Fusarium sp. infection in a patient with Acute Lymphoblastic Leukaemia

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SUMMARY

In the past two decades, *Fusarium* species have been increasingly recognized as serious pathogens in immunocompromised patients. The outcome of fusariosis in the context of severe persistent neutropaenia has been almost universally fatal. The treatment of fusariosis in immunocompromised patients remains a challenge and the prognosis of systemic fusariosis in this population remains poor. This report presents a case of fatal fusariosis in a 37-year-old patient who was diagnosed with precursor-B cell Acute Lymphoblastic Leukaemia (ALL).

INTRODUCTION

Species in the genus *Fusarium* are commonly found in soil and organic debris and cause disease in plants. Disease in the healthy human host is rare. Inhalation or minor trauma can lead to fusariosis in immunocompromised patients. *Fusarium,* usually *Fusarium* solani, is one of the more common causes of fungal keratitis, onychomycosis, endophthalmitis and skin and musculoskeletal infections (including mycetoma). Since the early 1970s, pneumonia, fungemia, and disseminated infection with *Fusarium* have become increasingly common problems in persons with haematological malignancy and other immunocompromised disorders.

CASE REPORT

A 37-year-old gentleman was referred to our hospital with a diagnosis of Precursor B cell ALL in January 2012. Induction chemotherapy was started and the recovery was complicated with one episode of neutropaenic sepsis which recovered with intravenous antibiotics. A repeat marrow examination confirmed complete remission had been achieved. Subsequently, he had further consolidation chemotherapy and this was complicated with *Klebsiella pneumoniae* sepsis. This resolved with antibiotics treatment and his neutrophil counts returned to normal level. However, he complained of blurring of vision of his right eye in April 2012, and was diagnosed of possible right subretinal abscess by the ophthalmologist. A vitreal tap and intravitreal antibiotics was given but this was complicated with vitreous haemorrhage. Cultures of the vitreous fluid did not yield any organism. He was treated with intravenous Ceftriaxone for about 2 weeks and he had another cycle of chemotherapy comprising of Methotrexate. He recovered well without further complications. In July 2012, he was again admitted to hospital with one day history of fever. He has had another further consolidation chemotherapy 3 weeks prior to this admission. Full blood counts showed pancytopaenia with suspicious blasts cells seen in peripheral blood film. A bone marrow examination confirmed a relapse of the leukaemia. Chest X-Ray showed left lung haziness and he was treated with intravenous Piperacillin-Tazobactam and Gentamicin which was later upgraded to Imipenem when his fever did not settle. He remained neutropaenic(absolute neutrophil count (ANC) of $<0.5x10^9$/L) and febrile despite the change of antibiotics. A CT scan of thorax showed ground glass appearance and lung nodules (Picture 1). In view of the persistent fever and prolonged neutropaenia, a diagnosis of presumed fungal infection of lung was made. Intravenous Voriconazole was started and subsequent bronchoscopic alveolar lavage did not grow any organism. After counseling with family members and patient, a decision to treat his relapse disease with intensive chemotherapy was made. This was given on 15/7/2012. There was defervescence after 10 days of Voriconazole and he appeared clinically better. Intravenous Voriconazole was then changed to oral formulation. However, he had another spike of fever a week later, a Chest X-Ray showed worsening right consolidation changes. A repeat CT thorax showed worsening changes with right pleural effusion. His neutrophil counts remained less than $0.5x10^9$/L. Antibiotic was again restarted and his antifungal therapy was changed to intravenous Caspofungin. He remained febrile and generalized body rash was noted subsequently. The rash was unfortunately not biopsied. Blood cultures taken during the recent febrile episode showed fungal elements and the growth was identified as *Fusarium sp.* DNA analysis done two weeks later via polymerase chain reaction (PCR) and sequencing confirmed the isolated organism as *Fusarium solani* species complex.

In view of the blood fungal results, the antifungal therapy was reverted to Voriconazole. His fever settled and his neutrophil counts recovered 4 weeks after the reinduction chemotherapy and he was able to return home. A week after discharge, he was readmitted with 3 days history of fever and cough. A Chest X-Ray showed right midzone and lower zone pneumonia. Intravenous Piperacillin-Tazobactam was started and oral Voriconazole was continued. A repeat blood count revealed platelet counts of $17x10^9$/L and total white cells counts of 45.8x109/L with 95% blasts.

