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TOPICAL COLLECTION: GLOBAL PEDIATRIC RADIOLOGY - PERSPECTIVE FROM INDIA

Endemic pediatric fungal infections in India: clues to diagnosis

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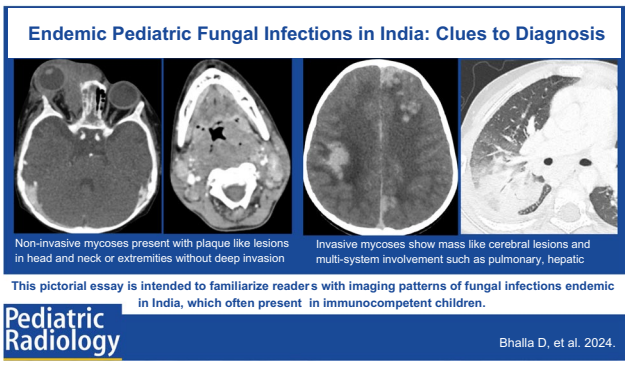
Abstract

This review is intended to familiarize readers with an emerging group of fungal infections that mostly manifest in immunocompetent individuals. This group was initially considered endemic to the tropics, but increasing worldwide prevalence has been reported. The organisms have been divided into dominant non-invasive forms and dominant invasive forms for ease of understanding. The non-invasive organisms include the group Entomophthoromycota, under which two genera *Basidiobolus* and *Conidiobolus*, have been identified as human pathogens. They present with plaques in the extremities and rhinofacial region, respectively. The invasive organisms are dematiaceous fungi (phaeohypomycosis), which includes *Cladophialophora* and *Exophiala* among others. They cause invasion of deep tissues, with the central nervous system being the most common target. The mycology, epidemiology, diagnosis, and treatment options have been summarized in brief. The clinical presentation, imaging manifestations, differentiation from other common infections and malignancies that show similar features have been detailed.

Graphical Abstract



Keywords *Basidiobolus* · *Conidiobolus* · Entomophthorales · *Exophiala* · Fungal infections · Mycology · Pediatric · Radiology

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Introduction

The most familiar manifestations of fungal infection in the pediatric population are in immunocompromised children, such as those receiving immunosuppression for malignancy or solid organ transplantation, hematopoietic stem cell transplantation, or congenital immunodeficiency. Another group that has been recently recognized as having susceptibility to fungal infections is neonates, particularly preterm and low birth weight infants [1, 2]. The common pathogens implicated in these settings are *Aspergillus*, Mucorales, *Candida*, and *Histoplasma*, which are responsible for invasive mycoses.

Another group of emerging fungal infections is being recognized, which present in apparently immunocompetent patients [3]. The fungi responsible are ubiquitous, often present in soil and excreta of animals. These include the recently classified Entomophthoromycota group as well as dematiaceous fungi responsible for phaeohyphomycosis. Worldwide distribution varies, although a predominance in the tropics has been reported. Subcutaneous infection caused by *Basidiobolus* species (sp.) is endemic in many parts of South India, including Pondicherry [4]. Similarly, among the cases of pediatric *Conidiobolus* multiple species (spp.) infection reported worldwide until 2022, 62% were from India [5]. In a study conducted by Dhawan et al. in North India, among 10,541 specimens prospectively analyzed over a one-and-a-half-year period, the prevalence of pheohypomycosis was found to be 0.2% [6].

The infection mechanism is postulated to be via direct subcutaneous route in case of trivial trauma such as abrasions and pricks or via ingestion/inhalation. The manifestations are also peculiar based on pathogenic organisms, which are often non-invasive, but invasive forms have also been recognized.

In this review, we summarize the imaging manifestations of these emerging infections, with emphasis on characteristic organ infliction by patterns of certain species, which would help the reader to recognize these in practice and guide early therapy. The classification of these organisms is shown in Table 1.

Non-invasive mycoses

Entomophthoromycota

Mycology

These were previously classified into the phylum Zygomycota along with Mucorales. However, important differences were recognized between Entomophthorales and Mucorales, which led to the formation of a separate phylum, Entomophthoromycota. They present with non-invasive subcutaneous infections and have a much better prognosis than Mucorales.

Basidiobolomycetes is a newly recognized class under the phylum Entomophthoromycota. It has been found via antigen and restriction enzyme analysis that all species isolated from infected humans belong to the species *Basidiobolus ranarum* [7].

The first human infection caused by *Conidiobolus* spp. was reported out of Jamaica and Congo simultaneously in 1965. This has been recently separated from *Basidiobolus* to a separate genus under the class Entomophthoromycetes under the phylum Entomophthoromycota. Human affliction is caused by the species *C. coronatus*, *C. incongruous*, and *C. lamprauges* [8, 9].

Epidemiology

Most notably, these are reported in immunocompetent individuals. There is also a striking predilection for tropics, though with increasing international travel, infections have also been reported from the USA [10], Australia [11], and the European mainland [12].

There is a characteristic demographic distribution of basidiobolomycosis, and children are most commonly affected (80% reported cases are in patients < 20 years old), with males affected three times as often as females.

Table 1 Classification and treatment strategy for endemic fungal pathogens

Infection pattern	Organism group	Genus	Species	Treatment
1. Dominant non-invasive	Entomophthoromycota	*Basidiobolus*	*B. ranarum*	• Amphotericin B (early resistance encountered), azole antifungals, potassium iodide • Surgery contraindicated
	Entomophthoromycota	*Conidiobolus*	*C. coronatus*, *C. incongruous*, and *C. lamprauges*	
2. Dominant invasive	Phaeohyphomycosis	*Cladophialophora*	*C. bantiana*	• Combination of amphotericin B and azole antifungals • Surgery often performed to reduce disease burden
	Phaeohyphomycosis	*Exophiala*	*E. dermatitidis*	
	Phaeohyphomycosis	*Alternaria*	Multiple species	
	Phaeohyphomycosis	*Rhinocladiella*	*R. mackenziei*	

Similar to the basidiobolomycosis demographics, conidiobolomycosis is also a disease of young adults and shows an even more striking male preponderance, with a male to female ratio of 10:1 [7].

