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Case Report

Pulmonary Alveolar Microlithiasis and Rheumatoid Arthritis with Pulmonary Tuberculosis

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Abstract: Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive disease, characterised by widespread intra-alveolar accumulation of microliths. A 30-year-old male patient, known case of rheumatioid arthritis on treatment, presented with occasional complaints of cough with expectoration, since 1 year. He was found to be sputum AFB positive for which AKT was started, and a chest xray was advised, which showed diffuse bilateral micronodular calcific opacities having sand-like appearance distributed throughout the lungs, with a evident black pleural sign, which made us suspect PAM. An HRCT chest showed, multiple dense micronodular opacities in bilateral lung parenchyma prominently in the middle and lower lung zones giving a classical sandstorm appearance with sparing of a thin peripheral subpleural rim of parenchyma, giving a black pleura sign. The patient was symptomatically treated and was counselled for lung transplant and presents for regular follow up.

Keywords: Alveolar Microlithiasis, Rheumatoid Arthritis, Sputum Positive Pulmonary Tuberculosis

1. Introduction

Pulmonary alveolar microlithiasis is a rare diffuse lung disease characterised by deposition of calcium phosphate within the alveolar airspaces. the disease is usually discovered from birth up to 40 years of age and is often diagnosed incidentally during radiography of chest for other reasons. Many patients are asymptomatic and the majority of patients either have normal or restrictive pulmonary function. The clinical course of the disease varies, while it remains static in some patients, it can progress into pulmonary fibrosis, respiratory failure and cor pulmonale in others.

2. Case Report

A 30-year-old male patient, known case of rheumatioid arthritis on treatment. Patient was referred to the chest department in view of incidental Chest Xray findings (Figure 1). On history, the patient was having occasional complaints of cough with whitish scanty sputum, since last 1 year. The patient denied history of breathlessness, fever, chest pain, haemoptysis. the patient had complains of pain and swelling in his knees, ankles, and hands since 5 years. The pain initially started over Ankle than progressed to calf- knee joint-than involving all 4 small proximal and distal joints of both upper limbs developing a swan neck deformity (Figure 4). Now since one year patient also has stiffness and restriction of movement in the cervical joint. Pain and stiffness of joints, classically is more in morning and the pain gets aggrevated on movements and relieves on rest. Patient was diagnosed with rheumatoid arthritis 1 year back, and the patient has been on methotrexate and Hydroxycholoroquininone for 1 year intermittently.

Patient gives history of pulmonary tuberculosis 10 years and was started on AKT, but defaulted after 2 months. There was no family history of similar illness. He was vitally stable. There was swelling and tenderness on palpation of his knees and slightly diminished breaths sounds on auscultation at the both lung bases, however there were no adventitious sound.

Table 1. *These were the basic investigations.*

Investigations	
HB	13.8mg/dl
TLC	11300
CRP	96.6
ESR	60
RA	100
CALCIUM	10.2
PHOSPHORUS	4.2
VITAMIN D	15.8ng/ml

A chest roentgenogram "Figure 1" was showing diffuse bilateral micronodular calcific opacities- sandstorm appearance, distributed throughout the lungs, with a evident black pleura sign, which made us suspect PAM. A further HRCT scan "Figure 2, 3" confirmed the diagnosis and it was reported by our radiologists as a fine diffuse reticulonoduler pattern most prominent in the middle and lower lung zones with greatest concentrations in the subpleural paranchyma, extensive areas of ground glass opacities witin interspersed interlobular septal thickening are noted involving bilateral lung parenchyma predominantly in lower lobes with sparing of thin peripheral subpleural rim of parenchyma. multiple calcified modules are noted in bilateral lower lobe and right middle lobe, black pleura sign, few subcentimeter sized pretracheal/paratracheal and subcrinal lymph nodes and bilateral axillary lymph nodes are seen".

