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Case report

Skull base osteomyelitis: A case report of Garcin syndrome due to mucormycosis in COVID pandemic

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ABSTRACT

Garcin syndrome is characterized by progressive unilateral multiple cranial nerve palsy without the presence of intracranial hypertension. In this case, we present a patient who experienced lower cranial nerve (CN 9–12) involvement attributed to post-mucormycosis osteomyelitis of the skull base. The osteomyelitis resulting from mucormycosis led to the development of Garcin syndrome, which manifested as progressive paralysis of the cranial nerves. It is important to recognize this rare complication and consider it in the differential diagnosis when evaluating patients with lower cranial nerve palsy following mucormycosis-related skull base osteomyelitis.

Introduction

Mucormycosis, a lethal fungal infection, mostly involves immunocompromised patients. Factors affecting mortality rate include site of infection, underlying disease, anti-fungal treatment and organism species [1]. In recent years, it has become more prevalent among patients with covid-19 disease, who are vulnerable to opportunistic pathogens, partly due to excessive prescription of corticosteroids [2,3].

Mucormycosis can manifest with Rhino-orbital-cerebral (ROC) symptoms. In the Sino-nasal area, it may present with mucosal erythema, mucosal necrosis, facial pain, rhinorrhea, sinusitis, and decreased sensation in the cheek or frontal area. If the orbit is involved, symptoms such as ophthalmoplegia, reduced visual acuity or blindness, and periorbital swelling or pain may occur. Brain involvement can lead to brain abscess, cavernous sinus thrombosis, headache, stroke, and seizures [4,5].

Garcin syndrome is a progressive, unilateral multiple cranial nerve palsy that is not accompanied by intracranial hypertension. It was first described by Raymond Garcin in 1926. This condition is commonly associated with malignancies of the head and neck, resulting from slow

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localized tumor growth. On the other hand, mucormycosis is a rare cause of this syndrome [6,7].

We present a case of ROC mucormycosis with an uncommon cause of Garcin syndrome.

Case presentation

The case presentation was approved by the local ethics committee and the National Ministry of Health (license no. IR.TUMS.IKHC.REC.1401.084). Detailed information about the study was provided to the patient's wife, and informed written consent was obtained.

A 54-year-old man presented with a three-month history of headache during the fourth wave of the Delta variant of COVID-19 in Iran. The headache was progressively worsening and intensified during exertion or walking but improved when lying down. Additionally, for the past week, he had been experiencing speech difficulties, hypernasality, swallowing difficulties due to loss of gag reflex, and purulent otorrhea on the right side.

During detailed history taking, the patient did not mention any accompanying diseases, current medication consumption, trauma, or recent COVID-19 infection, despite receiving the Sinopharm vaccine. However, he did have a history of previously treated Tuberculosis and Brucellosis several years ago. Three months ago, during initial evaluations at another medical center, sphenoid sinusitis was detected. Despite receiving maximum medical treatment with antibiotics, the patient did not respond, leading to the decision of performing endoscopic endonasal sinus surgery. However, there were no obvious mucosal changes except for discharge from the sphenoid sinus. Histopathologic examination results showed no specific findings other than inflammation.

During the physical examination, the patient appeared ill but was conscious and oriented. There was no evidence of orbital involvement, and cranial nerve 7 (facial nerve) was intact. The patient presented with trismus (difficulty in opening the mouth) and unilateral deviation of the uvula to the left, indicating involvement of cranial nerves 9 (glossopharyngeal), 10 (vagus), and 12 (hypoglossal). Due to the patient's general condition, it was not possible to examine cranial nerve 11 (accessory nerve). Additionally, there was loss of sensation in the region innervated by the V2 branch of the trigeminal nerve (maxillary nerve), but no mucosal changes were observed in the palate or nasal cavity.

A comprehensive work-up was conducted, taking into account the differential diagnosis. The initial laboratory data showed anemia and elevated levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fasting blood sugar (FBS) at 229 (Table 1).

A brain CT scan was performed, which revealed a destructive lesion forming sequestration in the skull base. The lesion involved the clivus, occiput, greater wing, and pterygoid process of the left-sided sphenoid, indicating the presence of skull base osteomyelitis. Additionally, mucosal thickening was observed in the sphenoid sinus (Fig. 1).

To further evaluate the condition, a multiplanar contrast-enhanced brain MRI was conducted. The results showed abnormal bone marrow infiltration in the clival, skull base, and pterygoid plates, with the most prominent involvement on the left side. The post-contrast enhancement was heterogeneous, suggesting skull base osteomyelitis. However, the possibility of neoplastic infiltration could not be completely ruled out. Furthermore, the right cavernous sinus, Meckel's cave, and oval foramen showed involvement, and abnormal enhancement of leptomeninges and dura was observed (Fig. 2).

