



Early Multidisciplinary Management of the First Case of Post-COVID-19 Mucormycosis in Bolivia: A Case Report

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Abstract

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Background: The current COVID-19 pandemic has highlighted various complications arising from the treatment and management of SARS-CoV-2 infected patients. One of these pathologies is mucormycosis, an angioinvasive, destructive, rare and rapidly progressive fungal infection that mainly affects immunocompromised patients.

Case Report: The aim of this study is to present the multidisciplinary clinical/surgical management of the first case of mucormycosis associated with COVID-19 in Bolivia. The particularity lies in the fact that this is a patient with no risk factors or relevant history who, after being infected by SARS-CoV-2, presented nasal-palatal-sinus mucormycosis with a rapid and aggressive evolution, but with a successful outcome.

Conclusion: The pioneering experience carried out in this case has made it possible to develop multidisciplinary teams and comprehensive care protocols adapted to the context that will make it possible to replicate the assistance received in the event of new cases in Bolivia.

Keywords: SARS-CoV-2; COVID-19; Mucormycosis; Opportunistic fungal infections; Corticosteroids

Abbreviations

ICU: Intensive Care Unit; PAS: Periodic Acid-Schiff; CT; Computed Axial Tomography; VMV: Mechanical Ventilation in VMV; PRF; Platelet-Rich Fibrin; CAM: Mucormycosis Associated with COVID-19

Introduction

The COVID-19 pandemic has revealed that patients who develop COVID-19 may be infected by opportunistic bacteria and fungi [1]. Mucormycosis is the third most common invasive fungus in existence [2]. It is a severe, rapidly progressive disease that is very rare in the general population and with a case fatality rate estimated at around 40% to 80% [3,4].

The most common appearance is rhinocerebral, initially affecting the nose and paranasal sinuses, which may extend to the orbit and brain [5]. Treatment and management of mucormycosis is a

complete challenge mainly because of delayed diagnosis due to a non-specific presentation [6], the rarity of the disease and the difficulties in microbiological identification [7].

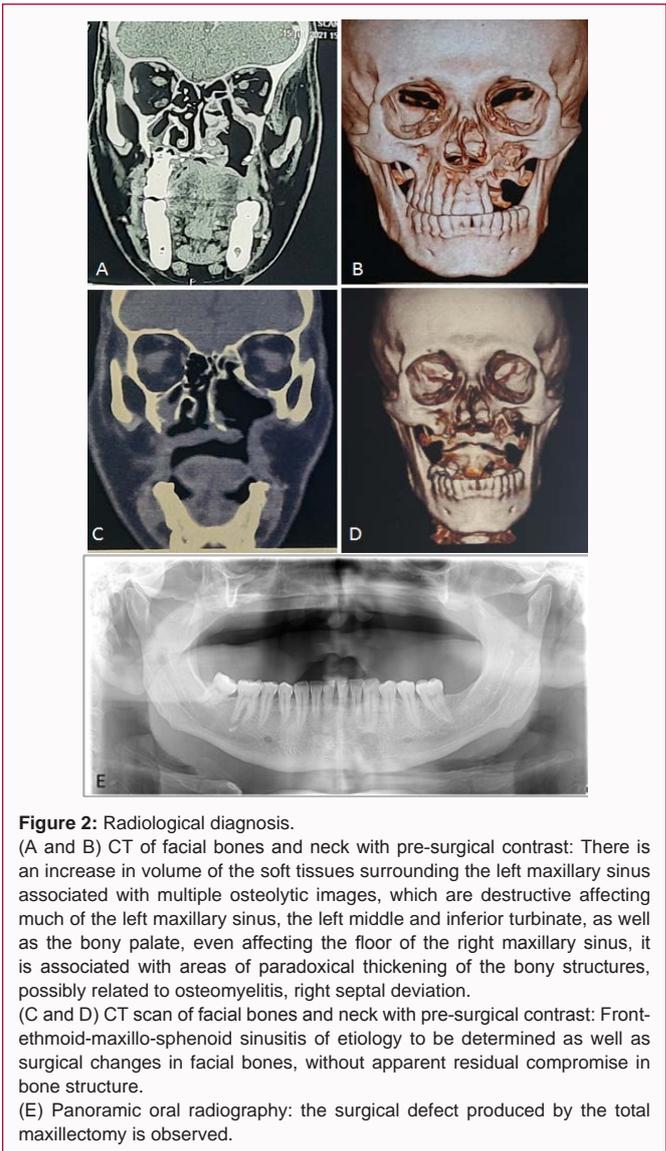
Therefore, patient recovery depends on the speed with which specific antifungal treatment is diagnosed and initiated, and in many cases surgical resection of necrotic tissue, which may include oral, nasal, and ocular bone tissue [8].

