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COVID-19 as a critical risk factor for osteonecrosis of the jaw: diagnostic challenge and surgical treatment

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Introduction

Aspergillosis encompasses a spectrum of clinical diseases, ranging from asymptomatic infection and colonization to life-threatening invasive conditions. Typically, this infection first affects the respiratory tract, leading to nonspecific signs, such as rhinosinusitis, up to more aggressive pulmonary infections.[1]

Aspergillus hyphae can spread through the blood vessels, resulting in a vessel lumen occlusion often evolving in a secondary thrombosis, leading to subsequent tissues necrosis.[2] Bone-invasive aspergillosis, a rare form of osteomyelitis, can lead to significant morbidity with an extensive destruction of both soft and hard tissues.[3]

Mucormycosis is a serious fungal infection caused by species from the Mucorales order, a group of fungi that thrive in moist environments. These fungi can invade and destroy the anatomy and function of various tissues and organs in the human body, including the sinuses, lungs, skin, and brain.[4]

The primary risk factor for contracting aspergillosis and mucormycosis is the severe alteration of the host immune system, caused, for example, by bone marrow transplantation, aplastic

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anemia, acquired immunodeficiency syndrome, and prolonged steroid use. Interestingly, COVID-19 infection has been also correlated to such opportunistic diseases, gaining interest within the scientific community.[5-7] COVID-19 has been a disease that affected millions of people all over the world in the last 3 years, mainly causing otolaryngological (ORL) symptoms, but also other nonspecified symptoms as headache, fatigue, myalgia, arthralgia, olfactory and taste alterations.[8] Moreover, the COVID-19 is linked to an elevated occurrence of venous thrombosis and pulmonary embolism/thrombosis, contributing to cerebral and cardiovascular complications.[9] Although the mechanisms under this process have not completely understood, the concept of COVID-19-associated coagulopathy (CAC) is currently considered among the potential drawbacks of this respiratory disease.[10]

Another downside is that patients affected by the so called "long COVID" syndrome, now described as a Postacute Covid-19 syndrome (PACS),[11] typically show an imbalanced immune system that is responsible for the occurrence of opportunistic bacterial and fungal secondary infections. Candidiasis, aspergillosis and mucormycosis are the 3 most common mycotic infections.[12] Opportunistic fungi colonize the arteries compromising the blood circulation, and causing severe local infections, such as osteomyelitis and sinusitis.[13]

In detail, osteonecrosis of jaws is a multifactorial pathology that has been frequently noticed in the last years in different type of patients, including those affected by Coronavirus (SARS-CoV-2).[14-16] Its pathogenesis recognizes an ischemic status induced by several factors such as trauma or infection, radiotherapy, assumption of antiresorptive, antiangiogenic medications or corticosteroids, diseases affecting the immune or vascular systems. Osteonecrosis of the jaws is typically asymptomatic in the first 8 or more weeks. Clinical features may require the presence of a prolonged ache in the jaw and oral cavity, loose teeth, gingival swelling, erythema, ulceration, soft tissue infection, and paresthesia or anesthesia in case of nerve involving.

Main complications as superinfections, pathologic fracture, extraoral or oral-antral fistula, or radiological evidence of osteolysis extending to the inferior border of the mandible or the maxillary sinus floor may occur.[17]

Over the last year, this condition has recurred so frequently that it has been named as COVID-19 Associated Fungal Osteomyelitis of Jaws and Sinuses (CAFOJS).[18] CAFOJS is able to affect patients even after a successful management of the COVID-19 infection, influencing on several levels their general health status.

