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*Case Report*

# *Aspergillus tracheobronchitis* in an immunocompetent critically ill patient

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***Aspergillus tracheobronchitis* (ATB) is a rare cause of respiratory failure in the critical care unit. Most commonly occurring in immunocompromised patients with underlying haematological malignancy, solid organ transplant, or HIV/AIDs, ATB is infrequently encountered in patients without underlying immunologic derangement. This brief report describes a single case of ATB in a critically ill patient with no known history of immunosuppression. Bronchoscopy confirmed the diagnosis of ATB and *Aspergillus fumigatus* was cultured from bronchoscopy and autopsy specimens. The diagnostic features of *A. tracheobronchitis* are highlighted with bronchoscopic and post-mortem images. A literature review highlights the diagnostic and therapeutic challenges associated with *A. tracheobronchitis* in the critically ill.**

**Key words:** *Aspergillus tracheobronchitis*, respiratory failure, fungal infections.

## INTRODUCTION

*Aspergillus tracheobronchitis* (ATB) is a devastating manifestation of invasive pulmonary aspergillosis, with mortality rates approaching 100% amongst critically ill patients (Tasci, 2006). Occurring most frequently in immunocompromised hosts, ATB is an uncommon etiology of respiratory failure in those without underlying immunodeficiency. Cases involving patients with normal immunologic function are limited to individual reports (Angelotti, 2002; Chang, 2005; Boots, 1999). The diagnostic and therapeutic challenge associated with ATB is notable and despite aggressive treatment, outcome remains poor. We present a case report of ATB Caused by *Aspergillus fumigatus* in a mechanically ventilated, immunocompetent patient. This case provides additional evidence that *Aspergillus* is an important pathogen in critically ill patients without underlying immunologic derangement.

## CASE REPORT

A 50 year old male was transferred from the operating theatre to the intensive care unit for evaluation and management of shock secondary to intra-abdominal sepsis. The patient required a Hartmann's resection for management of anastomic leakage occurring 3 days following low anterior rectosigmoid resection with diverting loop ileostomy for primary colonic adenocarcinoma. At the time of re-operation feculent

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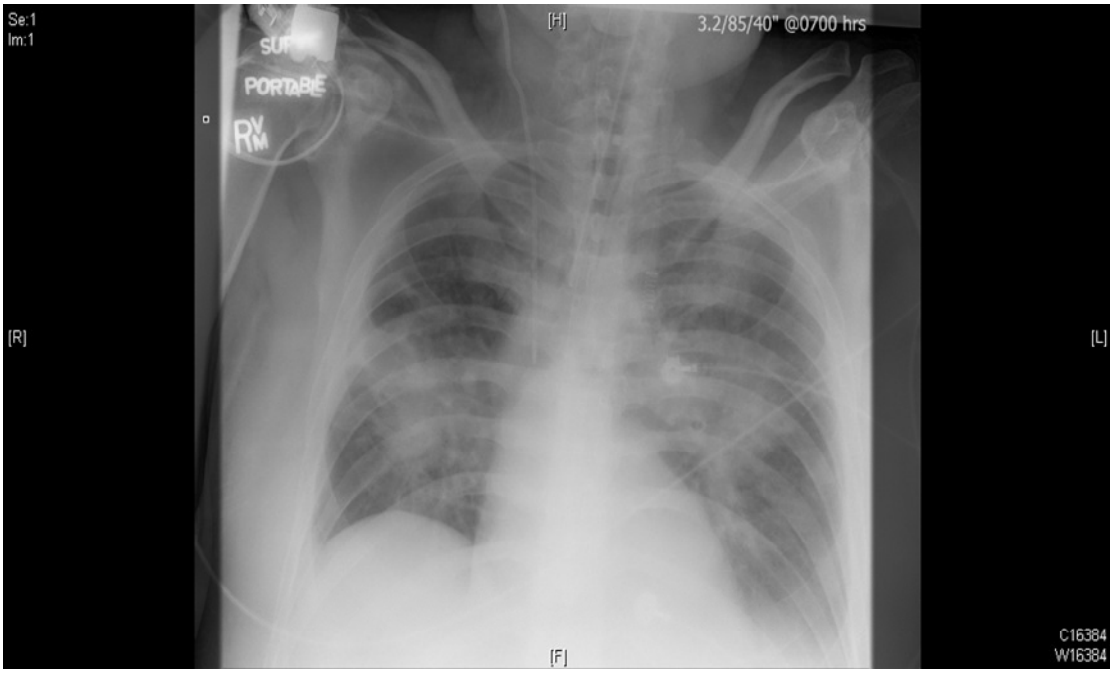


