Case Report

Hemorrhagic sarcoid pleural effusion: A rare entity

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ABSTRACT

Involvement of pleura by sarcoidosis remains a rare manifestation and varies from pleural effusion, pneumothorax, pleural thickening, hydropneumothorax, trapped lung, hemothorax, or chylothorax. Sarcoid pleural effusions presenting as hemorrhagic effusions are even more rare. We report a case of active pulmonary sarcoidosis presenting as hemorrhagic pleural effusion requiring tissue diagnosis to rule out malignancy. The rarity of the presentation prompted us to report this case.

KEY WORDS: Atypical presentations of sarcoidosis, hemorrhagic pleural effusion, pleural sarcoidosis

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INTRODUCTION

Sarcoidosis is a multisystem disorder of granulomatous origin, commonly involving lungs, lymph nodes, skin, eyes, and liver though it can affect virtually most of the organs in the body. Though rare and atypical presentations of this disease appear in the literature, it not only delays diagnosis but leads to frequent mistreatment. Conundrums in sarcoidosis never fail to surprise either by an atypical presentation from commonly affecting organ system or by affecting unusual organ.

Involvement of pleura by sarcoidosis remains a rare manifestation and varies from pleural effusion, pneumothorax, pleural thickening, hydropneumothorax, trapped lung, hemothorax, or chylothorax.[1] The incidence of sarcoid pleural effusion ranges from 2.8% to 3%.[1,2] It is usually paucicellular, lymphocyte predominant exudate, with a pleural fluid/serum protein ratio that is more consistently in the exudative range than with the pleural fluid lactate dehydrogenase (LDH) criterion.[1] Sarcoid pleural effusions presenting as hemorrhagic effusions are even more rare. We report a case of active pulmonary sarcoidosis presenting as hemorrhagic pleural effusion requiring tissue diagnosis to rule out malignancy. The puzzling clinical presentation prompted us to report this case.

CASE REPORT

A 65-year-old male presented with 4 months history of a dry cough, progressive shortness of breath and intermittent fever with associated chills and sweat and cough with minimal expectoration. He also had a history of redness of eyes and 15 kg weight loss over 4 months. He is an ex-smoker with a history of hypertension for 30 years and type-2 diabetes mellitus on the oral hypoglycemic agent for 15 years with poor glycemic control at presentation. His family history was significant for the gastrointestinal stromal tumor to his son. His chest X-ray (CXR) showed right lower zone nonhomogeneous opacity. His sputum smear was negative for acid-fast *Bacilli* (AFB). Contrast enhanced computed tomography (CECT) chest was done which showed multiple discrete and conglomerating heterogeneous mediastinal and bilateral hilar lymphadenopathy with few showing calcification and nonhomogeneous attenuation. There were ill-defined right lower lobe ground glass opacities

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.188975

How to cite this article: Jha O, Nair V, Talwar D. Hemorrhagic sarcoid pleural effusion: A rare entity. Lung India 2016;33:532-6.

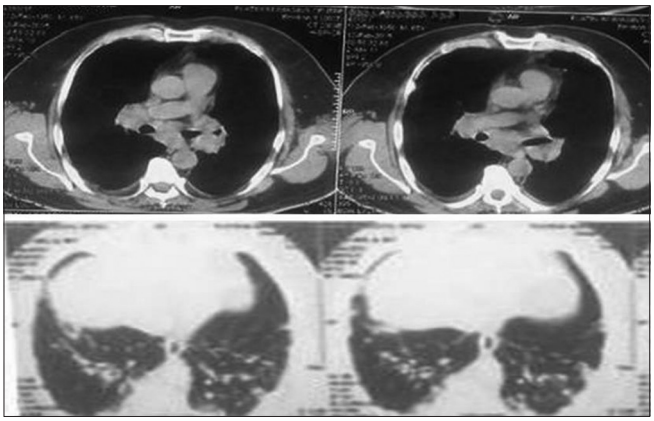

Figure 1: Contrast enhanced computed tomography showed multiple discrete and conglomerating heterogeneous mediastinal and bilateral hilar lymphadenopathy with few showing calcification and nonhomogeneous attenuation. There were ill-defined right lower lobe ground glass opacities with minimal pleural effusion

