



Invasive pulmonary aspergillosis in a patient with cirrhosis

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ABSTRACT

Aspergillus molds are ubiquitous environmental molds that can cause devastating invasive infections in immunocompromised patients. These infections often go unrecognized in critically ill patients. This case describes a 68 year-old female resident of a long-term nursing facility with history of dementia, nonalcoholic fatty liver disease with cirrhosis, chronic kidney disease stage III and insulin-dependent type 2 diabetes who presented with vomiting, diarrhea and leg swelling. She developed hypotension and was treated for sepsis but found to have negative routine infectious workup. Chest imaging showed nodular densities and bilateral opacities. She developed acute renal failure and hypoxic respiratory failure followed by acute decompensated cirrhosis with refractory volume overload and hypotension and was eventually transitioned to comfort care measures. Autopsy ultimately showed invasive pulmonary aspergillosis. Here we review the diagnosis and management of invasive fungal infections in critically ill patients without typical risk factors or clinical findings for invasive fungal disease. Invasive fungal infections are frequently missed and carry high mortality rates, therefore warranting consideration in critically ill populations.

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Introduction

Aspergillus molds are ubiquitous in the environment and can cause a spectrum of disease from colonization of airways to invasive pulmonary aspergillosis (IPA) which carries mortality rates exceeding 60 % [1,2]. Classically invasive fungal infections (IFIs) such as IPA were thought to be seen only in the setting of severely immunocompromised states including hematologic malignancy, neutropenia or T-cell suppression. However, increasingly these infections are seen in other patient populations including those with cirrhosis, COPD and ESRD as well as critically ill patients without a specific immunocompromised state [3]. Heightened suspicion is needed to identify these commonly missed infections in ICU patients [4].

Case presentation

A 68 year-old female resident of a long-term nursing facility with dementia presented to the ED with new onset of vomiting and diarrhea. The patient was oriented to self and place but unable to

provide an accurate history of present illness due to memory loss. She denied nausea, abdominal pain, bleeding or fevers, but complained of bilateral leg swelling with vague leg discomfort. Her diuretic dose had been increased over the previous three days due to increasing lower extremity edema. The patient denied focal leg pain or redness, trauma, rash, shortness of breath or chest pain. Her medical history was significant for nonalcoholic fatty liver disease with cirrhosis, chronic kidney disease stage III and insulin-dependent type 2 diabetes. She had never smoked cigarettes and had no history of alcohol or substance abuse.

On arrival, the patient was afebrile, with a heart rate of 55, BP of 96/43 mm Hg, a respiratory rate of 16 breaths/min, and an oxygen saturation of 96 % on room air. BMI was 36 kg/m². Patient was alert and conversant but oriented to self and place only. Mucous membranes were dry and sclera were anicteric. Cardiopulmonary exam revealed regular heart rate without an S3, normal JVP and clear lungs. Abdomen was benign and stool hemocult was negative. There was pitting lower extremity edema to the level of the knees without focal tenderness or erythema. No common findings of cirrhosis were present.

Hemoglobin level was 8.7 g/dL, WBC count was 12,400/ μ L with 91 % segmental neutrophils and no bands, and platelets were 77,000/ μ L. Sodium level was 138 mM, potassium level was 4.4 mM, bicarbonate level was 15 mM, BUN level was 72 mg/dL, and creatinine level was 4.16 mg/dL prior baseline of 1.7 approximately 5 months earlier. Total bilirubin was 1.9 mg/dL, aspartate

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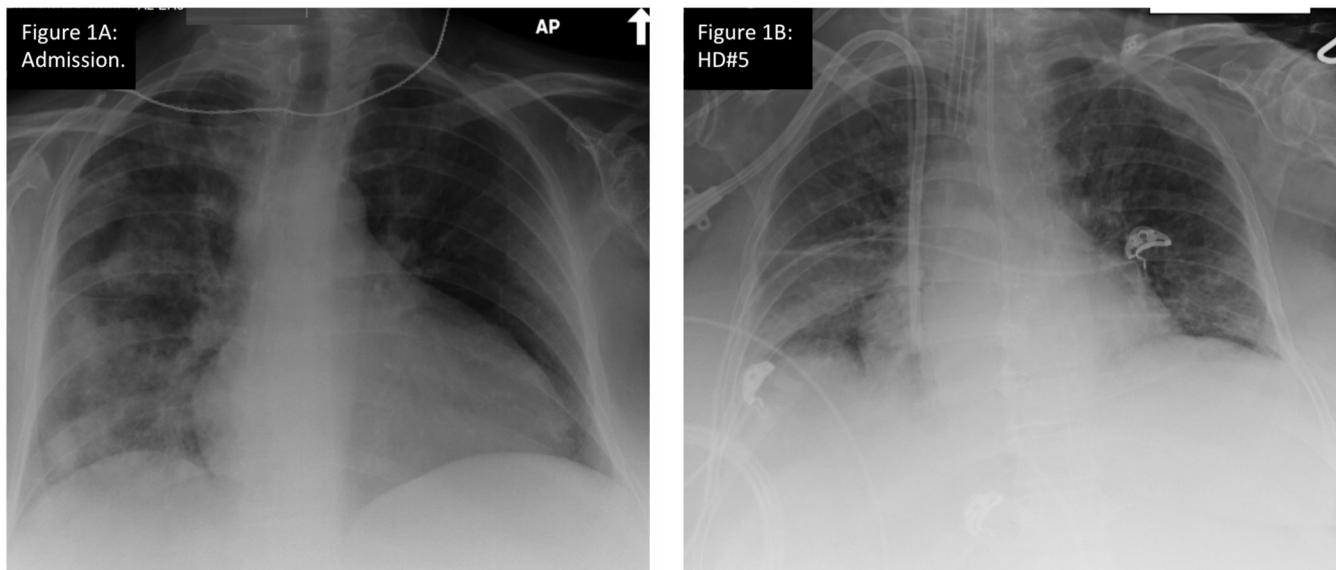


