Multifarious Relationship between Tuberculosis and Pulmonary Alveolar Proteinosis: Bronchoalveolar lavage cytological study with clinicopathological correlation

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ABSTRACT

Background: Pulmonary alveolar proteinosis (PAP) is a rare disorder which is categorized into congenital, idiopathic and secondary types. There is a marked paucity of literature from the Indian subcontinent that analyses the causation of PAP.

Methods: We studied clinical features, histopathological findings and cytological features in 19 bronchoalveolar lavage (BAL) cytology confirmed cases of PAP diagnosed over a 28-year period.

Results: One or more risk factors for PAP were noted in 11 cases (57.89%) and included exposure to silica dust, chemicals, smoke and flour, immunological diseases, tuberculosis, retroviral disease and monoclonal gammopathy. Three patients had more than one risk factor. Only one patient was tested for anti-granulocyte-monocyte colony-stimulating-factor (anti-GM-CSF) antibodies. Elevated anti-GM-CSF antibodies and absence of an identifiable risk factor was noted in this patient. Super-infection was noted in three (15.79%); with tuberculosis in two and aspergillosis in one. Six patients had a recent past history of anti-tuberculosis therapy but only one among them had documented acid fast bacilli positivity confirming tuberculosis and autopsy revealed tuberculosis in one patient.

Conclusion: The present study observed that a considerable proportion of cases were associated with known risk factors for PAP. A variable relationship of PAP and tuberculosis was observed where the latter was noted as a possible risk factor, a co-existing disease at presentation, a superinfection, or even a possible cause of a misdiagnosis of PAP as tuberculosis. These findings are of great relevance in view of the endemicity of tuberculosis in India.

Keywords: Pulmonary Alveolar Proteinosis, Bronchoalveolar Lavage, Tuberculosis

Introduction

Pulmonary alveolar proteinosis (PAP) is an uncommon disorder characterised by accumulation of lipoproteinaceous material in the alveoli and is classified into congenital, idiopathic and secondary categories[1]. Secondary PAP is reported to be less common as compared to idiopathic PAP[2]. PAP can be identified on correlating clinical findings and computerized tomographic scans[3]. But only bronchoalveolar lavage (BAL) cytology and/or lung histopathology provides a definitive diagnosis[4]. However, it may have an unusual presentation leading to a misdiagnosis as a more common respiratory disorder that includes even tuberculosis[5,6]. This study presents the data of clinical features and cytological / histological findings of PAP with emphasis on the multifarious association of PAP with tuberculosis.

Materials and Methods

We retrospectively reviewed a total of 19 cases from 1991 to 2018 wherein BAL fluid cytology had revealed the characteristic exudate of PAP - granular to clumpy, dark pink, paucicellular, proteinaceous material on routine hematoxylin and eosin (H & E) staining (Figure 1) with diastase resistant periodic acid-Schiff (PAS-DR) positivity (Figure 2). All patients had been subjected to diagnostic fibreoptic bronchoscopy to obtain BAL fluid. Documented details related to age, gender, clinical history, pulmonary function testing (PFT), radiological investigations, laboratory tests including microbiological workup, histopathology and treatment protocols were retrieved from records wherever available.

Results

Out of the total 19 patients included in the study, 13 (68.42%) were males and 06 (31.58%) were females. Their age ranged from 14-60 years with a mean age of 36.19 years. All patients had presented with dry or productive cough with mucoid or mucopurulent expectoration and exertional breathlessness, ranging from Grade 1 to 4. Eight patients (42.11%) had low grade fever. Comorbidities noted included autoimmune hepatitis, glomerulonephritis, rheumatoid arthritis and retroviral disease (RVD) in one patient each, while two patients had type 2 diabetes mellitus. As depicted in Table 1, occupational exposure...
to chemicals, farming dust and smoke or flour were noted in four patients (21.05%) and occupational exposure to silica in another three (15.79%). One patient was a current cigarette smoker and another a smoker till his present respiratory symptoms began, though he discontinued smoking thereafter.

