Aspergillus Tracheobronchitis With Airway Obstruction
A Case Series With Positive Patient Outcomes

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Background: *Aspergillus* tracheobronchitis (ATB) is a relatively rare and potentially fatal manifestation of *Aspergillus* infection in the tracheobronchial tree. The diagnosis of ATB may be delayed because of insidious onset and nonspecific signs and symptoms. On the basis of appearance, ATB is categorized into ulcerative, pseudomembranous, and obstructive type. We present 3 cases of ATB with obstruction of airways in immunocompromised patients with a history of malignancy and describe their clinical course. Two of the cases we present had a mixed pattern with pseudomembranous/obstructive type and one had ulcerative type of ATB. All showed nonspecific radiographic evidence of pathology and were ultimately diagnosed by a bronchoscopy. After bronchoscopy, voriconazole was prescribed to all the patients and 1 patient showed paradoxical worsening of a nodule with new cavitation.

Key Words: *Aspergillus* tracheobronchitis, obstruction, immunocompromise, hematologic, cancer

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Aspergillus is a ubiquitous mold, which is present in water, indoor surroundings, soil, organic debris, and other sites. The spores of *Aspergillus* are present practically everywhere in the atmosphere and are constantly being inhaled into the lower airways.[1,2] However, infections in immunocompetent or otherwise healthy individuals are rare because of active defense mechanisms against fungal organisms in the form of a mucosal barrier, macrophage, and neutrophil activity. On the contrary, impairment of these mechanisms increases the risk of colonization and progression to *Aspergillus*-related infections.[3–5]

Aspergillus tracheobronchitis (ATB) is a relatively rare pattern of aspergillosis and predominantly affects the trachea and bronchi. It is more commonly seen in patients with malignancy, solid organ transplant (especially lung transplant), and AIDS.[6,7] *Aspergillus fumigatus* is the most frequent subtype associated with ATB.[8] Previous studies have shown that ATB could present as an isolated finding or may be an indication of initial infection, which progresses to involve distal parts of lung and the parenchyma.[9,10] Therefore, it is of utmost importance to recognize ATB early and start appropriate treatment. Herein, we report 3 cases of ATB with obstruction seen in relatively immunocompromised patients with history of hematologic malignancy, lung cancer, renal cell carcinoma (RCC), or chronic obstructive pulmonary disease (COPD). We also briefly review the diagnosis and management of ATB.

CASE PRESENTATION

Case 1

The first patient is a 31-year-old woman with a history of Li Fraumeni syndrome with multiple cancers (liposarcoma of the left thigh, melanoma of the left shoulder, left parietal astrocytoma, colon cancer, and ductal carcinoma in situ of the left breast), myelodysplastic syndrome (MDS) status postallogenic hematopoietic stem cell transplant (HSCT), posttransplant relapse AML (3 months), and adrenal insufficiency. The patient came to the hematology clinic for follow-up of MDS and reported worsening productive cough, dyspnea, and multiple skin lesions on the lower extremities with no history of fever. She was admitted to the ward and examination revealed tachycardia, wheezing, and scattered rhonchi bilaterally and nonlabored respirations. The extremities showed multiple erythematous macular lesions with scabs.

Six weeks before her presentation, she had a dry cough and was found to be neutropenic (absolute neutrophil count, 260) for which cefepime, acyclovir, and micafungin were prescribed. At that time, isavuconazole was also added to her regimen for mold prophylaxis. Five days before this presentation, she reported that the cough had become productive of yellow and green sputum. On the computed tomography (CT) scan of the chest, nodular opacities suggestive of fungal pneumonia were observed.

NOTE: Patients with neutropenia and invasive aspergillosis have a mortality rate of more than 95%.

Because there was no improvement while taking isavuconazole after 4 weeks of therapy, it was discontinued and liposomal–amphotericin B was started. Over the course of next few days, cough and shortness of breath worsened and voriconazole (300 mg twice daily [BID]) was added to the regimen. Serum Galactomannan (GM) testing was performed and found to be negative. The white blood cell count was 1.71 cells/uL and fever developed with a maximum temperature of 100.7 F. While on this regimen, sputum fungal culture grew *Aspergillus fumigatus* and CT scan of the chest showed worsening perihilar consolidation on the right side. Two weeks later, she had an episode of intense coughing and respiratory distress. Chest x-ray showed increasing left and right lower lobe consolidation. A bronchoscopy for airway examination/therapeutic intervention demonstrated 100% obstruction of distal right mainstem bronchus and proximal bronchus intermedius by pale-yellow and green tissue with surrounding white friable lesions highly suggestive of ATB. The images taken during bronchoscopy are shown in Figure 1. The obstruction was relieved through bronchoscopic debulking and the tissue specimen sent for microbiology and pathology. Histopathology demonstrated multiple septate hyphae and grew *Aspergillus fumigatus*. The patient felt much better after the procedure with marked reduction of dyspnea and chest x-ray showed improved air expansion of the lungs. In the next few days, the absolute neutrophil count rose greater than 500 cells/uL. Upon discharge, oral voriconazole was continued for 3 months and liposomal–amphotericin B intravenously thrice weekly for 6 weeks. Several months later, lung findings cleared with no evidence of mold infection, but she died from refractory leukemia.

