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Manifestations and risk factors of COVID-19 and mucormycosis: A mini-review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has become a pandemic disease. It also increases the risk of co-infections. Mucormycosis is a severe fungal infectious disease and its causative agent, mucormycetes, belongs to an opportunist fungus Mucoraceae family. Mucormycosis in COVID-19 patients with mucormycosis presents an additional challenge worldwide. Mucormycosis shares certain risk factors and signs and symptoms with COVID-19. In this review, we summarize manifestations and risk factors of mucormycosis and COVID-19.

KEYWORDS: COVID-19; Mucormycosis; Manifestations; Risk factors

1. Introduction

Mucormycosis, a rare severe fungal infection, shows a high risk in immunocompromised patients, particularly patients with uncontrolled diabetes mellitus, iron overload, major trauma, and patients who are treated with high-dose of corticosteroid, and patients with large open wounds contaminated by Mucorales[1,2]. Normally elevated levels of inflammatory cytokines have been observed in COVID-19 patients. The immune response dysregulation is associated with coronavirus disease, with reduced T-lymphocytes (CD4⁺T and CD8⁺T) cells, and also may alter the innate immunity. That may permit secondary fungal infections[3,4]. In this review, we summarized highly destructive fungal infection (mucormycosis) with globally affected COVID-19 disease.

2. Manifestations of COVID-19 and mucormycosis

The COVID-19, a global pandemic infectious disease, is a life-

threatening respiratory disease that can affect near all organs of our body and is also associated with venous thrombosis, strokes, renal failure, cardiomyopathy, systemic vasculitis, and coronary[5,6]. The common symptoms in COVID-19 disease are fever, nasal congestion, sore throat, shortness of breath, fatigue, muscles pain, headache, weight loss, gastric disturbances, and rashes on the skin. These infection symptoms may arise in the human body between 2 to 14 days. Some patients' chest CT scans may show bilateral ground-glass opacity changes and lymphopenia, and the liver and heart specimens are likely to present some interstitial mononuclear inflammatory infiltrates. Otherwise, asymptomatic or mild symptoms also were noted in a large number of populations[7,8]. In the beginning, the viral reproduction numbers could be higher within the lower position of the respiratory tract, and infected cells are released causing inflammation signal molecules. Finally, pulmonary edema can be loaded in the alveolar spaces by hyaline membrane formation[9].

Mucormycosis or zygomycosis, a fungal infectious disease, is

Significance

The mini-review focuses on the manifestations and risk factors of concurrent COVID-19 and mucormycosis.

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highly severe, often acute. This disease is caused by ubiquitous and opportunist fungi belonging to the Mucoraceae family[10]. Normally the mucormycetes are found in dust and soil in the form of spores. These spores can be inhaled by a humans through the upper respiratory tract and finally spread toward the sinuses and invade into the brain, causing rhinocerebral mucormycosis and symptoms like fever, one side facial swelling, headache, sinus congestion, and black lesions outside the face or inside the mouth. While spores infection incorporates into the digestive system, it will induce gastrointestinal mucormycosis and symptoms such as abdominal pain, gastrointestinal bleeding, nausea, and vomiting. If infection occurs in dermal deep lacerations, it can cause cutaneous or disseminated mucormycosis, and the symptoms are the same with other types[11,12]. Chakrabarti *et al.*[13] divided mucormycosis into 3 clinical stages as stage I (signs and symptoms into the sino-nasal area), stage-II (sino-nasal area and sino-orbital infection), and stage III (intracranial involvement). Sugar also reported an uncommon presentation of renal infection. Initial computed tomography (CT-scan) of lung mucormycosis, the most common radiological pattern is a halo sign and then may deteriorate into mass/nodule. The standard roentgenograms and CT scans often reveal distinct degrees of swelling (soft-tissue) and, finally, bone damage that is typical of progressive mucormycosis[14,15].

