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Skull Base Osteomyelitis Complicating COVID-19: A Novel Secondary Infection?

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ABSTRACT

Background: Data from the onset of the Coronavirus Disease 2019 (COVID-19) pandemic has revealed a broad spectrum of clinical conditions and comorbidities. Secondary infections, such as sinonasal mucormycosis, have become more frequent due to COVID-19-related immunosuppression and its subsequent treatments. Skull base osteomyelitis is another potentially fatal infection that is prevalent among immunocompromised individuals. Angiotensin-Converting Enzyme 2 (ACE2) receptors in the external auditory canal may also be implicated in cases of external otitis linked to COVID-19.

Case Report: This report discusses two cases of treatment-resistant external otitis and skull base osteomyelitis in two elderly, immunosuppressed patients (with diabetes mellitus and chronic renal failure) who had previously been treated for COVID-19. In both cases, neither topical nor intravenous antibiotic treatments were effective, leading to referrals for hyperbaric oxygen therapy.

Conclusion: For patients exhibiting persistent ear discharge and a history of COVID-19, it is imperative to avoid underestimating a potential diagnosis of skull base osteomyelitis and to pursue early imaging.

Keywords: Skull base osteomyelitis, COVID-19, otitis externa, external ear, ear infection

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INTRODUCTION

There have been reports of a surge in superinfections and increased severity of infectious disorders following Coronavirus Disease 2019 (COVID-19). The rising prevalence of mucormycosis after COVID-19 has garnered attention in recent months of the pandemic.[1,2] Besides the immunosuppression induced by COVID-19, the use of steroids in its treatment can pave the way for opportunistic infections. Especially when patients with diabetes undergo steroid treatment for COVID-19, severe bacterial and fungal infections are observed due to deteriorated blood glucose or ketoacidosis.[1]

Skull base osteomyelitis (SBO) is a rare condition resulting from an infection that spreads from adjacent tissues, most commonly from malignant or necrotizing otitis externa.[3] Patients with SBO may exhibit signs of cranial nerve involvement since certain cranial nerves run proximate to the skull base.[4,5]

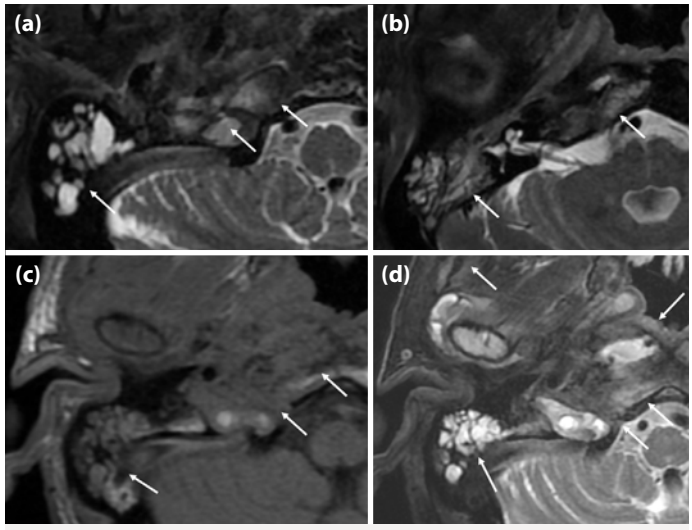

Figure 1. Pretreatment axial T1 **(a)**, T2 **(b)** and posttreatment axial T1 **(c)**, T2 **(d)** weighted magnetic resonance images of Case 1. White arrows indicate inflammatory signal changes in the mastoid air cells, clivus, and petrous apex.

