COVID-Associated Avascular Necrosis of the Maxilla—A Rare, New Side Effect of COVID-19

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Purpose: The purpose of this article is to present an interesting, rare case of a patient who experienced avascular necrosis of the maxilla associated with COVID-19 infection.

Methods and Results: Our team retrospectively evaluated this patient's chart after completion of surgical management. The patient is a 72-year-old male who presented to the University of Texas Health Science Center at Houston for surgical management of his infarcted maxilla, which developed as a sequela of infection with COVID-19. A literature review was completed using PubMed. Twenty-five articles are reviewed and discussed.

Conclusions: Infection with COVID-19 confers a hypercoagulable state in patients, leading to various complications in the head and neck region. In our case report, we present a patient who developed avascular necrosis of the maxilla secondary to infection with COVID-19. Thromboembolic prophylaxis is imperative in COVID-19 patients due to the high rate of potential systemic complications.

J Oral Maxillofac Surg 80:1254-1259, 2022

While colloquially thought of as a pulmonary disease, complications associated with COVID-19 infection have been observed in multiple other organs, including the heart, kidneys, and head and neck region. A systemic complication of COVID-19 is the development of a hypercoagulable state, which can lead to the development of thromboemboli and subsequently cerebral infarctions and myocardial infarctions. In the head and neck region, an observable occlusion on computed tomography angiography (CTA) has not been reported.

The aim of this article is to present a unique case of bilateral maxillary necrosis resulting from occlusion of the left internal maxillary artery secondary to COVID-19 infection. This phenomenon was confirmed with a CTA demonstrating occlusion of the left internal maxillary artery and branches of the pterygoid plexus. Surgical management of this patient and the pathophysiology based on available literature is reviewed. It is important for the head and neck surgeon to understand the pathophysiology of a hypercoagulable state induced by COVID-19 infection, how this affects the head and neck region, and how to prevent this complication in the perioperative period.

Methods and Results

CASE REPORT

In January 2021, a 72-year-old male with a past medical history significant for persistent atrial fibrillation

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Received February 9 2022

Accepted April 25 2022

0278-2391/22/00345-7

https://doi.org/10.1016/j.joms.2022.04.015

(status after ablation in 2009 and on daily 5 mg of warfarin), diabetes mellitus type II, coronary artery disease, and hypertension presented to an outside hospital with a chief complaint of headaches, blurry vision in the left eye, loss of taste, and an upper respiratory tract infection. His presenting international normalized ratio was 4.5. The patient's condition quickly deteriorated due to COVID-related pneumonia, and he was hospitalized in the intensive care unit (ICU) for approximately 1 month. Venous thromboembolic (VTE) prophylaxis included continuation of the warfarin at a therapeutic level and sequential compression devices. Temporal arteritis, cerebrovascular infarction, bilateral internal carotid stenosis, and deep vein thrombosis were ruled out via biopsy, head CT without contrast, carotid artery duplex scan, and bilateral lower extremity venous duplex, respectively. During the hospitalization, he also began to develop exposed bone in the right and left maxilla. After recovery, he was discharged from the hospital on 5 mg of apixaban twice daily and 81 mg of aspirin daily. He reports daily compliance with all medications.

After hospital discharge, he presented to a local oral and maxillofacial surgeon in May 2021 for exposed bone of the maxilla. He was subsequently referred to the University of Texas Health Science Center at Houston, Oral and Maxillofacial Surgery Department; he presented to the clinic in September 2021. No treatment was initiated prior to the referral; the patient attributed the delays in treatment to issues with insurance and finances.

