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Case Report

Atypical pulmonary alveolar proteinosis - A diagnostic challenge

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare syndrome, characterized by ground-glass opacities associated with reticulations giving a characteristic crazy paving appearance which is diagnostic but not pathognomonic in imaging. A 47-year-old male presented with breathlessness and dry cough. Arterial blood gas (ABG) showed hypoxemia and respiratory alkalosis with Alveolar- arterial (A-a) O_2 gradient of 82. HRCT thorax suggestive of crazy paving pattern along with solitary nodules of low density in right upper and lower lobes giving suspicion of malignancy with secondary PAP. The clinical probability of malignancy was moderate hence surgical lung biopsy was performed which suggested PAP. Granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody concentration was 118.7mcg/ml suggestive of autoimmune PAP. Patient was treated with inhalational GM-CSF with significant clinical response ((A-a) O_2 gradient improved to 24). Though crazy paving is characteristic for PAP, speculated low density atypical multi nodular appearance may also be possible which mandates biopsy for confirmation.

1. Introduction

Pulmonary alveolar proteinosis (PAP) is a rare syndrome, characterized by the accumulation and lack of resorption of surfactant in the air spaces. Ground-glass opacities associated with reticulations giving a characteristic crazy paving appearance is diagnostic but not pathognomonic in imaging. We describe auto immune pulmonary alveolar proteinosis presented in nodular form which was mimicking secondary pap with underlying malignancy. To our knowledge, nodular pap was reported very less in literature.

2. Case Details

47-year-old non-smoker, non-alcoholic male presented with breathlessness on exertion and dry cough for one month. Arterial blood gas (ABG) showed pH-7.47 with pCO_2-30 mmHg and PO_2-82 mmHg (FiO_2-30%), suggestive of hypoxemia and respiratory alkalosis with Alveolar- arterial (A-a) O_2 gradient of 82.

All routine blood investigations, HIV, HbsAg, HCV Serology, bacterial and fungal cultures were normal. High-resolution CT (HRCT) suggestive of bilateral ground-glass opacities with superimposed smooth interlobular and intralobular septal thickening suggestive of crazy paving pattern along with upper, lower lobe solitary nodules which were irregular in contour with spiculations, about 1.06 centimetres and 1.47cm low density with an average attenuation value of 15–60 HU [Figure-1A and 1B]. There was no associated effusion or lymphadenopathy. Due to the appearance of the lesions, malignancy with secondary PAP was suspected. Fiber optic Bronchoscopy (FOB) could not be performed because of hypoxemia. Initial trans thoracic needle biopsy from the lower lobe nodule was inconclusive. The clinical probability of malignancy based on a prediction model described in the British Thoracic Society Guidelines for the Investigation and Management of Pulmonary

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Nodule (Brock University cancer prediction equation) was 17.50, hence surgical lung biopsy was performed to establish the diagnosis.[1] Granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody concentration assay was done at Translational Pulmonary Science Center Laboratory, Cincinnati Ohio, USA [Courtesy: Dr. Bruce C. Trapnell; supported in part by National Heart, Lung and Blood Institute grant HL985453] using enzyme-linked immunosorbent assay. Spirometry (though poorly performed because of poor efforts) showed FEV1/FVC 75%; FEV1 59%; FVC 67%; and diffusing capacity for carbon monoxide (DLCO)62% suggestive of moderate restrictive lung disease. Histopathology of the resected specimen showed alveolar lumen filled with amorphous, homogenous, granular, eosinophilic material which is Periodic-acid–Schiff (PAS) positive which were consistent with PAP [Figure-2]. GM-CSF autoantibody concentration was 118.7mcg/ml (Normal-<3.1mcg/ml)], suggestive of Auto-immune Pulmonary Alveolar Proteinosis.

As patient was not giving consent for whole lung lavage (WLL), patient was treated with inhalational GM-CSF (dose of 125μg, twice daily for one week followed by one-week drug free interval for 12 weeks) and supportive measures.[2] Patient showed significant clinical improvement ((A-a) O_2 gradient of 24) during the treatment and lost follow up because of logistical reasons to evaluate further outcome.

