ORIGINAL RESEARCH PAPER

Pulmonary Medicine

PSEUDOMEMBRANOUS ASPERGILLUS TRACHEOBRONCHITIS PRESENTING AS PERI-BRONCHIAL MASS WITH SEGMENTAL COLLAPSE SECONDARY TO LEVAMISOLE INDUCED NEUTROPENIA

KEY WORDS:

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ABSTRACT

Pseudomembranous necrotizing bronchial aspergillosis is a variety of invasive pulmonary aspergillosis found in immunosuppressed patients. It is an uncommon clinical presentation of pulmonary aspergillosis (PA). Predisposing factors are similar to those for invasive pulmonary aspergillosis (IPA). Neutropenic or immunocompromised patients including patients with cytotoxic chemotherapy or corticosteroid therapy are at particular risk. Levamisole is known to cause severe agranulocytosis. We report a case of Pseudomembranous Aspergillus Tracheobronchitis (PMATB) presenting as hilar mass with lobar collapse in a patient who received Levamisole as an immunomodulator for the treatment of Alopecia totalis

INTRODUCTION:

Pseudomembranous necrotizing bronchial aspergillosis is a variety of invasive pulmonary aspergillosis found in immunosuppressed patients. It is an uncommon clinical presentation of pulmonary aspergillosis (PA). Predisposing factors are similar to those for invasive pulmonary aspergillosis (IPA). Neutropenic or immunocompromised patients including patients with cytotoxic chemotherapy or corticosteroid therapy are at particular risk. Levamisole is known to cause severe agranulocytosis. We report a case of Pseudomembranous Aspergillus Tracheobronchitis (PMATB) presenting as hilar mass with lobar collapse in a patient who received Levamisole as an immunomodulator for the treatment of Alopecia totalis.

Case Report

56 years old female, diagnosed case of type 2 diabetes mellitus on oral hypoglycemic agent presented with history of on and off fever for month, poor appetite, vomiting and cough with yellowish expectoration. Patient had several times watery loose stools with no blood or mucus. She had been suffering from alopecia areata for one and a half years and that had progressed to alopecia totalis. She was prescribed anthelminthic medicine Levamisole 150mg /week for 10 weeks for the same and was on the medication for the last few weeks before she presented to ER.

On Examination, Patient was febrile with stable vitals on presentation maintaining oxygen saturation of 97% on room air. She had features of alopecia totalis, however systemic examinations were within normal limits. Chest x-ray was unremarkable on presentation (Figure 1). Laboratory findings showed severe leucopenia (WBC 1200/mm3) with an absolute neutrophil count of zero. Hemoglobin was 13.1gm/dl and platelets were 512x 103/mm3.Biochemical tests showed raised ESR (105mm/1st hour) and C reactive protein was 150 mg/L. Urea electrolytes, creatinine and liver function tests were within the reference range. Blood and urine cultures were negative for any pathogens. Blood tests for various viral markers yielded negative results. For further evaluation the patient underwent contrast CT scan of chest, abdomen and pelvis.

CT scan of the chest showed right hilar mass surrounding the right lower lobe bronchus with significant narrowing leading to collapse of posterior basal segment of right lower lobe. No significant lymph node enlargement could be detected. CT scan of abdomen and pelvis were within normal limits (Figure 2). In view of the CT Chest findings the patient underwent fiberoptic bronchoscopy. Bronchoscopy showed multiple yellowish plaques in both main and some lobar bronchi, highly suggestive of pseudomembranous AT. There was extensive inflammation but no ulcerations of bronchial mucosa (Figure 3). . Histopathology of bronchial biopsy showed fibrinopurulent exudate and partially necrotic material with septate branching fungal hyphae consistent with Aspergillus species. PAS and GMS silver stain revealed numerous acutely branching septate, fungal hyphae morphologically consistent with Aspergillus species (Figure 4 A, B, C)

Detailed workup was done to find out the cause for neutropenia: all lab including serology viz. HCV, HIV, EBV, CMV, HSV, brucella titer, mycoplasma, parvovirus, Vasculitic and Connective Tissue disease profile were negative. Septic workup was negative for bacterial, TB and fungal source of neutropenia.

Immunoglobulin were elevated: IgG: 18.8, IgA: 2.84. IgM: 2.64. Hence bone marrow aspirate was done which revealed normal cellularity with marked increase in plasma cell which accounted 17% of mononuclear cells in the bone marrow hence bone marrow trephine biopsy was done which showed normal cellularity, markedly increased megakaryocytes including monolobed cells. granulopoetic and erythropoetic series were normal. Moderate increase in plasma cells with interstitial infiltration and primarily perivascular localization. CD138 + plasma cells were around 15-20% of mononuclear cells. No granulomas or non-hemopoietic infiltration seen hence concluded as non-diagnostic with reactive increase of plasma cells is probable as a cause.