Clinical exam revealed an edentulous maxillary ridge with exposed, infarcted bone on the labiobuccal surface extending from the left posterior maxilla anteriorly to the left canine region and from the keratinized gingiva mid-height of the alveolus to the depth of the vestibule. An isolated, 8-mm × 8-mm segment of the infarcted bone was also present on the labial surface of the right maxilla in the premolar region (Fig 1). The bone was mildly suppurative. The patient endorsed hypoesthesia in the distribution of left cranial nerve V-2; cranial nerve VII was grossly intact bilaterally. A maxillofacial CT without contrast revealed osteolytic changes of the hard palate, superior alveolar ridge, left maxilla, zygoma, zygomatic arch, left ethmoid air cells (lamina papyracea), pterygoid plates, and pterygoid palatine fissure (Figs 2*A-D*). A neck CTA demonstrated an abrupt cutoff of a small branch of the left internal maxillary artery located adjacent to the medial aspect of the left mandible, representing occlusion (Fig 3). Additionally, the left pterygoid plexus was nonfilling, indicating further occlusion of these branches.

The patient was taken to surgery and underwent debridement of the maxilla (Figs 4*A*,*B*). Cultures were obtained, yielding few *Pseudomonas aeruginosa*, few *Klebsiella pneumoniae* (with resistance to ampicillin), few *Candida tropicalis*, and few *Enterococcus* species. Biopsy of the specimen confirmed osteonecrosis of the maxilla. Primary closure was achieved (Fig 5). The patient was placed on amoxicillin/clavulanic acid 875mg/125mg twice daily for 10 days. The patient continued his regimen of apixaban 5 mg every 12 hours. The University of Texas Health Science Center at Houston Oral and Maxillofacial Surgery surgical team continues to follow the patient after surgical intervention.

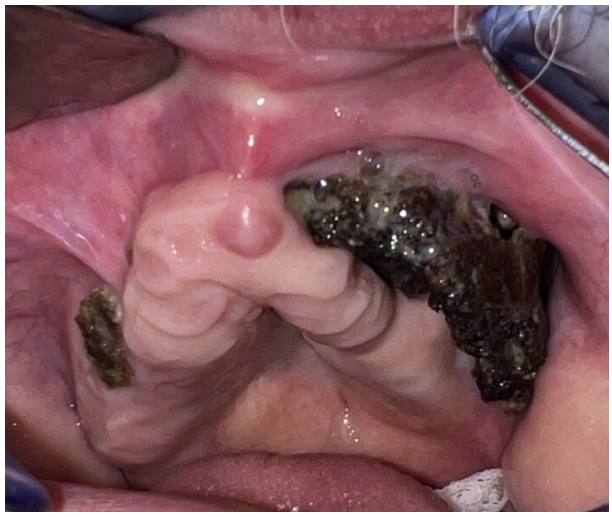

FIGURE 1. Clinical photo from the patient's initial presentation to the UTHSC-H OMFS clinic. There is necrotic, exposed bone on the labio-buccal surfaces of the left and right maxillary quadrants with suppuration. UTHSC-H OMFS, University of Texas Health Science Center at Houston Oral and Maxillofacial Surgery.

Mañón et al. COVID-Associated Maxillary Avascular Necrosis. J Oral Maxillofac Surg 2022.

Discussion

Emerging complications of COVID-19 in the maxillofacial region are being observed. It has been noted that patients treated for COVID-19 are at a higher risk for complications secondary to thromboemboli and fungal infections, including mucormycosis. The etiology of these complications is multifactorial and includes medication side effects, damage to endothelial cells, patient immobility, and other factors related to critical illness.[1,2] This patient demonstrated concerns for both of these complications. The authors of this paper believe this patient experienced multiple thromboemboli, as evidenced by the CTA and the exam results that ruled out giant cell temporal arteritis, deep vein thrombosis, and cerebrovasular accident. Complications from the thromboemboli include the patient's visual disturbances and necrosis of the maxilla. With a high suspicion for invasive fungal species, several biopsies and cultures were performed on

