Invasive Fungal Sinusitis and Its Orbital Morbidity in Pediatric Population

A Strategic Treatment Algorithm and Outcomes

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Background: Invasive fungal sinusitis, particularly mucormycosis, presents a significant clinical challenge, especially in pediatric populations. This retrospective epidemiologic study aimed to investigate the clinical characteristics, risk factors and outcomes associated with this rare but severe condition, with a focus on orbital morbidity.

Methods: Clinical data of 12 pediatric patients diagnosed with invasive fungal sinusitis between 2021 and 2023 were retrospectively analyzed. Diagnosis involved microbiological and histopathologic examinations, alongside radiologic imaging. Treatment comprised surgical intervention and antifungal therapy, with a detailed evaluation of orbital involvement. Statistical analysis included descriptive statistics and logistic regression.

Results: Predominantly affecting males, the median age of the patients was 8 years. Common symptoms included orbital swelling and impaired vision. Imaging revealed characteristic features of invasive fungal sinusitis, including fat stranding and bone erosions. Orbital involvement was extensive, with poor visual outcomes observed in several cases. Surgical debridement and antifungal therapy, including transcutaneous retrobulbar Amphotericin B, were administered. Risk factors associated with poor orbital outcomes included duration of diabetes and glycated hemoglobin levels. Mortality rate stood at 22.2%.

Conclusions: Early diagnosis, aggressive surgical intervention and combined antifungal therapy are essential for improving outcomes. Timely intervention showed stabilization of the orbital disease and better outcomes in pediatric patients. Further research with larger sample sizes is warranted to better understand and address this serious condition.

Key Words: pediatric invasive mycosis, invasive fungal sinusitis, orbital mycoses, mucormycosis, invasive aspergillosis

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This case was selected after obtaining informed consent of the patient for publication.The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.All authors were equally involved in conception of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article and final approval of the version to be published.

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Invasive fungal sinusitis poses a life-threatening risk, affecting the sinonasal tract, orbit and intracranium, across all age groups.[1] While commonly seen in immunocompromised individuals, it also affects immunocompetent patients.[2] Recent data highlight pediatric patients as an emerging vulnerable group to this infection, with significant morbidity and mortality.[3] Mucormycosis and *Aspergillus* are primary pathogens associated with orbital invasive fungal sinusitis, often transmitted from the sinonasal tract or via direct trauma.[4]

These aggressive infections often lead to poor survival rates and can spread to nearby structures like the cranial cavity. Timely diagnosis and treatment, typically involving intravenous administration of Amphotericin B (AMB) and other antifungal agents, are crucial. Surgical intervention aims to remove necrotic tissue caused by fungal invasion, which can lead to thrombosis and tissue infarction.[5,6]

The necessity and efficacy of radical surgeries, such as orbital exenteration, remain debated, especially in pediatric cases where preserving orbital volume is essential for normal facial growth.[7] Our study highlights the importance of evaluating patient risk factors, clinical presentation, causative pathogens, treatment options and outcomes in managing pediatric patients with invasive fungal sinusitis with special emphasis on orbital morbidity.

MATERIALS AND METHODS

Study Design and Setting

An ambispective epidemiologic profiling was conducted at apex tertiary care center in accordance with the principles outlined in the Declaration of Helsinki between 2021 and 2024 to analyze the clinical data of 12 pediatric patients who presented with invasive fungal sinusitis. The study aimed to identify potential risk factors, clinical presentations and outcomes associated with this rare but serious fungal infection with emphasis on orbital morbidity. Ethical approval was obtained from the institutional review board before data collection. Patient confidentiality was strictly maintained throughout the study by deidentifying personal information.

Patients Diagnosis and Treatment Algorithm

Twelve pediatric patients diagnosed with invasive fungal sinusitis were included in the study. Patients were identified through electronic medical records using appropriate diagnostic codes and key words related to mucormycosis.

Microbiology

Samples collected from the nasal cavity via diagnostic nasal endoscopy or from palatal ulcers/eschar undergo direct light microscopy examination using a 10% potassium hydroxide wet mount. Broad, hyaline, aseptate, right angle–branched hyphae indicate mucorales infection, while septate acute branching hyphae are characteristic of aspergillosis.

