Case Report

To immunosuppress or not: Behcet's syndrome presenting as an eosinophilic pleural effusion

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ABSTRACT

Etiologic diagnosis of an eosinophilic pleural effusion (EPE) presents a diagnostic challenge when intrapleural air and blood have been ruled out as its proximate causes. Among the causes of EPE, those that require immunosuppression for the underlying disease include connective tissue diseases, sarcoidosis, vasculitis, and eosinophilic pneumonia. We present a case of clinically suspected Behcet's syndrome based on a 10-year history of recurrent multiple oral ulcers and human leukocyte antigen-B51 positivity who presented with only an EPE. Computed tomography pulmonary angiogram ruled out central thoracic vein thrombosis but was inconclusive in ruling out a subsegmental pulmonary embolism. The patient declined immunosuppressants and while on follow-up developed bilateral extensive acute lower limb deep venous thrombosis and pulmonary embolism. Upper infrarenal inferior vena cava demonstrated chronic thrombosis suggestive of its antecedent role in pulmonary embolism-related EPE during the first instance. Behcet's syndrome-related EPE can be associated with venous thromboembolism, and immunosuppressive therapy prevents the subsequent thrombotic episodes.

KEY WORDS: Behcet's syndrome, eosinophilic pleural effusion, inferior vena caval thrombosis, pulmonary embolism

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INTRODUCTION

Etiologic diagnosis of an eosinophilic pleural effusion (EPE), defined as one whose differential count of nucleated cells demonstrates ≥10% of eosinophils, presents a diagnostic challenge when intrapleural air and blood have ruled out as its proximate causes.[1] Among the causes of EPE, those that require immunosuppression for the underlying disease include connective tissue diseases (CTDs), vasculitis, acute and chronic eosinophilic pneumonia, and sarcoidosis.[1] However, quandary prevails when the proximate cause of such an effusion is not definitely known and the patient, in high likelihood, needs immunosuppression. We present such a case.

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CASE REPORT

A 30-year-old nonsmoking male from South India presented to our institute with symptoms of dry cough, right-sided pleuritic chest pain, and dyspnea for 10 days in the background of a 10-year history of recurrent painful oral ulcers without associated history of recurrent genital ulcers, joint pains, red eyes, altered vision, altered bowel habits, fever, weight loss, or skin rash. Physical examination was unremarkable except for multiple oral aphthous ulcers on the tongue and buccal mucosa and reduced breath sounds with dull note on percussion in the right infra-axillary and infrascapular areas. Vital signs

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were normal. Chest X-ray revealed a small right-sided pleural effusion (PE).

Laboratory tests revealed peripheral blood eosinophilia (PBE) – 16% eosinophils (absolute eosinophil count 1440/cmm). Pleural fluid analysis revealed an exudate-pleural fluid protein 5.2 g%, pleural fluid lactate dehydrogenase (LDH) 1103 units/L), and glucose 106 mg%. Pleural fluid cell count revealed 39% eosinophils, 52% lymphocytes, and 55,000/cmm red blood cells. Medical thoracoscopy revealed inflamed visceral pleura with a few discrete yellowish pustules. Costal pleura was mildly thickened with two discrete whitish nodules. Biopsy of these nodules revealed organizing chronic pleuritis with fibrinous exudate and mesothelial proliferation.

Computed tomography pulmonary angiogram (CTPA) was negative for obvious filling defects up to the lobar and segmental levels. However, the opacification of segmental and subsegmental pulmonary artery branches bilaterally was not optimal and embolism in these vessels could not be excluded. Mild diffuse pleural thickening and enhancement measuring up to 5 mm was also noted [Figure 1a].

Among CTD markers, only antinuclear antibody was weak positive with nucleolar pattern. Specific markers anti-SSA, anti-SSB, dsDNA, anti-CCP, anti-RNP, and anti Jo-1, anti-Scl-70, antineutrophil cytoplasmic antibodies (ANCAs) were negative. Human immunodeficiency virus (HIV)-1 antibody was negative. Serum immunoglobulin (Ig) levels – IgG, IgA, and IgM – were normal. Specifically, IgE was <1.5 units/ml. Stool and pleural fluid were negative for parasites and upper gastrointestinal endoscopy was normal.

