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Case series of rare Interstitial Lung Disease (ILD).

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare lung disease where periodic acid Schiff (PAS)-positive eosinophilic material accumulates in the alveoli of the lungs. Here we describe two cases of young males who presented with dynpnoea and weight loss. The HRCT scan of the chest in both cases showed the typical "crazy-paving" pattern and lung biopsies confirmed the diagnosis of PAP. They showed remarkable symptomatic improvement with therapeutic whole lung lavage.

Keywords: Pulmonary Alveolar Proteinosis, Dyspnea, Whole Lung Lavage.

Introduction

Pulmonary Alveolar Proteinosis (PAP) was first described in 1958 as a disease of the lung that consists of the filling of the alveoli by a PAS-positive proteinaceous material rich in lipid.[1] It is a rare disease with the incidence of one case in every two million people. It is predominately found in males with a male to female ratio of 3:1.[2]

PAP is subcategorized into three types; congenital, secondary and acquired.Congenital PAP is related to mutations in the genes for surfactant and/or GM-CSF receptor. Acquired PAP is due to autoimmune production of anti-GM-CSF antibodies. Secondary PAP is attributable to multiple underlying conditions like infections, pneumoconioses, haematologic malignancies, immunodeficiency and autoimmune disorders. The disease process leads to accumulation of the lipoproteinaceous substances in the alveoli which compromise the gaseous exchange in the lungs.[3,4]

The disease presents with a wide array of symptoms but may be asymptomatic. Symptoms may include persistent dry cough, progressive dyspnoea, generalized weakness, malaise, weight loss, intermittent low-grade fever, pleuritic chest pain and rarely cyanosis and haemoptysis.[5]

A typical radiological picture of PAP on HRCT scan of the chest shows bilateral, patchy perihilar and infrahilar idiosyncratic ground-glass opacities with sparing of the lung periphery. This pattern is identified as crazy-paving pattern.[6] Positive findings on both HRCT and BAL (brochoalveolar lavage) studies provide a high diagnostic accuracy. A transbronchial or surgical lung biopsy is the definitive diagnostic test for PAP.[3]

Case Presentations

Case 1

A nineteen-year old male, non-smoker, presented to the pulmonology clinic in February 2014 with a one and half-year history of dyspnoea on exertion and right sided chest pain. He reported one episode of haemoptysis and a significant weight loss of 15 kg over the past year. There was no history of cough, orthopnoea, fever, night sweats or cyanosis.

He was treated for probable tuberculosis for 9 months, although the sputum studies were negative for acid fast bacilli. There was no significant family history. He was a

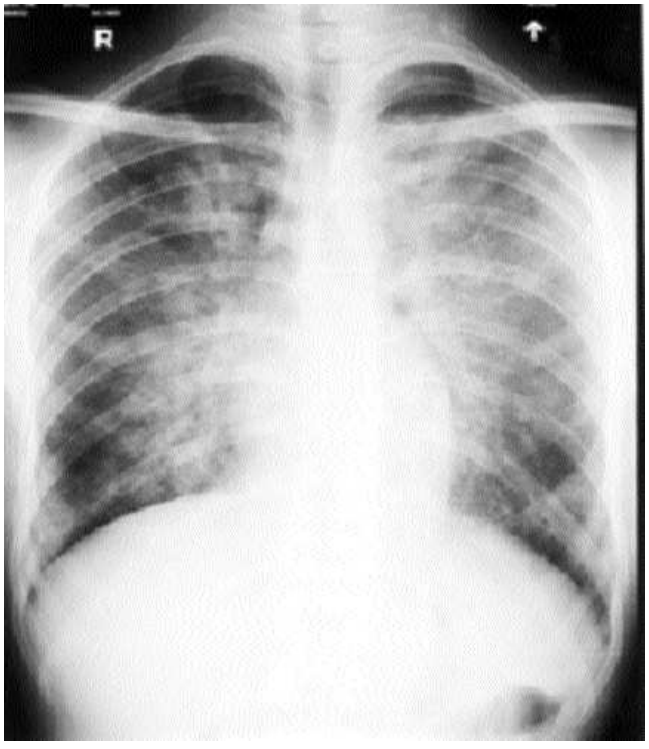

Figure-1: Chest radiograph of Case 1 shows bilateral interstitial lung infiltrates in a "bat-wing" pattern.

