Case Report

Surgical lung biopsy to diagnose Behcet's vasculitis with adult respiratory distress syndrome

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ABSTRACT

A 34-year-old female presented with fever and abdominal pain. Past medical history includes Crohn's and Behcet's disease. Examination revealed multiple skin ulcerations, oral aphthae, and bilateral coarse rales. She developed respiratory distress with diffuse bilateral alveolar infiltrates on chest radiograph requiring intubation. PaO_2/FiO_2 ratio was 132. The chest computed tomography revealed extensive nodular and patchy ground-glass opacities. Bronchoalveolar lavage demonstrated a predominance of neutrophils. Methylprednisolone 60 mg every 6 h and broad-spectrum antimicrobials were initiated. No infectious etiologies were identified. Surgical lung biopsy demonstrated diffuse alveolar damage (DAD) mixed with lymphocytic and necrotizing vasculitis with multiple small infarcts and thrombi consistent with Behcet's vasculitis. As she improved, steroids were tapered and discharged home on oral cyclophosphamide. Pulmonary involvement in Behcet's is unusual and commonly manifests as pulmonary artery aneurysms, thrombosis, infarction, and hemorrhage. Lung biopsy findings demonstrating DAD are consistent with the clinical diagnosis of adult respiratory distress syndrome. The additional findings of necrotizing vasculitis and infarcts may have led to DAD.

KEY WORDS: Adult respiratory distress syndrome, Behcet's disease, Behcet's vasculitis, diffuse alveolar damage, lung injury, vasculitis

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INTRODUCTION

Behcet's disease is an idiopathic vasculitis characterized by recurrent mucocutaneous ulcerations and uveitis. The diagnosis is made on the basis of clinical findings.[1-3] It is very prevalent in Turkey, but also seen worldwide.[4] Although Behcet's disease can affect any organ system, pulmonary involvement is uncommon and typically manifests as pulmonary vascular lesions. Pulmonary artery aneurysms involving the large proximal branches of the pulmonary arteries are the most common finding on chest computed tomography[5-8] and hemoptysis is a common presenting symptom. Pulmonary small vessel vasculitis and lung parenchymal involvement is rarely reported, although the true incidence is uncertain given that histopathologic correlation is seldom pursued.[9] This is an unusual case of Behcet's disease complicated by hypoxemic respiratory failure and acute respiratory distress syndrome. To our knowledge, this is the first case of adult respiratory distress syndrome associated with Behcet's disease with diffuse alveolar damage (DAD) and vasculitis on lung biopsy.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.142127

CASE REPORT

A 34 year-old, non-Turkish, Caucasian female with a history of Behcet's disease refractory to multiple immunosuppressive regimens presents with severe diffuse abdominal pain. She also reported a recent exacerbation of her Behcet's disease with skin ulcerations and orogenital aphthae. Past medical history included chronic sinusitis, migraine headaches, and Crohn's disease. She smokes one pack of cigarettes a day. Since the diagnosis of Behcet's, she had failed single-agent therapies, and therefore had required treatment with various combinations of immunosuppressants. Her current regimen included concomitant use of mycophenolate mofetil, methotrexate, azathioprine, infliximab, and prednisone at a dose of

50 mg daily. She self-discontinued methotrexate 2 weeks prior to her presentation due to gastrointestinal upset and the prednisone dose was increased to 80 mg given her current symptoms. The prednisone dose was then reduced to 50 mg several days later to avoid side effects from high-dose steroids. On day 2 of admission, she experienced rapidly progressive shortness of breath and hypoxemia requiring intubation and mechanical ventilation. She was febrile with a temperature of 102.7°F. Physical examination revealed a cushingoid-appearing female with a left mandibular healing ulcer, multiple punched out mucocutaneous ulcerations, and bilateral diffuse wheeze on auscultation. Her PaO_2/FiO_2 ratio was 132. An echocardiogram was normal. Chest radiography showed extensive bilateral alveolar infiltrates [Figure 1a]. Computed tomography of the chest revealed numerous small nodules and patchy areas of ground glass opacity [Figure 1b]. Bronchoscopy reveals numerous upper airway aphthous ulcers. Bronchoalveolar lavage showed a predominance of neutrophils. Intravenous methylprednisolone 60 mg every 6 h and empiric broad-spectrum antimicrobials were initiated. Bacterial, fungal, and viral cultures, including studies for Aspergillus and *Pneumocystis jirovecii* were unremarkable. Serology and immunology including polymerase chain reaction (PCR) for cytomegalovirus, flu antigens A and B, rapid human immunodeficiency virus (HIV) antibody, *Mycoplasma pneumoniae* antibody immunoglobulin (Ig) G and IgM, Legionella, and Cryptococcal antigens were negative. CD4 count was 96. Vasculitis panel, which includes serum myeloperoxidase antibodies (cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA)), serum proteinase 3 antibody (perinuclear-ANCA (p-ANCA)), rheumatoid factor, serum antinuclear antibodies (ANA) titers, creatinine kinase, and aldolase levels were all unremarkable. Urine analysis was normal and renal function remained stable. Antibiotics were subsequently discontinued several days later. On day 5, a surgical lung biopsy was performed that revealed areas of necrosis and DAD mixed with lymphocytic and necrotizing vasculitis with multiple small infarcts and thrombi [Figures 1c and d]. She recovered over the next 10 days and was successfully extubated. Steroids were slowly tapered and she was discharged home on combination therapy with cyclophosphamide and prednisone.