Histopathology

Tissue samples undergo fixation in 10% neutral buffered formalin before routine processing and sectioning. Four-micrometer-thick sections are stained with hematoxylin and eosin to observe fungal structures and morphology. Special stains like Grocott methenamine silver and periodic acid–Schiff highlight fungal structures, appearing black and magenta, respectively. Angioinvasion and perineural invasion, indicative of mucor infection, are visible in both hematoxylin and eosin and periodic acid–Schiff/Grocott methenamine silver–stained sections as fungal structures invading vessel walls and perineural spaces.

Staging and Treatment

Patients diagnosed microbiologically or histopathologically underwent radiologic imaging [computed tomography, magnetic resonance (MR) imaging or both] and were staged according to the institutional staging system.[8] Treatment included surgery and parenteral liposomal AMB (5 mg/kg/d). Patients with orbital involvement received transcutaneous retrobulbar AMB (TRAMB), administered as 1 mL of 3.5 mg/mL AMB with a 23-gauge 24-mm needle. Detailed treatment protocols are provided in Figure 1.

Cutaneous involvement was managed with intralesional AMB (2 mg/mL) administered using a 26-gauge half-inch needle in a 2-mL syringe. Daily doses were given for 7 consecutive days.

Orbit Evaluation

Orbital involvement was assessed for visual acuity, ophthalmoplegia and ptosis across 3 compartments: preseptal, bulbar and retrobulbar.

Best-corrected visual acuity was evaluated using the Snellen chart, supplemented by alternatives like Counting Fingers, Hand Movement (HM) and Light Perception when necessary. Counting Fingers involved counting fingers from a distance of 1 meter, HM assessed movement perception, and Light Perception evaluated light recognition from a 50-cm source.

Extraocular movement was assessed in 6 directions, categorized into 4 levels from full duction to full limitation.

Ptosis was defined by reduced upper margin-reflex distance 1, with severity classified as normal, partial or complete based on margin-reflex distance 1 measurement: ≥4 mm for normal, <4 mm for partial and complete eye closure for complete ptosis.

Data Analysis

Descriptive statistics were utilized to summarize the demographic and clinical characteristics of pediatric patients with rhino-orbital-cerebral mucormycosis. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as means with standard deviations or medians with interquartile ranges (IQRs), based on data distribution. Exact logistic regression was employed to identify risk factors associated with poor orbital outcomes. Visual acuity, ptosis and ophthalmoplegia were scaled uniformly from 0 to 10 using minimum-maximum scaling. Pre-treatment and post-treatment ophthalmological findings were compared using the Wilcoxon signed-rank test. All analyses were 2 tailed, with significance set at $P < 0.05$. The SPSS software, version 26.0 (SPSS Inc., Chicago, IL), was used for all analyses.

RESULTS

Clinical and Demographic Features

Table 1 describes the clinical and demographic features. During the period of 2020–2023, 12 pediatric patients were diagnosed with acute fulminant invasive mucormycosis. The median duration of chief complaints to first clinical visit was 13 (IQR 10–15) days. The median age was 8 (IQR 5–17) years. Ten were