PFT records available in 16 patients had revealed a restrictive pattern with diffusion defects and hypoxemia; these changes were severe in five (26.31%), moderate in eight (42.11%), mild in two (10.53%) and one demonstrated a normal PFT at presentation (5.36%). Records of high-resolution computerized tomography (HRCT) were available in 12 patients while only plain chest radiographs were available in six. HRCT had revealed ground glass opacities with interlobular septal thickening leading to a crazy pavement appearance in 9 patients, while one patient each had respectively shown crazy paving with nodular densities, crazy pavement appearance with cavitory consolidation and features suggestive of vasculitis or lymphangitis carcinomatosis. In the six patients where only records of chest radiographs reports were available, bilateral alveolar opacities and reticulonodular shadows were reported in three patients each.

Tests for tuberculosis performed by Ziehl-Neelsen staining for acid-fast bacilli (AFB), gene expert (GE) and Mycobacteria Growth Indicator Tube (MGIT) test respectively were documented in 17, seven and two patients each respectively. AFB was negative in 14, GE in six and MGIT in both patients tested.

The level of anti-granulocyte-macrophage colony-stimulating-factor (anti-GM-CSF) antibodies was available in only one patient who had an elevated level of 147.6 mcg/ml (normal = < 5.0 mcg/ml). No associated conditions or risk factors for secondary PAP could be identified in this patient. This case was categorized as idiopathic or autoimmune PAP. The patient improved significantly after a normal PFT at presentation (5.36%). Records of high-resolution computerized tomography (HRCT) were available in 12 patients while only plain chest radiographs were available in six. HRCT had revealed ground glass opacities with interlobular septal thickening leading to a crazy pavement appearance in 9 patients, while one patient each had respectively shown crazy paving with nodular densities, crazy pavement appearance with cavitory consolidation and features suggestive of vasculitis or lymphangitis carcinomatosis. In the six patients where only records of chest radiographs reports were available, bilateral alveolar opacities and reticulonodular shadows were reported in three patients each.

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seen in the lungs but they could not be considered as definite evidence of pulmonary tuberculosis. However, the left adrenal gland had shown large areas of caseation necrosis and inflammatory cells indicative of tuberculosis. Other organs were unremarkable.

Table 1 summarises salient features of risk factors for PAP observed in the study patients. Three patients (15.79%) had PAP associated with silica exposure: a driller and loader of rocks for 15 years had revealed silicoproteinosis on lung biopsy, a clay worker with exposure to silica for 10 years had been observed to have features consistent with silicosis on transbronchial lung biopsy and BAL fluid polarizing microscopy had shown numerous birefringent needle-shaped & tiny particulate crystals suggestive of silica, extracellularly and within alveolar macrophages in a flour mill worker with exposure to stone grinding for 15 years. Three patients (15.79%) had autoimmune diseases with immunosuppressive therapy while two (10.52%) had an occupational exposure to chemicals. One patient was a chronic smoker at presentation and another was a chronic smoker who has discontinued smoking when his respiratory symptoms began eight months ago. Another patient, a farmer who would have been exposed to farming dust had also given history of exposure to smoke for two months at the time of onset of his respiratory symptoms. Lastly, one patient each (5.26% each) had exposure to flour dust, retroviral disease and an incompletely worked up monoclonal gammopathy. As described in Table 1, more than one risk factor was noted in three patients. An occasional cyst of P. jiroveci was noted in Gomori methanamine silver (GMS) stained BAL cytosmears in two patients. However, both patients had no features suggestive of pneumocystis pneumonia (PCP) in the recent or distant past. One of these patients had a history of AFB positivity in bronchial wash and had been started on AKT one month prior to his diagnosis of PAP while the second patient was mechanic with exposure to diesel for 4-5 years. The significance of these occasional cysts is uncertain.

Thus, in our study, a total of 11 out of 19 (57.89%) patients had one or more identifiable risk factors for PAP (Table 1) and could belong to the category of secondary PAP. Excluded from this tally were eight cases where no identifiable risk factor for secondary PAP were noted including the patient with high anti-GM-CSF antibodies, the two patients who had taken AKT in recent past but had neither documentary evidence confirming tuberculosis nor the presence of any other identifiable risk factor and the two cases where tuberculosis superinfection had occurred later in the course of the disease but no identifiable risk factor at presentation.

