The Risk of Osseointegration in the Coronavirus Disease 19 Pandemic

*Gabriel Mulinari-Santos, PhD,**
Amanda Paino-Sant'Ana†, Roberta Okamoto, PhD,†
Juliana Zorzi Coléte, PhD, and João Lopes Toledo Neto, PhD**

Abstract: Coronavirus disease 19 (COVID-19) is associated with respiratory complications but also with alterations on bone metabolism. Coronavirus disease 19, therefore, might be a risk factor for osseointegration. Recent studies suggest that severe acute respiratory syndrome coronavirus 2 is related with bone abnormalities mainly for act via renin-angiotensin system. This report aims to list the bone alterations caused by coronavirus disease 19 and the possible consequences on the peri-implant bone healing. The current data add to the accumulating knowledge that coronavirus disease 19 may negatively impact the osseointegration and it requires further research.

Key Words: Bone, COVID-19, osseointegration, renin–angiotensin system

BRIEF REPORT

Coronavirus disease 2019 (COVID-19) is a major risk factor for respiratory death worldwide, mainly for causing pulmonary complications such as pneumonia and acute respiratory failure. In addition, patients with COVID-19 are already associated with low serum calcium level,[1] decreased bone mineral density[2] and osteonecrosis.[3] Given the search of a favorable bone for implant placement, it is crucial to understand the consequences of COVID-19 on bone metabolism. Even though there is a lack of studies identifying COVID-19 as a risk factor in implantology.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus strain affect enzyme angiotensin-converting enzyme 2 (ACE2) expressed in epithelial cells of the respiratory tissues.[3] Besides the lungs, osteoblasts and osteoclasts express ACE2 on bone tissue.[4] Severe acute respiratory syndrome coronavirus 2infection causes deficiency of ACE2 and low production of Ang-(1−7).[3] Angiotensin-converting enzyme 2 downregulates angiotensin II (Ang II) and synthetizes Ang-(1−7).[3] Angiotensin II is responsible for bone reabsorption[5] and Ang-(1−7) has essential function to maintaining bone structure.[4] Consequently, ACE2 targeted by severe acute respiratory syndrome coronavirus 2may decrease bone mass. Thus, the depletion of ACE2 on bone tissue could impair osseointegration.

Another point, severe hypocalcaemia was highly prevalent in severe acute respiratory syndrome patients.[1] Thus, it could implicate a down regulation of calcium delivered during the osseointegration. Furthermore, COVID-19 promotes an excessive inflammation by proinflammation cytokines as interleukin-1, interleukin-6, and tumor necrosis factor α.[6] In attempt to stop this extreme inflammation, one of most proposed treatment to COVID-19 is the corticotherapy.[6] Prolonged corticotherapy can suppress bone mineral mass and bone formation.[6] Additionally, diabetes, smoking, vitamin D deficiency are conditions associated with severe COVID-19 patients and risk factors for osseiointegration.

Our present report may encourage studies to analyze peri-implant bone healing in patients who have had COVID-19. Although the infected patient could be asymptomatic, diagnostic tests can be necessary to avoid metabolic effects of COVID-19 on bone tissue. This information reinforces the concerns about biosafety. In conclusion, the current article adds to the accumulating knowledge that COVID-19 is possible risk factor in implantology.

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From the *State University of Northern Paraná, Jacarezinho; and †São Paulo State University (Unesp), School of Dentistry, Araçatuba, São Paulo, Brazil.
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Address correspondence and reprint requests to Gabriel Mulinari-Santos, PhD, State University of Northern Paraná, Health Sciences Center-Dentistry, Padre Magno Avenue 134-318, zip code 86400-000, Jacarezinho, Paraná, Brazil; E-mail: gabriel_mulinari@hotmail.com
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Acute Invasive Fungal Rhinosinusitis and Coronavirus Disease 2019

Mosaad Abdel-Aziz, MD and Noha Azab, MD†*

Abstract: Acute invasive fungal rhinosinusitis (mucormycosis) is a rare, highly fatal disease. This opportunistic fungal infection causes

