Orofacial Mycoses in Coronavirus Disease-2019 (COVID-19): A Systematic Review

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ABSTRACT

Objectives: Studies reviewing orofacial mycoses in coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome 2 (SARS-CoV-2) infection are sparse. Here we review the major oral and maxillofacial mycoses of COVID-19, the associated comorbidities, and the probable precipitating factors.

Methods: English-language manuscripts published between March 2020 and October 2021 were searched using PubMed, OVID, SCOPUS, and Web of Science databases, using appropriate keywords.

Results: We identified 30 articles across 14 countries, which met the inclusion criteria of PRISMA guidelines. These yielded a total of 292 patients with laboratory-confirmed COVID-19, 51.4% (n = 150) of whom presented with oral and maxillofacial fungal infections, mainly comprising candidosis, mucormycosis, and aspergillosis. Candida infections were the most prevalent, present in 64% (n = 96), followed by mucormycosis, and only a single case of aspergillosis was noted. Oral and maxillofacial mycoses were predominantly seen in those with comorbidities, especially in those with diabetes (52.4%). Oral mucormycosis was noted in 8.6% (n = 13) and mainly manifested on the hard palate. An overall event rate of oral/maxillofacial mucormycosis manifestation in patients with COVID-19 with diabetes mellitus type 1/2 was about 94% (49/52; 95% confidence interval, 0.73%-0.89%), implying a very high association between diabetes mellitus and the latter condition. All fungal infections appeared either concurrently with COVID-19 symptoms or during the immediate recovery period.

Conclusions: SARS-CoV-2 infection–related immunosuppression, steroid therapy, as well as comorbidities such as diabetic hyperglycemia appear to be the major predisposing factors for the onset of oral and maxillofacial mycoses in patients with COVID-19 across all age groups.

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a wide range of opportunistic bacterial and fungal coinfections.1 The triad of the most
common secondary oral fungal coinfections seen in COVID-19 comprises candidosis, mucormycosis, and aspergillosis. Candida species are generally found as oral commensals in approximately one-half of the general population. They metamorphose into opportunistic pathogens when adverse conditions supervene, as in SARS-CoV-2 infection, causing both localised and systemic infections. COVID-19 itself and/or the associated contributory factors including corticosteroid therapy, lymphocytopenia, mechanical ventilator support, and other localised factors such as poor oral hygiene, xerostomia, and denture-wearing appear to favour Candida proliferation in the oral cavity.

On the contrary, mucormycosis (previously called zygomycosis) is an uncommon, angio-invasive disease caused by the fungi belonging to the group of molds called mucormycetes. The most common species that cause mucormycosis are Mucor and Rhizopus species. They are rarely isolated in health from the oral cavity, and their usual transmission mode is through inhalation of fungal spores common in air and dust. Recent data suggest a number of possible reasons that facilitate germination of mucorales spores in patients with SARS-CoV-2 infection. These include hypoxic conditions, diabetes-related conditions, and/or steroid-induced hyperglycemia and ketoacidosis, immune suppression, and several other risk mediators such as prolonged hospitalisation and mechanical ventilation. In addition, numerous reports of oral and maxillofacial mucormycosis in patients with COVID-19, particularly from the Indian subcontinent, with devastating outcomes leading to blindness are now available. Recently, Singh et al in a comprehensive review of oral and maxillofacial mucormycoses reported more than 100 such cases in patients with COVID-19.

The last of the COVID-19–associated triad of common oral and maxillofacial mycoses is aspergillosis. Some studies note that as many as 15% of patients with COVID-19 hospitalised in an intensive care unit experience aspergillosis infection. For instance, a German report observed COVID-19–associated invasive pulmonary aspergillosis in 5 of 19 (26.3%) patients with moderate to severe acute respiratory distress syndrome. Despite the relative commonality of oral and maxillofacial mycoses in COVID-19, there are no systematic reviews, to our knowledge, that specifically address the prevalence or aetopathogenesis of these diseases, and there is a need for clinically relevant information. Therefore, the aim of this systematic review was to identify the prevalence, aetopathogenesis, oral and maxillofacial manifestations, and management these infections either directly linked to COVID-19 or secondary to their treatment protocols.

Methods

Data sources

Three reviewers (L.P.S., K.S.F., and H.C.N.) executed an electronic data search using PubMed via OVID, SCOPUS, and Web of Science databases for the English-language manuscripts. Published reports were accessed between March 1, 2020, and October 1, 2021, to identify case series, observational studies, or case reports.