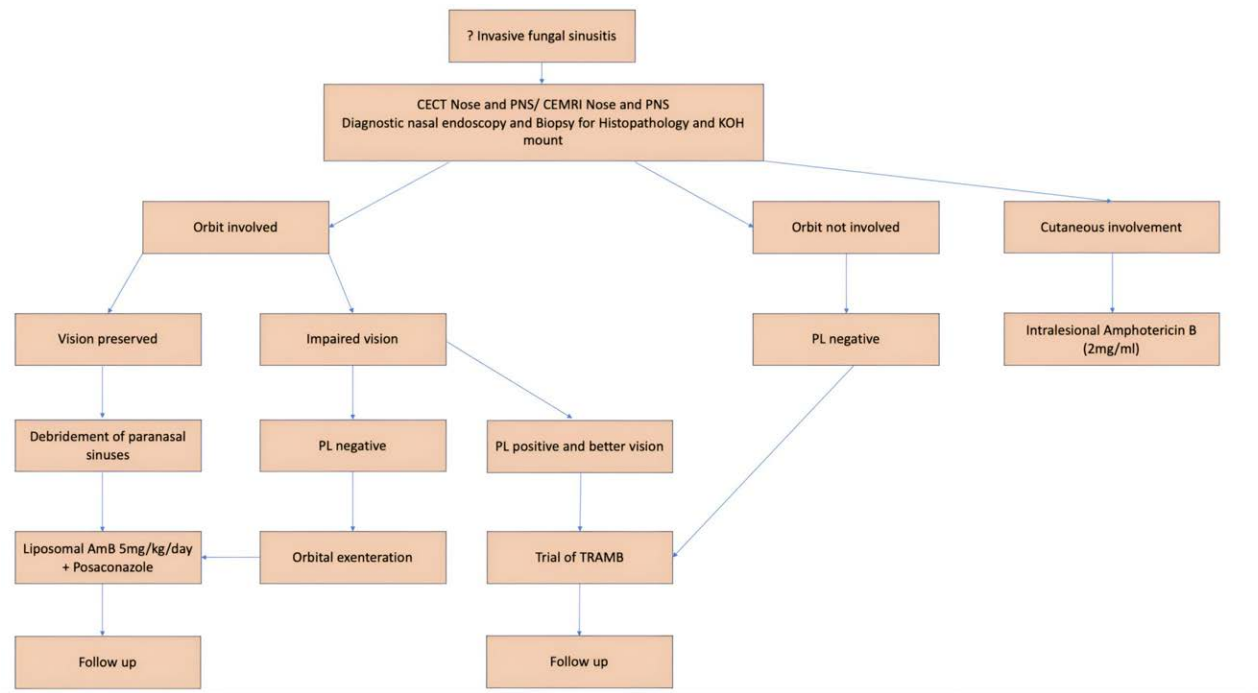

FIGURE 1. Schematic representation of treatment algorithm. CECT indicates contract enhanced computed tomography; CEMRI, contract enhanced magnetic resonance imaging; KOH, potassium hydroxide; PNS, paranasal sinuses.

TABLE 1. Clinical and Demographic Characteristics

Variable	Count (n)
Age	
≤12 yr	4
12–18 yr	8
Gender	
Male	10
Female	2
Chief complaints	
Orbital swelling	11
Impaired vision	10
Cheek swelling	10
Loss of facial sensation	9
Palatal ulcer	9
Comorbidities	
Type I diabetes	9
Hematological malignancy	2
No diagnosed comorbidities	1
HbA1c	
≤5.6	2
5.7–6.4	1
>6.4	9
History of COVID-19	
Yes	5
No	7
Stage of the disease	
I	1
II	1
IIIA	3
IIIB	5
IVA	1
IVB	1

male and 2 were female. Most common presenting symptoms were orbital swelling (91.6%), followed by impairment of vision (83.3%). The median duration of type 1 diabetes was 36 (IQR 32–46) months. The mean glycated hemoglobin (HbA1c) was 9.2 ± 2.8 g/dL. Common stage of presentation was IIIA (41.6%). Figure 2 shows the clinical images of common clinical presentation of invasive fungal sinusitis.

Important radiologic features of the invasive fungal sinusitis were, on computed tomography scan, fat stranding in the retroantral (maxillary antrum), extraconal, intraconal and premaxillary regions, as well as bone erosions are characteristics of invasive fungal sinusitis. These findings were present in all our cases. MR imaging showed black turbinate sign seen in post-contrast T1 sequence was defined as nonenhancement of nasal turbinates and nasal mucosa. Most common nerve showed perineural spread was maxillary division of trigeminal nerve. Three patients had brain abscess, and 4 patients had extensive skull base osteomyelitis changes. Figures 3 and 4 shows the radiologic findings of invasive fungal sinusitis. Rest of the clinical features are described in Table, Supplemental Digital Content 1, http://links.lww.com/INF/F581.

Risk Factors for Orbital Involvement

Extent of orbital involvement was divided as per the surgical spaces of orbit. Ten patients had orbital involvement, 5 patients had both preseptal and bulbar compartment involvement, 4 patients had all the 3-compartment involvement, and 3 patients had only retrobulbar compartment involvement. Figure 5 shows the stage based distribution of chief orbital complaints of invasive fungal sinusitis.

Six patients had poor visual acuity. Of these 6 patients, 3 patients presented with absent perception of light (PL) (negative PL), 1 patient had PL positive, and 1 patient had HMs. Rest 6 patients had a vision better than 20/200.

The degree of ophthalmoplegia was evaluated according to the degree of eye movement and divided into 5 sections: normal, <25%, >25% but <50%, >50% but <75% and >75% of limited eye movement. A total of 2 (16.6%), 3 (25%), 4 (33.3%), 1 (8.3%) and 2 (16.6%) patients were identified in each group.

On ptosis evaluation, no ptosis was observed in 4 patients, 5 patients had minimal ptosis, and 3 patients had complete ptosis. Figure 6 shows the pre and post treatment orbital outcomes.