From the *Department of Otolaryngology; and †Department of Rheumatology and Rehabilitation, Faculty of Medicine, Cairo University, Cairo, Egypt.
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Address correspondence and reprint requests to Mosaad Abdel-Aziz, MD, Department of Otolaryngology, Faculty of Medicine, Cairo University, 2 El-Salam St., King Faisal, Above El-Baraka Bank, Giza, Cairo, Egypt; E-mail: mosabeez@hotmail.com, mosabeez@cu.edu.eg
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angioinvasion and ischemic tissue necrosis. It mainly affects immunocompromised patients. Since the coronavirus disease 2019 (COVID-19) outbreak, many case reports have described the rhino-orbital-cerebral mucormycosis associated with COVID-19. However, the underlying predisposing factors are unknown. Several factors, other than diabetes, which is the most well-known contributing factor, may be involved in causing this severe fungal infection in COVID-19 patients. These factors may include steroid therapy, which is being used in severely dyspneic patients, the use of broad-spectrum antibiotics that may cause fungal flare-ups, and hospitalization with possible nosocomial infections. In addition, increased serum ferritin levels, possible endothelial damage, and pancreatic islets affection among COVID-19 patients may be implicated. Head and neck surgeons should be aware of the increasing prevalence of craniofacial mucormycosis among COVID-19 patients, as early diagnosis and prompt treatment are essential to improve the outcomes.

Key Words: COVID-19, fungal infection, mucormycosis, steroid therapy, tissue necrosis

Acute invasive fungal rhinosinusitis or mucormycosis is a rare, highly fatal opportunistic fungal infection. The disease mainly affects immunocompromised patients, and it has a rapid course with consequent ischemic necrosis of the affected tissue.[1] It is caused by Mucoraceae, which includes Mucor, Rhizopus, Rhizomucor, and Absidia.[2] These fungi are found in the soil, vegetation, and air; therefore, they frequently inhabit the upper airway mucosa but cause infections in immunocompromised people. They become pathogenic when the patients' general resistance declines.[3] Several clinical types, such as rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, and generalized are described in mucormycosis. Rhino-orbital-cerebral mucormycosis is the most common type of this life-threatening disease.[2]

In the pre-coronavirus disease 2019 (COVID-19) era, diagnosis of the disease was limited to patients with decreased immunity due to uncontrolled diabetes, end-stage renal failure, organ transplantation, and/or hematological malignancies. Since the COVID-19 outbreak, many case reports have described rhino-orbital-cerebral mucormycosis associated with COVID-19.[4] In our tertiary referral center, which is the largest university hospital in our country, many COVID-19 patients have been diagnosed with rhino-orbital-cerebral mucormycosis. Coronavirus disease 2019 may alter the cell-mediated immune response by decreasing T-lymphocyte levels, especially cluster of differentiation (CD) 4+ and CD8+ T cells, which may be involved in the pathogenesis of COVID-19 infection.[5] Most reported COVID-19 patients who developed craniofacial mucormycosis were diabetes patients, and most of them were treated with steroid therapy. In addition to the use of steroids, multiple risk factors associated with comorbid-illnesses in severe COVID-19 infection may predispose patients to invasive fungal infections.[4]

Steroids are widely used in the treatment of severe COVID-19 patients to reduce mortality, especially with hypoxemia, and have shown beneficial results.[6] However, their immunosuppressive and diabetogenic effects may increase the risk of developing mucormycosis in COVID-19 patients. Mucormycosis has even been detected in some COVID-19 patients treated with steroids without the presence of the traditional risk factors.[4] A reduced lymphocytic count has been detected in most COVID-19 patients. It is known that mucorales-specific T-cells (CD4+ and CD8+) secrete cytokines like interleukin (IL) 4, IL-10, IL-17 and interferon-gamma, which attack the fungal hyphae.[7] The decreased CD4+ and CD8+ T-cell populations, which are mediators of protective cell mediated immunity against fungal pathogens, may increase the tendency of opportunistic fungal infections in COVID-19 patients.[8] The aim of this study was to explore the potential underlying factors that may increase the incidence of mucormycosis among COVID-19 patients.