Study selection

Inclusion criteria

a. Study design: Case series, case reports, observational studies
b. Population: Laboratory-confirmed cases with asymptomatic, mild, moderate, or severe SARS-CoV-2 infection
c. Setting: Any healthcare setting (hospitals, dental clinics) that provides consultation or treatment for SARS-CoV-2 infection
d. Date or country enforced no limitations

Exclusion criteria

a. Review articles
b. Reports that present incomplete outcome details
c. Studies evaluating systemic fungal coinfection without data on oral or maxillofacial yeast manifestation
d. Studies that do not meet the set study objectives, grey literature, abstract only

Search terms

A particular search string was set up for each of the databases, which included the following search terms: COVID-19 OR coronavirus 19 OR novel coronavirus disease 19 OR nCoV-19 OR SARS-CoV-2 OR SARS-CoV-2 infection AND oral lesions OR oral manifestations OR oral fungal lesion OR oral yeast presentation OR oral mucormycosis OR oral black fungus OR oral aspergillosis OR orofacial manifestations OR orofacial fungal presentation OR orofacial yeast manifestation OR maxillofacial yeast manifestation AND mucormycosis AND Candida infection OR Candida infection AND aspergillosis.

Summary measure

The intended outcome was to review the prevalence, clinical presentation, temporality, and the likely etiology of oral and maxillofacial fungal coinfections in patients with COVID-19.

Electronic data search and analysis

The present review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for a systematic and comprehensive approach. During the first stage of the 3-staged electronic data search and analysis, 2 reviewers (L.P.S. and K.S.F.) examined the titles and abstracts of all published relevant reports that were in line with our set inclusion criteria. Next, a full-text review of all the related articles was performed to explore the data comprehensively during stage 2 of the review process. A detailed analysis of the full text of the selected literature ensured that the eligibility standards were met and the reported outcomes were in accordance with the preset outcome measures. In addition, references of the included reports were examined as a backward search. Finally, the reviewers (L.P.S. and K.S.F.) extracted and assessed the data during stage 2.
Upon completion of the full-text review, specific points linked to the characteristics of each individual included study were mapped and recorded. This assisted in classifying the study design, setting, intervention, and reporting jurisdiction. In addition, the sample size, assessment time, evaluation methods, and study conclusions were systematically analysed. Finally, the third reviewer (H.C.N.) cross-checked the data to validate its accuracy. Relevant reports with case presentations of oral and maxillofacial mucormycosis were evaluated. The frequency of occurrence of the mucormycosis manifestation amongst patients with COVID-19 with and without comorbid diabetic conditions was analysed with random-effects meta-analysis using a comprehensive meta-analysis tool (CMA v.3). The identified manuscripts were listed using a bibliographic software tool, Endnote version 20 (Clarivate Analytics). Summarised characteristics of the included reports are provided in Table 1.

Quality and the overall risk of bias assessment of the included reports

During stage 3 of the systematic assessment of the available records, 2 reviewers (L.P.S. and K.S.F.) independently performed the quality valuation of the eligible studies employing the Joanna Briggs Institute Critical Appraisal Checklist for (i) case reports, (ii) case series, and (iii) analytical cross-sectional studies’ critical appraisal checklists. The third and fourth reviewers (Y.Y.L. and M.H.M.N.B.) were referred to in case of any conflict. They evaluated reports were recorded as low-, moderate-, or high-risk, as shown in Table 1. Any case reports or case series with a high risk of bias were omitted from the present review. All the involved reviewers discussed decisions based on the cumulative scores. The report was deemed low-risk when the “yes” score was ≥70%, moderate-risk, when the score was between 50% and 69%, and high-risk when the score was ≤49%.

Results

Of the 108 full texts reviewed, 30 reported cases or case series were included in the present review, and they represented a total of 292 patients with COVID-19, of whom only 150 had fungal manifestations together with or without other comorbidities, such as cardiovascular diseases, renal ailments, and liver diseases. A few other patients exhibited an atopic immune condition. asthama, and mild hypothyroidism.

Overall, 8.7% of patients with asymptomatic/mild COVID-19 and 91.3% with moderate to severe COVID-19 were affected by candidiasis, aspergillosis, or mucormycosis. In addition, none of the patients displayed simultaneous oral coinfection with two different mycoses (Table 1).

In terms of the time of appearance of the fungal infections, 95.8% (92/96) experienced candidosis with their COVID-19 symptoms and 4.2% during the post–COVID-19 recovery period (Table 2). The time span of presentation of candidosis ranged from a few days to 1 month after initial COVID-19 symptom appearance. All patients with candidosis were on either antibiotic, antiviral, and/or steroidal therapy.

