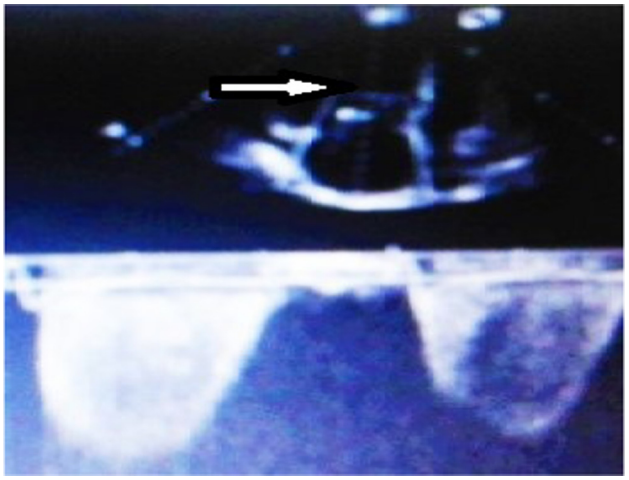

Figure 1 Echocardiography showing right chamber enlargement (arrow) and Doppler measurement of peak velocity of tricuspid regurgitation used for estimation of pulmonary artery systolic pressure.

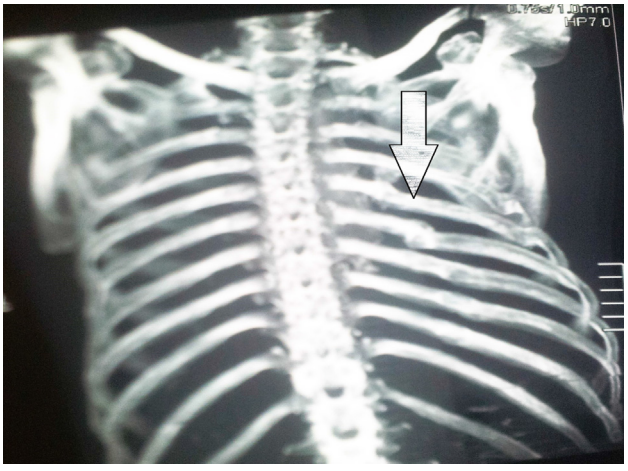

Figure 2 CT Scan: multiple rib fractures.

The cerebral Scanner was normal.

Cervical ultrasound showed a complete occlusion of the right internal carotid artery (ICA) from the middle part of the common carotid artery (CCA) up to the submandibular part of the ICA.

Neuro-vascular angiography showed the extend of the occlusion up to the intracranial portion of the ICA (Fig. 3a and b). The circle of Willis was not involved (Fig. 4).

The diagnosis of Angio-Behçet was retained according to the criteria for diagnosis of BD proposed by the International Group Study (ISG) for BD.[6]

As consequence, in addition to diuretics, statins and AVK, the patient received corticosteroids and colchicine.

Clinical course was good with substantial improvement of mucocutaneous and cardiac symptoms.

Improvement of dyspnea was noted but still present (NYHA 1-2) and echography findings remained unchanged except pulmonary artery pressure which was 60 mmhg in 2 months follow-up.