DIAGNOSIS

Rhino-orbital-cerebral mucormycosis is the most common type of Mucorales infection. The infection is transmitted by inhalation into the nose and sinuses. This severe form of fungal infection usually causes tissue necrosis via angioinvasion and thrombosis. Patients typically present with offensive black necrotic crusty nasal discharge, facial pain, blurring of vision, numbness, headache, and/or proptosis.[9] Without early treatment, visual loss, brain infarction with paralysis of the cranial nerves, and even death could be the ultimate result of the disease. The examination of the nose shows black necrotic tissue with possible orbital (Fig. 1A-B) and brain involvement, and similar black eschars are often seen over the hard palate.[3,9,10]

Computed tomography (CT) imaging is crucial for the diagnosis as it shows bone destruction (Fig. 1C). Magnetic resonance imaging is more sensitive than CT in the detection of orbital and brain involvement (Fig. 1D).[2] Sometimes, cerebro-vascular fungal invasion may cause fungal aneurysms, which can lead to hematogenous dissemination of the disease.[11] The ethmoid sinus is usually the most commonly involved area; however, fungal invasion may occur through the lamina papyracea to reach the orbit, extraocular muscles, and optic nerve. It may also extend through the cribriform plate to the brain.[2]

In the early stages of the disease, neither a CT scan nor magnetic resonance imaging can detect the lesions. Therefore, once a diagnosis is suspected, a biopsy should be performed using nasal endoscopy for direct microscopic examination and culture. Histologic examination and detection of mucorales fungi is very difficult. These organisms are not easily recognized on

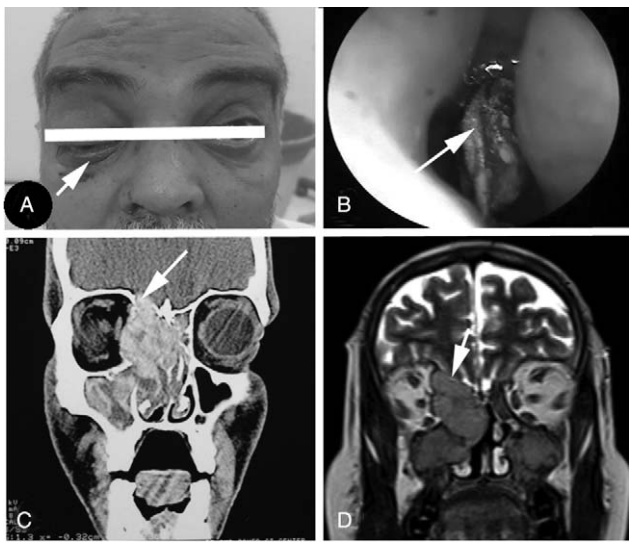

FIGURE 1. A patient with rhino-orbital-cerebral mucormycosis: (A) the arrow points to proptosis of right eye. (B) Endoscopic view of the right side of the nose with the arrow points to gangrenous middle turbinate. (C) Computed tomography shows the lesion that fills the right nasal cavity and sinuses with destruction of the medial orbital wall and cribriform plate (arrow). (D) Magnetic resonance imaging shows the lesion in the right side of the nose and sinuses invading the orbit and reaching the frontal lobe of the brain (arrow).

hematoxylin-eosin staining. Periodic Schiff acid and methanamine silver stains are the best methods for fungal detection, even they can highlight fungal fragments. Mucorales hyphae are characteristic. They are wide (5–15 microns), irregularly branched, with rare septations. This is in contrast to Aspergillus, which is narrow (2–5 microns) with regular branches and many septations.[11] Real-time polymerase chain reaction is sometimes needed to accurately detect fungi.[9,10]

TREATMENT

Patients with mucormycosis usually require combined medical and surgical therapies. Control of diabetes is very important for treatment, with starting systemic antifungal medications, such as amphotericin-B (the liposomal type is preferred) as early as possible to avoid nephrotoxicity. However, antifungal drugs cannot penetrate the devascularized tissue; therefore, they should be used in line with surgical debridement of this necrotic tissue, with restoration of aeration and drainage of involved sinuses using nasal endoscopy.[4,12] During debridement, it is essential to clean the margins to stop the spread of fungal infection.[9] Also, local irrigation of the nasal cavity with a mixture of normal saline and amphotericin B (1000 mL/50 mg) may be used.[3] As there is a high risk of infection transmission of the coronavirus, a surgeon who is dealing with debridement should take all necessary precautions during the procedure.

