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Case Report

A pediatric case and literature review of mucormycosis: Diagnostic and treatment challenges in a resource poor setting

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Abstract

Mucormycosis is an emerging disease that primarily affects immunocompromised patients; however, it has also been reported in immunocompetent individuals. Studies in the pediatric population are limited and reported mostly in case studies or series. The aim of this case report is to present a pediatric mucormycosis originated from Sumatra Island, Indonesia. A 13-year-old boy was referred to a tertiary hospital with facial necrosis involving the nasal, oral, and left maxillary areas, as well as left periorbital edema. No known underlying conditions were documented. The diagnosis was confirmed by histopathological findings of broad, pauci-septate, ribbon-like hyphae branching at 90°. The patient was managed by a multidisciplinary team consisting of the ear, nose, and throat, infectious diseases, dermatology, surgery, microbiology, and pathology departments. Management of the patient included debridement of the necrotic lesion and antibiotics and anti-fungal (fluconazole). Due to unavailability, the patient was not treated with amphotericin B. The patient died after 30 days of admission. This case highlights the importance of maintaining a high suspicion of invasive mucormycosis, even in immunocompetent children, when symptoms and signs are present, especially in resource-limited settings.

Keywords: Mucormycosis, Mucorales, invasive fungal infection, immunocompetent, pediatric case

Introduction

Mucormycosis is an emerging fatal invasive fungal disease. It belongs to the subphylum Mycoromycotina and order Mucorales, with eleven genus and 27 species have been documented to cause the infection [1-3]. The most common pathogens are *Rhizopus*, *Mucor* and *Lichtheimia*, accounted for 75% of infection [1-3]. Its diagnosis remains challenging due to the rarity of the disease, thus limiting information on its epidemiology, diagnosis and treatment. It primarily affects immunocompromised patients; however, it has also been reported in immunocompetent individuals [4]. Data in children is further restricted, and most information was acquired from case reports and case series [5].

Inhalation of spores is the most common route of mucormycosis infection, but infection can also be acquired via other routes including cutaneous, gastrointestinal, and injuries [6]. The rhino-orbital-cerebral, cutaneous, pulmonary, and disseminated are the most common manifestations, but less prevalent features may also occur including gastrointestinal mucormycosis and miscellaneous infections [1]. The disease progresses rapidly, and delay in

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diagnosis and treatment are associated with high mortality. The awareness of the disease, availability of diagnostic and therapeutic options varies between regions and influence the patient prognosis. Therefore, suspicion of the disease should be made by clinical manifestation and risk factors, supported by diagnosis tools such as microscopy, histopathology and imaging for early identification [6]. Direct microscopy and histopathology are the cornerstone of mucormycosis diagnosis; however, the diagnosis remains challenging and misidentification to *Aspergillus* spp. is common [4,7]. The use of molecular-based methods using paraffine-embedded or fresh tissue samples, and blood or serum have offered promising detection of Mucorales, and should be recommended to complement the conventional diagnostic methods [4,8-10]. Early treatment increases survival rates. This includes surgical intervention with administration of empiric antifungal drugs. Of the antifungals, amphotericin B, liposomal amphotericin B, posaconazole and isavuconazole have shown significant in vitro activity against Mucorales. Nevertheless, clinical response rates remain suboptimal [11-13]. In regards to the limitation of mucormycosis data from Indonesia especially in children, here, we report a case of mucormycosis in an immunocompetent 13-year-old boy.

Case

A 13-year-old boy was referred to a tertiary hospital with a facial necrosis involving the nasal, oral and left maxillary, and a left periorbital edema. The patient was initially complained of a red, painful nodule on the tip of his nose eight months earlier that ruptured, caused nasal bleeding and discharged purulent and necrotic debris. The patient continued to discharge crusted nasal purulent over several months and subsequently developed a significant nasal and left periorbital edema by four months since the first symptom. One month prior to admission, the disease rapidly progressed and caused perforation in the nasal, oral and left maxilla (**Figure 1**). There was no history of facial trauma, dental treatment, recent surgery, or known sinusitis. The patient had normal nutritional status without any known underlying conditions.

