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Case report and literature review

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Optimal care for rhino-orbital mucormycosis in child with myeloblastic leukemia. Case report and Literature review

Mucormycosis is an opportunistic and aggressive fungal infection that mainly affects immunocompromised patients who generally suffer from diabetes mellitus, immune impairment, hematological disease. It is a life-threatening infection and the management is not standardized.
The literature proposes aggressive and early surgical approach, even at the expense of mutilation. We report a case of rhino-orbital mucormycosis in a child with myeloblastic leukemia and the successful treatment using the instill negative pressure wound therapy combined with reconstructive surgery in order to reduce mortality and to avoid disfigurement.

KEY WORDS: Amphotericin B, Apex syndrome, Forehead flap, Instill NPWT, Myeloaplasia Mucormycosis,

Introduction

Mucormycosis is an infection due to Mucorales belonging to the class Phycomycetes, which results in necrosis and destruction of the involved structures and eventually leads to the decreasing of health-related quality of life [1].
This disease is usually observed in immunocompromised patients and its pathophysiology is multifactorial, however the predominant factor is neutropenia and a decrease in macrophages [2].
The third most common angioinvasive fungal infection is represented by Mucormycosis. This fungus can be found in soil, fruits, vegetable, manure and as bread mold.
As regards head and neck region, the infection initiates in the nose and paranasal sinuses (PNSs) because of the inhalation of fungal spores, subsequently it can disseminate to orbital and intracranial structures either by direct invasion or through blood vessels. The fungus invades arteries resulting in thrombosis that leads to necrosis of hard and soft tissues [3].
The Mucormycosis management is not standardized. A 2016 review of the Injury [4] proposes an aggressive and early surgical approach, even at the expense of mutilation, in the setting of cutaneous mucormycosis secondary to penetrating trauma.
The aim of this clinical report is to describe the management of a rhino-orbital mucormycosis in a myeloaplastic boy and to suggest a successful procedure based on two stages in order to reduce mortality and to avoid disfigurement.

Case Report

A 5 years Ukrainian boy was transferred to our Pediatric Hospital with a first diagnosis of jaundice.
After several episodes of recurrent fever and icterus, blood exams confirmed a liver impairment with hepatomegaly, requiring further diagnosis and treatment.
Previously the child was in good health, 21 Kg for 112 cm, BMI 16,7. On admission, ecographic exams showed hepatic and splenic edema, no involvement of hepatobiliar duct, pancreas or other organs. Hepatotropic viruses screening (HAV, HBV, HCV, HDV, CMV and B19 IgM and PCR) were all negative. Blood exams showed the inversion of leucocytes, ALT, AST and gamma-GT,

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LDH didn't show other alterations. After 10 days of stability and improvement he was discharged with a diagnosis of hepatitis ndd CMV-like. After a month and a half, he was re-hospitalised for fever and edema of right eye and nose area. Blood exams taken on re-admission showed a serious leukopenia, so a bone marrow biopsy was immediately performed revealing a severe aplasia. His conditions were getting worse, a septic state required intensive care and a tracheostomy was performed in order to support respiratory function.

Blood culture, urinalysis and nose swabs were taken, IgG and IgM for viruses were tested. HSV, VZV, B19, CMV, EBV, Adenovirus all IgM were negative. Fast response detected no presence of bacteria nor IgM alteration as well as PCR amplification detect no infection. Eye, nasal and throat swabs all negative. Autoimmune antibodies were tested (ANA, AMA, ASMA, anti LKM, ARA, APCA, anti-ribosomal Ab, ANCA, anti LC1) and they were all negative.

Furthermore, a blue spot appeared between the internal canthus and the nostril leading to the development of necrotic tissues. The lesion on the right cheek opened, showing a unique cavity (4 cm x 2,5 cm), communicating with the homolateral choana, and a septum perforation (Fig. 1). Consequently the biopsy of the sinus tissues diagnosed mucormycosis.

We performed a therapeutic algorithm based on two stages.