Diagnosis

In patients with non-invasive plaques like lesions in characteristic locations, extremity for basidiobolomycosis and the rhinofacial for conidiobolomycosis, tissue biopsy is a must for diagnosis [13]. Culture rates are also higher from biopsy specimens than from pus. This must be performed under image or endoscopic guidance as appropriate, based on the location of the soft tissue. Broad, sparsely septate hyphal elements are observed on histopathology sections, which display the "Splendore Hoeppli phenomenon" [14]. This refers to hyaline eosinophilic material clustered around the hyphae seen on hematoxylin-eosin stains.

Treatment

These organisms are usually quick to develop resistance to amphotericin B; therefore, alternative treatment strategies including azole antifungals and potassium iodide solution are employed, usually with a good success rate. However, disease recurrence and superadded infection often complicate the course of treatment [8]. In a series of three adult patients in Sri Lanka reported by Sigera et al. [15], one of the patients, who also had comorbidities, presented with orbital involvement and vision loss. He subsequently developed superadded infection by *Aspergillus* spp. and vision was not regained even after 6 months of therapy.

It is also noteworthy that the role of surgical excision in these patients remains limited to diagnostic purposes only. Once the diagnosis is suspected, any attempts at wide excision of the plaques must be discouraged as this leads to fungal seeding at lesion margins and thus facilitates recurrence.

Basidiobolomycosis

Clinical presentation

Cutaneous involvement is the most common form of the disease. In a series of seven cases in West Africa [16], all patients presented with similar findings of a single subcutaneous plaque that was easily separated from the underlying structures but not from the skin. In a series of 16 patients from India [3], lower limb predominance was once again noted, although few additional sites of involvement, such as the anterior chest and abdominal wall, were also documented. Only 6 of 16 patients could recollect trivial injury preceding the onset of swelling.

In the most recent literature, a gastrointestinal form of basidiobolomycosis is being reported in increasing numbers. In a literature review by Flicek et al. [17], 73 reported cases of gastrointestinal basidiobolomycosis were found.

Imaging features

These plaques tended to be sharply circumscribed and uniformly involve the lower limbs (thigh or buttock) with variable inguinal lymphadenopathy. Similar to the clinical presentation, imaging shows infiltrative lesions that involve the skin and subcutaneous plane, with no muscular or osseous involvement. Radiographs are occasionally performed in these patients, which show isolated soft tissue swelling. MRI is the mainstay of imaging due to its ability to differentiate between patterns of soft tissue involvement. The plaques are hyperintense on T2-weighted images and iso-hypointense on T1-weighted images. These lesions are most often misdiagnosed as soft tissue sarcomas. The lack of deep tissue invasion is a characteristic feature (Fig. 1) that must prompt a differential diagnosis in the appropriate clinical and geographical setting. The other important differential diagnosis, particularly in certain geographic locations in the tropics, is elephantiasis. However, localized involvement and "plaque" of soft tissue rather than edematous limb enlargement should point the physician to this etiology.

In patients with gastrointestinal involvement, CT is the mainstay of imaging. The most common imaging findings are multiple masses involving solid abdominal organs such as the liver; and multiple levels of bowel. Bowel involvement includes both the colon and small bowel and manifests as masses or bowel wall thickening. Reports have also described the extension of the mass across compartments, such as from the intraperitoneal compartment to the abdominal wall [18] or from the mesentery to the retroperitoneum, causing ureteric encasement. These masses cause luminal obstruction in encased hollow viscera, such as the bowel or ureter. These are often misdiagnosed as intra-abdominal manifestations of neoplasms such as lymphoma or rhabdomyosarcoma; however, pointers of inflammation such as fat stranding, collections, or fistulae guide the radiologist to the possibility of an infection and suggest biopsy. In the study by Flicek et al., all patients with abdominal masses had adjacent inflammation and/or abscess formation [17]. Intussusception has also often been reported with the bowel wall masses acting as lead points [19]. The obstruction of hollow viscera is also an important differentiator from lymphoma, which

