Orbital mycoses in a pediatric subtropical population: a case series

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PURPOSE To report our experience in the diagnosis and management of invasive fungal infections with orbital involvement in children from a subtropical population.

METHODS The medical records of children (<18 years of age) with orbital mycosis and treated by the senior author (TJS) from 1995 to 2017 in multiple pediatric tertiary centers were reviewed retrospectively.

RESULTS Six patients (aged 12 weeks to 15 years) were included in this series. Four patients had confirmed infection with isolated pathogens, including mucormycosis (3) and *Exserohilum* (2). One patient rapidly deteriorated and died before biopsy could be performed; however, the patient was presumed to have invasive fungal disease. Four patients had underlying hematological malignancy, and 1 presented in diabetic ketoacidosis. Orbital apex syndrome was observed in one patient. All patients received liposomal amphotericin B and five underwent at least one debridement surgery. One patient proceeded to orbital exenteration and survived. The overall survival rate was 67%.

CONCLUSIONS Orbital mycoses can affect children of all ages. Immunocompromised patients are particularly at risk, and mortality rates are high. In a subtropical population, these infections may be caused by a different spectrum of fungi compared to other climate zones. We believe extensive surgical debridement, including exenteration may still be necessary in the management of this disease in a young population, particularly if there is extensive orbital involvement. (J AAPOS 2019;23:270.e1-7)

Invasive fungal infections involving the orbit can affect patients of all ages. Although immunocompromised hosts are usually infected, cases involving immunocompetent individuals have been reported.[1,2] Mucormycosis and Aspergillus are the most commonly implicated pathogens in orbital mycoses.[3] Spread to the orbit typically occurs from the sinonasal tract; however, direct inoculation is also possible from trauma.[4]

Survival rates are often poor due to the fulminant, rapidly progressing nature of these infections, with potential propagation into neighboring structures, such as the cranial cavity.[5] Early diagnosis and treatment is crucial and have been shown to improve outcomes.[6] Medical management includes intravenous amphotericin B (AMB), usually in combination with other antifungal agents. Surgical management involves debridement of necrotic tissue that occurs as a result of fungal angioinvasion and subsequent vessel thrombosis and tissue infarction.[3]

The role of radical surgery, particularly orbital exenteration, is unclear and remains a controversial topic among orbital surgeons. Consequences of performing exenteration are more significant in children, as adequate orbital volume is necessary to maintain normal facial growth.[7] Here we report our experience in the diagnosis and management of pediatric patients with orbital mycoses from a subtropical population in Australia. Specifically, we evaluate patient risk factors, clinical presentation, pathogens, treatment, and outcomes.

Subjects and Method

The medical records of patients <18 years of age who were treated for fungal infection involving the orbit by the senior author (TJS) between 1995 and 2017 in a tertiary setting were reviewed retrospectively. Institutional review board approval for this study was obtained from the Children's Health Queensland Human Research and Ethics Committee. The following data were extracted from the record: age, sex, risk factors, presenting symptoms and signs, causative fungi, management, and outcomes.

Cases complied with the revised definitions for proven, probable, and possible invasive fungal disease proposed by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group

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(EORTC/MSG) Consensus Group.[8] Orbital involvement was determined on the grounds of clinical or radiographic evidence of orbital disease.

Results

Six pediatric cases of invasive fungal infection involving the orbit have been included in this series. Age, sex, patient risk factors, presenting symptoms and signs, management, and outcomes are summarized in Tables 1 and 2.