At the first stage, systemic antimycotic combined with instill negative pressure wound therapy (NPWT)[5] using AmBisomeâ was left in place (Fig. 2). The whole nose was covered by the PU membrane of the dressing, using hydrocolloid stripes. NPWT was set at 25 mmHg, with an instilling of 5 ml of AmBisomeâ, once per hour with 10 minutes of persistence. The AmBisomeâ solution used for instillation was the same used for endovenous infusion (5mg/Kg/die) to obtain a synergic action. Dressing changes were performed daily since the child's high fever, profuse lacrimation and salivation tend to dissolve the hydrocolloid unsealing the dressing. Aplasia was treated with EWOG-SAA 2010 protocol (Atgam, Methilprednisone, G-CSF, Ciclosporin), transfusions and neutrophil transplant from his mother. As first step, this hematological therapy was performed simultaneously with the NPWT Instill therapy.

At the second stage, only after histological diagnosis of fungus eradication, surgical debridement and reconstructive surgery were performed. Nasal reconstruction executed according to Menick [6,7]: 1) full-thickness forehead flap elevation; 2) excess soft tissue excision and cartilage graft placement; 3) pedicle division (Fig. 3).

A 30 months follow-up shows the surgery was successful and the patient is healthy (Fig. 4).

Discussion

Mucormycosis is caused by fungi of the order *Mucorales*. It is an opportunistic fungal infection which usually arises in immunocompromised individuals but can also infect healthy ones. Uncontrolled diabetes, malignancies such as lymphomas and leukemias, renal failure, long-term corticosteroid and immunosuppressive therapy, organ transplant, burns, cirrhosis, protein-energy malnu-

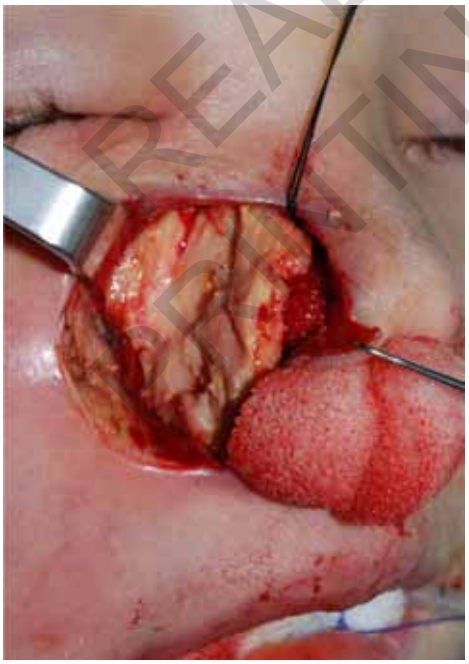

Fig. 1: Rhino-orbital Mucormycosis with severe tissue necrosis (nasal hemostatic swabs placed in the right nostril).

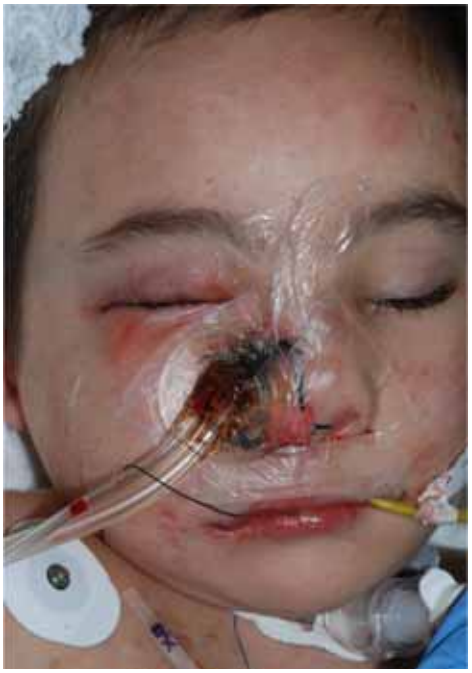

Fig. 2: NPWT Instill treatment.