**Figure 1.** Portable chest radiograph taken on the patients 10th day in the intensive care unit showing bilateral patchy areas of airspace disease in the central portion of each lung.


**Figure 2.** Bronchoscopic image demonstrating pseudomembranes consistent with *Aspergillus tracheobronchitis* at the level of the carina.

contamination was encountered requiring abdominal lavage and vacuum assisted closure. Past medical history was remarkable for a diagnosis of asthma made at 15 years of age. The patient had been assessed by a respirologist in 2002 with pulmonary function tests revealing reversible airway obstruction consistent with asthma. Chest radiograph in 2002 demonstrated persistent right upper lobe consolidation, which was further investigated with CT scanning. The CT showed a right upper lobe density with right hilar and mediastinal

adenopathy. Bronchoscopy was unremarkable with samples negative for both malignancy and infection. Specifically, fungal cultures were negative. Mediastinoscopy was performed and biopsy of station 4R and 10R lymph nodes revealed hyalinised granulomas. No organisms were seen on staining and cultures were negative. Clinically, the findings were felt to be consistent with sarcoidosis although the possibility of quiescent fungal infection was considered. Unfortunately, the patient was lost to follow up and no further investigation was performed. Prior to the elective abdominal surgery the patient was assessed in the pre-operative assessment clinic and felt to exhibit excellent functional capacity. The patient was started on salmeterol-fluticasone combination therapy to optimize his respiratory status pre-operatively. At the time of ICU admission the patient was treated empirically with piperacillin -tazobactam and fluconazole for nosocomial secondary peritonitis.

Hemodynamic support was achieved through the use of norepinephrine after appropriate crystalloid resuscitation. Chest radiograph demonstrated bilateral airspace disease thought to be consistent with ARDS (Figure 1). Definitive source control of abdominal sepsis was attempted with re-look laparotomy at 48 h. Unfortunately, on ICU day 9 the patients shock state acutely worsened after developing a necrotizing polymicrobial right lower quadrant abdominal soft tissue infection which required surgical debridement. Empiric hydrocortisone therapy was initiated on ICU day 10 for severe shock that was not responsive to high dose vasopressor therapy. The empiric hydrocortisone was weaned by ICU day 15; however hydrocortisone was restarted on ICU day 16 for severe shock and continued for the duration of the patients ICU stay. Microbiology from cultures taken from the peritoneal cavity grew mixed enteric gram negatives. Initial respiratory cultures taken on ICU admission were negative for bacterial and fungal pathogens. All blood cultures were negative for the duration of the patients ICU admission. Sputum cultures on ICU day 8 grew 2 colonies of *A. fumigatus*. On ICU day 9 antimicrobial therapy was broadened to Vancomycin, Meropenem, Fluconazole and Caspofungin due to the patient's ongoing dense septic shock and concern for untreated fungal and multidrug resistant organisms. Vancomycin and Caspofungin were both discontinued on ICU day 11 due to clinical improvement and lack of demonstration of MRSA or significant fungal infection. On ICU day 19 Fluconazole was changed to Voriconazole at a dose of 350 mg bid and continued for the remainder of the patients stay in the ICU as there was increasing concern that the few colonies of Aspergillus found in the sputum were truly pathogenic. This possibility was entertained due to ongoing low-grade shock requiring norepinephrine and ongoing respiratory failure. Caspofungin was restarted on ICU day 27 and continued for the duration of the patients stay.

