INTRODUCTION

Mucormycosis is a fungal infection with a high mortality rate (>50%) caused by the Mucorales often occurring in immunosuppressed patients, as with diabetes mellitus, hematopoietic stem cell transplants, or associated hematological malignancy. Mucormycosis usually develops as an acute infection and presents itself in rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated clinical types. Oral mucormycosis is rarely seen in clinical practice and reported cases are scarce [1-3]. Herein, we present the case of a male patient with L2 acute lymphoblastic leukemia (ALL) who suffered gingival mucormycosis due to Rhizopus arrhizus. Empirical treatment with amphotericin B deoxycholate (ABD) was prescribed with clinical and mycological healing on day 17. Unfortunately, the patient had an unfavorable outcome because of the ALL and died 49 days after the admission due to multiple organ failure.

CASE REPORT

A 31-year-old male, previously diagnosed with L2 acute lymphoblastic leukemia (ALL) since 2016, was admitted to our hospital in April 2019 because of the fourth disease relapse. On admission, the patient had pancytopenia, severe leukopenia (2,100 cells/μL), thrombocytopenia (99,000 cells/μL), and anemia (8.8 g/dL). Treatment was started with a Hyper-CVAD regimen (hyperfractionated cyclophosphamide doses, vincristine, doxorubicin, and dexamethasone) but without clinical improvement. The leukopenia persisted through day 2 and a progressive decrease in platelet levels was observed (3,000 cells/μL). During the hospital stay, several necrotic ulcers developed at the first and second premolars of the right maxilla in the gingival region, and an edematous plaque over the hard palate (Fig. 1). A direct microscopic examination revealed broad, dichotomic, coenocytic, and hyaline hyphae. Sabouraud dextrose agar media yielded hairy, cottony, grayish-white colonies with broad non-septate hyphae, sporangiophores, rhizoids, sporangia, and sporangiopores visualized. The fungus was mycologically identified as Rhizopus arrhizus (formerly R. oryzae) and confirmed by molecular biology according to the following regions: ITS:
99/99.2 (NCBI), 95.67/100 (ISHAM-ITS), 96.64/100 (MycoBank); and D1/D2: 99/99.1 (NCBI), 95.26/99.53 (MycoBank). Hence, we reached a diagnosis of gingival (oral) mucormycosis caused by *Rhizopus arrhizus*. A biopsy was not taken due to severe thrombocytopenia (Fig. 2). A CT scan of the head failed to show evidence of bone involvement. Surgical debridement was not performed because of the patient’s condition. Amphotericin B deoxycholate (ABD) was started at 1 mg/kg/day with clinical and mycological healing on day 17. Unfortunately, the patient’s condition worsened with disseminated intravascular coagulation and the patient died on day 49.

**DISCUSSION**

Mucormycosis is an invasive fungal infection characterized by the rapid growth of filamentous fungi, leading to thrombosis and tissue necrosis [1,4]. *Rhizopus arrhizus* is the most common etiologic agent, followed by *Mucor circinelloides* and *Lichtheimia corymbifera*, which together account for around 70% of all infections [1,4-7]. In 2005, Roden et al. conducted a review of 929 cases [4]. The mean age was 38.8 years with a prevalence of males (65%). DM was the most common underlying condition. One hundred fifty-four patients presented with a malignant neoplasm, among which 147 (95%) were hematological.

The *Mucorales* have the ability to cross physical barriers, finding innate immune cells: macrophages, neutrophils, and dendritic cells. Angioinvasion is a distinctive process in mucormycosis. Endothelium breakage causes thrombosis and tissue necrosis and allows for hematogenous dissemination. The *R. arrhizus* adhere directly to the endothelial cells and impels lesions through its internalization. The entrance to the endothelial cells is arbitrated by the endothelial cell surface receptor GRP78, which significantly increases acidosis and hyperglycemic conditions [5]. Patients with neutropenia have more extensive angioinvasion [8,9]. After crossing the endothelial tissue, *Mucorales* find platelets, recently identified as key effectors of the innate immune system, as they bear antimicrobial properties mediated by the release of platelet antimicrobial peptides such as platelet factor 4 (PF-4), as well as chemotactic properties mediated by the release of cytokines such as IL-1b. *In vitro* studies have shown that the platelets adhere to both spores and hyphae and significantly inhibit fungal germination and cause direct damage to hyphae [2,5].

