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Case Report

Mycotic clival osteomyelitis secondary to immunosuppression by SARS-CoV-2

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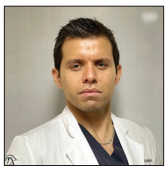

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ABSTRACT

Background: During the past 2 years, the use of systemic corticosteroids has increased due to COVID-19 atypical pneumonia management. Similarly, an increase in mycotic infection cases has been reported during the same period as a consequence of immunosuppression caused by corticosteroid overuse. Mycotic clival osteomyelitis is a rare clinical entity which presumably has increased its incidence during the pandemic.

Case Description: A 52-year-old woman who presented persistent headaches and unexplained weight loss after being hospitalized due to COVID-19 pneumonia treated with intravenous corticosteroids. Head computed tomography and magnetic resonance imaging showed extensive osteomyelitis at the clival region with no brain parenchyma involvement. Surgical excision through navigation-guided transnasal transclival endoscopic extended approach was performed for surgical debridement. Histopathological analysis revealed angulated hyphae, suggestive of *Aspergillosis.* Systemic antifungal treatment was administered for 30 consecutive days. Afterward, she was discharged without any remarkable neurological findings, reassessed during follow-up.

Conclusion: The COVID-19 pandemic has had an effect on the reemergence of mycotic infections due to corticosteroid immunosuppression. Clival osteomyelitis secondary to mycotic infection is an exclusion diagnosis that we encourage to be highly suspected within the persisting COVID-19 pandemic.

Keywords: *Aspergillosis*, COVID-19, Osteomyelitis

INTRODUCTION

Since the end of 2019, COVID-19 has infected more than 500 million people, with more than 6 million deaths up to date.[12] Incidence of mycotic infections has increased on account of the COVID-19 pandemic, the use of corticosteroids in the context of atypical COVID-19 pneumonia, and type 2 diabetes as a comorbidity.[13] The clinical scenario, where severe COVID-19 and type 2 diabetes converge, is optimal conditions for mycotic proliferation to develop in an immunocompromised host.[10]

Skull base osteomyelitis (SBO) is a rare, yet potentially treatable disease. Usually, the microorganisms involved are *Staphylococcus aureus*, and the most prevalent mycotic agent is *Aspergillosis*

fumigatus.[14] Within the still present COVID-19 pandemic, the coexistence of SARS-CoV-2 and *Mucormycosis* (also known as black fungus) has been reported, infecting nasal and orbital bone structures, occasionally with an extension to skull base brain parenchyma.[8] We present the case of an *Aspergillosis* infection with clival bone extension, within the context of a previously treated COVID-19 infection.

CLINICAL CASE PRESENTATION

A 52-year-old female with a previous medical history of hypertension in adherence to antihypertensive treatment (thiazide and angiotensin II receptor blocker), type 2 diabetes in adherence to Glargine insulin, and metformin treatment, arrived to the emergency room with ventilatory compromise and hypoxemia. *SARS-CoV-2* infection was diagnosed with a positive PCR test, clinically classified as moderate COVID-19 due to fever, dyspnea, and hypoxemia, which required 18 days of hospitalization and management with intravenous corticosteroids (6 mg dexamethasone q. d.) as well as subcutaneous low-molecular-weight heparin (60 mg enoxaparin q. d.). Hospital discharge was decided after stable and favorable clinical evolution, with prescription of continuous supplementary oxygen (5 L/h), dose adjustment of antidiabetic drugs, with no further required changes or complications.

Two weeks after hospital discharge, she presents a mild headache (visual analog scale 4/10). A month after discharge, she presents malaise and an unexplained weight loss of 8 kg. During follow-up, neurologic examination was unremarkable and there was no further need of supplementary oxygen. Nevertheless, cephalgia and intermittent nasal constipation were the patient's prevalent symptoms.

A head computed tomography (CT) scan was performed, which revealed a lesion within the paranasal sinuses. Bone window revealed demineralization with trabecular pattern, and cortical involvement of the walls of the ethmoid and sphenoid sinuses, pterygoid processes, turbinate bones, nasal septum, clivus, petrous apex, vomer, carotid foramina, greater wings of the sphenoid bone, frontal processes, orbital processes of frontal bone, and anterior and posterior clinoid processes, [Figure 1].

Magnetic resonance imaging (MRI) of the skull base at the level of the clivus and the petrous apex showed soft tissues as isointense to muscle tissue in T1-weighted sequence and hyperintense in T2-weighted as well as in fluid-attenuated inversion recovery sequence, with gadolinium enhancement in fat-saturated contrast-enhanced T1-weighted (T1+C+FAT) sequence, [Figure 2]. Loss of fat planes among soft tissue was identified with restriction in diffusion sequence, corroborated in apparent diffusion coefficient (ADC) sequence map, [Figure 3].