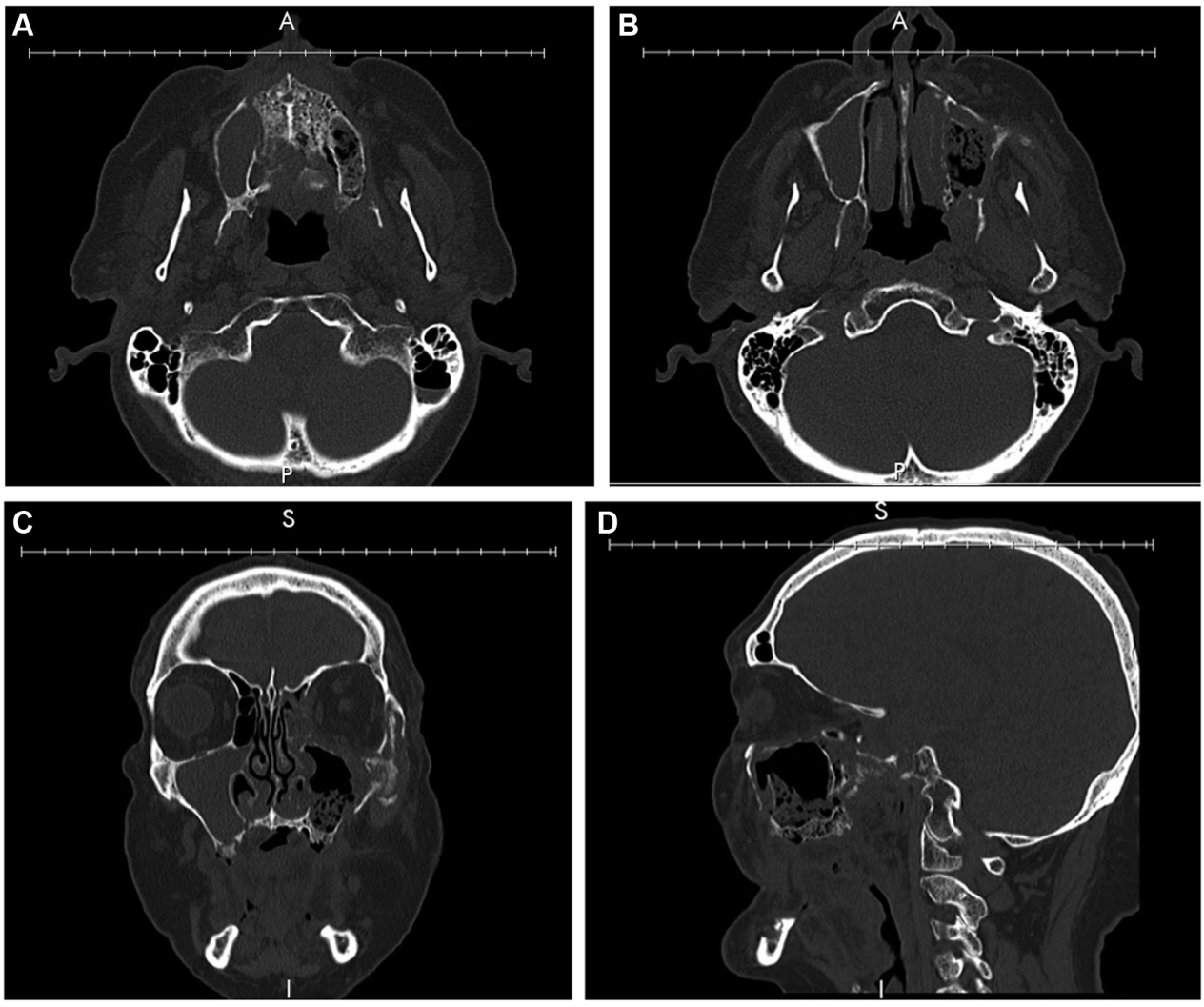

FIGURE 2. *A*, Axial view. There are osteolytic changes seen on the hard palate, superior alveolar ridge, and left maxilla. *B*, Axial view. There are osteolytic changes seen on the left maxilla, zygoma, and left ethmoid air cells. *C*, Coronal view. There are osteolytic changes seen on the hard palate, superior alveolar ridge, left maxilla, zygoma, zygomatic arch, and left ethmoid air cells. *D*, Sagittal view. There are osteolytic changes seen on the hard palate, superior alveolar ridge, left maxilla, and left ethmoid air cells.

