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Case Report

COVID-19 Associated Rhino-Orbital-Cerebral Mucormycosis: A Case Series

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Abstract

Rhino-orbital-cerebral mucormycosis is a unique secondary infection of COVID-19 pneumonia. We reported 2 cases diagnosed with COVID-19 pneumonia with polymerase chain reaction (PCR) test, presented with orbital swelling and ptosis without any nasal symptoms. Both patients were immunocompetent, except with a history of prolonged use of oral glucocorticoid as part of COVID-19 pneumonia treatment. Contrast-enhanced computed tomography noted skull base osteomyelitis and temporal subdural empyema. They were diagnosed with mucormycosis by either fungal PCR or tissue histopathology examination that shown to have fungal hyphae. Both cases have resolution of the symptoms after surgical debridement and at least 6 weeks of antimicrobial therapy. We discuss the contributary factors of secondary fungal infection related to COVID-19 as well as the uniqueness in these cases in term of clinical presentations and the disease progression.

Keywords: COVID 19, Mucormycosis, Fungal infection

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Coronavirus disease (COVID-19) caused by SARS-CoV-2 virus has greatly impacted human life. In many countries, there was additional challenge on top of COVID-19 infection, whereby the survivors from the first hit of COVID-19 pneumonia itself now suffered from secondary infections which were hitherto recognized only as opportunistic infections secondary to significant immunocompromise.

A significant number of patients affected with COVID-19 had mucormycosis with involvement predominantly at rhino-orbital region followed by cerebral region and pulmonary system.[1] Diabetes Mellitus is recognized as single most important risk factor associated with the disease.[2,3] While such condition was not similarly seen in any other countries, we had since seen more than a couple of mucormycosis cases with rhino-orbital-cerebral involvement within a month in Malaysia whereby it would not be so in pre-pandemic times.

Case Report

Case 1 – A 63-year-old female with no comorbidities presented with sudden onset left eye swelling associated with ptosis and blurring of vision on day 20 after being diagnosed with COVID-19 pneumonia verified with polymerase

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chain reaction (PCR) test. Besides anosmia, which was eventually attributed to COVID-19, she had no other nasal symptoms like nasal congestion, cacosmia, discolored nasal discharge or facial pain. She had no headache or other neurological deficit at presentation. She had history of being treated with oral prednisolone for a total of 17 days as part of her treatment for COVID-19 pneumonia.

Examination revealed a left periorbital swelling mainly over temporal part, which was erythematous, tender, and fluctuant, associated with partial ptosis and chemosis. The visual acuity was unaffected. Nasoendoscopy showed she had left polypoidal mass obliterating the entire osteomeatal complex (OMC) with posterior dripping of mucoid discharge.

A contrast-enhanced computed tomography paranasal sinus (CECT PNS) and orbit showed mucosal thickening involving the left frontal sinus, left ethmoid sinus, left maxillary sinus as well as left sphenoid sinus. The left maxillary sinus was mostly affected with complete opacification of the entire sinus cavity without bony erosion. Besides that, there was left eye subperiosteal abscess at the roof and lateral wall of orbit with 0.6 cm in maximum thickness.

She underwent emergency endoscopy sinus drainage as well as open incision and drainage of the left eye subperiosteal abscess. Intraoperatively there was 1cc pus drained, but the standard panel of bacterial culture showed no growth. There were nasal polyps from the left maxillary and ethmoid sinus with mucoid discharge mixed with whitish fungal material. Nasal tissue culture was negative for bacterial and mycobacterial staining and culture.

Intraoperative specimen histopathology examination (HPE) reported as inflammatory polyps with fungal infection. Post operatively she recovered well with intranasal corticosteroid and alkaline nasal rinse. Unfortunately, after 5 months later, she came back with left frontal headache and purulent discharge from the left supraorbital wound site. CECT scan showed opacity at left frontal and maxillary sinus with bony erosion to the left lateral frontal bone representing osteomyelitis of the frontal bone (Fig. 1).

Subsequently, an emergency debridement via left frontal craniotomy, left frontal sinus cranialisation with fascia duraplasty was performed. Intraoperatively there was osteomyelitic changes at left frontal bone (Fig. 2) and evidence of pus collection inside the diploic bone extending to the lateral part of frontal sinus and left temporal bone. The unhealthy bone and tissue were debrided.

The bony tissue HPE reported inflammation with foreign body response while the pus culture yielded *Pseudomonas aeruginosa*. A revision endoscopic sinus surgery was also performed on the same setting to remove the polypoidal mucosa obliterating the OMC and the HPE reported inflammatory polyp with the presence of fungal hyphae and yeast. She was treated with IV ceftazidime for 6 weeks in wad as decided by infectious disease team to clear the Pseudomonas infection from the skull base. She was found to have resolution of all symptoms at 3 months post op review in outpatient clinic.