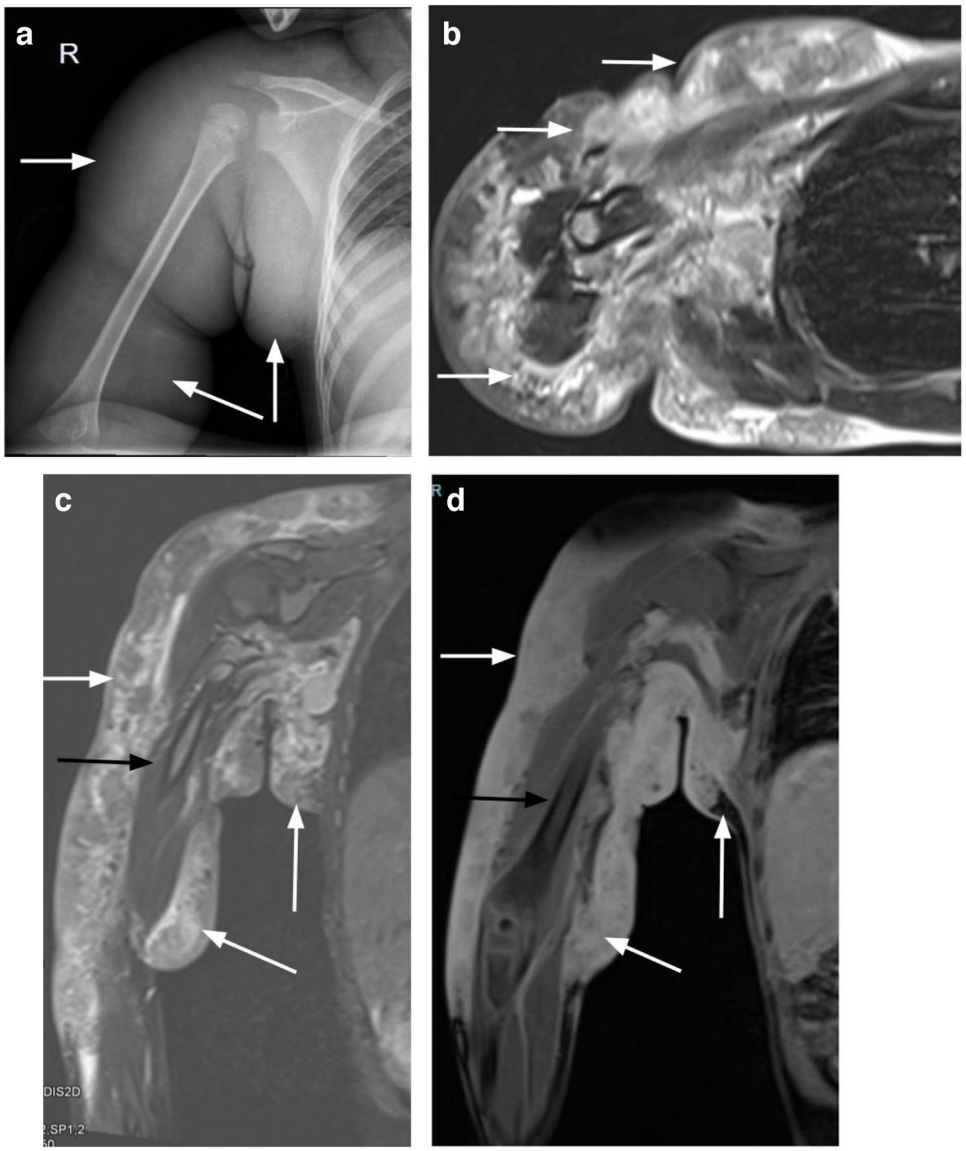

Fig. 1 Basidiobolomycosis. A 4-year-old boy with erythematous indurated plaque over the right arm, progressing to involve the chest wall. **a** Radiograph of the right arm reveals extensive soft tissue swelling along the entire length of arm (arrow) with extension into the axilla and chest wall. There is no bony irregularity or erosion. Axial (**b**) and coronal (**c**) STIR MRI of the right arm show thickened, hyperintense soft tissue (white arrow) which is localized to the subcutaneous plane. There is no involvement of the underlying muscles or bone (black arrow). **d** Coronal gadolinium enhanced image shows avid enhancement in the involved subcutaneous tissue of arm, axilla, and chest wall (white arrow) with normal bone (black arrow)

also presents with infiltrative masses but does not cause obstruction.

Conidiobolomycosis

Clinical presentation

The mode of transmission in these patients is by inhalation rather than inoculation; therefore, it is more prevalent in individuals engaged in outdoor activities. Post inhalation of fungal spores, there is involvement of the mucosa of the nasal cavity and paranasal sinuses and soft tissues of the face. Patients present with complaints of nasal stuffiness or epistaxis; occasionally, nasal discharge may also be noted. There is chronic granulomatous involvement of the subcutaneous tissues of the face and progressive swelling of the nasal bridge, upper lip, malar region, peri-orbital soft tissue, and forehead [15]. Rarely, more extensive involvement, such as in the shoulder and neck has also been reported [20]. Insidious progression is usually the norm, and patients usually complain of increasing swelling or obstructive symptoms over several months at presentation.

Cross-sectional imaging is usually performed at presentation to look for the origin of the swelling and extent of involvement. Although MRI performs better than CT, the latter is generally performed because of easier availability, particularly since these infections are common in low resource settings. Ultrasonography may be used for follow-up of superficial lesions, but it cannot adequately define deep or intracavitary extension.

CT shows plaque-like enhancing soft tissue in the affected regions. In some patients, enhancing nodules may also be noted. The most common sites of involvement are around the midline face. These include the external nose, nasal cavity,