Table 1
Basic laboratory data of the patient.

Investigation	Result	reference range	Unit
HB	9.6	12–16	g/dl
WBC	5.6	4.0–10.0	* 1000/mm^3
ESR	80	male 0–50 yr < 15 male 51–85 yr < 20 male 86–100 yr < 30	mm/h
CRP	103	< 6.0	mg/l
UREA	35		
CR	0.7		
FBS	229	0.7–1.4 70–100	mg/l

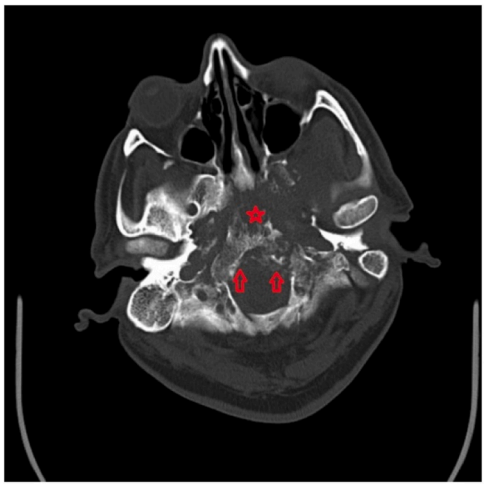


Fig. 1. Axial non-contrast CT scan of the skull base depicts bony attenuation and erosion of the clivus (red star), bilateral occipital condyles (red arrows), and the left greater sphenoid wing (brown arrows).

A cervical spine MRI study did not reveal any significant lesions. A neck MRV (Magnetic Resonance Venography) showed no evidence of thrombosis in the cervical venous system, and both jugular veins exhibited normal signal and diameter. A chest HRCT (High-Resolution Computed Tomography) scan did not show any remarkable findings.

Based on the imaging findings, osteomyelitis, tuberculosis (TB), and malignancy were considered more likely in the case of the patient, while fracture was ruled out. Mucormycosis was also considered as a possible differential diagnosis based on the patient's physical examination findings and the presence of the ongoing COVID-19 pandemic, along with the imaging data.

Due to the imaging findings and clinical presentation, the patient was admitted to the intensive care unit (ICU), where he gradually developed respiratory distress and required intubation. Neurosurgery and rhinology specialists consulted on the case and decided to perform skull base debridement and biopsy of the skull base lesion.

During endonasal endoscopy of the sinonasal cavity, the mucosa appeared normal without typical necrosis, except for the presence of purulent discharge from the sphenoid sinuses. Using the endoscopic endonasal trans-pterygoid approach, all the necrotic bone involved in the pterygoid palates, greater and lesser wings of the sphenoid, and clivus were resected extradurally. Macroscopically, the involved bone exhibited typical necrosis characteristic of an increasing number of mucormycosis cases. Additionally, through the endoscopic endonasal access to the craniovertebral junction, the remaining necrotic bone and sequestra, including the occipital condyles, were resected extradurally. The dura appeared thick and had adjacent granulation tissue near the involved bone. No cerebrospinal fluid (CSF) leak was observed, and considering the infectious nature of the disease, no reconstruction was performed.

Following the surgery, a tracheostomy was performed, and the patient's neck was stabilized using a collar. The day after the surgery, a percutaneous endoscopic gastrostomy (PEG) tube was inserted to provide nutritional support.

Surprisingly, both the KOH smear and culture of the surgical tissue sample revealed the presence of aseptate hyphae, consistent with Mucormycosis. The histopathologic examination confirmed the angioinvasion by fungal hyphae, further confirming the diagnosis