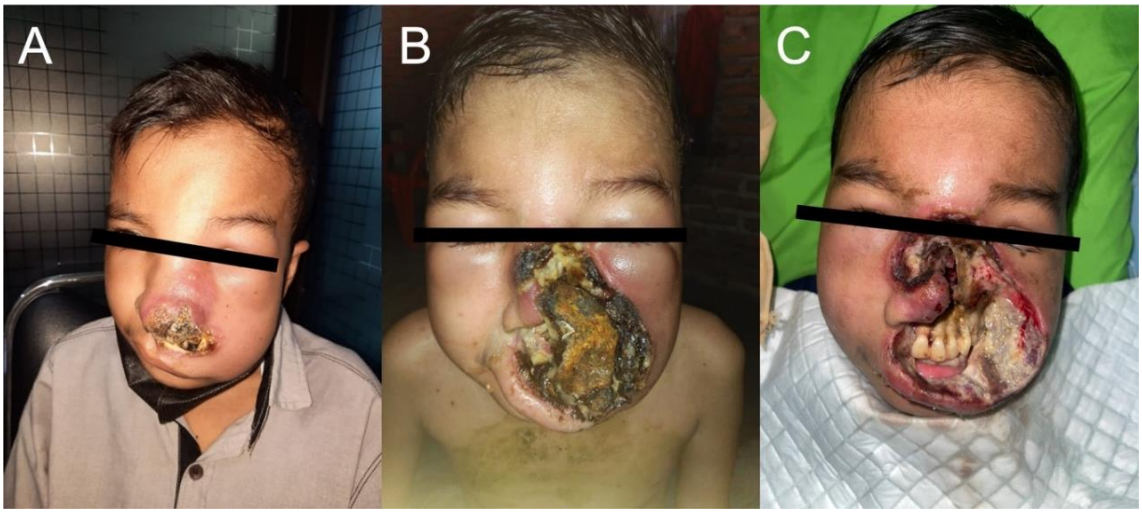

Figure 1. Progress of infection. (A) At 4 months since the first symptom. (B) At 8 months and on admission to the hospital. (C) Post debridement.

Laboratory tests yielded hemoglobin 12.5 g/dL, leukocytes 6.7×10^3 /µL (neutrophils 70.8%), thrombocyte 357×10^3 /µL, C-reactive protein 0.7 mg/L, procalcitonin 0.15 µg/L, random plasma glucose 85 mg/dL, urea 13 mg/dL, creatinine 0.45 mg/dL, ANA 0.7 IU/mL, and lactate dehydrogenase 771 U/L. The blood film did not show any signs of malignancy. Reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nasopharyngeal swab was negative. TB work up showed negative tuberculin test and negative Tuberculosis Nucleic Acid Amplification Test (NAAT) using sputum isolate. The HIV test was not performed due to family declined to consent. Histopathology findings from the necrotic tissue showed inflammatory smear with chronic granulomatous inflammatory process with a suspicion of fungal infection. Culture from the pus collected in the facial tissue revealed growth of *Proteus hauseri* and *Pseudomonas aeruginosa,* but no growth in the fungal culture. Head CT result showed soft tissue

defect on the left region of the nasal, maxillary, buccal to oral; bony erosion on the maxillary sinus wall with soft tissue swelling. Thorax CT images revealed multiple nodules with size up to 1.4 cm with a ground glass focus, suggesting a pulmonary infection.

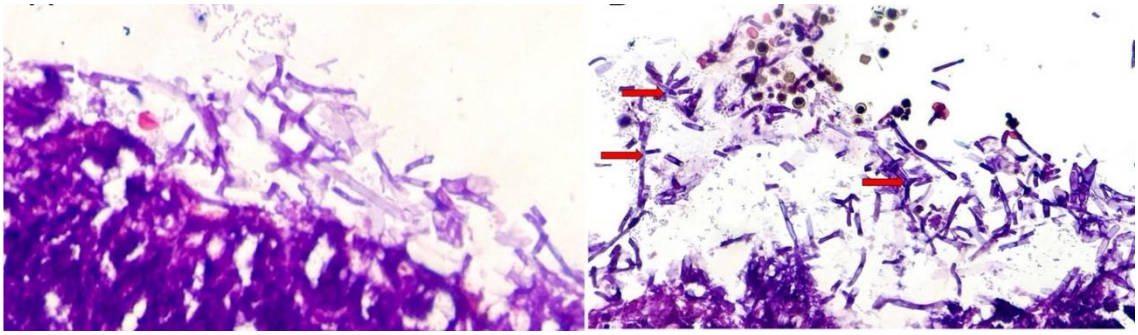

Figure 2. Histopathological findings showing broad, pauci-septate, ribbon-like hyphae branching at 90° with inflammatory cells (HE stain).