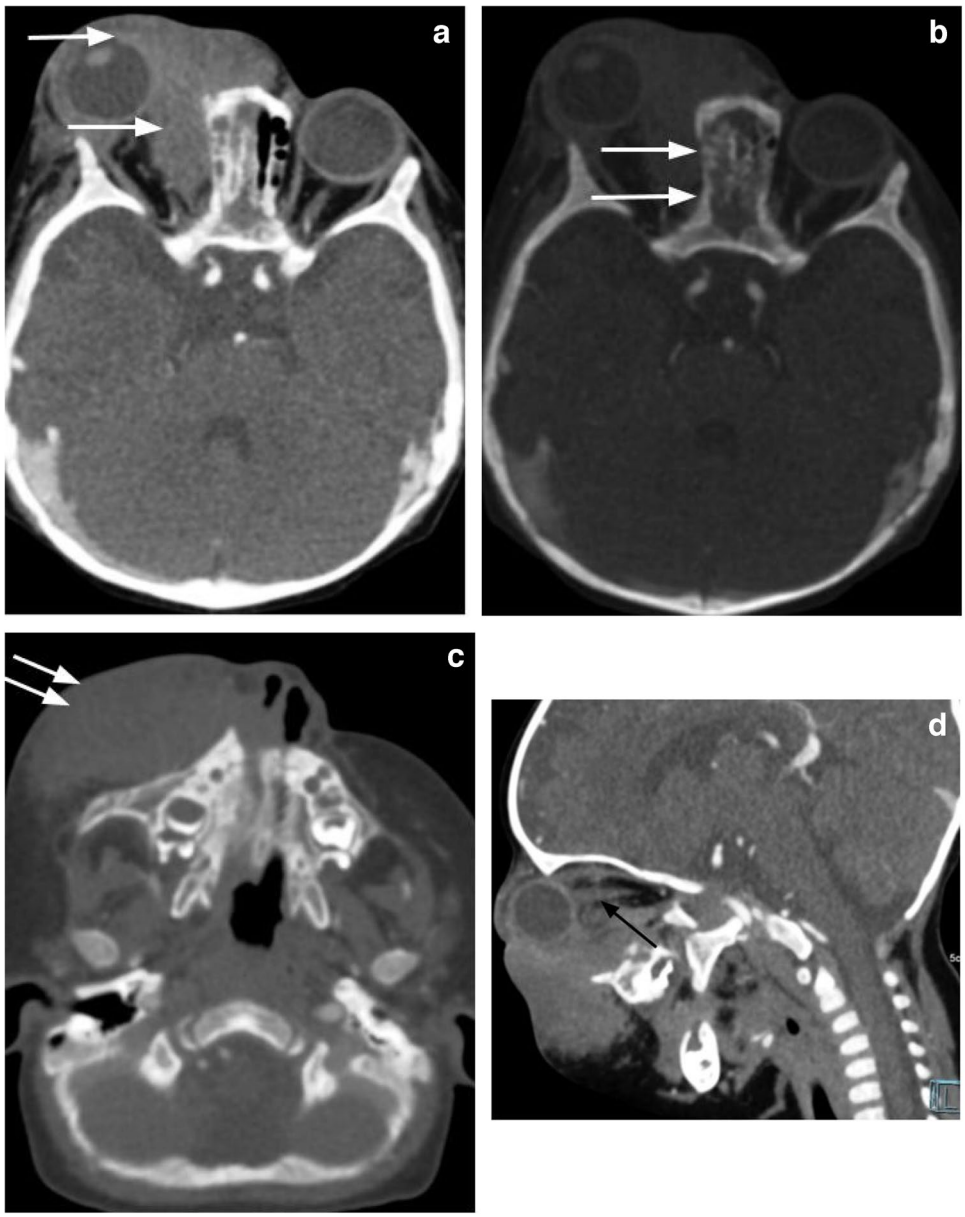

Fig. 2 Conidiobolomycosis. A 2-year-old boy with progressive right sided proptosis for 3 months. Axial CT orbit soft tissue window (**a**) shows infiltrating soft tissue along the nasal bridge, medial canthus, preseptal space, and lateral canthus with extension into the orbital fat (arrow). **b** Bone window at corresponding level shows intact bone with no erosion (arrow). **c** Axial CT at the level of maxillary alveolus shows extension of soft tissue into the subcutaneous fat of face (arrow). **d** In a sagittal section of the orbit, intact optic nerve (arrow) and surrounding fat plane are noted

and cheeks, which may spread to the glabella and upper lip [21]. Other uncommon regions of involvement include orbit (Figs. 2 and 3), causing proptosis. Furthermore, in advanced cases, there is involvement of the palate and oropharynx causing dysphagia or larynx, leading to laryngeal obstruction and stridor (Figs. 4 and 5). The plaques are usually homogeneous and infiltrative. They are usually localized to the subcutaneous tissue, which may extend into the neck fascia. Locoregional lymph nodes may also be involved.

Conidiobolomycosis mostly affects immunocompetent individuals, and there is no deep tissue or blood vessel invasion. Consequently, intracranial extension is also exceedingly rare unlike in patients infected by Mucorales.

Like basidiobolomycosis, these are often misdiagnosed as malignancies on initial imaging evaluation. Indeed, NK/T cell lymphoma remains an important differential for nasal cavity involvement in addition to granulomatosis with polyangiitis and squamous cell carcinoma of the paranasal sinuses in older patients. The lack of invasive features, particularly bone erosion and angioinvasion, as well as relatively infrequent nodal spread should indicate an alternative diagnosis.

With disease progression, there are striking deformities of the rhinofacial region. In immunocompromised patients, invasive forms of the disease may be seen. Disseminated disease with angioinvasion resembling Mucorales has rarely been reported, with involvement of the endocardium, liver, lungs, and brain [22].

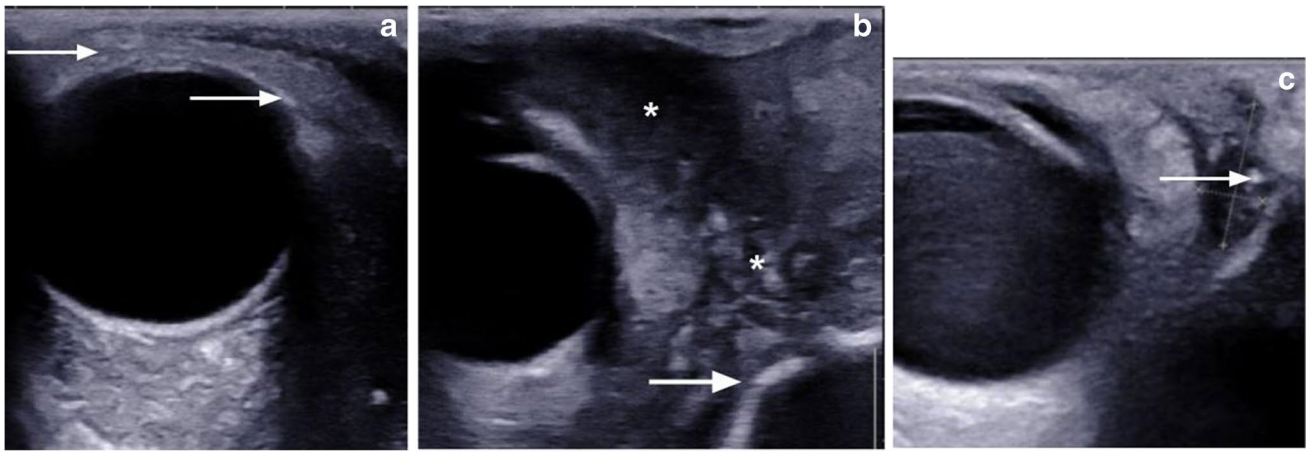

Fig. 3 Conidiobolomycosis. The same patient as in Fig. 2. Axial ultrasonography (US) of the right orbit. **a** The preseptal soft tissue swelling is noted (arrow). **b** Extensive hypoechoic soft tissue along the medial canthus (asterisk) with intact underlying cortex (arrow). **c** Follow-up scan performed post 6 months of therapy with azole antifungals showed only minimal residual lesion with specks of dystrophic calcification (arrow)