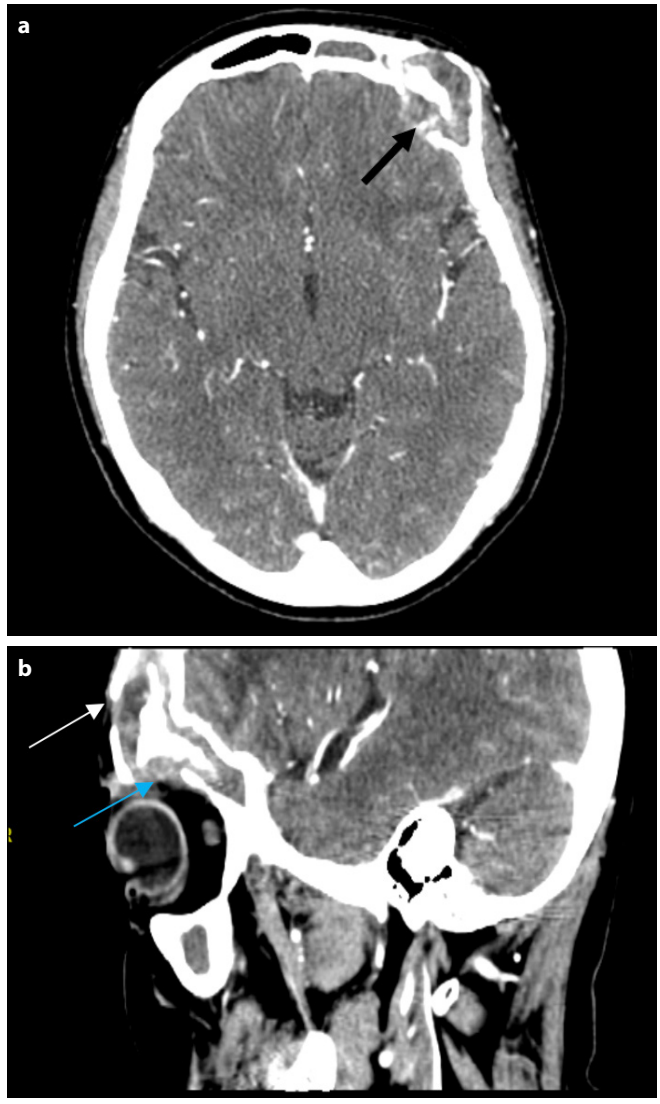

Figure 1 (a, b). Opacification of left frontal sinus with present of calcification within it. Black arrow shows erosion of inner table of frontal sinus. White arrow shows erosion of outer table of frontal sinus. Blue arrow shows erosion of the roof of orbit.

Case 2 – A 61-year-old man with no comorbidity presented with sudden onset right eye swelling associated with ptosis and blurring of vision at day 24 after diagnosed with COVID-19 pneumonia confirmed with a positive PCR test. He had no nasal symptoms like anosmia, congestion, cacosmia, discolored nasal discharge or facial pain. He also had right temporal headache but no other neurological symptoms. He had history of being treated with oral prednisolone for a total of 5 weeks as part of his treatment for CO-

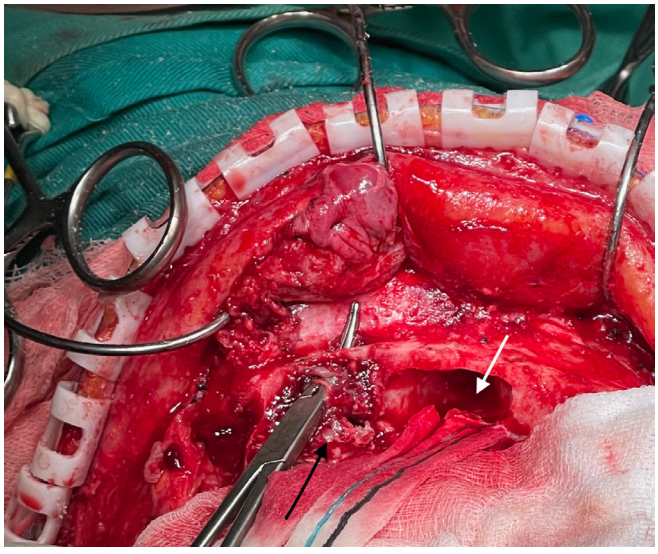

Figure 2. The lateral part of left frontal sinus (black arrow) with the presence of necrotic tissue extending through the dehiscent part of frontal bone (passed through by the artery forceps) to the subperiosteal region. The medial part of left frontal sinus (white arrow) is normal.