The patient was managed by a multidisciplinary team consisted of the pediatric, ear, nose, and throat, infectious diseases, dermatology, surgery, microbiology, and pathology teams. Management of patient include debridement of the necrotic lesion and empirical antibiotic (ampicillin/sulbactam and metronidazole) and anti-fungal (fluconazole) prior to culture findings to treat the presumably infection. Meropenem was given once the pathogens growth was shown in the culture and selected based on the antimicrobial sensitivity test result, where both *Proteus hauseri* and *Pseudomonas aeruginosa* were sensitive to meropenem. However, after one week of ongoing treatment with meropenem, the patient's condition did not improve, prompting the infectious disease team to request a follow-up histopathology and culture investigation focused on mold infection. The finding of broad, pauci-septate, ribbon-like hyphae with right-angle branching of 90° and chronic inflammatory cell infiltrate as seen in **Figure 2** lead to diagnosis of disseminated mucormycosis. Nevertheless, the fungal culture failed to show any growth. However, based on the histopathological result, a diagnosis of disseminated mucormycosis with bacterial skin and soft tissue infection were made.

The patient was scheduled to receive Amphotericin B. However, the drug was not available at the hospital and a request was promptly made. The patient continued to receive appropriate supportive therapy, antibiotic, and debridement. However the patient died after 30 days of admission.

Discussion

Epidemiology

Although the incidence of mucormycosis is rare, but the number has increased globally over the past decades which reflects the increased numbers of immunocompromised patients. The majority of cases reported are from Europe (34%), Asia (31%), North or South America (28%), Africa (3%), and Australia and New Zealand (3%) [1-3]. In Asia, India contributed to the highest prevalence with 0.14 case per 1000 population, higher than the infections reported from developed countries [1,14,15]. Very few case reports were found from Indonesia during our literature search, and only two articles obtained from the last forty years [16-22]. Recently, COVID-19 associated mucormycosis patients have also been increasingly notified [1]. The rise has been postulated due to many factors including dysregulated immune system due to COVID-19, prolonged duration of hospital stay and use of mechanical ventilation, use of immunosuppressants and corticosteroid during COVID-19 treatment, hyperglycemia and high ferritin observed among COVID-19 patients [1,23-25]. Therefore, this condition was mainly observed, but not limited to, patients with history of diabetes and with severe or critical conditions. Cases among individuals with no underlying conditions and post-COVID infection have also been reported [1,26].

The understanding of pathogens causing mucormycosis remains limited due to the difficulty to diagnose. The associations between the causative pathogens and the epidemiology, clinical characteristics and outcomes are yet elusive [15]. A recent systematic review found that Rhizopus (48%) was the most common pathogen, followed by Mucor (14%). Other noteworthy pathogens individually constituted less than 15% of the cases [5]. Nevertheless, despite the former study revealed Rhizopus being the predominant causative pathogen in every geographical region, there was a geographical variation for other Mucorales pathogens implying the importance of understanding the epidemiology of this disease. *Rhizopus* spp. was also frequently identified as a cause of rhino-orbital-cerebral infections when considering the site of infection.

In recent studies, several underlying/predisposing factors associated with increased risk of mucormycosis were identified including diabetes mellitus (40–91%), hematological malignancy (33–90%), solid organ transplantation (14%), hematopoietic stem cell transplantation (11%), corticosteroid use (3.7–90%), neutropenia (20–89%), trauma (20%), use of chemotherapy (18–87%), use of calcineurin inhibitors (16%), use of biological therapy (7%), use of renal replacement therapy (3%), and prior antifungal prophylaxis (11%) [3,6,14,27]. Additional risk factors were further documented in a large multicenter study in India, including chronic kidney disease (9%) and post-pulmonary tuberculosis (7%) [14]. Individuals without underlying conditions were reported in 18% and 10.6% in the global and Indian studies, respectively [3,14]. Mucormycosis may develop in these immunocompetent hosts via direct inoculation of spore into disrupted skin or mucosa, injury associated with natural disasters, and healthcare-associated mucormycosis [7]. A geographical variety in underlying factors was noted such as hematological malignancy that was more common in developed countries and uncontrolled diabetes mellitus in developing countries [3,4,14,28,29]. Diabetes mellitus was associated with the rhino-orbital-cerebral mucormycosis and rarely with pulmonary mucormycosis. Neutropenia and solid organ transplantation were associated with pulmonary mucormycosis. Solid organ transplantation was associated with gastrointestinal and disseminated mucormycosis, and trauma was associated with cutaneous infection [3,7,14,28,30].

