Behçet's Disease: Pulmonary Aneurysm Resolution with Oral Therapy and HLA B72 Allele Association

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We report the case of a woman who was diagnosed with a pulmonary artery aneurysm that was caused by Behçet's disease. The patient was initially diagnosed with community-acquired pneumonia and then pulmonary thromboembolism and aneurysm of the right pulmonary artery segmental branch was confirmed. The initial treatment consisted of anticoagulant drugs. After analysis of the family history and a positive pathergy test, the patient was diagnosed with Behçet's disease. Oral pharmacological treatment began with corticosteroids, cyclophosphamide, and anticoagulant suspension. The HLA B72 allele was identified in the patient and her two sisters, demonstrating the familial characteristic of the disease and the presence of this allele in a female patient with Behçet's disease. After 12 months of treatment, the clinical condition completely resolved.

Keywords: Behçet's disease; Pulmonary artery aneurysm; HLA B72

Behçet's disease (BD) is a multisystem inflammatory disease, characterized by a classic triad that consists of genital ulcers, oral ulcers, and uveitis, presenting recurrent episodes.¹ Other manifestations, include joints, gastrointestinal, and neurological involvement.^{2,3}

Behçet's disease is classified as vasculitis, with the involvement of both small and large arteries and veins in some organs.^{1,2} Vascular involvement in BD is found in approximately 25% to 30% of the affected population.⁴ Venous involvement is more common and may result in subcutaneous thrombophlebitis and deep venous thrombosis. Arterial involvement is less frequent, with aneurysms and occlusions of the abdominal aorta and carotid, femoral, popliteal, and coronary arteries.⁴⁻⁶ This disease is the second highest cause of pulmonary artery aneurysm, with a high mortality rate.^{4,7-9}

Many authors have recommended the use of immunosuppressants for the treatment of clinical

manifestations of BD, including vascular complications.¹⁰⁻¹⁴ However, to date, no standardized therapeutic regimen has been developed for the treatment of complications, which can be determined depending on the organ(s) affected and the extent and severity of the involvement.^{10,15}

Behçet's disease has a large geographic distribution and is endemic in the eastern Mediterranean region and Central and East Asian countries. It is less common in Australasia, the American continents, and sub-Saharan Africa.¹⁶ Brazil is a South American country where BD is relatively rare, but cases with clinical patterns that are similar to those found in endemic areas have been reported.¹⁷

Despite advances in human histocompatibility antigens (HLAs) and the identification of possible environmental factors that trigger the pathophysiological process of BD, the etiology of this disease is still not fully understood. Some studies have shown the involvement of genetic factors in its pathogenesis.^{1-4,18-21} The presence of the B51 allele as a

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genetic factor that predisposes individuals to BD has been reported by several authors.¹⁸⁻²¹ Other studies have reported a positive correlation between the A2, A26, A30, A68, B15, B27, B57, B58, and B72 alleles and BD.^{1,2,4,18-21} The B51 allele was associated with mucous and skin manifestations, early-onset uveitis, and low gastrointestinal involvement. The B58 allele was associated with cutaneous manifestations. The B72 allele was associated with vasculitis manifestations.^{20,22} The A2, A26, and A30 alleles were associated with (1) skin lesions and arthritis, (2) uveitis and vascular lesions, and (3) genital ulcers and a positive pathergy test, respectively.²³ Some studies have shown that the B51 allele predisposes to BD in both males and females. The A2 and B72 alleles are specific to men, and the A68 and B58 alleles are specific to women.^{18,20}

We describe a case of a female patient with pulmonary thromboembolism and pulmonary artery aneurysm associated with pneumonia and sepsis. An exhaustive clinical examination concluded that this was a complicated case of BD. Treatment consisted of corticosteroids and cyclophosphamide, and the clinical condition fully resolved. We identified the familial distribution of BD, indicating a genetic predisposition associated with the HLA B72 allele.

Case Presentation

We report the case of an unmarried, black woman, aged 45 years from a city in the state of Paraná, Brazil (a country with a multi-ethnic population). The patient was admitted on the third day of pharmacological treatment for community-acquired pneumonia in the lungs that was treated with antibiotics.

