Original Article

RARE OCCURRENCE OF PALATAL MUCORMYCOSIS IN AN INFANT WITH ORNITHINE TRANSCARBAMYLASE DEFECT: A CASE REPORT WITH SHORT REVIEW

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Abstract

Palatal mucormycosis in an infant is rare occurrence. Most commonly it is seen with hematological malignancy or solid tumors or immunodeficiency states like diabetes. Its association with urea cycle disorder is rarely reported. If left untreated mortality rate is very high. In our case KOH mount in view of unsual palatal growth was done which later confirmed with MRI brain to rule out any CNS involvement. All supportive measures were provided. But because of extreme hemodynamic instability with coexisting enterococcus sepsis the infant succumbed due to severe disseminated intravascular coagulation & septic shock. We should consider the possiblity of fungal infections in debilitating patients who are not improving on broad spectrum antibiotics & to consider the prophylactic use of iv amphotericin B whenever there is high index of clinician suspicion even if initial reports were normal.

Keywords: urea cycle disorder, mucormycosis, immunodeficiency.

Introduction

Mucormycosis is an emerging global disease with high morbidity and mortality. It is caused by saprophytic fungi belonging to Rhizopus and Mucor species and is mostly associated with immunocompromised conditions such as diabetes or neutropenia secondary to chemotherapy[1]. The etiopathology of this invasive fungal infection is attributed to the inhalation of fungal sporangiospores or the direct inoculation of organisms through the disrupted surface of skin or mucosa in vulnerable patients. The majority of these cases manifest as rhino-orbito-cerebral mucormycosis, but can also present as cutaneous, pulmonary, gastrointestinal, and disseminated diseases[2]. However, mucormycosis involving the hard palate or rhino-orbit in an infant is reported very rarely [3] Also, there are only a handful of reports in the literature about mucormycosis among children. This case report presents the clinical course of palatal mucormycosis with OTC defect in an infant with coexisting enterococcus sepsis.

Case Report

A 4 month old infant was shifted to pediatric intensive care unit (PICU) in view of persistant fever with GCTS. Fever is intermittent present since one month & associated with cold & cough. GCTS was sudden in onset, during awake state & lasted for 15 mins with no post ictal deficit. The infant was born by normal vaginal delivery at home with birth weight of 2.5 kg, cried immediately after birth with no signs of perinatal depression. Immunised at 2 months of age. Examination showed temp 100.1F heart rate 130/min RR 34/min along with nasal flaring and SpO2 97% on room air with central & peripheral pulses well felt. The child was on exclusive breast milk for 2 months. There was no organomegaly. Maintenance intravenous fluids were commenced, emperically started on iv antibiotics ceftriaxone, amikacin, antiviral acyclovir & anti epileptics leviteracetum and euglycemia was maintained. X-ray chest was normal. LP was done & CSF for viral panel report was normal. Eventually baby's blood pressure continued to drop & generalised edema had developed. Progressive abdominal distension with hepatomegaly was seen that lead us to the suspicion of metabolic disease mainly urea cycle disorder as ABG also s/o absence of metabolic acidosis. Serum ammonia level was around 205 µmol/L. Infant heart rate continued to drop & was intubated & put on mechanical ventilator with Fio2 80% pressures of 12/6 and rate 30/min with simultaneous ionotropic support. Antibiotics were upgraded to iv meropenam, iv vancomycin, iv collistin and iv lasix infusion, sedation & intravenous calcium gluconate was started and appropriate laboratory investigations were organized.

Table 1: Showing laboratory parameters assessed on day 1 of admission & day 5

Parameter	**Day 1 (admission)**	**Day 5**
Hb gm%	9.2	4.5
TLC	18500	10000
P/L/E/M	62/28/2/3	
Platelets	1.7 lakh	22,000
CRP	114	
Blood culture	Positive for enterococcus	
Serum albumin	2.1	
Total protein	3.5	
GGT		167.3
Serology	negative	
Covid igG	Negative	
Na/K/Cl/Ca	129/2.6/102/6.4	
Direct bilirubin	Normal	Increased
ABG	no metabolic acidosis	
PT/APTT/INR	21/33/1/1.74	

