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Case Report

Adult bronchiolitis obliterans in eosinophilic enteritis: a rare association

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ABSTRACT

We hereby present this rare disease in adult with eosinophilic enteritis. This case is reported since there are no published reports of bronchiolitis obliterans (BO) associated with eosinophilic enteritis. A 70yrs. old lady presented with sudden onset of dyspnea which was initially treated as pneumonia with anti-bacterial agents with poor result. She was provisionally diagnosed as small air way disease (Bronchiolitis obliterans) based on imaging and treated with parenteral steroids with empirical anti-bacterial agents. Infective workup was negative. Lung biopsy showed features of bronchiolitis obliterans. She showed partial response to high dose steroid therapy with relapse of severe dyspnea within short period. She was treated successfully with parenteral cyclophosphamide. Bronchiolitis obliterans is a rare cause for acute respiratory failure among adults in India. It manifests as pneumonia-like illness which is poorly responsive to broad spectrum antibiotics. Lung biopsy is usually required to confirm this non-infectious condition. Majority of patients respond to high dose steroid therapy. On rare occasion, steroid resistant cases require cyclophosphamide or cyclosporin therapy. Bronchiolitis obliterans should be considered as a possibility in acute or sub-acute unresolved pneumonia like illness especially in the absence of infective aetiology. Empirical therapy with steroids/ cyclophosphamide should be tried in cases with fatal respiratory failure. Bronchiolitis obliterans associated with eosinophilic enteritis is a novel thing, even though management of BO does not differ in this setting.

Keywords: Bronchiolitis obliterans, Methyl prednisolone, Cyclophosphamide, Trans-bronchial lung biopsy

INTRODUCTION

Bronchiolitis obliterans (BO) is a disorder of small airways of lung often seen after lung transplantation in developed countries. BO is a major cause of morbidity and mortality in post-lung transplantation patients. This disorder is also known by various pathological descriptions like bronchiolitis obliterans, bronchiolitis obliterans with organising pneumonia (BOOP), bronchiolitis with diffuse interstitial pneumonia, bronchiolitis fibrosa obliterans, follicular bronchiolitis and small airway disease.[1] In developing countries like India, this disorder is often seen as post-infectious form in paediatric population. It is the first ever published report of bronchiolitis obliterans associated with eosinophilic enteritis. We present a case of Bronchiolitis obliterans with fulminant respiratory failure, which was unresponsive to conventional medical therapy and high dose methylprednisolone, but was treated, successfully with the addition of cyclophosphamide.

CASE REPORT

A 70 yrs. old lady who is a known diabetic, hypertensive for past 4 years on oral medication. She was diagnosed as eosinophilic enteritis following ileal resection and anastomosis for sub-acute intestinal obstruction 7 years ago. She was presented to emergency department with

history of cough with scanty sputum for 2 weeks and sudden onset of breathing difficulty since morning. She was apparently normal 2 weeks ago, after which she developed viral prodrome-like illness which lasted for 3 days. She developed cough with scanty expectoration of yellowish white sputum associated with extreme fatigue. No history of fever or chest pain present. She was treated symptomatically. She developed sudden onset of dyspnea after 2 weeks of cough with expectoration.

On examination she was afebrile, tachypneic, no pallor, no icterus, no edema or lymphadenopathy. Vital signs showed blood pressure of 140/ 70 mmHg; pulse rate- 100 per min, regular; respiratory rate - 32/min. Respiratory and cardio vascular system examination revealed unremarkable findings. She was maintaining SpO2 -97% on ambient air. She was admitted in intensive care unit for respiratory distress with clinical diagnosis of "community acquired pneumonia with acute respiratory failure". Baseline investigations showed normal blood cell count, normal glucose, and normal renal and liver function tests. Her chest X-ray showed ground glass opacity of left lower zone with normal cardio-thoracic ratio. Sputum analysis for bacteria, fungus, acid-fast bacilli were negative. Sputum culture was negative. Throat swab for H1N1 was negative. Cardiac evaluation was normal. She was treated with nasal oxygen, empirical anti-bacterial agents (piperacillin, azithromycin) with inhalational beta2-agonist and inhalational steroid. Glycemic control was achieved with insulin. She improved partially hence shifted to general ward for further management.