Given the MRI findings, surgical excision through navigation-guided transnasal transclival endoscopic extended approach and later nasoseptal pediculated flap rotation was performed, [Figure 4]. Transoperative findings showed sphenoidal rostrum lysis with extension to lateral recesses, clival, and sella turcica osteolysis, with no dural invasion. Surgical debridement was performed in a conventional manner, with no apparent complications. The patient was discharged 48 h postsurgery, with no clinical signs of transnasal fistula.

Microbiology and histopathological analysis revealed 90° angled hyphae suspicious of *Aspergillosis*, [Figure 5]. A culture confirmation of the fungus was realized, with positive results to *Aspergillus* spp. Hospital readmission was suggested for antimicrobial treatment; intravenous fluconazole and liposomal amphotericin B treatment were prescribed for 30 days, which concluded with no further complications.

DISCUSSION

SBO is a rare entity with high risk of mortality, representing both a clinical and imaging diagnostic challenge. There are two categories of skull base osteomyelitis: typical and atypical (or central) osteomyelitis.[6]

Typical SBO is the most frequent type among these two. Most typical SBO cases present within diabetic and elder population, whose immunocompromise leads to external necrotizing otitis by *Pseudomonas* infection.[5] Atypical or central SBO invades the sphenoidal and occipital bones, with nonrelated previous otic infection.[11] *S. aureus* and *Pseudomonas aeruginosa* are some of the most frequently reported bacterial pathogens in atypical SBO. Likewise, *A. fumigatus* is the mycotic pathogen most frequently reported in the literature.[14] The known mechanism of skull base invasion by these microorganisms is through contiguous translocation through Santorini fissures and hematologic translocation through the venous plexus located within the temporal bone.[18] An established anatomical risk factor for clival osteomyelitis is a prominent navicular fossa, which is a known anatomical variant of clival morphology.[15]

Throughout the COVID-19 pandemic, clinical severity has been graded as asymptomatic, symptomatic, ventilatory compromise, severe ventilatory failure, and death. Within the context of COVID-19, bacterial and mycotic secondary infections are a clinical challenge due to its abrupt increase of morbidity and mortality.[19] *Candidiasis* and *Aspergillosis* were the most commonly reported fungi pathogens correlated to COVID-19 infection during the pandemic.[9] In addition, it has been also demonstrated that corticosteroids are an effective treatment as immune response modulators, resulting in a decrease in mortality in severe COVID-19 infection.[17] Nevertheless, the overuse of corticosteroids also conveys a higher risk of secondary opportunistic coinfections that may risk patient's survival.[13]

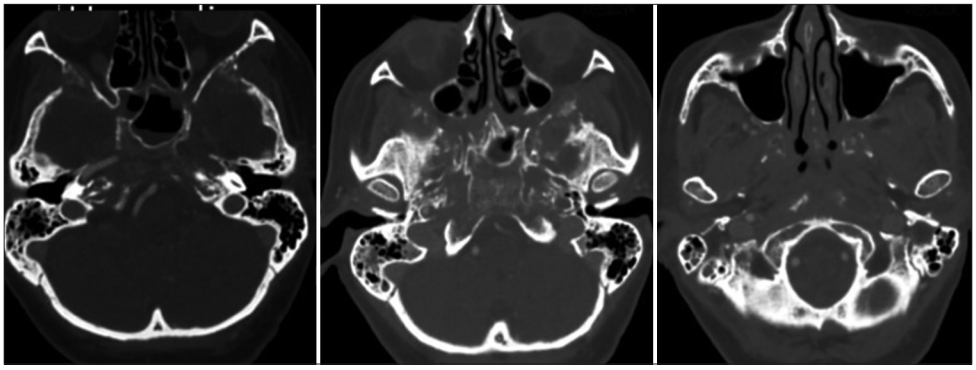

Figure 1: Axial computed tomography scan, bone window with osteomyelitis extension within the occipital bone base and the sphenoidal sinus.