VID-19 pneumonia.

Examination showed diffuse right peri-orbital erythematous swelling, which was tender, soft, but not fluctuant. The vision was unaffected, and he was diagnosed with preseptal cellulitis. Nasoendoscopy showed there was a small polypoidal tissue protruding from right sphenoid ostium.

Contrasted CT brain complimented with magnetic resonance imaging (MRI) showed subdural empyema at right temporal region. There was right sphenoiditis with bony erosion at right lateral sphenoid wall, right temporal bone, greater wing of right sphenoid bone, right frontal bone and skull base representing osteomyelitic process (Fig. 3).

Figure 3 shows Opacification of right sphenoid sinus with bony erosion of lateral sphenoid wall (orange arrow), right temporal bone (black arrow) and greater wing of right sphenoid bone (blue arrow).

He was empirically started with IV ceftriaxone for presumed bacterial sinusitis. During the right endoscopic transnasal sphenoidotomy, the polypoidal tissue was removed from the sphenoid ostium to reveal whitish chalky fungal material. The polypidal tissue that sent for fungal PCR reported to have *Rhizopus microsporus*. Pus and tissue bacterial culture reported no growth.

At the point of time when the fungal PCR resulted, patient had already given IV antibiotic for 2 weeks and he had resolution of all symptoms. He however refused neurosurgical intervention for his subdural lesion and took discharge against medical advice hence IV amphotericin was never started. The patient remained well with completely

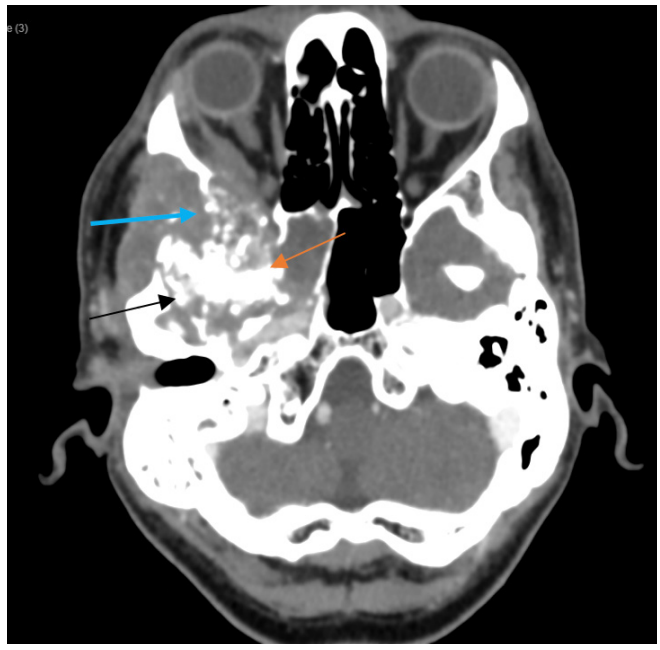

Figure 3. Opacification of right sphenoid sinus with bony erosion of lateral sphenoid wall (orange arrow), right temporal bone (black arrow) and greater wing of right sphenoid bone (blue arrow).

resolved symptoms during his most recent follow-up at 5 months post sphenoidotomy.

Discussion

Ever since glucocorticoid treatment was found to reduce mortality in hypoxemic COVID-19 pneumonia patients, it has been a mainstay in treatment worldwide.[4] Unfortunately, the widespread usage of such immunosuppressive treatment also saw a surge in cases of secondary infection, be it fungal or bacterial. This is relevant to both our cases whereby both had history of receiving oral glucocorticoid for prolonged period due to covid pneumonia. Corticosteroid therapy might also induce a hyperglycemic state at least during the period of treatment, which rendered the patients immunosuppressed. Hyperglycemia or diabetes mellitus is the most reported risk factor in coronavirus-linked microcytosis.[3] However, this does not occur in both of our cases as their glucose level were normal throughout the monitoring in wad.

Besides glucocorticoid related immune suppression, coronavirus disease itself also lead to immune dysfunction by affecting T lymphocyte especially CD4+ and CD8+ T cells which lead to lymphopenia and immunosuppression.[5] The hyperinflammation state of coronavirus disease also lead to hyperferritinaemia whereby the free iron can capture siderophores and helps in the growth of fungus especially Mucorales.[6] This explains the favoritism of secondary in-

fection by fungus in COVID19 patient which are also present in our case series.

Hypoxia as a consequence of COVID-19 pneumonia also is an important risk factor that promote secondary fungal infection especially Mucorales as it creates an ideal environment for the fungus to growth.[7] Both of our cases have significant hypoxia due to COVID-19 pneumonia.