In children, hematological malignancy (46%) was more common, followed by hematopoietic stem cell transplantation (16%) and solid organ transplantation (4.8%). Diabetes mellitus (5%) and trauma (5%) contributed to a low proportion of underlying conditions. A small proportion of 9.5% of children had no underlying medical conditions [5]. Risk factors for mucormycosis in children also vary by geographical area, where hematological malignancy was the most common condition in Europe, and no underlying condition was the most common condition in developing countries in the non-Europe region, different to findings in adults [3,5].

Clinical presentation

Patients with mucormycosis may develop various clinical forms that can be divided into six distinctive features including rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, disseminated and miscellaneous infection [11]. Rhino-orbital-cerebral is the most common form in adults [3,31], usually originated from the paranasal sinuses that eventually spread to the orbit, eye, and brain [7]. Initial symptoms may include symptoms of sinusitis, fever, purulent nasal discharge, nasal congestion and periorbital pain such as facial pain, facial numbness, headache and blurry vision [11,31,32]. A recent review documented the most common symptoms in rhino-orbital-cerebral being periorbital swelling, fever, decreased vision, ptosis, ophthalmoplegia and periorbital pain. A black eschar on the affected side is the hallmark of mucormycosis, and present of facial necrosis indicate an advanced disease [11,32]. The sign of infection reported in this case had similar description with the literature. The patient initially developed red and painful nodule which was eventually ruptured and produced purulent discharge and necrotic debris. However, we could not determine whether the initial infection was due to bacterial or fungal infection. The progression of the disease eventually led to periorbital swelling as seen in **Figure 1**.

Although cutaneous mucormycosis is more common in immunocompetent individuals, usually due to traumatic injury, it can also occur in immunocompromised hosts [7]. Cutaneous infection may appear with abscesses, skin swelling, necrosis, dry ulcers and eschar, and these features may remain localized or progress, affecting deeper tissue including muscles, bones or tendons [33]. The patient reported in this case had no remarkable risk factor and the patient was

considered healthy prior to the illness. However, we were not able to confirm HIV infection due to the patient's family refusal to take the test. The infection was also extended to deeper tissues, including bone tissue, based on Head CT scan, a characteristic often described in the literature, particularly when the diagnosis of mucormycosis is delayed. Mucormycosis was thought to be inoculated to the patient following a bacterial infection on the facial region which eventually allowed the penetration of mucormycosis.

In a study of 63 children with mucormycosis, the most common feature of mucormycosis was disseminated (38%), found in a much higher incidence compared to adults (13%) [3,5]. Disseminated infection was reported to involve three sites in 6% of cases including the gastrointestinal. Rhino-orbital-cerebral infection was divided according to the brain involvement; sinus-sinoorbital and rhinocerebral infections were reported in 15.9% and 7.9% of cases, respectively. Pulmonary and cutaneous infections were similarly common occurring in 19% of patients [5]. Clinical features of pulmonary mucormycosis have no clear distinction with pulmonary aspergillosis and bacterial pneumonia. However, several studies reported specific signs of mucormycosis that might include reverse halo sign, consolidation with ground glass. Nodules and cavitation are also commonly found in mucormycosis. Our present case report details a disseminated mucormycosis case with pulmonary involvement, wherein the identification of multiple nodules and ground glass foci on the patient's thoracic CT scan further supports this diagnosis.

Diagnostic challenges

Due to its high mortality, diagnostic tests to confirm mucormycosis should be recommended promptly when there are high suspicion, identification of host factors, and recognition of clinical manifestations. Required diagnostic tests can be determined according to the host's risk factors, initial symptoms or geographical areas. Confirmation of mucormycosis is made by biopsy of the affected tissue followed by direct microscopy, culture or molecular examinations [7]. Direct microscopy stained with fluorescent brighteners calcofluor white or blankophor allows presumptive diagnosis of mucormycosis when non-septate or pauci-septate, irregular, ribbon-like hyphae with a width of 6 to 25 µm appear. Using the hematoxylin and eosin, periodic acid-Schiff or Grocott-Gomori's methenamine silver staining, fungal hyphae can be described in detail. The histopathology of tissue is considered as the gold standard for mucorymycosis diagnosis; however, it requires pathologist with mycology expertise and species identification is not possible [4,7,34]. In histopathological examination, infected tissue is usually dominated by inflammation, neutrophilic or granulomatous [4].