IMPACT OF CORONAVIRUS DISEASE 2019

Little is known about the impact of COVID-19 on invasive fungal infections. Several reports have suggested a potential increased risk of developing mucormycosis in COVID-19 patients. John et al[13] found that 94% of COVID-19 patients who developed mucormycosis were diabetic, with 67% having poorly controlled diabetes. In addition, COVID-19 infection was severe in 95% of patients. It has further been suggested that patients with diabetic ketoacidosis are susceptible to fungal infections. Diabetic ketoacidosis is a serious, acute complication of diabetes. It may develop under stressful conditions, such as severe infection, surgery, noncompliance to insulin therapy, pancreatitis, vasculitis, and treatment with drugs that may aggravate hyperglycemia in diabetes patients.[2] Coronavirus disease 2019 has been reported to cause ketoacidosis even in patients without a prior history of diabetes. The exact cause is still unknown; however, excessive release of inflammatory cytokines caused by viral illness has been suggested.[14,15] Ketoacidosis is characterized by hyperglycemic crises, increased ketone body formation, metabolic acidosis, and dehydration. The high glucose level renders the patients prone to develop fungal infections.[2] Also, hyperglycemia has been suggested to alter the function of neutrophils, monocytes, and macrophages, including adherence, chemotaxis, and phagocytosis leading to decreased local immunity of the tissue.[11]

The severe acute respiratory syndrome coronavirus (SARS-COV) causes damage to the pancreatic islets, leading to acute diabetes and ketoacidosis. High levels of angiotensin-converting enzyme 2 receptors, which are the site of entry of SARS-COV-2 (the causative virus of COVID-19), were found in the pancreatic islets.[13] The virus may, however, directly induce beta cell injury and impede insulin secretion.[15] This observation could explain the diabetogenic state and diabetic ketoacidosis in some COVID-19 patients.

Dexamethasone and methylprednisolone have been incorporated into most protocols for the treatment of COVID-19, especially in moderate and severe cases. Steroids may reduce hospital stay and the mortality rates in COVID-19 patients, especially those with dyspnea. As glucocorticoids have an immunosuppressive effect, they could increase the susceptibility to fungal infections.[6,16] Al-Tawfiq et al,[17] stated that systemic steroids could exaggerate the underlying glycemic control and impede the body's immune system. It has also been suggested that steroids could impair migration, ingestion, and phagolysosome fusion in macrophages, which may explain their suppressive effects on the patients' immunity.[18] Garg et al,[4] advised avoidance of using steroids in mild COVID-19 cases (without hypoxemia) and Szarpak[19] reported that the use of corticosteroids should be carefully monitored to achieve a therapeutic effect with the lowest possible dose in the shortest possible time, in order to minimize the reduction of the patient's immunity.

The tendency of COVID-19 infection to form thrombi may provide iron availability to fungi, which enhances the growth of the organism. Increased serum ferritin and decreased iron binding capacity of transferrin in COVID-19 infection may supply the fungi with the iron needed for their growth.[20] Further, Jose et al,[18] reported that an increase in circulating ketone bodies in ketoacidosis with its high pH may increase the availability of free iron, by inhibiting the sequestration of iron by transferrin and ferritin. This high pH and increased availability of free iron may promote fungal growth in susceptible patients.