After 2 days, she developed dyspnea with minimal cough again and shifted to intensive care unit for O2 support. Arterial blood gas (ABG) analysis showed type I respiratory failure with mild hypoxemia. High resolution Computed Tomography (HRCT) chest showed mosaic attenuation pattern at bilateral lung fields with areas of air trapping (Figure 1). Left lung lower lobe showed fibrotic changes. She was provisionally diagnosed as "Bronchiolitis obliterans (post-infectious/Idiopathic)". Since HRCT chest findings are suggestive of small airway disease, she was treated with high dose steroids along with empirical broad spectrum anti-bacterial agents. Owing to poor response to steroids with antibiotics, she underwent CT pulmonary angiogram which was normal. Repeat Chest X-ray showed same findings. Repeat echocardiogram was within normal limits. ABG showed persistent type I respiratory failure. She was tachypneic, afebrile, maintaining spO2- 94% on ambient air. Antibiotics changed from piperacillin to Clarithromycin along with steroids. Bronchoscopy showed no gross abnormality. Broncho-alveolar lavage (BAL) culture showed *Klebsiella pneumoniae* (Extended spectrum beta lactamase producer). Gram stain, AFB stain and fungal smear of BAL were negative. Endo-bronchial biopsy showed non-specific inflammatory changes. She was given meropenem (sensitive to *Klebsiella*), linezolid along with parenteral steroids.

Despite effective dose of sensitive antibiotics, she developed fever, progressive dyspnea and severe hypoxemia. Repeat CT chest showed persistent mosaic pattern with areas of air trapping. No evidence of consolidation or mass seen. She was intubated and mechanically ventilated for type I acute respiratory failure. Endo tracheal aspirate culture showed acinetobacter baumanii sensitive to colistin, tigecycline. Antibiotics changed to colistin, tigecycline along empirical anti-fungal (voriconazole) with mechanical ventilation and other supportive measures.

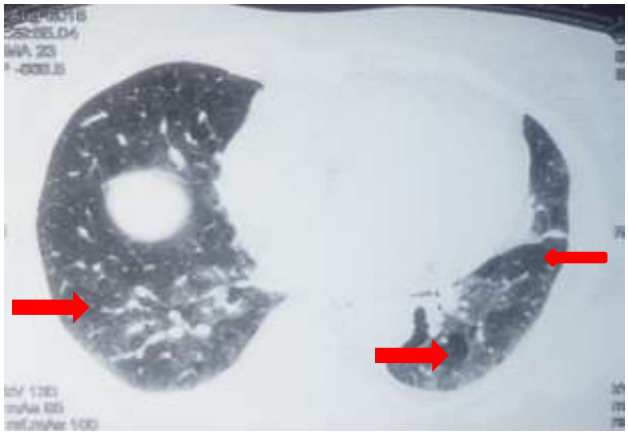

Figure 1: HRCT chest image showing areas of air trapping (noted with red arrows) with mosaic pattern.

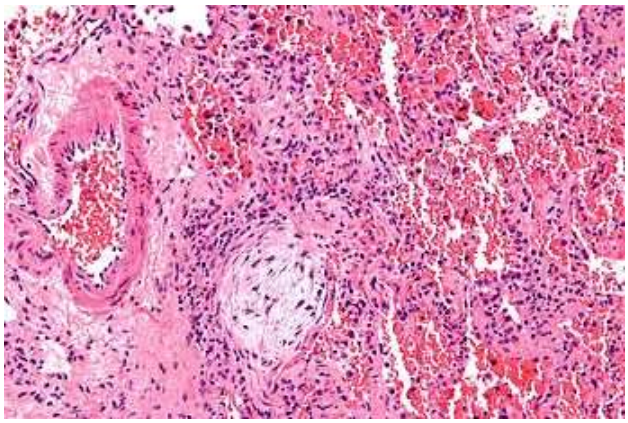

Figure 2: Histology showing Masson body (off center left/bottom of the image - pale circular and pauci cellular), as may be seen in bronchiolitis obliterans. Masson body plugs bronchiole shown with red arrow.

