Disseminated *Fusarium oxysporum* Infection in Hemophagocytic Lymphohistiocytosis

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Abstract

The portal of entry of disseminated *Fusarium* spp. infections is still not clearly defined. We report on a disseminated *Fusarium oxysporum* infection occurring during a long period of severe neutropenia in a child with hemophagocytic lymphohistiocytosis. A nasogastric feeding tube was the possible source of entry of the fungus.

Introduction

Fusarium spp. are soilborne fungi, known to be pathogenic for plants, animals, and humans [1]. In humans, *Fusarium* spp. can cause localized or invasive disease [2]. Disseminated infections only occur in immunocompromised patients, particularly those with severe hematologic disorders, and are usually related to severe and prolonged neutropenia [3–7].

Potential portals of entry reported include onychomycosis; the respiratory tract, in particular paranasal sinuses, the gastrointestinal tract, and a central venous line (CVL). However, in many cases the entry sites of disseminated *Fusarium* infections remain unclear. The present case suggests that nasogastric tubes (NGTs) should also be considered as possible mediators of entry of *Fusarium* infections in immunocompromised patients.

Case Report

A 2-year-old boy with hemophagocytic lymphohistiocytosis (HLH) was evaluated in our outpatient clinic because of a spiking fever lasting 2 days. Hemophagocytic lymphohistiocytosis was diagnosed 4 months earlier, when the child was evaluated for prolonged fever, hepatosplenomegaly, and pancytopenia. Upon diagnosis of HLH, the child had an intravascular catheter (Port-A-Cath®) inserted. Subsequently, treatment with high-dose prednisone and antithymocyte globulin was started, followed by continuous immunosuppression therapy with cyclosporin A.

Physical examination revealed an afebrile child in good general condition with hepatomegaly and splenomegaly of 1 cm and 2 cm below the costal margin, respectively. A complete blood cell count showed a white cell count of 2,900/mm³ with 33% neutrophils, and 31% lymphocytes, hemoglobin of 96 g/l, and platelet count of 196,000/mm³. Biochemistry showed a C-reactive protein concentration of 29 mg/l (norm: < 4), and a ferritin level of 4,250 µg/l (norm: 10–180), while fibrinogen and triglycerides were normal. Blood drawn from the Port-A-Cath® was cultured for bacteria, and the child was discharged home the same day.

Two days later, he was admitted to the hospital because the blood cultures grew *Staphylococcus epidermidis*. Antibiotic therapy with teicoplanin was started, and the Port-A-Cath® replaced with a CVL. Over the next 10 days, HLH relapsed with continuous fever, increasing pancytopenia with marked neutropenia (absolute neutrophil count < 500/mm³), hypofibrinogenemia, hypertriglyceridemia, and both ferritin and neopterin levels increasing up to 150,000 µg/l and 38.29 ng/l (norm: < 2.50), respectively. Empiric meropenem and liposomal amphotericin B at daily doses of 60 mg/kg and 3 mg/kg, respectively, were added to the antimicrobial regimen. The child's general conditions deteriorated. On day 12, he developed a respiratory distress syndrome requiring mechanical ventilation for 1 week. Immunosuppression with dexamethasone, vepeside, and intrathecally administered methotrexate was started according to the HLH-94 treatment protocol of the First International HLH Study 1994 [8]. The treatment resulted in clinical and biochemical remission within 10 days but severe pancytopenia with marked neutropenia persisted. Liposomal amphotericin B, meropenem, and teicoplanin were discontinued after 14, 20 and 22 days, respectively. During this time, the feeding was supported exclusively through an NGT.

On day 27, the child developed fever, progressive severe myalgias, vomiting, and diarrhea. Hematologic profile and biochemistry showed a persistent pancytopenia with profound neutropenia but no signs suggesting HLH relapse. Repeated microbiologic investigations including blood cultures drawn from the CVL, oral

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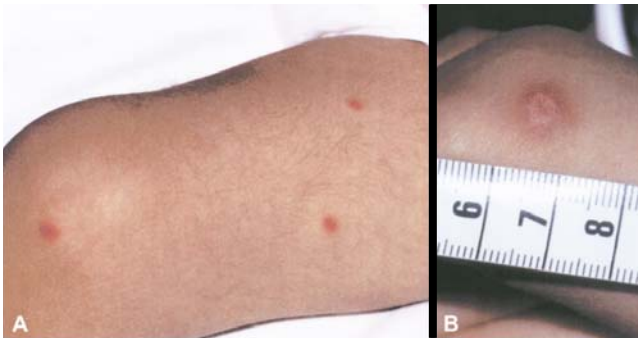
Figure 1. Typical skin lesions in disseminated *Fusarium oxysporum* infection in a 2-year-old boy with hemophagocytic lymphohistiocytosis. **A.** Erythematous macules and papules on the right upper leg. **B.** Erythematous subcutaneous nodule with necrotic area on the right elbow (scale is given in cm).

swabs, urine, and fecal samples remained negative. Empirical treatment with meropenem and teicoplanin was restarted. Ten days later, he developed multiple erythematous subcutaneous nodules, and painful erythematous macules and papules with progressive central infarction on the face, trunk, and extremities (Figure 1). A swelling of the right side of the face, eye, and neck, ipsilateral to the NGT, also occurred. Conventional radiography revealed a diffuse opacification of the maxillary sinuses.

