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Pathology

CYTOLOGICAL DIAGNOSIS OF PULMONARY ALVEOLAR PROTEINOSIS FROM BRONCHOALVEOLAR LAVAGE SPECIMEN -A CASE REPORT OF SILICOPROTEINOTUBERCULOSIS AND REVIEW OF LITERATURE

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ABSTRACT We present a case report of unusual association of silicosis, pulmonary alveolar proteinosis and tuberculosis occurring in a 30 year old stone quarry worker exposed to sand dust since 15 years. Pulmonary alveolar proteinosis (PAP) is an uncommon disease in which there is progressive and inappropriate occupation of the lung alveoli by an excessive amount of unprocessed surfactant. Untill recently the gold standard for diagnosis of PAP was considered to be open lung biopsy followed by histopathological and ultrastructural examination.With the introduction of improved bronchoscopic techniques, bronchoalveolar lavage (BAL) is now employed as a useful diagnostic and therapeutic modality in the management of PAP. The cytological features of BAL fluid in PAP are unique and with supporting clinical and radiological evidences a confident diagnosis of PAP can be given so that the patient can be spared of a more invasive diagnostic procedure. The authors present a case report where a cytological diagnosis of PAP was made possible by routine Papanicolaou stained smears and PAS-D stains. The utility of BAL cytology in the diagnosis of PAP is discussed.The conclusion is that study of the bronchoscopic lavage fluid is a useful diagnostic modality in PAP.

KEYWORDS :

Introduction

Pulmonary alveolar proteinosis was first described by Rosen et al in 1958.[1] It is a rare disease, also known as pulmonary alveolar phospholipoproteinosis and is a diffuse lung disease charecterized by the progressive accumulation of abundant granular extracellular material within the alveoli and terminal bronchioles. This material which represents surfactant distending the alveolar spaces is composed of protein and lipids and is periodic acid-Schiff (PAS) positive diastase resistant .Patient usually presents with cough and progressive dyspnoea. Imaging studies reveal alveolar opacities most often located centrally involving mainly the mid and lower lung zones usually described as ' bat wing' distribution. High resolution CT imaging shows scattered or diffuse areas of ground glass attenuation with superimposition of a linear pattern characterstically described as crazy-paving pattern [2]

Bronchoalveolar lavage specimens appear cloudy or milky and can be bloody rarely. Cytology smears prepared from these samples classically show paucicellular smears with abundant granular to amorphous globular material with only rare background macrophages and inflammatory cells.. Lung biopsy of these patients show alveolar spaces filled with granular eosinophilc material. Electron microscopy which increases the diagnostic accuracy shows whorled multilam ellate structures characterstic of surfactant.[3]

The basic pathogenetic mechanism in PAP is the dysfunction of the alveolar macrophages and hence causing impaired catabolism of the phagocytosed surfactant within the macrophages.Three different forms of PAP has been described.1. aPAP (autoimmune pulmonary alveolar proteinosis) wchich occurs as a result of production of GM-CSF autoantibodies. 2. Secondary PAP occurs in association with various other disorders like hematologic disorders including malignancies, dust-born lung diseases , infections and immunodefi ciencies. 3. Hereditary PAP caused by mutations affecting the GM-CSF receptor genes and less commonly by GATA2 mutations. This classification has relevance especially when it comes to management options as in the case of aPAP where a recently suggested therapeutic option is inhalation of GM-CSF as needed. [4]

Case Report:

A 30 year old male presented with a gradually progressing dyspnoea since 4 months . He had dry cough , loss of weight and a low grade fever since 3 months .He was treated elsewhere as a case of interstitial lung disease secondary to chronic exposure to silica. The patient who works as stone quarry worker is a smoker too since 15 years. There was no known co morbidities like tuberculosis , diabetes or asthma.On physical examination patient was tachypnoeic and showed bilateral scattered inspiratory crackles. Bronchogram was suggestive of interstitial lung disease and CT suggested bilateral lung parenchymal crazy-paving appearance indicating a diagnosis of pulmonary alveolar proteinosis with a differential diagnosis of PCP pneumonia, ARDS(acute respiratory distress syndrome) AIP(acute interstitial pneumonia) & tuberculosis. Sputum showed scanty AFB (1+) and BAL gene Xpert was positive for mycobacterium tuberculosis sensitive to rifampicin. BAL fluid received for cytological examination was thick ,creamy white with sediments . Microscopy of Papanicolaou stained smears showed amorphous granular orange coloured material(Fig1.a). Among this material were seen homogenous orange coloured globular masses in a background of very few inflammatory cells and cellular debri(Fig1b&c). No granulomas or epithelioid cells were seen.. The granular material and globular masses were stained reddish pink with PAS and were diastase resistant(Fig1.d) With this a diagnosis of pulmonary alveolar proteinosis was given. Whole lung lavage was given to the patient under GA. Repeated samples also showed similar material in the smears but less in quantity compared to the initial samples. Antituberculous treatment also started . Condition of the patient improved,fever subsided and was stable at discharge.