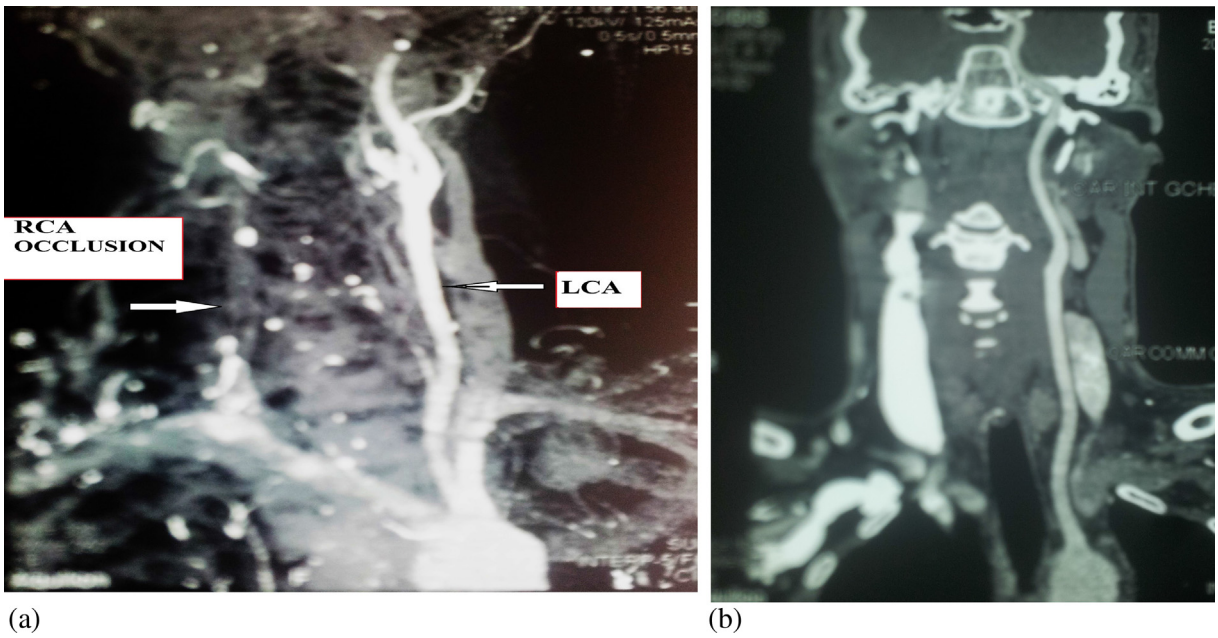

Figure 3 (a and b) Angiography: complete occlusion of the right ICA (LCA = left carotid artery, RCA = right carotid artery).

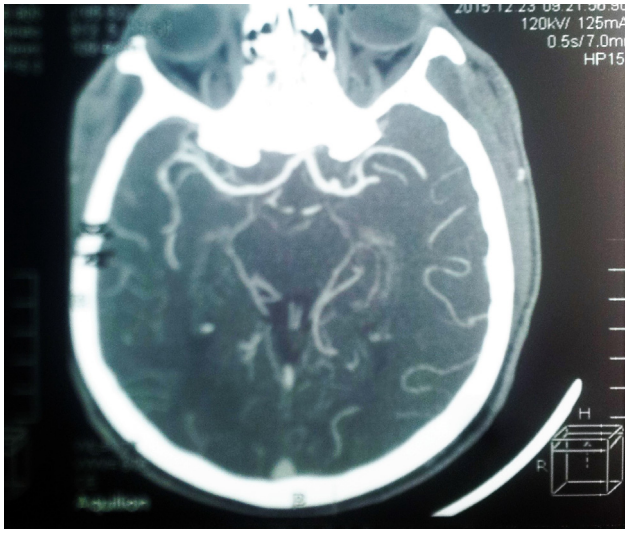

Figure 4 Angiography: intact circle of Willis.

The patient was discharged from hospital on the same treatment since there were no possibilities of surgery for his carotid occlusion because of its extension up to the intracranial portion.

3. Discussion

Behçet disease is a multifactory disorder. There have been many theories about its origin, including viral etiology, bacterial infections, autoimmuno mechanisms and genetic predispositions.

Although the medical understanding of this disease has been advanced, its cause is still unknown.[4,11] In our patient, it is suggested that his past medical history of road traffic accident with rib fractures and hemothorax and his long stay in intensive care unit, may constitute the triggering event.

