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REVIEW ARTICLE

Invasive pulmonary aspergillosis – case report and review of literature

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Invasive pulmonary aspergillosis (IPA) is a severe fungal infection with a high mortality rate. The incidence of IPA is on the rise due to an increase in the number of patients undergoing transplants and receiving chemotherapy and immunosuppressive therapy. Diagnosis is challenging due to the non-specific nature of symptoms. Voriconazole is the mainstay of therapy. We present a case of an elderly woman presenting with acute bronchitis and asthma exacerbation, who succumbed to overwhelming IPA. It is uncommon for IPA to develop in patients on short-term steroid therapy for asthma exacerbation. The possibility of aspergillosis in immunocompetent patients should be considered in those on systemic steroids and deteriorating pulmonary functions.

Keywords: aspergillus; *steroids*; *asthma exacerbation*; *vascular invasion*; *ground glass opacities*

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Aspergillus is a fungus which is commonly found in the soil, food, plant debris, and indoor environment. The spores are easily aerosolized and inhaled. In the respiratory mucosa, the spores may germinate into hyphae, which in turn can invade the mucosa leading to invasive pulmonary aspergillosis (IPA) (1). Both innate immune responses and inflammatory cells limit fungal growth and prevent disease in the majority of individuals. Depending on host's immune status and specific immune-deficiencies, *Aspergillus* may lead to different pulmonary manifestations (Table 1).

IPA usually occurs in severely immunocompromised patients. Classic at-risk patients are those with prolonged neutropenia, either due to chemotherapy or immunosuppressive therapy, post hematopoietic stem cell transplant (SCT), or solid organ transplant (1, 2). Risk factors for IPA are summarized in Table 2.

IPA has rarely been reported in patients on short-course steroid therapy without chronic lung diseases (3, 4). We describe the case of an elderly woman who was found to have extensive IPA, in the absence of classic risk factors.

Case report

A 73-year-old woman was admitted to our hospital with complaints of shortness of breath and malaise. Nineteen days prior to admission, she was treated with inhaled steroids and cefpodoxime for acute bronchitis. A week before admission, she complained of fever, chills, wheezing, and cough with yellow sputum. She received oral prednisone and levofloxacin. However her symptoms worsened, and she presented to our emergency department. Her medical history included asthma with infrequent exacerbations (three exacerbations in the previous 3 years), hypertension, hyperlipidemia, diabetes mellitus, hypothyroidism, gout, spinal stenosis, and chronic kidney disease. Her home medications included carvedilol, furosemide, atorvastatin, gemfibrozil, sitagliptin, levothyroxine, allopurinol, erythropoietin, montelukast, fluticasone, and albuterol inhalers. Vital signs in the emergency department were temperature 97°F, blood pressure 144/66 mm Hg, heart rate 80/min, respiratory rate 16/min, and oxygen saturation 99% on room air. Examination revealed bilateral diffuse wheezing and pharyngeal wall erythema. Laboratory data showed white cell count 2.8×10^3 cells/dl with 72% neutrophils, hemoglobin 8.7 g/dl, hematocrit 27.2%, blood urea nitrogen 67 mg/dl, and serum creatinine 2.73 mg/dl. Liver function tests and electrolytes were normal. Electrocardiogram was normal and chest X-ray was without any infiltrate. Peak expiratory flow rate was 200 L/min. Diagnostic impression was asthma

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Table 1. Clinical course following inhalation of *Aspergillus* spores

Normal immune competent host: No infection
Previous cavitary lung disease: Aspergilloma
Excess Th2 response (allergic response): Allergic broncho pulmonary aspergillosis
Mild immune compromised state: Chronic necrotizing aspergillosis
Severe immune deficiency: Invasive pulmonary aspergillosis

exacerbation secondary to acute bronchitis. Intravenous methylprednisolone 40 mg every 8 hours, bronchodilators, and levofloxacin were given. Serum mycoplasma antibody, urine legionella antigen, nasal swab for respiratory syncytial virus and influenza antigen, and rapid streptococcal throat tests were negative. On day 5 of admission, a high-resolution contrast tomographic (HRCT) scanning of the chest revealed bilateral multifocal ground glass opacities. On day 7 of admission, she complained of chest pain and had oxygen saturation of 80% on room air. Cardiac enzymes were undetectable and echocardiogram was normal. Perfusion lung scan showed perfusion defects highly suspicious for pulmonary embolism, and intravenous heparin was started. On day 10 of admission chest X-ray revealed new multifocal bilateral infiltrates, and ceftazidime and azithromycin were added. She was intubated for respiratory failure. Hemodialysis was done on day 11 of admission. Repeat HRCT showed development of new extensive bilateral pulmonary nodular infiltrates with ground glass opacities (Fig. 1). Antibiotics were switched to ertapenem and azithromycin. On day 13 of admission, sputum cytology showed *Aspergillus* species, and voriconazole was administered. She was extubated on day 14 of admission per the family's wishes and she died later that day. Autopsy revealed *Aspergillus* hyphae invading through the bronchial mucosa, almost completely obliterating the lumen of mid- to small-sized bronchi (Fig. 2). Vascular invasion by *Aspergillus* was also evident with concomitant widespread pulmonary arterial thrombi (Fig. 3). Acute tubular necrosis in the kidneys and centrilobular liver necrosis were also reported.

