



Case Report

Adventitious sporulation in *Fusarium*: The yeast that were notMatthew B. Lockwood^a, Juan Carlos Rico Crescencio^{a,b,c,*}^a University of Arkansas for Medical Sciences, Department of Internal Medicine, Little Rock, AR, USA^b University of Arkansas for Medical Sciences, Division of Infectious Disease, Little Rock, AR, USA^c University of Arkansas for Medical Sciences, Myeloma Institute, Little Rock, AR, USA

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ABSTRACT

In immunocompromised patients, *Fusarium* species cause infections that lead to high mortality. Our case report describes a case of disseminated fusariosis in a neutropenic patient with AML after myelosuppressive chemotherapy, and a neutropenic multiple myeloma patient with *Fusarium* fungemia awaiting stem cell collection. Both cases highlight the fact that *Fusarium* can grow as yeast-like structures in the blood causing a delay in diagnosis, and that *Fusarium* has a tendency to be a resistant organism. *Fusarium* was only susceptible to amphotericin B in both cases, but we chose to continue treatment with voriconazole in the first case with disseminated infection, despite culture results, in view of his good clinical response. Despite high mortality rates in disseminated infection, our two patients had good outcomes.

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Introduction

Fusarium are filamentous non-pigmented septated fungi ubiquitous in the environment. Fusariosis is a not uncommon invasive mold infection in patients with hematologic malignancies and hematopoietic cell transplants. Infection tends to spread rapidly in immunocompromised patients due to angioinvasiveness and fungemia but tends to remain localized in immunocompetent patients. Blood cultures are positive in almost half of the immunocompromised patients with *Fusarium* infection [1]. Fusariosis has high mortality rate once disseminated, and reversion of neutropenia is imperative along with antifungal therapy with voriconazole or amphotericin B.

Case report #1

A 63 year-old-male was admitted to our institution with the chief complaint of productive cough for 4 days, associated with fever up to 101.2°F, pleuritic chest pain, asthenia and emesis. The patient had history of acute myeloid leukemia, recently completed consolidation cycle #3 with high-dose cytarabine for 10 days prior to this admission, and was taking acyclovir, fluconazole and

levofloxacin for neutropenic prophylaxis. Past medical history was also remarkable for diabetes and DVT. He is a retired truck driver, lives with his wife and has no toxic habits or family history of malignancies.

Upon examination, the patient appeared ill, afebrile ($T 98.7^{\circ}\text{F}$), tachycardic (HR 122 bpm), normotensive (BP 120/62 mmHg) and tachypneic (RR 29 breaths per minute). His physical exam revealed respiratory distress with clear lung auscultation, and left arm PICC line with no signs of infection. Skin was intact. Laboratory results were remarkable for pancytopenia with profound neutropenia (WBC 0.02), severe anemia (Hgb 5.3), thrombocytopenia (plat 12), mild acute kidney injury, and elevated blood glucose. Chest X-ray showed bibasilar atelectasis and small right pleural effusion. Cefepime and vancomycin intravenously were started empirically for neutropenic fever. Fluconazole and acyclovir were continued as prophylaxis.

Chest CT was obtained the following day in view of persistent fevers and respiratory distress, and revealed bilateral nodular opacities (Fig. 1). Yeast-like forms were observed on gram stain on day 2 of incubation of the aerobic blood culture bottle, and the same bottle on day 4 also showed hyphae (Figs. 2 and 3). Fluconazole was stopped and amphotericin B 3 mg/kg intravenously daily was started until blood culture revealed *Fusarium* spp. four days after presentation to ED. At that time, amphotericin B was switched to voriconazole IV. Patient was discharged on oral voriconazole seven days after admission.

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Fig. 1. CT chest demonstrating multiple rounded nodular densities scattered throughout the both lungs.

Almost 3 weeks after initial blood cultures were obtained, fungal sensitivities showed azole-resistant *Fusarium*, only sensitive to amphotericin B. In view of good clinical response, it was decided to continue voriconazole PO for a total of 6 months. Repeated CT chest five months after starting antifungal treatment showed complete resolution of pulmonary nodules. During treatment course patient developed nausea and mild transaminitis that did not require discontinuation of the drug.

Case report #2

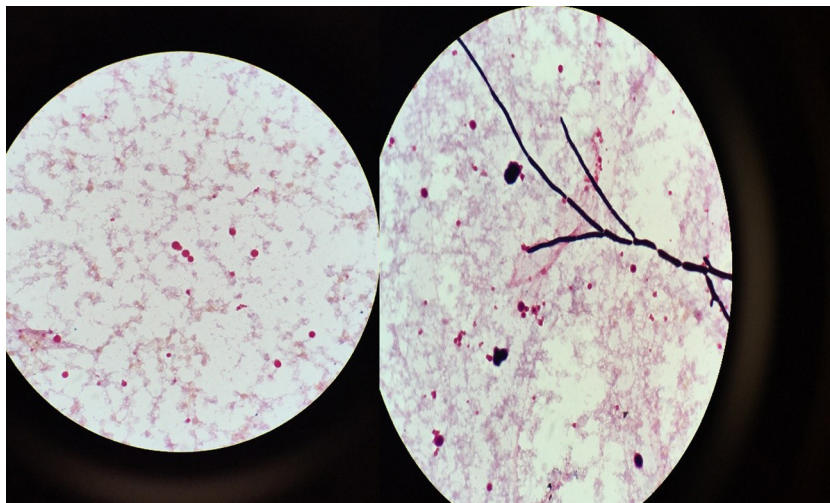
The patient in this case was a 46 year-old-male with high risk multiple myeloma with CNS involvement and heavily treated in the past who presented to our infusion center on day 13 post-chemotherapy with fever, chills, odynophagia, dysphagia and vomiting. He had completed a cycle of chemotherapy with cisplatin, adriamycin, cyclophosphamide, mesna, etoposide and dexamethasone. No other comorbidities were reported. Patient lived with his mother, was a former smoker, and uncle had history of cancer. He was on levofloxacin, fluconazole and acyclovir as standard precautions.

