Post COVID-19 Recovery- A Focus on Opportunistic Infections of Maxillofacial Region: Report of Two Cases

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Abstract: Severe acute respiratory syndrome coronavirus 2 infection might induce a significant and sustained lymphopenia, increasing the risk of developing opportunistic infections. We present our clinical experience with two cases of opportunistic infections with mucormycosis and actinomycosis leading to maxillary osteomyelitis in patients associated with uncontrolled diabetes mellitus in post-covid-19 status. One out of two cases had received steroid therapy during the treatment of COVID-19. Both the cases have a history of tooth extraction, following which they developed swelling over cheeks associated with nasal and intra-oral purulent discharge. On CT face, both the cases showed similar features of fungal osteomyelitis. But, when an incisional biopsy was performed, the first case revealed large, non-septate hyphae with 90° branching suggesting mucormycosis, whereas the second case showed inflammatory lesions suggestive of actinomycosis. Both the patients were later managed with oral antibiotics and planned for surgery. These cases highlight coronavirus might impair the immune response, exposing patients to a higher risk of developing opportunistic infections and hence the knowledge about the involvement of a wide spectrum of opportunistic microbes helps the surgeon in planning the surgery ranging from a more aggressive approach for fungal infections to less invasive management for bacterial infections.

Keywords: COVID-19, Mucormycosis, Osteomyelitis, Opportunistic infections, Actinomycosis.

INTRODUCTION

Opportunistic Infections are defined as, infections occurring due to bacteria, fungi, viruses, or parasites that normally do not cause a disease, but become pathogenic when the body's defense system is impaired. The immune dysregulation associated with COVID-19, with reduced numbers of T lymphocytes, CD4+T, and CD8+T cells, may alter innate immunity, exposing to opportunistic infections [1]. Mucormycosis is a rare opportunistic infection invariably affecting immunocompromised patients. The organism implicated to cause mucormycosis is a saprophytic fungus, mainly rhizopus or mucor. It is the most deadly and rapidly progressive form of fungal infection affecting humans [2]. Actinomycosis is also a rare disease favored by disruption of the mucosal barrier. The genus Actinomyces is a heterogeneous group of gram-positive bacteria, mainly anaerobic facultative or microaerophilic rods with various degrees of branching. Actinomyces species are frequently found as members of the normal microbiota in open cavities, especially the oropharynx, upper respiratory tract, gastrointestinal tract, and female genital tract. Various risk factors involved in the development of these opportunistic infections are tooth extraction, trauma, surgical therapy, radiation and systemic conditions such as diabetes, malignancy, anaemia, malnutrition, osteoporosis, osteopetrosis, and Paget’s disease [3].

CASE REPORT

Case report 1

A 47-year-old male patient reported with swelling in the left middle third of the face since 2 months, associated with pus discharge from the left upper teeth region since 15 days. The patient gave a history of extraction of teeth 23, 24,
and 25; 45 days ago due to pain and discharge. The patient was a known case of diabetic since 2 months and was on oral hypoglycemics, but with fasting blood sugar levels as high as 237mg/dl. Also, he gave a history of COVID-19 infection 1 month ago and he had not received any treatment for COVID-19. On extraoral examination, a diffuse swelling approximately 6cms x 6cms over the left middle third of the face with mild proptosis of the left eye and ptosis of the upper eyelid was evident (Figure 1). No loss of vision. Intraoral examination showed denuded necrotic alveolar bone from the left canine to the first molar region, crossing the midline up to 1cm and extending posteriorly to the junction of the hard and soft palate (Figure 2). Pus discharge with segmental mobility was evident in relation to 23 to 25 region. Complete blood count revealed neutrophil to lymphocyte ratio value of 11. The CT scans revealed erosion of superior alveolus on either side, anterior aspect of the hard palate, anterior and lateral walls of the left maxillary sinus extending to the floor of the left orbit including left zygoma, left lesser and greater wings of sphenoid, left medial and lateral pterygoid plates suggesting chronic osteomyelitis (Figure 3). Incisional biopsy revealed large, non-septate hyphae with 90° branching suggesting mucormycosis with areas of necrosis and hemorrhage (Figure 4) and large, aseptate hyphae with areas of necrosis and hemorrhage (Figure 5).
Case report 2

