CLINICAL PRESENTATION
A 50-year-old Latin American female patient complained of a painful lesion in the hard palate on a telephone consultation. The patient was isolated at home after receiving the diagnosis of coronavirus disease 19 (COVID-19), confirmed by the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA via polymerase chain reaction. The diagnosis was made approximately 8 days before the consultation. The only symptom related to COVID-19 was a persistent headache for 3 days, and no other medication was prescribed besides nonopioid analgesics. Her past medical history showed that she had type 2 diabetes. Because of the quarantine period, the patient was not able to go to the dental office and decided to send pictures of the lesion to the dentist. The patient reported no history of recent dental treatment or any type of trauma and wearing a removable partial denture. She described a chronologic sequence of the events, as follows: A small lesion appeared on the hard palate, with no symptoms, and she described it as an ulcer. At this point, she stopped wearing the prosthetic appliance by her own decision; 5 days later, she noted that the lesion increased in size and was accompanied by mild pain symptoms in the area of the lesion. However, on day 7, the pain became more severe and irradiated across the entire palate and middle third of the face. Examination of the clinical photographs taken 8 days after receiving the COVID-19 diagnosis and revealed a deep ulcerated lesion located at the center of the hard palate (over the midline). The bone was exposed, and the lesion measured around 2 cm at the widest diameter. The lesion was surrounded by an erythematous halo, the borders appeared lobulated, and focal areas were swollen (Figure 1).

DIFFERENTIAL DIAGNOSIS
Inflammatory conditions
Among several reactive and inflammatory conditions, necrotizing sialometaplasia (NSM) is known to present initially as an ulcer in the palate. This destructive inflammatory benign disease locally affects the salivary glands. People with NSM can feel pain or be asymptomatic, so it might be clinically and pathologically difficult to distinguish NSM from certain malignancies. Although NSM usually appears on the palate, there are reports of this condition in other intraoral sites, such as the retromolar area, labial mucosa, tongue, floor of the mouth, and buccal mucosa. In our case, NSM was first considered because the patient reported that the lesion started with a wound that did not heal. NSM frequently affects the palatal minor salivary glands, which might be related to the use of removable partial denture. Although the patient did not report whether the denture was ill-fitted and whether its use was interrupted in the first approach, one could assume that the prosthetic appliance could be related to the lesion. Moreover, it is unknown whether the rapid progression of the lesion and worsening of its appearance could be related to COVID-19 disease, because an exacerbation of the symptoms could occur mostly because of the inflammatory systemic condition. Besides NSM, other inflammatory conditions were not considered for differential diagnosis, mostly because of the rapid progression of the lesion and bone exposure after 7 days.

Malignant neoplasms
Malignant lesions were implied in the differential diagnosis in this case. Salivary gland tumors were considered because the lesion was located in the palate. These tumors are uncommon and account for 3% to 5% of all neoplasms in the head and neck region. A systematic review by Galdirs et al. showed that the majority of tumors in the minor salivary glands were malignant. In this present case, the lesion’s location in the hard palate was the only feature favoring the hypothesis of a malignant salivary gland neoplasm. Another aspect was observed: The borders of the lesion were raised and had a rolled appearance, suggesting an indurated (i.e., firm, hard) process and some neoplastic lesions could ulcerate as they progress. However, the rapid evolution and the absence of a mass (as seen in the pictures) were crucial to consider neoplasm as a less probable option in the differential diagnosis. Because of the impossibility to perform imaging exams at that time owing to the isolation of the patient, clinical presentation was the only source of information for diagnosis. Other hypothesis of malignant lesion for the present case was the possibility of a lymphoma. Lymphomas in the
oral cavity account for 3% of all malignant tumors of the head and neck, and they clinically present as a mass, with ulceration and with or without superficial necrosis.\(^3\) Regarding this information and clinical presentation, this hypothesis was included in the diagnosis list, considering that the palate is the most common intraoral location for extranodal malignant lymphomas.