Due to the lack of specific clinical and laboratory diagnosis tests, several sets of diagnostic criteria have ben proposed. Of these are the criteria of BD committee of Japan.[12]

Over the years, five major independent sets of criteria have been used for diagnosing BD, each characterized by its own clinical features and frequencies, as well as nature of criteria that should be met in order for the diagnosis to be positive.[6,13] All required a confirmation of the three major symptoms initially described by Behçet as a separate clinical entity (oral ulceration, genital ulceration, and eye lesions). The International Study Group (ISG) for BD proposed the main international standards for diagnosing BD.[6] These criteria, published in 1990 and last updated in 2013, provided simpler means for diagnosis of BD, excluded rare and subjective features, and showed more specificity with little or no loss of sensitivity to previously used tools.[4,14]

In 2004, Lawton et al. conducted a study in an attempt to define a set of clinical features that may be used as a standard index for measurement of BD activity.[15]

The incidence of vascular involvement in BD varies from 7% to 29%.[16] Cardiac involvement is present in 0.14% of patients.[16] Intraventricular thrombosis, regurgitant valvular heart diseases, coronary arteries aneurysms, and myocardial infarction are some of the reported manifestations of cardiac involvement in such disease.[17] Sporadic cases of myocarditis, pericarditis, aortic aneurysms, and conductive tissue disorders were also reported during BD.[18] In such a disease, arterial involvement is less frequent than venous lesions. However, it is markedly more dreadful, as it was correlated with an important morbimortality. There are two types of arterial manifestations: occlusive and more commonly aneurismal lesions.[19] Occlusive and stenotic lesions involve not only great vessels, but also vasa vasorum. Frequently involved arteries in decreasing order are pulmonary artery, femoral, popliteal, subclavian, and carotid arteries.

There are two mechanisms to explain thrombosis during Angio-Behçet: vasculitis and hypercoagulable state. BD's vasculitis involves usually all layers of a vessel and is characterized by the presence of lymphocytic infiltrate during the acute phase. At an advanced stage, an important fibrotic and scarring reaction develops.[20,21] Hypercoagulable state observed during BD is thought to be due to inhibition of fibrinolysis on the one hand and due to increased platelet aggregation on the other hand. The latter had been explained by endothelial dysfunction leading to increased production of von Willebrand factor and decreased levels of prostacyclin (PGI2).[21,22] Increased production of fibrinogen and factor VIII could also represent other etiological factors explaining hypercoagulable state.[23] In our case, both hypercoagulable state and vasculitis seemed to be involved in the ICA occlusion.

The annual risk of a major stroke varies from 1% to 3.2% in cases of luminal narrowing ranging from 50% to 99%.[24–26] This risk remains almost stable over a long period of time.[25] An increasing degree of luminal narrowing is associated with an increasing risk of stroke in asymptomatic ICA stenosis. For every 10% increase in luminal narrowing, the stroke risk increases by nearly 31%, or 0.6% per year.[26] After an ischemic event in the territory of the stenosed ICA, the annual major stroke risk increases to between 8% and 13%.[27,28] In symptomatic patients too, the degree of stenosis modulates the risk of stroke; for every 10% increase in ICA luminal narrowing, the stroke risk increases by approximately 10% (absolute risk increase of approximately 0.4%).[26] The annual risk of major ipsilateral stroke associated with ICA occlusion is approximately between 1.9% and 3.8% per year.[26]

Pulmonary hypertension in BD can be explained by 2 different mechanisms: complication of a connective tissue disease and following thrombo-embolism.

Pulmonary hypertension is a common complication of connective tissue disease (CTD) and confers a worse prognosis. Connective tissue disease associated pulmonary hypertension (CTD-PH) occurs most often with systemic sclerosis (SSc) but may also complicate mixed connective tissue disease (MCTD). Although the pathogenesis leading to CTD-PH may vary, the clinical presentation, treatment, and pathological lesions are often similar to those observed in idiopathic pulmonary arterial hypertension (IPAH), with intimal and medial thickening in small and medium-sized pulmonary arteries and plexiform lesions in some cases.[29] Fewer studies have examined the occurrence of pulmonary hypertension complicating MCTD, but one study with 26 patients found pulmonary hypertension in 7 patients (27%).[30] Others have found evidence of pulmonary hypertension in as many as 75% of patients with MCTD.[31] Pulmonary hypertension has also been reported as the most frequent disease-associated cause of death in patients with MCTD.[32]

Chronic thromboembolic pulmonary hypertension (CTEPH) represents a unique cause of secondary pulmonary hypertension by virtue of its potentially remedial nature.