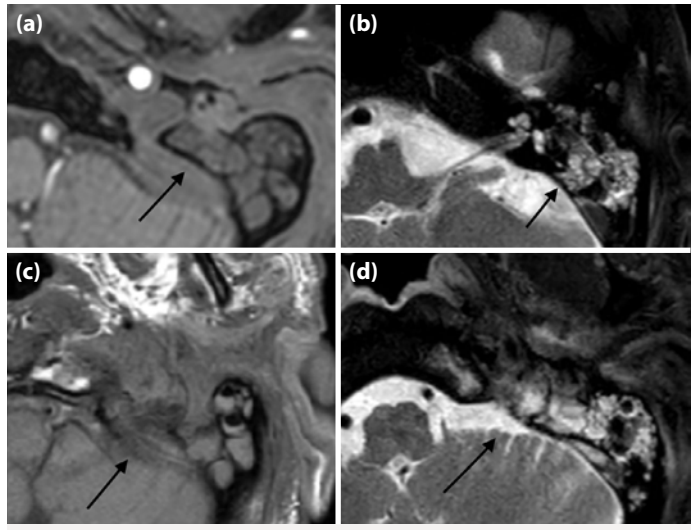

Figure 2. Pretreatment axial T1 **(a)**, T2 **(b)** and posttreatment axial T1 **(c)**, T2 **(d)** weighted magnetic resonance images of Case 1. White arrows indicate inflammation in the clivus and petrous apex, in addition to the mastoid air cells.

In this case report, we highlight two elderly diabetic patients who developed SBO following COVID-19 treatment. This report underscores the significance of early detection and management of severe post-COVID-19 infections, such as SBO, to minimize mortality.

CASE REPORTS

Case 1

A 65-year-old male patient presented with ear pain persisting for two months. The right external ear showed pronounced edema, and purulent discharge was aspirated. The initial culture taken from the external auditory canal (EAC) did not yield any identifiable bacteria. The patient 's history revealed that he had been treated for COVID-19 with 6 mg of dexamethasone daily and was discharged a week prior. Magnetic resonance imaging (MRI) of the temporal bone showed irregularly delineated diffuse enhancements in the middle ear, mastoid antrum, and mastoid cells. Additionally, the right side of the clivus and the right half of the sphenoid body were involved (Fig. 1). Owing to renal insufficiency, the nephrology department adjusted the dosage, initiating 2x1000 mg intravenous ceftazidime. Accompanied by topical ciprofloxacin (3.5 mg/mL, 3x5 drops) and dexamethasone (5 mg/mL, 3x5 drops) administration, daily aspiration of the EAC was carried out. A temporal Computed Tomography (CT) scan revealed extensive soft tissue presence in the middle ear cavity, near the ossicular chain adjacent to the oval and round windows, and within the mastoid cells. The patient also had diabetes mellitus (with blood glucose levels noted upon admission), coronary artery disease, chronic renal failure, and hepatitis B as comorbidities. Blood glucose regulation was managed in consultation with the endocrinology department, and insulin doses were adjusted upward. An MRI reevaluation of the patient was conducted in the third week of hospitalization. Due to a lack of radiological improvement, teicoplanin was added to the treatment regimen. During clinical follow-up, the patient developed abducent and glossopharyngeal nerve paresis. A simple mastoidectomy was performed for culture and debridement, revealing diffuse hypertrophic mucosa and purulent discharge in the middle ear. Given the lack of specific bacterial or fungal growth in the obtained cultures, the patient's existing antibiotic medication was continued, and he was referred to another hospital for hyperbaric oxygen therapy.

Case 2

A 78-year-old male patient presented with complaints of ear pain and discharge. Upon examination, the external auditory canal was found to be filled with polypoid tissue. His comorbidities included diabetes, epilepsy, hypertension, and renal failure.

He had been diagnosed with COVID-19 two weeks prior and was treated with steroids, specifically 6 mg of dexamethasone daily. A temporal MRI revealed inflammatory tissues infiltrating the external auditory canal and mastoid region, extending from the Temporomandibular Joint (TMJ) to the parapharyngeal area (Fig. 2). Mesh cotton was inserted into the external ear, and regular administration of ciprofloxacin and topical steroids was initiated. A culture sample was taken from the EAC. The patient was subsequently referred to an infectious disease specialist, and intravenous ceftazidime therapy was started.