Case 1

A 15-year-old girl was admitted to the Queensland Children's Hospital with a new diagnosis of T cell acute lymphoblastic leukemia (ALL). One week after starting induction chemotherapy, she developed fever, headache, facial pain, and nasal congestion. She was pancytopenic, with a neutrophil count of 0.08×10^9/L. The next day she developed a dark, nonblanching erythematous lesion on her left forearm and an ulcerated lesion of the right nasal septum. Computed tomography (CT) scan of the sinuses was normal. Liposomal AMB was prescribed for suspected fungal infection. A skin biopsy of the forearm lesion revealed thick-walled, broad hyphae with nerve and vessel invasion. Magnetic resonance imaging (MRI) showed increased signal and enhancement of the right nasal turbinates extending through the nasolacrimal duct (Figure 1). Oral posaconazole was added and nasal debridement was performed; tissue histopathology showed hemorrhagic necrosis and fungal elements consistent with mucormycosis. Fungal culture later identified the organism as *Mucor circinelloides*. She complained of left blurred vision; however, ophthalmic examination was otherwise normal. The patient underwent two further nasal debridements and received granuloctyte colony stimulating factor (G-CSF) for persistent neutropenia. Over the next 2 weeks, she improved and was discharged on oral posaconazole. She proceeded to consolidation chemotherapy and has had no evidence of disease recurrence at 2 years' follow-up.

Case 2

A 15-year-old boy with type 1 diabetes mellitus was admitted to Townsville Hospital with diabetic ketoacidosis. Initial blood pH was 7.22, with a bicarbonate of 4 mEq/L. The patient became febrile and developed painful left periorbital swelling and headaches. CT scan showed opacification of the left ethmoid and sphenoid sinuses with preseptal soft tissue inflammation. Histopathology from ethmoid sinus biopsies revealed necrotic inflammatory tissue containing numerous thick-walled nonseptate fungal hyphae consistent with mucormycosis. The patient was started on liposomal AMB and admitted to the ICU, where his diabetic ketoacidosis was reversed with an insulin infusion. The next day he developed sudden left-sided ptosis, proptosis, restricted elevation, and infraorbital hypoesthesia with preserved vision (left eye visual acuity, 6/7.5). Given the rapid worsening of orbital examination in spite of medical therapy and reversal of diabetic ketoacidosis, a decision was made to perform lid-sparing orbital exenteration. Culture from intraoperative specimens isolated the organism as *Rhizopus spp*. The patient underwent two further nasal debridement surgeries in addition to 34 dives of hyperbaric oxygen therapy. He clinically improved and was eventually discharged 1 month after initial presentation with no recurrence of disease.

Case 3

A 6-year-old girl was admitted to the Royal Children's Hospital with relapsed pre-B cell ALL after receiving an allogeneic bone marrow transplant the previous year. One week after starting chemotherapy, she developed nasal pain with bloody discharge, right-sided facial edema, skin discoloration, epiphora, fever, and decreased vision. Her neutrophil count was 0.23×10^9/L. Intravenous broad spectrum antibiotics, liposomal AMB, and G-CSF were initiated. CT scan showed diffuse opacification of the right paranasal sinuses, with associated preseptal soft tissue inflammation. Her symptoms rapidly progressed over the next day with development of proptosis, ptosis, and reduced ocular motility. Urgent examination by ophthalmology revealed right eye visual acuity of 6/60, with a relative afferent pupillary defect (RAPD) and complete ophthalmoplegia, signifying likely orbital apex syndrome. There was mild chemosis. Retinal examination was normal. Oral voriconazole was commenced. Unfortunately, the patient rapidly deteriorated further and died before any surgical intervention or tissue biopsy could be performed. An autopsy was not performed.

Case 4

A 12-week-old girl was admitted to the Royal Children's Hospital with newly diagnosed biphenotypic leukemia for induction chemotherapy. She developed left lower eyelid swelling and bruising with superficial ulceration of her hard palate measuring 5×7 cm. The patient was profoundly neutropenic with a neutrophil count of 0.00×10^9/L. CT scan showed subcutaneous edema of the left eyelids, left ethmoid opacification, and a 5 mm collection in the inner canthus (Figure 2). Intravenous liposomal AMB and antibiotics were initiated. Initial ophthalmic examination was normal except for periorbital and eyelid edema. The patient developed necrosis of her left nasal cavity, cheek, and hard palate. Initial biopsy showed necrotic material containing branching, septate fungal hyphae, with evidence of angioinvasion. The hyphae were long and slender and reported as not typical for *Mucor*. The patient received a further four surgical debridements of face, ethmoid sinus, and medial orbit, including resection of the nasolacrimal duct and part of the lacrimal sac. Culture of intraoperative specimens identified the fungus as *Exserohilum*