It was originally thought that 0.1% to 1% of patients who suffered from pulmonary embolism would subsequently develop pulmonary hypertension.[33] However, more data suggest that 0.8% to as many as 3.1% of patients may develop CTEPH after an initial episode of pulmonary embolism,[34,35] with an even higher occurrence after recurrent thromboembolic events.[34]

Although the mechanisms by which patients develop CTEPH are not fully understood, incomplete resolution of pulmonary emboli rather than in situ thrombosis of the pulmonary arteries appears to be the major contributor.[36,37]

Approximately 50% of patients presenting with acute symptomatic pulmonary embolism have echocardiographic evidence of right ventricular dysfunction.[38] Afterward, echocardiographic and pulmonary perfusion scan abnormalities typically stabilize over four to six weeks.[39,40]

In our patient the 2 mechanisms could be involved.

The main cause of morbidity and mortality in PAH is not injury to the lung, but rather progressive right ventricular (RV) dysfunction.

In most cases of PAH, PA pressure escalates faster than the RV can adapt. Although many patients develop significant RV hypertrophy, increased myocardial cell size and strength give way to apoptosis, fibrosis, and decreased contractility. The net result is a transition from a hypertrophic RV with preserved systolic function to a dilated, hypokinetic ventricle. As the RV enlarges, wall tension rises and free wall thickness decreases. The expanding RV widens the tricuspid annulus and causes chordal traction and tethering of the tricuspid leaflets, worsening tricuspid regurgitation and further compromising RV function. RV end-diastolic pressure rises, forcing the interventricular septum toward the LV during diastole and compromising LV filling.

Another finding in our patient was fertility abnormalities. Decreased fertility potential is not unusual among patients of both genders with rheumatic diseases, particularly in women.[41,42]

The reproduction potential of these male patients is impaired by the disease directly in the testicular tissue or by immunosuppressive therapy. A recent study evaluated fertility outcome of a larger retrospective cohort of BD patient's compared to a control Group.[43] They observed that 23 out of 130 subjects had infertility and the most common etiology was varicocele. In contrast, none of the 14 men with BD assessed for AntiSperm Antibodies (ASA) had antisperm antibodies.[44]

The evaluation of male subjects should rely on careful medical history, complete physical examination, semen analysis and sexual hormone profile.

The prognosis of mucocutaneous involvement in BD is generally good.[45] Vascular involvement represents the most important cause of mortality.[46] Neurological involvement is progressive among most patients, and is sometimes fatal. Annual mortality in BD varies between 2% and 4%. The most common causes of mortality are rupture of vascular aneurysms.[7]

Overall survival in BD patients with cardiac involvement is poorer than in those without. Complete remission of cardiac involvement has been associated with the use of immunosuppressants, colchicine, and anticoagulants.[46]

4. Conclusion

BD is a disease with multi-organ involvement and thus shows signs and symptoms in many systems. Angio-Behçet is one of the most severe and life-threatening facets of BD which predominantly appears in large blood vessels. Several cardiac manifestations may coincide in one patient. Cardiologists

should always bear in mind the potential threats of symptomatic cardiovascular involvement in BD and consider diagnostic measures for its timely detection. The prognosis of cardiac lesions is poorer than that of lesions in other organs involved in BD, but anticoagulation, immunosuppressant agents, and colchicine seem to improve the prognosis of cardiac manifestations in BD.

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