



Review article

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

Corrie E. Roehm^a, Juan C. Salazar^b, Nathan Hagstrom^c, Tulio A. Valdez^{a,d,1,*}^a University of Connecticut Health Center, Otolaryngology – Head and Neck Surgery, 263 Farmington Avenue, Farmington, CT 06030-6228, United States^b Department of Pediatrics, Division of Pediatric Infectious Diseases, Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106, United States^c Department of Pediatrics, Division of Pediatric Hematology and Oncology, Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106, United States^d Department of Pediatric Otolaryngology, Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106, United States

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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.

* Corresponding author.

E-mail addresses: corrie.roehm@gmail.com (C.E. Roehm), jsalaza@ccmckids.org (J.C. Salazar), Nhagstr@ccmckids.org (N. Hagstrom), Tvaldez@ccmckids.org (T.A. Valdez).

¹ Tel.: +1 860 545 9650; fax: +1 860 545 9651.

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/ μ l 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 Methenamine 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

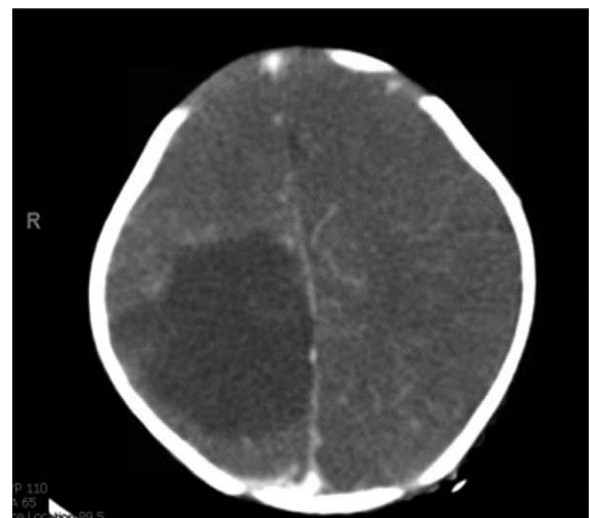


Fig. 3. Head CT shows a rim-enhancing low-density lesion in the right parietal lobe without significant surrounding edema.

findings were thought to be consistent with intracranial fungal extension. A third endoscopy revealed significant extension of fungal involvement over the right nasal floor, left nasal septum and left lateral nasal wall and palate. Discussion with the family and medical teams over the rapidly progressive infection with intracranial involvement and the poor response to induction chemotherapy led to a decision to provide palliative care and discontinue ventilator support. Nasal fungal culture results from intraoperative biopsies were finalized post-mortem, revealing *Acremonium* and *Phoma* species.

3. Literature review

An extensive literature search was performed for human infections caused by *Phoma* species resulting in seventeen papers [6–22] describing twenty total cases (Table 1) of *Phoma* spp., *Phoma hibernica*, *Phoma cava*, *Phoma eupyrena*, *Phoma minutispora*, *Phoma minutella*, *Phoma sorghina*, *Phoma exigua*, *Phoma glomerata* and *Phoma*

herbarum. Eighteen of the twenty cases included adults, with two pediatric cases, 6 females and 14 males ranging from 18 months to 77 years old. Sites affected included skin in cutaneous and subcutaneous infections in fifteen patients, nail or hair involvement in two, eyes in two, deep tissue compartments in two, and lungs in one patient. Treatment involved topical, oral to intravenous corticosteroids, and topical, oral to intravenous antifungal courses including griseofulvin, clotrimazole, dimethicone, miconazole, itraconazole, ketoconazole, bifonazole, amphotericin B, voriconazole, allylamine and sertaconazole. Involved deep tissue was debrided in five patients. Recovery was documented in 15 cases, clinical improvement in two patients, death from complications of *Phoma* infection in one and unknown outcomes in two cases.

4. Discussion

This case review presents several important clinical features including two unusual fungal pathogens and the specific

Table 1
Case details of all reported human infections caused by *Phoma* species.