As for the sites of candidal manifestations, the tongue was the most common focus of infection, followed by the soft palate, oropharynx, and the buccal/labial mucosa (Figure 2). Finally, all the candidal infections were managed with oral nystatin, miconazole, or systemic fluconazole therapy (Table 2).

As regards oral mucormycosis, we noted 13 cases of the disease predominantly manifesting as pallor or dry palatal mucosa with dry brown secretion to brownish-black ulcerative necrotic lesions, mainly on the hard palate (Table 2). Three patients with mucormycosis presenting with oral lesions were simultaneously diagnosed with COVID-19 symptoms. In addition, a number of other cases were fortuitous, incidental findings when examined for moderate/severe SARS-CoV-2 infection.

Furthermore, all moderate/severe cases of COVID-19 with the maxillofacial manifestation of mucormycosis were in hospitalised patients, mostly with comorbidities, and all were receiving systemic antibiotics, antiviral, and steroidal therapies for SARS-CoV-2 infection (Table 2). A noteworthy commonality amongst all patients with COVID-19 with oral/maxillofacial mucormycosis was their uncontrolled hyperglycemic condition. Thus, the overall event rate of mucormycosis was 94% (49/52; 95% confidence interval, 0.73%-0.89%) amongst patients with known diabetic type 1/2 conditions (Figure 3). The mucormycosis in the reviewed cohort was essentially managed with liposomal amphotericin B and surgical debridement of the necrotic tissue (Table 2). A single patient who had diabetes and mild COVID-19 presented with a painful deep-ulcerated lesion caused by *Rhizopus* species—belonging to the mucorales group. Additionally, only a single patient presented with histopathologically confirmed oral aspergillosis.

Discussion

Orofacial opportunistic mycotic coinfections are reported with increasing frequency at various stages of COVID-19. To our knowledge, the current review is the first report on the prevalence and aetopathogenesis of the major opportunistic, mycotic coinfections specific to the orofacial region in laboratory-confirmed COVID-19 cases. The available data clearly
| Study (country) | Number of patients | Age/sex | Comorbid conditions | Fungal test | Oral-maxillofacial manifestation | Oral-maxillofacial manifestationA | Oral-maxillofacial manifestation B | Risk of bias |
|----------------|--------------------|---------|---------------------|-------------|---------------------------------|------------------------------|-------------------------------|-------------|
| **Asymptomatic/mild COVID-19 cases** | | | | | | | | |
| Corchuelo J et al 2020 (Colombia) | 1 | Female = 40 y | An atopic patient with mostly on analgesics and antibiotics | NM | + | - | - | L |
| Glavina A et al 2020 (Croatia) | 1 | Female = 40 y | None | NM | + | - | - | M |
| Mirabela D et al (2020) (Romania) | 3 | Neonates (n = 3) Female (n = 1) Male (n = 2) | None | NM | + | - | - | L |
| Riad A et al (2020) (Czech Republic) | 1 | Female = 47 y | Mild hypothyroidism and on oral levothyroxine | NM | + | - | - | L |
| Diwakar J et al (2021) (India) | 2 | Male = 11 y Female = 13 y | Type 1 diabetes mellitus | Fungal culture showing Rhizopus arrhizus | - | - | + | L |
| Pauli MA et al (2021) (Brazil) | 1 | Female = 50 y | Type 2 diabetes | Histopathologic findings confirmed mucormycosis | - | - | + | L |
| Revannavar SM et al (2021) (India) | 1 | Female (Middle-aged, age not specified) | Uncontrolled type 2 diabetes without ketosis | Fungal culture-con-firmed Rhizopus species | - | - | + | M |
| Saldanha M et al (2021) (India) | 1 | Female = 32 y | Uncontrolled type 2 diabetes | Histopathologic examination | - | - | + | M |
| Verma V et al (2021) (India) | 2 | Female = 44 y Male = 35 y | Healthy patients | NM | + | - | - | M |
| **Moderate/severe COVID-19 cases** | | | | | | | | |
| Amorim dos Santos et al (2020) (Brazil) | 1 | Male = 67 y | Type 2 diabetes, hypertensive | Fungal culture | + | - | - | L |
| Baraboutis IG et al (2020) (Greece) | 49 patients, 2 of whom experienced a yeast infection | Female (n = 19) Male (n = 30) | NM | NM | + | - | - | L |
| Diaz Rodriguez M et al 2020 (Spain) | 1 | Female = 78 y | NM | There was a burning mouth sensation and pain | + | - | - | M |
| Salehi et al (2020) (Iran) | 53 | Sex = NM Age = NM | Cardiovascular diseases (52.83%), and type 2 diabetes (37.7%) | C albicans (70.7%); C glabrata (10.7%); C dublinsiensis (9.2%); C parapsilosis (4.6%); C tropicalis (3%); and C krusei (1.5%) | + | - | - | M |
| Alekseyev K et al (2021) (US) | 1 | Male = 41 y | Type 1 diabetes mellitus | Fungal culture shows Rhizopus | - | - | + | L |