In this clinical case we describe the successful and early approach to the first case of COVID-19-associated mucormycosis in Bolivia. This is a patient with no risk factors or relevant history who, after receiving corticosteroids for the treatment of SARS-CoV-2 infection, was admitted with a diagnosis of nasal-palatal-sinus mucormycosis with involvement of the oral cavity and maxillary sinus and was successfully treated by a multidisciplinary team.

Case Presentation

A 43-year-old male patient with no previous illness (non-diabetic, non-neutropenic, no malignant disease) and no relevant risk factors, with a history of pneumonia caused by SARS-COV-2. Due to his poor evolution, he was admitted to the Intensive Care Unit (ICU) at the beginning of April 2021 in a third level hospital in Bolivia. During admission he received invasive mechanical ventilation for ten days, as well as treatment with intravenous antibiotic therapy with Ceftriaxone, Imipenem and intravenous corticotherapy with Prednisone. After good evolution and recovery from pneumonia, he was transferred to the hospital ward where he was discharged after two months. During the days of hospitalization in the ICU, he began to present discomfort in the upper jaw teeth, which were extracted generating a wound that did not heal and he was diagnosed with possible oral cancer.

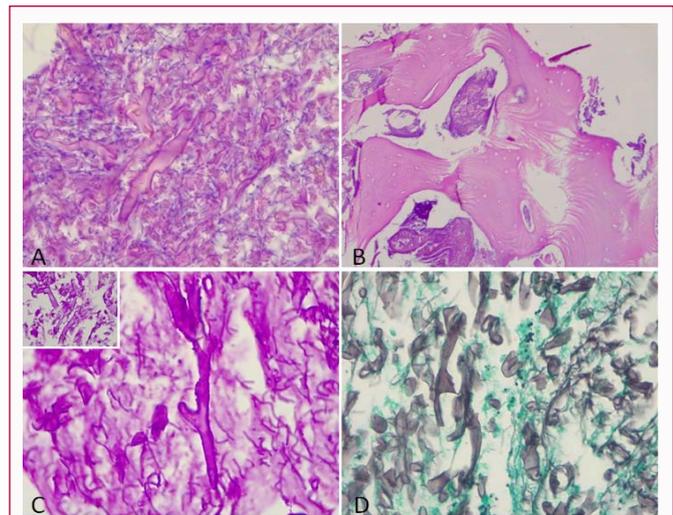
The patient went to the Maxillofacial Surgery office for a consultation with Otorhinolaryngology, a nasal-sinus endoscopic exploration was performed and a fistula was observed with extensive left maxillary oroantral communication with an important lesion



and alveolar bone with a moth-eaten appearance with necrotic bone edges, and a biopsy of the bone and the mucosa of the maxillary sinus was performed.

In Anatomic Pathology, microscopic inspection is performed by means of very sensitive special stains such as Periodic Acid-Schiff (PAS) and Grocott Gomori (Figure 1C, 1D) [9]. The results showed bony sequestrum, inflamed respiratory epithelium and extensive areas of large non-septate fungal hypha, some showing branching at right angles (PAS and Grocott Gomori positive) permeated by abundant hypha of *Candida* spp and Cocci (Figure 1A, 1B). Mucorales hypha are variable in width (6 μm to 25 μm), non-septate or sparsely septate, variable in branching angle and with 90° bifurcation [10,11]. This result allows us to give a definitive diagnosis based on the sensitivity of the histopathological examination [9].

Taking into account the histopathological results, the multidisciplinary team decided to admit the patient to hospital. Blood tests with different parameters were requested and were completely anodyne. An image test was performed with Computed Axial Tomography (CT) of the facial bones and neck with contrast prior to surgery where an increase of the soft tissues was described together