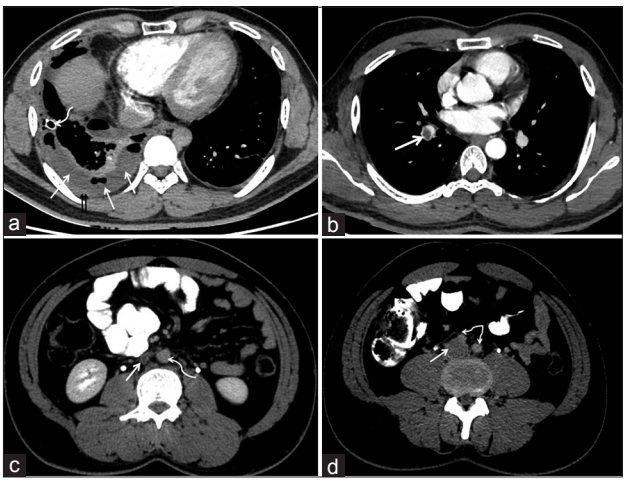

Figure 1: (a) Representative axial image from computed tomography pulmonary angiogram in mediastinal window showing loculated right pleural effusion with air pockets (arrows), mild pleural thickening and enhancement (double black arrows), intercostal drain tube (curved arrow). Although no definite pulmonary embolism could be detected, subsegmental pulmonary artery branches were not optimally assessed. (b) Representative axial image from computed tomography pulmonary angiogram in mediastinal window showing filling defects in the right lower lobe pulmonary artery (arrow) in keeping with acute pulmonary embolism. (c) Venous phase axial image at the level of the lower poles of the kidneys from contrast enhanced computed tomography abdomen showing narrowed caliber and nonenhancement of infrarenal inferior vena cava (straight arrow) suggesting a chronic thrombosis. Curved arrow – aorta. (d) Venous phase axial image at the level of the aortic bifurcation (bifid curved arrow) from contrast enhanced computed tomography abdomen showing dilated inferior vena cava with filling defect (straight arrow) suggesting an acute thrombus

With a history of recurrent and multiple oral aphthosis over the past 10 years, Behcet's syndrome was considered most likely[2] and human leukocyte antigen (HLA) typing was positive for B51 locus. He was provisionally diagnosed to have Behcet's syndrome with probable venous thromboembolism (VTE)-associated EPE. Immunosuppression was discussed with the patient, but due to unusual presentation of the disease and unclear evidence of thrombosis, he was not willing for immunosuppression or anticoagulation.

Two months later, he presented with sudden onset bilateral lower limb swelling associated with pain and tenderness, lower abdominal tightness, and sudden-onset breathlessness. He was tachycardic (105/min), but normotensive and normoxemic. Respiratory and abdominal examination was unremarkable. Ultrasound Doppler of the lower limbs revealed acute thrombus involving lower inferior vena cava (IVC), bilateral common iliac, external iliac, and common femoral veins. Electrocardiogram revealed sinus tachycardia. CTPA revealed hypodense filling defects in the descending branch of the right pulmonary artery and right lower lobar branches [Figure 1b]. Main pulmonary artery diameter was normal (24 mm). Previously seen PE had been resolved.

A CT scan of the abdomen revealed chronic thrombosis of the upper part of the infrarenal IVC [Figure 1c]. The lower part of infrarenal IVC and common iliac veins showed acute venous thrombosis [Figure 1d]. The previous diagnosis of Behcet's syndrome with VTE was now confirmed.

He was treated with pulse methylprednisolone for 3 days, followed by immunosuppression with deflazacort and azathioprine. Anticoagulation was started with enoxaparin, followed by oral warfarin. At the time of writing this report, the patient was doing well after 8 months of treatment with no recurrence of VTE or PE.

DISCUSSION

Our patient was worked up, during the first visit, from multiple angles to seek the etiology of the EPE.

The association of oral ulcers with pleural effusion

With a history of recurrent oral ulcers associated with a new-onset PE, the differentials considered were systemic lupus erythematosus, Behcet's syndrome, or celiac disease leading to VTE, an immunocompromised state or drug-induced PE.

Normal bowel habits, serum albumin of 4.2 g%, negative anti-tissue-transglutaminase antibody, and normal upper gastrointestinal scopy made inflammatory bowel disease or celiac disease unlikely. Negative HIV antibodies and normal serum immunoglobulins made an immunodeficient state unlikely. A negative CTD panel of markers and absence of specific symptoms or signs of a CTD made this diagnosis unlikely.

A history of recurrent and multiple aphthosis with positive HLA-B51 locus made Behcet's syndrome likely. The association of Behcet's syndrome and PE is rare. There are reports of chylothoraces secondary to thrombosis of central thoracic veins[3,4] and only two cases have been reported (in a series of 15 patients) of VTE[5]-related PE. Our patient had nonmilky, straw-colored, high LDH EPE. Pleural fluid triglyceride levels were not done. CTPA ruled out central thoracic vein thrombosis.