Osteomyelitis is defined as a progressive inflammatory process affecting the bones. It has an early onset in the medullary cavity, and then involves the most superficial parts of the bone, up to the soft tissues. It is an uncommon complication, and the mandible is the most frequently affected bone, in the head and neck area.[19,20]

The scientific literature has reported how the immune system can be somewhat compromised by the assumption of a long-term corticosteroid therapy,[21] as may commonly happen to treat an acute respiratory distress syndrome in patients with COVID-19. Mechanistically, steroids inhibit the production of IL-2 and interferon-γ (IFN-γ) in T lymphocytes, inducing programmed cell death in several immunologically critical cells, like T and B cells.[22] Beyond these effects, glucocorticoids can alter the local angiogenesis, induce an intravascular coagulation, and promote the apoptosis of bone cells: all these conditions are linked to ischemia, and related to the onset of bone necrosis.[14] Due to the risk of causing osteonecrosis, glucocorticoids have been not suggested as elective treatment in in COVID-19.[15]

This case report aims to describe a rare invasive rhinomaxillary aspergillosis and mucormicosis, with osteomyelitis of the maxillae, in a post-COVID-19 patient, treated with corticosteroids. We have speculated different potential etiopathological hypotheses, and we have also described the surgical treatment here performed, up to the functional rehabilitation of the patient.

Case presentation

The current case report was conducted in accordance to CARE (CAse REport) guidelines (https://www.care-statement.org).

Patient anamnesis and clinical examination

In November 2021, a 74-year-old male patient was referred with the complaint of unilateral rhinorrhea, cacosmia, persistent cough and frontal headache. A persistent oronasal communication was immediately observed by the clinicians; this anomaly was cause of alterations in eating and drinking.

The patient was a smoker with a medical history of hypertension, dyslipidemia, several venous thromboses, and cardiovascular diseases. During the first clinical investigation, the patient was not completely able to report all his clinical history; in fact, he forgot to report previous head and neck radiotherapy, and the assumption of antiresorptive and antiangiogenic drugs.

Importantly, the patient suffered from a severe form of COVID-19 infection 3 months before the access to our clinic During the viral infection, he was treated with dexamethasone (4 mg, 2 capsule/die) for 28 days, supported by antibiotics (azithromycin 500 mg os/die for 4 days then replaced by cefditoren pivoxil 400 mg os/12h for 6 days) for a total of 10 days.

Following the SARS-CoV-2, the patient developed a maxillary sinus bacterial infection; treatment included a 20-days of corticosteroids (mometasone 50 mg spray) to manage inflammation, 17 days of acetilcisteina to thin the mucus production, and 10 days of amoxicillin (1gr/12 h).

After extraoral examination, the clinical findings revealed diffuse edema on the left zygomatic and suborbital areas, with the alteration of surrounding skin due to the formation of a suborbital fistula (Fig. 1).

The intraoral examination showed an edentulous maxillary ridge, a left oro-antral fistula with purulent exudate, and a diffuse necrotic bone exposure (Fig. 2).

No alterations were pointed out after blood cell count, serum and urinary protein electrophoresis, measurements of the glycaemia and the electrolytes, presence of blood urea nitrogen, creatinine, serum and urinary proteins, iron, ferritin, vitamin B12, folic acid, and antinuclear antibodies levels. Specifically, the coagulation indices (PT, PTT, INR, d-dimer, fibrinogen) showed the increasing of d-dimer and fibrinogen values.

The swab of the purulent exudate was collected: it showed the significant presence of the aspergillus species, particularly *Aspergillus Niger*, and *Staphylococcus epidermidis*. Finally, the serum β-d-glucan and serum galactomannan levels were within the physiological cut-off.

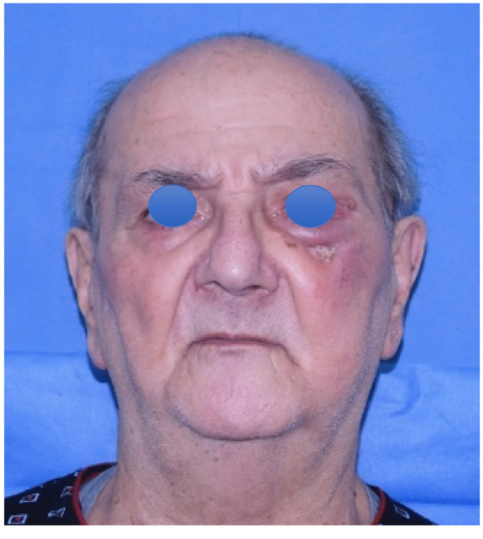

Fig. 1. Extraoral examination showing diffuse edema of the left zygomatic and latero-orbital areas with a suborbital fistula.