Mañón et al. COVID-Associated Maxillary Avascular Necrosis. J Oral Maxillofac Surg 2022.

the patient; no fungal contamination or colonization was found. It is also plausible that the prescribed anticoagulation was insufficient for the hypercoagulable state induced by COVID-19 infection.

There have only been a few reported cases of necrosis or osteomyelitis of the jaw after COVID-19 infection. One case series detailed osteomyelitis or necrosis of the maxilla in a series of 4 patients who had contracted COVID-19.[3] Another case report detailed maxillary necrosis in a single patient following COVID-19 infection.[4] Other oral cavity manifestations have been described including oral ulcers, petechiae, reddish spotting of the palate, desquamative gingivitis, and blisters.[3] No reported cases have described thrombosis of the internal maxillary artery.

Accumulating data suggest that COVID-19 infection can predispose one to a hypercoagulable state, increasing the risk for both arterial and venous thrombosis. A high incidence of thrombotic complications has been documented in the literature. There have been a number of reports for arterial thrombosis. In one large study of 3335 hospitalized patients with COVID-19, thrombotic events occurred in 16% of patients. Arterial events included ischemic stroke (1.6%), systemic thromboembolism (1.0%), and myocardial infarction (8.9%).[5] The pathogenesis of this prothrombotic state is currently incompletely understood. A myriad of factors may play a role, and different mechanisms have been proposed. Consequently, this phenomenon has been termed "COVID-associated coagulopathy".[6]

Endothelial injury and dysfunction (endotheliopathy) plays a role in COVID-19 thrombosis and coagulopathy. Autopsy studies have shown endothelial

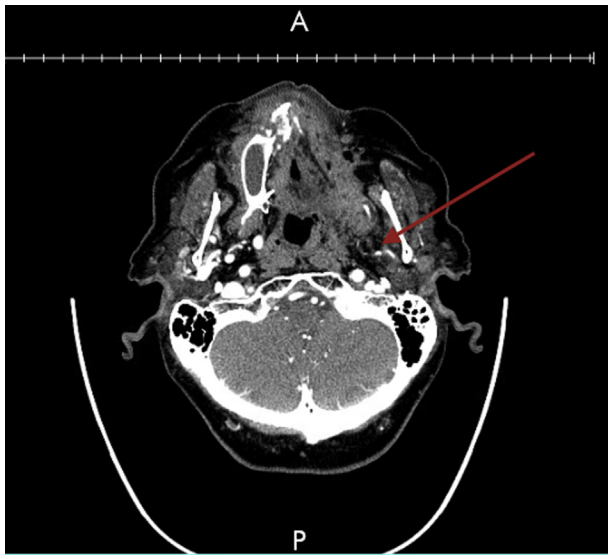

FIGURE 3. Neck CTA demonstrating occlusion of a branch of the left maxillary artery. Abbreviation: CTA, computed tomography angiography.

Mañón et al. COVID-Associated Maxillary Avascular Necrosis. J Oral Maxillofac Surg 2022.

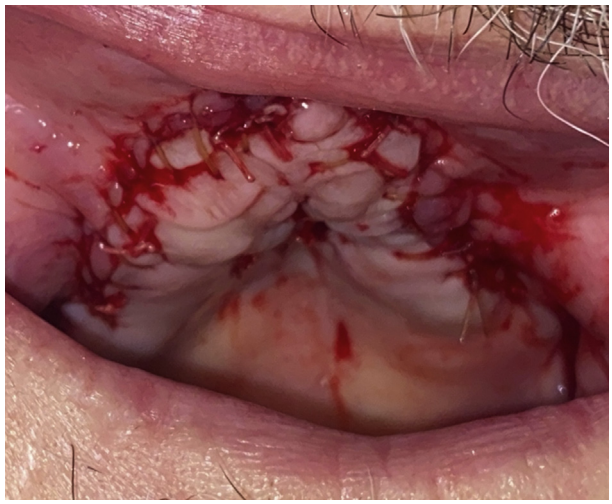

FIGURE 5. Primary closure of the maxilla after debridement.