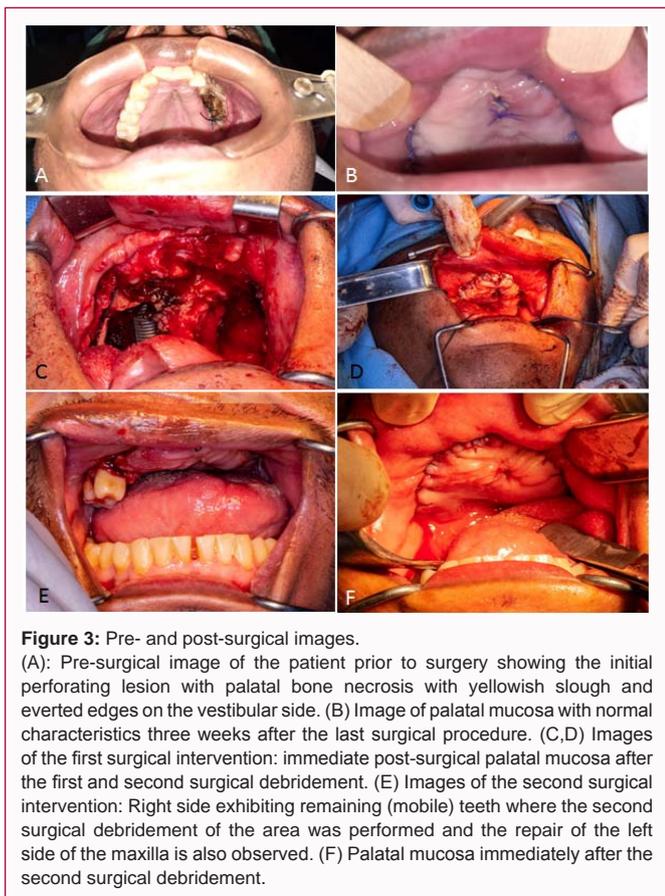


Figure 3: Pre- and post-surgical images. (A): Pre-surgical image of the patient prior to surgery showing the initial perforating lesion with palatal bone necrosis with yellowish slough and everted edges on the vestibular side. (B) Image of palatal mucosa with normal characteristics three weeks after the last surgical procedure. (C,D) Images of the first surgical intervention: immediate post-surgical palatal mucosa after the first and second surgical debridement. (E) Images of the second surgical intervention: Right side exhibiting remaining (mobile) teeth where the second surgical debridement of the area was performed and the repair of the left side of the maxilla is also observed. (F) Palatal mucosa immediately after the second surgical debridement.

with osteolytic images affecting a large part of the left maxillary sinus, the left middle and inferior turbinate, as well as the bony palate, even affecting the floor of the right maxillary sinus and associated with areas of paradoxical thickening of the bony structures and right septal deviation (Figure 2A, 2B). Treatment was started by Internal Medicine and Infectious Diseases Department with Liposomal Amphotericin B 50 mg and the patient was scheduled for surgical cleaning.

The first surgical intervention was performed by Maxillofacial Surgery and Otolaryngology Department with endoscopic exploration (Figure 3A) showing evidence of damage with palatal bone resorption. Partial maxillectomy of infrastructure was performed, with preservation of palatal mucosal tissue and nasal endoscopic surgery with permeabilization of the ostium of the left maxillary sinus plus endoscopic exploration and unilateral maxillary radical antrectomy (Figure 3C, 3D).

A week later the second surgery was performed with the extension of the infrastructure maxillectomy (total maxillectomy) and nasal endoscopic surgery with partial turbinectomy of the middle turbinate plus removal of necrotic tissue from the medial wall and second endoscopic revision of maxillary radical antrectomy with cleaning of necrotic tissue (Figure 3E, 3F). Postoperative control is performed with CT of facial bones reporting front-ethmoid and maxillo-sphenoid sinusitis without apparent residual compromise in bone structure.

During surgery, the work performed by the Anesthesia Service is noteworthy. Since it is an otorhino-orbital condition, it is considered a difficult airway. Being a much vascularized region and being a surgical cleaning there is a risk of bleeding with difficult hemostasis, so

it is decided to place a central line of three lumens of right subclavian access under ultrasound guidance for vasoactive management and possible transfusion of hemocomponents, in addition a peripheral venous access is obtained. Nasotracheal intubation is performed, so the nasal cavity with the least pathological condition is chosen using a tube with a steel arm to avoid kinking. Subsequently, a videolaryngoscopy is performed observing the tube in the oropharynx until entering the trachea, insufflation of the nasotracheal tube balloon by the minimum leakage method to minimize ischemia of the tracheal mucosa. Capnography is verified to ensure that the tube is in the airway, and the patient is connected to mechanical ventilation in VMV mode at a rate of 7 ml/kg of tidal volume and a respiratory rate of 12 per minute. It is also necessary to perform oropharyngeal packing with moist gauze to avoid the possible entry of fluids into the airway. Finally, after two hours of surgery the patient is transferred to the Post Anesthesia Care Unit with good recovery.

Two weeks later, surgical wound repair and repair of palatal mucosal tissue and gingival mucosa with Platelet-Rich Fibrin (PRF) membrane is performed (Figure 3B). PRF is a second-generation platelet concentrate that provides us, in a clot or membrane, with a large amount of growth factors, leukocytes and cytokines obtained by autogenous blood centrifugation which are necessary for soft and hard tissue healing processes [12]. These growth factors are considered to stimulate the mitogenic response in the periosteum and are responsible for bone repair during normal wound healing [13].

