

Fusarium Infection

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Organizer:	Social Hygiene Service, DH; Clinical Meeting

CASE SUMMARY

History

A 59-year-old woman had received liver transplant for idiopathic hepatic cirrhosis and was put on tacrolimus 4 mg twice daily and prednisolone 10 mg twice daily after operation. She noticed three tender nodules on the left shin on day 6 after the transplantation. The nodules later ulcerated. She had low-grade fever for only 2 days. Past illnesses included Coomb's positive anaemia and mild mitral regurgitation and tricuspid regurgitation.

Physical examination

Examination showed three tender, erythematous nodules on the left shin. The nodules later formed punched out ulcers with purulent discharge at the center (Figure 1).

Differential diagnoses

Differential diagnoses included deep fungal infection, skin tuberculosis, atypical mycobacterial infections, bacterial septic emboli, vasculitis and panniculitis.

Investigations

Blood tests showed a low haemoglobin (7.8 g/dl) and platelet count ($24/\text{cm}^3$). White cell count was normal post-operatively but dropped to $1.80/\text{cm}^3$ after ganciclovir treatment. It returned to normal after granulocyte colonies stimulating factor (GCSF) infusion was given. Creatinine was 167 mmol/L and liver function tests were mildly deranged. The C3, C4, and ANCA were normal.

Both blood and urine culture showed enterobacter species, sensitive to amikacin only. Pus swab from the ulcer showed mycelia in the smear and scanty fusarium species in the culture. Skin biopsy specimen again showed scanty fusarium species in culture. Blood tests for aspergillus antigen and penicillium marneffeii antibody were negative.

Skin biopsy demonstrated the presence of hyalophialides and conidia under H & E, PAS and



Figure 1: Tender erythematous centrally discharging nodules on the left shin

Grocott stain. The fungal hyphae showed branching and septation, suggestive of mould infection. There was dermal tissue necrosis, and granulomatous infiltration with lymphocytes, histiocytes, and some multinucleated giant cells (Figure 2 and 3).

Radiographs of left tibia, computed tomography scans of brain and thorax were negative.

Diagnosis

The diagnosis of fusarium infection was made.

Management

Prednisolone was maintained at 10 mg twice daily, and tacrolimus was decreased to 1 mg twice

daily. Initially cefalexin was given to cover for bacterial infection, then mevopenen and amikacin were given for the bacteraemia. Neutropenia occurred after ganciclovir treatment for cytomegalovirus infection. GCSF was given and white cell count gradually returned normal.

Amphotericin B was started against the fusariosis but later changed to liposomal amphotericin B (AmBisome) because of deteriorating renal function. Lipofuscin parenteral nutrition was given in the last 3 days of illness.

Progress

The general condition gradually deteriorated, with anorexia, myalgia, fatigue, confusion, shortness of

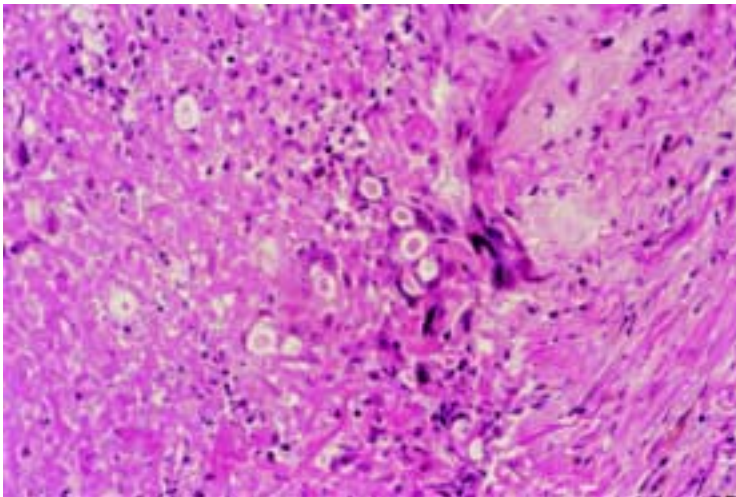


Figure 2: High power view showing focal necrosis and a mixed dermal inflammatory infiltrate with occasional multinucleated giant cells. Hyaline phialoconidia are noted within histiocytes. (H & E stain) (By courtesy of Dr. Nigel Trendell-Smith)

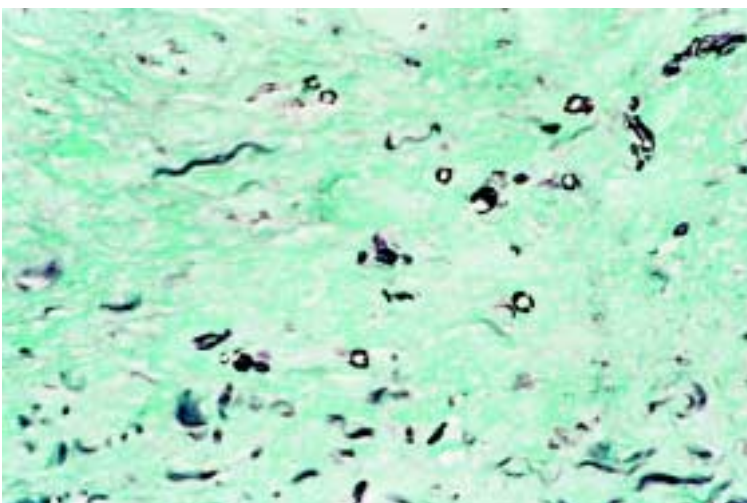


Figure 3: Many typical phialoconidia of variable sizes and occasional hyphae are demonstrated by Grocott modified silver methanamine stain. (By courtesy of Dr. Nigel Trendell-Smith)

breath, oliguria, increasing metabolic acidosis, and finally cardiac arrest.