Signs and symptoms of COVID-19 disease are similar to fungal diseases such as fever, shortness of breathing, and cough. Earlier laboratory testing is important to determine the COVID-19 and fungal infection. Patients can simultaneously suffer from fungal infection and COVID-19. Some authors have reported cases of invasive mucormycosis patients with COVID-19. Severe COVID-19 patients in an ICU (intensive care unit) are susceptible to fungal and viral infection[16]. Saldanha *et al.* reported a case of a 32-year-old lady who reported a 6 months history of uncontrolled diabetes and presented with complications in the left eye as well as facial pain. This patient was detected COVID-19 infection, and finally, histopathological examination showed mucormycosis[17]. Revannavar *et al.* reported a middle-aged woman newly detected diabetes, and she had a complicated fever and left-side facial pain. Initially, she was tested positive for COVID-19 disease, and then histopathological examination confirmed mucormycosis infection[18]. Khatri *et al.*[19] reported a case of a 68-year-old man who had undergone a heart transplant. Two months later, cough, fever, diarrhea, and mucormycosis occurred after COVID-19 (Table 1).

3. Risk factor of COVID-19 disease and mucormycosis

In recent decades, mucormycosis has increased due to the rising number of immunocompromised patients worldwide (mostly in developing countries). The highest number of cases was observed in India because of uncontrolled diabetes mellitus and trauma patients[32]. Rhinocerebral type of mucormycosis disease mainly occurs in diabetic ketoacidosis (two-thirds of the cases)[33,34],

and pulmonary mucormycosis most appear in patients who are already suffering from hematological malignancies[35]. Other long-proved risk factors of mucormycosis include AIDS, hematological disorders, liver cirrhosis, organ transplant, and high doses of steroids[36]. Uncontrolled diabetes ketoacidosis patients with iron overload take a higher risk of fungal infection, so do mucormycosis patients[37]. Most occasional cases of mucormycosis are reported in hospital lines, tornados, building construction, wooden tongue depressors, and adhesive bandages[12].

At the beginning of the COVID-19 pandemic, there was a heated discussion on whether a person with immunosuppressants is more vulnerable to COVID-19 infection[12,38]. The most notable risk factors for COVID-19 are comorbidities and advanced age. On the other hand, diabetes is one of the major risks at play[39]. Other common factors include cardiovascular disease, malignancy, hypertension, chronic respiratory diseases, kidney and liver diseases, and local immunodeficiencies. Other possible complication factors are acute kidney injury, thromboembolism, and coagulation disease[40-42].

The risk factors of both mucormycosis and COVID-19 are comorbidities, uncontrolled diabetes mellitus, and corticosteroids drugs[43]. The use of glucocorticoids produces various complex effects qualitative as well as quantitative immunosuppressive that influences cellular immunodeficiency and increases host possibilities to invasive fungal infection[44]. The extensive use of corticosteroids has increased glucose homeostasis. That may lead patients to mucormycosis. Corticosteroid drug use is a major risk factor for mycoses and mucormycosis[43]. A multicenter retrospective study in India from September to December in 2020, included 187 patients who suffered COVID-19 associated mucormycosis disease, and also observed diabetes mellitus and improper steroids use are quite common in these patients[45]. Seriously ill COVID-19 patients, especially those admitted into intensive care units and also in ventilation, or who had been hospitalized for longer periods, risk suffering fungal infection[46]. Monte Junior *et al.* represented a case of an 86-year-old male patient who suffered from fever, cough, acute diarrhea, and dyspnea, was admitted to an emergency room, and then tested positive for COVID-19 infection. This patient was treated with hydrocortisone, azithromycin, ceftriaxone, oseltamivir, and management with mechanical ventilation. After that, the patient blood report showed severe anemia (reduced hemoglobin level), thus, he was given 3 units of blood and omeprazole. According to the esophagogastroduodenoscopy report, two giant gastric ulcers and a deep hemorrhagic base were found. This patient died after one week and the pathological report showed mucormycosis[3]. Zurl *et al.* reported a case of 53-year-old male presented with obesity, depression, and myelodysplastic syndrome. Further, observation discovered other symptoms like fever, dysosmia, parageusia, soreness. Then polymerase chain reaction test was conducted, and the result confirmed COVID-19 infection. Therefore, treatment with high-dose of glucocorticoid and tocilizumab was initiated. Finally, the patient died after 24 days and a postmortem report was shown pulmonary mucormycosis[20]. In a case report by Maini

Table 1. Clinical profile, managements and outcomes of COVID-19 with mucormycosis.

