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Emerging coinfections: the intersection of mucormycosis, paracoccidioidomycosis, and COVID-19

Coinfecciones emergentes: la intersección de mucormicosis, paracoccidioidomicosis y COVID-19

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Palabras clave:
COVID-19, pandemia, infecciones fúngicas, mucormicosis, paracoccidioidomicosis, corticosteroides.

ABSTRACT

Introduction: the COVID-19 pandemic has led to global health consequences, including a high mortality rate and reports of secondary infections. Among these infections, the co-infection of mucormycosis and paracoccidioidomycosis has raised concerns, particularly in patients receiving corticosteroids. Prompt diagnosis and management of these fungal infections are crucial due to their potential complications and atypical clinical courses. **Material and methods:** to investigate the association between COVID-19, corticosteroid use, and fungal infections, we conducted a comprehensive literature review. Sequential searches were performed in electronic databases, selecting articles based on relevance, study design, and quality. The methodology and findings of each article were critically assessed to ensure reliability. Furthermore, we presented a case study of a patient who developed mucormycosis and paracoccidioidomycosis one year after recovering from COVID-19. The patient's medical history, laboratory findings, radiological images, and treatment outcomes were thoroughly documented and analyzed. **Discussion:** mucormycosis is difficult to diagnose and associated with high morbidity and mortality rates. Diabetes, corticosteroid use and COVID-19-mediated immunosuppression are common risk factors. Timely administration of antifungal agents and surgical intervention is essential for successful management. The COVID-19 pandemic has highlighted the potential complications associated with fungal infections, specifically mucormycosis and paracoccidioidomycosis. Our comprehensive literature review and case study

RESUMEN

Introducción: *la pandemia de COVID-19 ha tenido consecuencias graves para la salud global, incluyendo una alta tasa de mortalidad y reportes de infecciones secundarias. Entre estas infecciones, la coinfección de mucormicosis y paracoccidioidomicosis ha generado preocupación, especialmente en pacientes que reciben corticosteroides. El diagnóstico y manejo oportuno de estas infecciones fúngicas son cruciales debido a sus posibles complicaciones y cursos clínicos atípicos.* ***Material y métodos:*** *para investigar la asociación entre COVID-19, uso de corticosteroides e infecciones fúngicas, llevamos a cabo una revisión exhaustiva de la literatura. Se realizaron búsquedas secuenciales en bases de datos electrónicas, seleccionando artículos basados en su relevancia, diseño de estudio y calidad. Se evaluó críticamente la metodología y los hallazgos de cada artículo para garantizar su confiabilidad. Además, presentamos un estudio de caso de un paciente que desarrolló mucormicosis y paracoccidioidomicosis un año después de recuperarse de COVID-19. Se documentaron y analizaron detalladamente la historia médica del paciente, los hallazgos de laboratorio, las imágenes radiológicas y los resultados del tratamiento.* ***Discusión:*** *la mucormicosis es difícil de diagnosticar y se asocia con altas tasas de morbilidad y mortalidad. La diabetes, el uso de corticosteroides y la inmunosupresión mediada por COVID-19 son factores de riesgo comunes. La administración oportuna de agentes antifúngicos y la intervención quirúrgica son esenciales para un manejo exitoso. La pandemia de COVID-19 ha destacado las posibles complicaciones asociadas con las infecciones fúngicas, específicamente la mucormicosis y la paracoccidioidomicosis. Nuestra revisión exhaustiva de la*

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emphasize the importance of early detection and timely treatment. Increasing awareness among healthcare professionals is essential to improve the management of fungal infections in COVID-19 survivors and reduce mortality rates.

literatura y el estudio de caso enfatizan la importancia de la detección temprana y el tratamiento oportuno. Aumentar la conciencia entre los profesionales de la salud es fundamental para mejorar el manejo de las infecciones fúngicas en los sobrevivientes de COVID-19 y reducir las tasas de mortalidad.