Reference	Gender/age	Site	Pathogen	Treatment	Immune status	Outcome
Bakerspigel et al. [8]	F/22	Leg	<i>Phoma hibernica</i>	Oral griseofulvin	Topical steroids	Clinical improvement
Young et al. [21]	F/42	Subcutaneous, heel	<i>Phoma</i> spp.	Debridement	Suppressed, post-renal transplant	Resolution
Gordon et al. [13]	M/4	Left ear	<i>Phoma cava</i>	Oral griseofulvin and corticosteroid	Normal	Resolution
Bakerspigel et al. [9]	M/18 mo	Cutaneous, perioral	<i>Phoma eupyrena</i>	Clotrimazole, 15% zinc oxide paste, dimethicone	Normal	Resolution
Shukla et al. [19]	F/18	Face	<i>Phoma minutispora</i>	Topical clotrimazole	Topical steroids	Resolution
Baker et al. [6]	M/20	Neck	<i>Phoma minutispora</i>	Topical clotrimazole	Topical steroids	Resolution
	M/75	Subcutaneous, foot	<i>Phoma minutella</i>	Debridement	Suppressed	Required amputation for secondary gangrene, resolution
Rai et al. [16]	M/24	Face, neck, hands	<i>Phoma sorghina</i>	Topical miconazole	Normal	Resolution
Hirsh et al. [14]	M/19	Face	<i>Phoma sorghina</i>	Topical miconazole	Normal	Resolution
	M/45	Subcutaneous, hand	<i>Phoma</i> spp.	Itraconazole	Normal	Clinical improvement
Rosen et al. [18]	F/24	Cutaneous, facial	<i>Phoma</i> spp.	Ketoconazole	Normal	Resolution with 2-year follow-up
Zaitz et al. [22]	M/63	Subcutaneous, hand	<i>Phoma cava</i>	Amphotericin B, itraconazole	Suppressed, corticosteroids for sarcoidosis	Resolution
Arrese et al. [7]	M/49, sibling	Cutaneous, plantar	<i>Phoma</i> spp.	Topical bifonazole and ketoconazole	Normal	No improvement on topicals, lost to follow-up
	M/53, sibling	Cutaneous, plantar	<i>Phoma</i> spp.	Topical bifonazole and ketoconazole	Normal	No improvement on topicals, lost to follow-up
Oh et al. [15]	M/77	Subcutaneous	<i>Phoma</i> spp.	Oral itraconazole	Normal	Resolution
Everett et al. [12]	F/50	Hand deep compartment	<i>Phoma</i> spp.	Debridement, amphotericin B	Suppressed	Resolution, no recurrence after 2-year follow-up
Rishi and Font [17]	M/72	Keratitis	<i>Phoma</i> spp.	Debridement, keratectomy	Normal, history of globe trauma	Resolution
Balis et al. [10]	M/68	Lung	<i>Phoma exigua</i>	Amphotericin B, liposomal amphotericin B; left pneumonectomy	Suppressed; AML, diabetes mellitus	Death from cardiopulmonary arrest post-pneumonectomy
Errera et al. [11]	M/32	Endophthalmic following penetrating globe injury	<i>Phoma glomerata</i>	Failure of intravitreal amphotericin B, improvement with intravitreal voriconazole	Normal	Resolution
Tullio et al. [20]	F/36	Nail, toe	<i>Phoma herbarum</i>	Allylamine, sertaconazole	Normal	Resolution
This case	F/1 mo	Rhinosinusitis	<i>Phoma</i> spp., <i>Acremonium</i> spp.	Amphotericin B, posaconazole, voriconazole	Suppressed, leukemia, chemotherapy	Death with progressive rhinocerebral extension

implications of congenital leukemia within the broader scope of pediatric malignancies and immunodeficiencies. Congenital leukemia is a rare clinical condition, occurring in 8.5 per 1,000,000 births or approximately 1% of pediatric leukemia cases, with acute myeloid leukemia comprising 90% and acute lymphocytic leukemia only 10% of congenital leukemia cases [1]. Prognosis is poor for this disease with a 2-year survival of less than 30% compared to 70% survival in older pediatric patients with leukemia [2,3]. Patients with *MLL* gene rearrangement, as in this case, demonstrate more aggressive disease progression, including early central nervous system tissue involvement and hyperleukocytosis. Other poor prognostic indicators include newborn onset and high WBC at presentation [4], both of which affected this patient. A pathologic imbalance of immune cell types and the dysfunctional malignant cell populations associated with acute leukemia frequently lead to an acute immunosuppression. The baseline immaturity of the neonatal immune system and the additional systemic insult of chemotherapy treatment for leukemia further suppresses immunity, increasing the potential for neutropenia and leaving patients susceptible to opportunistic infections like invasive fungal rhinosinusitis.

This case also presents a unique polyfungal infection with two rare fungal species, *Phoma* spp. and *Acremonium* spp., when reports of rare fungal species infections in immunocompromised patients are emerging with increasing frequency [4,5]. Diagnosis and treatment of these unusual fungi is complicated by subtle morphologic differences between species, and varying resistance to common antifungal therapies. *Phoma* spp. are hyphomycetes of the class Coelomycetes, order Sphaeropsidales and family Dematiaceae, that are commonly isolated from the soil and represent phytopathogens. Morphologically, septate hyphae, pycnidia, conidia, and chlamydospores are often visualized and the hyphae vary from hyaline to brown in color. *Phoma* spp. is a ubiquitous fungus that inhabits the soil and plants. It is a common plant pathogen but rarely causes infection in humans. Only 18 cases have been reported in the literature, including primarily cutaneous or subcutaneous infections, one pulmonary and two ophthalmic infections [6–22]. Previous reports of infection caused by these fungi have occurred in patients with loss of local skin defenses or, as in this case, with systemic immunosuppression. To our knowledge this is the first reported case of invasive fungal rhinosinusitis associated with this opportunistic pathogen.

