CASE REPORT

Post-COVID-19 Disease Associated with Mucormycosis and Guillain-Barré Syndrome: A Causal Association or Just a Coincidence?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Originating from Wuhan, China, COVID-19 has rapidly spread worldwide. COVID-19 is primarily considered to be a respiratory illness, but with time there is enough evidence about the extrapulmonary manifestations of the disease. One of the neurological manifestations is Guillain-Barré syndrome (GBS). It may be associated with mucormycosis, with majority of cases occurring in India. Here, we report a case of a 40-year-old male patient, a known case of hypertension and diabetes mellitus who presented with the complaints of fever, cough and shortness of breath since May 10, 2021. He was found to be RT-PCR positive for COVID-19 on May 12, 2021. While recovering from COVID-19, on May 25, he was suspected to have rhino-orbital mucormycosis, which was confirmed on tissue specimen. While recovering from rhino-orbital mucormycosis, on July 26, the patient complained of weakness in bilateral lower limbs, followed by weakness in both upper limbs after 2 days. GBS was confirmed on nerve conduction study (NCS) and cerebrospinal fluid (CSF) examination. Patient was treated with intravenous immunoglobulin (IVIG), and while on treatment, the patient showed no significant improvement. Invasive ventilation was started in view of respiratory muscle involvement. The patient also developed autonomic dysfunction. He went into cardiac arrest and despite best efforts, couldn't be revived. Currently, to the best of our knowledge, there is no data to tell that both mucormycosis and GBS can occur in association with COVID-19. This case aims to raise awareness among the healthcare providers for this type of association. COVID-19 may be a cause or it may just be a mere coincidence, needs further study.

Keywords: COVID-19, mucormycosis, Guillain-Barré syndrome

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Originating from Wuhan, China, COVID-19 has rapidly spread worldwide. COVID-19 is primarily considered to be a respiratory illness, but with time there is enough evidence about the extrapulmonary manifestations of the disease, reports of which are increasing even today and is now considered to be a multisystem disorder. Extrapulmonary manifestations are as follows: neurological- headache, encephalopathy, Guillain-Barré syndrome (GBS), ageusia, anosmia, stroke; hematological- deep vein thrombosis, pulmonary embolism; cardiovascular- cardiomyopathy, myocardial ischemia, acute cor pulmonale; endocrinological- hyperglycemia, diabetic ketoacidosis (DKA); dermatological- livedo reticularis, urticaria; gastrointestinal- anorexia, nausea and/or vomiting, diarrhea and abdominal pain; renal- acute kidney injury, proteinuria, hematuria; hepatic manifestation- elevated aminotransferases, elevated bilirubin.[1]

As India continues to achieve stability over COVID-19, another imminent threat has emerged as a challenge to the country in the form of coronavirus disease-associated mucormycosis. Mucormycosis, caused by a group of molds called mucormycetes, is a rare but potentially fatal infection if inadequately treated. Commonly known as black fungus, the incidence of mucormycosis increased more rapidly during the second COVID wave compared to the first one in India.

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The most common causes reported to be accountable for the surge of mucormycosis in COVID-19 patients are likely to be uncontrolled diabetes, the rampant use of corticosteroids and longer stays in the intensive care unit (ICU). India contributed to more than two-thirds of the global cases of mucormycosis in patients with COVID-19.[2]

We report a case suffering from both GBS and mucormycosis associated with post-COVID-19. This case aims to raise awareness among healthcare providers for this type of association. To the best of our knowledge, this is one of the first cases of this association. COVID-19 may be a cause or it may be just an incidental finding.

CASE REPORT

A 40-year-old male patient, a known case of hypertension and diabetes mellitus, was admitted in some peripheral hospital with the complaints of fever, cough and shortness of breath since May 10, 2021. He was found to be reverse transcription-polymerase chain reaction (RT-PCR) positive for COVID-19 on May 12, 2021. The patient was suffering from moderate COVID-19 illness and DKA. He was given injection remdesivir and corticosteroids in that hospital. While recovering from COVID-19, on May 25, he complained of pain in teeth, facial swelling and headache. Contrast-enhanced computed tomography (CECT) paranasal sinuses (PNS)/orbit and brain was suggestive of left maxillary sinusitis with soft tissue thickening in the region of right lower buccal mucosa, likely due to fungal infection. Potassium hydroxide (KOH) mount from nasal secretions was negative for fungal hyphae. Punch biopsy was done from right lower buccal mucosa which was positive for fungal hyphae, suggestive of mucormycosis.

On June 8, the patient was brought to MBGH Hospital, Udaipur for further treatment of mucormycosis. Then, the patient was treated with injection liposomal amphotericin B. Magnetic resonance imaging (MRI) was done on June 10, which revealed invasive fungal sinusitis extending into right cheek, orbit and neck space (Figs. 1 and 2).

While recovering from rhino-orbital mucormycosis, on July 26, the patient complained of weakness in bilateral lower limbs, followed by both upper limbs after 2 days. Weakness was ascending and symmetrical in nature, not associated with bowel and bladder complaints.