Table 1. Sex, age, pathogens, risk factors and presenting clinical features

Case	Age	Sex	Pathogen	Risk factors	Presenting symptoms	Initial orbital signs	Symptom onset to orbital specialist review, days
1	15 yrs	F	*Mucor cicinelloides*	T-ALL, chemotherapy, neutropenia	Fever, headache, facial pain, rhinorrhea	Nil; right lacrimal duct enhancement on MRI	13
2	15 yrs	M	*Rhizopus spp.*	DKA	Fever, headache, facial pain, eyelid swelling, vision loss	Proptosis, ptosis, ophthalmoplegia, infraorbital nerve hypoesthesia	2
3	6 yrs	F	No biopsy	Pre-B cell ALL, BMT, neutropenia, chemotherapy	Fever, nasal pain and discharge, epiphora, periorbital/facial swelling, skin discoloration, vision loss	Orbital apex syndrome, ptosis, proptosis, eyelid edema, RAPD, chemosis	2
4	12 wks	F	*Exserohilum longirostratum*	Biphenotypic leukemia, chemotherapy, corticosteroids	Fever, periorbital swelling, nasal discharge, skin discoloration	Eyelid and periorbital edema 5 mm collection inner canthus	2
5	2 yrs	F	*Exserohilum rostratum*	Pre-B cell ALL, chemotherapy, neutropenia, corticosteroids	Fever, headache, rhinorrhea	Eyelid and periorbital edema	7
6	7 yrs	F	*Rhizopus spp.*	Pre-B cell ALL, BMT, GVHD, immunosuppressive therapy	Headache	Eyelid and periorbital edema, fixed dilated pupil with RAPD, chemosis, pale and swollen optic nerve, peripapillary choroidal infarction	15

ALL, acute lymphoblastic leukemia; *ALOC*, altered level of consciousness; *BMT*, bone marrow transplant; *DKA*, diabetic ketoacidosis; *GVHD*, graft versus host disease; *MRI*, magnetic resonance imaging; *RAPD*, relative afferent pupillary defect.

Table 2. Treatment and outcomes

	Sinus/nasal surgery		Orbital exenteration			Survival	Visual
Case	Y/N	No.	(Y/N)	Other	Medical therapy	(Y/N)	outcome
1	Y	3	N	Skin biopsy	Liposomal AMB; posaconazole; G-CSF	Y	Unchanged
2	Y	3	Y	—	Liposomal AMB; hyperbaric O_2 therapy	Y	No eye
3	N	—	N	—	Liposomal AMB; voriconazole; G-CSF	N[a]	Deceased
4	Y	5	N	—	Liposomal amphotericin B Voriconazole; G-CSF	Y[b]	Deceased
5	Y	5	N	—	Liposomal AMB; posaconazole; G-CSF	Y	Unchanged
6	Y	1	N	Maxillary sinus washings; lung biopsy	Liposomal AMB; capsofungin; rifampin	N[a]	Deceased

AMB, amphotericin B; *G-CSF*, granulocyte colony stimulating factor.
[a]Died from cerebral spread of infection.
[b]Died later from underlying malignancy.

