TREATMENT OF PULMONARY ALVEOLAR MICROLITHIASIS WITH ALLENDRONATE SODIUM

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Pulmonary alveolar microlithiasis (PAM) is a rare disorder with only about 200 cases having been BEEN reporting worldwide. No effective treatment has been evolved as yet and the disease is fatal. Allendronate Sodium has been reported to be effective in some cases. However each dosage, duration of treatment and clinical parameters in evaluating the patient response are not specifically given in available literature. Aims and objectives of the current study were to see the effect of allendronate sodium on the treatment of PAM. This is a prospective interventional study. Cases reporting to Medical OPD with symptoms of PAM were selected for study. Patients with shortness of breath, blue discoloration of lips and failure to thrive since childhood were included in the study. Twelve cases were initially short-listed with the suspician of PAM based on history, clinical examination and preliminary investigations including X-Ray chest. They were subjected to lung biopsy, CT scan and pulmonary function tests. Cases finally diagnosed as pulmonary alveolar microlithiasis were subjected to one year treatment with Allendronate Sodium. They had significant improvement clinically as well as in pulmonary function tests. However, there is no improvement in X-Ray of the chest.

INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is a rare disease, which is remarkable for a number of unusual if not unique features. There is probably a defect in calcium metabolism confined to the lungs which is characterized by the presence of calcific concretions composed of Hydroxyapatite in the alveolar spaces. Tiny 0.2- 0.5 mm calcified concretions, which may be concentrically laminated are found progressively in the alveolar spaces[1]. They produce a striking and truly unique appearance on chest radiograph. Pulmonary interstitium is usually not involved except perhaps late in the disease. Although a defect in the calcium metabolism is suspected, no specific abnormality in the calcium metabolism has been identified. A disproportionate number of cases occur in siblings which possibly points to a genetic rather than environmental basis.

PAM was first reported by Harbitz in 1918[2]. Up till now over 200 cases have been reported world-wide in medical literature.[3] The age of presentation is variable and whole age spectrum may be involved but there is some evidence that women are involved more than men in familial cases[4]. Peak incidence in western countries is 30-50 years but in Japan it is 4-9 years.

The patients are usually asymptomatic initially. They are usually diagnosed when an initial film is taken for incidental reasons. Patients eventually develop dyspnoea on exertion that limits their physical activity. Physical signs are conspicuous by their absence for most of its long course, though crackles, clubbing, cyanosis and signs of respiratory failure may be observed ultimately. Eventually respiratory failure and cor pulmonale supervene. Survival of 10-20 years is characteristic.

Plain X-Ray chest reveals fine sand like micro-nodulations (< 1 mm) involving both lungs diffusely and may appear confluent in areas (producing ground glass opacity). There is a predominant symmetric middle and lower lobe involvement. The borders of heart and diaphragm

are obliterated. The major finding on chest radiograph is ground glass opacification.[5]

On Computerized Tomography (CT) Scan there is a gradient in the distribution of the calcification which tends to cluster in posterior and inferior sub-pleural spaces and along the branches of vascular bundles. Calcific nodules larger than 1 mm are visible on high resolution computrized tomography (HRCT) image.[6]

In scintigraphy there is intense pulmonary uptake of radio-tracer on TcMDP bone scan. A chest radiograph is all that is needed for the diagnosis but confirmation with CT scan, scintigraphy and trans-bronchial lung biopsy can be done. No specific therapy is known to be effective. However allendronate may be effective in some patients.[7]

Aims and objectives of the current study were to see the effects of treatment of PAM with allendronate sodium.

SUBJECTS AND MEHTODS

Cases reporting to a medical OPD with symptoms of PAM were selected for study.

Patients with shortness of breath, blue discoloration of lips, failure to thrive since childhood and underweight were included in the study. Patients showing positive response to anti tuberculous treatment (ATT), antibiotics and having evidence of malignancy were excluded from the study.