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| Study (country) | Number of patients | Age/sex | Comorbid conditions | Fungal test | Oral-maxillofacial manifestation | Oral-maxillofacial manifestation | Oral-maxillofacial manifestation | Risk of bias |
|----------------|--------------------|---------|---------------------|-------------|----------------------------------|----------------------------------|----------------------------------|-------------|
| Ashour MM et al (2021) (Egypt) | Male (n = 5); ages 42-67 y; Female (n = 3); ages 41-65 y | Cases 1-2; 4, 5, 6, and 8: Uncontrolled type 2 diabetes mellitus; Case 3: CRD; Case 7: Uncontrolled diabetes mellitus, hypertension, and dialysis | Case 1: histopathology and culture revealed invasive Aspergillus species; Case 2-8: histopathology and culture shows Rhizopus | + | + |
| Bayram N et al (2021) (Turkey) | Female (n = 2); Male (n = 9); Mean age = 73. 1 ± 7.7 y | Type 2 diabetes | Fungal culture shows Rhizopus | NM | + | L |
| Dallalzadeh LO et al (2021) (US) | Male = 36 y; Male = 48 y | Uncontrolled type 2 diabetes mellitus | Fungal culture consistent with mucormycosis | NM | + | L |
| Favia G et al (Italy) | Female (n = 5); Male (n = 70); Median age 72 y; Male = 53 y | Type 2 diabetes | Fungal culture consistent with mucormycosis | NM | + | L |
| Farid HA et al (2021) (Iraq) | Male = 53 y; Uncontrolled type 2 diabetes on oral hypoglycemic Diabetic ketoacidosis at hospital admission | Fungal culture consistent with mucormycosis | | + | + |
| Karimi-Galougahi M et al (2021) (Iran) | Female = 61 y | No reported comorbidity | Histopathology and culture | NM | + | M |
| Mahan KM et al (2021) (US) | Male = 13 y | Type 1 diabetes mellitus | NM | + | M |
| Mehta S et al (2020) (India) | Male = 60 y; Diabetic (on oral hypoglycemic) | Uncontrolled insulin-dependent diabetes, asthma, hypertension, hyperlipidaemia | Fungal cultures show Rhizopus species | NM | + | M |
| Mekonnen ZK et al (2021) (US) | Male = 60 y | Uncontrolled type 2 diabetes mellitus | Fungal culture consistent with mucormycosis | NM | + | L |
| Mishra N et al (2021) (India) | Female (n = 1); Male (n = 9); Age = 55.8 y; (range = 37-78 y) | Case 1-3: type 2 diabetes mellitus; Case 4; CKD; Case 5: diabetes mellitus, hypertension, and IHD; Case 6: diabetes mellitus and CLD; Case 7: diabetes mellitus and hypertension; Case 8: diabetes mellitus, hypertension, | + | + | L |

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| Study (country) | Number of patients | Age/sex | Comorbid conditions | Fungal test | Oral-maxillofacial manifestation | Oral-maxillofacial manifestation A | Oral-maxillofacial manifestation | Risk of bias |
|----------------|--------------------|---------|---------------------|-------------|---------------------------------|---------------------------------|---------------------------------|-------------|
| Asymptomatic/mild COVID-19 cases |                     |         |                     |             |                                 |                                 |                                 |             |
| **Mohammadi F et al (2021)** (Iran) | 1 | Male = 59 y | Healthy | PCR test demonstrated *Rhizopus oryzae* NM | + | | + | M |
| **Riad A et al (2021a)** (Czech Republic) | 3 | Female (n = 3) | Case 1: 70 y Case 2: 25 y Case 3: 56 y | + | | | | L |
| **Riad A et al (2021b)** (Czech Republic) | 7 | Female (n = 2) Male (n = 5) | Case 2 & 3: healthy Case 1, 2, and 5: diabetes mellitus Case 3, 4, and 6: diabetes mellitus with hypertension, CVD, and vascular disease | RT-PCR | | | | L |
| **Veisi A et al (2021)** (Iran) | 2 | Female (n = 1); age 40 y Male (n = 1); age 54 y | Case 1: no comorbidity Case 2: well-controlled type 2 diabetes mellitus | Histopathology and culture | | | | L |
| **Waizel Haiat S et al (2021)** (Mexico) | 1 | Female = 24 y | Uncontrolled diabetes (severe diabetic ketoacidosis) | Direct exam (Sabouraud media isolating *Lichtenia* (Absidia) spp) | | | | L |
| **Werthman-Ehrenreich A et al (2021)** (US) | 1 | Female = 33 y | Hypertension and asthma | Fungal culture consistent with mucormycosis | | | | L |

