Case Report

Invasive sinonasal disease due to dematiaceous fungi in immunocompromised individuals: case report and review of the literature

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1. Introduction

Dematiaceous fungi are environmental pathogens, characterized by melanin in their cell wall.1,2 They are an uncommon yet increasingly recognized source of invasive sinusitis.3–5 Although destructive fungal sinus disease can occur in both immunocompetent and immunocompromised patients, disease in the latter is of greater severity and acuity.3,4 Improved prognosis is associated with surgical debridement, systemic antifungal use, and a reduction of immunosuppression. The optimal treatment for immunocompromised patients with invasive dematiaceous fungal disease is not known. The role of newer triazoles, posaconazole and voriconazole, appears promising, however more clinical data are needed. Definitive diagnosis requires tissue biopsy and successful treatment is associated with reduction of immunosuppression, aggressive surgical debulking, and systemic antifungal therapy.

SUMMARY

Invasive dematiaceous fungal sinusitis is an uncommon and aggressive disease in immunocompromised individuals. We report a unique case of invasive Exserohilum sinusitis in a pregnant, immunocompromised woman. After treating the woman with pregnancy-induced aplastic anemia and invasive Exserohilum sinusitis and pulmonary disease, we performed a Medline/PubMed review of invasive dematiaceous fungal sinonasal disease in immunocompromised individuals. Twelve cases of proven and one case of probable invasive sinonasal dematiaceous fungal disease in immunocompromised patients are reported in the English-language literature. The majority of patients had underlying hematological conditions. The crude mortality was high, with over half of the patients dying from presumed complications of the underlying immunosuppression. Successful outcomes were associated with surgical debridement, aggressive antifungal use, and a reduction of immunosuppression. The optimal treatment for immunocompromised patients with invasive dematiaceous fungal disease is not known. The role of newer triazoles, posaconazole and voriconazole, appears promising, however more clinical data are needed. Definitive diagnosis requires tissue biopsy and successful treatment is associated with reduction of immunosuppression, aggressive surgical debulking, and systemic antifungal therapy.

Keywords:
Invasive sinonasal disease
Exserohilum species
Immunosuppression
Dемatiaceous fungi
Phaeohyphomycosis
Aplastic anemia

2. Case report

A 32-year-old Caucasian woman was diagnosed with aplastic anemia and neutropenia during the second trimester of pregnancy. She was admitted to our tertiary care center at gestational week 26 for a bone marrow transplant evaluation. Upon admission, she had a fever of 39.5°C and a scabbing papule on her cheek. She was treated with broad-spectrum antibiotics. Blood cultures and a skin biopsy of the papule subsequently grew methicillin-susceptible Staphylococcus aureus (MSSA).

Despite treatment of the MSSA bloodstream and soft tissue infection, the high fever persisted and the patient reported nasal congestion. A computed tomography (CT) scan revealed significant mucosal thickening of the left maxillary sinus with associated hyperintense regions in the left frontal and bilateral sphenoid sinus, and a mucous retention cyst in the right maxillary sinus. A CT scan of the chest revealed multiple bilateral nodules with surrounding ground glass consolidation. A serum galactomannan antigen was negative. Broad-spectrum anti-infective coverage with imipenem and liposomal amphotericin B was initiated. Three days later she delivered a nonviable fetus.

After one week of antifungal therapy, a repeat CT scan of the chest revealed progression of the bilateral ground glass consolidation. A bronchoscopy and a video-assisted thorascopic lung biopsy were performed. Cultures were nondiagnostic. Due to significant electrolyte abnormalities from liposomal amphotericin B (total 3000 mg), the antifungal therapy was changed to combination posaconazole 200 mg by mouth four times a day and micafungin...
100 mg intravenously daily. After 28 days, the imipenem was discontinued and the patient was discharged home on posaconazole and micafungin.

One month later, the patient was readmitted with persistent neutropenia, right facial pain and swelling. A repeat CT scan of the sinuses revealed almost complete opacification of the left maxillary, left anterior, and left frontal sinuses. A CT scan of the lungs revealed improved but persistent multifocal airspace disease. The patient underwent a left maxillary antrostomy, left anterior and posterior ethmoidectomies, and left middle turbinate resection. Intra-operative findings included ulceration of the nasal septum and necrotic mucosa of the left middle turbinate. Histopathology was consistent with hyphal invasion of the sinonasal respiratory mucosa. Exserohilum species was identified; susceptibility testing was not performed.

The infectious diseases service subsequently expanded her antifungal regimen to combination liposomal amphotericin B and posaconazole. Three weeks later, a repeat sinus CT revealed worsening of the left maxillary sinus opacification. The patient underwent additional sinus debridement. Pathology was again consistent with a dematiaceous fungal infection. She developed rigors on liposomal amphotericin B (total 14 000 mg) prompting a change to micafungin 100 mg intravenously daily by the bone marrow transplant service. The posaconazole was continued. One month later, a CT scan revealed improvement in the sphenoid sinuses and left frontal opacification with ongoing disease in the left maxillary sinus. Due to her refractory disease, the bone marrow transplant service changed the posaconazole to voriconazole 300 mg by mouth twice daily. She was subsequently discharged home on micafungin and voriconazole.