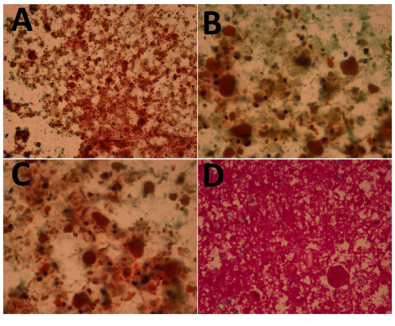

Figure legends

Fig 1

a) PAP stain x 100 showing amporphous granular orange coloured material.

b) & c) PAP stain x 400 showing orange coloured globular masses

d) PAS-D stain x400 showing masses of reddish pink diastase resistant material.

Discussion:

Clinical presentation of progressive dyspnoea and fever along with radiological detection of fluid material in the lung alveoli can occur in different conditions and the fluid content could be pus , blood , necrotic

tumor, gastric contents or a lipoproteinaceous material as occurs with PAP. Hence it is important to assess the nature of the material collected by laboratory methods so as to ensure the diagnosis and thereby to decide on the management strategy.

The golden yardstick for diagnosis of PAP was previously considered to be open lung biopsy or transbronchial lung biopsy where the lung tissue shows preservation of the alveolar architecture with the alveolar spaces filled by a granular eosinophilic PAS positive material. But with the advent of improved bronchoscopic techniques , bronchoalveolar lavage is shown to have both diagnostic and therapeutic advantages over open lung biopsy.With typical cytological findings, supported by radiological and clinical featurs , BAL specimen cytological examination is sufficient for a confident diagnosis of PAP.

In our case , the grossly milky appearance of the BAL specimen,typical cytopathological features of an amorphous granular material with orange coloured globules with Papanicolaou stain, PAS positivity and diastase resistance ,very well supported by the CT findings of bilateral significant central interstitial disease with a crazy paving appearance in a patient with a known history of occupational exposure to dust and a compatible clinical presentation were sufficient to give a conclusive diagnosis of PAP. Our patient although a probable candidate for dustborn lung disease complicated by PAP, the radiological diagnosis was not conclusive of PAP. The 'crazy-paving pattern' (resembling the structure of irregularly shaped paving stones) on CT was initially described as pathognomonic sign of alveolar proteinosis. But later , with high-resolution CT imaging , this pattern was described in a number of acute and chronic lung diseases thereby requiring cytopathological or histopathological correlation. In our case the BAL fluid study was very typical of PAP both grossly and microscopically. Hence the alternate radiological differential diagnoses were easily excluded.

PAP is an uncommon disease with a variable clinical course . It may undergo spontaneous resolution , may resolve with repeated whole lung lavages and may remain stable with persistent symptoms or may even progress to respiratory failure despite treatment depending various host factors. The intra alveolar material getting accumulated in PAP is considered to be surfactant proteins and the key mechanism in the pathogenesis of PAP is the excessive surfactant . Alveolar macrophages in the lungs are considered to play an important role in surfactant homeostasis. The granulocyte macrophage –colony stimulating factor (GM-CSF) appears to be the critical regulator of this homeostasis. . Auto immune PAP comprises 90 % of cases of PAP. Patients affected by autoimmune PAP have circulating neutralizing anti-GM-CSF antibodies . Diagnosis in such cases are increasingly made by X-ray and serological estimation of the GM-CSF antibody level. These antibodies cause a reduced localised GM-CSF activity in the lung thereby decreasing the alveolar macrophage surfactant degradation resulting in surfactant accumulation. GM-CSF is a cytokine stimulating the production of alveolar macrophages.

