A CASUAL RELATIONSHIP OR ASSOCIATION OF RARE PULMONARY DISORDER WITH DEAFNESS

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ABSTRACT
Pulmonary alveolar Microlithiasis (PAM) is a rare genetic disorder characterized by deposition of abnormal deposition of calcium in the alveoli. This results in the loss of surface area of alveolies for gas exchange leading to respiratory failure.

Key Words:
Pulmonary disorder; PAM; Pakistan

INTRODUCTION
Pulmonary alveolar Microlithiasis (PAM) is a rare genetic disorder characterized by deposition of abnormal deposition of calcium in the alveoli. This results in the loss of surface area of alveolies for gas exchange leading to respiratory failure. It was first described by Friederich in 1856. Upto 2014, there are only 1022 cases are reported. It is present throughout the world but it is more reported in Turkey and China. It has autosomal recessive pattern of inheritance, caused by mutation of the SLC34A2 gene encoding the type IIb sodium phosphate cotransporter in alveolar type II cells. Although radiology is sufficient to diagnose the condition but sometimes invasive investigations are required to make a diagnosis. PAM not only involves the lungs but also other organs, e.g. medullary nephrocalcinosis, pericardial calcification, gallstones, kidney stones and prostatic calcification.

This case report describes the condition in a young woman.

CASE REPORT
A 35 years old female from the rural areas of Kamoki, Punjab Pakistan, was referred to Gulab Devi chest hospital Lahore for evaluation of abnormalities on her chest x-ray. She is a non-smoker, non diabetic, non-hypertensive and house wife by profession. At that hospital, she presented with complains of progressive weakness of right side of the body for one hour. Her weakness improved spontaneously without any intervention during the stay in the emergency department. Her initial workup at that hospital showed abnormalities on chest x-ray which they were not sure whether it is tuberculosis or not. So they referred her to this hospital.

When evaluated regarding her chest symptoms, she has history of dry progressively increasing cough for seven years. Initially it is mild but now it is sometime severe enough to cause disturbance of her sleep. This cough occur through the day and night, partly relieved by cough supplements. During the hospital stay she coughed out sand like material which is whitish in color twice. There is no history of hemoptysis. There is history of progressive dyspnea for four years. Initially she could walk miles without any dyspnea but now she can only half a mile and had to stop to catch her breath. There is no history of orthopnea or paroxysmal nocturnal dyspnea. It is not associated with wheezing or chest tightness. There is no history of allergic rhinitis. She has a history of undocumentd low grade fever for four months.

Systemic inquiry reveal she has progressive loss of hearing for four months. She has more profound loss of hearing in right as compared to the left. There is no history of ear discharge, medication intake or exposure to loud sound in the past. Other systemic inquiry is unremarkable.

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She is married with five children, all are healthy and alive. Her both parents and brother and sisters are healthy and alive. There is no respiratory diseases, that are prevalent in the family.

Her general physical examination revealed she has pulse of 86/min, respiratory rate of 22/min, 120/80 mmHg of blood pressure and currently febrile. Her SpO₂ is 88% on room air. She has bilateral clubbing. Examination of chest reveal normal vesicular breathing with bilateral coarse crepts that change little with coughing. Examination of CNS is completely normal except for sensory neural hearing loss.

Her investigation revealed hemoglobin of 9gm/dl, TLC of 9.0/cmm and ESR of 40 mm/hr. Liver function tests, serum electrolytes, renal function tests, serum parathyroid hormone and vitamin D all are normal. Her serum calcium is 9.1mg/dl. Similarly her urinary calcium is also within normal limits. Her sputum pyogenic, AFB smear, culture & MTB-Rif and fungal culture revealed no growth. Her ABGs showed type 1 respiratory failure. Echocadography showed pulmonary hypertension with mean PASP of 56 mmHg. Her spirometry revealed restrictive type of defect. Her CXR showed increased calcifcarion bilateral more in basal region as compared to apices involving lung parenchyma.

Bronchoscopy guided transbronchial biopsy showed inflammatory cells with alveoli filled with calcified material, which are consistent with alveolar Microlithiasis.

**DIAGNOSIS**

Pulmonary alveolar Microlithiasis causing the sensori-neural deafness.

**DIFFERENTIAL DIAGNOSES**

Since PAM is idiopathic disorder, it should be differentiated from other causes of calcium deposition in tissue. The differential diagnosis includes infections (miliary TB, coccidiodomycosis, histoplasmosis, pneumocystis carinii pneumonia, CMV pneumonia and other disseminated viral infections) pneumoniais, lymphocytic interstitial pneumonia, haemosiderosis, pulmonary ossification, pulmonary blue bodies, tumour metastasis (e.g. thyroid carcinoma, lymphoma etc), sarcoidosis, pulmonary calcifications associated with chronic renal failure, amyloidosis and injection talcosis.

