Original Article

Hemorrhagic effusions in pleural tuberculosis: Need for correlation with pleural biopsy histopathological patterns

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Abstract

Pleural tuberculosis is a major treatable cause of exudative pleural effusions in India. Rarely these patients present with hemorrhagic effusion. Due to the similar constitutional symptoms, it becomes important to rule out malignancy in these patients by pleural biopsy. The lack of well formed granuloma formation in all cases of pleural tuberculosis leads to a diagnostic dilemma. Therefore, we retrospectively analyzed the histopathological features of pleural biopsies of tuberculosis patients who presented with hemorrhagic pleural effusion to the V.P Chest Institute from January 2009 to January 2015. These included 10 males and 2 females, age ranging from 33 to 80 years, mean of 65 years. The adequate biopsies (n=11) were histopathologically analysed and revealed, chronic lymphocytic pleuritis in 4 cases (44.44%), epithelioid granuloma formation in 3 cases (33.34%), necrosis in one case (11.12%) and fibrosis was seen in one case of nonresolving effusion (11.11%). The present study shows that the histopathological patterns of tubercular involvement of pleura vary depending upon the stage of involvement and epithelioid cell granulomas may not be identified in all cases. The knowledge of the histopathological patterns is necessary to accurately identify these cases who present with hemorrhagic pleural effusions and improve patient outcome.

Keywords: Pleural biopsies, tuberculosis, Pleural fluid analysis, pleural fibrosis.

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INTRODUCTION

The lung pleura is involved in tuberculosis by one of four routes: Primary pleural tuberculosis, post primary (reactivation) tubercular pleurisy, pleural tuberculosis secondary to pulmonary tuberculosis (miliary), tubercular empyema (Marcia *et al*., 2011). In developed countries tubercular pleurisy is becoming a form of reactivation rather than primary disease (Ibrahima *et al*, 2005). The mean age of the affected individual is also much higher than it was 50 years ago. In developing countries, however, pleural tuberculosis is considered to be a form of primary tuberculosis (Jessie *et al*, 2006) and observed to affect people of young age less than 45 year (Kumar *et al*, 2013). Also in developing countries the incidence of pleural tuberculosis is seen predominantly in males than in females. The pathogenesis of pleural tuberculosis is considered to be a delayed hypersensitivity reaction to the mycobacterial antigens when they enter the pleural space and interact with T-cells previously sensitized to mycobacteria (Doosoo, 2014). The accumulation of fluid, into the pleural space then occurs as a result of an increase in the permeability of pleural capillaries, leakage of serum proteins and increase in the oncotic pressure in the pleural fluid (Saptanaga, 2015). The other common causes of hemorrhagic pleural effusion include tumor which include both primary malignant pleural neoplasms as well as metastasis to the pleura, trauma (both iatrogenic and accidental) and tuberculosis. In hemorrhagic pleural effusions, an accurate identification of the pleural pathology and its correlation with clinical-radiological features is necessary to reach a definitive diagnosis. Pleural tuberculosis in the setting of

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hemorrhagic pleural effusion is a diagnostic challenge because of its nonspecific clinical presentation and paucibacillary nature. A definite diagnosis of tuberculous pleurisy is achieved when Mycobacterium tuberculosis is demonstrated in pleural specimens, or when caseous granulomas are found in pleural biopsies (Shirin *et al*, 2014). However these characteristic features are not seen in all cases, as they depend upon the stage of involvement of the pleura. The histopathological tissue reaction then needs to be carefully examined and correlated with cytology and other features. Therefore in the present study we studied the histopathological features seen on pleural biopsy in 12 cases of pulmonary tuberculosis who had presented with hemorrhagic pleural effusion.

MATERIAL AND METHODS

We retrospectively analyzed the histopathological features of pleural biopsies of pulmonary tuberculosis patients who presented with nonresolving hemorrhagic pleural effusion, received at department of Pathology, V.P Chest Institute, over a seven year period from January 2009 to January 2015. The pleural biopsies were obtained by Thoracoscopic biopsy technique (video assisted thoracoscopic surgery, VATS). The number of tissue bits varied from 3-5 and size of the biopsies ranged from 0.3cm to 0.8cm. At least three bits were submitted for histological studies and one bit sent for AFB culture. All biopsies were stained with Hematoxylin and eosin stain and adequacy of pleural tissue determined. The adequate pleural biopsies were histopathologically evaluated and correlated with pleural fluid analysis to identify the cause of effusion. Ziehl Neelsen stain was used to confirm the diagnosis of pleural tuberculosis. Pleural fluid was analysed and total and differential count was done. In hemorrhagic effusions, the cell block was prepared after lysis of RBC's to rule out the presence of atypical cells.