A histology of skin biopsy demonstrated a dermal inflammatory lymphocytic cell infiltrate. Both the periodic acid-Schiff and the silver stain revealed numerous septate branching hyphae around and within dermal blood vessels, many of which contained thrombi. Cultures of skin biopsy specimens grew *Fusarium oxysporum*, which was subsequently isolated also in fecal samples. Identification of *F. oxysporum* was based on the presence of sickled-appearing macroconidia, and short monophialides bearing single-celled microconidia in slide cultures [9]. The minimal inhibitory concentrations of amphotericin B and itraconazole, as determined by the colorimetric microdilution method [9], were 1 mg/l and 4 mg/l, respectively. Repeated blood cultures remained negative.

On day 46, concomitant intravenous administration of amphotericin B and granulocyte colony-stimulating factor at daily doses of 1.2 mg/kg and 5 µg/kg, respectively, was started. On day 49, the NGT was removed but neither studies to detect macroscopic or microscopic changes suggesting colonization by filamentous fungi, nor cultures were performed. After 10 days, progressive increase in the white blood cell count with simultaneous resolution of fever and cutaneous lesions occurred. After 6 weeks of intravenous antifungal therapy, the child was discharged home with oral itraconazole at a dose of 10 mg/kg while continuing immunosuppression according to the HLH-94 protocol [8]. Itraconazole was chosen for oral prophylaxis, since the compound voriconazole that can be also administered orally was then not available to us.

Discussion

Fusarium spp. are soil saprophytes causing diseases in plants and animals. While long known to cause localized infections also in humans, *Fusarium* spp. represent an increasing cause of disseminated infections among immunocompromised patients, especially those with severe hematologic disease [1–7]. As in our child, disseminated *Fusarium* infections usually develop during a profound and prolonged bone marrow aplasia, and show a typical clinical course including persistent fever despite adequate antimicrobial therapy, myalgia, and disseminated cutaneous lesions (Figure 1) [2]. Cutaneous lesions are present in more than 80% of patients with disseminated fusariosis, and usually develop at an early stage of the disease as widespread erythematous macules, papules, and nodules with progressive central infarction [2]. Occasionally, cellulitis of the face, or extremities with or without fasciitis has also been reported [10].

Portals of entry of disseminated fusariosis are not clearly defined. Most likely reported portals of entry include disrupted skin and respiratory tract mucosal barriers, particularly in patients with onychomycosis and sinusitis, respectively. Colonization of the gastrointestinal tract due to ingestion of contaminated food has also been reported [2, 11–13]. Also, indwelling catheters including CVL, and peritoneal dialysis catheters have been identified as potential entry sites of fusarial infection [1, 11–14]. In several of these cases, the role of indwelling catheters as portals of entry was supported by both the identification of *Fusarium* spp. by catheter tip cultures and the demonstration of the ability of *Fusarium* spp. to colonize and invade silastic catheters by electron microscopy, suggesting that other foreign-bodies may also represent an important source of disseminated fusariosis [1]. The presence of an NGT in our patient may have played an important role in promoting colonization of both the maxillar sinuses and the gastrointestinal tract with *F. oxysporum*, resulting in localized infection and subsequently dissemination during the long period of neutropenia. The present case strongly suggests that NGTs should be considered potential mediators of entry of *Fusarium* spp. in immunocompromised patients. Nasogastric tubes should therefore be used cautiously or probably proscribed in patients with severe neutropenia.

Disseminated *Fusarium* infections are associated with a high mortality rate [5]. Rapid diagnosis is an essential prerequisite for prompt antifungal therapy and survival of patients [3, 5, 13–15]. Although a high rate of isolation of *Fusarium* spp. from the bloodstream is reported, in several cases of invasive fusariosis, repeated blood cultures remain negative as in our patient [6–7, 12, 15]. The present case shows that knowledge of the cutaneous manifestations of *Fusarium* infections along with early histology and culture of skin biopsy specimens can accelerate the diagnosis, thus allowing prompt optimal treatment, and probably increasing the survival rate.

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