History including family and treatment history was taken from the patients. General physical and systemic examination was performed. Respiratoy system was especially examined in detail. Cases with pulmonary calcification and having suspician of PAM were resorted to CT scan, lung biopsy and pulmonary function tests before the start of the treatment. Positive cases for PAM were put on one year treatment of allendronate sodium (Osteopar 10mg 1 tablet/day). Clinical response, X- Ray chest and pulmonary function tests were repeated to see the effect of treating PAM with allendronate Sodium.

RESULTS

Twelve symptomatic cases with calcific spots on X-Ray chest were isolated with the suspician of PAM. CT scan and lung biopsy were performed on these cases. Two sisters of the same family were finally diagnosed as PAM on the basis of blood CP, X-Ray chest, pulmonary function tests, lung biopsy and CT scan. Both the cases had the past history of ATT and multiple courses of antibiotics.

Elder sister (patient 1) aged 18 years had haemoglobin (Hb) of 13 g/dL, total leucocyte count (TLC) was 5.9 x 10^9/L (neutrophils: 57%, lymphocytes: 38%, eosinophils: 3%, monocytes: 2%), erythrocyte sedimentation rate (ESR): was 42 mm fall at the end of first hour. Younger sister (Pateint 2) had Hb 11.6 g/dL, TLC 11 x 10^9/L, while ESR was 24 mm fall at the end of first hour. Urine routine examination, serum calcium, liver and renal function tests were normal. Blood gases did not show CO_2 retention. X- Ray chest report stated "High radio-opaque small opacities are seen in both lungs masking normal lung fields".

Pulmonary function tests of both the patients revealed a restrictive pattern as shown in fig 1.

Fig 1: Pulmonary function tests of PAM cases before the start of treatment.

Pulmonary Function Test	Pateint 1	Pateint 2
Vital capacity (VC)	48%	39%
Forced vital capacity (FVC)	44%	41%
Forced expiratory volume in first second (FEV1)	50%	43%
FEVI/VC	79%	69%

Review of the past investigations of patient 1 revealed an X-Ray chest done in 1995. It showed "coarse reticulo-nodular shadowing seen in both lung fields, all zones (Collagen disease/ fibrosing alveolitis"). Another X-Ray chest in 1992 was reported as miliary mottling. A lung biopsy was performed in 1992 and histopathogy reports were obtained. Lung biopsy of pateint 1 was from the laboratory of Pakistan Institute of Medical Sciences. It showed that alveoli are of normal size and there is no significant inflammation. Focal areas show presence of recent intra-alveolar haemorrhage and pulmonary oedema. There are numerous well circumscribed calcified areas. No granuloma or malignancy seen. Focal areas show the presence of non-specific chronic inflammation adjacent to pleura." The diagnosis was calcification, most likely metastatic.

The report of the patient 2 was from Armed Forces Institute of Pathology, Rawalpindi. It stated, that composed of a fragment of lung tissue. There are areas of laminated calcified nodules within the alveolar spaces. They are positive with Von Kossa stain (calcium). The remaining lung parenchyma is within normal limits. No evidence of tuberculosis could be seen," opinion: was pulmonary alveolar microlithiasis.

Pateint 2 had one X-Ray chest which was reported as miliary mottling but it appeared similar in finding to that of patient 1. Considering their history, examination and serial investigations over a period of 10 years and also comparing the X- Ray films of the two sisters, final diagnosis of PAM was made in them.

The patients were treated with Allendronate Sodium (Tab Osteopar 10 mg), which they tolerated well. They received treatment for one year. Their stamina improved and there was no shortness of breath on exertion. The cyanosis had disappeared and they look much healthier. They gained weight by up to two kg but the chest radiographs did not show any change. There was improvement in pulmonary functions after one year's treatment with Allendronate Sodium as shown in the table 2.

Table 2: Pulmonary function tests of PAM patients after the treatment.