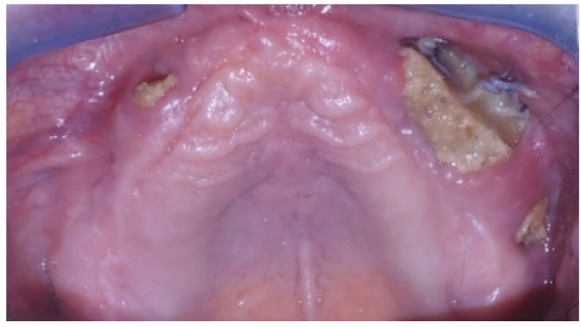

Fig. 2. Intraoral examination showing a left oro-antral fistula with purulent exudate and bone exposure.

Following the diagnosis of *Aspergillus niger*, and the patient underwent with a therapy based on oral administration of Isavuconazole 200 mg/day for 6 months.

Radiologic examinations

Infection affected multiple areas of the maxillary bone, as seen on a CT scan of the maxillo-facial region (Fig. 3A-C).

A severe bone erosion involves the entire maxillary bone and a significant part of the hard palate in both hemiarches. The infection has led in a wide vascular necrosis involving large part of the mucosa of the left maxillary sinus, as well as the hard palate, and the alveolar process, especially at the anterior sector.

The most infected portion of bone turns out to be the lateral wall of the left maxillary sinus, which also reaches the zygomatic arch, fronto-zygomatic suture, temporo-zygomatic suture, and lateral wall of the left orbit (Fig. 4A and B).

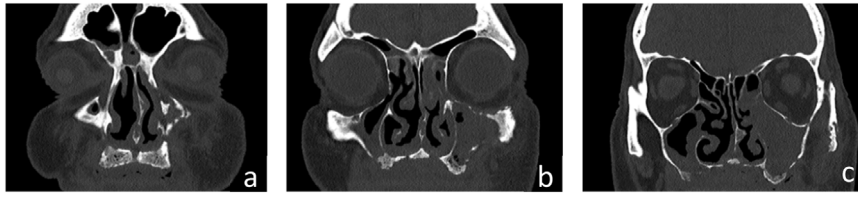

Fig. 3. (A-C) CT scan of the facial massif showed infective processes involved maxillary sinuses and nasal cavities.

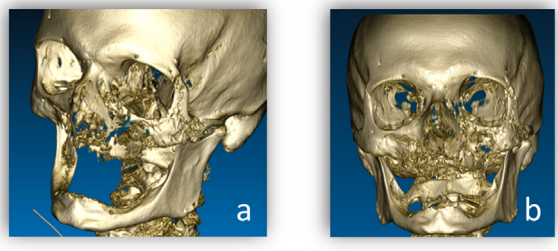

Fig. 4. (A, B) 3D facial reconstruction showed a structural remodeling and erosion involved the alveolar process of the maxillary bone bilaterally, zygomatic arch and latero-orbital region.

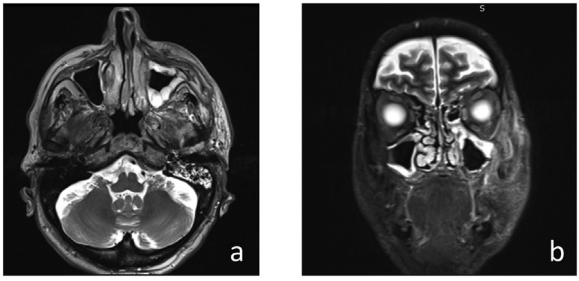

Fig. 5. (A, B) MRI shows on the left side, inhomogeneous perimaxillary, lateral periorbital, and perizygomatic soft tissue signal and the presence of phlogistic tissue affecting the parietal profiles of the maxillary sinus.