The patient was prostrated, had a low weight, and was hemodynamically stable (blood pressure: 110/84 mmHg; heart rate: 102 beats per minute; good peripheral perfusion; without vasopressor drug; spontaneous ventilation; grunting; oxygen saturation: 92%; Glasgow Coma Scale: 9) despite being in a condition of generally poor health.

Chest X-ray showed a nodular image in the perihilar right pulmonary artery. Laboratory tests indicated microcytic and hypochromic anemia (hemoglobin: 7.2 g/dL; hematocrit: 21.4%; mean corpuscular volume: 79.1 fL), without leukocytosis or a leftward shift. C-reactive protein was 189 mg/L. The patient was negative for anti-cardiolipin, non-reactive to anti-neutrophil cytoplasmic antibody, and non-reactive to anti-ribonucleoprotein.

On the next day, the patient presented a worsening of her clinical condition, which progressed to sepsis with a pulmonary source presenting fever, weakness, altered mental status (depressed level of consciousness), and altered pulmonary function (decreased O₂ saturation, respiratory frequency: 38 breaths per minute, effort breathing with furcula retraction). She was transferred to the Intensive Care

Unit (ICU) and endotracheally intubated with measures for volemic resuscitation initiated.

Computed tomography (CT) of the chest indicated pulmonary thromboembolism, left pleural effusion, and aneurysmatic dilatation of the right pulmonary artery segmental branch (Figure 1, panels A and B). Transthoracic echocardiography showed no intracavitary thrombi, a left ventricle with normal dimensions, preserved systolic and diastolic function, a tricuspid valve that exhibited discrete insufficiency, and signs of discrete pulmonary hypertension (RVSP: 40 mmHg). At this stage, measures were initiated for shock and enoxaparin for the treatment of pulmonary thromboembolism.

In a review of the patient's clinical history, there was a report of painful ulcerous lesions, frequent in the oral and genital areas, not only in the patient but also in her two sisters, referring to frequent skin lesions that are compatible with folliculitis. In the past, one of the patient's sisters required surgical intervention for the treatment of a cerebral artery aneurysm, and the other sister had already presented ocular symptoms, diagnosed as uveitis. Upon physical examination, the patient had oral ulcers. On the third day of hospitalization, a pathergy test was performed, which was positive in less than 24 hours.

When the criteria for a BD diagnosis were met, enoxaparin treatment was suspended, and corticosteroid treatment began (2 mg/kg methylprednisolone, intravenous route). The patient progressed favorably and was extubated after 24 hours. On the second day after the diagnosis of BD, the patient remained hemodynamically stable and comfortable with noninvasive ventilation and without vasopressor drugs. Glucocorticoid therapy was initiated and 86 hours later the patient was discharged from the ICU to complete the cycle of antibiotic therapy in the ward for 10 days.

Upon ambulatory follow-up, corticosteroid therapy (1 mg/kg prednisone, oral route, for 60 days, with progressive weaning) was combined with cyclophosphamide (2.5 mg/kg, oral route). The patient received was followed-up monthly with clinical and laboratory tests and followed-up quarterly with CT, showing total resolution of the lesion after 12 months of treatment (Figure 1, panel C).

During the 12-month follow-up period, the typing of HLA was performed for both the patient and her two sisters. The results indicated the presence of the HLA Class I B72 allele, suggesting a familial characteristic of this disease. The patient also presented the A1 and A23 alleles.

Discussion

Behçet's disease is characterized by systemic and necrotizing but not granulomatous vasculitis with an unknown etiology.^{1,2,9} In 1990, the International Behçet Disease Study Group published the most widely known and disseminated criteria for the disease (recurrent oral ulcerations accompanied by at

Figure 1. Chest tomography. (A) Coronal section of multidetector tomography (multislice) of the thorax with intravenous contrast, indicating a right pulmonary artery aneurysm and left pulmonary thromboembolism. White arrow: pulmonary artery aneurysm. (B) Axial section of multidetector tomography (multislice) of the thorax with intravenous contrast, showing a right pulmonary artery aneurysm and left pulmonary thromboembolism. White arrow: left pulmonary thromboembolism. (C) Axial section of multidetector tomography (multislice) of the thorax with intravenous contrast, not showing aneurysm of the right pulmonary artery.