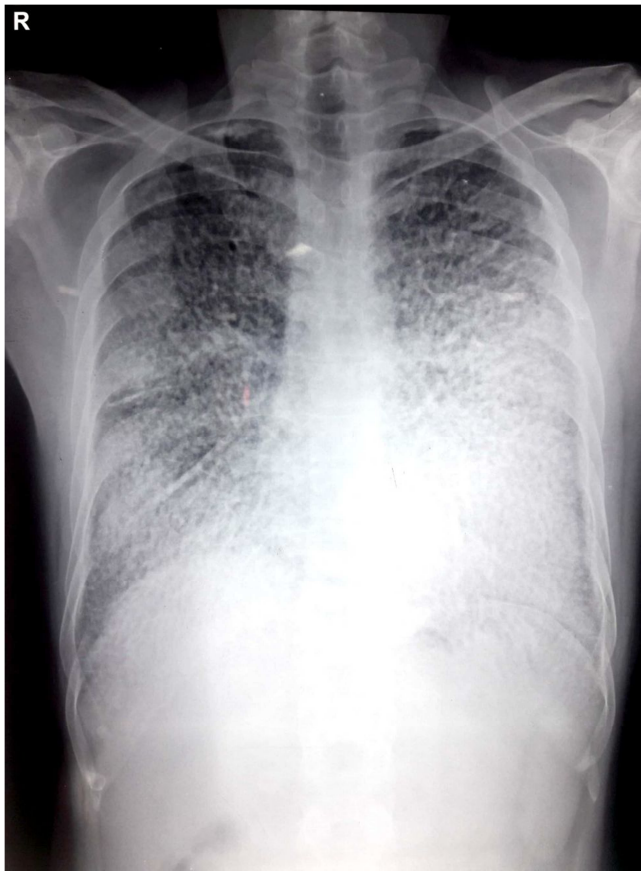

Figure 1. *Chest radiography shows diffuse bilateral micronodular opacities.*

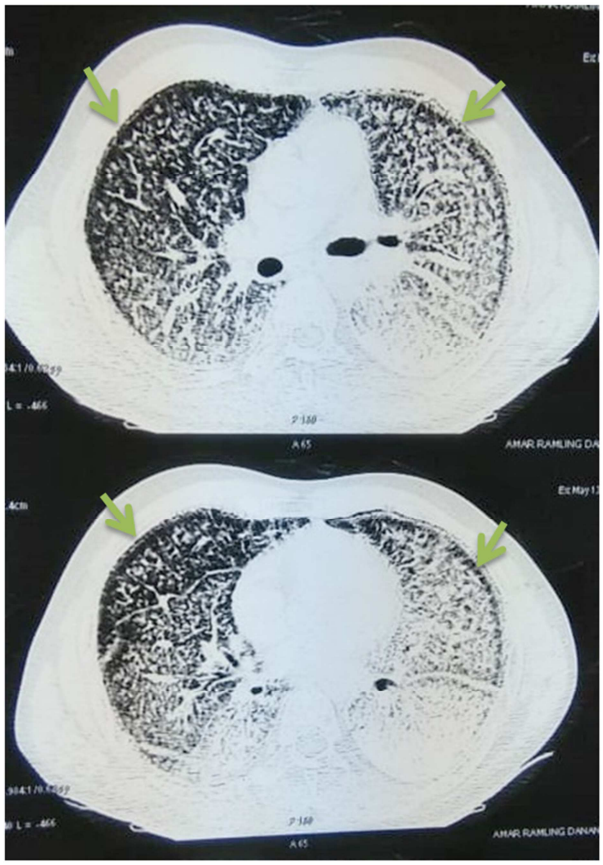

Figure 2. *Black pleura sign.*

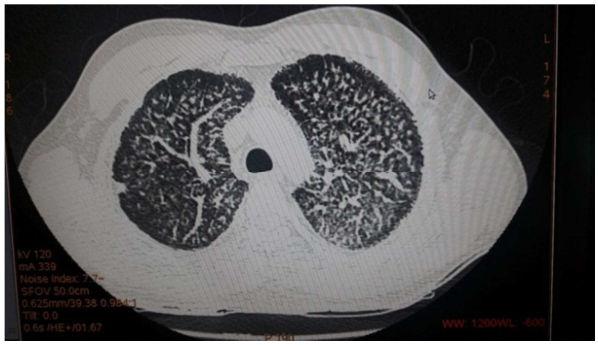

Figure 3. *CT scan shows diffuse distribution of micronodular calcific densities in the subpleural parenchyma and along the broncho-vascular bundles. black pleura sign.*