Oral mucormycosis usually develops after the transpalatal extension of rhinocerebral infection. Cases located in the periodontal tissue (gingival and alveolar bone) are rare [8-10]. In general, we have had experience of palatal ulcer formation in up to a third of our patients, but gingival presetting is extraordinary and must be kept in mind in the oral forms of mucormycosis [10]. Table 1 shows a comparison of the characteristics of the reported cases, including this case.

In our search through the English-language literature, we found merely ten cases of periodontal mucormycosis: nine in patients with hematological malignancies and one in a diabetic patient. All patients underwent extension studies and the diagnosis of aspergillosis was ruled out. All cases, including this case, had active hematological malignancies. All patients had neutropenia (<500 cells/μL) and four patients with hematological malignancy had associated thrombocytopenia. Clinical manifestations were similar: the patients complained of gingival pain while
seven patients had a fever. Physical examinations revealed bluish, grayish, or whitish edematous plaques as well as necrotic changes. All patients received amphotericin B as a first-line treatment and three patients underwent surgical debridement. Seven of the eleven cases successfully completed the antifungal treatment and two patients died of pneumonia whereas our patient died from multiple organ failure. In one patient, the evolution was unknown [11]. The diabetic patient received treatment with amphotericin B and surgical debridement with favorable results [12]. Unlike rhinocerebral mucormycosis, the gingival type was observed without central nervous system involvement and with slower progression [1,8,13].

Mucormycosis is diagnosed by direct examination with Calcofluor, Fungifluor, or Blankofluor. Calcofluor analysis is not performed in daily practice due to the need for fluorescence microscopy [9]. Laboratory diagnosis is necessary, although bearing low sensitivity. The Mucorales grow rapidly to 37°C (98.6°F) in selective and nonselective media. The diameter of coenocytic (non-septate) or pauci-septate hyphae ranges from 6 to 25 μm. The branch angle is variable and includes bifurcations with an angle of ≥90° [8]. Histopathological examination makes it possible to distinguish between Aspergillus hyphae and Mucorales hyphae, defining the treatment. Mucormycosis is characterized by necrosis and vascular and perineural invasion [1]. No standardized tests are available for detecting Mucorales-specific antigens. The results of negative serum galactomannan and bronchoalveolar lavage tests support the diagnosis of mucormycosis [14]. (1,3)-β-D-glucan is a common part of the cell wall of a wide variety of fungi, but not the Mucorales [1].

Amphotericin B deoxycholate is one of the drugs approved for treating mucormycosis. However, given the associated toxicities, it is often replaced by lipid formulas. Early treatment with amphotericin B and the surgical debridement of the infected areas is the treatment of choice [1,14]. Posaconazole has shown significant clinical efficacy against the Mucorales [8,15]. Isavuconazole is a novel azole showing in vitro and in vivo activity against the Mucorales when compared with posaconazole [1,15]. On the other hand, fluconazole, voriconazole, echinocandins, and fluocytosine show no in vitro activity against the Mucorales [1].

In hematologic patients, it is suggested to continue treatment until complete remission is achieved proved by imaging studies and reversing risk factors [1]. Alveolar osteonecrosis presents difficulty in surgical treatment since extensive debridement of the maxillary bones may trigger functional complications. In addition, the risks and benefits of surgical treatment should be carefully weighed in patients with neutropenia and thrombocytopenia [8]. During severe immunosuppression, primary prophylaxis with posaconazole has been recommended specifically for the prevention of mucormycosis, but a lack of controlled studies persists [1].

**CONCLUSION**

This was the case of a patient with L2 ALL displaying rare clinical primary gingival mucormycosis. The patient had an unfavorable outcome because, despite treatment, the ALL activity persisted, together with severe neutropenia and thrombocytopenia. The patient died due to multiple organ failure. In hematologic patients, prognosis usually depends on the response to treatment of hematologic neoplasia.

**Consent**

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

**REFERENCES**

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