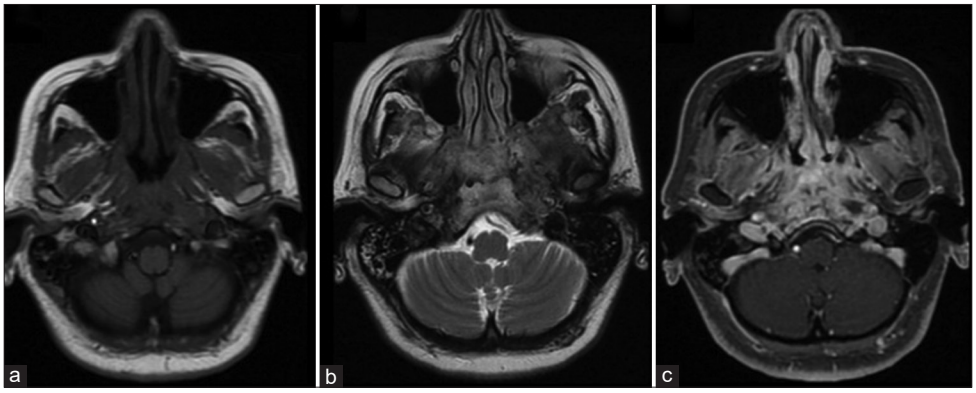

Figure 2: Axial magnetic resonance imaging demonstrating a hypointense lesion with sphenoid boy and clival bone involvement (a) infiltrating nasopharyngeal submucous tissue (b) with a hypointense appearance in T1 and T2 sequences. Gadolinium enhancement in T1 of sphenoid and clival bone tissue.

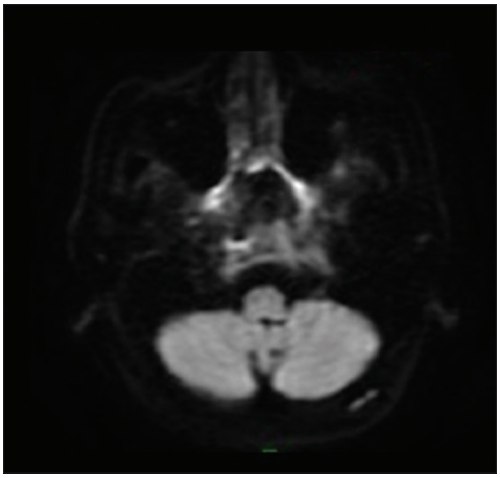

Figure 3: Axial diffusion-weighted imaging with focal fluid along the anterior wall of the sphenoid sinus persisting hyperintensity, suggesting focal abscess.

Cephalgia and facial pain are symptoms reported in most SBO cases. However, several cases with cranial nerves affection (VI, IX, X, XI, and XII) have been reported.[16] Due to the ambiguous signs and symptoms that may be present, difficulties to reach a diagnosis are common, as well as the misdiagnosis of malignant skull base tumors in different imaging studies.

Radio imaging correlation with the clinical presentation is fundamental during the diagnosis approach of SBO. In general, the use of contrasted CT scan and gadolinium-enhanced MRI is fundamental. In complex cases, the use of functional studies may provide us useful bone metabolism data, such as positron emission tomography CT scan with technetium 99.[6]

When atypical SBO is present, it is important to evaluate key areas including the bony external auditory canal, mastoid process, temporomandibular joint, petrous apex, petro-occipital fissure, foramen lacerum, jugular foramen, and clivus, where most frequently the origin of disease is clival infection.[1,6,16]

CT scan is the gold standard imaging study for SBO. It is a helpful tool to evaluate the extent and severity of infection, as well as to assess cortical bone erosion or trabecular demineralization related to osteomyelitis.[6,11,16] There is