**Infections of soft tissue**

Infectious diseases were the most emphasized group of lesions for differential diagnosis. Fungal diseases along with lesions in the oral cavity commonly occur in some regions of Latin America, especially in Brazil. The patient of this case lives in a countryside town. Oral manifestations related to a pathogenic microorganism

---

**Fig. 1. Clinical and imaging findings.** (A) Clinical aspect of the lesion just after the incisional biopsy procedure, revealing a deep ulcerated lesion, with bone exposure in the hard palate. (B) Three fragments measuring about 0.5 × 0.3 × 0.1 cm to 1.0 × 1.0 × 0.5 cm removed during incisional biopsy. All of the material collected was sent for histopathological analysis. (C) Cone beam computed tomography scan taken immediately following incisional biopsy. No significant alteration was noted in the maxillary bone. Hyperdense image covering the soft tissue corresponds to surgical cement applied for homeostasis during the biopsy procedure. (D) Clinical presentation 7 days after incisional biopsy. (E) Ten days following discharge from hospitalization and approximately 60 days after initial evaluation. The lesion appears to be resolving and the patient is asymptomatic.
infection were considered in the differential diagnosis list as follows: paracoccidioidomycosis, mucormy- 
cosis, and mucocutaneous leishmaniasis. de Castro Costa 
et al. reviewed cases of female patients with paracocc-
dioidomycosis and found that Brazilian white women 
aged 40 to 50 years were the most affected individuals, 
with the possible occurrence of a single painful lesion.4 
Almeida et al. concluded that the clinical presentation of 
oral leishmaniasis is unusual, which underlies the 
importance of considering leishmaniasis in the differ-
tial diagnosis of oral lesions, especially in endemic 
areas.5 According to a review study, the incidence of 
mucormycosis in South America is increasing: It 
appeared in 41% of 143 Brazilian patients. The mean 
age of the patients was 40.0 years (43.0 in Brazil, 37.5 
in the other countries of South America).6 In the case 
reported here, both clinical condition and prevalence 
rates were considered for inclusion of fungal and para-
site diseases in the differential diagnosis.

Bone infections
Because of bone exposure in this case, bone infections 
were also considered. At this point, we needed more 
information from the patient to determine whether to 
include bone necrosis in the diagnosis. Medication-
related osteonecrosis of the jaws is a bone necrosis 
induced by antiangiogenic and/or antiresorptive drugs, 
such as bisphosphonates, bevacizumab, and denosu-
mbab. The most common clinical presentation includes 
exposure of bone surfaces in the maxilla, local pain, 
sequestrum formation, and secondary local infection.7 
To distinguish the lesion from other delayed healing 
conditions, we reviewed the patient’s medical history 
to discard the possibility of previous use of bisphosph-
onates, bevacizumab, and denosumab. On a second 
call consultation, which was guided by a structured 
questionnaire, the patient reinforced the information 
that she was not on antiresorptive treatment; thus, the 
hyphysis of medication-related osteonecrosis of the 
jaws was rejected. Osteomyelitis was also considered. 
Osteomyelitis is an inflammatory, usually infectious 
bone marrow condition with a wide range of clinical 
presentations; it arises more often in the mandible than 
in the maxilla. Some symptoms of osteomyelitis are 
pain, edema, fever, adynamia, and cutaneous fistula.8 
We included osteomyelitis in the differential diagnosis 
because of the acute evolution of the lesion and 
because the patient had COVID-19 and diabetes; little 
is known about the evolution of these diseases in 
comorbidity, because both could be worsened by a bac-
terial infection progression.

Oral lesions related to SARS-CoV-2 infection
The main challenge was to include COVID-19-related 
lesions in the diagnosis process for this case. There is 
scarce information on oral findings for this condition, and 
the literature is mostly based on a few case series pub-
lished. Brandão et al. reported 8 cases of COVID-19 infec-
tion in patients who developed oral necrotic ulcers and 
aphthous-like ulcerations, which started early in the course 
of the disease. Lesions varied from clustered ulcers of 1 to 
1.5 cm in diameter covered with crusts to necrotic areas,9 
including painful ulcer and focal erythema/petechia. 
Amorim dos Santos et al. conducted a systematic review 
and reported that oral mucosal lesions are more likely to 
present as co-infections or secondary manifestations with 
multiple clinical aspects.10 In this specific case, COVID-19 
oral manifestations were included in the spectrum of possi-
dible diagnosis, although co-infection was likely to be con-
sidered. The patient reported mild symptoms of COVID-
19 disease (i.e., no fever, only headache and some discom-
fort) and, interestingly, no complaints of taste loss.