On admission to the ICU the patient was easily weaned to pressure support ventilation with PEEP of 7.5 cm $H_20$ and 30% $FiO_2$. On ICU day 4 the patient was switched to assist control ventilation and on ICU day 6 the patient's ventilatory pressures began to rise. By ICU day 10 the patient's peak airway pressures were consistently approaching 40 cm $H_20$ with plateau pressures above 30 cm $H_20$ despite a variety of ventilatory modes and deep sedation with no respiratory effort. Ventilatory pressures continued to rise, with peak pressures over 50 cm $H_20$ and plateau pressures over 40 cm $H_20$. The patients' abdomen was still open at this time and bladder pressures were normal. Gas exchange acutely worsened on ICU day 24. This was investigated with a CT thoracic angiogram which demonstrated scattered parenchymal scarring in both upper lobes with bilateral pleural effusions. Localized consolidation was noted in the lateral aspect of the right upper lobe. There was no radiological evidence of mediastinal adenopathy nor of pulmonary emboli. A bronchoscopy was performed to further investigate the respiratory failure on ICU day 25. The bronchoscopy demonstrated pseudomembranous tracheobronchitis with pseudomembranes covering the mucosa of all visible airways with sparing of only one small division of the left lower lobe bronchus.(Figure 2) Washings, cytology and biopsy were completed. Biopsy results showed necrotizing granulomas with numerous branching fungal hyphae, the morphology of which was consistent with aspergillus species. Fungal cultures grew *A. fumigatus*. Stains for acid-fast organisms were negative. The patient deteriorated with ongoing hemodynamic instability and respiratory failure. At the request of the family life support was discontinued on ICU day 27 and the patient died shortly thereafter. The family consented to a post mortem examination.

As demonstrated in Figures 3 and 4, the post mortem demonstrated evidence of invasive bronchopulmonary aspergillosis with pseudomembranous tracheobronchitis and this was determined to be the final cause of death. There was no evidence of occult malignancy nor were any other causes of immunosuppression found at autopsy. The post mortem examination also showed marked bilateral pneumonia. Two subpleural infarcts were at the right apex. Pulmonary vasculature was normal with no evidence of pulmonary thromboembolus.

## DISCUSSION

Invasive pulmonary aspergillosis (IPA) is now recognized as an important cause of pulmonary morbidity and death in the critical care setting (Trof, 2007). With a mortality rate approaching 80%, early diagnosis and initiation of appropriate therapy is critical (Trof, 2007). *A. tracheobronchitis* is a rare presentation of IPA occurring infrequently in the absence of pulmonary parenchymal involvement (Pornsuriyasak, 2009). The outcome for

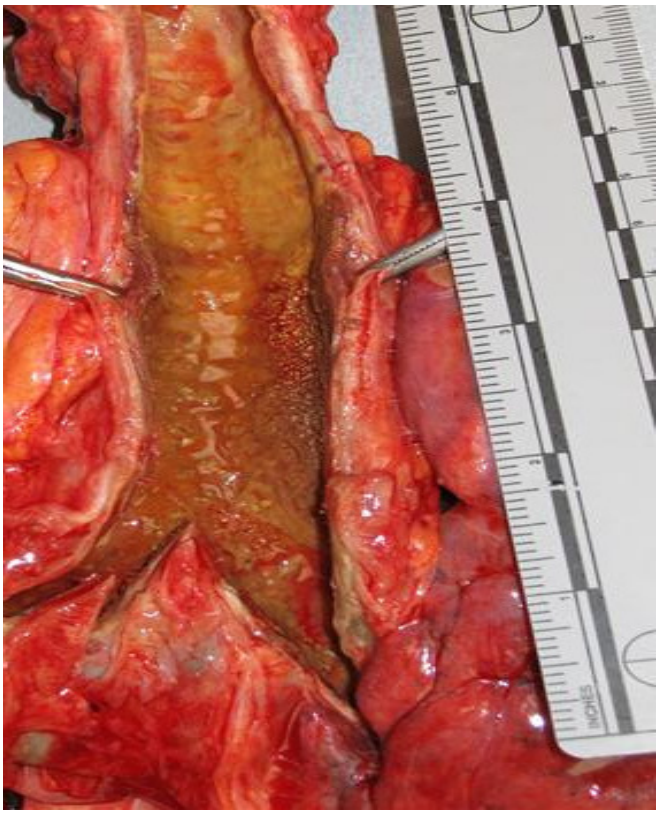

**Figure 3.** Coronal section from post mortem examination showing extensive yellow-brown pseudomembrane formation in the trachea and proximal bronchi characteristic of *Aspergillus tracheobronchitis*.