Despite above intensive measures for 7 days, her oxygenation not improved. She underwent trans-bronchial lung biopsy which confirmed histological features of bronchiolitis obliterans (Figure 2). She was diagnosed to have "steroid resistant bronchiolitis obliterans". She was given a pulse of intravenous cyclophosphamide (dose: 10 mg/kg). Her oxygenation status improved dramatically and she was weaned from ventilator after 5 days of cyclophosphamide administration. She was transferred to ward with minimal Oxygen support. Later she was discharged with an advice

to receive 6 cycles of pulse intravenous cyclophosphamide followed by reassessment of pulmonary status.

DISCUSSION

Bronchiolitis Obliterans (BO) is characterised by inflammation and fibrosis of small airways with various aetiologies, a wide clinical spectrum and diverse pathological appearances.[2]

Aetiology

BO is a common complication of lung and stem cell transplantation.[3] Adult cases of BO are often reported in connective tissue disorders, post-lung transplant rejection cases, toxic fume exposure and idiopathic form. Common connective tissue disorders associated with BO are systemic lupus erythematosus, Rheumatoid arthritis, sjogren syndrome, systemic sclerosis,[4] polymyositis and dermatomyositis.[5] Drugs causing BO are pencillamine, gold, amiodarone, Busulfan, sulphasalazine, acebutolol.[6] Inhalational injury in the form of toxic fumes (oxides of nitrogen), irritant gases like chlorine, organic dust and volatile agents may result in BO. Paediatric cases are reported often as post-infectious BO.[7] Our patient has no known etiological factor mentioned in literature. But she has underlying eosinophilic enteritis which could probably be related to it.

Pathogenesis

Microscopic injury to small airway epithelium results in inflammatory response. First, a florid alveolitis with edema occurs as a result of damage to the alveolar lining. The degree of alveolar lining destruction and disruption of the basal lamina, with resulting gaps on the basement membrane, appears to determine the extent of intra-alveolar fibrosis. After development of the alveolitis, fibroblasts migrate into the lesion, proliferate, and secrete matrix proteins. This results in the formation of Masson bodies, polypoid buds of fibroblasts, and extracellular matrix projecting into the lumina of respiratory bronchioles, alveolar ducts, and alveoli. The matrix of the Masson bodies stain positive for type III collagen and fibronectin (cell and plasma in origin). The fibroblasts in the Masson bodies also stain strongly for procollagen type I. Granulation tissue formed during repair causes obstruction of small airways. It is known as "proliferative" bronchiolitis. Intramural and intraluminal concentric fibrosis formed during repair results in obliteration of terminal and respiratory bronchioles. Hence it is called bronchiolitis obliterans (constrictive bronchiolitis).[8]

Trans-bronchial lung biopsy of our patient showed fibromyxoid plugs in alveolar ducts and alveoli. Interstitium showed moderate fibrosis with mild lymphocytic infiltrate. There are numerous macrophages noted in alveoli. Above findings are suggestive of bronchiolitis obliterans with organising pneumonia.