with minimal pleural effusion [Figure 1]. Empirical anti-tuberculosis treatment (ATT) (H_{300} R_{450} Z_{1500} E_{800} and levofloxacin 750 mg/d) was started by a local physician. Sputum smear for AFB stain was negative. Echo revealed normal left ventricular ejection fraction (60%) with mild concentric left ventricular hypertrophy and left ventricular diastolic dysfunction. Ultrasound whole abdomen revealed increased renal cortical echogenicity, mild prostatomegaly. Fiberoptic bronchoscopy (FOB) done was reported normal and bronchoalveolar lavage was negative for AFB stain, AFB culture, and gene Xpert for *Mycobacterium tuberculosis* but continued on ATT. However, he continued to have progressive breathlessness and cough, low-grade fever after 2 months. Pulmonary function test revealed mild restriction-forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) - 83%, FEV1-2.02L (75%) and FVC - 2.43L (70%). Repeat CXR showed bilateral new infiltrates in the lower zones [Figure 2] and due to further worsening he came to MCRD for further evaluation.

In view of previous CECT findings and nonresponse to ATT need of further evaluation considered looking into other possibilities such as sarcoidosis and malignancy. Combo positron emission tomography (PET) was planned to know the extent of the disease and to guide tissue sampling site and improving the diagnostic yield. FOB, endobronchial ultrasound (EBUS) and transbronchial lung biopsy (TBLB) planned. His complete blood count and liver function tests were normal. Serum creatinine was high (1.55 mg/dl). Combo PET-CT [Figure 3] showed multiple fludeoxyglucose (FDG) avid lymph node revealed in prevascular, aortopulmonary window, bilateral paratracheal (RLP: 2.7 × 2.6; SUV – 9.2), sub-carinal (3.6 × 2.6; SUV – 8.7), para-esophageal and bilateral hilar regions with FDG avid inter- and intra-lobular nodular septal thickening with multiple small nodules (SUV – 9.2) in perilymphatic distribution along the fissures and subpleural locations involving both lungs. Bilateral

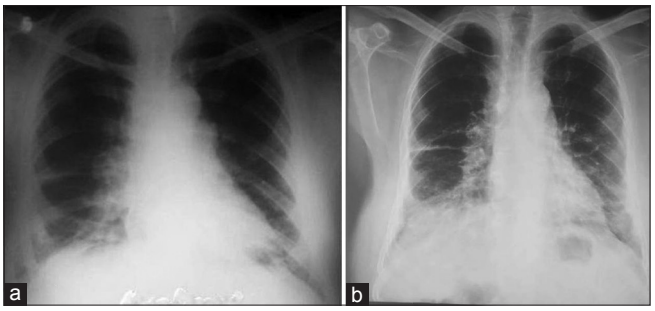

Figure 2: (a) Chest X-ray showed right lower zone nonhomogeneous opacity initially. (b) Repeat chest X-ray showed bilateral new infiltrates in the lower zones

pleural thickening with right pleural effusion was noted. His serum angiotensin converting enzymewas raised (95IU Normal up to 65 IU), Mantoux was negative and interferon-gamma release assays was positive.

FOB with EBUS-fine needle aspiration was done, the bronchial mucosa was edematous and endobronchial biopsy (EBB) taken. EBUS showed large heterogeneous lymph nodes at stations 7, 4R, 4L, 10R, and 10L. FNA smears from station 7; 4R and 4L showed scattered epithelioid cells with scant necrosis and Ziehl–Neelsen stain for AFB negative. Cell block showed nonnecrotizing granulomatous inflammation with no atypical cells [Figure 4]. EBB showed nonspecific inflammation. TBLB showed nonnecrotizing granulomatous inflammation in the interstitium and sub-bronchial mucosal granulomas [Figure 5]. Diagnosis of sarcoidosis was made. To evaluate the cause of pleural effusion pleural fluid aspiration and biopsy was done by medical thoracoscopy and 100 ml of frankly hemorrhagic fluid aspirated from right side and it was lymphocytic, exudative with high leucocyte count (total leukocyte count - 24,000, differential leukocyte count - Lymphocyte 98%; Polymorph 2%, glucose - 260, protein - 6.1 G, LDH - 643, packed cell volume - 1.4%, adenosine deaminase - 53.2, AFB stain and culture negative) with occasional large atypical cells and few binucleate cells, therefore, pleural fluid flow cytometry and immunohistochemistry (IHC) on cell block was done. Flow cytometry revealed 83% mature T lymphoid cells and 2.1% mature B lymphoid cells polyclonal for kappa/lambda and showed no definite evidence of lymphoma. IHC showed CD15, CD30 and Epstein-Barr virus negative, CD68 strongly positive consistent with reactive histiocytes with no evidence of lymphoma [Figure 6]. Both visceral, as well as parietal pleura studded with nodules, showed noncaseating granulomas on biopsy with mycobacterial smear and cultures being negative [Figure 7]. The patient was started on oral steroids, is currently in follow-up and improved clinico-radiologically [Figure 8].