Introduction

The COVID-19 pandemic has had a significant impact on global health, with millions of people infected and a high mortality rate reported in many countries. In addition to the direct effects of the virus, there have been reports of secondary infections and complications associated with COVID-19, including fungal infections. Of particular concern are rare cases of co-infection with mucormycosis and paracoccidioidomycosis, two invasive fungal infections that can be difficult to diagnose and treat.[1]

These co-infections are especially challenging in patients who have received corticosteroids, which are commonly used in the management of COVID-19. The immunosuppressive effects of corticosteroids may increase the risk of developing fungal infections, and the chronic use of these drugs may further complicate the clinical course of these infections.[1-3]

Despite their rarity, the increasing incidence of fungal infections in COVID-19 patients underscores the need for increased awareness and vigilance in their diagnosis and management. Fungal infections can present with a variety of symptoms and can mimic other conditions, leading to delayed diagnosis and potentially worse outcomes. Furthermore, the evolution of fungal infections in COVID-19 patients may be unique, with atypical presentations and unexpected clinical courses.[1-3]

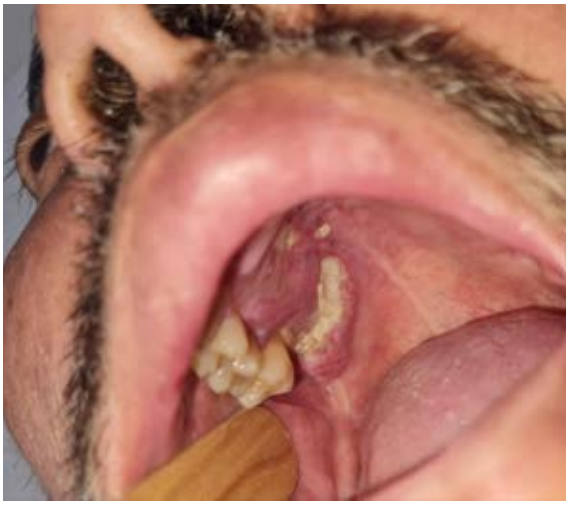

Figure 1: *Initial injury.*

Diagnosis

Referred as a product of right subtotal maxillectomy:
** soft tissue (maxillary sinus tissue) with:
- Presence of chronic granulomatous inflammation with foreign body type gigantocellular reaction and focal necrosis.
- Presence of microorganisms of fungal morphology suggestive of zygomycete: mucor
- Presence of microorganisms of fungal morphology: paracoccidioidomycosis.

Figure 2: *Histopathological report.*

In this article, we aim to explore the association between COVID-19, corticosteroid use, and fungal infections, with a focus on the rare co-infection of mucormycosis and paracoccidioidomycosis. Through a comprehensive literature review, we will highlight the challenges in diagnosing and managing these infections and provide insight into the unique features of their clinical course in the context of COVID-19. Ultimately, this article seeks to increase awareness of the potential complications of COVID-19 and the need for early recognition and prompt intervention in patients who develop fungal infections.

Zygomycosis infections caused by mucorales fungi are characterized by invasion of blood vessels and other adjacent organs or structures. Mucorales often cause infection at the orbi-torhinocerebral, pulmonary, cutaneous, digestive, or disseminated level, and their development is favored by certain underlying diseases such as diabetes and renal insufficiency. They are associated with high mortality rates and early diagnosis and antifungal treatment, combined in most cases with wide surgical debridement, are key to successful management. Isavuconazole is currently considered an alternative therapy for refractory or intolerant mucormycosis, especially in patients intolerant to liposomal amphotericin B.[4-6]

Mucormycosis is a rare but potentially life-threatening disease with high morbidity and mortality rates, and it is difficult to diagnose. It is caused by a group of molds called mucormycetes. Diabetes, corticosteroid use, metabolic/diabetic acidosis, and COVID-19-mediated immunosuppression are reported in more than 70% of cases in patients with mucormycosis. The coexistence of mucormycosis, COVID-19, and diabetes mellitus increases the likelihood of mortality. Despite its occurrence since

the beginning of the pandemic, there are still unanswered concerns regarding the origin of this fungal infection and its mortality rate and/or relationship with diabetic patients. Once mucormycosis is diagnosed, a combined treatment method consisting of administration of antifungal agents such as amphotericin B, together with surgical intervention to reverse the underlying condition, is required. Early detection of this potentially life-threatening infection and timely attention are necessary to reduce mortality rates.[6-8]