Six weeks after the second sinus surgery, the patient was readmitted with worsening headache, left facial pain and unresolved neutropenia. A CT scan of the sinuses revealed ongoing opacification of the left maxillary sinus with bony irregularity of the left maxillary sinus lateral wall and involvement of the inferior wall of the left orbit. No intracranial invasion was noted. A CT scan of the lungs revealed multiple areas of consolidation and nodular opacities. The bone marrow transplant service initially added lipid complex of amphotericin B (1800 mg total) to her prior regimen of micafungin and voriconazole. She underwent a left maxillary antrostomy and left sphenoidectomy. Pathology revealed tissue invasion by fungal hyphae. Cultures were non-diagnostic. After further consultation with the infectious diseases service, the patient’s antifungal regimen was changed back to micafungin and voriconazole.

Approximately six weeks after the third sinus surgery, the patient was readmitted for further treatment of the aplastic anemia. A CT scan revealed improvement in the right ethmoid, left maxillary and sphenoid sinuses; increased inflammatory changes in the left ethmoid sinuses; and no change in the right maxillary sinus. Despite a trial of antithymocyte globulin and two months of cyclosporine, the neutropenia persisted. She reported no additional headaches or fevers. The patient was not a candidate for bone marrow transplantation as adherence to her immunosuppressant and antifungal regimen was suboptimal. The patient ultimately left the hospital with ongoing aplastic anemia and neutropenia. She died approximately two months later from complications of the underlying aplastic anemia. The status of her sinonasal disease at the time of death was not known.

3. Literature review

A literature review of invasive sinonasal disease secondary to dematiaceous fungi in immunocompromised individuals was performed using the Medline/PubMed database. All searches were limited to English-language articles. Immunocompromised hosts were defined as those having neutropenia, a hematopoietic stem cell transplant (HSCT), solid organ transplant, or cell-mediated immunodeficiencies. The first search term ‘phaeohyphomycosis and invasive sinonasal disease’ yielded three articles, and a second search term ‘dematiaceous fungi and invasive sinusitis’ yielded 16 articles. Additional searches under ‘invasive sinonasitis’ or ‘nasal septum’ and individual genera of dematiaceous fungi yielded 36 articles. Sinonasal disease due to Scedosporium species was not included due to controversy regarding its classification as a dematiaceous fungus. Articles were reviewed to identify cases with proven or probable sinonasal disease based on criteria established by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group, and references from these articles were reviewed to identify additional cases. Cases with invasive nasal septum disease in the absence of concomitant sinonasal disease were omitted. A total of 12 relevant articles, and details on 13 immunocompromised patients with invasive sinonasal disease, were found. An additional case of sinonitis in a patient with aplastic anemia was omitted due to insufficient data available for classification. All relevant articles were published between 1987 and 2008.

4. Discussion

We report a unique case of acute invasive sinonitis due to Exserohilum species in a pregnant woman with aplastic anemia and prolonged neutropenia. Since 1987, there have been 14 (including the present case) published cases of invasive sinonasal infection due to dematiaceous fungi in immunocompromised individuals (Table 1). In addition to the present case, 13 other cases were biopsy ‘proven’ invasive sinonasal disease, although in three of these cases the invasive pathology was cited in the skin or nasal septum, rather than the sinuses. One case was considered ‘probable’ invasive sinonasal disease based on host and clinical factors in the presence of sinusitis on imaging; however no tissue or vessel invasion was described. Manifestations of both proven and probable invasive sinonasal disease included disease localized to one or more sinuses or sinonasal disease with dissemination. Twelve patients (86%), including the present case, had underlying hematological conditions. Three of these patients, including the present case, had aplastic anemia. Six patients with invasive fungal sinonitis had HSCTs, of whom four had infection diagnosed prior to the transplant. Sinusitis was caused by Exserohilum species in eight patients (including the present case), Alternaria species in four patients, and Scytalidium species in one patient.

The crude mortality in patients with invasive dematiaceous fungal sinusitis is high, with over half of reported cases dying during follow-up (9/14, 64%). Despite stabilization or improvement in the invasive sinonasal infection, most died from their underlying immunosuppression or other infections. Survival was associated in most cases with resolution of neutropenia and immunosuppression. Most patients who survived required a combination of surgical debridement and systemic antifungal therapy. Complications related to invasive dematiaceous fungal sinusitis are common. Six patients, including the present case, had associated pulmonary infiltrates. One patient with disseminated Exserohilum disease had cutaneous involvement manifesting as ecthyma gangrenosum. Another patient with invasive Curvularia species had co-infection with Fusarium solani in an orbital muscle abscess. Intracranial involvement complicating destructive sinus disease from dematiaceous fungi has been
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<td>Sinus, lung</td>
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<td>Surgery, L-AMB, AMB, voriconazole</td>
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<td>Surgery, L-AMB, voriconazole</td>
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*Note: L-AMB: liposomal amphotericin B; HCT: hematopoietic cell transplant; s/p: status post.*

5. Conclusions

Acute invasive sinonasal disease due to dematiaceous fungi is associated with immunosuppression and results in significant morbidity and mortality. Successful treatment requires reduction of immunosuppression, aggressive surgical debridement, and systemic antifungal therapy. Clinical experience with posaconazole and voriconazole is limited but promising. These agents may have a role either in disease unresponsive to intravenous amphotericin B or as first-line agents. Further clinical experience is needed to better define the use of these antifungal agents for the treatment of invasive sinonasal disease due to dematiaceous fungi.
management of invasive sinonasal disease secondary to dematiaceous fungi. In the setting of immunosuppression and pregnancy, the presence of invasive fungal sinusitis should raise concern about dematiaceous fungi and should trigger prompt antifungal therapy and urgent surgical evaluation.

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**References**