Authors	Locations	Age/Sex	Patient history	Signs and symptoms	Treatments	Outcomes
Monte Junior <i>et al.</i> [3]	Brazil	86/male	Arterial hypertension	Acute diarrhea, cough, dyspnea, fever, melena and severe anemia	Ceftriaxone, azithromycin, oseltamivir, hydrocortisone, antifungal agents not admin	Patient expired
Zurl <i>et al.</i> [20]	Austria	53/male	Myelodysplastic syndrome, depression, obesity (BMI 34)	Fever, sore throat, parageusia, dysosmia	Voriconazole, tocilizumab, glucocorticoids, piperacillin/tazobactam	Patient expired
Maini <i>et al.</i> [21]	India	38/male	No history of diabetes, debilitating condition	Fever, body ache, cough, shortness of breath, after 18 days swelling & pain (left eye)	Remdesivir, methylprednisolone, dexamethasone, piptaz metronidazole, fluconazole, amphotericin B, eyedrops tobramycin BD, nepalact	Patient was satisfied with the outcome
Placik <i>et al.</i> [22]	Yuma, USA	49/male	No significant past medical history	Fever, cough, shortness of breathing, acutely dyspneic	Ceftriaxone and azithromycin, dexamethasone, remdesivir, amphotericin B	Patient expired
Pasero <i>et al.</i> [11]	Italy	66/male	Arterial hypertension treated with ACE-inhibitors	Rapid & progressive deterioration of oxygenation, COVID-19 related symptoms	Hydroxychloroquine & lopinavir-ritonavi, piperacillin-tazobactam levofloxacin, liposomal amphotericin B	Patient expired
Khan <i>et al.</i> [23]	Texas, USA	44/female	Type II diabetes & no prior history of tobacco use	Fever, reduce oxygen level, respiratory rate of 26, heart rate of 126 bpm	Remdesivir & insulin drip methylprednisolone, cefepime & vancomycin, voriconazole, piperacillin/tazobactam, micafungin, liposomal amphotericin	Patient expired
Saldanha <i>et al.</i> [17]	India	32/female	Uncontrolled diabetes since 6 months	Complete ptosis (Left eye) & left facial pain	Amphotericin B	Decreased facial pain, no progress in vision
Revannavar <i>et al.</i> [18]	India	Middle-aged/ female	Newly detected diabetes	Fever, facial pain (left side), mild COVID-19 infection	Insulin therapy, amphotericin B	Decreased diffuse opacification
Mehta <i>et al.</i> [24]	India	60/male	Diabetic (more than 10 years)	Severe breathlessness, tachypnea, pyrexia, generalized malaise, complicated (right eye)	Dexamethasone, oseltamivir, meropenem, methylprednisolone, insulin, meropenem, vancomycin, amphotericin B	Patient expired
Alekseyev <i>et al.</i> [25]	USA	41/male	Diabetes mellitus	Loss of taste & cough, aching pain, pain medications alleviated & discomfort	Hydroxychloroquine, steroids, amphotericin B, surgery	Discharged after complete therapy
Kanwar <i>et al.</i> [26]	USA	56/male	End-stage of renal disease going on hemodialysis	COVID-19 complication, fatigue & shortness of breath	Methyl prednisone, tocilizumab & methylprednisolone, tocilizumab, vancomycin & piperacillin-tazobactam	Patient expired

Table 1. Clinical profile, managements and outcomes of COVID-19 with mucormycosis (continued).

