Lung Adenocarcinoma Presenting as Diffuse Alveolar Haemorrhage in a Young Adult

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Abstract: Diffuse Alveolar Haemorrhage (DAH), a potentially life threatening condition is associated with a number of clinical entities. It has been associated with various immune and non immune conditions but its association with primary lung malignancy has rarely been described. We report a case of a 25 year old male with adenocarcinoma of the lung presenting as DAH. To our knowledge this is the first case reported of its kind. A classification of DAH associated with malignancy is also proposed.

Keywords: Diffuse alveolar haemorrhage, lung adenocarcinoma, malignancy, young adult

Key Messages: Always consider malignancy whether primary or secondary as a differential diagnosis in all cases of haemoptysis and specially DAH.

1. Introduction

Diffuse alveolar haemorrhage (DAH) is a rare and potentially life threatening condition characterized by bleeding from the pulmonary microcirculation (pulmonary arterioles, alveolar capillaries and pulmonary venules) as a result of microvascular damage leading to extravasation of blood into the alveolar spaces. It is syndrome characterized by haemoptysis, anaemia, hypoxemic respiratory failure and diffuse pulmonary infiltrates on chest radiography. The diagnosis requires confirmation of the alveolar haemorrhage by bronchoscopy in which serial bronchoalveolar lavage samples reveal persistently hemorrhagic fluid.1,2,3 DAH is associated with a number of clinical entities and several histological subtypes of which pulmonary capillaritis is the most common. It has various immune and non-immune aetiologies but has been rarely been described as presenting feature of primary lung malignancy. We report a case of a young adult with adenocarcinoma of lung presenting as DAH.

2. Case History

25 year old male, construction site supervisor, presented to our centre with haemoptysis around 20cc per day since two months. He also gave history of dyspnea on exertion grade two (mMRC), subjective sensation of low grade fever, and loss of weight of four kgs in two months. He was a non smoker and had no significant past history. In view of haemoptysis and radiological changes, patient was started on anti tuberculosis treatment by his family physician as smear negative pulmonary tuberculosis. Patient was referred to higher centre in view of no response.

On presentation patient was in respiratory distress. He also had pallor and clubbing. Breath sounds were bilateral and equal, with bilateral coarse mid inspiratory crepitations throughout both lung fields. Rest of the systemic examination was normal and there was no clinical evidence of malignancy, vasculitis or connective tissue disorder elsewhere in the body. There was no history of exposure to toxic fumes or drugs. His haemoglobin had dropped from 15.4gm% to 5.3 gm% over the last two months. His total and differential leucocyte counts and coagulation profile were normal. Immunological investigations like ANA (anti-nuclear antibody), anti dsDNA (anti-double stranded DNA antibody), and ANCA (anti neutrophilic cytoplasmic antibody) and anti GBM (glomerular basement membrane) antibodies were negative. His routine urine, renal and liver function tests, ECG and echocardiography examination were normal. Ultrasonography of the abdomen and pelvis did not reveal any abnormality. His room air PaO2 was 64mmHg which did not show any improvement on supplementation of oxygen.

Chest X ray (Figure 1) revealed bilateral diffuse pulmonary infiltrates with haziness in left lower zone.

Figure 1
HRCT Chest (Figure 2a) was suggestive of diffuse ground glass opacities in bilateral lower lobes with consolidation in left lower lobe. Figure (2b) shows ground glass opacities in both upper lobes.

In this particular case, considering the young age and no significant history of drugs or toxin exposure, a working diagnosis of immune related DAH was considered. The patient was started on haemostatics, oxygen supplementation and intravenous pulse methylprednisolone awaiting the serological reports. However his haemoptysis continued. Bronchial artery embolisation was also unsuccessful. A diagnostic bronchoscopy was undertaken to localise the cause of bleeding, to rule out any endobronchial lesion and to confirm the diagnosis of diffuse alveolar haemorrhage. Bronchoscopy revealed fresh bleeding from right upper, right lower and left lower lobe bronchus with persistent bleeding on serial aliquots (Figure 3) and showed presence of haemosiderin laden macrophages on Prussian blue staining.

Bronchial washings were negative for infection in form of acid fast bacilli (AFB), pn eumocystis jiroveci cysts, aerobic and fungal cultures. The bronchial wash cytology and post bronchoscopy sputum showed d p resence of malignant cell is suggestive of ade ncarcinoma, however further categorisation of the type could not be made on cytology. On c onfirmation of malignancy, patient was referred to thoracic oncology for further management, where unfortunately he had a rapid fatal course and histopathological diagnosis was not possible.