A 38-year-old male diabetic patient reported with swelling over the right side of the face since 2 months. He gave a history of COVID-19 three months ago and a history of teeth extraction due to pain in the upper right quadrant 5 days after the hospital discharge. On extraoral examination, a diffuse swelling was seen approximately 4cms x 5 cms over the right middle third of the face with paraesthesia over the right cheek and right lateral wall of the nose (Figure 6). On intraoral examination, bony exposure was evident at the upper right vestibular region extending from maxillary tuberosity to 13 region with irregular borders and erythematous margins associated with pus discharge (Figure 7). CT face revealed deossification and erosive changes at the right maxillary alveolus, medial and postero-lateral walls of the right maxillary sinus. Also, erosive changes were noted in the right pterygoid body suggesting fungal osteomyelitis (Figure 8). But, interestingly incisional biopsy revealed acute on chronic inflammatory lesion (Figure 9) with bacterial colonies suggested of actinomycosis (Figure 10). Oral Clindamycin 300mg for a week and chlorhexidine mouthwash were advised until the histopathology report arrived. Partial maxillectomy was planned, but the intraoperative finding was suggestive of the intact maxilla and hence only the curettage of the lesion was done and the specimen was sent for histopathological examination. Post operatively patient was given intravenous inj. Imipenem 500mg for 4 days and inj. Ceftriaxone 1g for a week. Histopathological examination revealed chronic nonspecific inflammatory lesions with granulation tissue. The patient recovered well and is being followed up with regular imaging.
DISCUSSION

Coronavirus disease 2019 (COVID-19) infection may be associated with a wide range of bacterial and fungal co-infections. There are specific pathophysiologic features of COVID-19 that may permit secondary or opportunistic infections, including a propensity to cause extensive pulmonary disease and the subsequent alveolo-interstitial pathology that may enhance the risk of opportunistic infections. Second, the immune dysregulation associated with COVID-19, with reduced numbers of T lymphocytes, CD4+T, and CD8+T cells, may alter innate immunity [4]. High risk individuals include critically ill-patients, patients on mechanical ventilation and those with longer hospital stay are more likely to develop fungal co-infection[5]. Hence, it is important to notice that COVID-19 patients can develop further opportunistic infections during the middle and latter stages of this disease. And lastly, glucocorticoids have been used extensively to reduce hospital stay and mortality related to Covid-19. Dexamethasone and methylprednisolone have both been...
incorporated into most protocols in COVID-19 infection especially in moderate to severe cases [6]. The immunosuppressive nature of glucocorticoids, makes the patients more prone to secondary infections. Even though steroids was not administered in our case 1, he developed mucormycosis and the case 2 who had received dexamethasone during his treatment for COVID-19 developed actinomycosis.

Osteomyelitis occurring due to fungal infection is rare and occurs in an indolent manner. Osteomyelitis is commonly seen in males (80.36%) than in females (19.64%), with a peak incidence in 30–39 years of age[7]. The maxilla is the most common jaw bone being affected by fungal osteomyelitis and is more commonly associated with diabetes mellitus. Among fungal osteomyelitis, Candida is the most commonly encountered followed by aspergillosis and mucormycosis. These organisms are from an original infection that has not been treated properly, commonly from dental extraction [8]. Niranjan et al., in their ten-year study reported that 52% of all the osteomyelitis cases were that of fungal osteomyelitis, whereas 48% belonged to the nonfungal category [9].

The manifestations of mucormycosis include cutaneous, gastrointestinal, pulmonary, and disseminated forms; however, rhinocerebral mucormycosis, involving the nose, paranasal sinuses, orbit, and central nervous system, is the most common and has been subclassified into rhinomaxillary and rhinocerebral/oral mucormycosis. Malaise, headache, swelling, facial pain, and mild fever are common clinical symptoms of rhinocerebral mucormycosis. Clinical features of osteomyelitis may include local pain, fever, swelling, purulent discharge, intra-oral and skin fistula, the unhealed soft tissue in the oral cavity, paraesthesia in the involved area, pathological fracture, and trismus[10].