Table 2. Risk factors for developing IPA

Stem cell transplant or solid organ (especially lung) transplant
Hematologic malignancies
Prolonged neutropenia
Critically illness in intensive care unit
Steroid use
Hemodialysis
Liver disease
Chronic obstructive pulmonary disease (COPD)/chronic lung diseases
Chronic granulomatous diseases

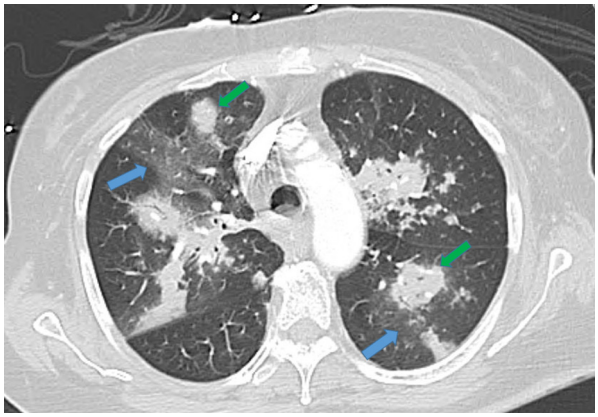

Fig. 1. High-resolution computed tomographic scan of the chest revealing multiple foci of ground glass opacities (blue arrows) and bilateral pulmonary nodular infiltrates (green arrows).

Discussion

IPA is caused by one of the four species of *Aspergillus*: *A. fumigatus*, *A. flavus*, *A. niger*, *and A. terreus* (5). It is increasingly seen due to a rise in the number of patients undergoing SCT and solid organ transplants, and also due to increasing number of patients on chemotherapy (6). Construction work in the vicinity of susceptible patients may increase spore aerosolization and is an independent risk factor (7). Mannose-binding lectin deficiency has also been associated with IPA (8).

Lower respiratory tract symptoms such as cough with or without sputum production, respiratory distress, wheezing, and fever are common. *Aspergillus* has a predilection for invading vasculature, especially in the neutropenic patients, leading to thrombosis, tissue infarction, and

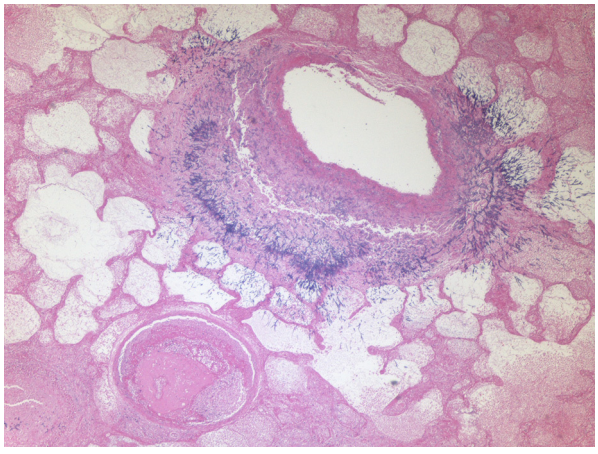

Fig. 2. Light microscopic findings of lung specimen (40 ×) stained with hematoxylin and eosin showing *Aspergillus* hyphae invading through the bronchial wall. A blood vessel is visible in the lower left field with an occluding thrombus and inflammatory cells in its lumen.

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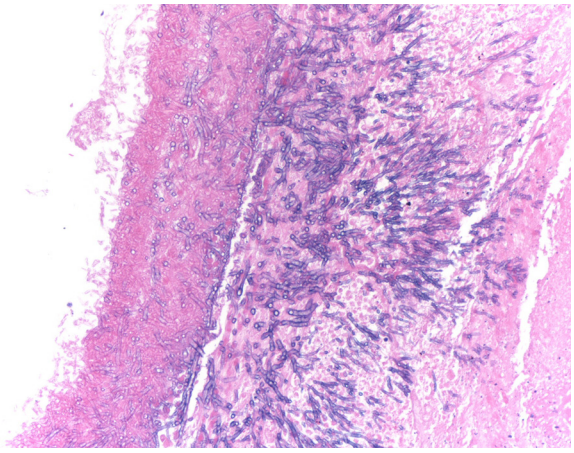

Fig. 3. Hematoxylin and eosin stain of the lung specimen under a light microscope at 200 × showing typical branching, septate *Aspergillus* hyphae, invading through the mucosa of a distal bronchi.

necrosis. In such cases pleuritic chest pain and hemoptysis may be present (2).

