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Review article

Phoma and *Acremonium* invasive fungal rhinosinusitis in congenital acute lymphocytic leukemia and literature review

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ABSTRACT

Objective: Invasive rhinocerebral fungal infections are a difficult and often fatal problem in children with hematologic malignancies, with increasing reports of rare pathogens. We describe a case of congenital acute lymphoblastic leukemia (ALL) and invasive fungal rhinosinusitis involving *Acremonium* and *Phoma* species, not previously reported in invasive pediatric fungal rhinosinusitis, and review all published cases of human *Phoma* infections.
Methods: A literature and institutional review for *Phoma* spp. was completed including patient demographics, infection site, immune status, treatment and outcome.
Results: A female neonate with acute lymphoblastic leukemia presented with hyperleukocytosis and advanced invasive *Phoma* and *Acremonium* spp. rhinosinusitis. Despite aggressive medical and surgical therapy, the disease progressed to a rhinocerebral infection with a fatal outcome. Twenty cases of *Phoma* spp. were found in a complete literature search, including 6 females and 14 males from 18 months to 77 years old. Infections were superficial in fifteen patients and involved deeper tissue in five patients, with sites including cutaneous, subcutaneous and deep tissue sites (eye, lung, extremity deep tissue compartments).
Conclusions: This case highlights the risks and grave prognosis of fulminant invasive fungal rhinosinusitis in the context of congenital leukemia, and the potential for rare fungal species in neonates with immunosuppression.

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1. Introduction

Patients with congenital leukemia, as with other hematologic malignancies, are at a significantly higher risk of developing invasive fungal infections [1–3]. The inherent dysfunction of innate and adaptive immune responses in these children is compounded by chemotherapy-associated severe neutropenia. Opportunistic fungal infections including candidiasis, aspergillosis and mucormycosis can spread and progress rapidly. Invasive fungal rhinosinusitis with these common opportunistic fungal species is a well-known complication of immunosuppression following chemotherapy for hematologic malignancies. More recently, an increasing number of cases of fungal rhinosinusitis have been linked to uncommon fungal opportunistic pathogens [4,5]. In this report, we discuss a case of fatal invasive fungal rhinosinusitis due to *Phoma* and *Acremonium* species in an infant with congenital leukemia, and review *Phoma* infections published in the literature.

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To our knowledge, this is the first case in the literature involving *Phoma* species as an etiologic agent in rhinosinusitis.

2. Case

Following approval from the Connecticut Children's Hospital Institutional Review Board, a case was reviewed involving a newborn female who presented in the neonatal period with a markedly elevated white blood cell count of 40,700/μl with 84% leukemic blasts, leading to diagnosis of congenital pre-B cell acute lymphoblastic leukemia. The diagnosis was confirmed with flow cytometry and cytogenetic analysis showing a t(4;11) translocation consistent with *MLL* gene (myeloid/lymphoid or mixed-lineage gene) rearranged infant leukemia. Chemotherapy treatment was initiated with vincristine, daunorubicin and cyclophosphamide, but peripheral blood smears and subsequent marrow aspirates showed persisting blasts with minimal granulocytes despite therapy.

Nine days after initiating chemotherapy, the patient developed rhinorrhea, fever and left periorbital swelling and erythema (Fig. 1). Initial computed tomography (CT) of the head and sinuses revealed mild mucosal thickening of the left nasal septum and lateral nasal wall with no evidence of bony destruction or significant sinonasal, orbital or intracranial abnormalities. A fiberoptic nasal endoscopy revealed crusting and blackened, necrotic tissue in the left nasal cavity including the inferior and middle turbinates, the nasal floor, lateral nasal wall and lateral portion of the nasal ala and inferior nasal septum (Fig. 2). An endoscopic surgical procedure was performed to remove the necrotic tissue involving the circumference of tissue from the left nasal cavity from the nasal septum to the nasal floor and lateral nasal wall and turbinates, reaching margins of vascularized, healthy tissue. The right nasal cavity disease was minimal with a small area of septal involvement, which was also removed. Intraoperative frozen-section and permanent Periodic Acid Schiff (PAS)- and Grocott Methemanime Silver (GMS)-stained sinonasal biopsies showed necrotic septated hyphal elements with 45°, dichotomous branching, morphologically consistent with *Aspergillus* species on preliminary smears.

Antifungal treatment was simultaneously initiated with intravenous (IV) liposomal amphotericin B. Due to a lack of clinical response, IV voriconazole and posaconazole were added.