Paracoccidioidomycosis is an endemic systemic granulomatous disease in Latin America that is acquired through the respiratory tract by inhaling propagules found in the soil. In the human body, the propagules cause the infection. Paracoccidioidomycosis can affect any organ, especially the lungs, upper aerodigestive tract mucosa, and skin. Blackberry-like ulcers on oral mucous membranes are one of the first manifestations of the disease. The infection can remain subclinical, localized, or occasionally disseminated. Hematogenous dissemination of paracoccidioidomycosis to abdominal lymph nodes, spleen, liver, adrenal glands, skin, or brain can lead to potentially fatal complications. When the disease manifests with systemic signs and symptoms without its classic features, initial confusion among physicians can occur, leading to a delay in diagnosis and treatment of the disease and its associated comorbidities.[3,5,9]

The COVID-19 pandemic has had a profound impact on global health, leading to an increased awareness of infectious diseases and their complications. In recent months, reports have emerged of a rare and potentially deadly combination of fungal infections in COVID-19 survivors, including mucormycosis and paracoccidioidomycosis. This article presents a case study of a patient who developed mucormycosis and paracoccidioidomycosis approximately one year after recovering from COVID-19. In addition, a comprehensive literature review is conducted to explore the current understanding of the relationship between COVID-19 and fungal infections, and to provide insight into the management of these rare and complex cases. The aim of this article is to increase awareness of the potential complications of COVID-19 and to highlight the importance of early detection and treatment of fungal infections in COVID-19 survivors. Thousands of cases of severe and often fatal invasive fungal infections were reported in the wake of the second wave of COVID-19 cases, bringing global attention to this deadly but neglected disease.[10,11]

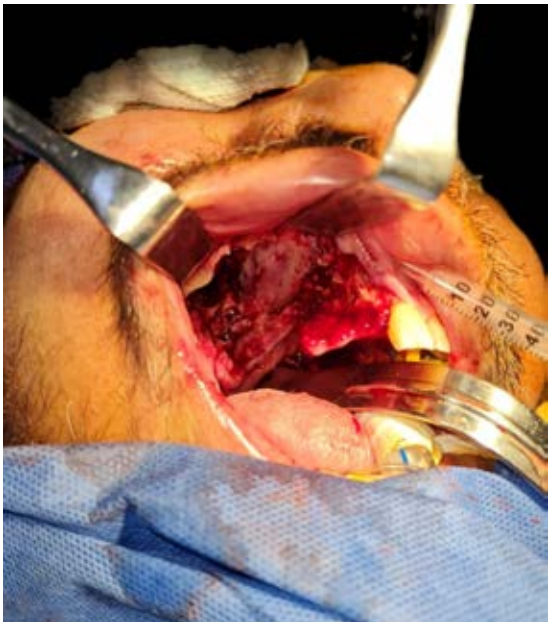

Figure 3: *Maxillectomy.*

Material and methods

The methodology for this article involved a comprehensive literature review and a clinical case study focused on the relationship between mucormycosis, paracoccidioidomycosis and COVID-19. To begin, we conducted sequential searches in electronic databases (PubMed, EBSCO, ScienceDirect, The Cochrane Library, ClinicalKey) using the search terms «Mucormycosis, OR paracoccidioidomycosis» and «SARS-CoV-2». We analyzed the selected articles and identified the most relevant ones based on their relevance to the topic, study design and quality. Additionally, we critically assessed the methodology and findings of each article to ensure that the information presented was reliable and valid.

Furthermore, we presented a rare case study of a patient with both mucormycosis and paracoccidioidomycosis, which involved a detailed clinical evaluation, diagnostic procedures and treatment plan. The patient's medical history, laboratory findings, radiological images and treatment outcomes were all thoroughly documented and analyzed.

We present the case of a patient who presented to a public hospital with a maxillary region volume increase that had been evolving for 21 days. The patient's medical history is relevant, as he had been using corticosteroids chronically for joint pain, was hypertensive and had suffered from COVID-19 one year approximately. The patient reported that his condition began with tooth pain, which then progressed to inflammation in the area. The patient also lost sensitivity in the region and experienced increased pain. On intraoral clinical examination, a necrotic area adjacent to the left upper second molar was observed *(Figure 1)*, and the tooth presented grade III mobility.