All the 9 patients received TRAMB.

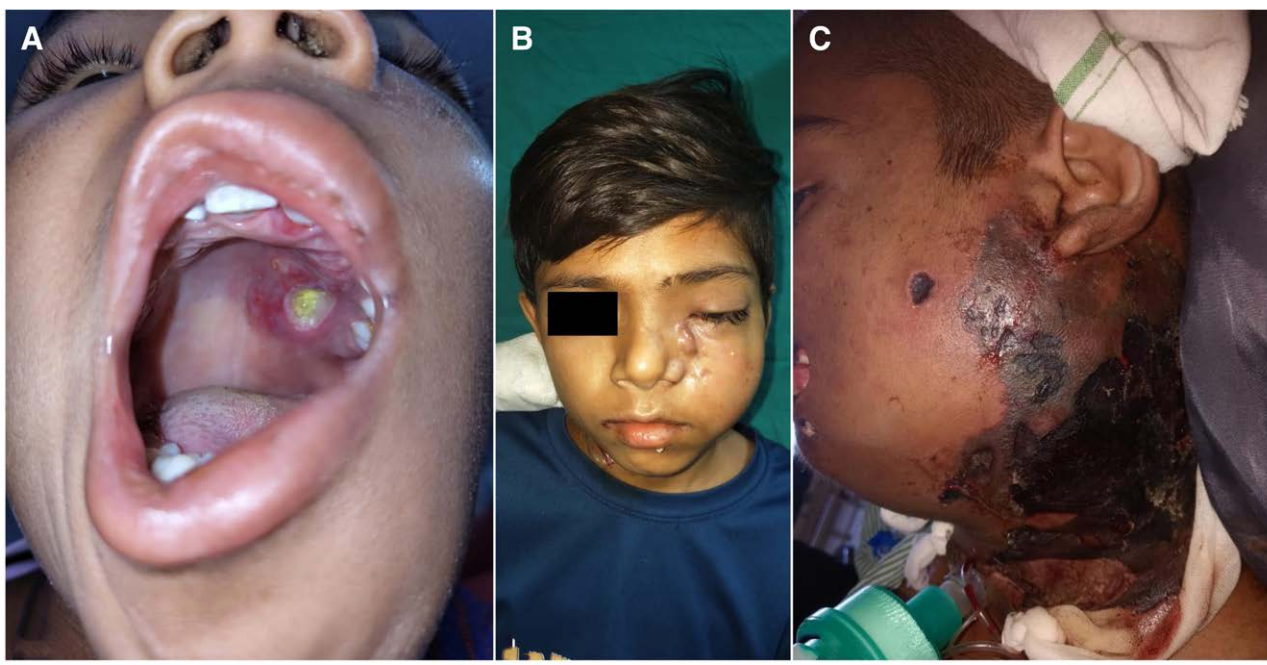

FIGURE 2. Clinical presentation of Invasive fungal sinusitis. Clinical photographs showing (A) palatal ulcer, (B) orbital involvement and (C) extensive cutaneous involvement.