DISCUSSION

Pleural sarcoidosis is still considered a rare manifestation of the disease, even though the first report on this

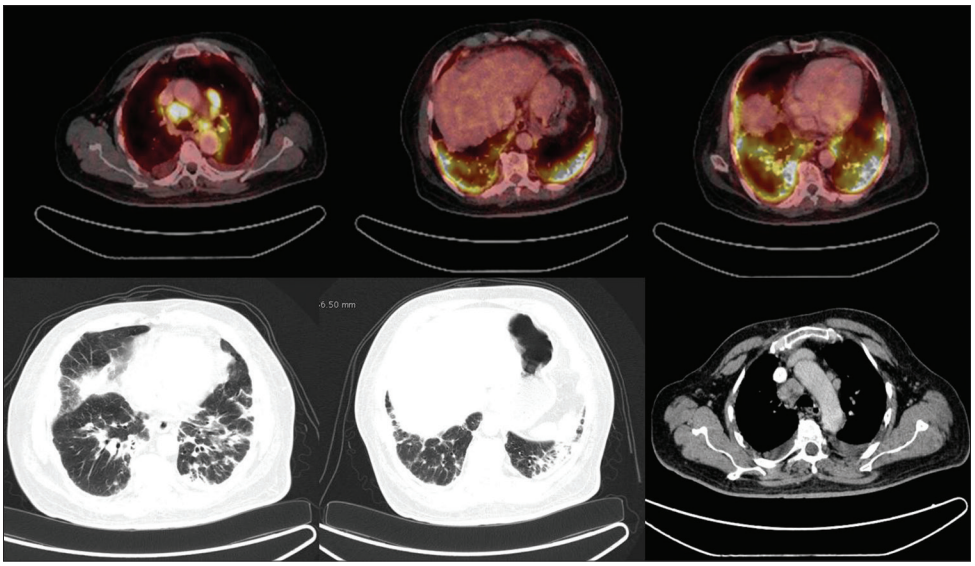

Figure 3: Multiple fludeoxyglucose avid lymph node revealed in prevascular, aortopulmonary window, bilateral paratracheal (RLP: 2.7 × 2.6; SUV – 9.2), sub-carinal (3.6 × 2.6; SUV – 8.7), para-esophageal and bilateral hilar regions with fludeoxyglucose avoid inter- and intra-lobular nodular septal thickening with multiple small nodules (SUV – 9.2) in perilymphatic distribution along the fissures and subpleural locations involving both lungs. Bilateral pleural thickening with right pleural effusion

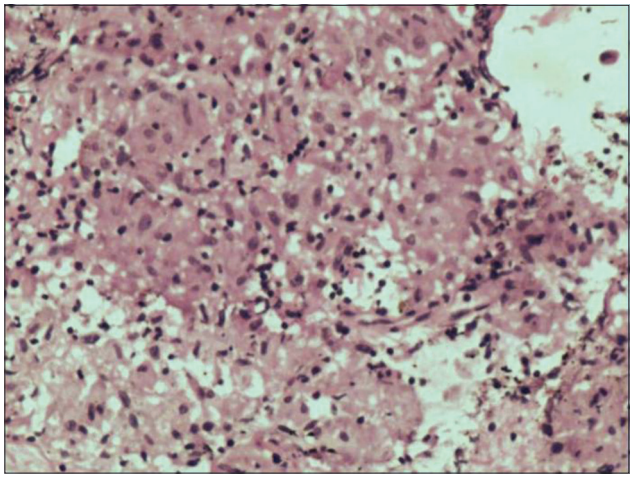

Figure 4: Endobronchial ultrasound-guided cell block showed nonnecrotizing granulomatous inflammation with no atypical cells