Identification of Mucormycosis genus and species by culture are essential to provide better epidemiological understanding [7]. However, the use of susceptibility testing to guide treatment has limited evidence, despite a variety of susceptibility has been reported in some studies [7,12,34,35]. Mucorales is usually susceptible to amphotericin B, but less susceptible to posaconazole [34]. A recent Mucorales susceptibility study from the United States showed variability of sensitivity at the genus level, where most Mucorales were sensitive to amphotericin B. However, the *Cunninghamella* spp. was not as susceptible. Different susceptibility of different genus to azoles were also noted. The importance of having accurate identification of the infection to provide useful information regarding the appropriate treatment [12]. However, half of mucormycosis cases culture resulted in false negative, providing a suboptimal sensitivity [36]. Loss of viability of the hyphae may occur during homogenization of the tissue and reduce culture sensitivity, therefore it should be avoided. Culture at 30°C and 37°C may increase the yield of culture as some strains grow better at the lower temperature [7].

The introduction of molecular-based methods has improved the detection of Mucorales [34]. It is superior to culture, and both fresh and formalin-fixed paraffin-embedded tissue can be used for diagnosis [11,33,34,37]. The performance of detection using fresh tissue is nevertheless superior, as formalin destroy the DNA in the formalin-fixated tissue [8,11,33]. Thus, fresh tissue is preferable over formalin-fixed paraffin-embedded tissue. Various techniques have been utilized and showed clinical values including PCR with and without sequencing, semi-nested PCR, and qPCR with and without high-resolution melting, with the DNA targets of the internal transcribed spacer, 18S, 28S, cytochrome B, and CotH. However, all the molecular methods previously

mentioned are still in-house assays and lack of standardization, thus should not be used as a single assay [7,11,33]. Early diagnosis using blood and serum have yielded promising performance. It provides early detection prior to the detection using standard diagnosis thus may lead to early initiation of therapy and higher survival rates [4,6,7,11].

Biomarkers for mucormycosis are currently not commercially available. The available biomarkers for detection of fungal infections are available for other infections but have limitations to detect Mucorales. Galactomannan can be used for detection of *Aspergillus, Penicillium, Paracoccidioides, Histoplasma, Fonsecaea*, and *Cryptococcus*. 1,3-ß-D-glucan can detect *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Trichosporon* spp., *Saccharomyces cerevisiae*, *Acremonium* spp., *Coccidioide immitis*, *Histoplasma capsulatum*, *Sporothrix schenchkii* and *Pneumocystic jirovecii*. While *Candida* mannan can be used for *C. albicans*, *C. glabrata*, and *C. tropicalis*. Most Mucorales have low amounts of 1,3-ß-D-glucan, thus below the limit of detection. While negative galactomannan result may be interpreted as an invasive mucormycosis [6,11,33,38]. With the absence of appropriate biomarkers for rapid detection of mucormycosis, the development of mass spectrometry for the detection of d Liposoihexasaccharide in serum [6,7,39] and the use of ELISA for the detection of *Rhizopus*-specific antigen have shown promising results [6,40].

Treatment

Identification of mucormycosis, reversal of risk factors, surgical intervention and administration of antifungal are key management to improve survival rates [4,11]. A multidisciplinary team involving microbiology, pathology, radiology, infectious diseases, surgery, pediatrics, hematology, intensive care, dermatology and pharmacology are important to prevent delay in diagnosis and treatment. Surgical intervention of mucormycosis can be divided into debridement of skin and soft tissue, debridement of rhino-orbito-cerebral region, orbital exenteration, lung resection, debridement of bone and visceral resection [7]. However, the mortality rates of surgical intervention or antifungal therapy alone were high [1, 2], therefore combined modality approach is the preferred therapy to improve outcomes.

Amphotericin B deoxycholate has been the drug of choice for decades due to its effectiveness against mucormycosis [7,11,12]. However, its use has been limited due to the substantial toxicity which can be worsened by the duration and doses needed for mucormycosis [7]. Further, the safety and tolerability are acceptable in neonates. However, the use is discouraged due to the inferior efficacy compared to the liposomal amphotericin B. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) recommended the use of liposomal amphotericin B over the amphotericin B deoxycholate [33]. The liposomal amphotericin B is dose-dependent, and the current recommended daily doses ranged from 1 mg/kg per day to 10 mg/kg/day, with higher dose associated with better response [7,41,42]. However, increased dose caused significant nephrotoxicity, although it is reversible [41,43]. Amphotericin B lipid complex has shown successful results in a study where there is no CNS involvement. However, this formulation still has limited evidence [33].