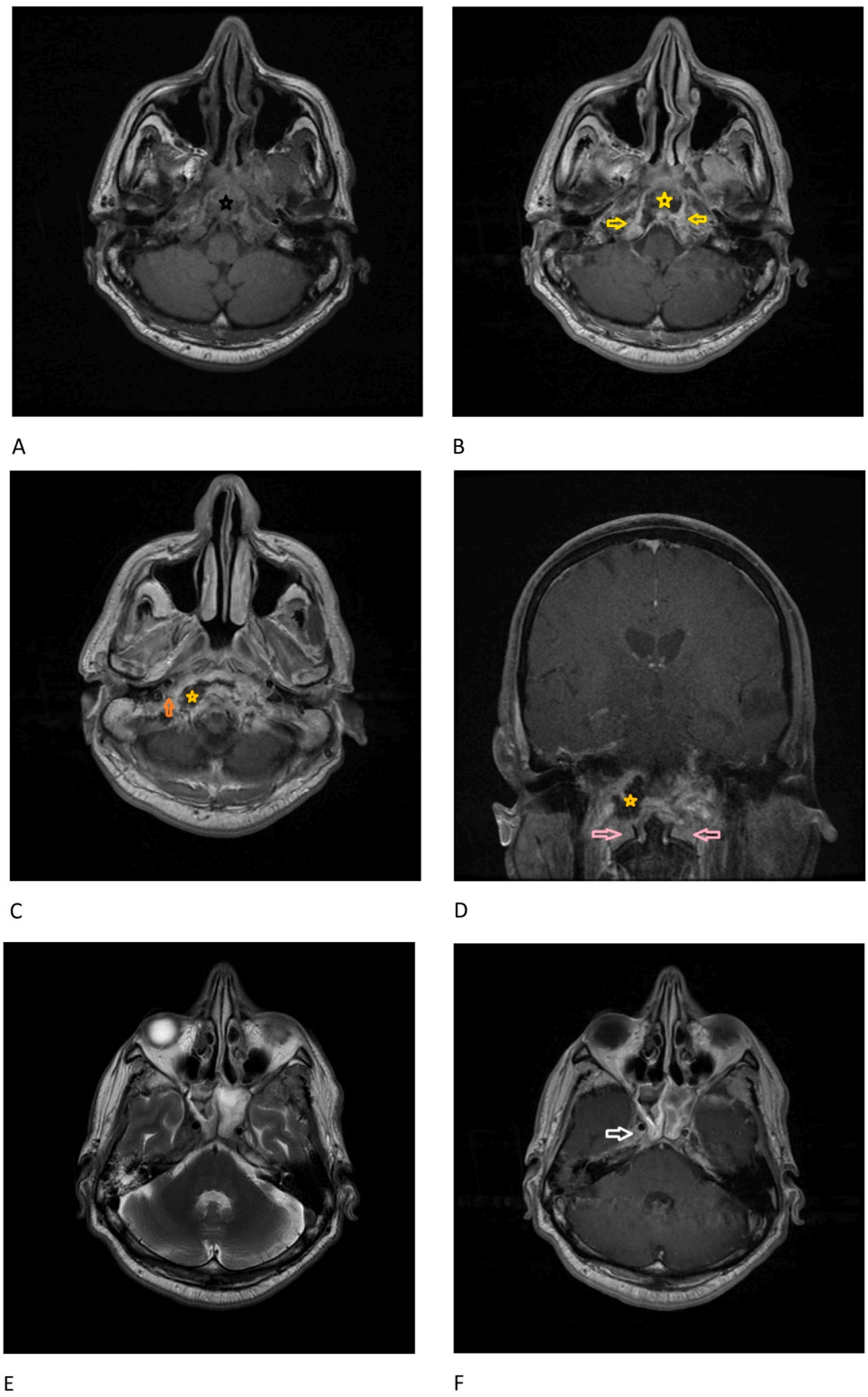


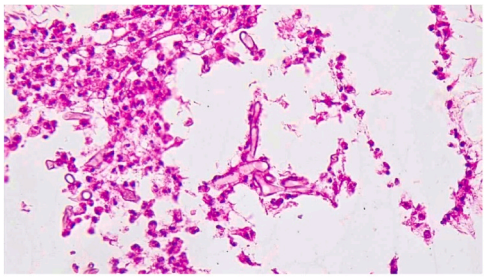
Fig. 2. Axial non-contrast and contrast-enhanced T1-weighted MR images of the skull base reveal replacement of normal fatty marrow in clivus with heterogenous low signal (black star) that depict hyperenhancement in peripheral parts (yellow arrows) and non-enhancing irregular areas in the center (yellow star) implying necrosis (A,B). Axial and coronal contrast-enhanced T1-weighted image at a lower level (C,D) show extension of necrosis to the right occipital condyle that contains hypoglossal canal (gold star), abnormal enhancing tissue at the right jugular fossa(orange arrow) and abnormal diffuse enhancement in the C1 (pink arrows). Axial T2-weighted and contrast-enhanced T1-weighted brain MRI (E,F) depicts the replacement of the normal CSF signal of Meckels cave with enhancing tissue on the right side (white arrows).

(Fig. 3).