Routine urine microscopy was normal. Serum ammonia was 206, serum lactate 13. Stool for occult blood was positive. GA for AFB negative. Lipid profile showed triglycerides 98, HDL 9. Urine for reducing substances was positive. Clinical examination showed progressive & rapid discolouration of left eye & bridge of the nose. Fundus examination showed cherry red spot with right retinal artery occlusion. We observed whitish fluffy growth under palate during routine oral hygiene care. Hence, KOH mount was sent & it showed positive for mucormycosis. USG abdomen s/o hepatomegaly with mild ascites. Cranial ultrasonography was normal. MRI brain was normal. Urine for GCMS was negative. Blood for TMS was positive for ornithine transcarbamylase deficiency. The patient despite of strong broad spectrum antibiotics & antifungals succumbed. Studies conducted by Silene MS et al. Says immune alternations in a patient with hyperornithine hyperammonemia homocitrullinuria syndrome: A case report. Frontiers in immunology. 2022;(13): 1-10 [19] says functional & phenotypic immune alterations can render the patient immunocompromised and might be related to the high frequency of inter current infections in patients bearing urea cycle disorders.

Figure 1: Showing Palatal growth of mucormycosis

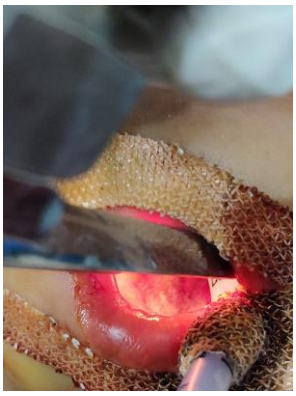
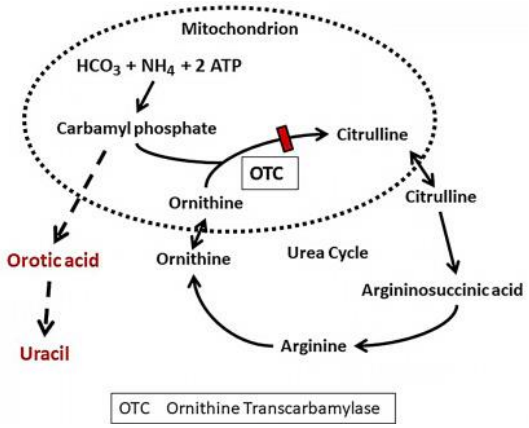


Figure 2: Showing involvment of orbit & bridge of the nose.

Discussion

Ornithine transcarbamylase deficiency affects the liver's ability to convert ammonia into urea. OTC combines carbamyl phosphate with ornithine to make citrulline which is subsequently processed to urea (see: figure 3 diagram).

Figure Showing OTC deficiency of Urea Cycle



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OTC deficiency is the most severe form of urea cycle disorders. Patients with complete OTC deficiency rapidly develop hyperammonemia in the newborn period. But in our case surprisingly serum ammonia levels were not raised. Studies showed patients who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia[4]. OTC is located on the X-chromosome & follows X linked recessive mendelian inheritance.

The term mucormycosis (zygomycosis) is used to refer to infections due to moulds belonging to the Order Mucorales. These organisms can cause rhinocerebral, pulmonary, gastrointestinal, cutaneous or disseminated infection in predisposed individuals, the different clinical forms often being associated with particular underlying disorders. Most cases of human infection are caused by members of the Mucoraceae. These include the genera Mucor and Rhizopus. The commonest cause of human infection is Rhizopus arrhizus. The species isolated from cases of human infection are thermotolerant & ubiquitous in nature. Most human infections follow inhalation of spores and the lungs and nasal sinuses are the commonest initial sites of infection. Less frequently, infection follows ingestion of contaminated food or traumatic inoculation of organisms into the skin and soft tissue.

The major risk factors predisposing individuals to mucormycosis include profound neutropenia, uncontrolled diabetes mellitus, metabolic acidosis, burns, use of corticosteroids and treatment with the iron chelating agents like desferrioxamine (deferoxamine).

