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Disseminated Infection Due to *Neocosmospora (Fusarium) falciformis* in a Patient with Acute Myelogenous Leukemia

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INTRODUCTION

Fusarium species are ubiquitous in soil, plants, organic matter, and water; they are important plant pathogens associated with vascular wilt, rots, and damping-off diseases.[1] Some species are animal and opportunistic human pathogens. *Fusarium solani* species complex (FSSC), recently renamed *Neocosmospora*,[2] accounts for half of human infections caused by *Fusarium*. Some of the species are associated with severe infections in transplant recipients and patients with hematological malignancies, persistent neutropenia, or immunosuppression caused by corticosteroid therapy.[3] We present a case of disseminated *Neocosmospora (Fusarium)* infection in a 55-year-old male who developed febrile neutropenia on day four post induction chemotherapy for acute myelogenous leukemia. This case highlighted the clinical presentation and treatment for disseminated *Neocosmospora (Fusarium)* infection and the importance of clinical examination allogenic stem cell transplant recipients.

CASE REPORT

A 55-year-old male presented to his primary care provider with fatigue and diarrhea. Initial work-up showed a white blood cell count (WBC) of 103,600 cells/uL prompting admission. Acute myelogenous leukemia (AML) with monocytic differentiation was diagnosed by bone marrow biopsy and he was started on induction chemotherapy on admission (day one), in addition to prophylactic acyclovir 400 mg twice daily, levofloxacin 500 mg daily, and micafungin 50 mg daily. He became neutropenic on day four. On day 16, he developed febrile neutropenia and a new painful grey lesion was noted between his right fourth and fifth toes (Figure 1); otherwise, examination was unremarkable. WBCs were 200 cells/uL, hemoglobin 6.9 g/dL, and platelets 8,000/uL. Renal and liver function tests were within normal limits. Serum beta-D-glucan and *Aspergillus* galactomannan antigen tests were within normal range.

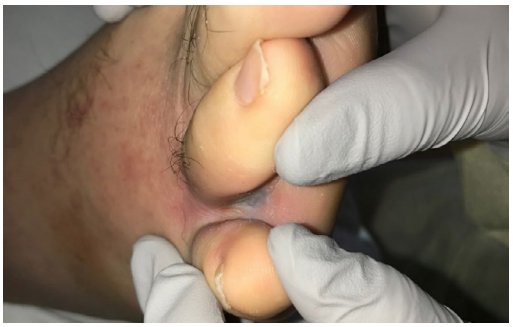

Figure 1. Skin lesion between the right fourth and fifth toes.

The patient was started on liposomal amphotericin B 5 mg/kg daily. Routine blood cultures were positive after four days of incubation. Hyphal elements were reported on the blood culture (Figure 2).

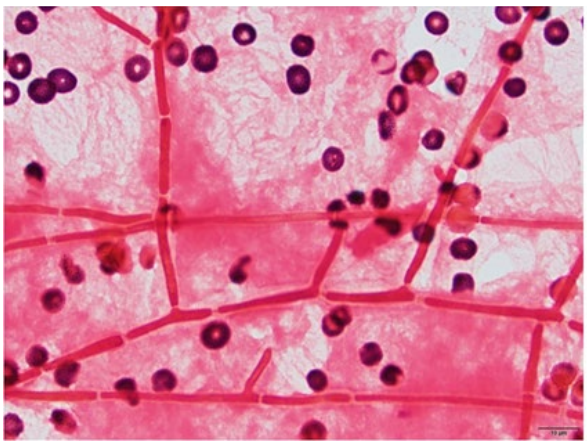

Figure 2. Gram stain of positive blood culture bottle showed septate hyphae (on BD BACTEC Aerobic medium; 20x).

Additionally, the dermatology consult team performed a shave biopsy, which was sent for aerobic, anaerobic, and fungal cultures. Routine culture grew *Staphylococcus epidermidis*. No tissue was sent for histopathology. After three days of incubation, the fungal culture of the tissue grew a mold identified as *Neocosmospora falciformis* by combined morphology and DNA sequencing of the TEF and RPB2 genes at the reference lab (Figure 3). The patient developed acute hypoxic respiratory failure requiring 4 L/min of oxygen by nasal cannula. Chest computed tomography (CT) showed innumerable nodular opacities throughout both lungs, which were greatest in the apices with surrounding ground-glass opacities suggestive of multifocal fungal pneumonia (Figure 4). Two weeks after broad spectrum antifungal therapy, a fungal Grocott's methenamine silver (GMS) stain of bronchioalveolar lavage fluid demonstrated similar looking septate hyphae, but fungal culture remained negative. A transbronchial lung biopsy remained culture negative as well.

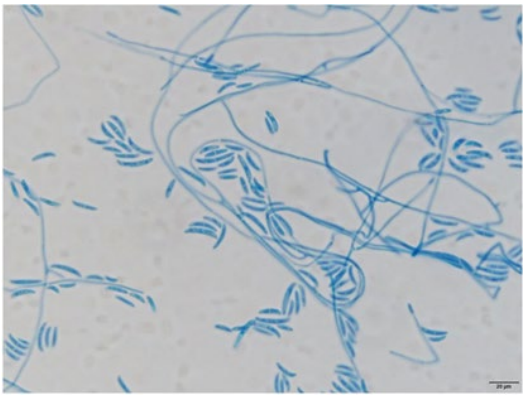

Figure 3. Lactophenol cotton blue stain of the culture prep, 40x.