REVIEW ON FUSARIUM INFECTION

The first case of disseminated fusariosis was reported in 1973. Most cases have occurred in patients with haematological malignancies.¹ There have been an increasing number of deep tissue and disseminated infections in recent years, presumably due to the increased use of immunosuppressive treatments for malignancies and transplants.

Up to 1995, 15 species had been reported to cause human and animal diseases. Common species includes *F. solani* (commonest), *F. oxysporum*, *F. verticilloides*, *F. proliferatum*, and *F. anthophilum*.¹

Source and Portal of entry

Fusarium is a ubiquitous saprophytic fungus in the soil. It causes diseases in plants and animals. In immunocompetent patients it may cause eumycetoma, onychomycosis or harmlessly colonize ulcers. However, in immunocompromised patients, it may cause deep and disseminated infections. It enters the body through the skin, by following a localized infection, wound contamination, indwelling venous catheter,² trauma, or even spider bite. It may also enter by inhalation of spores.

Predisposing factors

Invasive fusariosis occurs almost exclusively in immunosuppressed patients.³⁻⁵ Among invasive fungal infections of post-marrow transplant patients, candidiasis is the commonest. Among moulds, aspergillosis is the commonest and fusariosis is the next commonest.²

Clinical features

Fever, fungaemia, and myalgia may occur. Skin, blood, lung and sinuses infections are most common but most other body organ systems can also be affected.⁶

Skin lesions are present in 80% cases of disseminated infection. They may be primary or metastatic. They are important for early diagnosis

because of accessibility for biopsy and culture. Typical skin lesions are painful, erythematous, subcutaneous nodules and plaques, which later undergo central necrosis, forming "black eschar" or "ecthyma gangrenosum-like lesions". Other reported morphology included lesions with a surrounding rim of erythema, erythematous macules with or without central necrosis, palpable or non-palpable purpura, flaccid pustules, and cellulitis overlying sinusitis or osteomyelitis. Sometimes there is associated digital cellulitis or superficial white onychomycosis.

Diagnosis

Definitive diagnosis depends on the presence of both hyphae in histology and positive culture. Positive culture from non-sterile sites, such as skin or sputum needs to be differentiated from colonization. Repeated positive culture in high risk patients are suggestive of infection.

Investigation

Histopathology

It is important for early diagnosis because cultures take at least 7 days. Fungus can be seen under H & E or PAS stain, but Gomori methenamine silver (GMS) or Grocott is best for showing adventitious sporulation.

Histology shows dermal necrosis and acute inflammation. Blood vessel invasion with hyphae and thrombosis occurs more frequently than in aspergillus. Granuloma is sometimes present. Hyalohyphomycosis, which means the presence of hyaline hyphae filaments (phialides) and unicellular form spores (phialoconidia) in the histology, is present in specimens with fusarium, paecilomyces, acromonium and aspergillus species. In aspergillosis, only 45-degree hyphae branching are present and hyphae are uniform in diameter. In paecilomyces, acromonium and fusarium, hyphae branching of both 45 and 90 degree are present, and hyphae diameter is smaller and irregular. Differentiation between fusarium, paecilomyces and acromonium are usually impossible. Candida yeast cells may resemble conidia, but can be distinguished by their rounded apex and broader truncate basal scar.⁷

Microbiology

Fungal culture is done in Sabouraud agar without cycloheximide for a maximum of 21 days. Blood culture

is positive in 50% of fusarium cases, compared with 5% in aspergillus.

Radiology

Chest radiography most commonly shows non-specific infiltration, but nodular and cavitating lesions are sometimes seen. Sinuses and bone involvement can also be shown to be involved radiologically.

Treatment

Early treatment is important for invasive fusariosis, and modalities of treatment include:

Correction of neutropenia

Correction of neutropenia is the most important therapy.^{3,7} Granulocyte colony stimulating factors (G-CSF) and Granulocyte-macrophage colony stimulating factors (GM-CSF) had been reported to be useful. Granulocytes transfusion from donor who had been stimulated with G-CSF was found to be most effective.

Antifungal therapy

All the available antifungal drugs show only low activity for fusarium. Amphotericin B has the highest in vitro activity and is therefore regarded as the treatment of choice.¹ However, in vitro susceptibility to amphotericin B is a poor predictor of clinical outcome. Amphotericin B is needed in high dose for fusariosis and amphotericin B lipid complex such as liposomal formulation (AmBisome) had been reported to give good response. However, on a study of 31 cases of invasive fusariosis, none of the nine antifungal therapies used was unambiguously superior to the others. They included amphotericin B, ketoconazole, itraconazole, fluconazole, flucytosine, Schering 39304, G-CSF, GM-CSF, and surgery in various combinations.⁴ Combination treatment is often needed.

Others

Surgical debridement and excision of localized invasive infection had been tried. Colonized intravenous catheters need to be removed.²

Prognosis

Prognosis of disseminated infection is much worse than localized invasive infection. For disseminated infection, mortality rate is 50-90% despite antifungal treatment. Prognosis is correlated with marrow improvement. There is high risk of recurrence with subsequent myelosuppression. Therefore, prophylactic G-CSF-stimulated-granulocyte transfusion before restarting chemotherapy had been advocated.

Learning points:

Disseminated fusarial infection occurs almost exclusively in immunocompromised patients. Prognosis is poor and correction of neutropenia is most important for recovery.

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