Case 2

The second patient is a 76-year-old man with COPD who had previously undergone radical left nephrectomy for RCC diagnosed 4 years earlier. He presented with a chronic cough for 4 months. The cough was productive with brown sputum and occasional blood. One-year before this, a new lesion was noted in his

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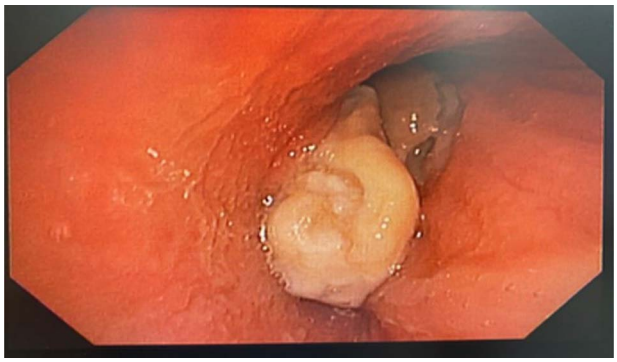


FIGURE 1. The figure shows a bronchoscopy image demonstrating complete right mainstem bronchus obstruction by pale-yellow tissue with necrotic material.

right kidney, which was positive for RCC, the patient was started on sunitinib and was tolerating the drug well.

On examination, the patient was afebrile and found to have decreased breath sounds at the base of lungs bilaterally. Laboratory analysis showed a white blood cell count: 4.7 K cells/uL and absolute lymphocyte count: 690 cells/uL consistent with lymphopenia. Computed tomography scan of the chest performed 1 month prior revealed left lower lobe mass (2.2 × 5.5 cm), which upon repeat CT scan did not change in size. In addition, bronchiectasis of left lower and right upper lobe with some mucus impaction was noted. Serum GM testing was negative.

Ultimately, a bronchoscopy was performed, which demonstrated right mucosal pit in the distal tracheal wall, a right upper lobe ulcerative lesion, and an endobronchial lesion in the left upper lobe. Purulent secretions were noted and removed with suctioning. The cultures grew *Aspergillus fumigatus*, a few colonies of *Candida albicans*, 4+ group beta hemolytic *streptococcus* and 4+ upper respiratory flora. Pathology of the tissue revealed bronchial wall with fungal organisms and marked acute inflammation with necrotic debris. The fungi had septate hyphae with 45-degree angle branching consistent with *Aspergillus*. The patient was prescribed oral voriconazole 200 mg BID for 3 months. At follow-up after 40 days of treatment, patient was asymptomatic and repeat CT scan of the chest showed increase in size of the left lower lobe mass by 0.5 cm with a new cavitation (Fig. 2). After changing voriconazole to isavuconazole for 3 months, the lung consolidation was resolved.

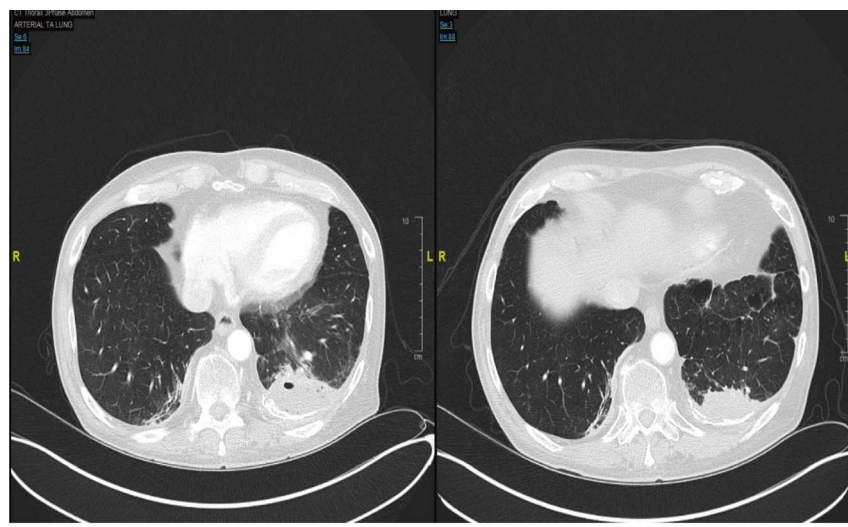
Case 3

A 60-year-old female smoker with Crohn disease and COPD presented with a nonproductive cough for 3 months. She had been diagnosed with stage 4 nonsmall cell lung cancer and had undergone 1 year of chemoradiation. As the cough was initially thought to be related to underlying COPD and/or radiation changes causing gastroesophageal reflux and pneumonitis, she was treated with inhaler therapy and a tapering course of corticosteroids without improvement in her cough. There was no history of fever.