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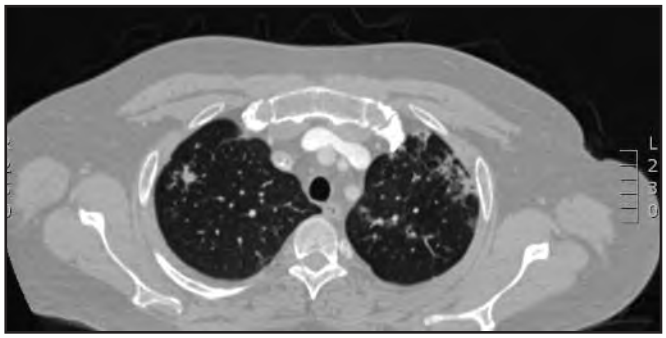

Fig. 1 : The patient's CT scan of thorax showing right lung nodules and ground glass appearances.

He remained febrile despite a change of antibiotic to Imipenem and a repeat Chest X-Ray showed worsening of his pneumonia, his antifungal therapy was changed to intravenous Amphotericin B. A repeat blood culture did not yield any organisms. His fever settled but his white cell counts became higher at $148x10^9$/L. The patient and family members were again counseled of the grave prognosis and family decided on another trial of further intensive chemotherapy. This was given on 3/9/12. He continued to have supportive transfusion of red cells and platelets. Unfortunately, on 7/9/2012, he became acutely drowsy and a CT scan of brain showed intraventricular bleed with mass effect. He subsequently passed away on the same day.

DISCUSSION

Neutropaenia is one of the most important risk factors for acquiring fusariosis. The portal of entry in most of these cases of disseminated infection is not known. Inhalation, ingestion, and entry through skin trauma have been suggested. This leukaemic patient underwent chemotherapy 5 months prior to the infection. He had prolonged neutropaenia due to the chemotherapy.

Patients with *Fusarium* infection can present with a broad spectrum of symptoms, ranging from keratitis and onychomycosis to sinusitis, pneumonia and systemic infection. Skin lesions are also commonly seen in patients with *Fusarium* infection. In this case, the patient's signs and symptoms are consistent with disseminated fusariosis with severe lung infection and a generalized skin rash.

Fusarium species possess several virulence factors. They produce mycotoxins, proteases and collagenases, and also have the ability to adhere to prosthetic material. Among the *Fusarium* species, *Fusarium solani* is the most virulent species, as shown in a murine model of fusariosis in immunocompetent animals[3].

The diagnosis of fusariosis depends on the clinical form of the disease. Two characteristics suggest the diagnosis of disseminated fusariosis in the severely immunocompromised host: skin lesions (either cellulitis or metastatic lesions) and positive blood cultures of *Fusarium sp*. On Potato Dextrose Agar, cultures of *Fusarium solani* are usually white to cream with sparse mycelium. Many isolates do not produce pigments in the agar although some violet or brown pigments may be observed. Macroconidia are relatively wide, straight, stout and robust. Microconidia are oval, ellipsoid, reniform and fusiform with 0 or 1 to occasionally 2 septa. The confirmatory diagnosis of fusariosis may require histopathology. In tissues, the hyphae show hyaline and septated that typically dichotomize in acute and right angles. Although the genus *Fusarium* can be identified by the production of hyaline, banana-shaped, multicellular macroconidia with a foot cell at the base, species identification is difficult and may require molecular methods. A PCR sequencing approach was used, utilizing ITS (internal transcribed spacer) regions for sequence comparison. Using the Basic Local Alignment Search Tool (BLAST) provided by the NCBI (National Centre for Biotechnology Information), we were able to confirm that the species belonged to *Fusarium solani species complex*.

Fusarium sp. manifests an inherent resistance to a multitude of antifungal agents, making the treatment of fusariosis difficult, especially in severely immunosuppressed individuals with haematological malignancies. Amphotericin B (ABD) remains the drug of choice for the management of disseminated fusariosis. Resistance is usually associated with inherently different species-specific antifungal susceptibility profiles, making *Fusarium* identification at the species level important for optimal treatment[1]. This patient was treated with Voriconazole and Caspofungin which initially showed some response but with the subsequent worsening clinical and X-Ray findings, this was changed to intravenous ABD. Unfortunately, due to his underlying refractory disease, he passed away due to intracranial bleed.

The prognosis of fusariosis in the immunocompromised host is directly related to the immune status of the patient, with high death rates in patients with persistent immunodeficiency.

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