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trition and AIDS are the predisposing factors for mucormycosis [8].

Although it affects not only the immunocompromised host, but also the immunocompetent one. Two meta-analysis [9,10] describe immunocompetent patients with cutaneous mucormycosis after trauma, surgery, burns, use of contaminated dressings and injection. In China and India, several cases of isolated renal mucormycosis were observed in apparently healthy individuals [11].

The pathogens causing mucormycosis are Rhizopus arrhizus, which is the most common one, ichtheimia, Apophysomyces, Rhizomucor, Mucor and Cunninghamella species [11]. The pathogen's port of entry reflects the site of infection and the most frequent is the sinus disease (39%), followed by pulmonary (24%), cutaneous (19%), cerebral (9%), other sites (9%), gastrointestinal (7%) and mortality ranges from 17% to 66% depending on predisposing risk factors. Otherwise the majority of immunocompetent patients are infected by *Apophysomyces* species [12].

According to Jeong et al. study, the most common underlying condition in mucormycosis is %) [9].

As regards the prevalence of mucormycosis, it is round about 10.000 cases globally excluding India. Including Indian data, the prevalence of the disease rises to 910.000 cases in the world. Therefore, incidences per million populations are: diabetes mellitus (40%) and in particular for the rhino-orbital-cerebral type. Disseminated infection is associated with haematological malignancy; although gastrointestinal, pulmonary or disseminated mucormycosis is associated with solid organ transplantation. Rhizopus species causes mainly rhino-orbital-cerebral mucormycosis and the mortality rate is 46%. Mortality rate in Cunninghamella infections (which cause mostly pulmonary or disseminated disease) is considerably higher than those caused by other Mucorales (71% versus 44Europe (from 0.2 cases in Denmark to 95 cases in Portugal), USA (3.0 cases) and India (140 cases and the average mortality is of the 38.2%) [11].

The most frequent localization was the rhino-orbital-cerebral (ROCM) coupled with an Orbital Apex Syndrome, OAS, sometimes evolving down in palatal perforation or in an upper cerebral dissemination. ROCM with OAS at the beginning is reported to have no more than a 24% of survival rate [13,14]. The invasive mucormycosis causes necrotic and gangrenous lesions due to the peculiar angiolymphatic invasion (100%) perineuronal invasion(90%) while the lungs disease presents 100% of angioinvasion as well, followed by hemorrhagic (90%), coagulative necrosis (85%), intra-alveolar hemorrhages (85%). The angioinvasion is more represented in neutropenic patients compared to not neutropenic ones [15].

OAS form represents often the beginning of a rhino-orbital cerebral mucormycosis, it's more frequent in immunocompromised male patients, it's rapidly fatal due to the vague sign and symptoms which lead to a late diagnosis: swelling lid, nasal stuffiness and vision loss. For those who survive, ocular, nasal sinuses and soft tissues involvement has a destroying effect on facial shapes which have to be restored after the resolution of the infection. Forehead flap is the most appropriated technique used to restore volumes of nose [16].

Late diagnosis in immunocompromised patients may lead to a fatal outcome, mostly until three months from diag-

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Fig. 3: Reconstruction with forehead flap.

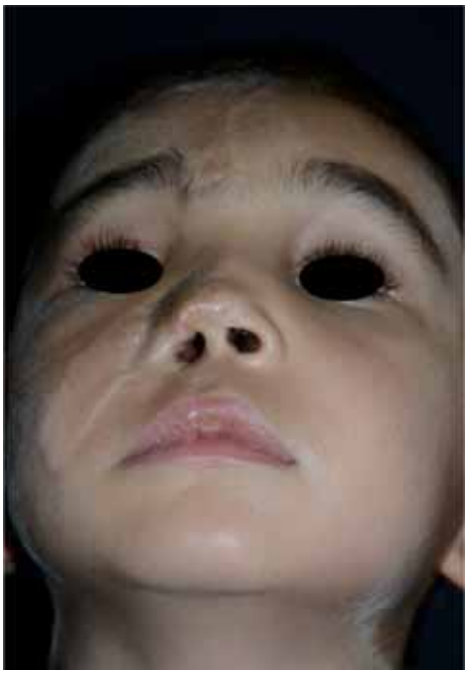

Fig. 4: One year follow-up.