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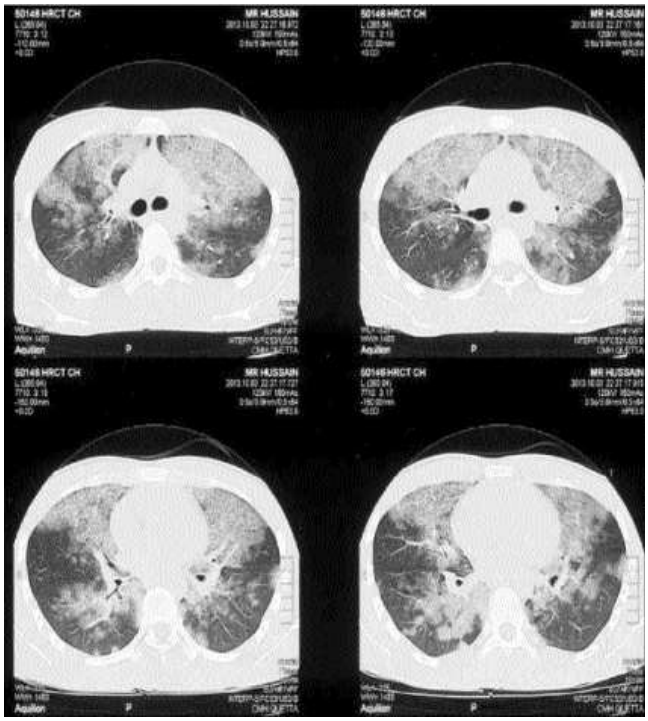

Figure-2: Chest HRCT of Case 1 shows extensive areas of ground glass opacities with interlobular septa thickening.

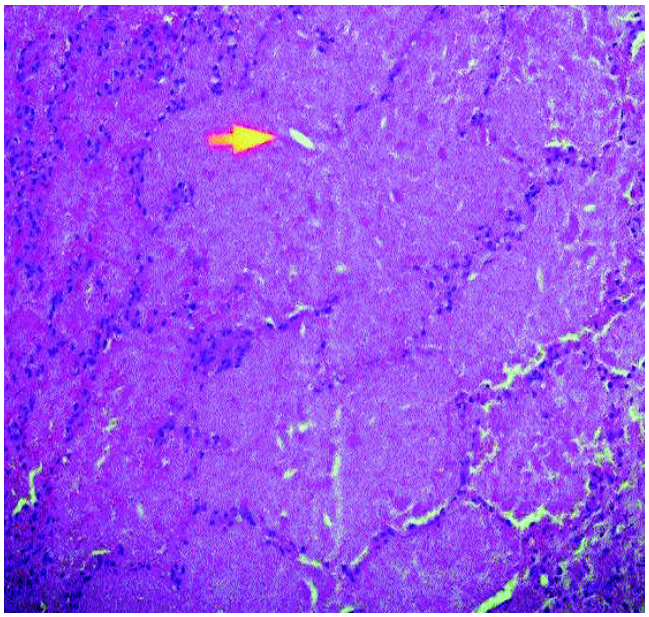

Figure-3: Histological section from open lung biopsy of Case 1: Alveolar Lipoproteinosis; The alveoli are filled with finely granular material with a cholesterol cleft (arrow) 20x10; Haematoxylin and Eosin stain.

tailor by profession. There was no history of drug allergies or illicit drug use.

Clinically he appeared comfortable. His general physical examination and vital signs were within normal limits. On chest examination, maculopapular blanching rash was noted over the posterior chest and fine end-inspiratory crackles were heard on the posterior lower one-third of the chest. The rest of the physical examination was within normal limits.

The lab tests including complete blood counts, HIV screening and autoimmune workup was normal. The chest x-ray showed bilateral perihilar infiltrates (Figure-1). A high-resolution computed tomography scan showed characteristic areas of patchy ground-glass opacifications with interlobular septal thickening and intralobular reticular thickening (Figure-2).

The broncho-alveolar lavage [BAL] was negative for gram-stain and acid-fast bacilli and few macrophages were seen on cytology. A transbronchial lung biopsy revealed focal histiocytes which highlighted with CD 68 immunostain, with surrounding haemorrhage. An open lung biopsy was performed for confirmation of the diagnosis (Figure-3). The histopathology revealed lung tissue exhibiting variable sized lung alveoli containing amorphous eosinophilic material. Some of the alveoli also showed foamy histiocytes, hemorrhage and cholesterol clefts. The diagnosis of PAP was made. He underwent therapeutic alveolar lavage with 12 liters of normal saline in each lung. On follow up visit the patient had improved significantly and dyspnoea had almost completely resolved.

Case 2

A 24 year old male, non-smoker was referred to our hospital from Defense Military Hospital in Bahrain in October 2014. He presented with a 5 month history of dyspnoea and undocumented weight loss. The HRCT scan of the chest showed the classic "crazy paving" pattern (Figure-4) and he was diagnosed to have PAP on a transbronchial lung biopsy. Autoimmune markers and HIV testing were negative.

He received several courses of Prednisolone for over 5 months with dosages ranging between 40-60 mg per day and had progressively developed the need for supplementary oxygen over the past year. He was now on ambulatory oxygen of 2 liters per hour and had also developed polycythemia. He had no significant past medical or family history. There was no history of drug allergies or illicit drug use.