In terms of clinical feature, nasal congestion, facial pain and nasal discharge are the early signs for rhino-orbital-cerebral mucormycosis.[8] Surprisingly, this doesn't occur in both of our cases as they have no noticeable nasal symptoms as well as no facial pain. Both cases share the similarity of orbital symptoms, such as peri-orbital swelling, partial ptosis and blurring of vision, came in as the earliest presenting symptoms. As the disease progress to skull base or brain, they developed headache. The involvement of sinuses in COVID-19 associated mucormycosis is heterogeneous in most of the existing literature and this also appear to the same in our series whereby one of the cases affected predominantly anterior group of paranasal sinus namely maxillary, ethmoid, and frontal sinus, and the other case only affect sphenoid sinus.

Orbital complications of rhinosinusitis usually occur in pediatric age group rather than adult.[9] This is because the boundary between orbit and nasal cavity (lamina papyracea) is thinner in children and this facilitates the spread of infection from ethmoid sinus to orbit.[9] Nevertheless, the first case in our series developed right eye subperiosteal abscess due to ethmoid sinus involvement. This shows the secondary infection precipitated by the above-mentioned factors has result in significant inflammation, spreading through the thicker lamina papyracea in adult leading to abscess formation. Typically, orbital complication occurs in acute form of rhinosinusitis rather than chronic rhinosinusitis.[9] The first case in the series has nasal polyps signify chronic rhinosinusitis, but he developed subperiosteal abscess of right eye properly can be explained by acute in chronic rhinosinusitis precipitated by secondary fungal infection and pseudomonas infection linked to COVID-19-related immunosuppression.

Skull base osteomyelitis is a serious and recognized complication of rhinosinusitis typically occur in acute setting.[9] After functional endoscopic sinus surgery for chronic form of rhinosinusitis, the first case patient came back again with osteomyelitis involving the lateral wall of frontal sinus in continuation with ipsilateral temporal bone. However, the frontal sinus outflow tract was found to be normal intraoperatively signifies the skull base osteomyelitis is not related to rhinosinusitis but rather an acute, sporadic form of fungal osteomyelitis of skull bone probably secondary to COVID-19-linked immune dysfunction, glucocorticoid related immunosuppression or other fungal promoting growth factors as discussed above.

The second case had temporal subdural empyema with extensive osteomyelitis involving temporal bone extending from sphenoid bone caused by acute sphenoid sinusitis. Being the commonest intracranial complication, subdural empyema is usually occur in frontal sinusitis.[9] But this can occur in with acute sphenoid sinusitis as in our second case.

Mucormycosis is an extraordinary uncommon fungal infection caused by the fungi of order Mucorales. Mucorales species are Rhizopus (the most common genus associated with mucormycosis), Lichtheimia and Mucor.[2] Fungal infection among COVID-19 patients can be diagnosed by several methods. HPE is the most sensitive method and fungal culture being the least sensitive method of identification.[1] This finding is consistent with the first case in our series whereby the patient had fungal hyphae and yeast present in HPE but the fungal culture was negative. The second case had neither HPE evidence of fungal infection nor culture growth of fungus, but fungal PCR was positive for Rhizopus microspores. Hence, fungal PCR has its role in in suspected fungal infection especially in patients with history of COVID-19 infection if the HPE and conventional fungal culture were negative.

Timely management of COVID-19-associated rhino-orbital-cerebral mucormycosis is important to firstly limit the damage caused, and secondly to avoid further vital organ failure such as blindness and loss of brain function and neurological deficit or even death. Antifungal therapy and surgical debridement are the mainstay treatment to improve survival rate.[8] A study in India with 187 cases of COVID-19 with mucormycosis, 70.1% patients are treated with antifungal as well as surgery, yet the mortality rate is significant which 44.1 % death within 3 months.[1] In our series, IV antifungal was not initiated for both cases due to resolution of symptoms, even before the laboratory results come back with evidence of fungal infection, hence the joined decision with infections disease (ID) team is no need to start IV antifungal. However, both patients did somewhat recover from the acute illness, partly due to early detection and treatment. While antifungal treatment is essential for extensive disease, early disease as in our series, can probably be managed without it, provided good clinical control of the disease.

Conclusion

COVID-19 associated rhino-orbital-cerebral infection is a unique secondary infection caused by glucocorticoid related immunosuppression, COVID-19-induced immune dys-

function, as well as fungal growth promoting factors such hypoxemia as a result of pneumonia. There is not particular group of paranasal sinus is prone to this disease. Patients can have COVID-19-associated rhino-orbital -cerebral infection even without noticeable nasal symptoms and further workout with imaging study is needed if such condition is suspected. Early detection and timely treatment of the disease are important to ensure survive and prevent full bloom complication of the disease.

Disclosures

Informed Consent: Written informed consent was obtained from the patients for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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