nosis. Eye or facial pain and facial numbness can be the initial symptoms, then infection might diffuse to the orbit, causing chemosis, ptosis and proptosis. The dissemination to the cavernous sinus involves cranial nerve III, IV, V, VI palsies and permanent blindness. Consequently, histopathologic diagnosis of the fungus is crucial and the extension of involvement might be valuated with MRI or CT [17,18].

Three principles are fundamental in mucormycosis treatment. The first one is early diagnosis, the second one is that necrotic or infected tissues might be debrided or resected. The third one is the use of antimycotic medication. Moreover, Tedder et al. described that the mortality rate was 11% in patients treated with surgery, though 60 % in patients without surgical treatment [19].

The therapy includes treating the underlying pathology (ketoacidosis in diabetics, neutropenia with growth factors, avoiding iron overload or acidosis, corticosteroids supplies, control the viral load) treating the mycosis with antifungines as liposomial Amphotericin (B-AMP), 5mg/Kg/die up to 10mg/Kg/die for rescue treatment, administred for weeks (4-6 weeks) or others as suggested in guidelines [20]. The wound care approach consists of surgical debridement of non-viable or necrotic tissues which very often need to be repeated several times, particularly suggested is the decompression of the ocular nerve in the OAS via anterior nasal endoscopy (ethmoidal) [21] and contemporarily biopsy and excision [22].

Zahoor et al. review concluded that aggressive and early surgical approach, even at the expense of mutilation, is necessary in the setting of cutaneous mucormycosis secondary to penetrating trauma [4]. Even Akers et al. proposed aggressive surgical debridement as primary therapy, but they performed antifungal medications and negative pressure wound therapy as an adjunctive role in the care of wound infection.

Finally, Lewandowski et al. proposed the addition of dilute Dakin's solution with negative pressure wound therapy to treat angioinvasive fungal infection in the combat wounded [23].

We suggest an optimal care based on Negative Pressure Wound Therapy (NPWT) and local instillation of Amphotericin B using the same preparation of the endovenous dosage, this synergic action eradicates the mycotic infection and, only after negative histology, we can perform surgical debridement. Then we succeed with a minimally extensive surgery and reconstruction simultaneously in order to avoid facial disfiguration.

Conclusion

The survival of the patients with mucormycosis and myeloblastic leukemia is a rare result [24]. The drainage and reclaim of affected area through the wound instillation coupled to the systemic Amphotericin B therapy allowed to contain the diffusion. No vision loss nor other cerebral impairment occurred. The onco-hematological therapy supported immune system until its reactivation. Multidisciplinary approach between Onco-Hematology and Plastic and Reconstructive Surgery is essential.

We suggest this approach for cutaneous mucormycosis, in children and adults, not only secondary to myeloaplasia but also to trauma. This therapeutic algorithm is an optimal care not only because demolition and reconstruction phases can be performed in sequence during the same surgical sitting, but also because it can restore the disfiguring facial sequelae.

Riassunto

La mucormicosi è un'infezione fungina opportunistica e aggressiva che colpisce principalmente i pazienti immunocompromessi che generalmente soffrono di diabete mellito, compromissione immunitaria, malattie ematologiche. È un'infezione pericolosa per la vita e la gestione non è standardizzata.

La letteratura propone un approccio chirurgico aggressivo e precoce, anche a scapito della mutilazione.

Segnaliamo un caso di mucormicosi rino-orbitale in un bambino con leucemia mieloblastica e il trattamento di successo utilizzando il trattamento delle ferite a pressione negativa instillata combinata con la chirurgia ricostruttiva al fine di ridurre la mortalità ed evitare deturpazioni.

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