Acremonium species are emerging as an increasing cause of local and disseminated fungal infections, with over eighty cases described in the literature, and two-thirds of those cases published since 2000 [5,23,24]. Approximately 50% of the papers involve invasive or systemic infections, but very few pediatric cases are described. *Acremonium* spp. (also called *Cephalosporium*) are opportunistic saprophytic molds found ubiquitously in the environment in soil and plant debris, demonstrating small conidia on thin phialides that resemble early *Fusarium* growth [5]. The fungi have a colorless, septated filamentous appearance that classifies them as hyaline (nonpigmented) hyphomycetes with other non-*Aspergillus* filamentous fungi including *Fusarium*, *Rhizopus*, *Paecilomyces* and *Scedosporium* [5]. One important difference in *Acremonium* infections compared to other hyaline fungi is their ability to infect immunocompetent patients, causing keratomycosis in contact lens wearers and subcutaneous infections – mycetomas – after trauma. *Acremonium* can also cause sinusitis, arthritis, osteomyelitis, peritonitis and pneumonia, but invasive *Acremonium* infections usually occur in immunocompromised hosts with neutropenia.

Accurate diagnosis is important among hyaline fungi, since *Acremonium*, *Fusarium*, and *Paecilomyces* species are frequently resistant to available antifungal treatments [23]. Morphologic variations in this group are very difficult to distinguish on

histologic smears and they are often misdiagnosed as *Aspergillus*, requiring isolation of the organism by culture for species differentiation. In this case, initial tissue pathologic diagnosis from surgical debridement suggested *Aspergillus*, with the final accurate diagnosis only determined through fungal cultures from these intraoperative specimens. Important clues indicating non-*Aspergillus* fungi include pleomorphic variations in size and filament diameter, conidia, phialides, and the presence of both 45° and 90° septations instead of only 45° branching [24]. Frozen sections are particularly useful during surgical debridement to confirm negative margins for full resection of invasive fungal infections. However histopathology evaluations have poor reliability in identifying specific fungal species, except in rare cases when unique fungal features can be visualized (e.g. fruiting head of *Aspergillus* or an intact endospore-filled spherule of *Coccidioides*), since subtle morphologic characteristics like the angle of hyphal branching or septations can be affected during specimen processing. Immediate identification of fungal elements in a specimen can provide an initial differential diagnosis for fungal species involved in an infection, and differentiate acute, chronic and invasive fungal processes by evaluating local inflammation and vascular infiltration. Final speciation, however, should be confirmed with fungal cultures.

Clinical presentation of invasive fungal disease in the head and neck can include persistent unexplained fever, facial or orbital swelling and pain, pale or dusky sinonasal mucosa or persisting symptoms of acute sinusitis despite appropriate antibiotic treatment. Radiologic abnormalities can be minimal in the early stages, showing only mucosal thickening, or in more advance cases may show evidence of bony and local tissue destruction, vascular thrombosis or central nervous system CNS invasion [25]. Management of invasive fungal rhinosinusitis involves multimodal therapy including antifungal treatment, surgical removal of affected tissue, and supportive therapy to help reverse the predisposing factors. In high-risk patients, any clinical suspicion of invasive fungal rhinosinusitis should prompt immediate and aggressive treatment with intravenous antifungals and urgent planning for surgical debridement. *Phoma* spp. have shown resistance to fluconazole and 5-flucytosine with sensitivity to amphotericin B, ketoconazole and itraconazole in some cases, although response rates in systemic or invasive infections has been minimally addressed in the literature due to the rarity of these infections [15]. Similarly, treatment of *Acremonium* is difficult due to its poor response to common antifungals, and research determining the effectiveness of different antifungals in invasive infections has not been extensive due to the rarity of this infection as well. Current recommendations for treatment include Amphotericin B (1–1.5 mg/kg/day) or lipid formulations of Amphotericin B (5 mg/kg/day starting dose) for patients resistant to non-lipid Amphotericin B, however, recent reports have described *Acremonium* having consistent susceptibility to voriconazole [23]. Ultimately, debridement of affected tissue and improvement in neutropenia is the most important factor to gain control of the infection, although this must be pursued early in the infection process for the best chance of preventing further progression.

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