She was evaluated for low Hemoglobin and found to have interno-external hemorrhoids. The case was discussed with the Infectious Diseases department and treatment with meropenam and fluconazole was advised, along with filgrastim, to which the patient responded well. Repeat CT scan of chest showed marked improvement and patient was discharged home (Figure 5).

DISCUSSION:

TBA was first described in 1991 by Kramer et al 1 as invasive Aspergillus tracheobronchitis after lung transplantation. After

that, cases of TBA in immunocompetent hosts have also been reported in post-tuberculosis tracheal stenosis and anastomosis site after lobectomy.

Most recently, Wu et al2 classified isolated invasive TBA (IITBA)–TBA without invasive parenchymal disease–according to the bronchoscopic findings as superficial infiltration, full-layer involvement, occlusion, and mixed type in 2010.

Pseudomembranous ATB (PMATB) typically shows extensive inflammation of the tracheobronchial tree, with a membrane overlying the mucosa containing Aspergillus spp. The diagnostic criteria include Aspergillus isolation from the cultures of tracheobronchial tree samples, or the histological confirmation of Aspergillus in the affected tissue, along with confirmation of the absence of alternative diagnosis, as well as the absence of radiological, clinical and histological evidence of invasive parenchymal aspergillosis3. It occurs in 10% of invasive aspergillosis. Invasive pulmonary aspergillosis makes 90% of all clinical forms of pulmonary aspergillosis, and 7-20% of these infections are manifested by a concurrent involvement of the tracheobronchial tree 4 . As an isolated form of invasive pulmonary aspergillosis, PNBA is found in 7-10% of the affected patients5. ATB may be manifested in the form of aspergillus bronchitis, obstructive tracheobronchitis, ulcerative tracheobronchitis, and PNBA [4,5,6,7,8,9.]

New classification divides ATB in immunodeficient patients into three forms 6 . 1) mucous deposits and plaques with no inflammatory response signs in the bronchial mucosa (this form is usually found in the patients with heart transplantation and AIDS); 2) pseudomembranous aspergillosis of the tracheobronchial tree accompanied by an extensive inflammation with pseudomembranous deposits covering the mucosa and containing Aspergillus; 3) ulcerous aspergillosis of the tracheobronchial tree manifested as a local infection in the region of the pulmonary transplant suture – this form has a good prognosis and a good response to instillation of antifungal drugs during bronchoscopy and to surgical debridement [1].

Pseudomembranous necrotizing Aspergillus tracheobronchitis (PNTB) is a rare form of invasive pulmonary aspergillosis which occurs in immunocompromised patients, primarily those with neutropenia, hematological disorders, acquired immunodeficiency syndrome (AIDS), and patients who underwent bone marrow or organ transplantation10. The diagnostic criteria include Aspergillus isolation from the cultures of tracheobronchial tree samples, or the histological confirmation of Aspergillus in the affected tissue, along with confirmation of the absence of alternative diagnosis, as well as the absence of radiological, clinical and histological evidence of invasive parenchymal Aspergillosis [1].

Levamisole acts as an immunomodulator and immune-enhancer used as disease modifying agent in treatment of rheumatoid arthritis works by increasing macrophage chemotaxis and T-cell lymphocyte function 11.17 It has also been shown to stimulate neutrophil chemotaxis, up-regulate toll-like receptors, and enhance dendritic cell maturation 12,13,14,15,16. Notable adverse effects of levamisole include severe agranulocytosis, retiform purpura, and seizures [17,18,19].

Our patient was on levamisole for last few weeks with severe agranulocytosis (severe leucopenia with an absolute neutrophil count of zero) with resultant immunosuppression with subsequent PMTBA. On bronchoscopy, patient had multiple yellowish plaques in both main and some lobar bronchi, highly suggestive of pseudomembranous AT. There was extensive inflammation but no ulcerations of bronchial mucosa suggesting superficial TBA.

TBA can cause nonspecific symptoms as fever, cough, purulent sputum and hemoptysis with or without parenchymal infiltration. Hence high clinical suspicion and early bronchoscopic evaluation is important especially in immunocompromised hosts where it can lead to high mortality rate up to 70% if left undiagnosed and untreated20. Key factors for favourable outcome are an early diagnosis and adequate antifungal therapy.