Fig. 1. A. Chest X-ray on admission demonstrates focal right-sided infiltrates. B. By hospital day (HD) 5, the patient is intubated and scattered bilateral infiltrates are present.

aminotransferase was 63 u/L, alanine aminotransferase was 34 u/L, INR was 2.1 and ammonia was 94 umol/L. Venous lactate drawn peripherally was 1.6 mmol/L. ECG revealed sinus bradycardia. Chest radiograph demonstrated multiple nodular densities and ill-defined airspace opacities in the lungs, mainly on the right (Fig. 1A).

While in the Emergency Department, the patient became hypotensive (BP = 78/34 mm Hg), and intravenous received fluid resuscitation and empiric broad spectrum antibacterials (vancomycin and piperacillin/tazobactam) for possible sepsis. She was admitted to the hospital for further management, and received additional IV fluids for hypotension, but had a normal lactic acid level and negative blood and urine cultures. She was unable to produce sputum for analysis. A nasal swab for methicillin resistant *Staphylococcus aureus* was negative, and vancomycin was stopped after 48 h. Liver enzymes were elevated and a bedside portable ultrasound was consistent with cirrhosis but showed no evidence of biliary obstruction. Echocardiogram showed normal systolic and diastolic function. She developed progressive oliguric renal failure with urinary sediment demonstrating acute tubular necrosis and dialysis was initiated.

On hospital day #3, the patient developed hypoxic respiratory failure and was admitted to the Intensive Care Unit and subsequently intubated. A follow up chest X-ray demonstrated worsening bilateral airspace disease or pneumonia (Fig. 1B). The patient was supported with mechanical ventilation, pressors, and dialysis. Intravenous piperacillin/tazobactam was continued, and vancomycin was resumed, with doses adjusted for renal failure. She was initiated on CVVHD due to worsening hypotension. Over the next two weeks, respiratory function stabilized with PEEP of 5 cm H₂O and FiO₂ of 40% but she was unable to be weaned from the ventilator due to weakness and waxing and waning encephalopathy. Despite clinical evidence of hypervolemia, she remained hypotensive and pressor-dependent, which interfered with dialysis, and was treated with stress-dose steroids. She developed hematologic abnormalities including thrombocytopenia, anemia, and coagulopathy consistent with liver failure. At the request of her family, she was transitioned to comfort care and died on hospital day #18. Permission for an autopsy was granted.

The autopsy demonstrated a shrunken liver weighing 750 g with findings of hepatic cirrhosis, massive abdominal ascites (8100 mL)

and esophageal varices. Histologic examination of the kidneys demonstrated intratubular oxalate crystals consistent with acute kidney injury. Additionally, there was nodular glomerulosclerosis and arterial and arteriolar nephrosclerosis present, indicative of an underlying nephropathy consistent with the patient's history of diabetes mellitus and hypertension. Mild to moderate aortocoronary atherosclerosis was identified with mild cardiomegaly and myocyte hypertrophy. Acute and chronic pancreatitis were also present.

Gross examination of the lung demonstrated heavy lungs (right: 900 g; left: 600 g) with mostly ill-defined areas of consolidation throughout the right lung except for a more well-defined 3 cm consolidation in the right upper lobe (Fig. 2A and B). Histologic analysis of the areas of consolidation in the right lung demonstrated septated hyphae with acute angle branching, consistent with *Aspergillus* species, including foci of fungal hyphae invading into vessel walls (Fig. 2C). These findings are consistent with invasive pulmonary aspergillosis (IPA). There were no fungal infiltrates identified in the right lung or other organs. Bilateral organizing pulmonary thromboemboli were also identified histologically within medium-sized vessels, although without discernable fungal organisms. The immediate cause of death was determined to be pulmonary aspergillosis with underlying end-stage renal and liver disease.