For the detection of mucormycosis, CT is the initial imaging method generally selected. However, CT findings can be non-specific in the early stages of disease; even if a patient is infected with invasive mucormycosis, they can present a normal sinus on a CT scan. Bone erosion and extra sinus spread are distinct features of mucormycosis and therefore comprise strong evidence for its diagnosis [11]. Histopathologically, the lesion demonstrates broad aseptate fungal hyphae that show branching at right angles [12]. As per the guidelines from the 3rd European Conference on Infections in Leukemia, the first line treatment of mucormycosis is depicted in Table 1[13].

<table>
<thead>
<tr>
<th>First line of treatment</th>
<th>Second line of treatment</th>
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<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>Posaconazole 400 mg bid</td>
</tr>
<tr>
<td>Liposomal Amphotericin B 5–10 mg/Kg</td>
<td>Combination lipid Amphotericin B and caspofungin</td>
</tr>
<tr>
<td>Posaconazole 400 mg bid</td>
<td>Combination lipid Amphotericin B and posaconazole</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>Combination deferasirox not recommended</td>
</tr>
<tr>
<td>Control of the underlying condition</td>
<td>Maintenance therapy Posaconazole</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
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<tr>
<td>Hyperbaric oxygen therapy</td>
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Actinomycoses are part of the normal flora commonly seen in the human oral cavity, female urogenital tract, and GI tract. The organism has low virulence and only invades the body to cause deep-seated infections when there is tissue injury or following a break in the normal mucosal barrier. Infection is mostly polymicrobial, established with the help of a companion bacteria by inhibiting host defense, reducing oxygen tension, or by toxin production which facilitates the inoculation of actinomycoses [14].

The infection sets in after a breach in the mucosal barrier, the human host responds by initiating an intense inflammatory response which is supplicative and granulomatous. The infection spreads contiguously irrespective of tissue planes which present with draining sinus tracts, discharge of sulfur granules, and lead to intense fibrosis of tissue. Different species of Actinomycoses include Actinomyces israelii, Actinomyces naeslundii, Actinomyces viscous, and Actinomyces odontolyticus among which Actinomyces israelii is the most common. The predisposing risk factors are infection in erupting teeth, dental caries, gingivitis, and dental extraction, diabetes, alcohol use disorder, malnutrition, and malignancy. In the present case, it was due to dental extraction. Imaging findings are nonspecific and are non-contributory in diagnosing the disease but will help in assessing the degree of soft tissue and bone involvement. CT and MRI studies may show osteolytic changes in the chronic form of infection. Antibiotics remain the mainstay of treatment. Surgery can be an adjunctive procedure.

Medical management in the form of antibiotics is depicted in table 2. The duration of therapy is usually 6 to 12 months but can be shortened if surgical resection of the infected site has been performed. The type of surgery will depend upon the site and extent of the disease, but it usually involves incision and drainage of abscesses, curettage, decompression of closed space, and excision of sinus tracts.
Table-2

<table>
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<tr>
<th>Penicillin G</th>
<th>Clindamycin</th>
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| Beta-lactams with a long course of oral amoxicillin | • Macrolides. (erythromycin, clarithromycin, or azithromycin)  
• Doxycycline. |
| Cephalosporin | A combination of metronidazole and a beta-lactamase inhibitor may be tried in polymicrobial infections. |

**CONCLUSION**

In conclusion, these cases highlight that new coronavirus might impair the immune response, exposing patients to a higher risk of developing opportunistic infections and hence the knowledge about the involvement of a wide spectrum of opportunistic microbes helps the surgeon in planning the surgery ranging from the more aggressive approach for fungal infections to less invasive management for bacterial infections.

**REFERENCES**