At the time of our evaluation, he appeared chronically ill, afebrile ($T 96.7^{\circ}\text{F}$), tachycardic (HR 95 bpm), normotensive (BP 113/73 mmHg) and normal respiratory rate. His physical

exam revealed mild mucositis, and pedal edema. He had an Ommaya reservoir, an implanted port, and a subclavian central venous catheter with no signs of infection. No skin lesions were identified. Laboratory results were remarkable for pancytopenia with profound neutropenia (WBC 0.02), anemia (Hgb 8.6), thrombocytopenia (plat 14), hyponatremia (Na 125 mmol/L), hypophosphatemia (P 1.8 mg/dL) and elevated CRP (199 mg/L). A PET/CT showed no infection. Cefepime and vancomycin intravenously were started empirically for neutropenic fever, and fluconazole and acyclovir were continued as prophylaxis.

Four days after a blood culture was obtained from central venous line, yeast grew in the aerobic bottle. Central venous line was removed but lport was kept in view of negativity of repeated culture studies. Fluconazole was switched for micafungin intravenously until culture revealed *Fusarium* spp. 8 days after blood culture collection. Micafungin was stopped, and patient was started on combination therapy with amphotericin B intravenously and voriconazole intravenously.

Culture results revealed azole-resistant *Fusarium* with amphotericin B MIC of 2. Patient received a total of 6 weeks of amphotericin B for *Fusarium* fungemia. Infection resolved, but unfortunately patient died 8 months after the fusariosis due to a relapse of end-stage, refractory multiple myeloma.



Figs. 2 and 3. Gram stain initially showing spores describe as yeast forms, and later septated hyphae.

Discussion

Fusarium is the second or third most common invasive mold infection in immunocompromised patients. It is especially prevalent in patients with hematologic malignancies and hematopoietic cell transplants. A recent study found that smoking was the only significant variable associated with invasive fusariosis in AML patients [2]. In the immunocompromised host, the principal portal of entry for *Fusarium* spp. is the airways, followed by the skin at site of tissue breakdown and mucosal membranes [1]. In the first case, the most likely portal of entry was the airway, whereas mucosal membrane due to mucositis would be the most reasonable focus in the second patient.

Although sometimes similar in the population at risk, presentation and radiological imaging, aspergillosis and fusariosis are different in that fusariosis has a much higher rate of blood culture positivity. In one study looking at 294 patients with fusariosis, 41% had positive blood cultures yielding *Fusarium* [1]. In our report, blood cultures were initially reported with yeast-like structures, delaying correct treatment in both patients due to adventitious sporulation in the blood culture bottle. Adventitious sporulation is the presence of fungal reproductive structures within infected tissue. Those reproductive structures include, fertile cells known as phialides, and the conidia (spores) that arise serially from the apical orifice of each phialide [3]. Schell also hypothesized that the sustained release of fungal spores into the bloodstream, via angioinvasion and adventitious sporulation, may explain the higher prevalence of positive blood culture results and rapid rate of dissemination associated with fusariosis [3]. Adventitious sporulation in *Fusarium* spp. was first observed by Wolf in 1955, and erroneously described as a phenomenon of dimorphism by Kidd and Wolf in 1973 in a patient with mycotic keratitis caused by *Fusarium moniliforme* [4,5]. They incorrectly thought *Fusarium* spp. grew in two different morphological forms depending on the culture media, distinguishing a mycelial phase on solid and liquid media, and a yeast phase on liquid media upon agitation at 25 °C and 37 °C.

Both patients were neutropenic due to myelosuppressive chemotherapy for their underlying hematological malignancy. Rapid reversion of neutropenia along with appropriate therapy with either amphotericin B or voriconazole are key to prevent a fatal outcome. Posaconazole is considered salvage therapy, and isavuconazole, a new broad-spectrum triazole, has shown limited

in vitro activity against *Fusarium* species, with a MIC₉₀ of $\geq 16 \mu\text{g/mL}$ [6]. Removal of infected catheters and surgical debridement of large single lesions are also recommended. In a study of 84 patients with fusariosis and hematologic malignancies, only 18 of 84 patients (21%) survived after 90 days. Of those 66 deaths, 59 died of fusariosis [7]. Another study showed only 13% of patients with fusariosis and hematopoietic cell transplants survived after 90 days [8]. Despite both isolates showed high MIC for voriconazole, the first patient was managed with voriconazole in view of his good clinical response. Different species may have different patterns of susceptibility. The relevance of these in vitro data is not clear, because there are not enough data documenting a correlation between MICs and the clinical outcome [1]. In one study of 26 patients with a *Fusarium* infection, 46% were cured or improved with Amphotericin B lipid complex [9]. Another retrospective study with 73 patients with proven or probable *Fusarium* infection in France showed a 47% success rate with voriconazole [10]. The optimal duration of therapy remains unclear due to the lack of trials. We chose to use antifungal treatment for 6 months in disseminated fusariosis, and 6 weeks in isolated fungemia.

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