Discussion

Aspergillus is a ubiquitous fungus that causes a broad spectrum of pulmonary disease, from a mild hypersensitivity reaction to invasion of the blood and lymphatic system. Exposure to aspergillus is widespread by way of inhaled conidia, or spores, from the environment that reproduce asexually by forming hyphae [1]. Airway epithelial cells and alveolar macrophages recognize cell wall components in the hyphae that form during germination and initiate an innate immune response characterized by neutrophil recruitment and activation [5]. Through these processes, immunocompetent hosts will clear the organism without difficulty, however when immunity is impaired, the opportunity for invasive pulmonary aspergillosis (IPA) emerges [5]. The term 'invasive' is defined by progression of aspergillus across tissue planes with destruction of local tissue and angioinvasion with passage to other parts of the body. On tissue sections, *Aspergillus* appears as

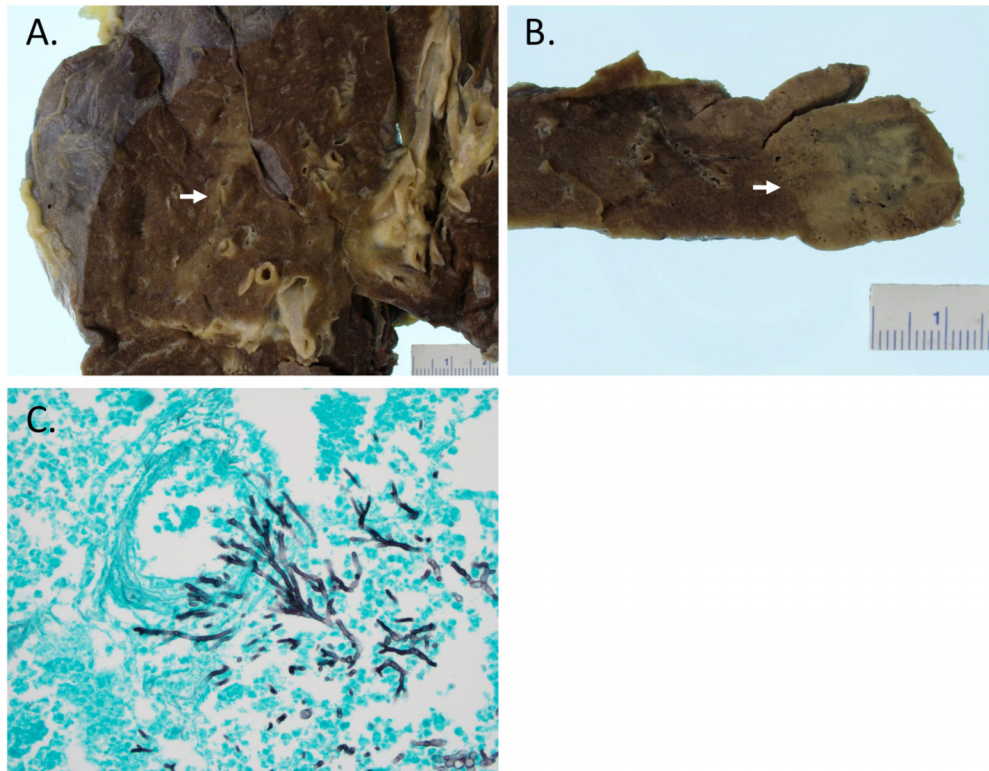


Fig. 2. A. Autopsy demonstrated ill-defined consolidation in the right lower lobe (arrow), and focal consolidation in the right upper lobe (arrow, B). C. Right lung section demonstrating septated hyphae with acute angle branching invading a vessel wall, consistent with IPA (GMS, original magnification $\times 400$).

septated hyaline hyphae with acute angle branching. Lung parenchyma often develops nodules and central liquefactive necrosis [1]. The immune system plays a key role in how aspergillus exposure and infection are manifested clinically and histologically. For example, in neutropenic patients there is less cellular inflammation and neutrophilic infiltrate [1].

Diagnosis of invasive fungal infections (IFI) such as IPA can be challenging and a high index of suspicion is needed particularly in critically ill patients without typical risk factors or clinical findings, as reported mortality rates exceed 60 % [1,2]. The 2008 revised definitions of invasive fungal disease from the EORTC/MSG consensus group provide some direction in identifying proven, probable or possible IFIs, although the criteria proposed are designed for enrolling patients in research studies rather than guiding clinical diagnosis. “Proven” fungal infection requires definitive identification of fungal elements in tissue or culture. “Probable” IFI requires that a combination of host, clinical and mycological evidence described below, whereas “possible” IFI includes host and clinical factors but lacks mycological evidence [6]. A separate algorithm has been suggested for identifying IPA in an ICU population, taking into account mycological data, signs and symptoms, host factors and imaging [7].