The patient, due to the suborbital skin fistulas, underwent to a surgical debridement of the infected tissues, removing the comminuted fragments of avascular bone completely necrotic and contaminated by anaerobic bacteria.

In this scenario, the complete obliteration of the maxillary sinus and osteo-meatal complex (OMC) was evident, due to the production of microbiological material of homogenous density, spreaded up to the anterior region of the ethmoid.

On MRI, on the left side, nonhomogeneous soft tissue is visible above the periorbital area; moreover, structural alteration of the maxillary bone was reported also in the MRI investigations, with the involvement of the palatine process and the most part of the maxillofacial bones. In part, such alterations were also found in the right palatine process, highlighting a deep and overall involvement of the entire facial complex. Mainly in the left side, there was the presence of abundant phlogistic tissue: on the maxillary sinus, it takes on a polypoid appearance, reaching also the orbital region and the left lower slope of the ethmoidal cells. Of course, also the contiguous muscles, such as the masticatory and temporalis muscles, were subjected to edematous-congestive phenomena (Fig. 5A and B).

Surgical treatment

The patient was prepared for the bone sequestrectomy surgery at the Operative Unit of Maxillofacial Surgery: this surgery aimed at removing the necrotic bone tissue above described in detail.

The surgical approach started with an access from the oral cavity, reaching the nasal fossa, supported with local endoscopy. From the oral cavity and lower orbital frame, it was possible to rapidly debride the vast majority of the necrotic avascular bone, and the inflammatory tissue as well as the fibrotic mucosa (Fig. 6A-D).

Afterward, a Functional Endoscopic Sinus Surgery (FESS) was conducted, commencing with the initial procedures of maxillary uncinectomy and antrostomy to release the Osteomeatal Complex (OMC). Upon accessing the inner cavity of the left maxillary sinus, a thorough removal of infected material and inflammatory mucosa was successfully carried out (Fig. 7A-C).

Throughout the endoscopic approach, it was enough to perform minimally invasive accesses to completely remove the necrotic comminuted bone fragments

At the end of the surgical procedure, single stiches were used to suture mucosa (Vicryl 3-0) and skin wounds (Prolene 3-0) (Fig. 8A and B).

Histological examination

Bone tissue removed during surgery underwent histologic analysis at Department of Advanced Biomedical Sciences, Pathology Section, University of Naples “Federico II” (Fig. 9).