Table 1. Clinical, laboratory, and radiological findings of the patients at the time of admission and before referral

	Case 1		Case 2	
	Day 1	Day 67	Day 1	Day 81
Symptoms	Two months of right ear pain and discharge	Mild pain in the right ear and right side of the neck	Four months of right ear pain and discharge Left EAC full of	Left ear pain
Ear examination	Right EAC severely edematous, purulent discharge, membrane could not be evaluated	Granulation tissue in right EAC, membrane hyperemic and intact	granulation tissue, tympanic membrane not visible	Granulation tissue on left EAC base, tympanic membrane normal
Blood glucose level (mg/dL)	126	112	303	207
CRP (mg/L)	21.8	24.1	55.7	17.8
Hemoglobin (g/dL)	9.3	11.9	13.0	13.1
Creatinine (mg/dL)	2.60	1.64	1.75	1.85
Radiological findings	External ear canal, temporomandibular joint, middle ear, and mastoid were involved.	Disease propagated to the clivus, petrous apex, odontoid process, and parapharyngeal space.	External ear, middle ear, mastoid cells, and sigmoid sinus wall were involved.	Propagation to petrous apex, parapharyngeal fatty tissue, and carotid space.

CRP: C-reactive protein; EAC: External auditory canal.

While there was a reduction in edema and polypoid tissues in the external auditory canal, a follow-up MRI in the third week of hospitalization identified sinus thrombosis. Treatment with low-molecular-weight heparin was then initiated. Based on the culture results, Staphylococcus epidermidis was found to be susceptible to quinolones and sulbactam-ampicillin. Consequently, the antibiotic regimen was adjusted to include IV ciprofloxacin and ampicillin. The patient refused to undergo mastoidectomy and was referred for hyperbaric oxygen therapy. The insulin dose was increased. The blood glucose, clinical, and laboratory findings of both patients are presented in Table 1.

DISCUSSION

Numerous complications have been described both during and after a COVID infection. The combination of the virus's effect on cell-mediated immunity, immunocompromised comorbidities, and immune-suppressive treatment protocols creates optimal conditions for invasive bacterial or fungal infections. A COVID-19 infection can lead to significant and lasting lymphopenia, elevating the risk of opportunistic infections.[6] Mady et al.[7] reported a heightened incidence of otitis externa in patients with COVID-19 (18%) compared to those without (1% to 10%).

The pathophysiology of otitis externa in individuals with COVID-19 remains unclear. It could be directly related to the accumulation of immune complexes, or it might be associated with the presence of Angiotensin-Converting Enzyme 2 (ACE2) in the skin.[8] However, it remains challenging to pinpoint why this infection is particularly severe in the external ear canal based solely on ACE2 receptors. SBO is common among immunocompromised individuals, with diabetes serving as an independent risk factor.[5] The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) inherently diminishes Cluster of Differentiation 4 (CD4)-positive and Cluster of Differentiation 8 (CD8)-positive T cells.[9] This combination of factors places COVID-19 patients at an elevated risk for secondary infections. Symptoms of SBO are nonspecific and can be mistaken for malignancy. While CT is the preferred modality for evaluating bone erosion and decalcification, MRI is superior for identifying the anatomical location and spread of the infection.[8] Immediate antibiotic administration is critical, with antipseudomonal agents selected as first-line treatments. Moreover, rigorous ear dressing with antibiotic drops and boric acid was administered daily to eliminate ear discharge and sustain the acidic pH of the EAC. The primary cause of tissue necrosis is the microangiopathy of small vessels. The infection spreads to the dural sinuses and extends intracranially through venous circulation. Moreover,

necrotic changes in the bone reduce the effectiveness of antibiotics.[5] Consequently, anticoagulants should be incorporated into the treatment when necessary. We initiated low molecular weight heparin due to thrombotic foci in the sigmoid sinus in our patients. Regrettably, SBO is a deadly condition; hence, it must be diagnosed and treated promptly.[3] We recommend conducting CT and MRI scans promptly to detect bone damage and soft tissue infiltration, ensuring early diagnosis and treatment.

To the best of our knowledge, this study is the first to highlight the association between SBO and COVID-19 infection. Clinicians should be made aware of the characteristics of this rare yet potentially fatal condition to facilitate timely management during the ongoing pandemic.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept – ET, HCB, ED, SA; Design – ET, HCB, ED, SA; Supervision – ET, HCB, ED, SA; Resource – ET; Materials – ET; Data Collection and/or Processing – ET; Analysis and/or Interpretation – ET; Literature Search – ET, ED; Writing – ET; Critical Reviews – ET.

Conflict of Interest: The authors have no conflict of interest to declare.

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