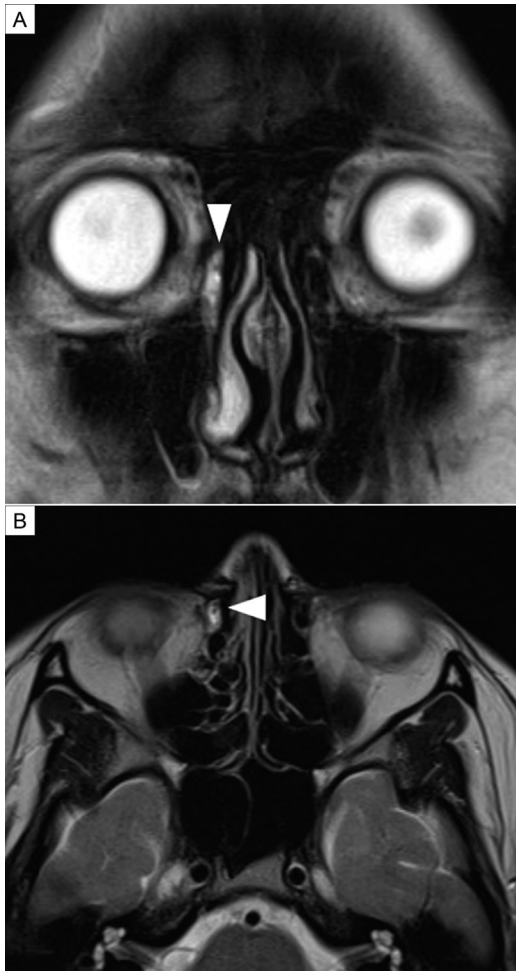

FIG 1. T2-weighted magnetic resonance imaging (MRI), coronal (A) and axial (B) slices, of patient 1 showing increased signal of right nasolacrimal duct (arrowheads).

longirostratum. Oral voriconazole and G-CSF were commenced. The patient clinically improved over the next month and follow-up MRI showed no evidence of remnant disease. She received a bone marrow transplant; however, unfortunately, she relapsed and died the next year from her hematological malignancy.

Case 5

A 2-year-old girl was admitted to the Queensland Children's Hospital with high-risk pre-B cell ALL. After starting induction chemotherapy, she became febrile, with a neutrophil count of 0.07×10^9/L. She developed rhinorrhea, increased irritability, and recurrent headaches. CT scan showed minor mucosal thickening of the right ethmoid but was otherwise normal. Five days later, she suddenly developed right-sided periorbital edema. Liposomal AMB was promptly initiated for suspected invasive fungal infection. MRI showed significant subcutaneous premaxillary edema. Exploration under anesthesia revealed necrotic debris within the nose extending to the ethmoid sinus, which was debrided. Histopathology showed necrotic tissue with angioinvasive fungal hyphae branching at 60°. The fungus was later identified as *E. rostratum* from cultures. Ophthalmology consultation noted marked periorbital and eyelid swelling, with a sluggish pupillary reflex, but normal fundus. Intravenous posaconazole and G-CSF were initiated. Chemotherapy was temporarily delayed by the oncology team. The patient underwent four further sinus and facial debridement surgeries including a midface degloving approach. She improved clinically and was discharged approximately 2 months after initial symptom onset on maintenance oral posaconazole.

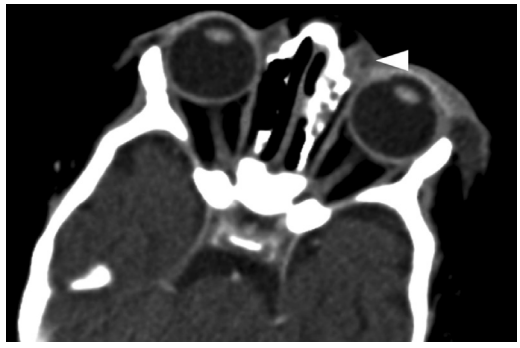

FIG 2. Computed tomography, axial slice, of patient 4 showing left inner canthal collection shown by arrowhead.

Case 6

A 7-year-old girl was admitted to the Royal Children's Hospital with poorly controlled graft-versus-host disease of the skin. She previously received an allogeneic bone marrow transplant for relapsed precursor B-cell ALL. Immunosuppressive regime included mycophenolate, cyclophosphamide, and prednisolone. A CT was performed due to severe headaches, which showed severe left-sided sinusitis. Intravenous antibiotics but not antifungal therapy were initiated. Two weeks later, she developed sudden-onset right arm hypotonia and left periorbital edema with altered level of consciousness. She was febrile with a left-fixed dilated pupil and chemosis (Figure 3). Repeat CT showed extensive left maxillary and ethmoid disease with fat stranding in the retroorbital tissue and infratemporal fossa. There was a 2.6 cm diameter dense lesion in the left lung lower lobe with central cavitation. Liposomal AMB was initiated. On ophthalmic review, the left optic nerve head appeared pale and swollen with peripapillary infarction. MRI showed thickening of the optic nerve (Figure 3) and high signal within the left frontal lobe and pons. The patient underwent urgent tissue biopsy of her left ethmoid sinus and lung lesion. Histopathology revealed numerous PAS-positive non-septate fungal hyphae. Culture later isolated the organism as *Rhizopus spp*. Capsofungin and rifampin were prescribed and her immunosuppressive medications