Pulmonary function tests	Patient 1	Patient 2
FVC	61%	56%
FEV1	63%	59%
FEVI/VC	93%	89%

Symptomatology of these patients was markedly improved. Cyanosis has been cleared with the treatment and there is no dyspnoea on exertion after the treatment. However there is no change in pulmonary calcification on X-Ray chest.

DISCUSSION

PAM is a defect in calcium metabolism confined to the lungs. It is characterized by the presence of calcific concretions composed of hydroxyapatite in the alveolar spaces. Pulmonary interstitium is usually not involved, except perhaps late in the disease. The chest radiograph is characteristic and may even allow diagnosis without the aid of other investigations.[8] The diagnosis in these patients was, in fact suspected based solely on chest radiographic abnormalities. Bone scan or trans-bronchial lung biopsy are useful in confirming the diagnosis.[9] The disorder is slowly progressive and there is no definite therapy.[10] So far no reversible treatment of this disorder is known. It has been proposed that a combined heart/lung transplant might be the possible way to prolong the life of the patients. Diphosphonates have been used to inhibit the microcrystal growth formation.[11, 12]

Pulmonary functions have been studied in a few patients with this disorder, and are usually normal or only slightly impaired for a long period following diagnosis. A restrictive ventilatory defect (also seen in our patients) and diminished diffusing capacity are the most frequently reported abnormalities. This is largely related to alveolar filling. But there is hardly any information on the physiological assessment of alveolar involvement.[13]

Exponential analysis of pressure-volume data has been reported to adequately describe the nonlinear static lung mechanics over a wide range of lung volumes. The shape constant of this curve (K), the single most important variable describing this curve, is an index of lung compliance. Unlike compliance, it is largely independent of ethnicity, patient effort and lung size. Exponential analysis also helps to differentiate restriction due to reduced elastic properties (low value for K) from that due to loss of lung volume (normal K). Also, in the former situation, lungs can theoretically achieve a normal maximal volume if a supranormal distending force is applied, hence maximum lung volume (Vmax) is close to predicted total lung capacity (TLC). In contrast, Vmax is decreased in the latter case. In our patients, K was nearly normal and Vmax was only marginally greater than the observed TLC. This indicates absence of any significant interstitial involvement in our patients; diminished compliance was related to loss of alveoli. In fact, this also correlates well with the pathology observed microscopically in this disease, in which the alveoli are filled with calcific material and the interstitium is largely spared.[14]

Most patients are asymptomatic on presentation. There is a striking contrast between the paucity of signs and symptoms and the marked radiographic features. The initial symptoms are dyspnea on exertion and a nonproductive cough. Auscultation may reveal diminished breath sounds and fine inspiratory crackles. Subsequently, they may develop respiratory failure with cyanosis and signs of right ventricular failure.

In addition to the chest radiograph, other methods can be used to establish the diagnosis of PAM. Surprisingly, microliths in the sputum and BAL are not diagnostic, because patients with COPD and tuberculosis expectorate microliths as well. CT and the ^{99m}Tc diphosphonate scan have been used to confirm diffuse calcifications in PAM. CT scan of the chest reveals a diffuse infiltrative pattern, and the ^{99m}Tc diphosphonate scan reveals increased uptake of the isotope throughout both lungs.[15]

CONCLUSION

PAM is a rare cause of bilateral pulmonary infiltrates and should be considered in the differential diagnosis. The most common findings are calcific nodules on X-Ray chest and decreased vital and total lung capacity. There is no specific treatment of PAM. Allendronate sodium has provided symptomatic relief in our patients but has not reversed the X-Ray findings. Corticosteroids and broncho-pulmonary lavage has no effect. More research is required to discover an absolute cure of this life threatening disorder. Lung transplantation may be tried in selected cases. Patients should be counseled about prevention from dust, fumes and smoking. Yearly influenza vaccine and immunization to measles, pertussis and tuberculosis should be completed.[16]

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