The patient was admitted to the maxillofacial surgery department, where antifungal management with Amphotericin B was provided, given the clinical features compatible with mucormycosis, with the aim of preventing disease progression and awaiting the results. In the operating room, with the patient

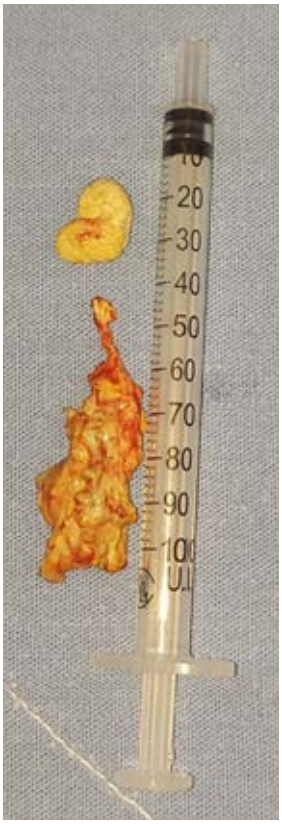

Figure 4:

Necrotic buccal fat pad.

under general anesthesia, hemimaxillectomy was performed, leaving a Brown type B defect. The surgical procedure was successful in terms of disease progression, as it was completely removed and limited in its expansion *(Figures 2 to 4)*.

Upon receiving the biopsy results (product of maxillectomy), the diagnosis of mucormycosis was confirmed, with the peculiarity that there was also the presence of microorganisms from the paracoccidioidomycosis family. The histological report also indicated local necrosis and granulation tissue, which is a response of the organism *(Figure 5)*.

The patient was initially progressing well. However, due to his pre-existing conditions and the necessary pharmacological management, he experienced systemic decompensation, and unfortunately, he died of cardiac problems days later in his room.

Discussion

Mucormycosis and paracoccidioidomycosis are two different fungal diseases that affect different parts of the body. They mainly affect patients with diabetes mellitus (60-80%) in the rhino-orbital-cerebral region, producing bone necrosis, vascular damage, and invasion of the orbit, eye, and brain. Patients usually present with facial pain, sinusitis, proptosis, or amaurosis 3, which may be exacerbated by dental extraction. It is difficult to determine whether dental extraction creates a portal of entry for fungal infection in these patients or if mucormycosis was the original cause of the pain and was confused with dental pain.[2,4,5,12]

Mucormycosis is an opportunistic fungal infection caused by fungi of the genus Mucorales, which usually affects immunocompromised patients, such as those with diabetes, HIV, or those who have received transplants. On the other hand, paracoccidioidomycosis is a chronic fungal infection caused by the fungus Paracoccidioides brasiliensis, which is mainly found in Latin America and primarily affects the lungs. When associated with the SARS-CoV-2 virus, they are usually observed during the recovery period of COVID-19.[6,13]

The presence of a combination of mucormycosis and paracoccidioidomycosis in the oral cavity of a patient would be a very rare and unlikely condition. Each of these infections usually occurs independently and affects different parts of the body. However, it is possible for a patient to have multiple fungal infections if their immune system is weakened and unable to effectively fight infections.[2-4]

Mucormycosis in the oral cavity can present as an infection in the palate, gums, or teeth. Symptoms may include pain, swelling, tissue ulceration, and necrosis. On the other hand, paracoccidioidomycosis in the oral cavity can present as a lesion in the oral mucosa, which may or may not be painful. In severe cases, paracoccidioidomycosis can spread to lymph nodes and other organs, such as the lungs.[14,15]

The treatment of mucormycosis should be based on rapid and accurate diagnosis, control of predisposing factors, potential improvement of immune status, and a combination of appropriate antifungal treatment along with extensive surgical debridement and excision, sometimes very aggressive and mutilating. In addition, in neutropenic patients, the recovery of the number and functionality of neutrophils is very important.

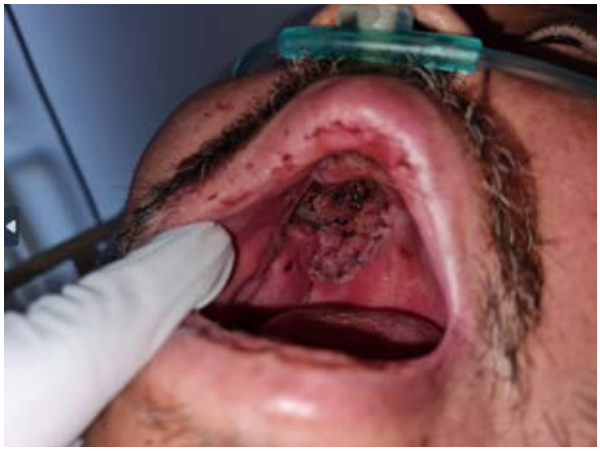

Figure 5: *Wound in healing process.*

The recommendations of different European guidelines are summarized in the table. Most of them are based on expert opinion consensus or studies with scarce evidence.[16]