Table 1: Salient features of risk factors for PAP observed in the study group.

| S.No | Risk factor                  | N  | Salient relevant details                                                                 |
|------|------------------------------|----|-----------------------------------------------------------------------------------------|
| 1    | Silica dust exposure         | 03 | Driller and loader of rocks – 15 years. Lung biopsy: silicoproteinosis                   |
|      |                              |    | Clay worker exposed to silica dust - 10 years. Lung biopsy: consistent with silicosis   |
|      |                              |    | Exposure to stone grinding in a flour mill worker - 15 years. Birefringent particles on polarizing microscopy of BAL* |
| 2    | Autoimmune disorder          | 03 | Rheumatoid Arthritis on treatment – 15 years                                            |
|      |                              |    | Anti-smooth muscle antibody positive hepatitis treated with Prednisolone*               |
|      |                              |    | Glomerulonephritis treated with prednisolone **                                        |
| 3    | Tuberculosis                 | 02 | Co-existing PAP and adrenal TB at presentation: AKT for 4 months, started 1 year before diagnosis of PAP. Autopsy: PAP, invasive pulmonary aspergillosis, pneumonia, ill-defined pulmonary granulomas and adrenal TB |
|      |                              |    | Recent past history of TB: Bronchial wash AFB positive& started on AKT 1 month before PAP diagnosis. No AFB in BAL at time of diagnosis of PAP. |
| 4    | Exposure to chemicals        | 02 | Fabric industry worker for 20 years exposed to chemical fumes                           |
|      |                              |    | Mechanic with exposure to diesel for 4-5 years                                           |
| 5    | Cigarette smoking            | 02 | Cigarette smoker (current)                                                              |
|      |                              |    | Chronic smoker till 8 months ago; quit after onset of symptoms of present illness***    |
| 6    | Exposure to farming dust and smoke | 01 | Farmer with exposure for farming dust and smoke**                                     |
| S.No | Risk factor               | N  | Salient relevant details                                                                 |
|------|--------------------------|----|----------------------------------------------------------------------------------------|
| 6    | Exposure to flour dust   | 01 | Flour mill worker* – 15 years                                                           |
| 7    | Monoclonal gammopathy    | 01 | Monoclonal gammopathy detected after diagnosis of PAP but incompletely worked up and lost to follow-up** |
| 8    | Retroviral disease       | 01 | Known case of retroviral disease presented when undergoing AKT***                       |

Abbreviations: PAP = pulmonary alveolar proteinosis, N = number of cases, BAL = bronchoalveolar lavage, TB = tuberculosis, AKT = anti-tuberculosis therapy, AFB = acid fast bacilli.

More than one risk factor was noted in three patients: * A flour mill worker with (a) exposure to flour dust, (b) exposure to stone dust while grinding (birefringent particles in BAL on polarizing microscopy), (c) anti-smooth muscle antibody positive hepatitis treated with prednisolone (d) unconfirmed TB (no documentation available) with AKT taken 6 months before diagnosis of PAP and negative for AFB at time of diagnosis of PAP. ** Farmer with (a) exposure to farming dust (b) exposure to smoke for 2 months (c) Glomerulonephritis treated with prednisolone (d) Monoclonal gammopathy – detected after diagnosis of PAP but incompletely worked up and lost to follow up. *** A patient with (a) retroviral disease (b) exposure to cigarette smoke till 8 months ago; quit after respiratory symptoms started (c) unconfirmed tuberculosis – undergoing AKT for tuberculosis diagnosed in recent past (no documentation available of chronology or confirmation of tuberculosis) and negative for AFB at time of diagnosis of PAP.

Fig. 1: Bronchoalveolar lavage cytosmear - paucicellular, granular to clumpy proteinaceous material characteristic of pulmonary alveolar proteinosis (Hematoxylin and Eosin x40, inset x400).

Fig. 2: Bronchoalveolar lavage cytosmear - Periodic Acid Schiff positive diastase resistant material diagnostic of pulmonary alveolar proteinosis (x 400).