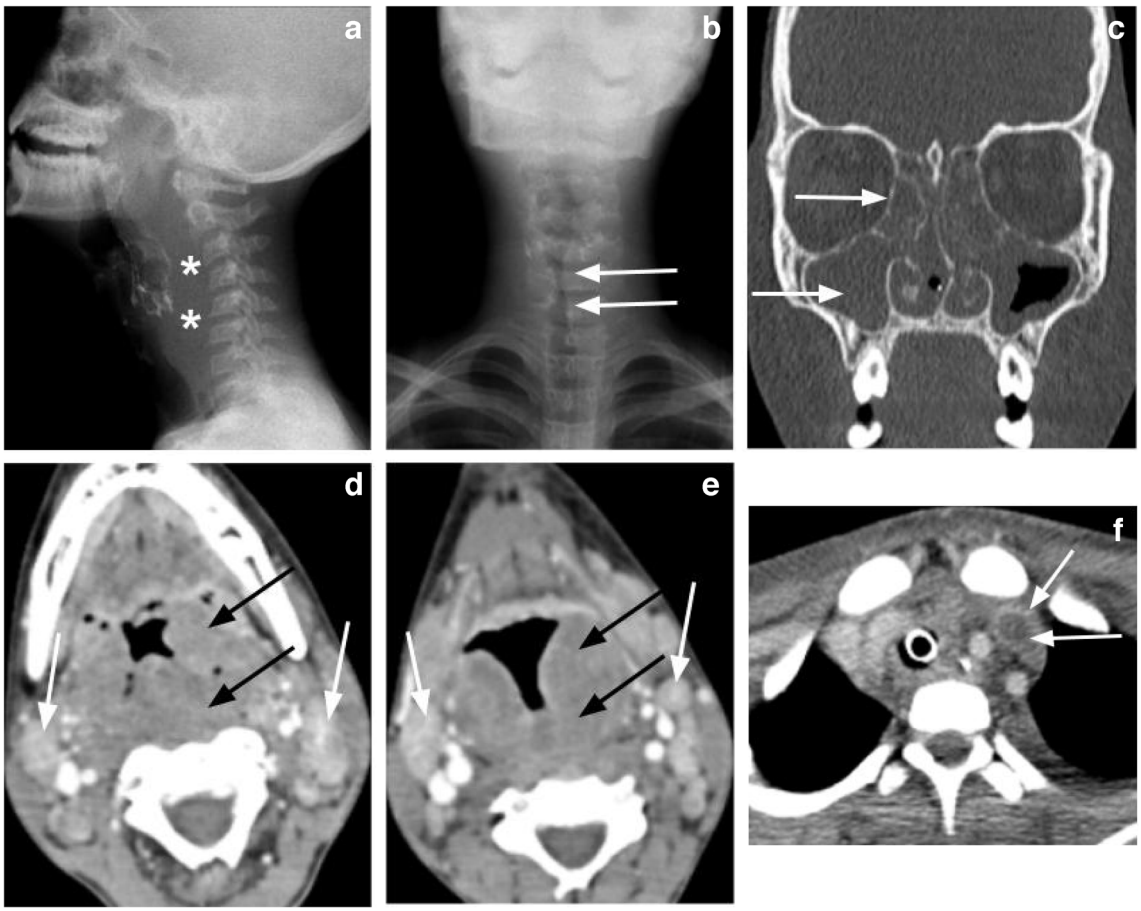

Fig. 4 Conidiobolomycosis. A 14-year-old girl with 2 months history of dysphagia, presented with acute onset stridor. **a**, **b** Lateral (**a**) and frontal (**b**) radiographs of the neck show retropharyngeal soft tissue (asterisk) from the skull base to thoracic inlet, causing severe narrowing of the airway at the C5-C6 level (arrow). **c** Coronal CT bone window shows extensive soft tissue filling the nasal cavity and maxillary and ethmoid sinuses without any bone erosion (arrow). **d**, **e** Axial CT of the neck shows marked thickening of the oropharyngeal wall with retropharyngeal soft tissue (black arrow). Multiple enhancing cervical lymph nodes are also seen (white arrow). **f** Axial CT of the thorax shows thrombosis of the left brachiocephalic vein (arrow) which extended from the internal jugular vein (not shown)