The other important clinical form of the disease is secondary PAP (nonimmune) which occurs in association with various conditions like toxic/dust exposure , infections like tuberculosis , pneumocystis carinii pneumonia , nocardiasis, malignancies like leukemia or lymphoma and in immunodeficiency states . In all forms of the disease there is a quantitative and /or qualitative dysfunction of the alveolar macrophages.

Another very important thing to be considered is occupation of the patient. This patient was initialiy diagnosed as a case of interstitial lung disease from the clinical history and image findings. It is a well known fact that silicosis is the most prevalent of the pneumoconiosis and the incidence of tuberculosis among patients with silicosis is upto 40 times or more higher when compared with general population. Coexistence of mycobacterial infection is always a possibility in patients with chronic exposure to silica. Experimental studies have shown that silica modifies the immune response of the lungs by impairing macrophage function and causing macrophage apoptosis. Surfactant protein A has been shown to be at high levels in the BAL fluid of patient of silicosis.Considering the prolonged history of occupational exposure to silica dust , our patient possibly falls in the category of secondary PAP . The pathogenetic mechanism suggested in silicoproteinosis is that silica dust mechanically irritate type II pneumocytes producing an excessive surfactant material.

In view of the sputum positivity for mycobacterium tuberculosis , an important question which arises in our case is whether the patient had mycobacterial infection secondary to which he developed PAP or is it tuberculosis occurring in a case of silicoproteinosis. With established tuberculosis, cytological examination usually reveals granulomatous reaction or even the caseous material. In our case these two were not to be seen but still the patient was proved to be harbouring mycobacteria as revealed by microbiological examination .Since there was no history or physical findings suggestive of a pre-existing tuberculosis at the time of admission,it is highly probable that this patient might have contracted tuberculosis as a superinfection on PAP . The relationship between PAP and infections including tuberculosis is attributed to the defective function of alveolar macrophages. So also the fluid filling the alveolar spaces in a case of PAP can be a rich culture medium for the growth of mycobacteria. PAP has been described in association with various infections and tuberculosis is one among them. . Our patient was was diagnosed as silicoproteinosis with simultaneous detection of tubercle bacilli in the sputum and the patient responded to whole lung lavage plus antituberculous theapy. So this may be considered as a case of silicoproteinotuberculosis. The co- existence silicosis , secondary pulmonary alveolar proteinosis and tuberculosis in a patient presenting with respiratory distress is quite uncommon[5] .

Bronhoalveolar lavage is a relatively safe and noninvasive procedure compared to open lung biopsy and the results can be obtained on the same day itself. With transbronchial biopsy , the material may not be sufficient enough to do special staining procedures and also there will be delay in getting the histopathology report. Moreover open Lung biopsy or trsnsbronchial biopsy specimes may not always represent the area of lung tissue affected by the disease process and false negative results may occur due to sampling errors [6] . Morbidity and mortality is also more with invasive procedures.

Conclusions :

Respiratory tract cytopathology has its main application in the diagnosis of neoplastic disorders and it has only limited value in the diagnosis of non-neoplastic lesions. But in the appropriate clinical and radiological setting cytopathological examination can be very useful in establishing the diagnosis even in nonneoplatic lesions .Cytological examination of BAL fluid is the best diagnostic tool in the diagnosis of PAP . By this BAL technique a larger area of the lung is sampled and the amount of fluid obtained as specimen is also more so that in addition to cytology other tests like culture , mycological & virological studies can be done simultaneously . With BAL fluid cytology , delay in reporting is almost nil so that the patient gets adequate initial therapy at the appropriate time thereby avoiding the adverse effect of diagnostic delay on morbidity and mortality of the patient It is well known from various studies that chronic exposure to silica can be associated with silicosis , tuberculosis. PAP & lung cancer and the occurrence of these adverse health effects is very well related to the concentration of silica dust[7] Hence it is very important that measures are to be taken to provide respiratory protection to those engaged in industries with increased risk of chronic and excessive exposure to silica. In any case of PAP coexisting tuberculosis has to be ruled out especially in countries with high prevalence of tuberculosis.

Conflicts of interest :none declared.

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