The CT findings of necrotizing bronchial aspergillosis include bronchial wall thickening, which is often nodular, and narrowing of the bronchial lumen, which is often associated with distal atelectasis 21 It has been reported invasive aspergillosis can present as multiple nodules with or without halo sign, masses and consolidations[22].

Conclusions: Neutropenic or immunocompromised patients including patients receiving cytotoxic chemotherapy or corticosteroid therapy are at particular risk of developing Aspergillosis and PMATB. Levamisole is known to cause severe agranulocytosis. Hence, a very high index of suspicion should be kept for the possibility of invasive aspergilosis and PMATB in patients taking levamisole for the treatment of many autoimmune skin disease especially in the developing world where it is quite often used.

A detailed workup including CT scan and with a low threshold for bronchoscopy including full investigation for aspergillosis must be done while treating such patients with agranulocytopenia specially those patients who has slow or no clinical and / or radiological improvement.

Figure 1. CXR at presentation was within normal Limits

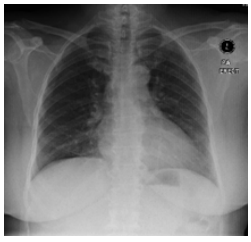


Figure 2. CT scan of Chest before bronchoscopy

showed right hilar mass surrounding the right lower lobe bronchus with significant narrowing leading to collapse of posterior basal segment of right lower lobe.

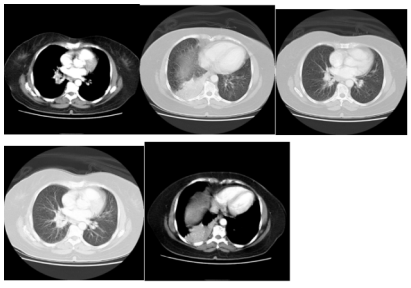


Figure 3. bronchoscopy

showed multiple yellowish plaques in both main and some lobar bronchi, highly suggestive of pseudomembranous AT.

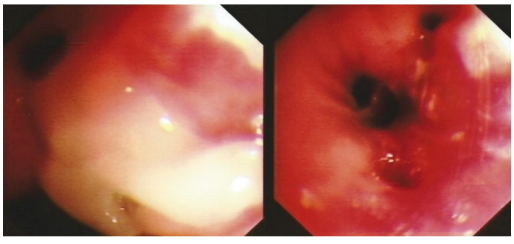
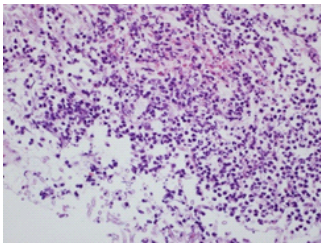
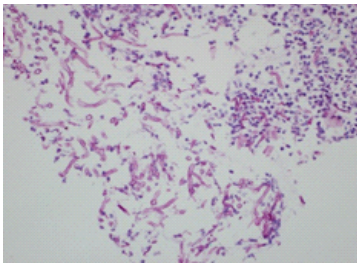


Figure 4 (A, B, C) Histopathology:

(A) Endo bronchial biopsy of the right lower lobe bronchus (H&E X 400) : - Fibrino-purulent exudate and partially necrotic material with septate branching fungal hyphae: consistent with Aspergillus species lung infection.



(B) PAS (special stain X 400): Numerous acutely branching septate, fungal hyphae morphologically consistent with Aspergillus species are seen



(C) Grocott methenamine silver stain (X400): Numerous acutely branching septate, fungal hyphae morphologically consistent with Aspergillus species are seen

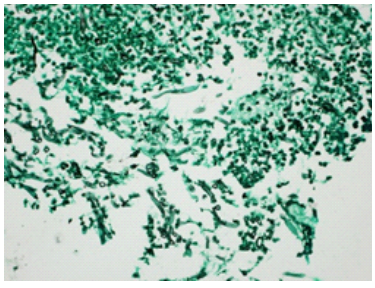
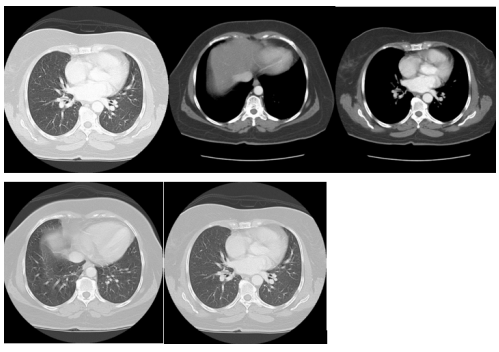


Figure 5 : CT AFTER (Same cuts has to be included)



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