Mañón et al. COVID-Associated Maxillary Avascular Necrosis. J Oral Maxillofac Surg 2022.

inflammation[7] after COVID-19 infection. Marked increases of endothelial activation and injury markers including von Willebrand factor (vWF), angiopoietin 2, P-selectin, and thrombomodulin have been noted, where vWF and thrombomodulin correlate with mortality.[8-12] COVID-19 may directly (through the ACE2 receptor) or indirectly trigger endothelial exocytosis of prothrombotic/proinflammatory factors, which drives microvascular inflammation and thrombosis.[9] Hyperactivation of the complement system has been seen in COVID-19, with increased circulating markers correlating with severe disease. Thrombotic microvascular injury with extensive deposition of complement proteins has been seen in autopsy.[13] Activation of complement may be direct from COVID-19 or as a sequela of endotheliopathy, which, in turn, activates the complement system.[14] In line with this, studies of Middle East respiratory syndrome coronavirus in C3-deficient mice or in those with blockage of the distal complement system show less systemic pathology.[15,16] Terminal components of the complement cascade may promote endothelial injury and dysfunction through multiple processes.[14] Complement system targets are currently being studied.

Laboratory analysis has been consistent with a hypercoagulable state in COVID-19. Increased D-dimer, fibrinogen, factor VIII, and vWF and decreased antithrombin have been noted in the critically ill.[8,17] In addition, thromboelastography results are consistent with a state of hypercoagulability, with shortened reaction time (R) and clot formation time (K), increased maximum amplitude (MA), and decreased clot lysis at 30 minutes (LY30).[8] Although critical illness is known to cause a hypercoagulable state, COVID-19 appears to cause a profoundly proinflammatory state, escalating prothrombotic factors.[18] In addition, plasma hyperviscosity has been observed in critically ill patients with COVID-19 pneumonia.[19] Neutrophil extracellular traps, web-like structures of chromatin, proteins, and oxidant enzymes, have been described

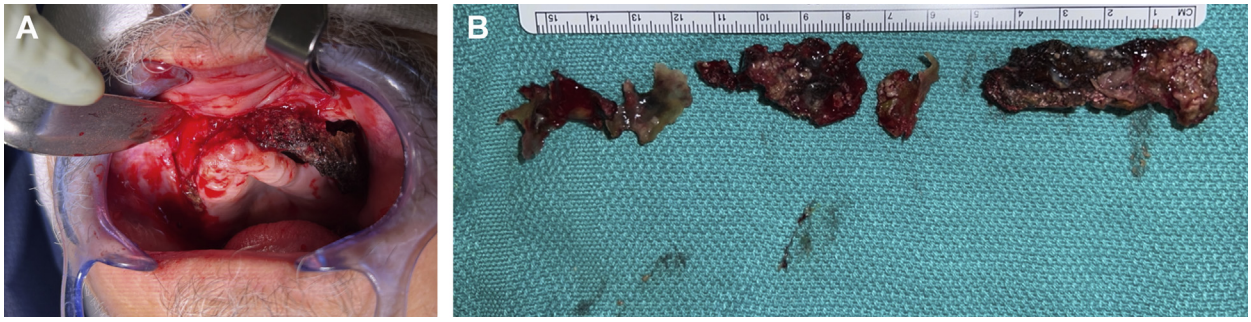

FIGURE 4. *A*, Surgical debridement of the right and left maxillary necrotic bone. *B*, Necrotic bone debrided from the right and left maxilla.

Mañón et al. COVID-Associated Maxillary Avascular Necrosis. J Oral Maxillofac Surg 2022.

