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Title: A Critically Ill Patient with Aspergillus Fumigatus Sepsis Related Ischemic Colitis

Running Title: Invasive aspergillosis and critical illness

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Abstract

Background: Invasive aspergillosis (IA) is an opportunistic infection generally encountered in patients with hematological malignancies. However, IA is increasingly recognized in nonneutropenic and critically ill patients in the absence of classic risk factors.

Case report: An 81-year-old man with diabetes mellitus (DM), chronic renal failure (CRF) and heart failure, who had had one-week complaints of diarrhea, nausea and vomiting, was admitted to the intensive care unit with septic shock, acute respiratory failure and acute kidney injury. Chest computed tomography showed cavitary lung lesions and colonoscopy revealed ischemic ulcers in the descending colon. Other causes of cavitary lung lesions were excluded and all cultures were negative, except for bronchoalveolar lavage yielding *Aspergillus fumigatus*. Thus, *Aspergillus fumigatus* sepsis with multiorgan failures was diagnosed.

Conclusion: Inhaled *Aspergillus* conidia are kept under control by alveolar macrophage. DM, CRF and aging are the conditions that disrupt phagocytic activity of macrophages and predispose to IA.

Keywords: Critically ill patient, invasive aspergillosis, ischemic colitis, sepsis, phagocytic function.
**Introduction**

Invasive aspergillosis (IA) is an opportunistic infection that mainly occurs in immune compromised patients (1,2). *Although the lung is the main site of infection, almost every organ or system of the body can be infected* through the hematological spreading after blood vessel invasion by Aspergillus hyphae (1,3). IA has increasingly been diagnosed in patients admitted to the intensive care unit (ICU), even in the absence of a classic predisposing immunodeficiency. The incidence of IA in the ICU ranges from 0.3% to 5.8% (4,5). *The complex underlying conditions in the patients and nonspecific presentation of the symptoms can confound* IA diagnosis in the ICU (5). We report a patient with multiorgan failures admitted to the ICU where lung IA was detected as the cause of sepsis although the patient did not have definitive risk factors for IA.

**Case report**

An 81-year-old male patient with coronary artery disease, heart failure, diabetes mellitus (DM), pace maker and chronic renal failure (basal creatinine, 1.6-1.9 mg/dL) was admitted to the hospital with one-week complaints of nausea, vomiting and watery diarrhea with no blood or mucus. On admission, his blood pressure was 96/45 mm Hg, respiratory rate 26 per minute and room-air oxygen saturation 84% by pulse oximeter with normal temperature and heart rate. The initial abnormal laboratory tests were creatinine, 3.1 mg/dL; urea, 164.5 mg/dL: sodium,122 mEq/L; C-reactive protein, 22.3 mg/dL; partial thromboplastin time, 51 seconds; prothrombin time, 16.7 seconds; leukocytes, 13.7x10⁹; hemoglobin, 8.4 gr/dl; pH, 7.196; PCO₂, 20.1 mm Hg; HCO₃, 10.1 mEq/L; lactate, 2.4 mg/dL; base excess, -19.2 mg/dL. The patient was hospitalized with the diagnosis of diarrhea and acute kidney injury (AKI). The patient was intubated 24 hours later due to hypotension and respiratory failure, and admitted to the ICU with the diagnosis of septic shock. Chest computed tomography (CT) demonstrated cavitary lesions mainly located at the left lung along with the left pleural effusion (Fig. 1). Deep tracheal aspirate (DTA), blood, urine and stool cultures, and acid-fast bacilli (AFB) staining of DTA on 3 consecutive days were negative. Stool examination showed leukocytes, but was negative for
Clostridium difficile enterotoxin, ova and parasites. Pleural fluid was in transudate with negative AFB staining, culture and cytology. The possibility of rheumatologic was excluded by autoantibody panels. Lung septic embolism from infective endocarditis was ruled out by esophageal echocardiography. Neck and abdominal CT were normal as bronchoscopy. Studies of human immunodeficiency virus (HIV), hepatitis virus C and B, severe acute respiratory syndrome coronavirus-2, protein electrophoresis, and blood smear were unremarkable. Colonoscopy, done on day 4, showed ulcers with sharp borders and centrally located exudates in the descending colon and ischemic colitis was assessed (Fig. 2). Since the abdominal examination of the patient was unremarkable along with normal abdominal CT and ultrasonography, the perforation was not considered. Tazobactam-sulbactam, metronidazole and linezolid were prescribed in the ICU, but the patient did not improve. Mold growth in BAL culture was determined on day 6 and amphotericin B was begun. The patient benefited from the therapy and noradrenaline infusion was stopped on day 10. The patient deteriorated on day 17 because of ventilator-associated pneumonia, did not responded to antibiotic therapy and died on day 20. The family refused an autopsy. BAL culture yielded Aspergillus fumigatus. Mycobacterium and colon tissue cultures resulted negative. Pathology of the colon delineated ischemic colitis with no Aspergillus hyphae.