In addition, widespread vascular endothelial injury has been noted in postmortem autopsy in COVID-19 patients.[21] Indeed, endothelial damage is well known to be the first step in the pathogenesis of mucromycosis.[13] Jung et al,[22] reported that SARS-COV-2 enters endothelial cells by endocytosis via the binding of its spike glycoprotein to angiotensin-converting enzyme 2, which is abundantly expressed in the respiratory epithelium. This endothelial damage could lead to local ischemia and necrosis. Necrotic tissue may thus provide fertile media for fungal growth and also impair leukocytic function.[2]

The use of broad-spectrum antibiotics, which may cause fungal flare-ups, and hospitalization with possible nosocomial infection might contribute to the causation of mucormycosis among COVID-19 patients.[1,4,13] Jose et al,[18] stated that many COVID-19 patients may develop respiratory complications that could require hospitalization and long-term mechanical ventilation with strong antibiotics as a part of the treatment protocol. This may predispose the patients to various nosocomial infections and/or superinfections (bacterial or fungal), especially if the host is immunocompromised. Indeed, nosocomial mucormycosis of the thigh in a COVID-19 patient has been described by Boodman and Cheng,[23] yet it has not been reported in rhino-orbital-cerebral mucormycosis.

All these factors alone or in combination could be included in increasing the prevalence of mucormycosis among COVID-19 patients.

CONCLUSIONS

Mucormycosis is an aggressive fungal infection with a high mortality rate. Early diagnosis and treatment are crucial for this life-threatening disease. Classically, it occurs in immunocompromised patients, and uncontrolled diabetes is the most common risk factor. Steroid therapy for COVID-19 may increase the incidence of this disease. Severe acute respiratory syndrome coronavirus 2 may cause damage of the pancreatic islets leading to acute diabetes and ketoacidosis. Increased serum ferritin may supply fungi with the iron needed for their growth. Vascular endotheliitis with tissue necrosis may provide fertile media for fungal growth and impair leukocytic function. In addition, the use of broad-spectrum antibiotics may cause fungal flare-ups and hospitalization with possible nosocomial infections. In high-risk patients with unilateral facial/orbital swelling, pain, and/or proptosis, a diagnosis should be suspected. Tissue necrosis is often a late sign of the disease. Biopsy

is an important diagnostic tool; however, it carries a risk of airborne transmission of SARS-CoV-2 during aerosol-generating endoscopic procedures. In addition, caution should be taken during surgical debridement of the lesions. Head and neck surgeons should be aware of the increasing prevalence of mucormycosis among COVID-19 patients, especially in high-risk individuals.

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Pregnancy Promotes the Recurrence of Cerebellar Hemangioblastoma?

Shiqiang Zhang, MD, Yue Wang, MD,† Xiaoxiang Yu, MD,* Bo Chen, MD,* and Bo Zhang, MD, PhD‡*

Abstract: Cerebellar hemangioblastomas with pregnancy is rare, but coexistence of pregnancy and recurrent cerebellar hemangioblastomas is rather rare. And coexistence of other diseases during pregnancy usually leads to misdiagnosis because of pregnancy reaction. A 29-year-old woman, at the 8th week of pregnancy, complained of nausea, vomiting, and episodic posterior occipital pain and was misdiagnosed pregnancy reaction without any special treatment during her several visits to local hospital. The patient was diagnosed cerebellar hemangioblastomas 14 years ago, after surgery, she received regular re-examination without recurrence. At the 15th week of pregnancy, the situation of the patient got worse, and she was admitted to our hospital. Brain magnetic resonance imaging showed a lesion in cerebellum. It was considered to be cerebellar hemangioblastomas and was confirmed finally by postoperative pathological examination. In clinical practice, differential diagnosis is of great importance during pregnancy because many other diseases can mimic pregnancy reaction. In this patient, the intracranial hypertension caused by recurrent cerebellar hemangioblastomas was misdiagnosed as pregnancy reaction and it was suggested that the change of hormones, neuroendocrine, and

From the *Department of Neurosurgery of Wuhan Third Hospital; †Department of Surgery and Anesthesia, Taikang Tongji (Wuhan) Hospital, Wuhan; and ‡Department of Neurosurgery of Shenzhen People's Hospital, Shenzhen, China.

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Address correspondence and reprint requests to Bo Zhang, MD, PhD, Department of Neurosurgery of Shenzhen People's Hospital, Shenzhen 518020, China; E-mail: zhangbodl@126.com; Bo Chen, MD, Department of Neurosurgery, Wuhan Third Hospital, Wuhan 430061, China; E-mail: 22467513@qq.com
SZ and YW are co-authors, they contributed equally to this work.

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