least two of the following signs: recurrent genital ulceration, ocular lesions with uveitis or retinal vasculitis, papulopustular skin lesions or skin with erythematous nodules, and a positive pathergy test).²⁴ These criteria were reassessed and validated by the International Committee on Behçet Disease in 2006. These new criteria increased diagnostic accuracy and sensitivity by adding vascular manifestations of the disease, such as phlebitis, venous or arterial thrombosis, and aneurysms.³

Pulmonary aneurysms in BD are most commonly expressed as wedge-shaped alveolar and subpleural infiltrates or poorly defined rounded areas that are surrounded by an increase in opacity, representing focal vasculitis and thrombosis of pulmonary vessels and resulting in infarction, hemorrhage, and focal atelectasis.^{8,13} These manifestations can be detected on radiographs and confirmed by CT or magnetic resonance imaging.⁹

Behçet's disease has a good response to immunosuppressive drugs, but the existing evidence is based only on case reports, anecdotal case series, and a few randomized clinical trials. Thus, the pillar of treatment is still the empirical use of steroidal antiinflammatory and/or immunosuppressive drugs, adjusted for the severity of the case.^{10,11-14} Therapeutic strategies have not yet been well established, particularly for pulmonary artery aneurysm. The European League Against Rheumatism recommends the use of cyclophosphamide and corticosteroids.¹⁰ A therapeutic regimen that consisted of intravenous pulses of corticosteroid and cyclophosphamide, followed by oral corticosteroids and azathioprine, was recently reported to successfully improve a pulmonary artery aneurysm in a patient with BD.¹¹ It is important to emphasize that pharmacological therapy should be early instituted, even before the BD definitive diagnosis is established, once

aneurysm rupture is one of the causes of death.²⁴ In addition, the control of inflammation and prevention of end-organ damage can reduce the risks of other complications.^{1,3,24} The therapeutic regimen that was used for the case of the female patient reported herein consisted of oral corticosteroids and cyclophosphamide to improve her clinical condition. Pulse therapy was contraindicated because she had a septic condition.^{25,26} The use of anticoagulants was also reduced after the diagnosis of BD because therapy with this medication remains controversial as there are no data from randomized controlled trials.^{2,10} Although venous thrombosis has been reported to be common in BD, it is uncommon to form emboli because of thrombus adhesions to the vessel wall.¹¹ Another reason to discontinue the use of anticoagulants is the frequent presence of coexisting arterial aneurysms that can result in fatal hemorrhage.^{11,14}

The patient presented complete resolution of the aneurysm, even without the use of corticosteroid pulse therapy, a decision that was made because of the lack of guidelines for the treatment of critical patients with exacerbated BD concomitant with pulmonary sepsis. The successful outcome that was observed in this case is similar to the findings of other reports and corroborates studies that reported the complete resolution of aneurysms in more than 75% of patients who received immunosuppressive treatment.^{8,11,27}

A relevant finding in this case study was the presence of the HLA B72 allele in both the patient and her two sisters, demonstrating the familial characteristic of BD and the presence of this allele in female patients with BD and emphasizing the importance of detecting this allele, which is usually found only in men.²⁰ The patient also presented the A1 and A23 alleles, which seemingly have a low association with the disease.²⁰ Although the presence of HLA B51 may help the

differential diagnosis of BD,^{1,5,20} in the present case the patient was HLA B51 negative. To our knowledge, this is the first report of the presence of the B72 allele in a female patient with BD, which may be a predisposing factor for BD with vascular, neurological, mucocutaneous, and ocular involvement.

Conclusion

The patient presented complete resolution of the pulmonary artery aneurysm after oral treatment with corticosteroids and cyclophosphamide, without the use of pulse therapy. The HLA typing of the patient and her two sisters indicated the presence of the HLA Class I B72 allele, suggesting a familial characteristic of BD and demonstrating the presence of this allele in a female patient.

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