He was in respiratory distress with a respiratory rate of 28 breaths per minute and oxygen saturation of 88% on 2 liters of oxygen per minute. He was using his accessory

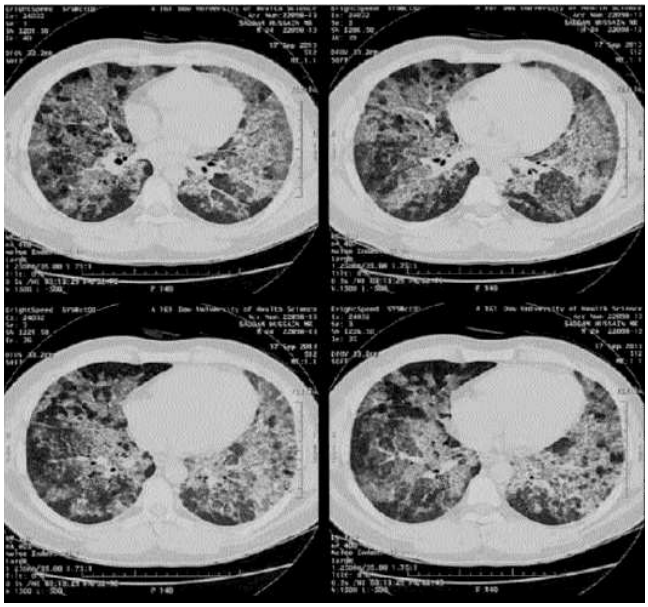

Figure-4: Chest HRCT scans of Case 2: These images show a symmetric combination of extensive ground-glass opacities and interlobular septa thickening in posterior areas of the lungs.

Figure-5: Whole Lung Lavage washouts of case 2. The image displays the fluid aspirate in the series of lung lavages from a patient with PAP.

muscles of respiration and had a pulse of 110 beats per minute. Rest of the general physical examination was normal. On chest auscultation there were decreased breath sounds bilaterally and mid-inspiratory crackles were present across both the lung fields. The cardiovascular, abdominal and CNS examinations were unremarkable.

He underwent therapeutic lung lavage with 11 Liters in the right lung and 18 liters in the left lung (Figure-5). His condition improved significantly upon discharge and on follow up he had oxygen saturation of 98% on room air.

Discussion

PAP has a variable presentation and disease course. The chest radiographs are usually non-specific and showed prominent interstitial infiltrates in our patients. The HRCT revealed the classic "crazy paving" pattern in our patients.

In the presence of hypoxia or respiratory distress as was the case with both our patients the treatment of choice is a whole lung lavage with a double-lumen endotracheal tube.[7] It was performed under general anaesthesia and before the lavage was started 100% oxygen was used for ventilation. The solution used was isotonic sodium chloride; which is considered the ideal choice of fluid in all cases of PAP. The amount of solution used for whole lung lavage is dependent on the series of washouts. A clear lavage is indicative of a successful washout (Figure-5). We used 12-20 liters per lung but up to 50 liters of fluid per lung can be used safely for the lavage. Both the lungs were lavaged 24 hours apart in our patients.

The outcome of our patients was excellent, as it usually is for primary PAP. Our first case showed complete remission and resolution of symptoms following whole lung lavage, while the second case showed dramatic improvement in symptoms and was weaned off the oxygen.

Although there is a lack of randomized controlled clinical studies, evidence shows that response rates are around 60%, less than 15% cases require lavage every 6 months and less than 10% of cases fail to respond.[7] Research also suggests that patients who require repeat lavages usually have progression to pulmonary fibrosis.[7] This treatment modality however is both time-intensive and requires technical skills.

A relatively novel approach of using GM-CSF therapy in the treatment of pulmonary alveolar proteinosis in humans is being studied after murine studies showed resolution of a PAP-like syndrome in mice with GM-CSF deficiency on administration of local GM-CSF therapy.[8] However up till now only a few human cases have been reported in literature to have shown response to this treatment.[9] The exact mechanism of action of this therapy is yet to be determined and proper treatment guidelines need to be established.

Conclusion

PAP is a rare disorder which is usually seen in young otherwise healthy patients. This condition may present with a spectrum of symptoms and can be a diagnostic challenge. It is imperative to determine which patients require extensive workup including diagnostic tools such as HRCT and open lung biopsy which is considered the gold standard for diagnosis.

Treatment options are limited. Whole lung lavage has produced excellent results, with most patients experiencing almost complete remission post lavage.

Further evidence is required to establish GM-CSF as an alternative or an adjunct to whole lung lavage in the treatment of PAP.

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Conflict of Interest: None.

Funding Disclosure: None.

Ethical Review: Exempted.

Informed Consent: Verbal consent was obtained from both patients.

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