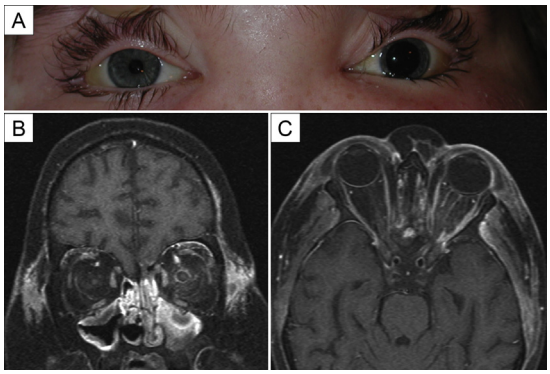

FIG 3. A, Clinical photograph of patient 6 on initial examination. B-C, T1-weighted MRI with gadolinium contrast, coronal (B) and axial (C) slices.

were weaned. Unfortunately, the patient further deteriorated and died 4 days after clinical onset of orbital and intracranial involvement.

Discussion

We have reported 6 children from a subtropical population who had invasive fungal infections involving the orbit. Patient 3 was not biopsied because of rapid clinical deterioration and death, precluding histological or microbiological confirmation of fungal infection. However, we have included this case in this series because host factors and clinical presentation meet the EORTC/MSG consensus group criteria for possible invasive fungal disease.[8]

Most of our patients required an orbital specialist review for orbital signs that developed only several days after initial symptom onset. This reflects the rapidly progressive nature of this disease from sinus to orbital involvement and highlights the importance of timely diagnosis and treatment in order to optimize patient outcomes.[6] Infection usually originates in the sinonasal tract before spreading to the orbit and subsequently the intracranial cavity, at which point the disease is often fulminant with dismal prognosis.

Infections often occur in immunocompromised hosts, typically neutropenic patients with underlying hematological malignancy receiving chemotherapy.[9,10] Five patients in our series had underlying hematological malignancy, and 3 survived. Temporary interruption of the child's chemotherapy or immunosuppressive regime may be required, particularly if they are neutropenic, under the guidance of their hemato-oncologist. Previous hematopoietic stem cell transplant (HSCT) is also another risk factor in children, associated with increased mortality.[9] Two patients in our series had previous HSCT, and both died. In immunocompromised patients, early inflammatory signs on clinical examination or imaging may be absent due to an impaired immune response, which can contribute to a delayed diagnosis. In cases 1 and 5, both patients had relatively normal initial CT findings early in the course of their disease.

The recent introduction of novel targeted chemotherapy agents such as blinatumomab may influence favorably the survival of patients with hematological malignancies who develop invasive fungal infections. Blinatomomab is a bispecific T cell engager antibody construct that targets specifically CD-19 positive tumor cells, thereby avoiding generalized immunosuppression seen with traditional chemotherapeutic regimes.[11]

Diabetes mellitus with or without diabetic ketoacidosis is a risk factor specific for mucormycosis. Hyperglycemia and acidosis decreases the host's fungal defense system through multiple mechanisms, such as impairing neutrophil chemotaxis and oxidative burst ability.[12] Therefore, early glycemic control and normalization of blood pH is key in the management of these patients. In neonates, prematurity is a unique risk factor for mucormycosis and mortality rates have been shown to be higher compared to older children.[5]

Several cases of invasive orbital mycoses affecting immunocompetent, nondiabetic children have also been reported.[2,13] Therefore, this disease should always be included in the treating clinician's differential diagnosis for patients presenting with orbital symptoms or signs, regardless of age and immune status.