Persons with immune deficient states often develop fulminant rhinocerebral mucormycosis or pulmonary or disseminated disease. Impairment of macrophage and neutrophil function has been identified as the principal factor responsible for the increased risk of developing mucormycosis in diabetic individuals. some studies says patients will recover if underlying ketoacidosis can be reversed. Nosocomial outbreaks of mucormycosis are not common but have sometimes been linked to construction or renovation work, contaminated ventilation systems, biomedical devices, or use of non-sterile surgical dressings and splints. Hospital aquired infections are sporadic in nature and difficult to determine whether these infections are acquired inside or outside the hospital setting.

PATHOGENESIS

The key factor in pathogenesis of Mucor are host defense mechanisms, fungal endothelial interaction and role of iron. In individuals with normal immune function, mononuclear and polymorphonuclear cells generate oxidative metabolites which kill mucorales. This is the reason for neutropenia and dysfunctional phagocytes being risk factors in causing mucormycosis[8].

Mucormycosis have a predilection for vascular invasion causing thrombosis, infarction and necrosis of the surrounding tissue. The clinical hallmark of mucormycosis is the rapid onset of necrosis and fever. In most cases, progress is rapid and death follows unless aggressive treatment is initiated.

TYPES

Rhinocerebral mucormycosis

It begins in the paranasal sinuses and then spreads to involve the orbit, face, palate and/or brain. The clinical presentation is similar to that of acute invasive Aspergillus sinusitis. It is the commonest clinical form of mucormycosis, and is often fatal within a week of onset if left untreated. Necrotic black lesions on the hard palate or nasal turbinate & drainage of black pus from eye are a characteristic diagnostic signs. Orbital infection may spread into the brain leading to frontal lobe necrosis and abscess formation.

Pulmonary mucormycosis

This form of mucormycosis is most commonly seen in neutropenic cancer patients undergoing remission induction treatment. It develops in the lungs as a result of aspiration of infectious material, inhalation, or from haematogenous or lymphatic spread during dissemination. The infection is fatal within 2-3 weeks. There are no characteristic symptoms or clinical signs to distinguish mucormycosis from aspergillosis. Pleural effusion is uncommon

Gastrointestinal mucormycosis

This is a rare condition that has usually been encountered in malnourished infants or children. All segments of the gastrointestinal tract can be involved. Complications include gastric or intestinal perforation, perirenal abscesses and renal infarction. Intestinal mucormycosis is a fulminant illness ending in death within several weeks due to bowel infarction, sepsis or haemorrhagic shock

Cutaneous mucormycosis

Although inhalation is the usual route of infection in patients with mucormycosis, traumatic inoculation of spores can lead to extensive necrotic cutaneous infections. This form of disease is most often seen inpatients with burns or other forms of local trauma. Necrotizing cutaneous mucormycosis has also been reported in patients who have had contaminated surgical dressings or splints applied to their skin[6]. Cutaneous mucormycosis is an aggressive disease & can lead to necrotizing fasciitis or to widespread disseminated infection. The lesions begin as an erythematous, indurated painful cellulitis, then evolve into ulcers covered with a black eschar.

Disseminated mucormycosis

This may follow any of the four forms of mucormycosis described so far, but is usually seen in neutropenic patients with a pulmonary infection. The commonest site of spread is the brain, Cerebral infection following haematogenous dissemination is distinct from the rhinocerebral form of mucormycosis. The lesions often lead to focal neurological signs. Isolated mucormycotic brain lesions have been reported in parenteral drug abusers. Rhinocerebral mucormycosis can be confused with cavernous sinus thrombosis, bacterial orbital cellulitis, and other forms of acute invasive fungal sinusitis, such as aspergillosis.