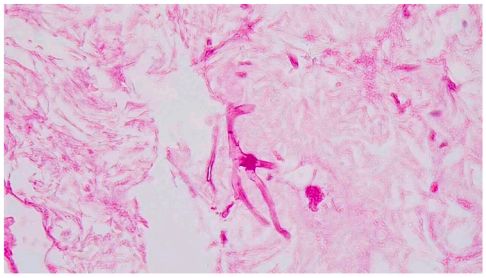
The patient received amphotericin B treatment for 38 days following the surgery. After spending 12 days in the ICU, the patient regained consciousness and achieved physical stability, leading to a transfer to the ward. However, he developed high blood sugar levels and was diagnosed with new-onset diabetes. Unfortunately, after 30 days, his general condition deteriorated due to uremia, due to acute renal injury (AKI), and he passed away 8 days later.

Discussion

During the COVID-19 pandemic, Mucormycosis infection became more prevalent, primarily due to several factors. Firstly, the hyperglycemic state induced by the Delta variant of COVID-19 contributed to an increased susceptibility to Mucormycosis. Additionally, the widespread prescription of corticosteroids and immunosuppressive agents to manage inflammatory conditions associated with COVID-19 played a



(A)



(B)

Fig. 3. (A and B): × 400 magnification, Hematoxylin and Eosin stain. Under microscopic examination infiltration of fungal elements with broad pauci-septate hyphae and irregular branching at 90° angles is seen.

role in weakening the immune system. Furthermore, the disease itself has an immunosuppressive nature, further increasing the risk of Mucormycosis infection [3].

In cases of progressive aggressive rhinocerebral mucormycosis, involvement of the cavernous sinus can lead to paralysis of cranial nerves III–VI [3]. However, facial nerve palsy is considered a rare occurrence in these cases.

When encountering lower cranial nerve palsy, it is essential to consider and rule out various other potential causes. Neoplasms located in the posterior fossa, vascular malformations at the base of the skull, traumatic injuries, brainstem infarction, and degenerative disorders like amyotrophic lateral sclerosis should be considered and evaluated [8]. Skull base osteomyelitis and Garcin syndrome are rare conditions that can also lead to cranial nerve palsy. According to Garcin, nearly all cranial nerves can be involved in Garcin syndrome [6].

There have been reports of skull base osteomyelitis resulting from mucormycosis, with involvement observed in various areas such as the maxillary bone [9], orbits, infratemporal fossa and parapharyngeal space [10], nasopharynx [11], and temporal bone [12]. However, in our patient, the initial presenting symptom was lower cranial nerve paralysis, without typical necrosis of the paranasal sinus mucosa or orbital involvement. Instead, aggressive osteolytic lesions were evident in the sphenoid, clivus, and C1 bone on imaging studies.

The standard treatment approach for mucormycosis involves a combination of systemic antifungal therapy, extensive debridement of necrotic tissue, and addressing the underlying disease if possible, especially when diagnosed early [13].

In our case, based on the physical examination findings and radiologic features, it was determined that the lower cranial nerves, including nerves IX, X, and XII, as well as the nerves in Meckel's cave, were involved. Garcin syndrome associated with mucormycosis has been reported in several previous cases. These include a 47-year-old man who initially presented with symptoms of phonophobia, photophobia, and headache [14], a case with infiltration of mucormycosis into the dura mater and intact skull bone [15], a 45-year-old woman with diabetes mellitus and hypertension who experienced unilateral cranial nerve palsy [7], a patient with a history of pulmonary tuberculosis, diabetes mellitus, and hypertension with involvement of eight cranial nerves (excluding I, II, VIII, and XI) [16], and a 60-year-old poorly controlled diabetic man with a history of hepatitis B and nephropathy who presented with cranial nerve (CN) IX, X, and XII palsy [8].

Although treatment was initiated promptly upon confirmation of the diagnosis, unfortunately, our patient succumbed to complications associated with the disease.

Tuberculosis can indeed be a leading cause of misdiagnosis in cases of cranial nerve palsy. Yang et al. reported a case of tuberculosis meningitis presenting with cranial nerve palsy and low-grade fever, where pansinusitis was observed on imaging [16]. However, in the case of our patient, although tuberculosis was initially considered as a possible diagnosis due to the past medical history, further imaging studies and laboratory tests excluded tuberculosis as the cause of the symptoms.

Conclusion

In cases of unilateral progressive cranial nerve palsy, particularly in immunocompromised or diabetic patients, it is important to consider Garcin syndrome as a potential manifestation of mucormycosis. Prompt diagnosis and treatment are crucial in this life-threatening condition. To aid in the exclusion or confirmation of Garcin syndrome, appropriate laboratory tests, imaging studies, and histological examination of tissue samples should be conducted. Early detection and intervention are essential to improve patient outcomes and prevent further complications associated with mucormycosis.

CRediT authorship contribution statement

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing, others, who have contributed in other ways should be listed as contributors.

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Ethical approval

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Consent

Informed consent was taken that is sent to journal.

Conflicts of interest

There is no conflict of interest.

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