Mucorales and *Aspergillus* are the predominant pathogens implicated in invasive sino-orbital fungal disease. However, 2 of our patients (patients 4 and 5) were infected with *Exserohilum* in the context of hematological malignancy. Patient 4 was a young infant who unfortunately died despite her infection being controlled by multiple antifungal agents and sinus debridement surgeries. *Exserohilum* are environmental dematiaceous fungi, which, like *Aspergillus*, may cause invasive or noninvasive disease (eg, allergic fungal sinusitis).[14] Most commonly reported types of infection include systemic (often with sinus involvement), cutaneous, and corneal infections.[13] Azoles such as itraconazole and posaconazole appear to demonstrate better activity than AMB against *Exserohilum*, however combination therapy is often employed, particularly in immunosuppressed individuals.[15,16] To our knowledge, there have only been 2 previously reported cases of invasive *Exserohilum* infection involving the orbit in children.[15,16] These patients lived in Israel and India, suggesting that this particular pathogen is more common in warmer tropical or subtropical regions.

Involvement of the lacrimal system appears common in a pediatric population.[17-19] This is potentially due to the higher prevalence of certain predisposing conditions, such as congenital lacrimal duct obstruction (CLDO). Lithander and colleagues[17] reported a case of an immunocompetent infant with CLDO presenting with a lacrimal sac mass extending into the orbital apex secondary to *Conidiobolus coronatus*. Successful management included systemic antifungals combined with AMB irrigation via intraorbital drain. Two pediatric cases of invasive *Aspergillus* presenting as dacryocystitis are also described by Davies and colleagues.[19] Both patients survived with systemic

antifungal therapy and dacryocystectomy. Patient 1 in our series developed mucormycosis in the context of receiving chemotherapy for ALL, with nasolacrimal duct enhancement shown on MRI. Involvement of the lacrimal system was subtle in her case, as she demonstrated no suggestive signs on initial examination such as medial periorbital erythema or swelling. This case highlights the utility of MRI as part of the initial diagnostic work-up, particularly for evaluating soft tissue involvement in fungal disease.

The most common presenting clinical features of orbital mycoses in our series include proptosis, restricted ocular motility, periorbital or facial edema, and fever. Patients also often describe preceding symptoms of nasal discharge or congestion, headache, or sinusitis. The development of orbital apex syndrome (OAS) may represent advanced disease and signal imminent propagation of infection to the cavernous sinus and intracranium.[4] Patient 3 in our series developed OAS only 2 days after initial symptom onset and died prior to any surgical intervention, presumably from cerebral spread of infection. This case again highlights the potentially acute, rapidly progressive nature of this disease. Other serious sequelae include orbital ischemia, as demonstrated by patient 6 who developed choroidal infarction and ischemic optic neuropathy.

Surgical debridement of necrotic, devitalized tissue represents an important part of management of sino-orbital mycoses.[3] This is because the tissue serves as an infection source, which is poorly penetrated by systemic antifungals due fungal angioinvasion and vessel thrombosis.[3] Numerous studies have demonstrated reduced mortality with combined surgical and medical intervention compared to medical treatment alone.[9,20] However, the role of extensive debridement including orbital exenteration remains a topic of debate amongst orbital specialists, arguably more so in a pediatric population. There is insufficient evidence to say that exenteration definitively improves mortality in orbital mycoses. Some authors advocate and report successful outcomes from a more conservative management approach without exenteration.[21,22] Patient 2 in our study was exenterated for mucormycosis in the setting of diabetic ketoacidosis and survived. From our experience in managing invasive orbital mycoses, we believe exenteration is warranted as a last resort in cases where there is significant burden of disease involving the orbit, seen either clinically, on imaging, or intraoperatively, that is progressive despite medical therapy and aggressive sinus debridement.

Early instigation of systemic antifungal therapy is vital in treating orbital mycoses. Ideally, this involves intravenous liposomal AMB combined with another agent such as voriconazole or posaconazole, depending on culture and sensitivities. Hyperbaric oxygen therapy (HBO) and intraorbital irrigation or injection with AMB are also occasionally used, particularly for mucormycosis. HBO theoretically improves neutrophil oxidative fungicidal ability and relieve areas of ischemia, while the rationale behind topical application of AMB is direct drug delivery to targeted, infected tissues.[23,24] There have been 6 reported cases of retrobulbar AMB injection for invasive orbital fungal infection with generally favorable outcomes; however, all the patients were adults.[25] Granulocyte colony-stimulating agents are also often used as adjunctive therapy in neutropenic patients with hematological malignancy.[26]

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