DIAGNOSIS
Until the end of the mandatory isolation period, the 
patient was prescribed antibiotics (amoxicillin with 
kalium clavulanate for 7 days) along with a nonste-
roidal anti-inflammatory drug and tramadol (centrally 
acting analgesic) because of the intense pain. Antisep-
tic mouthwashes were also indicated 3 times a day. 
During isolation, the patient reported one episode in 
which she received intravenous medication in an emer-
gency medical service to control the pain. After this 
period, the patient attended the dental office for intrao-
ral examination. Imaging exams were requested, and 
an incisional biopsy was performed under local anes-
thesia. Next, the patient underwent a cone beam com-
puted tomography scan. Tomographic images revealed 
a maxilla with normal contour, without signs of signifi-
cant eroded areas. She was advised to seek a consulta-
tion with a physician to check her diabetes status. A 
fasting blood sugar test revealed a glucose level of 
218 mg/dL. The patient signed a written informed con-
sent form for the present study.

Histologic examination of the biopsy showed an ulcer-
ated lesion with coagulative necrosis, hemorrhage, and 
abundant neutrophils. In the necrotic material, especially 
in blood vessels walls, there were many large nonseptate hyphae with thin walls and branches at 90°, which were 
well visualized with hematoxylin and eosin staining 
(Figure 2). These hyphae were evidenced with Grocott’s 
menenamine (Figure 2) and special stains for fungi-like 
periodic acid–Schiff (Figure 2). The morphologic diag-
nosis of mucormycosis was confirmed. A high-resolution 
version of the examined slides is available as eSlides 
VM06234, VM06235, and VM06236 for assessment via 
Virtual Microscope.
MANAGEMENT AND FOLLOW-UP
After the diagnosis of mucormycosis, the patient was quickly referred for hospitalization to start treatment. At the hospital, a series of tests was carried out to identify whether the disease had compromised the lungs and other organs. Imaging exams revealed no other affected sites. The patient started the treatment with intravenous amphotericin B in association with hydrocortisone. After 10 days of intravenous medication, superficial debridement of the lesion was conducted. In addition, the patient presented a respiratory allergic reaction, so an antihistamine therapy was introduced. Diabetes was also controlled during hospitalization. After approximately 1 1/2 months of hospitalization, the patient was sent home with no pain or any other symptoms. The patient attended the dental office for clinical evaluation of the hard palate, which seemed recovered 10 days after discharge from the hospital.

DISCUSSION
Mucormycosis is a rare and potentially lethal invasive fungal infection caused by saprophytic aerobic fungi *Rhizopus, Rhizomucor,* and *Cunninghamella* genera of the or order Mucorales, now called Rhizopodaceae, which colonize the oral and nasal mucosa and paranasal sinuses. The disease usually evolves rapidly in immunocompromised or debilitated patients; that is, those with uncontrolled diabetes, uncontrolled human immunodeficiency virus infection, malignant hematological diseases, and solid organ transplantation. This disease rarely affects patients with no underlying condition. The epidemiology of mucormycosis is difficult to determine, mostly because of its rarity. However, owing to the increasing number of immunocompromised patients, aging of the population, and better health care with higher overall survival rates, there has been an increase in the incidence of this disease in the last decades.

Disease transmission seems to occur mainly via inhalation of spores from environmental sources. Mucormycosis usually presents a worse outcome compared to other invasive fungal infections. The most common clinical presentation of mucormycosis is sinusitis (rhinocerebral infection), followed by pulmonary, cutaneous/subcutaneous, and disseminated diseases. Tissue necrosis is the hallmark of mucormycosis, resulting from angioinvasion and subsequent vascular thrombosis. Oral manifestations of mucormycosis usually include bone exposure and necrosis, which demands histopathological examination to confirm the diagnosis because of its nonspecific features and possible similarities to bacterial osteomyelitis, trauma, and iatrogenic infections.

Oral mucormycosis without any other systemically compromised organs is quite uncommon. In our case, the patient had both a debilitating condition resulting from poorly controlled diabetes and acute inflammatory immune response due to COVID-19.
reports of oral manifestations related to mucormycosis identified triggering or predisposing factors for local and systemic conditions. Rajashri et al. reported oral mucormycosis in a patient with diabetes after tooth extraction. Srivastava et al. reported a case of mucormycotic osteomyelitis in the nasomaxillary zygomatic complex, resulting from a trauma in a 42-year-old male patient with poorly controlled diabetes. Vahabzadeh-Haghi et al. described a case of invasive oral tongue mucormycosis after orthotopic liver transplant due to a history of hepatitis C cirrhosis and hepatocellular carcinoma. Boras et al. reported a case of oral mucormycosis and aspergillosis in a patient with acute leukemia. All of these cases of oral mucormycosis share a debilitating condition, and we initially considered COVID-19 as one of these, besides diabetes.