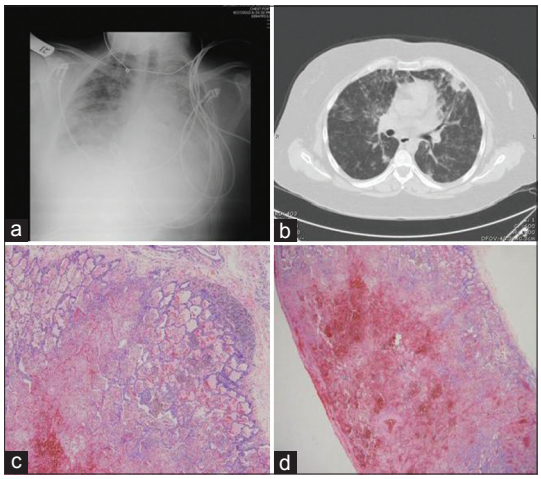

Figure 1: (a) Extensive bilateral infiltrates. (b) Numerous patchy areas of ground glass opacities. (c) Diffuse alveolar damage characterized by intra-alveolar fibrin and hyaline membranes (hematoxylin and eosin stain (H and E)). (d) Multiple thrombi and infracts (H and E)

DISCUSSION

This is a case of Behcet's disease complicated by an acute fulminant pulmonary syndrome. The findings of necrotizing vasculitis with multiple infarcts and thrombi are consistent with previously described pulmonary manifestations of Behcet's disease.[10] The literature pertaining to pulmonary involvement in Behcet's disease is mostly limited to case reports and case series describing large vessel vasculitis such as pulmonary artery aneurysms and their sequelae. Data on lung parenchymal involvement in Behcet's disease is scarce. The various pathologic findings reported include pulmonary infarction, hemorrhage, interstitial lung disease, and small vessel vasculitis. DAD in association with Behcet's disease has rarely been described.[11] As surgical lung biopsy in Behcet's disease is seldom pursued, true incidence of pulmonary Behcet's disease is likely underdiagnosed. To our knowledge, this is the first case of Behcet's disease with pulmonary involvement manifesting as DAD mixed with necrotizing vasculitis on lung biopsy.

DAD is a well-described lung injury pattern which can occur in many settings including infection, collagen vascular disease, drug toxicity, inhalational injury, and uremia. It may be idiopathic. In the absence of any identifiable cause, the clinical diagnosis of acute interstitial pneumonia is appropriate. In this case, the coexistent vasculitis with multiple small infarcts consistent with lung involvement by Behcet's disease may have triggered the onset of DAD, and it provides an explanation for the clinical presentation. It is possible the abrupt tapering of steroids prior to her presentation led to an exacerbation of Behcet's disease.

Diffuse alveolar hemorrhage (DAH), another diagnosis to consider in the setting of vasculitis, is a syndrome characterized by injury or inflammation of the pulmonary arterioles, venules, or alveolar septal capillaries, and is associated with three different histologic patterns, including pulmonary capillaritis, bland alveolar hemorrhage, and DAD. DAH can result from a variety of conditions, such as coagulation disorders, drugs, toxins, collagen vascular diseases, and mitral stenosis. DAH is also commonly associated with ANCA positive vasculitis presenting as a pulmonary renal syndrome. Alveolar hemorrhage in Behcet's vasculitis is rare but may occur in the setting of DAD.[12,13]

Drug-induced lung injury is another possible explanation for her presentation. Immunosuppressive therapy is the

mainstay of treatment for Behcet's disease, although evidence supporting specific agents is limited. Several immunomodulators and biologic agents, some of which our patient was using, have been reported to cause lung injury. Methotrexate, azathioprine, mycophenolate mofetil, as well as the tumor necrosis factor alpha inhibitor infliximab, have all been associated with varying degrees of pulmonary toxicity, including DAD.[14] A cohort study of 514 patients with acute lung injury reported an incidence of drug-associated lung injury of 9.5%.[15]

Pulmonary involvement in Behcet's disease, although uncommon, is a real entity and can be life-threatening. Physicians who treat patients with Behcet's disease, especially those with unexplained respiratory complaints, must keep this in their differential. Patients with Behcet's disease, especially those on immunosuppressant therapy should be frequently evaluated for any such evolving respiratory complications as well as drug-related pulmonary toxicity. For those on chronic steroid therapy, abrupt withdrawal or rapid tapering of steroids should be avoided to prevent an exacerbation of underlying vasculitis. High-dose corticosteroids appeared to have benefited our patient who had a complete recovery. Future lung biopsy-confirmed cases of DAD in association with Behcet's disease may help elucidate pathophysiologic mechanisms and optimize treatment.

In conclusion, this is a case of pulmonary Behcet's disease presenting as adult respiratory distress syndrome with DAD and vasculitis on lung biopsy. Physicians must maintain a high index of suspicion and early lung biopsy may help in the diagnosis and management of patients with Behcet's disease who present with unexplained respiratory failure.

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How to cite this article: Vydyula R, Allred C, Huartado M, Mina B. Surgical lung biopsy to diagnose Behcet's vasculitis with adult respiratory distress syndrome. Lung India 2014;31:387-9.

Source of Support: Nil, **Conflict of Interest:** None declared.