The patient remained in hospital for two more months with treatment of liposomal amphotericin B up to a cumulative dose of 5 grams with follow-up and treatment by the multidisciplinary team and with favorable evolution until discharge. The patient is currently at home in good condition and awaiting reconstructive surgeries in the following months.

Discussion and Conclusions

COVID-19 cases treated with corticosteroids are effective and mortality is highly reduced but paradoxically, this form of treatment increases the risk of secondary fungal infection, including mucormycosis, which has a high mortality rate [14-16].

The literature shows that most of the mucormycosis associated with COVID-19 (CAM) published to date correspond to patients with advanced age, uncontrolled diabetes, prolonged neutropenia, organ transplant recipients and hematological malignancies [17]. This study describes an atypical case since it is a middle-aged patient with no relevant history except for having suffered from bilateral COVID-19 pneumonia with corticosteroid therapy as treatment who presented with an unusual and rapid mucormycosis infection. Most of the cases correspond to the rhino-orbital type of mucormycosis in our case; the manifestation was nasal-palatal-sinus [18].

More than 200 cases of mucormycosis have been described in Latin America, some of them associated with COVID-19 in recent years and this is the first case in Bolivia and the eighth country in the Americas to report a case [19,20].

In the case of Bolivia, there are several aspects worth highlighting, the probable cause of this opportunistic co-infection due to the excessive, prolonged and unmonitored use of corticosteroids [21]. Early action allowed a differential diagnosis in relation to other previous diagnoses of the lesion, such as oral cancer, which made it possible to identify mucormycosis by means of special histochemical techniques and direct microscopic examination [9,22].

Different control measures were also carried out, such as analytical follow-up through blood laboratories, radiological imaging tests, mainly cranial CT scans, which have made it possible to assess the progression of the disease or invasion of other systems, as well as to evaluate the pre- and post-surgical process [23]. The corresponding epidemiological investigations were also carried out with the study of contacts, which made it possible to rule out the presence of more suspected cases of mucormycosis, with special emphasis on environmental contamination [24].

It is also worth mentioning the sophisticated surgeries that were performed following international protocols but adapted to the characteristics of the lesion and pathology of our patient, as well as the anesthetic approach that allowed hemodynamic control of the patient and mainly because it is a disease with severe destruction by fungal invasion of small blood vessels producing consequent infarction and necrosis of the tissue, against a minimal inflammatory response of our patient to infection because he is immunosuppressed by the use of corticosteroids [25]. Unlike the surgical protocols used in the current literature, the use of PRF to optimize the immune response, decrease the bacterial load and stimulate the repair process of the patient's tissues locally "*in situ*" has been considered a pioneering and successful work in the treatment of mucormycosis [26].

The pioneering experience carried out in this case has made it possible to develop multidisciplinary teams and comprehensive care protocols adapted to the context that will make it possible to replicate the assistance received in the event of new cases in Bolivia [27].

We are confident that early and timely detection, antifungal therapy, aggressive surgical debridement and stimulation of local healing together with a committed and specialized multidisciplinary team [28] have been factors that contributed to the favorable and successful evolution of the first case of mucormycosis associated with COVID-19 in Bolivia.

Declarations Ethics Approval and Consent to Participate

All authors have confirmed that they maintained confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement and assignment of rights to the journal.

The patient and family members signed the informed consent to participate.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing Interest

The authors declare that they have no conflicts of interest in relation to this article according to the rules of the International Committee of Medical Journal Editors (ICMJE).

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Authors' Contributions

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Conceptualization: QCV, GRRA, GSJ, RBJL. **Data Curation:** GRRA, RBJL, CSMR, DGC, DCRLJ, RGE, GSJ. **Formal Analysis:** QCV, GRRA, RBJL, CSMR, DGC, DCRLJ, RGE, HUA, GSJ. **Funding Acquisition:** QCV, GRRA, RBJL, CSMR, DGC, DCRLJ, RGE, HUA, GSJ. **Investigation:** QCV, GRRA, GSJ, RBJL. **Project Administration:** GSJ. **Resources:** QCV, GSJ, HUA. **Supervision:** QCV, GSJ. **Visualization:** QCV, GRRA, GSJ. **Writing – Original Draft Preparation:** QCV, GRRA. **Writing – Review & Editing:** QCV, GRRA, RBJL, CSMR, DGC, DCRLJ, RGE, HUA, GSJ

All authors read and approved the final manuscript and to have agreed both to be personally accountable for the author's own contributions.

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