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Pulmonary Alveolar Microlithiasis in an Elderly: A Case Report with Brief Review of Literature.

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ABSTRACT

Pulmonary alveolar microlithiasis (PAM) is a rare chronic lung disease characterized by presence of 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 co-transporter (SLC34A2) expressed primarily in alveolar epithelial type II cells. It is most frequently diagnosed from birth to 40 years of age with a mean age of 27-30 years at the time of diagnosis. Most of patients are asymptomatic or having mild symptoms and are usually diagnosed incidentally. Chest radiograph and high-resolution CT of thorax are nearly pathognomonic for diagnosing PAM and histopathological confirmation is required only in few cases. This disease has slow progressive course ultimately leading to death by causing pulmonary fibrosis and cor pulmonale. Currently, there is no medical or gene therapy capable of reducing disease progression. Lung transplantation remains the only possible treatment for end-stage disease. Herein,we report a case of PAM in a 60-year-old gentleman who presented with a 5-year history of shortness of breath on exertion and intermittent cough with expectoration. His sister had similar respiratory symptoms and died 10 years back of which no details are available. The rarity of this disease and late age of presentation prompted us to report this case.

Keywords: HRCT, Pulmonary alveolar microlithiasis, Microlith, SLC34A2 gene.

INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is a rare disease, characterized by presence of diffuse innumerable minute calculi called microliths or calcospherites in the alveoli of the lungs. This rare entity was first described by Friedrich in 1856 and subsequently by Harbitz in 1918. The disease was named PAM by the Hungarian pathologist Puhr in 1933.[1,2]

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As of 2014, 1022 cases have been described worldwide, the majority of cases being in Asia (576 cases; 56.3%) and in Europe (285 cases; 27.8%). Turkey has the highest number of cases , followed by China, Japan, India, Italy and the USA. Eighty cases have been reported from India till 2014.[3-5] It was first reported from India by Viswanathan.[6] The disease affects both sexes, with a slight predominance among males worldwide. The female sex seems to be predominant in familial cases where as sporadic cases show male predominance. The clinical traits are heterogeneous, ranging from totally asymptomatic to respiratory failure. Recently it has been considered a genetic disease linked to mutations of the SLC34A2 gene, with a pattern of autosomal recessive inheritance with high penetration.[7,8]

We present a case of symptomatic PAM in a 60-year-old man, emphasizing the role of high-resolution lung CT (HRCT) in the diagnosis of this rare disease with a brief review of literature.

CASE REPORT

A 60-year-old man presented to our department with mild to moderate shortness of breath and cough with expectoration for the past five years. He had no other complaints like history of fever, chest pain, hemoptysis, or weight loss.. He had no significant medical or past history. He was a nonsmoker.

On physical examination, Vitals were within normal range. Auscultation of the lungs revealed random wheezes and coarse crackles. No cyanosis, clubbing, peripheral edema was observed. Cardiac auscultation was normal. The routine blood examination was found to be normal. His sister died of some

respiratory disease 10 years back as said by the patient for which no documentations are available.
Chest radiograph revealed bilateral diffuse symmetric dense, micronodular pattern causing ''sand-storm'' appearance. Computed tomography scout image revealed similar findings with predominant involvement of the posterior and basal regions with obscuration of the mediastinal, cardiac, and diaphragmatic borders [Figure 1].

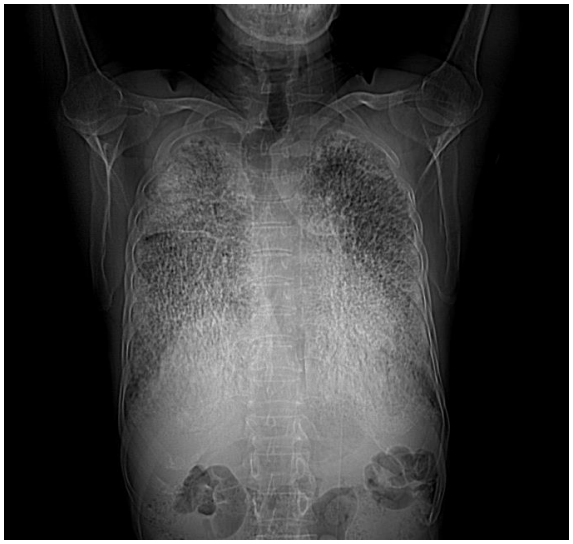

Figure 1: CT scout image showing classic "sand-storm" appearance, with a symmetric pattern of diffuse fine micronodules in both lungs with obscuration of the mediastinal, cardiac and diaphragmatic borders.