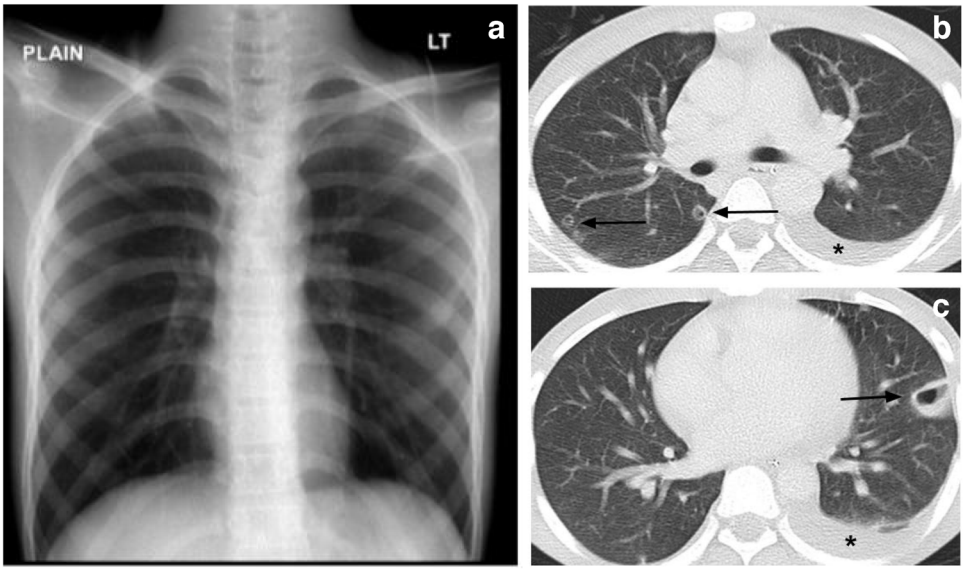

Fig. 5 Conidiobolomycosis. The same patient as in Fig. 4. **a** Radiograph performed at the time of presentation did not show any lung lesions. **b**, **c** Axial CT lung window shows multiple cavitating lung nodules due to septic emboli from the thrombosed jugular vein. There is also a small left sided pleural effusion (asterisk)

Invasive mycoses

Phaeohyphomycosis

Mycology

Phaeohypomycosis refers to infection by dematiaceous fungi, characterized by the presence of melanin-like pigments in their walls. Their growth is in the form of septate mycelium, and this morphology separates them from other dematiaceous fungi, such as those in chromoblastomycosis or mycotic mycetoma. The melanin in their walls is an inhibitor of phagocytosis and thus contributes to their virulence. The commonly implicated species in humans include *Cladophialophora bantiana*, *Exophiala dermatitidis*, *Rhinocladiella mackenziei*, *Alternaria* spp., and *Ochronis gallopavum* [23–25].

Diagnosis

Diagnostic methods vary, including cultures from pus aspirates or resected specimens and molecular techniques involving Sanger and next-generation sequencing from CSF, plasma, or pus.

Treatment

An aggressive multi-pronged strategy must be employed for treatment, with most authors using a combination of intravenous voriconazole and intravenous or intramedullary amphotericin B for prolonged durations. Surgical resection is also performed to reduce the disease burden. However, the mortality rate remains as high as 70% [26], even after adequate treatment, mostly attributed to delays in the initiation of therapy. Persistent neurological deficits are also often observed. Hence, it is imperative for radiologists to be aware of this entity and alert the clinician to this possibility to improve patient outcomes.

Clinical presentation

Similar to the non-invasive mycoses, this is commonly observed in immunocompetent hosts. However, unlike conidiobolomycosis and basidiobolomycosis, it follows a fulminant course with high mortality, which approaches 100% in untreated cases and 65–70% in patients treated with surgery and antifungal agents [27]. Recently, an association of caspase recruitment domain family member 9 (CARD 9) deficiency with isolated fungal infections in patients has been reported. CARD 9 deficiency has also been found in otherwise apparently immunocompetent children who developed phaeohypomycosis [23].

CNS infection is the most frequent presentation; however, other systemic manifestations including hepatitis and lymphadenitis, have also been reported. CNS infection is postulated to be secondary to hematogenous spread from the lungs, although no pulmonary focus has been identified in most reports [28].

Another peculiar manifestation is verrucous, plaque-like lesions in the head and neck. These are often reported in immunocompromised patients [29]. There is crusting and ulceration along the superficial aspect of the wound along with extensive deep-seated necrosis.

Imaging features

Multiple reports have described CNS imaging features [23]. Some authors have described areas of focal cerebritis that

may be observed, with gyral enhancement and white matter edema [25]. Others have reported the formation of intracerebral masses that may mimic malignancy (Fig. 6) and even show a choline peak on magnetic resonance spectroscopy (MRS). However, cerebral perfusion is usually normal, unlike malignancy. On MRI, due to the melanin in these fungi, areas of T1 hyperintensity and T2 hypointensity may be noted, particularly along the rim, which may indicate the diagnosis. Post-gadolinium enhancement is usually the norm [26]. Often, abscess-like lesions may also be seen in these children in the cerebral parenchyma with rim enhancement and extensive perilesional edema. The imaging findings resemble those of other fungal abscesses in such cases. The wall shows T2 hypointensity with intracavitary projections that are also hypointense. There is no diffusion restriction in the cavity, but is seen in the wall of the abscess. Blooming is seen in the wall on susceptibility weighted-imaging, which on phase images does not correspond to blood products [30]. On MRS, a trehalose peak is seen in addition to the lipid-lactate peaks. When hepatic involvement is observed, focal hypodense hepatic lesions [24] (Fig. 7) are seen with variable degrees of abdominal lymphadenopathy.

Although the initial route of infection in most cases is presumed to be respiratory, pulmonary phaeohypomycosis is rarely encountered clinically. In a systematic review of 120 cases of *Cladophialophora* infection, only three cases were found to have pulmonary involvement [31]. The findings in reported cases often point to a fungal etiology, although not specific to any organism. These include nodules which may show a ground glass halo, to segmental and even lobar consolidation [32] (Fig. 8). When ulcerated plaques are present over the head and neck region, the key differentiating feature in these from previously reported non-invasive mycoses is the presence of erosion and propensity for invasion of deep structures. However, they show slower progression, over months or years, compared to Mucorales [33].