The antifungal triazoles including posaconazole and isavuconazole are recommended as salvage therapy or as a first-line or combination therapy for mucormycosis [33]. The recommended oral dose of posaconazole is 200 mg every 6 hours and survival rates reached 80% among refractory patients and patients intolerant to previous therapy [33,44]. Various studies also reported satisfying response rates from 72% to 80% [4,33,45,46]. Isavuconazole at dose of 200 mg every eight hours for six doses, followed by daily doses showed comparable outcomes to amphotericin B, therefore can be considered as first-line treatment [4,11,13]. However, further consideration should be made as the study size was small. Two combinations of liposomal amphotericin B and caspofungin, and liposomal amphotericin B and posaconazole have been studied with only moderate results [33].

Recommendations of treatment for children are similar to adults. These are due to the absence of data on many variables of mucormycosis treatment including pediatric pharmacokinetic data and dosing recommendations, pediatric safety and efficacy data, and the regulatory approval for use in pediatric. Recommendations in children are extracted from

observational findings in adult trials and case series. When antifungal drugs are available, the recommended treatment pathway is surgical debridement with clean margins plus immediate treatment initiation. The choice for first-line treatment in neonates and children include liposomal amphotericin B (neonatal dose 5–<10 mg/kg/day and pediatric dose ≥5 mg/kg/day from day 1) and amphotericin B lipid complex (neonatal and pediatric doses 5 mg/kg/day from day 1), with the former being favored for infections involving the CNS due to its pharmacokinetic and pharmacodynamic. Response to treatment should be evaluated weekly, before patient continue to salvage treatment. There are several recommendations for salvage therapy with isavuconazole iv or po and posaconazole iv or delayed released being moderately recommended. Amphotericin B lipid based plus posaconazole or caspofungin, and posaconazole alone with therapeutic drug monitoring have marginal recommendation [7,33]. However, all the mentioned antifungals are not available in our setting. Amphotericin B was planned; however, due to limited resources, the antifungals were not immediately available, resulting in delayed treatment and poorer outcome.

Mortality rates

Overall mortality in mucormycosis is high up to 80%, and association with underlying conditions and certain type of infection have been reported [3,7]. Disseminated mucormycosis reported to have the highest mortality at 68%, followed by gastrointestinal (54%), pulmonary (51%), rhino-orbital-mucormycosis (42%), and cutaneous mucormycosis (31%) [3]. *Cunninghamella* (71%) has been associated with an increased mortality compared to other Mucorales in adults. However, the proportion in children was 33.3%, lower than *Lichtheimia* spp. (50%) and *Rhizopus* spp. (45.8%) [3,5]. The independent predictors of death in children were hematopoietic stem cell transplantation (aOR 13.6, 95% CI 1.8–98.9, p=0.01) and disseminated disease (aOR 4.2, 95% CI 0.9–18.5, p=0.05) [5]. While combined treatment of surgery and antifungal therapy reduced risk of deaths (aOR 0.37, 95% CI 0.1–0.9, p=0.035) [5].

Early diagnosis and prompt management, including surgical intervention and antifungal therapy improve survival. However, the lack of awareness of the disease remains substantial due to the rarity of the disease. The incapability to suspect mucormycosis leads to delay in diagnosis and treatment and eventually cause poorer outcome, as seen in this case. In resource-poor settings, diagnostic tools and treatment are often restricted especially for fungal infection. In our setting, the patient was late presented due to sociocultural factor and upon diagnosis, the patient did not receive any recommended treatment due to the unavailability of antifungal therapy.

Conclusion

This patient was admitted to the tertiary hospital in a very advanced stage due to financial, social and cultural constraints The diagnosis was delayed due to non-specific early sign that could mimic other bacterial invasive infection and the lack of the usual risk factors (e.g., immunocompromised. Other challenging factors include lack of expertise and low sensitivity of conventional diagnostic tools. Late diagnosis is also further impacted by limited options of antifungals, which then increased the mortality rates, as seen in this case [3]. This study highlights the importance of considering invasive mucormycosis when symptoms and signs encompassing the nose, orbital and cerebral present, even in patient with no underlying cause or are immunocompetent. Early management and multidisciplinary teams are crucial to improve the outcome of invasive mucormycosis.

Ethics approval

Informed consent has been acquired from the guardian.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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