On laboratory testing, her complete blood count, liver function test, and kidney function were normal. A CT scan of the chest done 2 weeks prior showed increasing consolidation around the right hilar area, especially posteriorly. Serum GM testing was also performed and found to be negative. After experiencing an episode of respiratory distress, a bronchoscopy was performed, which demonstrated right mainstem bronchus obstruction by pale-yellow material adherent to the posterior lateral and anterior walls with pooled secretions. A 75% obstruction of that area was noted; furthermore, there was a 2-mm opening at the distal bronchus intermedius with a yellow adherent material with 90% obstruction. The bronchoscopy images are shown in Figure 3. The pathology of biopsy material was positive for necrotic tissue in fibrin with no evidence of tumor and the fungal culture grew 2+ *C. albicans* and colonies of *Aspergillus flavus* and *Aspergillus niger*. There was marked improvement in the patient's condition after bronchoscopy. Recommendations were made to continue oral voriconazole 200 mg BID for a period of 3 months. At 1-month follow-up, the patient was tolerating the drug well with improvement in his symptoms.

DISCUSSION

Aspergillus tracheobronchitis continues to be a potentially lethal complication of *Aspergillus* infection in the immunocompromised as well as immunocompetent patients. When compared with other patterns of aspergillosis, ATB is a relatively rare manifestation of the disease. The risk factors of ATB include neutropenia, chronic steroid use, hematologic malignancy, and solid organ



After Before

FIGURE 2. The figure on the left shows worsening of nodular lesion with new cavitation associated with ATB after receiving 40 days of voriconazole therapy.

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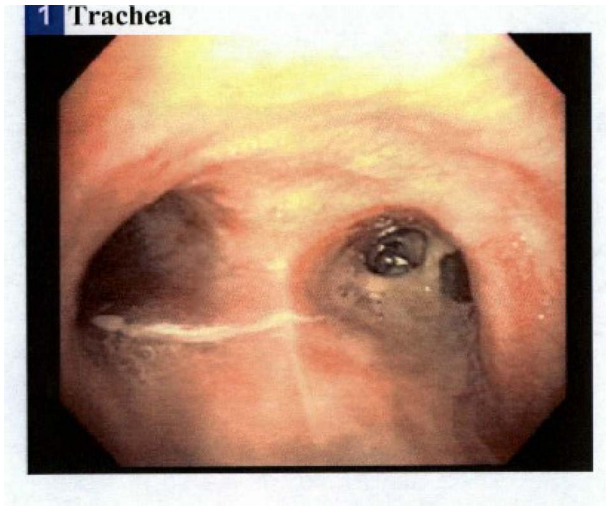

FIGURE 3. The bronchoscopy image shows 90% obstruction of the right mainstem bronchus and surrounding pale-yellow lesions.

transplant or HSCT and AIDS patients.[11,12] In lung transplant recipients, ATB is frequently observed at the anastomotic site, which may be due to the presence of suture material eliciting a localized immune reaction.[13] Although more commonly seen in immune compromised patients, some recent studies show that ATB can occur in immune competent patients with no known risk factors as well and may even be associated with a higher risk of mortality.[14–17] The higher mortality in these patients may in part be due to low suspicion of *Aspergillus* infection given their immune competent or relative immune compromised status. Herein, we have presented 3 cases of ATB with obstruction seen in immunosuppressed patients with a history of different underlying conditions.

The first case we presented is ATB in a neutropenic patient with a history of hematologic malignancy and HSCT. It is worth noting that patient was being managed for her MDS and there was a long gap between the HSCT and ATB infection. Our second patient was on sunitinib chemotherapy for RCC, and to our knowledge, only two case reports of pulmonary aspergillosis on sunitinib chemotherapy have been previously published with Visvardis et al[18] elucidating a possible mechanism of infection.[19] The patients in the second and the third case had a history of COPD, and interestingly, some studies have demonstrated that *Aspergillus* colonization in patients with structural lung disease like COPD may carry a significant risk for the development of ATB but the exact mechanism is not well understood.[20] Last, the patient in the third case had a history of nonsmall cell lung cancer having received chemotherapy and radiation therapy 1 year before his diagnosis.