The diagnosis of IPA is challenging due to the nonspecific nature of the symptoms and is often delayed due to lack of clinical suspicion in patients without classic risk factors. Tissue biopsy with histopathologic demonstration of tissue invasion by fungal hyphae is considered the 'gold standard' (9). However, obtaining tissue specimens from critically ill, often intubated, and hemodynamically unstable patients is not always feasible. Identification of *Aspergillus* species in the sputum could represent colonization, especially in immunocompetent patients (1, 10). On the contrary, isolation of *Aspergillus* from sputum in patients with leukemia, or in those who have undergone SCT, has a positive predictive value of 80–90% for the presence of IPA (1, 11, 12). With regard to imaging studies, Patterson et al., in their review of 595 cases of IPA, reported that 85% of the cases had computed tomographic (CT) scan findings suggestive of IPA (13). HRCT is recommended in all cases of suspected IPA. Pulmonary nodules are the most commonly seen abnormality whereas the 'halo sign' is relatively more specific with a high predictive value for IPA in patients with neutropenic fever after SCT (14). Laboratory tests to detect *Aspergillus* antigens in body fluids, either serum or bronchoalveolar lavage fluid (BAL), are increasingly helpful in the diagnosis of IPA. Galactomannan (GM) testing or *Aspergillus* polymerase chain reaction (PCR) assay in BAL has good sensitivity and specificity for IPA (2, 15). Testing for both GM and PCR may increase sensitivity without compromising the specificity (2). BAL GM testing is part of the diagnostic criteria for IPA (16).

Definitions for proven, probable, and possible IPA for the susceptible population of immunocompromised patients with cancer and recipients of SCT have been stated (16). A criterion has also been suggested for the diagnosis of IPA in chronic obstructive pulmonary disease (COPD) patients (17).

The mortality rate of IPA continues to be very high, exceeding 50% in neutropenic patients (14), and 90% in SCT recipients (18). Amphotericin used to be the preferred antifungal, until a large randomized clinical trial comparing amphotericin with voriconazole for primary treatment of IPA showed a better response rate and higher survival (71 vs. 58%) at 12 weeks of therapy in the voriconazole group. Voriconazole also has a better side effect profile and is generally better tolerated. Echinocandins, such as caspofungin, are used as salvage therapy in patients not responding to or not tolerating first-line therapy (1). Due to differences in their mechanisms of action, combination therapy with azoles, trienes, and echinocandins could be a strategy to treat IPA (1). At present, voriconazole is considered the therapy of choice (19).

Prolonged and high-dose corticosteroid therapy is an established risk factor for the development of IPA (1, 2). Steroids inhibit macrophage killing of *Aspergillus* by nonoxidative mechanisms (20). Steroids may also promote the growth of *Aspergillus* (21). Although IPA is seen in patients with chronic lung diseases on long-term steroids, it is rarely seen with short use of corticosteroids (1, 2, 22). To the best of our knowledge, diagnosis of IPA after short-course steroid therapy for asthma in a 31-year-old man is the only other case of IPA in a similar clinical scenario (3). Relatively few cases of IPA are observed in truly immunocompetent patients without classic risk factors (3, 4).

Conclusion

Short duration steroid therapy may be a risk factor for IPA in certain individuals. Classic risk factors for IPA were absent in our patient, and thus IPA was not high on the differential diagnosis. In our patient, hypoxia raised the possibility of pulmonary embolism, and perfusion lung scan further supported this diagnosis. Angioinvasive IPA can lead to thrombosis and create perfusion defects (2, 23). Thus, the diagnosis of pulmonary embolism confounded the clinical picture by giving an alternate explanation for the patient's symptoms, preventing further investigations such as bronchoscopy.

Refractoriness to therapy manifested as worsening clinical symptoms, progressive hypoxia, and increasing pulmonary infiltrates despite aggressive antibiotic therapy should raise suspicion for IPA. In our opinion, bronchoscopy should be considered in such patients along with antigen detection with GM and PCR testing. Early treatment with voriconazole is the only hope, and treatment should be initiated as soon as IPA is suspected. Every effort should be made to taper off steroids in these patients.

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