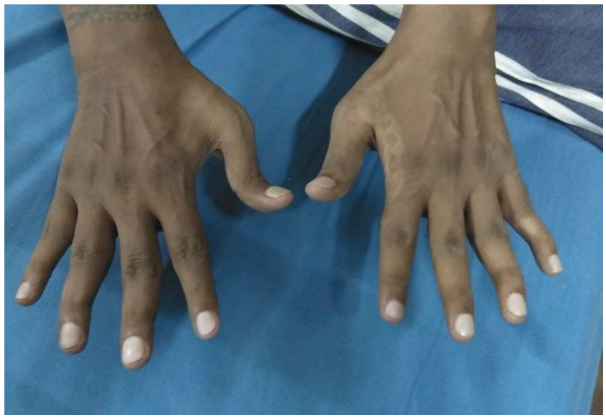

Figure 4. *Phalangeal and metacarpo-phalangeal deformi-ties.*

BAL, Biospy was not done as our patient did not consent for any invasive procedure.

3. Discussion

Pulmonary alveolar microlithiasis (PAM) is a rare autosomal recessive disease, characterised by widespread intra-alveolar accumulation of innumerable minute calculi called microliths. It is caused by inactivating mutations in the gene "solute carrier family 34 member 2", encoding a sodium-dependent phosphate cotransporter (SLC34A2, Npt2b, NaPi-2b). [1] SLC34A2 is expressed primarily in alveolar epithelial type II cells and is responsible for the uptake of phosphate released from phospholipids in outdated surfactant. The formation of calcium phosphate microliths in PAM could be explained by the inability to clear phosphate from the alveolar space, PAM can be seen in any age group, and disease typically follows a protracted course. The mean age at diagnosis is 35 years. Males and females are affected with equal frequency. The cause of this process remains unclear. One hypothesis is that an abnormal inflammatory response to irritants or infection leads to formation of an exudate that is not easily absorbed and ultimately undergoes calcification [2, 3]. In our country infectious diseases such as measles in childhood and tuberculosis in both childhood and adulthood are very common. As we know, these infections may easily infect the other children of the family and then a post infectious autoimmune inflammatory process develops. So this could explain the reason for familial association in approximately half of the reported cases and that the affected relative is sibling [4, 5, 6].

4. Diagnostic Procedures

Diagnostic procedures can be classified into two main groups: imaging and anatomopathological. The former include chest radiography, chest computed tomography and high-resolution computed tomography (HRCT); the latter, listed in increasing order of invasiveness, bronchoalveolar lavage (BAL), transbronchial biopsy, open lung biopsy and autopsy.

The first cases of PAM were reported in the 1950s and 1960s in patients with respiratory failure; they were most often diagnosed by autopsy.

4.1. Chest Xray

The typical finding on chest roentgenogram of bilateral infiltrates with a fine sandlike micronodular appearance and greater density in the lower and middle lung fields is considered to be diagnostic (figure 1).

4.2. High–Resolution Computed Tomography Thorax

CT scan demonstrate diffuse distribution of micronodular calcific densities which are usually most prominent in the middle and lower lung zones with greatest concentration in the subpleural parenchyma and along the broncho-vascular bundles (figure 2, 3). Although usually asymptomatic at the time of presentation, alveolar microlithiasis rarely produces functional abnormalities. When it does, these findings are restrictive pulmonary function tests or exercise-induced pulmonary hypertension. Respiratory function tests are often normal even with extensive radiographic changes. With progression of disease, a restrictive pattern of lung volumes develops, and gas transfer is disturbed and respiratory failure ensues.