Diagnosis of ATB in the early stages may be difficult and delayed because nonspecific symptoms and imaging findings, and this may lead to a worse prognosis.[8] In all the cases, we have presented there was a significant time lapse between onset of symptoms and diagnosis of ATB. Most commonly reported symptoms of ATB include cough, fever, and dyspnea.[6] The main symptoms in our patients were cough (frequently productive) and progressive dyspnea, which ultimately prompted bronchoscopy. Some studies suggest that neutropenic patients with unilateral wheezing and unremitting fever despite broad-spectrum antibiotic coverage may benefit from early bronchoscopy.[21–23]

Galactomannan is a component of *Aspergillus* cell wall, which is widely used to diagnose invasive *Aspergillus* infections nowadays because of its higher sensitivity when compared with cultures. The GM test can be carried out on serum as well as bronchoalveolar lavage fluid. The sensitivity of serum GM ELISA test when performed in patients with hematologic malignancy is 60% to 80%, whereas it is less 50% in nonneutropenic patients. The specificity of the test is approximately 90% according to most studies. Serum GM testing was negative in all the patients we presented. However, false-negative result is not uncommon especially when patients are on antimold prophylaxis. Similarly, false-positive results are also observed, which may be attributed to cross-reactivity between other fungal infections. Thus, GM testing may help in diagnosing ATB, but additional large-scale studies may be required to further study its role in diagnosis.[24,25]

Initial radiologic evaluation of patients with ATB through x-ray may aid in diagnosis but has low sensitivity and specificity.[6,26] It may be negative or show nonspecific findings, which include scattered pulmonary infiltrates, consolidation, or centrilobular nodules.[6] Computed tomography scan of chest as an initial radiologic test has higher diagnostic value when compared with x-ray of the chest.[11] In the cases we presented, CT chest mainly revealed nodular opacities and perihilar consolidation. Some radiologic findings, which may be considered specific for ATB (tracheobronchial wall thickening, atelectasis and endobronchial mass),[27,28] were not observed in any of our cases. For diagnosis of ATB, bronchoscopy with microbiology and histopathology is the criterion standard as sputum cultures are not reliable in immunosuppressed patients.[26] However, transbronchial biopsy may be contraindicated in patients with hematologic malignancy due to increased risk of bleeding. For this select group of patients, endobronchial ultrasound–guided transbronchial needle aspiration may be a useful alternative to achieve a diagnosis.[29]

Based on the bronchoscopy findings, Denning[30] proposed a classification for ATB in 1995, which consisted of 3 patterns: pseudomembranous, ulcerative, and obstructive. This classification is widely accepted. Recently, Wu et al[31] proposed another classification in 2010, which is similar to the previous one but focuses more on the depth of invasion by *Aspergillus* and consists of 4 types: (a) superficial infiltration, (b) full layer involvement, (c) occlusion type (airway occlusion of >50%), or (d) mixed type. The clinical relevance of the recent classification is still unclear. Although these classifications exist, different patterns or subtypes often coexist in a single patient. The ulcerative type usually presents as a discrete ulcer or plaque like lesion in the bronchial wall and is most commonly seen in lung transplant and AIDS patients.[6,32] Meanwhile, the pseudomembranous type is seen more frequently in severely immunosuppressed patients with hematologic malignancy or HSCT, and it manifests as thick membranes on the surface of tracheal and bronchial mucosa. In the cases, we have presented 2 patients who had the pseudomembranous/obstructive type and 1 patient who had the ulcerative type of ATB.

The ideal pharmacologic treatment for ATB is still unclear, but voriconazole is currently the drug of choice for invasive aspergillus infection. Voriconazole achieves higher concentration in interstitial space and bronchial mucosa, has fewer serious adverse effects, and has better survival when compared with Amphotericin-B in treating *Aspergillus* infections.[11] The mainstay of treatment for obstructive type ATB is bronchoscopic debulking followed by 3 months of systemic antifungal therapy with or without aerosolized Amphotericin-B.[33] After bronchoscopy, all of our patients were prescribed voriconazole for 3 months or until resolution of infection. However, our patient in case 2 had a paradoxical worsening of his lung nodule with new cavitation after 40 days of voriconazole therapy. Interestingly, a case report by Kim et al[34] demonstrated complete resolution of mass-forming ATB with only 19 days of voriconazole therapy and no bronchoscopic intervention. This report may highlight the importance of medical management especially with voriconazole

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in ATB patients with contraindications to surgical or invasive airway procedures.

To summarize, ATB is a rare manifestation of *Aspergillus* infection especially in immunocompetent patients because it is more common in immunocompromised patients. The symptoms and imaging findings of ATB are nonspecific, which may lead to a delay in diagnosis and treatment. Galactomannan testing for *Aspergillus* may aid in diagnosis of ATB; however, the mainstay for diagnosis as well as treatment remains to be bronchoscopy. Voriconazole therapy may be an effective treatment in patients with contraindications to invasive procedures.

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