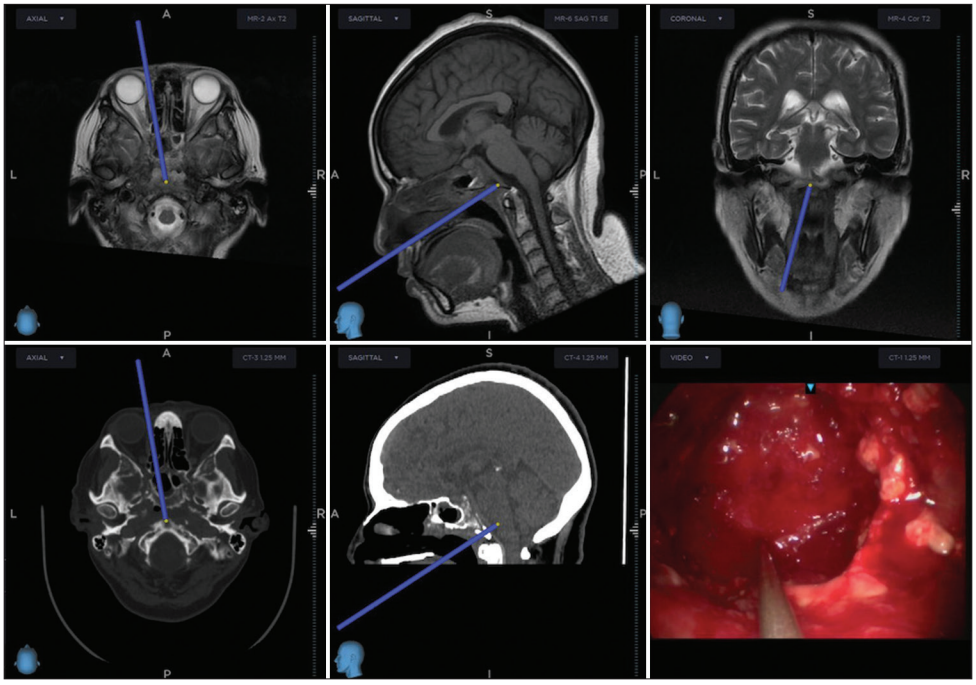

Figure 4: Navigation-guided transnasal transclival endoscopic extended approach with clival drilling.

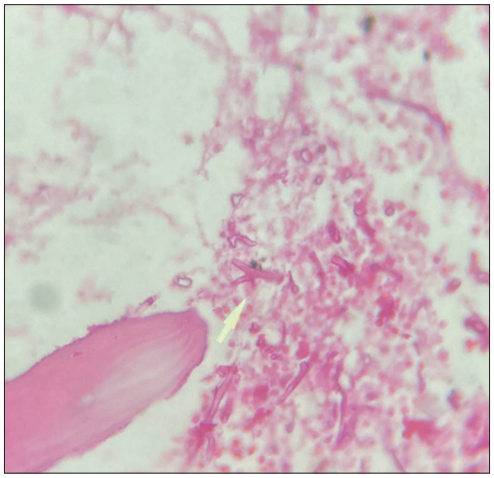

Figure 5: Microphotography of histopathological bone tissue sample with hematoxylin and eosin staining. Numerous angled hyphae of *Aspergillus* spp. are identified (yellow arrow).

often evidence of invasive sinusitis with cortical erosions of the paranasal sinuses, particularly the sphenoid or ethmoid sinuses, anterior clivus, and foramina of the central skull base.[6,16] Contrast-enhanced CT scan can be of additional benefit for the evaluation of vascular complications, including cavernous sinus thrombosis or stroke.[6]

MRI is complementary for soft-tissue analysis around the skull base and medullary cavity of the bone.[6,11] On T1-weighted sequence, the ill-defined soft issue demonstrates either hypo- or isointense signal of the muscle, causing fat plane obliteration. When osteomyelitis affects the bone marrow, there is loss of normal fat signal within the bone marrow space. Infiltration may precede edema and phlegmon, which are evidenced as hyperintensity in T2 sequence and heterogeneous enhancement in T1-weighted fat-saturated and contrast-enhanced sequences.[6,11] In severe osteomyelitis, bone marrow may progress from necrotic tissue into an abscess, producing a ring-enhanced lesion.[6] Diffusion restriction in nonenhanced fluid collections can help confirm an abscess. In addition, ADC sequence may allow distinction between SBO and neoplastic lesions.[6]

Nuclear medicine provides both functional and metabolic data of the osseous tissue, complementing for localization of skull base infection. Specifically, technetium 99m-methyl diphosphonate (Tc99m MDP) demonstrates a higher osteoblastic activity whenever an infectious process is present within the bone.[2]

Surgical debridement and antimycotic treatment are the standard therapy on invasive SBO caused by *Aspergillosis*.[3] The main objective of surgical treatment is to perform a safe and maximum debridement with posterior long-term antimycotic treatment.[4] In the previous decades, liposomal amphotericin B used to be the treatment of choice for invasive *Aspergillosis*.[7] Voriconazole, a second-generation triazole, has demonstrated a greater efficacy as treatment proposed for *Aspergillosis*. The previous studies have demonstrated an effective soft tissue and bone distribution of voriconazole, which is convenient due to bone, meningeal, and central nervous system damage held by invasive *Aspergillosis* infection.[3]

CONCLUSION

Clival osteomyelitis secondary to mycotic infection is a rare clinical infectious entity with a challenging diagnosis and treatment approach. It is usually considered an exclusion diagnosis and is finally confirmed with histopathological and microbiological analysis. Within the still present COVID-19 pandemic, we encourage a high suspicion of this entity to be considered in elder, diabetic patients treated with corticosteroids, with atypical signs and symptoms. Surgical debridement is not only vital part of the treatment but also part of the definite diagnosis approach.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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