Clinical features

Disease onset is usually in the fifth or sixth decade, with a mean age of 58 years; men and women are affected equally.[9] Almost three-fourths of patients have symptoms for less than 2 months; few have symptoms for more than 6 months before diagnosis. Cigarette smoking is not a precipitating factor, since approximately 50 per cent of subjects are never-smokers, 25 per cent are ex-smokers, and only 25 per cent are current smokers. The clinical presentation may mimic that of community-acquired pneumonia. A recent retrospective study of patients with an underlying diagnosis of cancer showed a treatable cause of lung disease with variable manifestations. This group showed that BOOP can mimic pulmonary malignancy and pulmonary infection.[10] A persistent and usually non-productive cough is the most common presenting symptom (72 per cent of subjects). Frequently, patients experience dyspnea with exertion (66 per cent). Disease onset is usually described as a flulike illness, with fever (51 per cent), malaise (48 per cent), fatigue, and cough. Weight loss of greater than 10 lb. is a common complaint (57 per cent). Physical examination reveals inspiratory crackles (74 per cent); wheezing is rare and is usually present in conjunction with crackles. Clubbing is rare (fewer than 5 per cent of patients). Twenty eight per cent of patients in one series had normal pulmonary function. Dyspnea, fatigue, minimal cough with scanty sputum with non-specific clinical and radiological findings is noted in our patient.

Diagnosis

Even though post-transplant bronchiolitis and toxic fume exposure related disease are identified without much difficulty, idiopathic bronchiolitis cases pose diagnostic challenge. High index of suspicion is important to identify such cases in community. Most patients present with acute or sub-acute interstitial pneumonia like illness which is unresponsive to broad spectrum antibacterial agents without any evidence of infective etiology. Our patient too had pneumonia like illness which was unresponsive to antibiotics.

Radiological features are variable according to stage and severity of disease. Nodular densities, alveolar opacities, hyperinflation, mosaic attenuation, air trapping are notable features of bronchiolitis in HRCT chest.[11,12] Air trapping more than 1/3 (32%) of lung parenchyma is virtually diagnostic and early predictor of BO with high sensitivity and specificity.[13] HRCT chest classical features are sufficient to make diagnosis of BO and eliminate need for lung biopsy. In difficult cases open lung biopsy is used to confirm diagnosis since the yield of trans-bronchial lung biopsy is poor.[14] False negative biopsy may result due to patchy nature of the disease. Bilateral multifocal consolidation along with alveolar

infiltrates predominantly in the lower lobes, which are migratory in nature, is another common radiological finding but for confirmation of diagnosis, histopathology is required. Trans-bronchial biopsy is diagnostic in most cases but open lung biopsy is needed in doubtful cases[15.] In our patient, diagnosis was inconclusive until we did trans-bronchial lung biopsy. In our case, histo-pathological features were very much consistent with BOOP.

Management

Bronchiolitis especially proliferative type is usually responsive to corticosteroids. Constrictive bronchiolitis (bronchiolitis obliterans) is usually shows poor response to steroids. Long term use of steroids is also associated with significant morbidity. Clinical trial using fluticasone, azithromycin, montelukast in diagnosed cases of BO helped to reduce steroid exposure and its ill effects of long term use.[16] But its clinical application requires further study. Recent case reports show successful management of steroid resistant BO with the use of potent immunosuppressive agents like cyclophosphamide, cyclosporin, and azathioprine along with anti-fibrotic agent like pirfenidone.[17,18] Newer therapies like Tumour necrosis-alpha blockade and inhalational cyclosporin were used successfully.[19,20]

Our patient was successfully treated with cyclophosphamide pulse therapy since response to steroid was suboptimal. She was advised to undergo 6 cycles of cyclophosphamide pulse therapy and minimum of 6 months of oral immunosuppressive agent.

Prognosis

Bronchiolitis obliterans has indolent course but may prove fatal if there is rapid progression to respiratory failure. Clinical response to steroid therapy depends on histological features. Proliferative bronchiolitis has very good response to steroids but constrictive type has poor response. Early diagnosis and treatment of this rare entity results in better clinical outcome.

CONCLUSIONS

Bronchiolitis obliterans usually has an indolent course and good prognosis, but it may rapidly worsen and respiratory failure may develop. Fatal respiratory failure should be treated aggressively with a combination of intravenous high-dose corticosteroids and immunosuppressive agents like cyclophosphamide and cyclosporin. Even though lung biopsy is the confirmatory test, an early therapeutic trial of cyclophosphamide should be considered in patients with BO who fail to respond to steroids. Management of BO does not differ in the setting of eosinophilic enteritis.

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