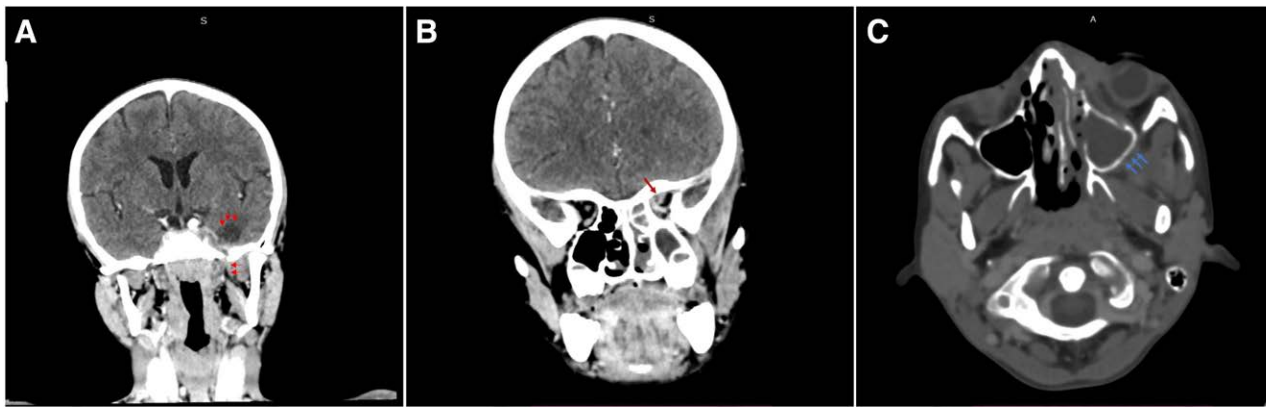

FIGURE 3. Computed tomography imaging. A: Coronal section showing temporal lobe abscess with perineural spread along the mandibular division of trigeminal nerve. B: Coronal section showing the fat stranding in the left orbital apex as shown by the red arrow indicating the disease involvement. C: Axial section showing fat stranding in the retroantral fat.

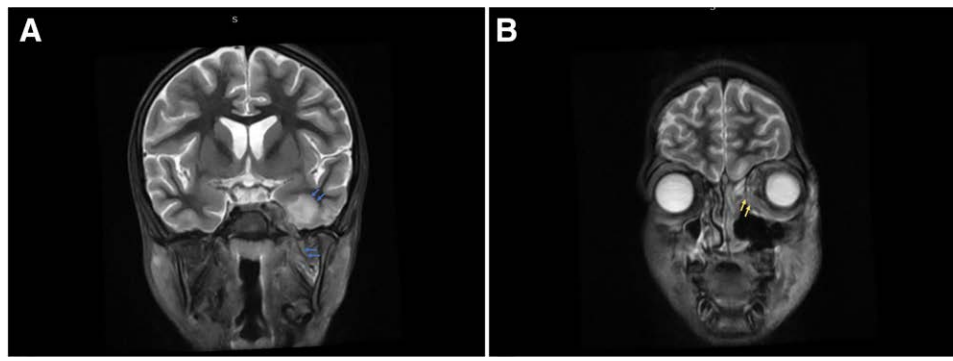

FIGURE 4. Magnetic resonance images of paranasal sinuses. MR imaging showing (A) T_2W sequence showing temporal lobe with perineural spread along the mandibular division of trigeminal nerve on the right side with right cavernous sinus thrombosis (blue arrow) and (B) T_2W sequence showing the extraconal fat stranding in the left orbit (yellow arrow).T_2W indicates T_2 weighted.

A median of 5 (range, 3–7) doses was received by the patients. Three patients underwent orbital exenteration following no response to TRAMB. Two patients expired from the extensive spread of the disease. One patient had stable vision following 7 doses of TRAMB.

On comparing the pre and post treatment, the differences in visual acuity ($P = 0.98$), ptosis ($P = 0.08$) and ophthalmoplegia ($P = 0.09$) were statistically insignificant by Wilcoxon signed-rank test.

One patient with primary rhino-orbito-cerebral mucormycosis extending to involve periorbital soft tissue and skin received 7 doses of intralesional AMB.

We performed an exact logistic regression analysis to see the risk factors associated with poor orbital outcome. HbA1c, duration of symptoms and status of perineural spread were strong predictors of poor orbital outcome (results are given in Table 2).

Long-term Prognosis and Follow-up

Two patients expired during the treatment due to the extensive disease. One of these 2 patients had primary invasive sinonasal mucormycosis with uncontrolled type 1 diabetes (HbA1c > 10), and the second patient was immunocompetent. Rest of the patients were discharged on oral posaconazole at a median duration of 45 (IQR 42–52) days of hospital stay. Patients with brain abscess were monitored by means of serial MR scans, at median interval of 15 (IQR 13–18) days. All the patients with brain abscess were decided to discharge when the abscess was walled off with resolution of perilesional edema. All the patients were reviewed once in 3 weeks for strict glycemic control and cavity inspection. The median duration of follow-up was 18 (range, 9–24) months. Radiology was repeated at 6 months or prior in case of suspicion of recurrence of disease. Patients received posaconazole for a median duration of 7 (range, 6–8) months. One patient who received intralesional AMB at the first month of follow-up, his periorbital lesion resolved completely. None of the patients developed recurrence of the disease during the follow-up period.

DISCUSSION

We conducted an ambispective analysis spanning 2 years, examining various aspects including patient demographics, clinical presentation, imaging findings, treatment approaches and outcomes. Notably, there has been limited documentation of mucormycosis cases in pediatric populations, making our report a substantial contribution to the literature from our region.

