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 especially DAH.

1. Introduction

Diffuse alveolar haemorrhage (DAH) is a rare and potentially life threatening condition characterised by bleeding from the pulmonary microcirculation (pulmonary arterioles, alveolar capillaries and pulmonary venules) as a result of micro vascular damage leading to extravasation of blood into the alveolar spaces. It is syndrome characterised 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 immunological and non-immunological aetiologies but has been rarely described as a presenting feature of primary lung malignancy.4 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 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 pul monary tuberculosis. Patient was referred to our centre in view of no response.

On presentation patient was in respiratory distress. He also had pallor and clubbing. Breath sounds were bilaterally equal, with bilateral coarse mid inspiratory crepitations throughout both lung fields. Rest of the systemic examination was normal. Full coagulation profile was 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.
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 bronchi 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), pneumocystis jiroveci cysts, aerobic and fungal cultures. The bronchial wash cytology and post bronchoscopy sputum showed a pleural effusion, however further examination 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 is often difficult to differentiate from bleeding from other causes. It is a diffuse phenomenon simultaneously affecting multiple areas in both lungs and is recognized by the clinical constellation of haemoptysis (which may be absent in one third of the cases due to distal location of the bleeding source), anaemia, diffuse bilateral radiographic pulmonary infiltrates, and hypoxemic respiratory failure. All causes of DAH have the common denominator of widespread injury to the alveolar microcirculation which may be localized to the lung (inhalation injuries, diffuse alveolar damage) or associated with a systemic disorder (vasculitis or connective tissue disease). The underlying histopathology of DAH includes the presence of intraalveolar RBCs and fibrin and the eventual accumulation of haemosiderin-laden macrophages.

Diffuse alveolar haemorrhage is not a single disease but a clinical syndrome that may have numerous causes. Autoimmune disorders account for fewer than half of cases, whereas the majority are due to nonimmune causes such as left heart failure, infections, drug toxicities, coagulopathies, and malignancies.

Histologically it is classified as pulmonary capillaritis, bland pulmonary haemorrhage and diffuse alveolar haemorrhage. Bronchoscopy revealed fresh bleeding from right upper, right lower and left lower lobe bronchi with persistent bleeding on serial aliquots (Figure 3) and showed presence of haemosiderin laden macrophages on Prussian blue staining.

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

Pulmonary function test typically shows increased DLCO and restrictive pattern with reduced FVC. The setting of breathlessness and haemoptysis is investigated by bronchoscopy with BAL fluid and histology. The specific aetiology needs to be established for autoimmune antibodies like ANA, 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.
the form of haematuria, proteinuria or renal failure or 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 rec ommended, however immunosuppressive agents like cyclophosphamide and azathioprine can also be used in cases of re nal involvement. Other possible management measures include supplemental oxygen, bronchodilators, reversal of coagulopathy, intubation with tracheal intubation and mechanical ventilation.

There have been isolated cases of renal 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 bone marrow transplantation. Amongst malignancies metastasizing to lungs and presenting as DAH, angiosarcoma is the most common which can arise from ovary and heart. Re nal cell carcinoma can also metastasize to lung 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.

Table 1: Diffuse alveolar hemorrhage associated with malignancy

<table>
<thead>
<tr>
<th>Treatment induced by</th>
<th>Drug induced</th>
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<tbody>
<tr>
<td>Hematological malignancies</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>Drugs used in other malignancies-all trans retinoic acid, Bortezomib, filgastrin, 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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