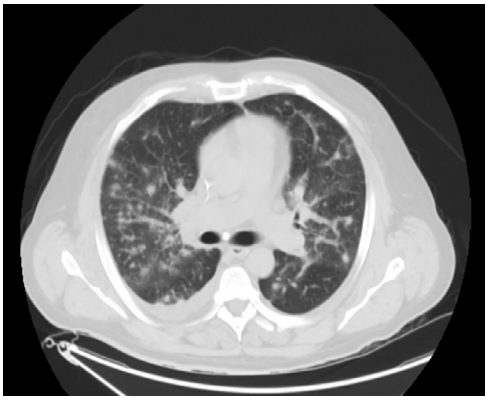

Figure 4. Computed tomography scan of the chest with bilateral multiple nodules.

Repeat CT of the chest two weeks after starting liposomal amphotericin showed slight increase in size of nodules with cavitation, as expected with neutrophil recovery. Antifungal susceptibility testing for the *Neocosmospora (Fusarium) falciformis* recovered showed low minimal inhibitory concentration (MIC) only reported to amphotericin B (amphotericin B MIC 0.5 mcg/mL, voriconazole MIC > 16 mcg/mL, isavuconazole MIC > 16 mcg/mL, posaconazole MIC > 16 mcg/mL, caspofungin MIC > 8 mcg/mL, terbinafine MIC > 2 mcg/mL). The patient was treated with antifungal therapy for a total of five months. At five months, the patient had resolution of symptoms and was breathing well on room air. Repeat CT of the chest showed significant improvement with residual patchy nodular infiltrates throughout both lungs. Eventually, the patient had relapsed AML and transitioned to hospice care as he was no longer a candidate for intensive chemotherapy.

DISCUSSION

The classification of fungi historically was based on morphology of the sexual forms.[4] Many fungi are known to reproduce only asexually, and some have both asexual (anamorph) and sexual (teleomorph) states causing confusion in fungal taxonomy as several were inadvertently given two separate names. Since January 2013, each fungus can have only one name, as the system of permitting separate names to be used for anamorphs ended.[5] However, confusion continues since many medically important fungi still are known by their established anamorph names (i.e., *Candida*). In this case study, the mold from both shave biopsy and blood culture was identified as *Neocosmospora falciformis*. The genus *Neocosmospora*, previously under *Fusarium solani* species complex (FSSC), contains at least 60 species.[2,6] Taxonomy changes to *Fusarium* species have caused scientific opposition,[7] due to the confusion it generated, and clinical laboratories are encouraged to continue to use the term *Fusarium* until conflicting viewpoints are resolved.[2]

Infections with *Fusarium* species may result in a broad spectrum of clinical manifestations, including superficial keratitis and onychomycosis (second most common pathogen after dermatophytes), locally invasive or disseminated disease. Infection severity and location depends on the immune status of patients and the pathogen portal of entry. Invasive and disseminated infections occur almost exclusively in severely immunosuppressed patients, particularly among those with hematological malignancy with prolonged neutropenia.[3] Allogeneic stem cell transplant recipients with graft-versus-host disease on steroid treatment are at particular risk for disseminated or invasive infection. Between 1986 and 1995 the incidence of *Fusarium* species infection was 1.2% among 750 allogeneic and 0.2% among 1,537 autologous marrow transplant recipients at M.D. Anderson Cancer Center in the U.S.[8] *Fusarium* is reported to be the third most common mold infection in hematology patients and organ transplant recipients after *Aspergillus* and Zygomycetes.[9]

The limited diagnostic tools available to diagnose invasive fungal infections lead to a delay in the diagnosis and treatment of these infections. Any clue to the early diagnosis of these infections may lead to changes in antifungal therapy and may be critical for an improved outcome. One of the most frequent, and frequently the only clinical sign, aspect of infections with *Fusarium* species is the development of skin lesions. Recognition of the skin manifestations will lead to early administration of antifungal therapy and obtaining biopsies for histopathology and fungal cultures.

Colonies of *Neocosmospora* (FSSC) grow rapidly within a few days and display aerial white to cream mycelium that turns bluish-brown when sporodochia develop. Curved, fusiform macroconidia with three to five septa (characteristic of *Fusarium* species) develop after four to seven days of incubation, while small, oval, one- or two-celled microconidia are usually abundant (Figure 3).[10] *Fusarium* and *Neocosmospora* species are unique among other commonly identified clinical filamentous molds (e.g., *Aspergillus* and *Zygomycetes* species) in their ability to grow in routine blood cultures.

With unpredictable response to therapy, high virulence seen in case reports and animal models, *Neocosmospora* (FSSC) infections often are associated with poor prognosis in patients.[11] Our patient's specimen displayed significant resistance to antifungals with low MIC only reported to amphotericin B. *Fusarium* and *Neocosmospora* species are relatively resistant to most antifungals,[12] therefore antifungal susceptibility testing is recommended while managing these infections, even though a correlation between MICs and clinical outcomes is not established. Treatment is typically a combination of surgical debridement, source control, and high dose liposomal amphotericin B, voriconazole with or without terbinafine.[3] Novel antifungals like olorofim are being evaluated.[13]

CONCLUSIONS

This case demonstrated the importance of a detailed physical examination for patients especially immunocompromised with fever. It also illustrated the changing fungal nomenclatures and the relatively high degree of antifungal resistance seen in *Neocosmospora (Fusarium)* infections.

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