RESULTS

Total 12 pleural biopsies from patients of V.P. Chest Institute were analysed. These included 10 males and 2 females, age ranging from 33 to 80 years, mean of 65 years. These 11 biopsies were adequate for histopathological analysis, and one biopsy was inadequate. The adequate biopsies (n=11) were classified into two group: Group I: malignant (2/11=18.18%) (Figure 1), Group II-nonmalignant (9/11=81.81%). The histopathological spectrum seen in the adequate pleural biopsies in Group II included Chronic lymphocytic pleuritis- in 4 cases (44.44%), Epithelioid granulomatous inflammation- in 3 cases (33.34%), Pleural Fibrosis- in 1 case (11.11%) (Figure IIa, IIb,IIc). Only necrotic material was obtained in 1 case (11.12%). X-ray revealed Massive pleural effusion which was hemorrhagic on gross examination in all these cases.

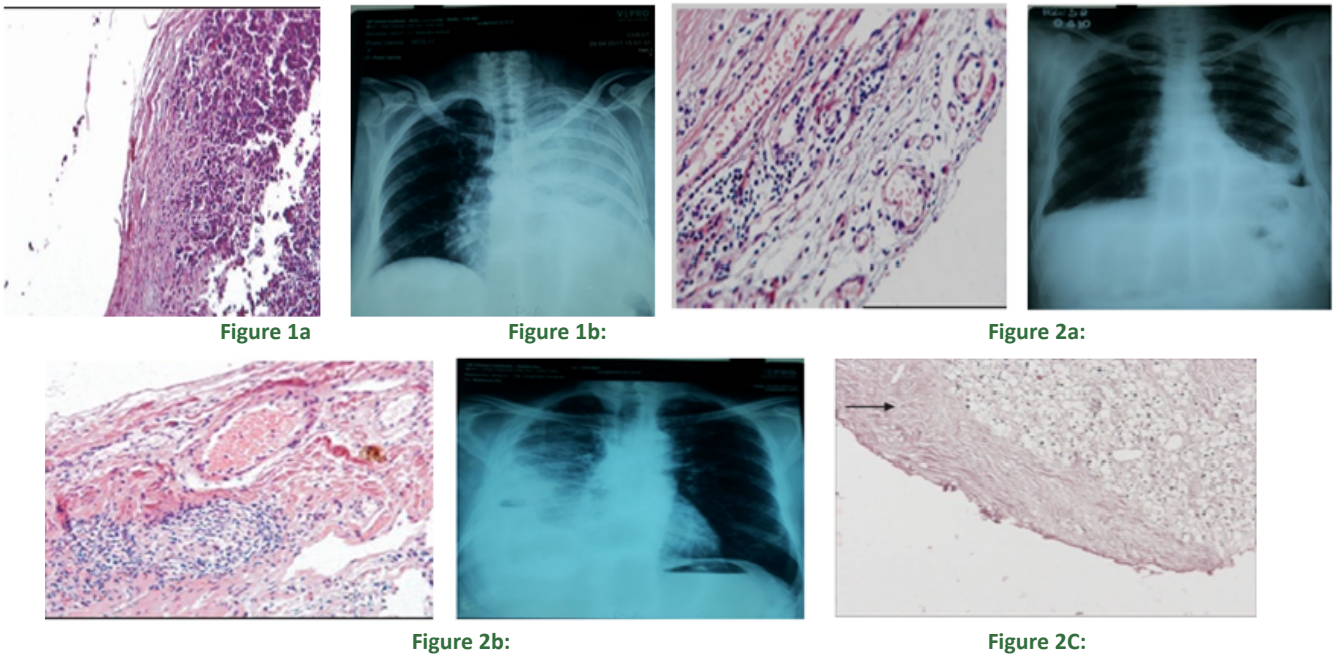

Figure 1: In Group I: (a) Pleural biopsy showing the neoplastic infiltration of pleura from underlying small cell carcinoma lung. (b) X Ray Chest showing massive pleural effusion. Pleural fluid aspirated showed hemorrhagic effusion with clusters of reactive mesothelial cells.

Figure 2 a: Group II: Histopathology of pleura showing chronic lymphocytic infiltrate in the pleura. Pleural Effusion seen on X-ray Chest which showed lymphocyte predominance on microscopy.
Figure 2 b: Group II: Well formed Epithelioid cell granulomas in the pleura associated with hemorrhagic pleural effusion. Atypical cells were not seen in Cell block prepared.
Figure 2 c: Thickened fibrotic pleura with typical basket weave pattern of collagen fibres seen in H and E stain. The total and differential count could not be performed because of the hemorrhagic nature of the pleural effusion. Atypical cells were not seen.