CKD, chronic kidney disease; CLD, chronic liver disease; CRD, chronic renal disease; CVD, cardiovascular disease; IHD, ischemic heart disease; NM, not mentioned; PCR, polymerase chain reaction; RT-PCR, reverse transcription-polymerase chain reaction.

Joanna Briggs Institute critical appraisal tool for CR (Case Reports): low (L) risk of bias = >70% scores; moderate (M) risk of bias = scores between 50% and 69%; and high (H) risk of bias = scores <49%.宁静
Table 2 – Oral and maxillofacial manifestation of (I) mucormycosis and (II) candidosis and their respective management modalities in the reviewed studies.

| Study (No. of patients) | Oral mucormycosis in asymptomatic/mild COVID-19 cases | Maxillofacial mucormycosis in asymptomatic/mild COVID-19 cases | Oral mucormycosis in moderate/severe COVID-19 cases | Maxillofacial mucormycosis in moderate/severe COVID-19 cases |
|-------------------------|------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------|
| Pauli MA et al (2021)   | Ambulatory COVID-positive patients with hyperglycemia | None             | Case 1: Naso-paranasal, orbital apex mucormycosis    | Bayram N et al (2021)                                 |
| (n = 1)                 | and diabetic ketoacidosis                             |                 | (Of n = 11, 1 has palatal mucormycosis involvement) |                                                           |
| Alekseyev K et al (2021)| Hospitalised                                         |                 | VeiSi A et al (2021)                                 |                                                           |
| (n = 1)                 |                                                     |                 | (n = 2)                                         |                                                           |
| Ashour MM et al (2021)  | Hospitalised                                         |                 | Waizel Haiat S et al (2021)                         |                                                           |
| (n = 6)                 | 2 weeks to about a month                             |                 | (n = 1)                                         |                                                           |
| Riad A et al (2021b)    | Hospitalised                                         |                 | Werthman-Ehrenreich A et al (2021)                  |                                                           |
| (Of n = 7, 1 has palatal |                                                     |                 | (n = 1)                                         |                                                           |
| mucormycosis involvement)|                                                     |                 | Maxillofacial mucormycosis in moderate/severe COVID-19 |                                                           |
| Drohakar J et al (2021) | Ambulatory COVID-positive case with history of type 2 | None             | Dallalzadeh LO et al (2021)                         |                                                           |
| (n = 2)                 | diabetes and diabetic ketoacidosis                   |                 | (n = 2)                                         |                                                           |
| Revannavar SM et al (2021)| Hospitalised                                |                 | Farid HA et al (2021)                               |                                                           |
| (n = 1)                 |                                                     |                 | (n = 1)                                         |                                                           |
| Saldanha M et al (2021) | Ambulatory COVID-positive case with uncontrolled | No exposure to systemic steroids or antibiotics     | Before hospital admission: Injectable steroids and antibiotics, without medical prescription |                                                           |
| (n = 1)                 | diabetes                                               |                 | At hospital admission: Favorspravas, anticoagulants, and antibiotics |                                                           |
| Oral mucormycosis in moderate/severe COVID-19 cases | Case 1: and 2: Remdesivir and levofoxacin day 1-6 | Pain in the left midface region left lid edema with extension to the upper lip and malar area | Symptom of COVID-19 diagnosis | Rhinofacial-orbital-cerebral mucormycosis | 7 rhino-orbital and 3 patients of rhino-orbital-cerebral mucormycosis | IV and retrobulbar liposomal amphoterin B |