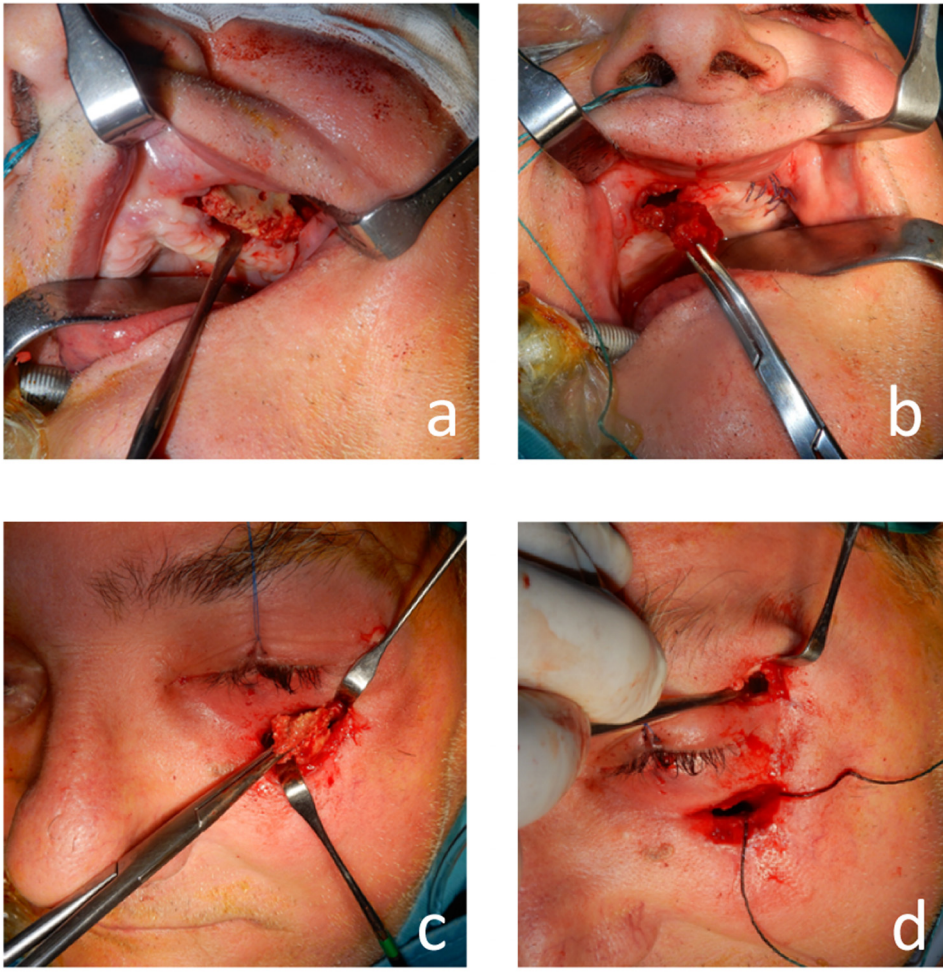

Fig. 6. Images (A-B) shows a bone sequestrectomy from oral cavity while images (C-D) shows bone sequestrectomy from upper maxillary wall and fronto-zygomatic suture.

Specimens were processed after 24 hours into formalin (10% neutral buffered formalin solution): 5 µm slices were cut and stained with hematoxylin and eosin. A Grocott's staining was also performed. In detail, histologic examination revealed, in both sinuses, the presence of severe lymphoplasmacytic infiltrate, bone necrosis, and broad aseptate hyphae, highlighted also by Grocott's stain. These aspects were consistent with the diagnosis of Mucormycosis (Fig. 10A-D). Moreover, the bone sample, taken from the suborbital region, also showed the presence of septate hyphae with dichotomously branching (acute angle branching), suggesting an Actinomyces-like bacteria coinfection.

Functional rehabilitation and follow-up

The patient was informed about how to maintain a good oral hygiene and he has been followed up monthly. Three months after surgery, hard and soft tissues showed an adequate health status, and the patient referred no complaints. Thereby, he was esthetically and functionally rehabilitated by a prosthetic obturator (Fig. 11A-C).

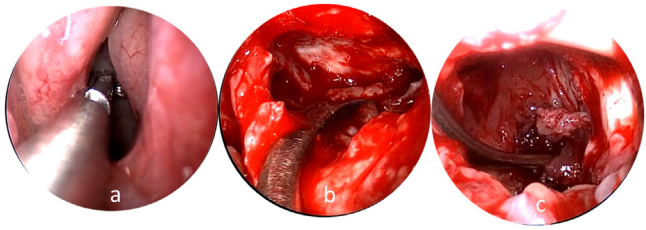

Fig. 7. (A-C) Antrostomy of the maxillary sinus with removing of inflamed tissue and avascular bone.

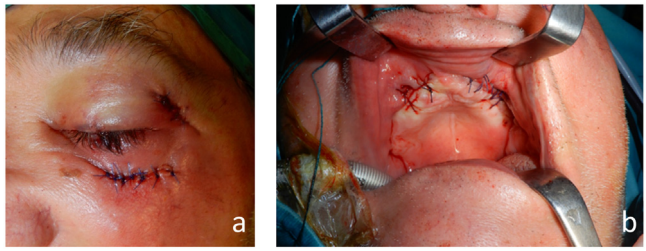

Fig. 8. (A, B) Cutaneous and mucosa sutures.

Fig. 9. Maxillary bone sample undergone histological examination.

Particularly, the prosthetic obturator was able to support the majority of soft tissues, achieving a better facial profile (Fig. 12A-D).