Authors	Locations	Age/Sex	Patient history	Signs and symptoms	Treatments	Outcomes
Khatri <i>et al.</i> [19]	USA	68/male	Undergo heart transplantation	Fever, cough, diarrhea, fungal mucormycosis	Prednisone oral, mycophenolate mofetil, tacrolimus prophylactic atovaquone, nystatin, valganciclovir, immunosuppressive agents, remdesivir, hydroxychloroquine, vancomycin & meropenem, liposomal amphotericin B	Patient expired
Johnson <i>et al.</i> [27]	USA	79/male	Diabetes & hypertension	Fevers, dry cough, shortness of breathing	Antibiotics, remdesivir, dexamethasone, antifungal treatment AmB 400	Discharged with long-term acute care facility
Ahmadikia <i>et al.</i> [28]	Iran	44/female	Uncontrolled diabetes, heart disease, asthma, hypertension, tuberculosis	Fever, dry cough, malaise, partial dyspnoea, toothache, headache, nasal congestion, facial swelling	Dexamethasone metronidazole, penicillin V & naproxen liposomal amphotericin B	Patient's clinical situation improved
Werthman-Ehrenreich [29]	Buffalo, USA	33/female	Suffering mental status, hypertension, asthma, proptosis	Ptosis (left eye) dry (mucous membranes were), palate had brown, dry appearing secretions	Vancomycin & piperacillin-tazobactam, remdesivir amphotericin B	Patient expired
Mekonnen <i>et al.</i> [30]	USA	60/male	Insulin-dependent diabetes, hypertension, hyperlipidema, asthma	Dyspnea & hypoxia, worsening symptoms, prominence (right eye)	Antibiotics, remdesivir, hyperglycemia, vancomycin & cefepime, liposomal amphotericin B, dexamethasone	Patient expired
Nehara <i>et al.</i> [31]	India	59/female	Diabetic	Mild proptosis, headache, ptosis, chemosis, loss of vision, nasal cavity (blackish discharge), hard palate (black crust)	Azithromycin, liposomal amphotericin B Inotropes, remdesivir, oxygen supplementation, meropenem, dexamethasone, enoxaparin, insulin	Patient expired day 10 of admission
		62/female	Type II diabetes (twelve years)	Loss of vision & painless swelling (right eye), facial swelling (right side), black patch (right eye)	Antibiotics, liposomal amphotericin B	Under treatment, lost right eye completely
		68/female	Diabetes	Facial swelling, loss of vision, ptosis, headache, proptosis, black crust (hard palate), blood-tinged black discharge (nostrils)	Antibiotics, Inotropes, liposomal amphotericin B	Patient expired
		52/male	Diabetes mellitus	Diminished vision headache, chemosis, mild proptosis, blood tinged black discharge (nasal cavity), mild limit of ocular movement (right eye)	Antibiotics, posaconazole, liposomal amphotericin B	Patient recovered
		70/female	Type II diabetes (fifteen years)	Mild proptosis, lid edema, decreased vision, chemosis, black crust (nasal cavity)	Antibiotics, liposomal amphotericin B, basal-bolus insulin	Stable condition

et al., a 38-year-old male (no history of diabetes) hospitalized COVID-19 patient case was represented. This patient was treated with remdesivir IV injection. Dexamethasone injection was started after 11 days and continued for 12 days. After 18 days, the patient complained of pain, and his left eye showed chemosis. Consequently, diagnosis with mucormycosis[21]. Nehara *et al.* reported a case series of mucormycosis in a COVID-19 infection patient during his/her course of treatment[31]. Recently, 101 cases of COVID-19 with mucormycosis disease have been reported, of which 82 cases were from India and 19 from other countries, until May 13, 2021[47].

4. Conclusion

As COVID-19 disease has swept over the whole world and is making a recurrence, threats from the fungal co-infection disease such as mucormycosis become higher. Most of the signs and symptoms are same for both COVID-19 and mucormycosis diseases like cough, shortness of breathing, and fever. Early detection can reduce the severity as well as the mortality rate of the two diseases. On top of this, most of the risk factors are similar to both diseases. Management of COVID-19 by steroids, monoclonal antibodies, broad-spectrum antibiotics may develop mucormycosis. The recent paper provides new information on COVID-19 and mucormycosis disease this will help to motivate researchers and healthcare professionals.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

B.R.S.: contributed the supervision, validation, visualization, review, and editing; J.S.: contributed towards the writing-original manuscript, literature searching and editing.

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