In any case, the treatment of these fungal infections will depend on the severity of the infection and the overall health of the patient. Treatment may include antifungal medications, such as amphotericin B, fluconazole, or itraconazole, and may require surgical interventions to remove infected tissue. The surgical treatment of fungal infections requires early diagnosis, aggressive surgical debridement, and early reconstructive surgery. Debridement should continue until clear resection margins are obtained, based on microscopic findings of hyphae, fungal cultures, and fungal DNA detected by PCR.[4,17] Treatment is based on surgical debridement of the damaged tissue, effective antifungal medication (monotherapy or combination therapy), reversal of immunosuppression, and possible control of predisposing comorbidities, taking into account that systemic conditions in patients with this pathology involve a challenge for clinical management.[18,19]

COVID-19 is often associated with secondary infections, both bacterial and fungal, possibly due to immune dysregulation. In addition, the widespread use of broad-spectrum antibiotics, steroids, or monoclonal antibodies in the management of COVID-19 can lead to the development or exacerbation of pre-existing fungal diseases.[20]

In a 2023 systematic review, Ozbek et al. reported that the most frequent post-pandemic combination of fungal infections related to COVID-19 was mucorales and aspergillus. They also reported that risk factors for *Aspergillus* coinfection were a history of obesity, neutropenia, and the use of corticosteroids, dexamethasone, hydrocortisone, or tocilizumab for COVID-19.[15]

In 2021, Meher et al. concluded that the increase in mucormycosis associated with COVID-19 was mainly observed in patients with uncontrolled diabetes, a dysfunctional immune system due to SARS-CoV-2 infection, and imprudent use of corticosteroids.[12]

The case of the patient with mucormycosis and paracoccidioidomycosis is a rare entity that highlights the need for heightened awareness of these fungal infections in clinical practice; to the best of our knowledge, this is the first reported case of simultaneous mucormycosis and paracoccidioidomycosis in a patient. Our review of the literature also suggests an increased incidence of these infections in the post-COVID-19 era. It is essential for healthcare professionals to remain vigilant for the signs and symptoms of these conditions, particularly in patients with a history of COVID-19 or other immunosuppressive conditions. Further research is needed to better understand the pathophysiology of these infections and to develop more effective treatments. In the meantime, early diagnosis and prompt initiation of appropriate therapy are critical for improving outcomes in patients with these challenging fungal infections. The findings presented in this study are compatible with the literature and support the idea that COVID-19 may increase the risk of fungal infections. It is important for clinicians to be aware of this possibility and to consider fungal coinfection in patients with COVID-19, especially those with preexisting comorbidities.

Conclusion

The case presented in this article highlights the rare and potentially lethal combination of mucormycosis and paracoccidioidomycosis in a patient who had recovered from COVID-19 approximately one year earlier. The association between COVID-19 and fungal infections, particularly in immunocompromised patients, has been reported in recent studies, and the chronic use of corticosteroids may further increase the risk of developing fungal infections.

Given the rarity and severity of these infections, it is crucial to maintain a high index of suspicion and to promptly initiate appropriate diagnostic and therapeutic measures. Fungal infections can manifest in various forms, and their clinical presentation may be challenging to distinguish from other pathologies. Furthermore, the management of these infections may require a multidisciplinary approach, including antifungal therapy, surgical intervention, and supportive care.

In light of the ongoing COVID-19 pandemic, it is essential to recognize the potential complications of this disease and to closely monitor patients who have recovered from COVID-19, especially those who have received immunosuppressive therapy. Further research is needed to better understand the pathogenesis of these fungal infections in COVID-19 survivors and to develop effective strategies for prevention and management. Overall, this case underscores the importance of early detection, prompt intervention, and vigilant follow-up in patients who present with rare and complex fungal infections.

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Conflicts of interest: there are no conflicts of interest.

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