CT images taken 1 year after surgery demonstrated how the choice of an “open” surgical approach, combined with a minimally invasive endoscopic surgery, played a key-role in the full recovery of the anatomy of the oral mucosa and the related bony structures. in fact, despite a

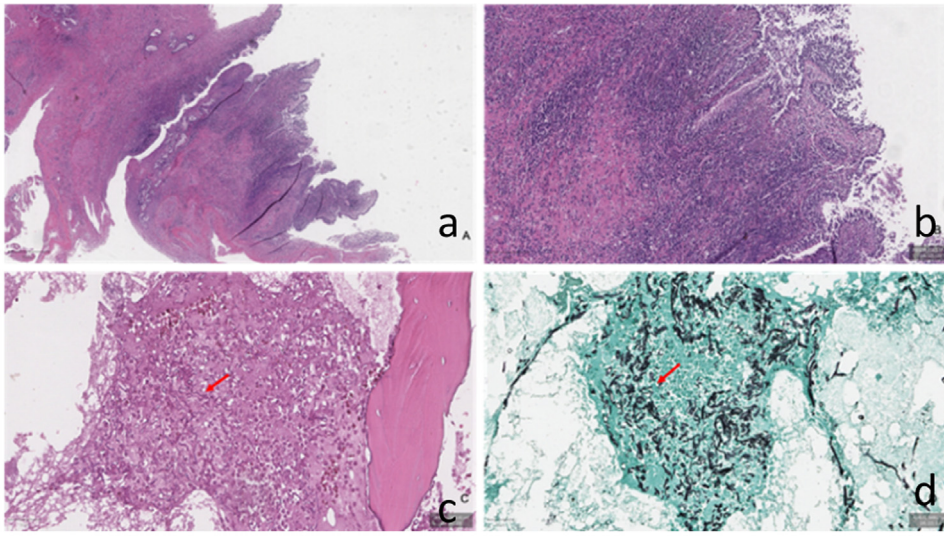

Fig. 10. (A, B) Histological sections revealed a severe inflammatory process (H and E 5 and 10× respectively); (C, D) The presence of nonseptate hyphae (red arrow) was confirmed by Grocott's stain (H and E 20× and Grocott's stain 20× respectively).

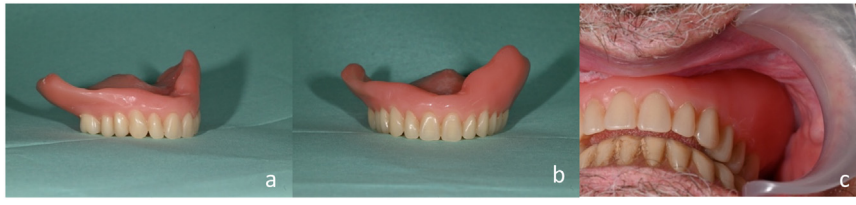

Fig. 11. (A-C) Prosthetic obturator.

huge amount of necrotic bone, 1 year after surgery the patient was able to retain his masticatory, respiratory, and phonatory functions (Fig. 13A-C).

After 2 years from the first surgery, the patient is still strictly followed every 6 months, through clinical and radiographical examinations, in order to prevent potential complications. During the follow-ups, the patient received no further treatment.

Discussion

This case report aimed to describe a rare invasive rhinomaxillary aspergillosis and mucormicosis, with osteonecrosis of the maxillae, in a post-COVID-19 patient, treated with corticosteroids.

A compromised blood supply to bone tissue renders it vulnerable to secondary infection encompassing bacterial, viral and fungal pathogens, with Aspergillosis and Mucormycosis being the most common angio-invasive microbes.[23-26]

These pathogens, typically environmental saprophytes, become pathogenic in the presence of immune deficiency,[27] often transmitted via inhalation of spores. Risk factors include xerostomia, type 2 diabetes mellitus, immunosuppression, and prolonged corticosteroid or antibiotic therapy.[28] In immunosuppressed patients, the infection may rarely lead to an invasive aspergillosis