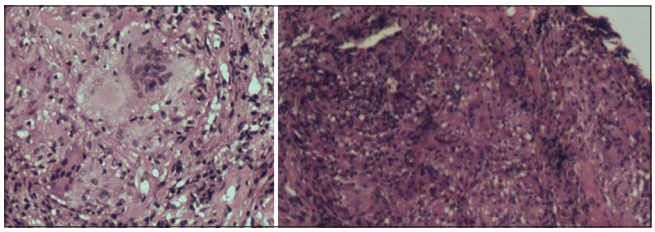

Figure 5: Histopathological examination of transbronchial lung biopsy showed nonnecrotizing granulomatous inflammation in the interstitium and sub-bronchial mucosal granulomas

entity was done by Schaumann in 1933.[3] Over the past few decades, despite the advent of newer diagnostic modalities and greater knowledge regarding the various atypical presentations of pulmonary sarcoidosis, the disappointingly meager data on sarcoid pleurisy is rather astonishing, to say the least. Four major patterns of pleural involvement have been noted: Pleural effusion, pleural thickening, pleural micro-nodules, and pneumothorax. It is not entirely certain as to why pleural involvement is scarce, despite the fact that pulmonary parenchymal and nodal involvement is virtually present in almost all reported cases. In 2005, Szwarcberg *et al*.[4] found that out of the 61 patients of sarcoidosis they studied, 25 (41%) had pleural involvement by CT (20 thickening, 5 effusions), compared to 7 (11%) by standard CXR (3 thickening, 4 effusions). The frequency of occurrence of pleural effusion in patients with sarcoidosis has been reported by Huggins *et al*.[1] as 2.8% (5 of 181 patients) with only 2 of the 181 PEs (1.1%) caused by sarcoid pleural involvement. Thereby proving the fact that even with newer diagnostic modalities the reported incidence is less. The reasons could be multifactorial; (a) mere presence of pleural effusion associated with sarcoidosis cannot be considered to be caused by sarcoidosis, (b) small pleural effusions can be missed on routine CXRs, (c) in a tuberculosis (TB) endemic country like ours, most pleural effusions are wrongly diagnosed as tubercular and empirically treated with ATT and hence missed, (d) lack of histopathological evidence of pleural involvement, (e) lack of awareness regarding this rare manifestation thereby missing the diagnosis. In a recent study, Wang *et al*.[5] retrieved from CNKI and PubMed database during the period 2004–2014, 92 cases of pleural involvement in sarcoidosis which included 59 cases of pleural effusion, 29 cases of pleural thickening, 3 cases of pneumothorax, and 1 case of nodules in pleura.

Pleurisy in sarcoidosis has been considered to be related to either inflammation of visceral and parietal pleura caused by peripheral lung granulomas, or disturbance of venous and lymphatic circulations. They are typically paucicellular,