Peripheral blood eosinophilia with pleural fluid eosinophilia

Common causes

The association of peripheral blood eosinophilia (PBE) with pleural fluid eosinophilia (PFE) is common.[1] Common conditions include eosinophilic granulomatosis with polyangiitis, Hodgkin's lymphoma, fungal and parasitic infections, Hypereosinophilic syndrome (HES), drug-induced PE, and Loeffler's syndrome.[1] The absence of a wheeze, other vasculitic symptoms, negative antineutrophilic cytoplasmic antibodies, absent hepatosplenomegaly or mediastinal adenopathy, and PBE <1500/cmm made vasculitis, hematological malignancies, and HES unlikely. The absence of travel history to paragonimiasis endemic regions along with negative pleural fluid, pleural biopsy, and stool parasites made a parasitic etiology of EPE unlikely. Loffler's syndrome or tropical pulmonary eosinophilia was considered unlikely due to the absence of parenchymal infiltrates (in CTPA) and normal serum IgE.

He was not on any drugs that are associated with EPE.[1] He had been treated in the past for his recurrent oral ulcers with infrequent courses of multi-vitamins and local benzocaine gel application. The absence of an immunosuppressive condition made fungal etiology unlikely. He was unwilling for bone marrow examination.

Uncommon causes

Uncommon causes of PBE with EPE include effusions associated with longstanding parapneumonic PE (PPE), tuberculosis, malignancy, and pulmonary embolism.[1]

Longstanding (>1 month) PPE has been known to have PFE.[1] Visceral pleural inflammation on medical thoracoscopy, diffuse pleural thickening on the CTPA, and chronic pleuritis with fibrinous exudates in histopathology made PPE a possibility. However, normal peripheral blood white blood cells, 9% pleural fluid polymorphs, and a 10-day symptom duration were inconsistent.

Pleural biopsy was negative for tuberculosis and malignancy. Malignancies account for one-third of causes of EPE, but PFE ≥32% reduces the likelihood of malignancy.[6]

In a series of cases presented by Bower,[7] four out of five patients with VTE-related EPE has PBE. Although CTPA was negative for obvious filling defects up to the lobar and segmental level, opacification of subsegmental pulmonary artery branches bilaterally was suboptimal. Among patients with VTE, PEs can be detected in 36%–47% of patients by CTPA[1,8] and such effusions can exist even if the CTPA cannot identify embolism in subsegmental vessels.[8] In a series of 423 patients, Liu *et al*.[9] found that VTE-related PEs are not related to location of the embolism (central or peripheral pulmonary arteries), obstruction index of embolism, or the side of the embolism. In a meta-analysis of 392 patients, PFE was found to be present in 4% of cases of PE related to VTE.[1] In another series of 60 patients, Romero Candeira *et al*. found PFE in 18% of patients.[10] Overall, literature estimates the incidence of EPEs in patients with VTE to be between 0% and 33%.[10] As our patient had no clinical signs or symptoms of deep venous thrombosis (DVT), ultrasound Doppler of the lower limbs were not ordered for. However, in retrospect, this was an error. As the IVC and lower limb veins were not imaged during the evaluation of the EPE, it is possible that an acute or subacute asymptomatic thrombosis of upper infrarenal IVC at this time (which was seen later as chronic thrombosis in the CT abdomen) could have been missed. Although CTPA has a high sensitivity and a high specificity of detecting pulmonary embolism, its negative predictive value in excluding embolism is 60% in high-risk patients. Hence, in patients with high risk of VTE, such as ours, a negative CTPA or inconclusive CTPA should be followed by CT venography of femoral and popliteal veins or serial Doppler ultrasonography of the lower limb deep veins.[11]

Diseased pleura in eosinophilic pleural effusions

Diseased pleura is a consistent feature of EPE.[1] Nonspecific pleural inflammation is the most common biopsy finding in patients with EPE.[1,7,12] Interestingly, Bower described five cases of VTE-related EPE;[7] two of three patients, among the five, who underwent closed pleural biopsies showed chronic inflammation. In elucidating the biochemical and cytological characteristics of PE associated with VTE, Romero Candeira *et al*.[10] found that LDH levels ranged from 228 to 2783 units/L and that mesothelial proliferation was a frequent occurrence. Multi-loculated PEs have been described in up to 20% of cases of embolic effusions.[8] All these features suggest significant pleural inflammation in EPE- and VTE-associated PEs.

CONCLUSION

We present a rare case of Behcet's syndrome with an EPE as one of the presenting features. The EPE was most probably due to VTE from a missed asymptomatic

thrombosis in the IVC. Lessons learnt from this case are (a) Behcet's syndrome can rarely be associated with PE – chylothorax (due to thrombosis in central thoracic veins) or VTE-related PE; (b) EPE may occur in cases of VTE-related PE; (c) Commencement of immunosuppressive therapy early in the first instance may have prevented the subsequent occurrence of extensive DVT and VTE.

Behcet's syndrome-related PE (eosinophilic or otherwise) is usually a manifestation of its prothrombotic nature and along with EPE related to vasculitis, eosinophilic pneumonia, sarcoidosis, and CTD presents a clinical situation where treatment with immunosuppression is beneficial.

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Conflicts of interest
There are no conflicts of interest.

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