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| Study (No. of patients) | Ambulatory/hospitalised patient | Length of stay in the hospital | COVID-19 therapies | Symptoms at the time of presentation | Fungal manifestation (time of onset) | Mucormycosis manifestation | Treatment for fungal infection |
|-------------------------|---------------------------------|-------------------------------|-------------------|-------------------------------------|-----------------------------------|---------------------------|-----------------------------|
| Karimi-Galugahi M et al (2021) (n = 1) | Hospitalised | 2 weeks | Remdesivir, interferon-alpha, and systemic corticosteroid | Symptoms of SARS-CoV-2 infection | Readmitted for fungal infection after 1 week of hospital discharge | Rhino-orbital-cerebral mucormycosis | Insulin (raised blood sugar without ketoacidosis) and systemic antifungals |
| Mehta S et al (2020) (n = 1) | Hospitalised | 10 days | For COVID-19: IV meropenem and oral oseltamivir with parenteral methylprednisolone | Severe breathlessness, pyrexia, tachycynes, and generalised malaise | On the 10th day of hospitalisation, patient developed sinusitis, bilateral lid edema, and right-eye prominence | Rhino-orbitisitis, cerebral mucormycosis | Amphotericin B was added |
| Mekonnen ZK et al (2021) (n = 1) | Visit 1: Tested negative for SARS-CoV-2 given antibiotics for bronchitis | 31 days | Antibiotic for a week on suspicion of bronchitis | After one week, pt. presented with ARDS and hyperglycemia | 1 day after hospitalisation | Rhino-orbitalisitis with orbital involvement | Antifungal (liposomal amphotericin B), caspofungin |
| Mishra N et al (2021) (n = 10) | Hospitalised | NM | Cases 4–9: Steroid treatment Case 10: Both remdesivir and tocilizumab | Nasal blockage, eye, and facial pain | NM | Rhino-orbital-cerebral mucormycosis | IV amphotericin B |
| Mohammadi F et al (2021) (n = 1) | Visit 1: Hospitalised for SARS-CoV-2 infection | NM | Visit 1: Remdesivir and methylprednisolone | Visit two: Nasal obstruction and left side facial and orbital swelling | After 10 days of hospital discharge after COVID-19 treatment | Rhino-orbital-cerebral mucormycosis | IV liposomal amphotericin B |
| Riad A et al (2021b) (Of n = 7, 6 cases had rhino-orbital mucormycosis) II Candidosis Study (No. of patients) | Hospitalised | 4–6 weeks | Azithromycin, dexamethasone, saline, enoxaparin sodium, zinc | Symptoms of SARS-CoV-2 infection | From a few days to a month of COVID-19 diagnosis/recovery | Rhino-cerebral mucormycosis | Liposomal amphotericin B |
| Asymptomatic/mild COVID-19 cases Cortchoule J et al 2020 (n = 1) | Ambulatory COVID case | None | Ibufrofen and azithromycin twice for 5 days (1st and 3rd week) | 3 weeks post–lab confirmation of COVID-19 infection | Whitish plaque at the back of the tongue and the attached gingiva near the first lower premolar | Nystatin for 2 weeks Use of CHX 0.12% |
| Glavina A et al (2020) (n = 1) | Ambulatory COVID case | None | Systemic acyclovir | After a week of COVID-positive symptoms | White lesion on the ventral side of the tongue | Local therapy with nystatin, panthenol, local anesthesia |
| Mirabela D et al (2020) (n = 3; neonatal cases) | Case 1 and 2: asymptomatic but hospitalised for care Case 3: symptomatic and hospitalised | 2–3 weeks | Case 1: vitamin D Case 2: vitamin A, eye drops, topical cream for erythema Case 3: ampicillin, gentamicin, human immunoglobulin, amphotericin | During hospitalisation | Oral candidosis on the tongue, erythematous lesions | Case 1 and 2: topical nystatin Case 3: IV fluconazole and topical nystatin |
| Riad A et al (2020) (n = 1) | Ambulatory COVID case | None | Azithromycin, linezolid, and ceftriaxone | A few days post-SARS-CoV-2 infection | Multiple pseudo-membranous lesions with white plaques over the dorsal surface of the tongue | NM |
| Verma V et al (2021) (n = 2) | Case 1 and 2: hospitalised with mild COVID-19 symptoms | A week for fungal infection | Case 1 and 2: antiviral therapy | Presented with dysphagia. Upon investigation, SARS-CoV-2 infection was confirmed | Case 1: whitish patch on the back and lateral surface of the tongue Case 1: whitish patch on | Case 1: oral fluconazole and antiviral Case 2: oral fluconazole and antiviral (remdesivir) |