DISCUSSION

Pleural tuberculosis is one of the most common forms of extrapulmonary tuberculosis in developing countries and remains a major health problem in Asian and African countries. It has been reported to account for up to 25% of tuberculosis infected adults and for up to 30% of exudative pleural effusions (Pickering *et al*., 2013). In countries with high tuberculosis incidence, the mean age of tuberculous pleural effusion patients ranges from 32 to 34 years (Arriero *et al*, 1998) and 70% are under the age of 40 (Valdés *et al*, 2012). In the developed countries too, its incidence has risen in parallel to the increasing incidence of HIV (Lawn *et al*, 2013). In the United States, mean age at presentation is 49 years with nearly 50% of patients under 45 years of age and approximately 30% patients, who are over 65 years of age (Baumann *et al*, 2007). To explain these differences, it has been suggested that in developed countries, tubercular pleural effusion is the result of reactivation, while in countries where it appears in a younger population, it is a primary form of the disease (Moudgil *et al*, 1994). The immunological status of the patient influences the outcome of primary tuberculosis or reactivation of dormant foci and depends to a major extent on the T helper cells (Th1) immune response. A strong Th1 response, limits the bacillary dissemination with the formation of granulomas (Zhang *et al*, 1995; Hernandez-Pando *et al*, 1996). On the other hand, immune response with strong Th2 bias fails to restrict multiplication of the bacilli and their spread leading to multiple bacterial foci with disseminated pathology (Somoskovi *et al*., 1999). Localized form of tuberculosis is characterized by an intense chronic granulomatous inflammation at disease site, involving activation of Th1 cells and their preferential recruitment to disease sites. Tubercular pleural effusion is characterized by a strong granulomatous inflammatory response to M. tuberculosis inflicting either lung parenchyma and/or adjacent pleura. This is associated with a high level of interferon-α (IFN-α) in tubercular pleural fluid as opposed to pleural effusions caused by neoplastic and autoimmune diseases. Pleural fluid in tubercular pleural effusion may additionally be rich in mononuclear cells. These are mainly CD4 lymphocytes, which are recruited from the peripheral blood into the pleural space (Somoskovi *et al*., 1999). Recent studies are also indicative of the active role of mesothelial cells in immunologic tissue reactions (Dobos *et al*, 2000). Histopathological and microbiological analysis of the pleural fluid and/or tissue remain to be the Gold standard for diagnosis of pleural pathologies. Detection of tuberculosis in tissue is based on the histological pattern of the granuloma (Khalid *et al*., 2014) and confirmed with Ziehl Neelsen stain. On histopathology, the granulomatous tubercular reactions have been subdivided into typical caseating and nontypical noncaseating granuloma. Recently immunohistochemistry using pAbBCG has been used and positive coarse granular cytoplasmic stain of epithelioid cells and round, fragmented mycobacterial/ bacillary staining have been demonstrated (Shirin *et al*, 2014). Inaddition positive staining is seen in endothelial cells, fibroblasts, plasma cells, lymphocytes, and macrophages outside the granuloma. In the present study we demonstrate that in tuberculous pleurisy, the pleural biopsy can demonstrate a spectrum of pathologies that range from non-specific lymphocytic inflammation, granulomatous inflammation, caseation necrosis, or fibrosis. These patterns vary depending upon the stage of the disease and the immunological response and epithelioid cell granulomas may not be identified in all cases. Definitive diagnosis cannot be reached in approximately 20% of these specimen (Sharma *et al*, 2012). Thus emphasizing the significance of identification of all types of histological patterns (Patterson *et al*., 1917). Previously also, Stead *et al*.1955 have described, the presence of sparse granulomas along with an extensive transformation of the submesothelial tissue into granulation tissue in patients with tuberculous pleurisy. These findings may justify the larger amount of granulation tissue recovered by the Cope needle when compared to granulomas (Purohit *et al*., 2007). The presence of mycobacterium both intracellularly in macrophages as well as extra cellularly in the granuloma and even in lymphocytic fragments around the granuloma have been reported. The differential cell count in pleural fluid have been analysed (Light *et al* 2001). In tubercular pleural effusion, the pleural fluid lymphocyte is usually more than 50% and mesothelial cells are occasionally found (28.9% cases), and account for only approximately 3% cells. The mesothelial cell differential count of more than 5% has been observed to strongly argue against a tubercular etiology in pleural effusion (Fishman *et al*., 1988). In the present study, the characteristic granulomas were seen in 33.34% cases only. However when combined with Ziehl

Neelsen stains and culture studies were seen to yield a confirmatory diagnosis in 88.89% cases. This is similar to previous studies in patients with tubercular pleural effusions which have shown that pleural biopsies in combination with culture have a diagnostic yield of 60 to 95%. In 11.11% cases, pleural fibrosis characterised by an excessive deposition of matrix components, resulting in the destruction of normal pleural tissue architecture and compromised function was seen to develop as the consequence of a haemorrhagic tubercular effusion.

CONCLUSION

In patients presenting with hemorrhagic pleural effusion it is important to differentiate tubercular effusion from malignancy by pleural biopsy. The histopathological patterns of tubercular involvement of pleura vary depending upon the stage of involvement and epithelioid cell granulomas may not be identified in all cases. The knowledge of the histopathological patterns is necessary for systematic approach to accurately identify these cases in a step wise manner and improve patient outcome.

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