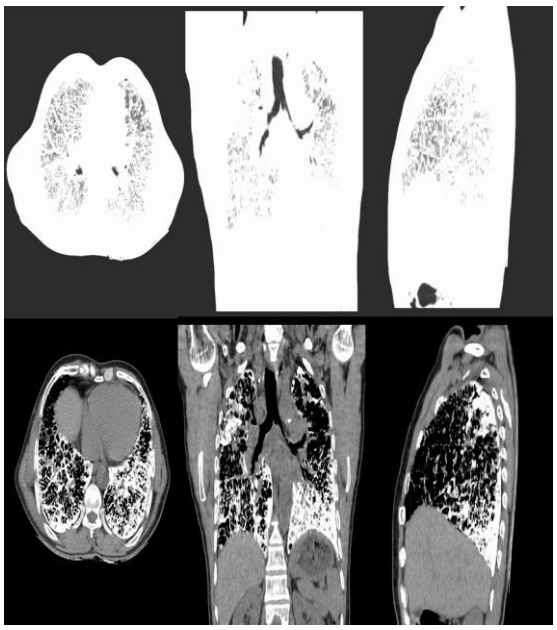

Figure 2: HRCT image lung window (upper row) and mediastinal window(lower row) in axial, coronal and saggital reformat showing widespread nodular intra-alveolar calcific density with diffuse ground-glass attenuation, calcifications along the interlobular septa, bronchovascular bundles and subpleural regions, more pronounced in lower and posterior pulmonary regions.

HRCT thorax [Figure 2] revealed widespread nodular intra-alveolar calcific density with diffuse ground-glass attenuation, calcifications along the interlobular septa, bronchovascular bundles and subpleural regions. The calcifications are most prominent in peripheral, mediastinal and fissural subpleural regions. Visualised bones are normal. CT Volume rendered (VR) image in transparent mode revealed the abnormality to best advantage [Figure 3]. Bronchoalveolar lavage fluid was negative for microliths. Patient did not opt for transbronchial biopsy. However based on characteristic HRCT findings with clinico-radiological dissociation, diagnosis of PAM was made.

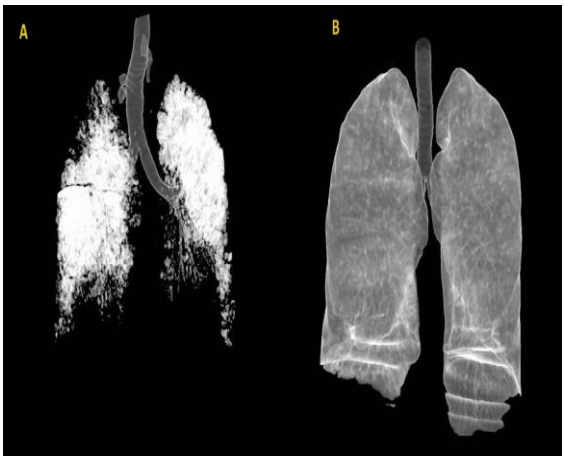

Figure 3: CT Volume rendered (VR) image in transparent mode of the patient (A) shows the extent of the microlithiasis. VR image in transparent mode of a healthy individual (B) is shown for comparison.

DISCUSSION

Pulmonary alveolar microlithiasis (PAM) (OMIM 265100) is a rare disorder characterised by widespread laminated calcospherites in the alveolar spaces in the absence of any known disorder of calcium metabolism. Most of the cases described in the literature were presented as case reports. In 1957, Sosman et al. published the first world review of 45 cases.[9] Three exhaustive reviews of world case series have been published, by Castellana and Lamorgese , who reported 424 cases up to 2001, by Mariotta et al. , who documented 576 cases up to January 2003 , and by Castellana G et al. who reviewed 1022 cases upto December 2014 which give insight to this disease.[3-5]
Though PAM is seen in all age groups, it is usually discovered from birth up to 40 yrs of
age with a mean age of 27-30 years at the time of diagnosis.[3,4,10-12] The youngest reported cases were premature twins and two newborns (an 8-month-old infant and an 18-month-old infant), while the most elderly was an 84-year-old female.[5] Patients may remain asymptomatic for many years and usually become symptomatic between the third and fourth

decades. Symptomatic patients present with dyspnoea, non-productive cough, chest pain and asthenia. Some patients have finger clubbing and pneumothorax in the advanced stages of the disease. In few patients the disease remain stationary in terms of both symptoms and of the radiological and functional findings, while in the majority it worsens over time leading to pulmonary fibrosis, respiratory failure and cor pulmonale.[3-5,10,13] The disease presents as both sporadic and familial cases, with familial cases accounting for 30–50% of the reported cases.[3,4,11,12]

High incidence of familial links, signifying the presence of a hereditary factor in pathogenesis of PAM was first described by Sosman et al. Both horizontal accumulation of the patients in a family and the presence of consanguineous marriages in the parents suggest that PAM is an autosomal recessive disease with a high penetrance.[5,9-11]

Recently, a few reports have described the role of mutation in the type IIb sodium-phosphate cotransporter gene (SCL34A2 gene) expressed in alveolar epithelial type II cells to be the cause of the disease. This gene is involved in phosphate homeostasis in several organs, including the lung. This protein transports the phosphorus ion from the alveolar space into the alveolar type II cells. Loss of function of the gene due to mutations may lead to a decreased cell uptake of phosphate, which in turn may lead to formation of intraalveolar microliths as a result of phosphate-chelating calcium in the extracellular fluid.[5,8,11]