Fig. 3: Bronchoalveolar lavage cytosmear - Numerous acid-fast bacilli in a 46 years old housewife who developed superinfection 18 months after the onset of pulmonary alveolar proteinosis. The background shows the exudates of alveolar proteinosis (Ziehl Neelsen, x1000).
**Discussion**

PAP is a rare disease worldwide and also in India. A total of 19 cases diagnosed with PAP by BAL cytology over a 28-year period were analysed in the present study. To the best of our knowledge, only one series of PAP published from India had analysed five cases diagnosed over a 6.5-year period [7]. Idiopathic PAP considered to have an autoimmune aetiology, is associated with high levels of anti-GM-CSF antibodies and is therefore also referred to as autoimmune PAP [1, 8, 9]. Secondary PAP is known to be associated with a variety of conditions [1, 9, 10]. Studies have observed that idiopathic PAP is far more common than secondary PAP [2].

Anti-GM-CSF antibody testing was done in only one patient in the present study. Markedly elevated anti-GM-CSF antibody levels and no other identifiable risk factor were noted in this patient. Thus, in the present study, this is the only case that could be definitely categorized as idiopathic or autoimmune PAP.

In our study, one or more risk factors known to be associated with secondary PAP, were noted in a considerable number of cases: 11 out of the 19 patients (57.89%). These risk factors were occupational exposure to silica, autoimmune disorders, tuberculosis, exposure to chemicals or smoke, retroviral disease and monoclonal gammapathy. These risk factors have been associated with secondary PAP [1, 9, 10]. It has also been noted that exposure to various dusts, chemicals and cigarette smoke occurred in considerable numbers of patients studied in Korea and that farming dust was significantly associated with severity of PAP [11]. However, the contribution of this risk factors to the evolution of the PAP disease process in our study is uncertain. Furthermore, in the absence of an anti-GM-CSF antibody test in these patients it would not be possible to definitely categorize them as secondary PAP.

A striking feature noted in our study was an association of tuberculosis with PAP in eight patients. It occurred as a superinfection during the course of persistent PAP in two patients (10.52%) and AKT had helped in recovery from tuberculosis as well as PAP in both. While six other patients had a history of tuberculosis in the recent past only one among them had a report of AFB positivity and tuberculosis was noted at autopsy in one patient albeit most evidently in the adrenals. Lack of documentary evidence made the diagnosis of tuberculosis uncertain in the remaining four patients. Thus, a definite association with tuberculosis either as a pre-existing or concurrent disease or a superinfection occurred in four patients (21.05%). Tuberculosis is a known micro-organism among infections reported to be causes of secondary PAP [8, 9]. However, tuberculosis is more commonly observed to be a complication of PAP as reported in several cases in world literature [12, 13, 14, 15, 16]. One of the patients with tuberculosis superinfection in the present study was a diabetic on oral hypoglycemics. An association of PAP with tuberculosis and diabetes mellitus has also been documented in literature [13]. Our study underscores that the absence of adequate documentary evidence of a diagnosis of TB in a proportion of cases who had been administered AKT without much response to the treatment might reflect that these are cases of PAP misdiagnosed as TB.

PAP has been reported in patients recovering from pneumocystis pneumonia [17]. While two cases in our study showed an occasional cyst of P. jiroveci in BAL cytosmears, in view of the absence of pneumonia and thereby the uncertainty of the clinical significance of these cysts in these cases, this was not considered a risk factor in our study.

Thus, the salient findings of our study were that risk factors for secondary PAP were observed in a considerable proportion of cases (57.89%) and superinfection was noted in three cases; with pulmonary tuberculosis in two and invasive pulmonary aspergillosis in one. To the best of our knowledge despite the endemcity of tuberculosis and its association with PAP only two cases with tuberculosis superinfection have been reported in patients in India; both from our centre and included in the present series [18, 19]. The study also highlights the possibility of PAP masquerading as tuberculosis [6].

**Conclusion**

Our study observed that risk factors that could underlie PAP were observed in a large proportion of cases. Also importantly, the relationship of tuberculosis with PAP appears to be multifarious wherein tuberculosis could occur as a superinfection, as a co-existent condition at presentation, as a pre-existing disease leading to secondary PAP and also a possible reason for a missed diagnosis of PAP. The endermcity of tuberculosis in India makes these findings important to note.

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