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| Study/No. of patients | Ambulatory/hospitalised patient | Length of stay in the hospital | COVID-19 therapies | Symptoms at the time of presentation | Fungal manifestation (time of onset) | Mucormycosis manifestation | Treatment for fungal infection |
|-----------------------|---------------------------------|-------------------------------|-------------------|--------------------------------------|-----------------------------------|---------------------------|-----------------------------|
| Moderate/Severe COVID-19 cases Amorim dos Santos et al (2020) (n = 1) | Hospitalised | 24 days | Initially: hydroxychloroquine, ceftriaxone, and azithromycin. Later: meropenem, sulfamethoxazole, trimethoprim, immunosuppressants, and anticoagulants. | After 24 days of ICU admission, opportunistic fungal infection. | The white plaque on the tongue dorsum. | Mucormycosis manifestation | Systemic fluconazole and oral nystatin |
| Baraboutis IG et al (2020) (n = 2) | Hospitalised | NM | Azithromycin, teicoplanin, dexamethasone | At 7-10 days of hospital admission, since hospital admission for SARS-CoV-2 symptoms. | Oral candidosis. | | NM |
| Diaz Rodriguez M et al 2020 (n = 3) | Hospitalised | NM | Antiviral, antibacterial, and corticosteroids | During hospital stay for SARS-CoV-2 infection treatment. | Pseudo-membranous candidosis and angular cheilitis. | Oropharyngeal candidosis. | Fluconazole, nystatin, and caspofungin |
| Salehi et al (2020) (n = 53) | Hospitalised | NM | Antiviral and corticosteroids | During hospital stay for COVID-19 treatment. | Moderate COVID: candidosis (18). Severe COVID: candidosis (4). Critical cases: candidosis (6). | | Miconazole nitrate |
| Favia G et al 2021 (Italy) | Hospitalised | NM | | | | | |
| Riad A et al (2021) (n = 3) | Case 1: hospitalised | 2-3 weeks | Case 1: azithromycin, levofloxacin, rivaroxaban, and lactoferrin. Case 2: moxifloxacin, pantoprazole, and multivitamins. | Case 1: 3 days after release from the hospital for COVID-19 treatment. Case 2: 2 weeks. Case 3: After 2 weeks. | | | Case 1: nystatin and 0.2% CHX. Case 2: topical miconazole. Case 3: systemic fluconazole and topical miconazole. |

ARDS, acute respiratory distress syndrome; CRD, chronic renal disease; CHX, chlorhexidine; ICU, intensive care unit; IV, intravenous; NM, not mentioned; NSAIDs, nonsteroidal anti-inflammatory drugs.
indicate that such coinfections in COVID-19 are due to 3 major fungal groups, *Candida* spp, *Aspergillus* spp, and mucorales, a group of common zygomycotic fungi. These infections manifest with a spectrum of clinical presentations, ranging from erythematous and edematous mucosae to pseudo-membranous lesions and, on occasions, to extensive focal tissue necrosis involving the alveolar bone.

**Candidosis**

Oral candidosis due to several pathogenic candidal species is perhaps the commonest human fungal infections seen in debilitated individuals.43,44 *C albicans*, the most common agent of oral candidosis, as well as several non-albicans *Candida* species have been reported in our cohort of COVID-19 cases, especially in hospital-bound patients.20,23 In general, these manifestations could be explicable in terms of diabetic ketoacidosis that promotes yeast growth and lymphocytopenia, especially the T lymphocytes, due to SARS-CoV-2 infection. Other causative factors include the use of broad-spectrum antibiotics and steroid therapy and neglected and poor oral hygiene.45 It is known that oral candidal infections are common amongst the "very young, the very old, and the very sick,"44 and this aphorism has been, once again, proven to be the case in COVID-19. For instance, candidosis was present in 3 full-term neonatal patients with COVID-19 infection, with no history of receiving antibiotics.15 Characteristically, neonates exhibit immature cellular immune responses, resulting in increased susceptibility to infection,46 and this, together with the SARS-CoV-2 infection, are the likely causes for such manifestations. Nevertheless, more comprehensive studies are needed to better understand the oral mycoses of COVID-19 in the neonatal population.

**Aspergillosis**

It is now known that bronchopulmonary aspergillosis is the another common opportunistic systemic infection seen in COVID-19.47,48 In general, it is frequently seen in those who are immunosuppressed and may lead to life-threatening complications.59 A solitary case of aspergillosis with maxillary sinus invasion in a patient with uncontrolled diabetes with severe COVID-19 was noted in our review.29.
The disease usually ensues after inhalation of Aspergillus spores, and their subsequent germination and proliferation in the bronchopulmonary system. However, on occasions, the infection may manifest in nasal sinuses, the oral cavity, and the eyes. The most common agent of the disease known to cause invasive oral and maxillofacial lesions is A. flavus. In the absence of a robust immune response, the angioinvasive hyphal elements of Aspergillus species usually cause thrombosis, leading to tissue infarction and necrosis. The other virulence traits of the fungus include the production of hemolysins, proteases, phospholipases, and the toxins, aflatoxin and gliotoxin.