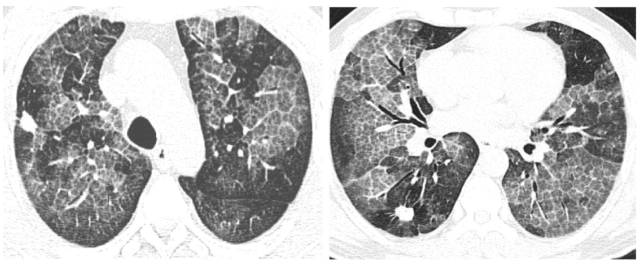

Fig. 1: Chest computed tomography scan showing bilateral crazy paving pattern and upper lobe 1.06 cm (1A) and lower lobe 1.47cm (1B) irregular contour nodules

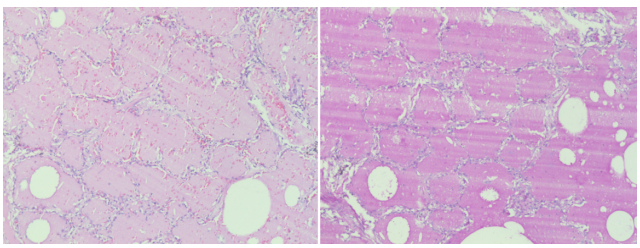

Fig. 2: Histopathological examination of lung nodule showed dilated alveolar spaces were filled with granular eosinophilic material (A) which was positive for periodic acid-Schiff (PAS) stain (B).

3. Discussion

PAP usually results from failure of surfactant clearance by macrophages in the alveolar air spaces. The commonest cause of PAP is autoimmune (90% of cases) relevant to the presence of anti-GM-CSF. HRCT scan with symmetrical, diffuse, or predominantly basal characteristic crazy paving appearance is essential to the diagnosis but not pathognomonic.[3,4] Asymmetrical or predominantly apical forms are rare and are described very less in literature.[3]

Atypical forms of pap are reported in the form of solitary nodule (1.0cm) by Nosaka et al., in 2011.[5] Seon et al., in 2014 described pap presenting as unilateral "crazy paving" type and solitary nodule type (1.2 cm).[6] Mediastinal lymphadenopathy is possible in cases of complications (infections) or another associated lesion. Multinodular form of PAP is very rare and reported less.[7] Our case presented with crazypaving pattern with two nodules, one in upper and one in lower lobe of right lung which is not classical in PAP.

Flexible bronchoscopy with BAL showing opaque or milky appearance and, when possible, TBLB is a key step in the diagnosis of PAP.[8,9] Diagnosis can be made by surgical lung biopsy where FOB is not possible and risky like our case.[9] Surgical lung biopsy is usually considered as the gold standard for the diagnosis of PAP. Due to non-conclusive evidence from HRCT, BAL, and TBLB, 10-20% of patients has to undergo surgical lung biopsy to establish the diagnosis. Since our patient is in hypoxemia and having moderate clinical probability of malignancy based on Brock University cancer prediction equation, surgical biopsy was performed for the diagnosis and biopsy features was consistent with PAP.

As the patient did not have any evidence of secondary causes of pap, measurement of serum anti-GM-CSF antibody titer was done, which is 100% sensitive and 91-98% specific for the diagnosis of autoimmune PAP and the titer levels were suggestive of auto immune pap.[10] Serial measurements of BAL or serum anti-GM-CSF antibodies proven to be useful in monitoring disease activity and response to treatment.[11] In some special situations where HRCT thorax and BAL findings were suggestive of PAP, but do not have serum antibodies to GM-CSF, abnormal GM-CSF receptor function and signaling analysis can be done.

The choice of treatment depends upon the severity of disease and risk benefit balance. Asymptomatic PAP patients would most likely to have spontaneous remission.[9,12] Patients who have moderate to severe disease are the candidates for WLL which is most widely accepted and effective form of treatment. If there is progression despite of WLL recombinant nebulized recombinant GM-CSF (sargramostim) can be given which improves lung function and PaO2 by facilitating clearance of the GM-CSF-antibody complex[2]. Supportive therapy in the form of vaccination against influenza, pneumococcal pneumonia and supplemental oxygen to be provided. Patients should

also be advised not to smoke cigarettes as patients with cigarettes smoking require twice as many sessions of WLL as nonsmokers.[12]

In our case, patient did not give the consent for WLL, he was treated with inhalational GM-CSF along with other supportive measures with significant clinical improvement.

4. Conclusions

Although crazy paving is the characteristic radiological appearance of PAP, speculated low density, non-enhancing multi nodular appearance may also be possible in some cases. Open lung biopsy, if transthoracic sampling is not possible or inconclusive along with histopathological confirmation is essential in such atypical presentations for confirmation of the diagnosis.

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7. Conflict of Interest

The authors declare they have no conflict of interest.

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