One case with PAM has been reported by Olauson et al. where no disease-causing mutations or single nucleotide polymorphism were found in the SLC34A2 gene.[14] The authors suggested that PAM might be a polygenic disorder arising from mutations other than those in SLC34A2. Smoking accelerate the development of symptoms on PAM.[7,11]

Elevated serum concentrations of surfactant protein (SP)-A and SP-D have been found in PAM. As the disease progresses, serum levels of SPA and SP-D tend to rise, suggesting these to be useful serum markers in monitoring the disease activity and progression.[5,11, 15]

Since the SLC34A2 gene is also expressed in many extrapulmonary sites like the mammary glands, small intestine, kidneys, pancreas, ovaries, liver, testes, placenta and prostate ; this can explain systemic manifestation of disease in few patients.[16]

Of importance are microcalcification in testes (testicular microlithiasis), medullary nephrocalcinosis, nephrolithiasis, calcification of the lumbar sympathetic chain, seminal vesicles, epididymal and periurethral calcifications , pericardial calcification, gallstones, kidney stones and prostatic calcification.[5,9,11,17,18]

The main comorbidity associated with PAM is tuberculosis.[19] Other reported associated diseases include milk alkali syndrome, pericardial cyst, lymphocytic interstitial pneumonitis, diaphyseal aclasia, autosomal recessive Waardenburg-anophthalmia syndrome, hypertrophic pulmonary osteoarthropathy, pectus excavatum, rheumatoid arthritis, psoriasis, osteopetrosis, non-Hodgkin lymphoma, antiphospholipid syndrome and discoid lupus after Varicella zoster infection and Sjögren's syndrome.[11,20]

A striking feature is lack of significant symptoms despite extensive radiological changes (clinic-radiological dissociation). Chest radiographs usually reveal diffuse, bilateral areas of micronodular calcifications ("sand storm") that predominate in the middle and lower lung areas with obliteration of diaphragmatic, mediastinal, and cardiac borders. The HRCT is highly characteristic showing the extent of disease and helps in assessing the severity of disease. HRCT findings in decreasing order of frequency are diffuse ground-glass attenuation and subpleural linear calcifications (90%), small parenchymal nodules, nodular fissures, subpleural nodules, calcifications along the interlobular septa, dense consolidations, and subpleural cysts. Small thin-walled subpleural cysts are described as well, and they are responsible for the "black pleura" sign seen in the chest radiographs which refers to a zone of hyperlucency between the lung parenchyma and the ribs. It was first described by Felson. Paraseptal emphysema, air cysts in the upper lobes, as well as pneumothorax and areas of ossification are noted in advanced stage.[13,20-22]

A "crazy paving" or mosaic pattern on chest HRCT due to ground-glass opacities along with superimposed interlobular septal thickening and calcification is very specific for PAM.[23] (18) F-sodium fluoride PET/CT is a superior modality in characterization and assessment of the extent of disease in PAM compared to all other non-invasive imaging modalities.[24]

Dense consolidations with calcified nodules can also be found in tuberculosis, metastatic osteosarcoma, amyloidosis, silicoproteinosis, metastatic pulmonary calcification, talcosis and amiodarone lung toxicity and are differential diagnoses of PAM. But these patients have a variety of clinical manifestations unlike PAM.[25]

Broncho-alveolar lavage (BAL), trans-bronchial biopsy, open lung biopsy and autopsy are sometimes required to confirm the diagnosis. The characteristic periodic acid–Schiff-positive intraalveolar concentrically laminated (onion skin-like appearance) microliths in the lung tissue establish the diagnosis. Variable degrees of fibrosis are also noted in the lung interstitium. The microliths are 50 to 1000 μm in diameter and are mainly composed of calcium and phosphorus (phosphorus:calcium ratio of 1:2) with varying amounts of iron, magnesium, potassium and copper.[11,16,20]

There is no known effective treatment for PAM, with the exception of lung transplantation.[26]

Systemic corticosteroids, hydroxychloroquine, disodium etidronate and serial bronchopulmonary lavage[27] have been shown to be largely ineffective are used as palliative treatments. Only a few authors have reported on the beneficial effect of these drugs. In patients with respiratory failure and hypoxia, palliative treatment with oxygen improves subjective daytime function and oxygenation.[28]

CONCLUSION

Pulmonary alveolar microlithiasis is a rare autosomal recessive disorder associated with mutation of the SLC34A2 gene. The radiographic picture of PAM is highly characteristic. Confirmatory diagnosis is established by trans-bronchial or open lung biopsy revealing widespread laminated intraalveolar calcospherites. There is no specific treatment for PAM and the long-term prognosis is poor leading to respiratory failure, cor pulmonale and death. Most patients have minimal symptoms and are diagnosed incidentally on imaging. Novelty of our case is that he was diagnosed at 60 years of age. To the best of our knowledge from India, the most elderly reported case at diagnosis is a 55-years-old male.[29] It is hoped that new therapies to halt or slow the formation of microliths and interstitial lung disease will become available in the future.

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