4.3. BAL and Biopsy Show the Characteristic Calciospherocitis (Microliths) in the Alveoli

Histologically, the microliths are periodic acid–Schiff (PAS)-positive and consist of calcareous concentric lamellae around a central nucleus with an amorphous or granular aspect. This appearance is distinct from those of metastatic and dystrophic calcifications, which are located in the interstitial or vascular compartments [7].

The microliths usually range from 50 to 1000 μm in diameter, although microliths up to 5000 μm in size have been reported, and are mainly composed of calcium and phosphorus (phosphorus:calcium ratio of 1:2), with varying amounts of iron, magnesium, potassium and copper [7].

4.4. Biopsy also Shows Variable Degrees of Fibrosis in the Lung Interstitium

To date, the best diagnostic schedule for PAM is the association of BAL and chest HRCT, as the former investigation can document the diagnosis while the latter provides further information about the degree of inflammation and/or fibrosis or calcification of the interstitium. This association makes it possible to avoid performing transbronchial and open lung biopsy, burdened by higher complication rates [8]. Identification of the *SLC34A2* gene mutation could clinch the diagnosis.

Biopsy generally shows the calcified spherules filling the alveolar spaces. There may or may not be interstitial fibrosis and inflammatory cell infiltration. There are usually no changes in other organs although calcium deposits have been reported in one patient [8].

4.5. Therapy and Lung Transplantation

Currently, there is no medical or gene therapy capable of reducing disease progression. Systemic corticosteroids, calcium-chelating agents (alendronate sodium can have palliative role) and serial bronchopulmonary lavage have been shown to be ineffective and are used as palliative treatments [8, 9, 10]. The use of diphosphonates has also been proposed to reduce calcium phosphate precipitation in PAM, however, this therapy remains controversial given the limited number of reports in the literature [11-15].

In 1988, the Toronto Lung Transplantation Group reported a successful double lung transplantation in humans. The first bilateral lung transplant in a patient with PAM was described in 1992 in France [16], followed by a second one in 1993 in Germany [17] and two others in 1997 in the USA [18]. Single transplants were reported in 1996 in Saudi Arabia [19] in 2001 in Canada [20], in 2009 in Iran [21] and in 2014 in Italy [22].

Four other bilateral transplants were performed in France in 2009 [22], in Brazil in 2010 [23], in the USA in 2010 [24] and 2011 [25] and five in Vienna between 1989 and 2013 (one of these was also published by GÜÇYETMEZ *et al.* [26]). The longest-living transplanted patient is a 63-year-old female [27].

A striking feature of this disease is the frequent discordance between the clinical and radiographic manifestations. Many patients display only minor symptoms despite impressive radiographic features, as also seen in our patient.

In the differential diagnosis, pulmonary dystrophic and metastatic calcification should be taken into consideration. Dystrophic calcification refers to the deposition of calcium salts in dead tissue, such as within the healing granulomas of tuberculosis. Metastatic calcification refers to the deposition of calcium salts and occurs in association with some derangement of calcium salts metabolism, such as hyperparathyroidism, hypervitaminosis D, the milk alkali syndrome, sarcoidosis, increased bone turnover due to multiple myeloma or metastatic carcinoma, or chronic renal failure [1].

In this patient we think that PAM itself caused an autoimmune rheumatic process to start. The patient complained mostly of symptoms of polyarthritis. Clinical and laboratory findings strongly suggested a rheumatic process. Results revealed Rheumatoid Arthritis. In our knowledge, this is the first report on PAM associated with RA and pulmonary tuberculosis. We think that further cases are needed to explain this association.

5. Conclusion

PAM is an "orphan" disease and lung transplantation is currently the only effective therapy. However, since the demonstration of the gene responsible for PAM, it is hoped that in the future new therapies may become available, that can reduce the phosphate ions in the alveolar spaces and so arrest or delay the formation of microliths and the progression to interstitial disease. Future evaluations are needed to investigate patient survival rates and the risk of PAM recurrence after lung transplantation.

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