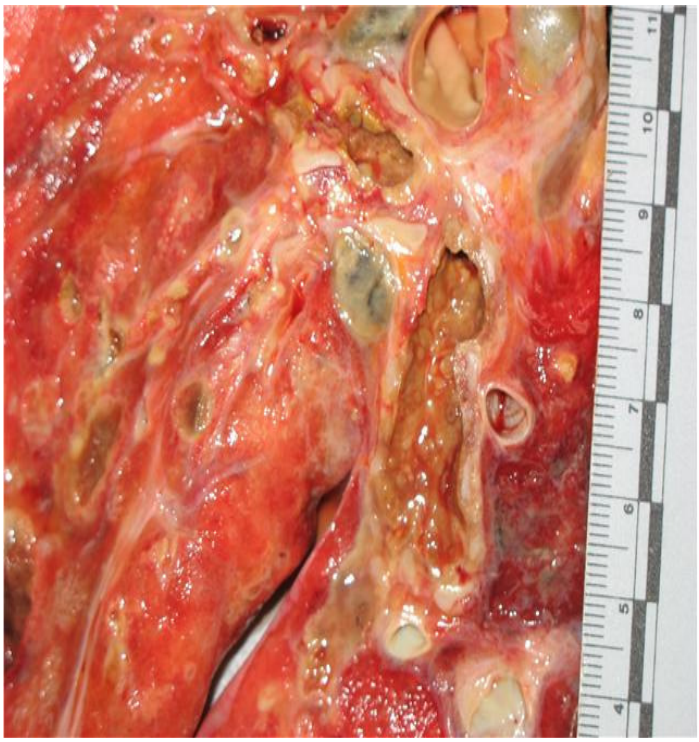

**Figure 4.** Sagittal section from post mortem examination demonstrating extensive pseudomembranous involvement of bronchi with surrounding acute airspace disease.

patients with *ATB* requiring ventilatory support is dismal and considered to have a near universal fatal outcome (Tasci, 2006). Patients affected with ATB are most often immunocompromised secondary to haematological malignancy, AIDS, solid organ transplant or chronic corticosteroid therapy. ATB has also been described in patients with systemic lupus erythematosus, hepatic failure and obstructive lung disease (Angelotti, 2002; Pornsuriyasak, 2009; Hines, 2009; Samarakoon, 2008). A comprehensive literature review revealed 4 cases of ATB in patients who did not have the described risk factors of solid organ transplantation, HIV, haematological malignancy, obstructive lung disease or hepatic failure (Angelotti, 2002; Chang, 2005; Boots, 1999). In 2 patients diabetes mellitus was identified by the authors as a risk for ATB. In this case series, 1 patient succumbed to respiratory failure and one was successfully treated, never requiring mechanical ventilation (Chang, 2005).

A second case report documented a 35 year old, previously well female patient, who developed acute respiratory failure attributed to ATB.This patient presented with symptoms consistent with severe asthma. Bronchoscopy revealed a thick membrane adherent to the trachea and proximal bronchi. Biopsy and lavage specimens confirmed the diagnosis of ATB. The patient required prolonged mechanical ventilatory support but survived to hospital discharge (Boots, 1999). An additional case report of ATB developing in a 23 year old female who had been diagnosed with systemic lupus erythematosus (SLE) 5 months prior to developing ATB was reported. This patient had not received any immunosuppressive therapy prior to her presentation. This young patient developed respiratory failure requiring mechanical ventilation which subsequently led to her death on hospital day 9. The authors suggest low complement levels associated with SLE may have been the predisposing factor to ATB in her case. This patient was treated with corticosteroids and cyclophosphamide for less than 7 days prior to her death (Angelotti, 2002). Aspergillus is a common mould to which many humans are exposed. Transmission occurs via inspiration of aerosolised spores (Meersseman, 2007). The suspected pathogenesis of IPA in immunocompromised patients; specifically those following lung transplant has been well described (Tasci, 2006; Trof, 2007; Meersseman, 2007). Invasion is facilitated by impaired local defense mechanisms and systemic immunodeficiency, especially impaired macrophage and neutrophil function. The critical care patient may not exhibit classic risk factors for IPA or ATB, but remain susceptible due to the immunomodulation that is known to occur in critical illness. Other risk factors include concomitant pulmonary

