Fatal disseminated fusarium infection in acute lymphoblastic leukaemia in complete remission

B Austen, H McCarthy, B Wilkins, A Smith, A Duncombe

Abstract

Fusarium species are increasingly recognised as serious pathogens in the immunocompromised. The outcome in the context of persistent severe neutropenia has been almost universally fatal. However, there have been several case reports of successful treatment if neutrophil recovery can be achieved. This report presents the case of a fatality that occurred despite neutrophil recovery. A 67 year old man developed disseminated fusariosis during the neutropenic phase of induction chemotherapy for acute lymphoblastic leukaemia. Fusarium dimerum was isolated from blood cultures. This species is highly unusual and very few case reports exist in the literature. An initial response to amphotericin treatment coincided with neutrophil recovery but a subsequent relapse occurred, despite adequate neutrophil counts, which proved fatal. It is postulated that reseeding of the blood from an occult site, namely the right vitreum in this case, led to this secondary relapse despite achieving complete leukaemic remission.

(J Clin Pathol 2001;54:488–490)

Keywords: fusarium; disseminated; neutropenia; remission

A 67 year old man presented with a three to four week history of general malaise, weight loss, intermittent high fevers, and spontaneous bruising. An initial full blood count demonstrated neutropenia and thrombocytopenia, and subsequent investigations confirmed a diagnosis of acute lymphoblastic leukaemia (ALL). He was treated on the MRC UK ALL 12 induction protocol, which includes high dose steroids. This was given via a tunnelled intravenous catheter. Fluconazole was given from day 1 and the patient was nursed on an open ward without HEPA (high efficiency particulate air) filtration. His absolute neutrophil count fell to zero by day 5 of treatment.

On day 22 during absolute neutropenia, the patient developed a painful macule on the dorsum of his right hand. Over the next few days this evolved, developing a necrotic centre and an ecthyma gangrenosum-like appearance (fig 1). He remained afebrile but was treated with broad spectrum antibiotics. New lesions subsequently appeared on his face, trunk, and limbs, initially appearing as erythematous macules and subsequently developing into flaccid vesicles and then into necrotic lesions (fig 2). Empirical intravenous conventional amphotericin was commenced. Blood cultures subsequently grew Fusarium dimerum and so the

Figure 1 Initial lesion on dorsum of right hand, which developed an ecthyma gangrenosum appearance.

Figure 2 Multiple skin lesions on patient’s face and thorax. Initially, many had a vesicular appearance and later developed central necrosis.
Fusarium species are saprophytic moulds that are ubiquitous in the soil and increasingly recognised as serious pathogens in the severely immunocompromised. Prolonged severe neutropenia (<0.5 × 10⁹), corticosteroids, broad spectrum antibiotics, and indwelling intravenous catheters are all important risk factors for the development of disseminated fusariosis.¹ Several reviews in the literature, including the large series by Boutati et al, highlight the very poor prognosis in the absence of recovery from myelosuppression.¹³ In this series of 43 patients with disseminated fusariosis, only 13 patients responded to treatment and all of these responders obtained neutrophil recovery and remission from their underlying disease. Of the 30 non-responders, only three were in disease remission at the end of infection and all were still neutropenic.³ Similar results were seen in a smaller series by Musa et al.⁷ Seven patients developed fusarial infection during chemotherapy induced neutropenia. Two patients subsequently developed locally invasive infection, but following resolution of neutropenia made a recovery on antifungal treatment. The remaining five patients had persistent neutropenia and developed disseminated systemic fusariosis, which proved fatal.

The poor prognosis of disseminated disease highlights the importance of early recognition and treatment of localised disease. Reports suggest that the skin is one of the most common sites of presentation of fusarial infection: this was the case in more than 55% of patients in several literature reviews.¹³ Primary skin lesions included cellulitis at the site of onychomycosis or at a wound site. There was no evidence of fungal nail infection in our patient and no evidence of previous skin break-down at the site of his primary lesion on the dorsum of his hand. Metastatic skin lesions reported included both subcutaneous nodules and ecthyma gangrenosum-like lesions, as seen in our patient.⁷

Distinguishing fusarium from other types of fungus, such as the more common aspergillus species, is also very important because of the poor sensitivity that fusarium often shows to amphotericin.¹² Therefore, any suspicious lesion should be biopsied urgently to aid rapid diagnosis. Fusarium has been grown from blood cultures in a high proportion of patients (45%) with disseminated disease, so blood cultures should also always be taken to facilitate the correct diagnosis.¹³ High dose liposomal amphotericin is the current recommended treatment and should be started without delay if fusarial infection is suspected in a patient with known risk factors. Because of the poor prognosis with continued neutropenia, G-CSF is usually added, as in our patient, to stimulate neutrophil recovery.¹²

Our patient died from overwhelming fungaeemia despite complete remission from ALL, a normal neutrophil count, and an initial response to treatment. One explanation might be related to the poor central nervous system penetration of intravenous amphotericin preparations. Eradication of the fungal infection could not be achieved despite local intravitreal antifungal treatment. This may have allowed reseeding of the blood from the right vitreous with secondary dissemination. We have found no reports of a similar secondary relapse in the literature. In those few cases where patients have developed a second episode of fusarial infection, having apparently cleared an initial...
infection, it has been in the context of a further
neutropenic episode.1,3

The early diagnosis of fusarium may be bet-
ter facilitated in the future with the develop-
ment of polymerase chain reaction (PCR)
based techniques. The detection of fusarial
DNA by PCR in spiked blood and tissue from
a mouse model has recently been reported to
have a high sensitivity.7 These techniques might
also aid correct species identification, although
as yet there is no information to suggest this
alters prognosis. *Fusarium solani* is the most
common species reported, *F dimerum*
being highly unusual, and contributing to less
than 2% of cases.1,4–6 Current treatment remains
disappointing, with amphotericin being the
only available agent. Its activity is often limited
against fusarial infection, although this can be
improved by using high dose treatment with a
lipid formulation. An improvement in treat-
ment might be realised using one of the new
investigational triazoles such as voriconazole or
SCH 56592, which have shown promising
potential in the treatment of fusariosis accord-
ing to in vitro and preliminary animal stud-
ies.1,2 This case demonstrates the urgent need
for new agents.

1 Boutati E, Anaissie E. Fusarium—a significant emerging
pathogen in patients with haematologic malignancy: ten
years’ experience at a cancer centre and implications for
2 Musa MO, Elaa AA, Halim M, et al. The spectrum of
fusarium infection in immunocompromised patients with
haematological malignancies and in non-immuno-
compromised patients: a single institution experience over
3 Gamis AS, Gudnason T, Giebink GS, et al. Disseminated
infection with fusarium in recipients of bone marrow trans-
infections: a retrospective study of 31 cases. *J Med Vet
5 Merz WG, Karp JE, Hoagland M, et al. Diagnosis and suc-
cessful treatment of fusariosis in the immunocompromised
solani infections in patients with acute leukaemia. *Rev Infect
7 Hue FX, Huerre M, Rouffault MA, et al. Specific detection
of fusarium species in blood and tissues by PCR technique.
Fatal disseminated fusarium infection in acute lymphoblastic leukaemia in complete remission

B Austen, H McCarthy, B Wilkins, A Smith and A Duncombe

doi: 10.1136/jcp.54.6.488

Updated information and services can be found at:
http://jcp.bmj.com/content/54/6/488

These include:

**References**
This article cites 7 articles, 2 of which you can access for free at:
http://jcp.bmj.com/content/54/6/488#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Immunology (including allergy) (1664)
- TB and other respiratory infections (74)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/