At present, there are only 3 studies investigating the possible correlation between COVID-19 and mucormycosis. Hanley et al. conducted a postmortem study involving 10 patients with fatal COVID-19 and found the case of a 22-year-old man with disseminated mucormycosis affecting lymph nodes, heart, brain, and kidney. Werthman-Ehrenreich reported the case of a 33-year-old woman with altered mental status and proposis who was ultimately diagnosed with COVID-19 along with invasive rhino-orbital-cerebral mucormycosis, which led to an orbital compartment syndrome. In a review study on the association between COVID-19 and fungal infection, Song et al. suggested that invasive mycoses are more likely to occur in patients with COVID-19, especially those who are severely ill or immunocompromised. According to their study, the most important risk factors of invasive mucormycosis in these patients are trauma, diabetes, glucocorticoid use, hemopoietic malignancies, prolonged neutropenia, allogeneic hematopoietic stem cell transplant, and solid organ transplant.

Co-infections in patients with COVID-19 are an emerging concern, especially because of their complex diagnosis, severity, and increased mortality. In a systematic review, Rawson et al. reported that 8% of patients experienced bacterial or fungal co-infection during hospitalization. Co-infections can primarily occur through the following: When the pathogenic organism is carried by patients themselves before the viral infection, when patients have an underlying chronic infection, or when the patient is hospitalized. Oral lesions in patients with COVID-19 seem more likely to be induced by co-infections, immunity impairment, and adverse reactions instead of direct SARS-CoV-2 infection.

Regarding COVID-19, some studies also revealed the presence of oral necrotizing lesions among affected patients. Patel and Woolley reported the case of a 35-year-old patient with suspected COVID-19 and diagnosis of necrotizing gingivitis. The main signs found were severe halitosis, nonprovoked bleeding from the gingival sulcus, and necrotic interdental papillae. Singh et al., in their case series, reported the case of a 71-year-old woman diagnosed with COVID-19 who was admitted to the intensive care unit for intubation because of respiratory distress. The patient presented discoloration on the upper lip and tongue, which progressed to swelling, full discoloration, and finally necrosis with dark eschar formation. Brandão et al. reported 3 cases of patients with COVID-19 in the eighth and ninth decades of life who presented aphthous-like lesions and superficial necrotic areas in the hard palate, upper and lower lips, and tongue. Those authors suggested that the high prevalence of oral necrotic lesions in patients with COVID-19 may be because of the increased permeability of the cell walls to pathogens and to the viral replication in the oral mucosa lining provoked by the infection of oral tissues.

In the context of severe acute respiratory syndrome (SARS), which is primarily caused by a coronavirus type, a possible relationship with avascular osteonecrosis (AVN) has been suggested. Hong and Du evaluated diagnostic imaging exams of 67 patients with SARS with pain in the large joints during or after hospitalization and 28 patients were identified with AVN (41%). Those authors believed that administration of corticosteroids (which is frequently prescribed to severely ill patients) in patients with SARS could be the major predisposing factor for AVN development and recommended that steroids should be administered cautiously. Considering that the disease can be severe in patients with COVID-19, it is important to know the possible effects of the medicines being prescribed to these patients to avoid major systemic complications.

Early diagnosis is the best way to manage oral mucormycosis, along with reversal of the underlying predisposing factors and systemic disorders, surgical debridement, and prompt administration of active antifungal agents. Because patients with COVID-19 may need to quarantine and socially isolate, tele-healthcare and/or tele-dentistry can be the best way to provide early diagnosis. Initial evaluation of pictures and clinical images is crucial to start the diagnosis process. In our case, the pictures of the patient along with her medical history and major complaints allowed us to recognize her oral condition and conduct the differential diagnosis. Martins et al. reported that literature evidence supports the use of tele-consultation and tele-education as effective alternatives in this period of pandemic to avoid the spread of SARS-CoV-2 and its collateral damage. The authors also emphasized that dental care delivery needs to be redesigned.
mucormycosis. Mucormycosis, along with other deep fungal infections, should be considered as an important outcome of SARS-CoV-2 infection. Because COVID-19 is still under investigation, all possible associations with the disease should be reported. In addition, the possibility of obtaining information from non-in-person consultation could be an alternative for patients in quarantine.

REFERENCES


Reprint requests:

Prof. Dr. Gustavo Davi Rabelo
Departamento de Odontologia
Universidade Federal de Santa Catarina
Rua Delfino Conti
1240 Bairro Trindade
 Florianópolis
Santa Catarina 88040-900
Brazil.
drgustavorabelo@yahoo.com.br