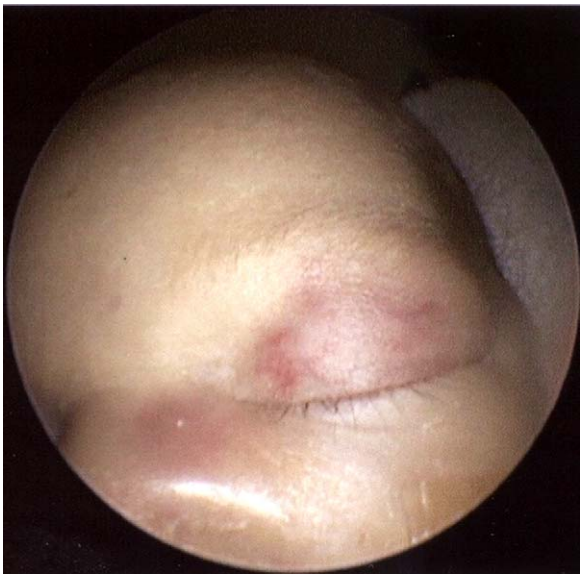

Fig. 1. Left periorbital swelling and erythema extending to the left lateral nasal bridge, medial canthus and superior lid.

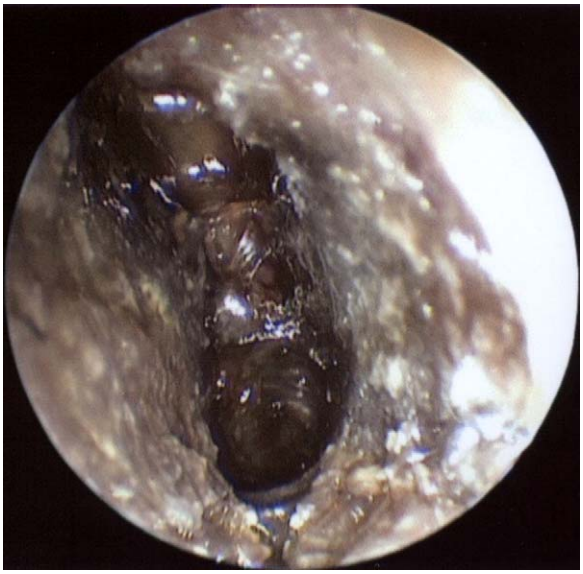

Fig. 2. Endoscopic view of nasal aperture with circumferential area of darkened and necrotic tissue including the left nasal septum (left of picture) and inferior turbinate to the nasal floor and lateral nasal wall (right of picture).

The patient returned for a second intraoperative endoscopy and further endoscopic resection of necrotic tissue. Nasal endoscopy showed large extension of necrotic involvement which had progressed to include the left lateral nasal wall and the anterior ethmoid sinuses, and the middle turbinate of the right nasal cavity. A left anterior ethmoidectomy and debridement of the left lateral nasal wall removed any visibly necrotic tissue. Necrotic tissue in the right nasal cavity was then excised from the right anterior septum and middle turbinate, with a right middle turbinectomy to the basal lamella and a right anterior ethmoidectomy to reach a margin of healthy tissue. After the second surgical procedure, the patient continued to deteriorate with persisting fevers and increasing difficulty weaning the patient from ventilator support following each operative intubation. Repeat CT imaging and magnetic resonance imaging (MRI) of the brain showed a new rim-enhancing low density region in the right parietal lobe without significant surrounding edema and no evidence of anatomic continuity with the sinonasal disease process (Fig. 3). These

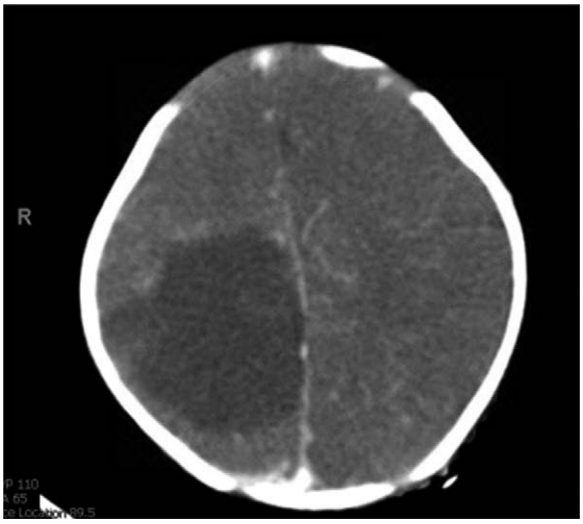

Fig. 3. Head CT shows a rim-enhancing low-density lesion in the right parietal lobe without significant surrounding edema.