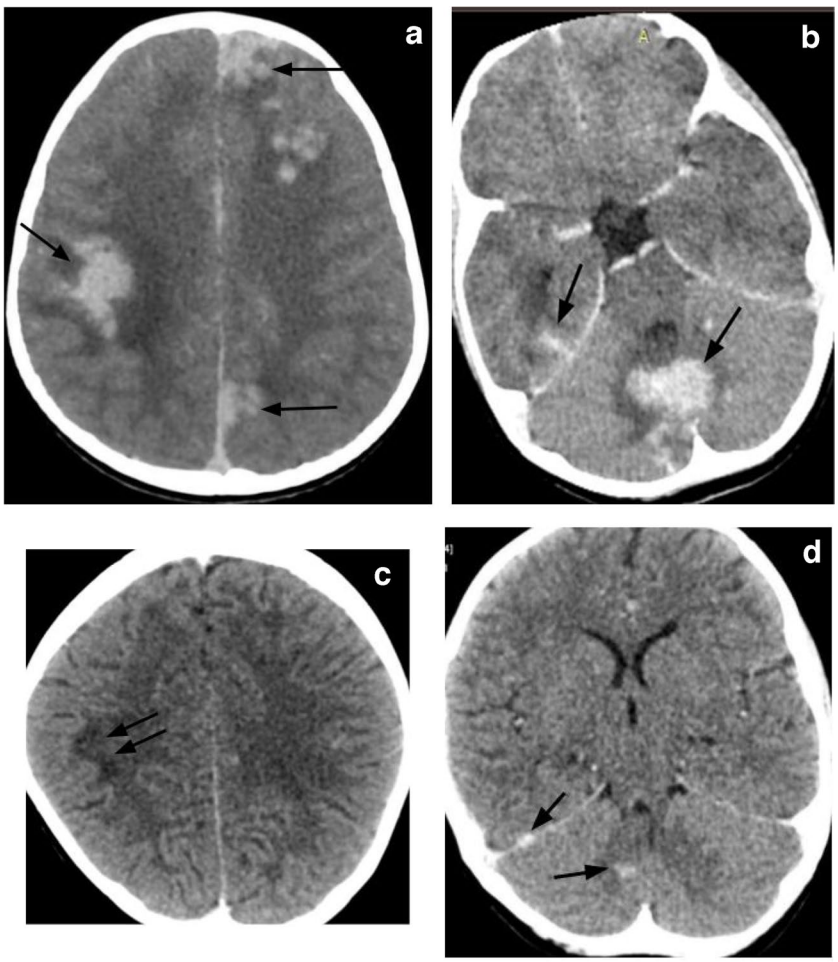

Fig. 6 Phaeohyphomycosis. A 3-year-old boy who presented with seizures. **a**, **b** Pretreatment axial enhanced CT of the brain shows multifocal cortical-subcortical enhancing masses in both the cerebral hemispheres and in the vermis (arrow) with significant perilesional edema. **c**, **d** CT done at 2 months post treatment with intravenous liposomal amphotericin B and voriconazole shows significant reduction in the size of the enhancing lesions as well as resolution of the edema (arrow)

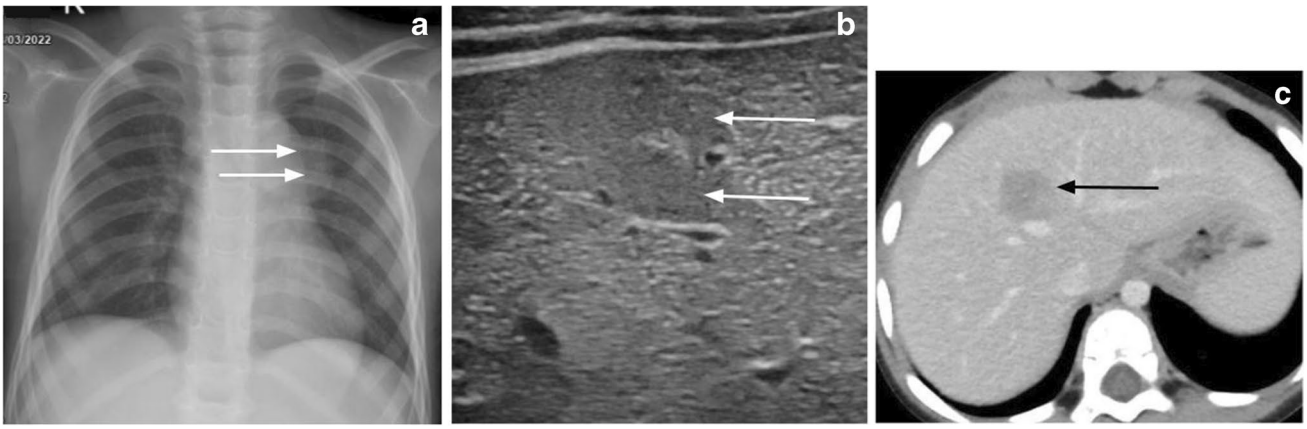

Fig. 7 Phaeohyphomycosis. The same patient as in Fig. 6. The child developed cough and abdominal distension a few days after presentation. On investigation, elevated leukocyte count was found with eosinophilia. **a** Frontal radiograph showed mediastinal lymphadenopathy along the left heart border (arrow). **b** Axial section of US performed via intercostal view for liver shows ill-defined hypoechoic lesions with no well-defined capsule. **c** Axial enhanced CT sections show the homogeneous hypodense liver lesion with no surrounding edema (arrow)