DIAGNOSIS:

Microscopy The microscopic demonstration of Mucorales in clinical material taken from necrotic lesions is more significant than their isolation in culture. These organisms are identified by their characteristic broad, non-septate hyphae with right-angled branching. Despite their predilection for angioinvasion and haematogenous dissemination, blood cultures in all forms of mucormycosis are always negative. Serological tests There are no routine serological tests for mucormycosis available at present[7]

MANAGEMENT

To treat it successfully, the underlying metabolic or immunological disorders that precipitated the infection must be corrected with high doses of iv amphotericin B. Other antifungal drugs have no role in the management. Iron chelation treatment should also be discontinued. Shortening the duration of neutropenia with colony stimulating factors might be beneficial, but it remains unclear whether this improves outcome. Amphotericin B remains the drug of choice for mucormycosis. In individuals with sino-orbital infection, aggressive surgical debridement of the necrotic lesions and surrounding infected tissue is the single most important component of treatment [8]. In individuals with cutaneous mucormycosis, aggressive surgical debridement of the necrotic lesions and surrounding infected tissue is an essential component of treatment [9]. The duration of antifungal treatment should be guided by clinical response rather than the total drug dose administered [10].

PREVENTION

Prevention measures to reduce the incidence of mucormycosis are of major importance in the management. In the non-immunocompromised individual, preventive measures should focus on the underlying risk factors. Immunocompromised patient should reduce or eliminate obvious sources of environmental exposure. The most effective, and expensive, method of protecting these individuals from nosocomial infection is to confine them to hospital rooms provided with high efficiency particulate air (HEPA) filtration.There is currently no effective antifungal prophylaxis available for prevention of mucormycosis[11].

PALATAL MUCORMYCOSIS

Contrary to the classical clinical manifestations of rhinoorbital mucormycosis that aid the diagnosis in most of those cases, the clinical diagnosis may not be so straightforward in cases of limited palatal mucormycosis [12]. The presence of mucosal ulceration or necrosis on the palate without any sinonasal manifestations rather mimic a malignancy or osteomyelitis. However, the onset of palatal growth is quite dramatic, and the progression is relatively rapid in invasive fungal disease. Despite the drastic clinical evolution of mucormycosis, the actual ulceration or necrosis of the hard palate is generally preceded by a slight discoloration of the mucosa or mucosal swelling. Such preceding clinical signs have also been reported in cases of rhino-orbital mucormycosis with palatal involvement. In other words, the regular monitoring of oral cavity mucosa by the clinicians or by oneself, or by parents in the case of infants & children can aid in the early diagnosis of palatal mucormycosis in vulnerable patients. As such, the oral mucosa is prone to many inflammatory conditions and opportunistic infection in immunodeficient children would require regular surveillance. The treating team should have a high index of suspicion, and any doubtful lesion or growth of the palatal mucosa is to be sent for microbiological examination at the earliest to rule out the possibility of mucormycosis[13]

The chances of recovery seem to reduce if active surgical debridement is not considered early in the course. Some of the reasons for not considering the surgical debridement in previous reports were poor general condition, low platelet count. Although the surgical intervention for palatal mucormycosis could pose a greater challenge in younger infants with respect to restoring oral feeding, it needs to be done in confirmed cases of invasive fungal disease to prevent further disease progression and corresponding poorer outcome. Besides, there are several reports of successful rehabilitation of larger palatal defects even among infants as young as 2 to 3 months.

Posaconazole and isavuconazole, both second-generation triazoles, are the only antifungals in their class with efficacy against mucormycosis and are often reserved for salvage therapy in patients who cannot tolerate amphotericin B.

Table 2 Showing: Previously published cases of mucormycosis in children & neonate

Author	demographics	comorbidity	Treatment	outcome
David etal,2018	25 wks/ fch	Premturity	AmphotericinB	recovered
Mahanjan etal,2019	2 yr/ mch	High ferritin	Amphotericin B	expired
Sps yadav,2010	10 yr/mch	nil	Amphotericin B	recovered
Rizzo et al, 2021	5 yr/ mch	Myeloblastic leukemia with apex syndrome	AmphotericinB & debridement	expired
Mohamed et al, 2021	12 yr/fch	Diabetes type1	AmphotericinB &surgical debridement	recovered

Conclusion

A case of palatal mucormycosis in which underlying urea cycle disorder has been described. This association of mucormycosis with metabolic disorder in an infant is often challenging to treat. In all urea cycle disorders cases we should consider the possibility of underlying immunodeficiency that might be a predisposing risk factor for mucormycosis. The main treatment is prophylactic use of anti fungals with supportive care in Pediatric intensive care. Novel finding in this case is borderline rise in serum ammonia level where as in urea cycle disorders its level usually rise above 1000 & ABG analysis showed no metabolic alkalosis. Probably the underlying acidosis that developed due to cellualr dehydration due to ongoing sepsis & disseminated coagulation made the infant prone to develop mucormycosis. By our case we also conclude that routine oral hygiene in ICU setting & immunodeficiency screening in urea cycle disorders can help us in early tracing of serious fungal infections for better outcome.