Mucormycosis

Mucorales that cause mucormycosis are common saprophytic fungi found in air, dust, and wet, organic materials. They cause infection predominantly in patients with poorly controlled diabetes mellitus or those who are immunocompromised due to disease or drugs. Hence, it is not surprising that the prevalence of mucormycosis has increased during the COVID-19 pandemic. Oral mucormycosis was reported in 7 reviewed cases of mild to moderate SARS-CoV-2 infection, and most of them involved patients with either controlled or uncontrolled diabetes. Their clinical presentation...
included malaise, facial pain, swelling, irregular black eschar, exudation of pus from the eye and nose, and low-grade fever.

As noted above, mucormycosis is the third most reported opportunistic fungal infection in patients with SARS-CoV-2 infection. It has 4 to 5 categories: rhinocerebral, cutaneous, disseminated, gastrointestinal, or pulmonary, depending on the infected tissues. Of these, rhinocerebral mucormycosis is relevant in the current context as it affects the oral cavity, sinuses, nasal passages, and brain. The infection usually begins in the nasal mucosa or palate and spreads via nearby vessels to the paranasal sinuses, often involving the maxillary and ethmoidal sinuses. Previous literature from the pre–COVID-19 era also indicates that rhinocerebral mucormycosis affects patients with poorly controlled diabetes and immunosuppressed patients. Many of the cases in our review had documented mucor invasion of cranial nerves III, IV, and VI, leading to ptosis, pupillary dilatation, proptosis, and vision loss. In addition, hematogenous spread to the cavernous sinus led to fatal cavernous sinus thrombosis in a few cases.

In cases in which mucormycosis is suspected, prompt diagnosis and treatment are critical because of the angioinvasive nature of the fungus and its rapid systemic dissemination. A number of recent cases, particularly from the Indian subcontinent, report fungal invasion seeded in the maxillary sinus and progressing into maxillary alveolar bony tissues and then the oral cavity as well as the orbits, with eventual blindness of the individual. Late diagnosis of the disease with orbital invasion needs to be managed by radical surgery of the affected regions and removal of the orbital contents.

Apart from the Mucor genus, other disease-causing genera in this group include Rhizopus and Absidia. In the oromaxillofacial region, Mucor and Rhizopus species account for most of the oral and rhinocerebral mucormycosis in COVID-19 cases. In contrast, a single case from Mexico reported isolating Absidia (Lichteimia) spp (belonging to mucorales) from the biopsy of a young female patient with severe diabetic ketoacidosis secondary to steroidal therapy for COVID-19 treatment.

In clinical terms, it should be noted that most oral mycoses in COVID-19 may present as innocuous red patches on the hard palate or the buccal mucosa, as shown by incidental findings in SARS-CoV-2 infection. However, as some of these lesions may lead to impairment of vision and/or even removal of the affected bony tissues and eventual disfigurement, all clinicians examining the oral cavity should maintain a high index of suspicion and be cognisant of the oral and maxillofacial mycoses that may pose a threat to the long-term health and the quality of life of these patients, particularly after recovery from SARS-CoV-2 infection. Indeed, oral and maxillofacial mycoses in COVID-19 could be construed as a little-known silent manifestation of the pandemic.

Study limitations

Our review has a few limitations. First is the disparate and heterogeneous nature of the reported cases emanating from various geographic locales, a significant proportion with limited and incomplete data. For instance, only a few case reports or case series included microbiological or histopathologic data of the fungal lesions confirming the diagnoses, and mere clinical observations were reported. In addition, most reports documenting oral candidosis did not elaborate on the species differentiation of Candida species. Additionally, it should be noted that the majority of fungal infections reported thus far have been diagnosed in hospitalised patients with severe COVID-19, and the data presented cannot be extrapolated for all patients with COVID-19 who mostly have mild symptoms.

Conclusions

Patients with SARS-CoV-2 infection are susceptible to oral fungal superinfections. The most likely reasons for this could be the impaired immune defenses due to the underlying viral infection, immunosuppressive and steroid therapy for COVID-19, ventilator-associated fungal infection, xerostomic conditions, and/or extant diabetes mellitus. Oral and maxillofacial mycoses, when present, appeared either concurrently with COVID-19 symptoms or during the immediate postrecovery period. Attending clinicians must maintain a high degree of suspicion of the possibility of these mycoses, particularly in patients with underlying comorbidities such as diabetes. A full and complete oral examination of patients with COVID-19 leading to early identification and treatment of secondary oral and maxillofacial mycoses can considerably reduce morbidity and improve their long-term health and quality of life.

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Supplementary materials

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