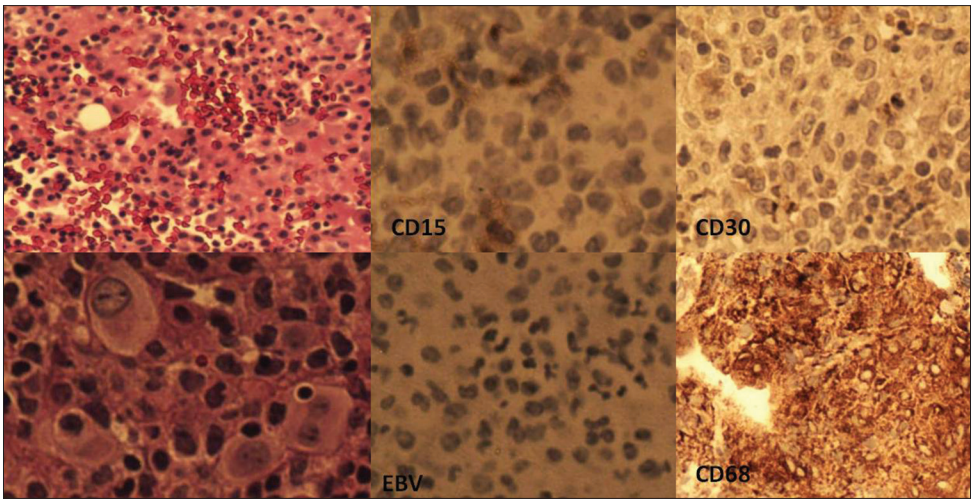

Figure 6: Frankly hemorrhagic pleural fluid aspirated, cytology showing occasional large atypical cells and few binucleate cells, immunohistochemistry done on pleural fluid cell block showed CD15, CD30 and Epstein-Barr virus negative, CD68 strongly positive consistent with reactive histiocytes with no evidence of lymphoma

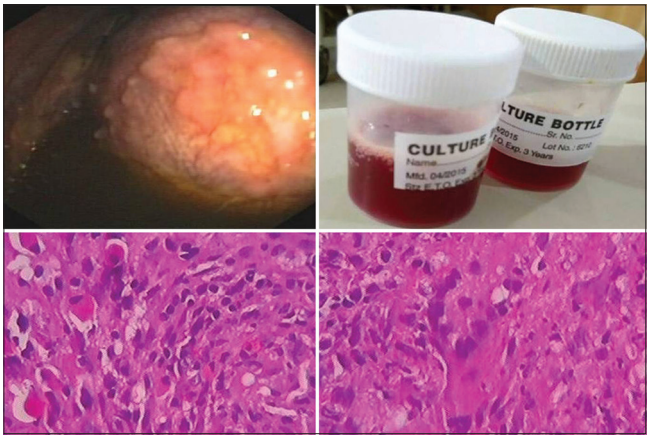

Figure 7: Both visceral, as well as parietal pleura studded with nodules, showed noncaseating granulomas on biopsy

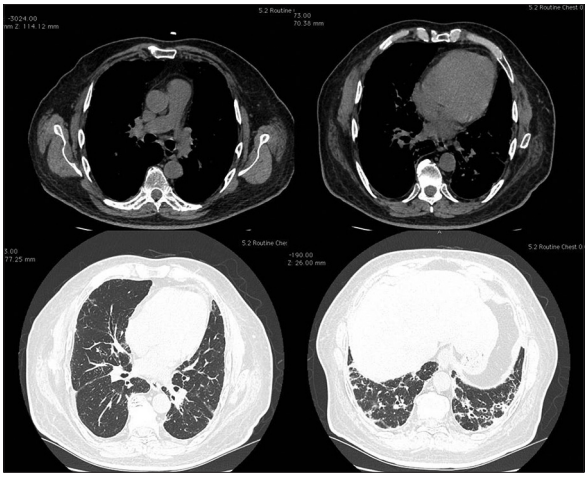

Figure 8: Computed tomography done after treatment showing significant resolution of ground glass opacities, septal and interstitial infiltrates, mediastinal lymph nodes and complete resolution of pleural effusion

lymphocytic-predominant, and exudative-protein discordance with low LDH further supporting the view of increased capillary permeability with minimal pleural space inflammation being the causative mechanism in the formation of pleural fluid in sarcoidosis, reinforcing the hypothesis of a few advocates of a "protective pleural mechanism" keeping pleural spaces dry.