disease, diabetes mellitus, multi-organ failure and broad spectrum antimicrobials (Trof, 2007).

The patient treated in our institution was treated with broad spectrum antimicrobials as well as hydrocortisone, but did not have an underlying immunocompromised state as seen in the majority of patients with IPA. Sputum cultures from endotracheal aspirates were positive for aspergillus 48 h prior to initiation of hydrocortisone therapy. Studies have suggested that a 7 day course of hydrocortisone may be enough to predispose to IPA, but further study in this subject is required (Meersseman, 2007; Crean, 1992). The decision to use empiric steroids in this patient was based on his severe illness and distributive shock which was refractory to conventional doses of vasoactive agents. Attempts to wean off hydrocortisone therapy were unsuccessful due to the patient's refractory hemodynamic instability. The post-mortem examination revealed a 4 x 3 x 2 cm circumscribed zone of dense fibrosis in the central portion of the right upper lobe, possibly correlating tothe right upper lobe opacity noted on chest radiograph in 2002. No fungal organisms were detected histologically. Extensive investigation, including both bronchoscopy and mediastinoscopy were performed and were non-diagnostic. In addition to the aforementioned described scarring, post mortem examination confirmed hyalinized granulomas in mediastinal lymph nodes. There were areas of nonspecific interstitial fibrosis accompanied by rare multinucleated giant cells, though no interstitial granulomas were detected. The findings could represent quiescent fungal infection which may be related to the development of ATB during the patient's critical illness in 2009. Nevertheless, pre-existing *Aspergillus* infection could not be clearly established. The diagnosis of *ATB* may be elusive. In a series of 20 patients with *A. tracheobronchitis* 12 patients had pathological radiographs but only 2 had findings characteristic of *ATB* (Tasci, 2006).

The utility of chest computed tomography in achieving the diagnosis of IPA in the critical care patient has been questioned in previous studies (Herbrecht, 2002). Bronchoscopy remains a useful diagnostic tool by directly visualizing pseudomembranes or obtaining specimens for cytology and culture. Characteristic findings on bronchoscopy include tracheal ulcers, raised nodules and the presence of pseudomembranes in the distal trachea and or bronchi (Angelotti, 2002). In the presented case, the patients worsening compliance and increasing plateau pressures may have been an early clue to the diagnosis of ATB. Amphotericin B has been the first line therapy in the treatment of invasive Aspergillus infections (Trof, 2007). In a randomized, unblinded clinical trial, Voriconazole demonstrated superiority over Amphotericin B for the initial treatment of invasive Aspergillus infection with an excellent tolerability profile (Herbrecht, 2002).

Anecdotal evidence suggests potential improved outcome with the use of capsofungin (Tasci, 2006). The high mortality rate associated with IPA has lead to the development of successful animal models using combination therapy of Amphoteracin B with an echinocandin (Herbrecht, 2002). The low incidence of ATB would make randomized investigation into the most effective treatment difficult. However, the high case fatality rate mandates aggressive antifungal therapy. The mainstay of therapy remains early diagnosis and initiation of antifungal therapy and supportive care in the intensive care unit. Invasive pulmonary aspergillosis is increasingly recognized as an important clinical entity in the critical care setting and one which may be encountered in an immunocompetent host.

*A. tracheobronchitis* is a rare form of IPA which when encountered in a mechanically ventilated patient has a guarded prognosis. This rare case of pseudomembranous *ATB* in an immunocompetent host demonstrates the diagnostic and therapeutic challenges associated with its management.

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