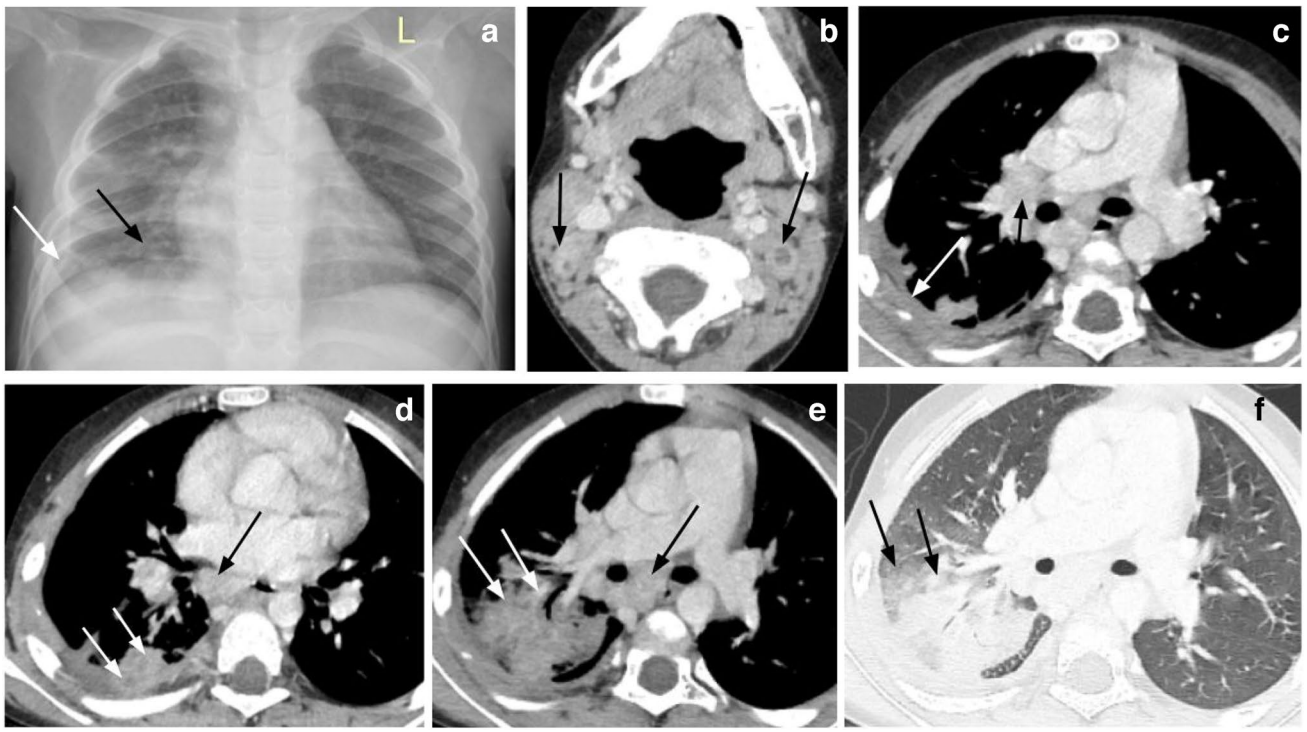

Fig. 8 Pheohypomycosis. A 5-year-old boy with immune deficiency who presented with fever and chest pain. **a** Frontal radiograph shows right sided airspace opacity (black arrow) and pleural collection (white arrow). **b** Axial CT of the neck shows cervical lymphadenopathy with necrotic centres (arrow). **c** Axial CT of the chest shows right hilar lymphadenopathy (black arrow) and right sided empyema (white arrow). **d** Subcarinal lymphadenopathy is also seen (black arrow). Consolidation in the right lung shows internal hypodense areas suggesting necrotising pneumonia (arrow). The patient underwent thoracotomy with excision of the affected right lower lobe segment and empyema drainage. CT repeated post-surgery due to persistent fever. **e** Axial CT of the chest shows new onset consolidation in the right upper lobe (white arrow) with persistent subcarinal lymphadenopathy (black arrow). **f** On the lung window, there is a ground glass halo seen (arrow) surrounding the consolidation due to angioinvasion

Table 2 Summary of diagnostic features of endemic fungal infections

Organism	Imaging features	Differential diagnosis	Differentiating features
Entomophthoromycota - basidiobolomycosis	1. Sharply circumscribed, homogeneously enhancing plaques in subcutaneous plane 2. Localized to limbs (lower > upper) 3. Multicompartmental abdominal masses with bowel and solid organ involvement	1. Soft tissue sarcoma	No deep tissue invasion, muscles and bones spared
		2. Elephantiasis (filariasis)	Discrete plaques of soft tissue composition compared to diffuse edema in filariasis
		3. Abdominal lymphoma	Inflammatory changes in adjacent fat, hollow organ obstruction with upstream dilatation unlike lymphoma
Entomophthoromycota - conidiobolomycosis	1. Enhancing plaque like or nodular soft tissue 2. Facial soft tissue, orbit, pharynx, larynx	1. NK/T-cell lymphoma	No bone destruction, no midline predilection unlike lymphoma
		2. Granulomatosis with polyangiitis	No bone destruction
		3. Mucormycosis	No bone destruction or intracranial extension. Uniform enhancement compared to necrotic areas in mucormycosis
Phaeohyphomycosis	1. Brain abscess/cerebritis- most well recognized form 2. Multi-organ involvement 3. Ulcerative plaques in head and neck	1. Pyogenic cerebral abscess	Rim is T1 hyperintense on MR due to melanin compared to hypointense rim in pyogenic abscess
		2. Mucormycosis	Slower progression [33]

Conclusion

While radiologists are familiar with typical imaging manifestations of invasive mycosis, particularly in immunocompromised patients, it is important to be aware of these emerging infections that present in peculiar geographic and demographic distributions. In particular, because they may be often mistaken for malignancy, diagnosis is often delayed in these patients, precluding adequate therapy. The common organisms and their imaging features are summarized in Table 2. The radiologist plays a crucial role in improving patient outcome by suggesting the diagnosis and performing image-guided sampling where necessary.

Author contributions DB and MJ conceived and supervised the study. DB, MJ, SM, ASB, PN, SKK, and RS collated and analyzed the data. DB, MJ, SM, ASB, and PN drafted the initial manuscript and interpreted the images. SKK and RS helped supervise the project. All authors reviewed and approved the final manuscript.

Declarations

Conflicts of interest Manisha Jana is an editorial board member for *Pediatric Radiology*. Other authors: None.

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