3. Discussion

Diffuse alveolar haemorrhage (DAH) is a rare syndrome characterised by bleeding from the pulmonary microcirculation (pulmonary arterioles, alveolar capillaries and pulmonary venules) which needs to be differentiated from bleeding from other causes. It is a diffuse phenomenon simultaneously affecting multiple areas in both lungs and is recognised by the clinical constellation of haemoptysis (which may be absent in one third of the cases due to distal location of the bleeding source), a anaemia, diffuse bilateral radiographic pulmonary infiltrates, and d hypoxemic respiratory failure. All cause s of D AH ha ve t he com mon denominator of wi despread injury t o the al veolar microcirculation which may be localized to the lung (inhalation injuries, diffuse alveolar damage) or associated with a systemic di sorder (vasculitis or c onnective tissue disease). The underlying histopathology of DAH includes the presence of intraalveolar RBCs and fibrin and the eventual accumulation of haemosiderin laden macrophages.

Histologically it is classified as pulmonary capillaritis, bland pulmonary haemorrhage and diffuse alveolar damage however lung biopsies are rarely performed as it does not consistently provide etiological diagnosis. The patient may be a known case of autoimmune disorder or may give history of exposure to drugs and toxins. It is important to clinically look for any other systemic manifestation.

Chest X ray shows extensive bilateral alveolar infiltrates and HRCT chest shows bilateral ground glass opacities with relatively central involvement with peripheral lung sparing.

Pulmonary function test typically shows increased DLCO andrestrictive pattern in absence of any improvement in the setting of breathlessness and haemoptysis. A macroscopically haemorrhagic BAL fluid, especially with increasing blood content on successive aliquots, is considered diagnostic of DAH and haemosiderin laden macrophages represent greater than 20-30% of total macrophage count. The specific aetiology needs to be established by testing for autoimmune antibodies like ANA, ANCA, anti dsDNA, APLA and anti GBM and also careful history of drug exposure. Infectious aetiology also needs to be ruled out by sending cultures of BAL fluid. If the underlying cause remains elusive then a histological diagnosis can be confirmed by renal biopsy in cases of renal involvement in
the from of haematuria, proteinuria or renal failure by lung biopsy when the disease is confined to the lung. Immunosuppressive therapies are the mainstay for treatment of immune related DAH. Pul se dos es of intravenous methylprednisolone a re generally recommended. O ther immunosuppressive agents like cyclophosphamide and azathioprine can also be used in cases of renal involvement. Other possible management measures include supplemental oxygen, bronchodilators, reversal of a coagulopathy, intubation with or without mechanical ventilation.

There have been isolated case reports of lung malignancy presenting as DAH. Amongst primary lung malignancies, there have been case reports of choriocarcinoma and angiosarcoma presenting as DAH. It can also present as a complication of various treatment modalities of lung malignancy. However, it has not been described in treatment naïve lung adenocarcinoma patients till date. Amongst malignancies metastasizing to lungs and presenting as DAH, angiosarcoma is the most common which can arise from ovary and the head and neck. If entr cell carc inoma can also metastasize to lungs and present as DAH. It can also be a manifestation of cytotoxic drugs related toxicity or more commonly as a complication of bone marrow or stem cell transplantation. A classification of malignancies associated with DAH has been proposed in table 1. This case highlights the importance of considering malignancy whether primary or secondary as a differential in all cases of haemoptysis and specially DAH.

### Table 1: Diffuse alveolar hemorrhage associated with malignancy

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<thead>
<tr>
<th>Treatment naïve</th>
<th>Treatment related</th>
<th>Drug Induced</th>
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<tbody>
<tr>
<td>Hematological malignancies</td>
<td>Bone marrow transplant related</td>
<td>Drugs used in lung malignancy like Gemcitabine, Bevacizumab</td>
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<tr>
<td>Primary lung malignancies like Angiosarcoma, Choriocarcinoma &amp; Adenocarcinoma</td>
<td>Hematopoietic stem cell transplant related</td>
<td>Drugs used in other malignancies like all trans retinoic acid, Bortezomib, filgrastim, Gemcitabine, gemtuzumab ozogamicin, lenalidomide &amp; sunitinib</td>
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<td>Metastasis to lungs from Angiosarcoma &amp; Renal carcinoma</td>
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### References


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