Our study found a predominance of male patients, consistent with previous research indicating mucormycosis primarily affects males.[9,10] Additionally, most affected children were over 5 years of age, with a concerning 22.2% mortality rate in our series. Recent research by Francis et al identified hematologic malignancy, transplantation and diabetes as key risk factors for mucormycosis in older infants

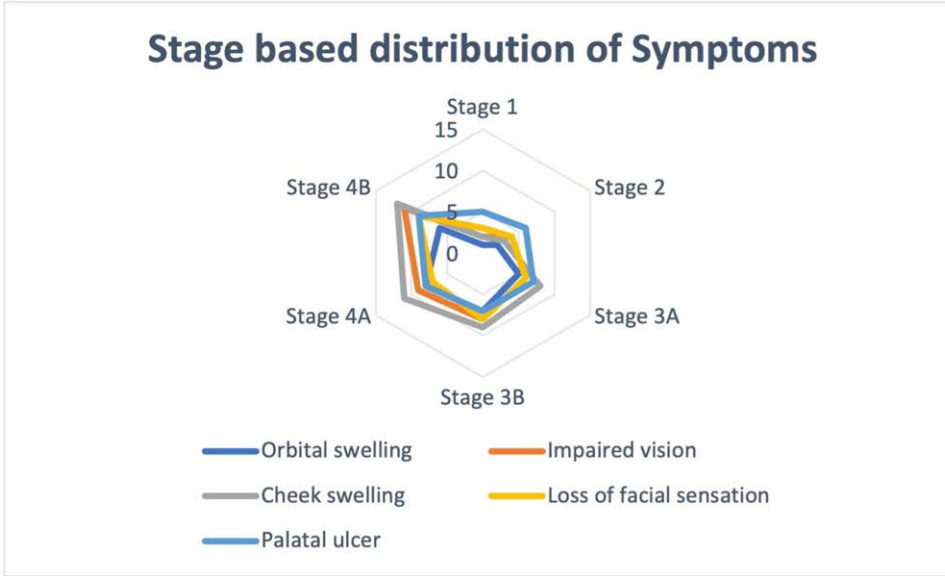

FIGURE 5. Spider graph showing the stage-based distribution of symptoms.

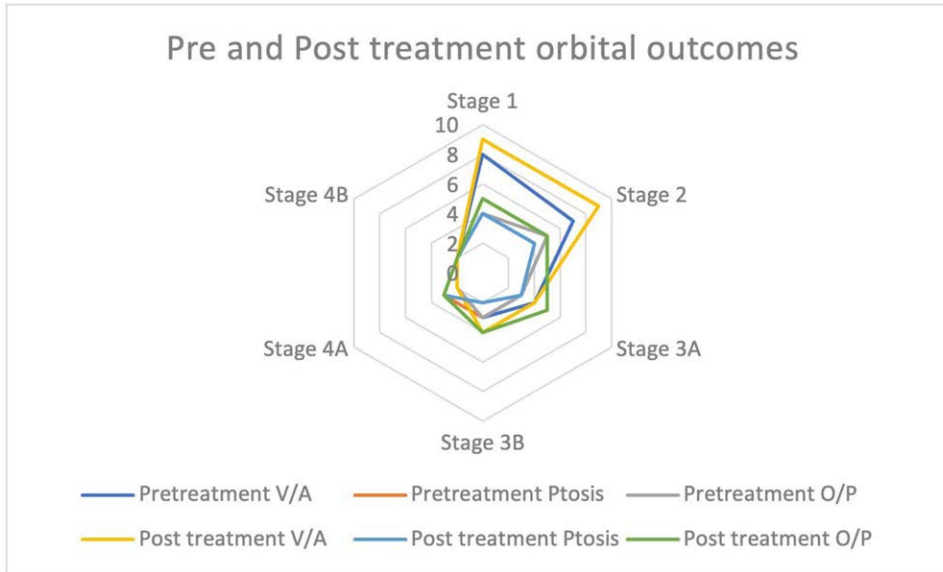

FIGURE 6. Spider graph showing the stage-based distribution of orbital outcome. O/P indicates ophththalmoplegia; V/A, visual acuity.