The most common appearance of pleural fluid among most published case series was serous and less commonly yellow. Our patient had presented with highly cellular, hemorrhagic exudative effusion with a hematocrit of 1.4% which was perplexing, raising the suspicion of associated malignancy as bloody pleurisy in sarcoidosis is extremely rare. Though noncaseating granulomas seen in lung parenchyma and mediastinal lymph nodes made sarcoidosis as the most likely diagnosis, but such lesions have been reported in malignancies and represent sarcoid-like reactions. Furthermore, the finding of occasional large atypical and binucleate cells, in the pleural fluid analysis, led to a further diagnostic dilemma. In addition, lymphoma, mesothelioma, and lung cancer have been sometimes reported in patients with sarcoidosis. Though, pleural fluid flow cytometry and pleural fluid cell concentrate histopathology and IHC did not reveal any evidence of lymphoma but ultimately noncaseating granuloma in the pleural biopsy proved it to be hemorrhagic sarcoid pleural effusion. This is rarest as only four cases have been reported in literature so far to the best of our knowledge. De Vuyst *et al*.[6] in 1979 first reported a case of bloody pleural effusion in sarcoidosis with extensive lung parenchymal involvement and in 1992, Takahashi *et al*.[7] reported a case of Heerfordt's syndrome with bilateral bloody pleurisy, bloody ascites, and hepatosplenomegaly. A decade later, Watarai *et al*.[8] published a case of sarcoidosis with bloody pleural effusion, bilateral hilar lymphadenopathy, and

parenchymal nodules. Kumar *et al*.[9] published a case of deep cervical lymphadenopathy, bilateral hilar adenopathy with left sided bloody pleural effusion. All cases responded to oral corticosteroid therapy and did not report any recurrence.

Capillary permeability cannot explain bloody pleurisy in sarcoidosis and pleural granulomas demonstrated on medical thoracoscopy either compressing or eroding the blood vessels is more likely to explain frankly bloody sarcoid pleural effusions like seen in our case. As pleural sarcoidosis is rare, TB, malignancy must be excluded despite the histopathological evidence. After initiation of oral steroids, the patient reported significant clinical improvement with resolution of pleural effusion along with lung opacities, further cementing diagnosis of hemorrhagic sarcoid pleural effusion.

CONCLUSION

Sarcoid pleural effusions are unusual, and hemorrhagic ones are even rarer. In a country like ours, it can be overlooked or misdiagnosed as TB as happened in our patient prior to coming to our center. A broader clinical approach and suspicion is required to effectively diagnose this rare entity, the lack of which leads to delay in appropriate therapy. To add to the problem, hemorrhagic effusions pose diagnostic challenges as evaluation of more common causes like associated lung malignancy or lymphomas becomes pertinent. Therefore, any pleural effusion in a patient of sarcoidosis should not be presumed to be pleural sarcoidosis without histopathological evidence of sarcoidosis or have effectively ruled out other causes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Huggins JT, Doelken P, Sahn SA, King L, Judson MA. Pleural effusions in a series of 181 outpatients with sarcoidosis. Chest 2006;129:1599-604.
2. Soskel NT, Sharma OP. Pleural involvement in sarcoidosis. Curr Opin Pulm Med 2000;6:455-68.
3. Schaumann MJ. Etude anatomo-patholgique et histologique surles localizations vicerales de la lymphogranulomatose benigne. Bull Soc Fr Dermatol Syphiligr 1933;40:1167-78.
4. Szwarcberg JB, Glajchen N, Teirstein AS. Pleural involvement in chronic sarcoidosis detected by thoracic CT scanning. Sarcoidosis Vasc Diffuse Lung Dis 2005;22:58-62.
5. Wang F, Tong Z, Wang Z, Wang X, Xu L. Sarcoidosis related pleural effusion: 6 case reports and literatures review. Zhonghua Jie He He Hu Xi Za Zhi 2015;38:99-104.
6. De Vuyst P, De Troyer A, Yernault JC. Bloody pleural effusion in a patient with sarcoidosis. Chest 1979;76:607-9.
7. Takahashi N, Enomoto T, Hagiwara T, Horie T, Amagi S, Tanaka N, *et al*. A case of sarcoidosis presenting with Heerfordt's syndrome, associated with hepatosplenomegaly, pleural effusion, and ascites. Nihon Kyobu Shikkan Gakkai Zasshi 1992;30:684-8.
8. Watarai M, Yazawa M, Yamanda K, Yamamoto H, Yamazaki Y. Pulmonary sarcoidosis with associated bloody pleurisy. Intern Med 2002;41:1021-3.
9. Kumar S, Verma SK, Singh R, Prasad R. Hemorrhagic pleural effusion secondary to sarcoidosis: A brief review. Ann Thorac Med 2009;4:27-31.