Discussion
Species of the genus Aspergillus are ubiquitous fungi. The conidia (spores) are easily aerosolized and lung infections are caused by inhalation of airborne conidia (2). They are most commonly found in the upper respiratory tract, including the external ear. IA is an opportunistic infection that mainly occurs in patients having allogeneic stem cell transplantation, solid organ transplantation, HIV/acquire immunodeficiency syndrome and immunosuppression by chemotherapy or corticosteroids, and is mostly caused by Aspergillus fumigatus (1-3). However, IA has been recognized in patients in the absence of an apparent predisposing immunodeficiency. Other conditions seemed to be associated with IA are chronic obstructive pulmonary disease, emphysema, autoimmune disease, DM, acute/advanced liver failure, renal failure, aging, and being in intensive care unit (2,6). IA in the ICU can be two types; the patients can have the disease of IA when admitted to the ICU or develop IA in the ICU after the airways

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are colonized by the microorganism, and critical illness induced immunosuppression leads to the microorganism to invade the alveoli (4,5). A high index of suspicion is needed to diagnose IA in critically ill patients without known predisposing risk factors, especially when the pulmonary infiltration was persisted despite the broad-spectrum antimicrobial therapy (4). IA in the ICU carries a high mortality rate reaching 80% (7). The diagnosis of IA in non-neutropenic critically ill patients is difficult as signs and symptoms are not specific, and importantly, low clinical suspicion lead to delayed initiation of diagnostic tests. In the present case, we first focused on tuberculosis and septic emboli, and then, on rheumatologic diseases. When mold growth from BAL was reported, IA was moved to the top of the list of possible diseases as the cause of cavitary lesions, ischemic colitis, shock and AKI. Since microbiologic and pathological studies of the colon did not show Aspergillus invasion, the ischemic colitis was considered to be sepsis-related.

Aspergillus conidia are kept under control by alveolar macrophages in immune competent individual. Defects in phagocytic function of macrophage as seen in chronic granulomatous disease, or prolonged neutropenia impair killing and result in continued fungal growth within the host (1,2). Once conidia germination occurs, Aspergillus invades lung parenchyma and arteriole, and causes ischemic necrosis (2). Although our patient did not have classic risk factors, he was older, and had DM and renal failure that all three conditions cause abnormalities in phagocytic function of leukocytes (8-10). Voriconazole is the first choice of the drug for IA treatment. Intravenous voriconazole includes the vehicle sulfobutylether-beta-cyclodextrin that can accumulate in moderate-severe renal impairment (5). Amphotericin B is the second line drug which was ordered in our case as the patient had renal impairment.

IA in critically ill patients represents a challenge for the clinicians. The complex underlying conditions in the patients, nonspecific presentation of the signs, and lack of clear identification criteria can confound the diagnosis. Therefore, a high index of suspicion is needed to diagnose IA in critically ill patients.

References

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Figure legends

Figure 1: Chest computed tomography demonstrate a left cavitary lesion (white arrow), left pleural effusions (black arrow) and air around thoracic aorta and esophagus (short white arrow).

Figure 2: Colonoscopy showed the longitudinal ulceration at descending colon.
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