TABLE 2. Exact Logistic Regression to Evaluate the Risk Factors for Poor Orbital Outcome

Variable	Unadjusted OR (95% CI)	*P*
Duration of diabetes	1.91 (1.01–2.12)	0.023
Duration of chief symptoms	1.38 (1.09–2.84)	<0.001
HbA1c	2.41 (1.23–4.21)	0.01
Presence of perineural spread	2.13 (1.33–3.98)	0.04

OR indicates odds ratio.

and children.[3] In our study, untreated or undertreated type 1 diabetes was the most common underlying cause, followed by acute leukemia. Notably, 1 patient with extensive involvement had normal immunity. Regression analysis revealed diabetes duration and HbA1c levels as significant predictors of poor orbital outcomes.

Most cases in our study were caused by Mucorales, except for one attributed to *Aspergillus*. Mucorales commonly enter through inhalation, often leading to rhino-orbito-cerebral involvement, which can escalate to disseminated disease if not treated promptly.[2] In our research, sinus involvement was prevalent (88%), followed by cutaneous cases.

Imaging techniques provide additional diagnostic insight, although they do not consistently align with surgical and pathologic findings.[11] Yadav et al in her study described various spectrum of radiologic features of COVID-19–associated mucormycosis. The typical imaging characteristics included the presence of the "black turbinate sign" alongside nonenhancing sinonasal mucosa (82%),

orbital engagement (76%) and restricted diffusion in the optic nerve (24%). Intracranial manifestations included perineural extension into the brain (42%), cerebritis (30%) and involvement of the internal carotid artery (16%).[12]

Orbital involvement in invasive fungal sinusitis causes significant morbidity via direct bone erosion and perineural spread.[1] The fungus's angioinvasive nature leads to localized necrosis and bone lysis, often affecting the lamina papyracea of the ethmoid bone.[7] Perineural spread, particularly through the maxillary division of the trigeminal nerve, including the infraorbital nerve, is also significant.[13] Studies suggest the mandibular division of the trigeminal nerve can serve as a pathway for temporal lobe abscess formation.[14] Orbital involvement not only affects vision but also poses a risk of intracranial complications.[15] Studies indicate a higher incidence of cavernous sinus involvement and intracranial complications in patients with orbital mycoses.[16] In our study, 2 patients were diagnosed with temporal lobe brain abscesses that radiologically originated from the orbit.

The standard treatment involves early surgical sinus debridement paired with systemic broad-spectrum antifungal therapy, typically liposomal AMB (5 mg/kg/d).[8,10] Evidence suggests potential benefits from adding dual-antifungal agents like posaconazole, particularly in advanced cases.[17,18] In our series, all patients received both AMB and posaconazole, with treatment duration based on disease severity and discontinued upon clinical resolution and immune recovery in successfully treated pediatric cases. In our investigation, surgery was undertaken in all patients, yielding a favorable response rate of 77%.

During the COVID-19 pandemic, mucormycosis cases, often involving the orbit and brain, have surged. TRAMB has shown efficacy in such cases.[19] In our series, all 9 patients received TRAMB, including those with negative PL (presumed local dissemination) before considering orbital exenteration. Shakrawal et al reported improvements in visual acuity and ophthalmoplegia with TRAMB.[20] However, in our study, comparing pre and post treatment, there were no significant changes in visual acuity, ptosis or ophthalmoplegia, suggesting disease stabilization or no worsening from baseline.

In this study, we also reported the first case of cutaneous mucormycosis successfully treated with intralesional AMB. Traditionally, intralesional AMB is used for cutaneous leishmaniasis.[21] In a randomized controlled trial by Goswami et al, comparing the efficacy of 2 concentrations of AMB (2.5 vs. 5 mg/mL), the difference in efficacy between the 2 concentrations was statistically insignificant.[22]

Fungal skull base osteomyelitis is another worrying presentation of fungal sinusitis. This complication typically requires an extended period to stabilize pathologically, necessitating prolonged antifungal therapy.[8] Current guidelines recommend a treatment duration of 6–8 weeks, though this remains under investigation.[23,24] In our experience with 4 patients displaying extensive skull base involvement and uncontrolled type 1 diabetes, we employed a dual-antifungal approach. During hospitalization, all patients received a combination of Amphotericin and posaconazole. Upon discharge, they continued oral posaconazole treatment for at least 6–8 weeks.

In summary, the increasing reports of mucormycosis underscore improved awareness among the at-risk groups. Early diagnosis and treatment are vital for better outcomes in children. Management strategies should prioritize surgical debridement, combined antifungal therapy and restoring underlying immune function. Effective management of risk factors such as neutropenia and hyperglycemia is essential in preventing this disease.

Limitations

The small sample size is one the limitation of the study.

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