**DISCUSSION**

PAM is a rare disorder and in Pakistan it is even further less reported. Marriota and et al in 2004 presented series of 576 cases published in literature, which showed only two cases were reported from Pakistan.³ Up to 2015 only six caes were further reported from Pakistan, six were male and two were females.²

Most of the patient who are diagnosed remain asymptomatic and diagnosis is most often incidental. The exact epidemiology is largely unknown. There is no sex prediliction of the disease although some show a female predominence.² Similarly there is no specific age distribution. It been reported in new born to late ages.³

It has two types of inheritance. Many studies support the hypothesis of familial transmission as autosomal recessive.²⁴ Other reports as sporadic cases. In 2006 a PAM locus was first mapped at 4p15 and then by a candidate-gene approach SLC34A2 was identified as the gene responsible for the disease.³ It consists of 13 exons, the first of which is noncoding. The remaining exons code for a 690-amino acid protein, a type 2 phosphate transporter, which is expressed in several human tissues of epithelial origin. This gene causes a defective sodium phosphate-IIb transporter protein, and consequently, alveolar epithelial type II cells are no longer able to clear phosphorus ions, and calcium phosphate deposits (microliths) form in the extracellular fluid.³ In our patient screening of family showed that her eldest child, which is 20 year female,
has alveolar shadowing in lungs, but she refused further workup with HRCT.

Most of patients remain asymptomatic and diagnosis of often incidental.\textsuperscript{10-12} Children are often diagnose on the absis of stunted growth. Adults are diagnosed usually for routine checkup or for insurance purpose. Dyspnea is the most frequent symptom followed by cough, chest pain and asthenia.

SLC34A2 gene is also expressed inbody organs. It is expressed in mammary glands, small intestine, kidneys, pancreas, ovaries, liver, testes, placenta and prostate;\textsuperscript{10} this can explain the systemic involvement in PAM. We hypothesize that deafness in our patient is due to involvement of internal auditory apparatus resulting in deafness, as there is no such history or drug can be traced to cause the deafness.

**RADIOLOGY**

Giuseppe et al, recently published review of 1055 cases worldwide. In this he discussed the classification by Castellana G and et al, classified the PAM into four stages. These are actually four evolutionary stages that disease progresses. First is precalcific stage. It represents early stage. The lesions on CXR is difficult to define, as they are non calcific micronodules. This is predominantly described in children. The second phase shows the typical radiological picture. Lungs appear “sandy”, featuring diffuse, scattered calcific micronodules with a diameter of <1 mm. They have typically clearly outlined and bright, with a uniform size and distribution throughout the lungs. Calcification tends to be a greater concentration in the medial and inferior regions. Overall appearance resembles to that of sandpaper. Outlines of the heart and diaphragm are still clearly visible. As disease progress, the number and volume of the opacifications increases (third stage). Micronodules become more granular, more nodular and confused due to the initial thickening of the interstitial weave. This causes loss of vision of some micronodules. Heart and diaphragm borders are no more clearly visible. It is usually seen in adults. In last stage (fourth stage) the lungs become ‘white’. This is due to intense deposition of calcium in alveoli and surrounding pleural involvement. There may be some apical sparing. There may be parasetal emphysema along with cysts formation which may resemble pneumothorax. Pneumothorax may also be presenting feature of this stage. This is advanced stage and patients are older and usually symptomatic.

**TREATMENT**

PAM is an orphan lung disease so development of drugs to treat this condition is currently not under progress. Different authors try different drugs and procedure to sure or slow down the progression, but results are unsatisfactory. Some authors tried bronchoalveolar lavage, but no change in CXR or CT scan seen.\textsuperscript{17, 18} Other authors have tried to treat with sodium etidronate, but again results are not encouraging.\textsuperscript{19-22} There was no improvement in CXRs. Similarly use of corticosteroids have no effect in slowing or reversing the disease. Bisphophonates have been tried and with claim of some success, but considering small number of patients it is to early to comment any benefit from them.\textsuperscript{21, 25-26} Lung transplantation is only definitive option for patients with PAM. Both the single\textsuperscript{27}and double lung transplantation\textsuperscript{28-30} has been successfully performed in PAM. The longest living transplanted patient is a 63-year-old female.\textsuperscript{31} The longest survival for PAM treated by transplantation is 15 years without recurrence.\textsuperscript{32} Double lung transplantation is preferred over single transplant, for fear of carrying of microlith from disease side to normal transplanted side by blood or by air way communication. However, so far in transplanted lung there is no recurrence of the disease.

**CONCLUSION**

In our case report we suggest that the loss of hearing is due to the PAM, probably by involving the chochlear apparatus, as there is no cause identified for the loss of hearing. Considering the multi system involvement, this is quite possible. We suggest further studies to confirm or negate this hypothesis.

**REFERENCES:**