Signs and symptoms of IPA include fever refractory to antibacterials, respiratory insufficiency, chest pain and hemoptysis [2,5]. All of these are highly non-specific in critically ill patients and furthermore IPA may develop in patients with pre-existing lung injury including pneumonia, ARDS and inhalation injuries [2]. Non-neutropenic patients may have a more prolonged course without fever making IPA a frequently missed diagnosis in the critically ill population [4,8,9]. It is important to note that we did not perform post-mortem fungal cultures in this case, and it remains possible that the pathologic findings were due to *Pseudallescheria boydii* or related fungi.

The majority of patients with IPA have a known underlying defect in immunity, which the EORTC/MSG host factors specify as neutropenia, allogeneic SCT, prolonged steroid use, T-cell immunosuppressant or inherited immunodeficiency [6]. Other conditions associated with IPA include renal failure, hemodialysis, diabetes mellitus, HIV/AIDS, ARDS and COPD [3], but in one recent study Blot et al. found that almost 30 % of ICU patients with IPA lacked obvious host risk factors [7]. Our patient had cirrhosis, which is known to affect both humoral and cellular immunity in what is termed cirrhosis associated immune dysfunction and immune paralysis [10,11]. One observational study found a prevalence of 14 % for probable IPA in critically ill patients with cirrhosis and another found that 28 % of ICU patients with cirrhosis had proven or putative IPA [9,11]. Our patient had both renal failure and diabetes in addition to liver cirrhosis. It would seem logical that the co-existence of multiple host factors would further increase risk of IPA, but we are not aware of studies that have examined this question systematically.

Clinical evidence for IFI includes primarily CT imaging findings which are classically a “halo sign” of groundglass surrounding a macronodule, air-crescent sign, or cavitation [5]. However, reportedly 70 % of critically ill patients with proven IPA did not show classical radiographic findings [1,11]. Other findings may include centrilobular nodules and branching opacities with “tree-in-bud” appearance. Invasion into blood vessels may produce wedge-shaped infarcts [1,12]. Our patient exhibited nodules which can be seen in IPA but are non-specific and not included in current EORTC/MSG criteria [6].

Mycological criteria include direct observation of mold in fluid samples or serologic tests that recognize fungal cell wall components, such as ELISA of galactomannan antigen for Aspergillosis or 1,3-Beta-D-glucan assay for unspecified IFI [6]. Isolation of *Aspergillus* can be completed by sputum culture, or more invasively via bronchoscopy with bronchoalveolar lavage and

lung biopsy. In non-neutropenic patients galactomannan in BAL shows higher sensitivity than in serum due to antigen scavenging, although repeated serum measurements may increase sensitivity [13]. In one study of cirrhotic patients, galactomannan from BAL was found to have sensitivity of 90 %, specificity of 85 % [11].

In critically ill patients, it is difficult to distinguish between asymptomatic colonization of the respiratory tract versus true invasive infection. Often, empiric treatment is elected because IPA carries a high risk of mortality with delayed treatment, although colonization reportedly carries a mortality rate as high as 40 % [13]. However, only half of *Aspergillus* isolates (of which 90 % are due to *Aspergillus fumigatus*) in the intensive care unit turn out to be IPA. Different algorithms have been proposed to help with clinical decision making, and discriminate between “putative” IPA vs. colonization [7].

Voriconazole is the mainstay of treatment for confirmed or suspected IPA due to increased efficacy and less toxicity, particularly with therapeutic drug monitoring [14,15]. Isovucanazole is a newer alternative which is non-inferior to voriconazole. Liposomal amphotericin B is most appropriate if mucormycosis infection and also in patients with liver insufficiency, where voriconazole may have increased toxicity [15]. Combination of azoles with an echinocandin has also shown benefit in some studies [14]. Extended treatment is typically required depending on the anticipated state of the immune system.

This case illustrates that IPA can occur even in the absence of obvious systemic immunosuppression. In our patient, fungal elements were confined to the lung and not detectable in other organs. At the time of her death, the major clinical issues were persistent hypotension and failure to wean, and it is difficult to know whether specific anti-fungal treatment would have changed the outcome. Nonetheless, this case reminds us to remain vigilant for IPA in the setting of critical ill patients with sepsis and pulmonary infiltrates of unknown cause. Our case also underscores the utility of the autopsy in identifying previously unsuspected medical diagnoses.

Consent

Consent for submitting this case report was provided by the patient’s family.

Authors contribution

Heather Clark prepared the final manuscript and performed the literature review. Hugo Valencia and Steve Georas cared for the

patient and prepared the initial manuscript draft. Jennifer Findeis-Hosey performed the autopsy and interpreted the autopsy material.

Declaration of Competing Interest

Nothing to declare.

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