Table 1. SUMMARY OF NIH TREATMENT GUIDELINES PANEL'S STATEMENT ON ANTICOAGULATION IN HOSPITALIZED PATIENTS WITH COVID-19

Patient	Antithrombotic Therapy	Contraindications	Other
Hospitalized, nonpregnant adults who require low-flow oxygen and are not receiving an ICU level of care, with elevated D-dimer and without increased risk of bleeding	Therapeutic-dose heparin (anticoagulation dose) LMWH preferred over UFH	Platelet count <50×10⁹/L, hemoglobin <8g/dL, need for DAPT, known bleeding within the last 30 days, and known bleeding disorder (inherited or active acquired)	Continue for 14 days or until hospital discharge, whichever comes first Recommends against use of intermediate-dose and therapeutic-dose anticoagulation
Hospitalized, nonpregnant adults who are receiving an ICU level of care (including patients requiring high-flow oxygen) without elevated D-dimer.	Prophylactic-dose heparin unless requires an anticoagulation dose for other clinical indications		Recommends against use of therapeutic-dose oral anticoagulants
Hospitalized, pregnant adults	Prophylactic-dose anticoagulation		There is inadequate evidence to recommend for or against therapeutic anticoagulation

Abbreviations: DAPT, dual antiplatelet therapy; ICU, intensive care unit; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Mañón et al. COVID-Associated Maxillary Avascular Necrosis. J Oral Maxillofac Surg 2022.

as also possibly contributing to immunothrombosis.[20,21] These factors have been confirmed to cause thromboembolism despite appropriate thromboembolic prophylaxis.[6,22]

VTE prophylaxis is imperative given the elevated risk of complications. The National Institutes of Health COVID prophylactic guidelines are in Table 1.[23] The use of therapeutic versus prophylactic doses of anticoagulation has been reviewed in clinical trials. In ICU settings, therapeutic heparin did not reduce mortality and may lead to a higher risk of bleeding events; therefore, standardized use of therapeutic doses of heparin is not recommended. Other trials (RAPID and HEP-COVID trials) evaluated VTE prophylaxis in non-ICU COVID-19 patients and found that therapeutic doses of heparin may be beneficial in patients who have elevated D-dimer levels, require low-flow oxygen, and have no increased bleeding risks. The use of direct oral anticoagulants (DOACs) has also been reviewed; Testa et al (2020) found that the simultaneous use of DOACs and antiviral medications can lead to supratherapeutic levels of DOACs; therefore, the authors recommended the transition from DOACs to low-molecular-weight heparin or unfractionated heparin if antiviral therapy is necessary.[6,24] There are clinical trials currently investigating the use of antiplatelets for the use of COVID-associated coagulopathy. The concomitant use of corticosteroids and nonsteroidal anti-inflammatory medications in addition to prophylaxis has limited and/or conflicting evidence to support their use.[6,23] In February 2021, the American Society of Hematology guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 suggested the use of prophylactic-intensity over therapeutic-intensity anticoagulation for patients with COVID-19.

Thromboembolism of the internal maxillary artery secondary to a hypercoagulable state from COVID-19 infection can lead to bilateral maxillary necrosis. Infection with COVID-19 and immobility can increase the complication risks of hospitalized patients, even with prophylactic doses of anticoagulation therapy. In this report, we document this complication, confirmed with CTA and biopsy of the maxilla. Other potential causes of necrosis and ophthalmologic complications (giant cell arteritis, CVA) were ruled out. The pathophysiology of COVID-induced hypercoagulability is caused by multiple factors, including an increase in D-dimer, fibrinogen, factor VIII, and vWF and a decrease in antithrombin. Other cellular changes, including neutrophil extracellular traps and changes in enzymatic proteins and oxidants, may also contribute. These changes are exacerbated in the critically-ill, immobile patient. If necrosis of the

maxilla, or any other bony structure, develops, the patient should be managed surgically; biopsy and cultures should be obtained to rule out superimposed infections and confirm diagnosis. NIH guidelines for VTE prophylaxis should be reviewed by the surgeon and managing team to prevent potential complications.

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