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Conflicts of interest

There are no conflicts of interest.

References

1] Prakash H, Chakrabarti A. Epidemiology of Mucormycosis in India. Microorganisms. 2021 Mar 4;9(3):523.

2] Hosseini SM, Borghei P. Rhinocerebral mucormycosis: pathways of spread. Eur Arch Otorhinolaryngol. 2005 Nov;262(11):932-8

3]AK AK, Gupta V. Rhino-orbital Cerebral Mucormycosis. [Updated 2022 Sep 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022

4] Gropman AL, Summar M, Leonard JV. Neurological implications of urea cycle disorders. J Inherit Metab Dis. 2007;30:865–79

5] Krivitzky L, Babikian T, Lee HS, Thomas NH, Burk-Paull KL, Batshaw ML. Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders. Pediatr Res. 2009;66:96–101.

6] Oh D,Notrica et al; Primary cutaneous mucormycosis in infants and neonates: case report and review of the literature. Journal of Pediatric Surgery.2002;(37):1607-1611.

7] Ribes, J.A., Vanover-Sams, C.L. & Bakel; D.J. (2000) Zygomycetes in human disease. Clinical Microbiology Reviews 13,236-301.

8] Yohai, R.A., Bullock, J.D., Aziz, A.A. et al. (1994) Survival factors in rhino-orbital-cerebral mucormycosis. Survey of Ophthalmology 49 (RR-lo), 1-125. 49,385-390. 39,3-22.

9] Fatterpekal; G., Mukherji, S., Arbealez, A. et al. (1999) Fungal diseases of the paranasal sinuses. Seminars in Ultrasound CTand MRI 20,391-401.

10] Adam, R.D., Hunter, G., DiTomasso, J. et al. (1994) Mucormycosis: emerging prominence of cutaneous infections. Clinical Infectious Diseases 19, 67-76

11] Centers for Disease Control and Prevention (1997) Guidelines for prevention of nosocomial pneumonia. Morbidity and Mortality Weekly Report 46 (RR-Ol), 1-79.

12] De Shazo, R.D., Chapin, K. & Swain, R.E. (1997) Fungal sinusitis. New England Journal of Medicine 337,254-259.

13] Losee, J.E., Selber, J., Vega, S. et al. (2000) Primary cutaneous mucormycosis: guide to surgical management. Annuls of Plastic Surgery 49, 385-390.

14] Prasad PA, Vaughan AM, Zaoutis TE. Trends in zygomycosis in children. Mycoses. 2012;55(4):352–6.

15] T.T. Riley, C.A. Muzny, E. Swiatlo, D.P. Legendre Breaking the mold: a review of mucormycosis and current pharmacological treatment options Ann Pharmacol., 50 (9) (2016), pp. 747-757

16] E. Roilides, T.E. Zaoutis, T.J. Walsh Invasive zygomycosis in neonates and children Clin Microbiol Infect, 15 (Suppl. 5) (2009), pp. 50-54

17] A.S. Ibrahim, T. Gebremariam, Y. Fu, J.E. Edwards, B. Spellberg Combination echinocandin-polyene treatment of murine mucormycosis Antimicrob Agents Chemother, 52 (4) (2008), pp. 1556-155

18] P. Agrawal, U. Saikia, S. Ramanaathan, R. Samujh Neonatal small intestinal zygomycosis misdiagnosed as intussusception in a two day old child with a review of the literature Fetal Pediatr. Pathol., 32 (2013), pp. 418-421

19] Silene MS et al.Immune alternations in a patient with hyperornithine hyperammonemia homocitrullinuria syndrome: A case report. Frontiers in immunology. 2022;(13): 1-10