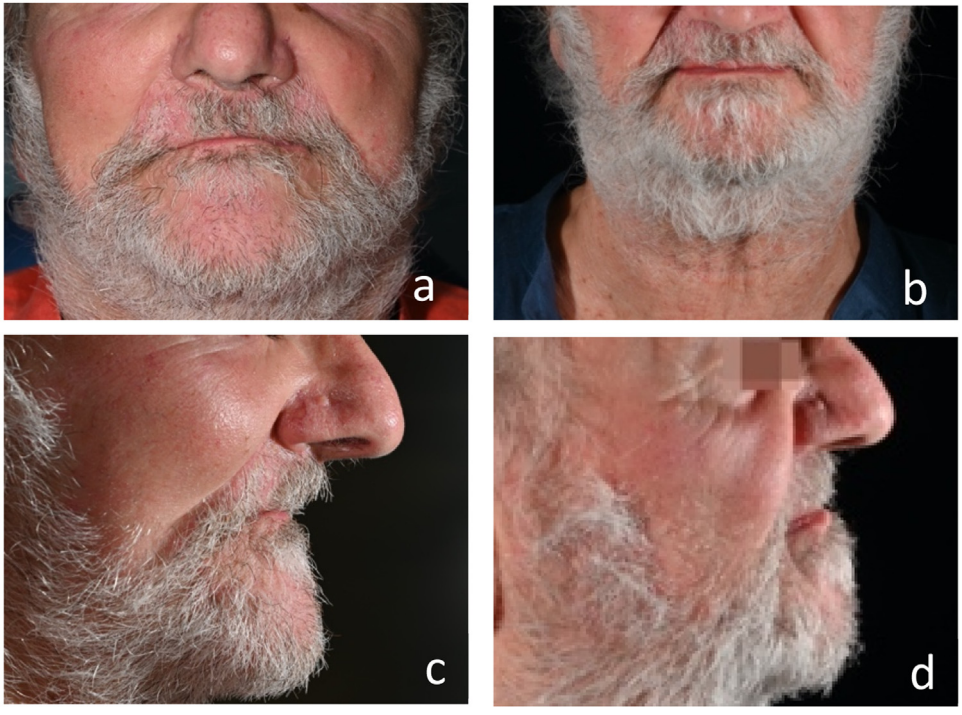

Fig. 12. (A, B) Frontal clinical images showed the difference between the time before and after prosthetic rehabilitation; (C, D) profile clinical images showed the difference between the time before and after prosthetic rehabilitation.

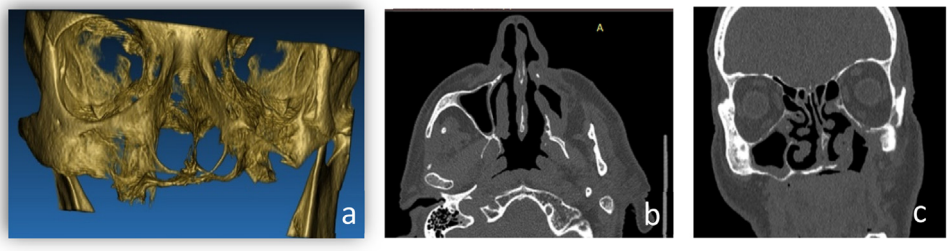

Fig. 13. (A-C) CT scans and 3D reconstruction 1 year after surgery.

that starts from respiratory tract and nasal sinuses. Then, it could spread via blood damaging distant tissues and organs.[29-32]

Mucor is the primary cause of the rhino-orbito cerebral syndrome characterized by face pain, facial numbness, headache, diplopia; blackness on the skin and mucosa, along with ulcer and palate drainage. Mucor damages necrotic tissue and thrombosis in nearby arteries of the nervous system like the internal carotid artery and cavernous sinus.[33]

Stated the way of transmission of these fungi, the type of patient's job (geologist) may would have played a critical role in exposing these people at a major risk to develop infection. In fact, many studies verified that different environments, like outdoor and occupational settings, have been recognized as at high risk of fungal infection occurrence, even in patients with intact immune system.[34,35]

Establishing the role of SARS-CoV-2 is essential. Even after recovering from the infection, it's crucial to recognize the potential for distant complications. The ACE2 receptor, the target of SARS-CoV-2, is not only prevalent in the human epithelia of the lungs and small intestine but is also abundantly found in vascular endothelial cells and arterial smooth muscle cells.[36] Therefore, considering the involvement of the vascular system, as highlighted in this case report, is imperative.

To clarify the reasons of the osteonecrosis, the authors suggest 2 different etiopathogenetic hypotheses based on the recent literature reported below.

The first hypothesis takes into account the link between the Coronavirus and the high hypercoagulability status of the patient while the second one pointed out the immune suppressant effect of corticosteroid drug capable of make a latent infection clear

Firstly, the thrombogenic effect of Coronavirus was identified as a critical comorbidity in addition to the patient's history of past episodes of venous thrombosis. In such case, aspergillosis and mucormicosis have been detected as over-infections.

Regarding to this first hypothesis, Coronavirus' strong thrombogenic effect would seem to play a crucial role in the pathogenesis of osteonecrosis even if the patient followed an antithrombotic therapy during the COVID-19 period. On the other hand, a primary role is covered by the patient's specific immune response. In fact, corticosteroid therapy was prescribed to the patient for the treatment of the coronavirus infection. It resulted in a reduction of immune defenses that caused the appearance of aspergillosis and mucormycosis that were in a latent state until then.[37-41]

Patients with a history of thrombo-embolism and ischemic cardiopathy are more prone to develop a status of hypercoagulability.[42,25,43] With, biomarkers of coagulation (D-dimer, fibrinogen, platelet count), inflammation (interleukin-6) and immunity (lymphocyte count) are critical to prevent the formation of blood clots and run the illness properly. Corticosteroids-induced osteonecrosis of jaws is a rare condition that occurs after a history of long corticosteroid therapy (for example, for treatment of LES, psoriatic arthrosis or mycosis) in association with a recent dental extraction. Due to these reasons, the role of corticosteroids would be led only to their depressing effects on the immune system.[41,44-46]

Although this study reports a rare presentation of osteonecrosis of the jaws after COVID-19, contributing constructively to the medical literature, it has several limitations that need to be considered. Firstly, as it focuses on a single patient, the findings may not be generalizable to a broader population. The specific medical history and unique circumstances of the patient may limit the applicability of the results to other cases. In addition, there is no possibility to establish a strong cause-effect relationship of the analyzed variables, influencing the observations and interpretations. Finally, while this case provides valuable insights, further research involving larger sample sizes and diverse populations is necessary to validate the findings and explore their implications in different contexts.

Conclusion

Our case report highlighted a potential association between SARS-CoV-2 infection and osteonecrosis of the jaws, as complication arising from COVID-19-induced coagulopathy, particularly prevalent in long-COVID patients. Furthermore, SARS-CoV-2 infection may amplify the risk of superinfections by opportunistic pathogens like Aspergillus and Mucor. Consequently, it is imperative to integrate these findings into screening and prevention protocols, utilizing a comprehensive approach encompassing surgical, methodological, pharmacological, and multidisciplinary strategies.

Future perspectives

Given the aforementioned hypotheses, it is crucial for clinicians to explore alternative therapies for Coronavirus disease to reduce the adverse complications associated with corticosteroid

drugs. The literature urgently needs high-quality studies to guide clinicians in the effective management of osteonecrosis of the jaws and associated superinfections in COVID-19 patients. Future research should:

- Conduct long-term studies to understand the progression and outcomes of osteonecrosis in COVID-19 patients, which will help develop effective management protocols.
- Explore the underlying mechanisms by which SARS-CoV-2 contributes to osteonecrosis and other complications, focusing on its thrombotic and immunosuppressive effects.
- Promote integrated treatment strategies that combine surgical, pharmacological, and supportive care to enhance patient outcomes.

Patient's consent

Authors declare that the patient provides a written consent to use his image in the current article.

Declaration of competing interest

Authors declare there is not conflict of interest.

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