On examination, deep tendon reflexes of both upper and lower limbs were absent and power was noted as 3/5 in all four limbs. Proprioception was abnormal; no cranial nerve involvement was seen at that time. Next day,

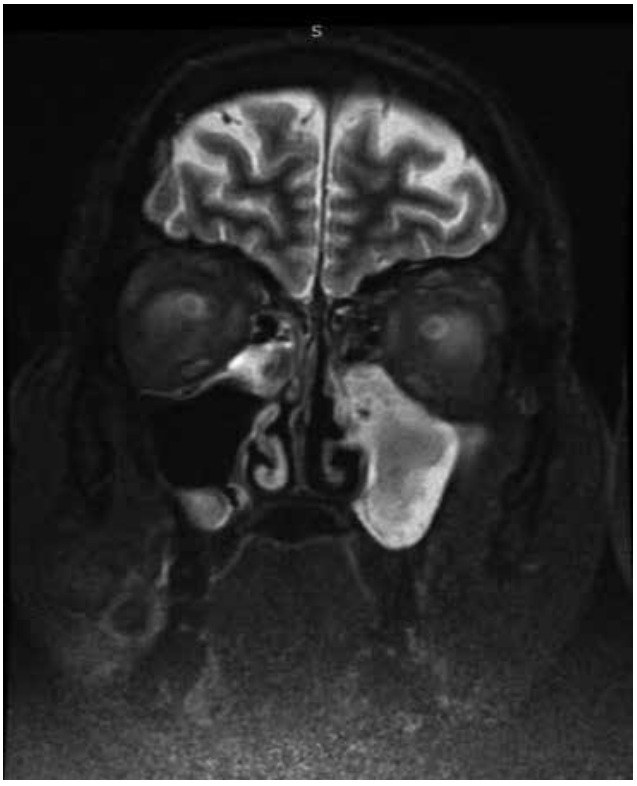

Figure 1. STIR-weighted coronal MRI image shows polypoidal mucosal thickening in bilateral maxillary sinuses.

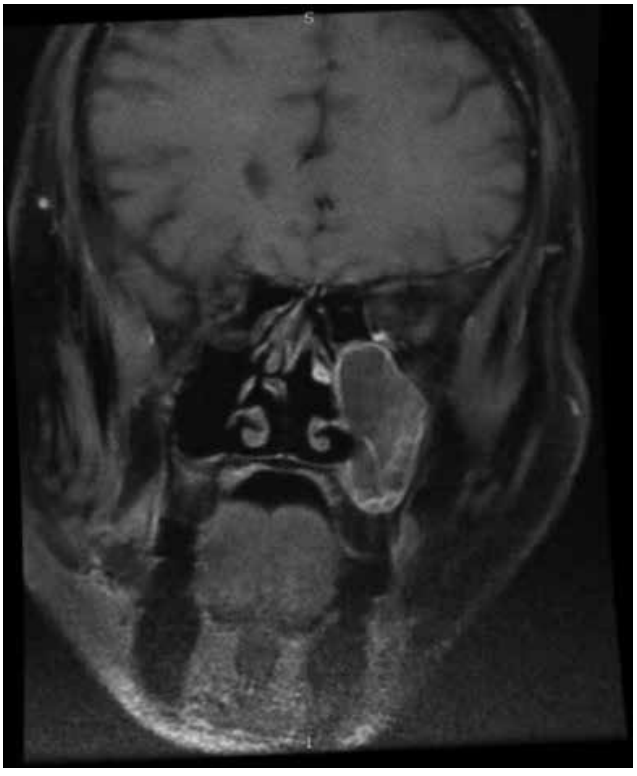

Figure 2. Post-contrast T1-weighted coronal MRI image shows heterogeneous post-contrast enhancement in the mucosa of bilateral maxillary sinuses.

the patient developed dysarthria and dysphagia and difficulty in opening mouth. On examination, bilateral facial nerve and right-sided 9th and 10th cranial nerve palsy was found. Electrolytes were within normal range. Clinically suspected to be a case of GBS, the patient was shifted to ICU. Nerve conduction study (NCS) revealed sensory motor severe axonal polyradiculoneuropathy. The patient was started on intravenous immunoglobulin (IVIG).

On investigation, serum electrolytes were: Na - 132 mEq/L, K - 3.8 mEq/L, Cl - 100 mEq/L. Other findings included: ESR - 53 mm/hr, Hb - 13.1 g/dL, TLC - 12.7 K/µL, platelets - 3.23 lakh/µL, N/L ratio - 12, D-dimer - 1026 ng/mL, ferritin - 1237 ng/mL, LDH - 447 units/L, urea - 42 mg/dL, creatinine - 2.0 mg/dL, CRP - 143 mg/L, HbA1c - 12.4%. Cerebrospinal fluid (CSF) examination was done on Day 6 of illness which showed albumino-cytological dissociation with protein - 128 mg/dL, glucose - 85 mg/dL and no nucleated cells. Patient was human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) negative. Thus, the diagnosis of acute motor sensory axonal neuropathy (AMSAN) variant of GBS was confirmed. IVIG was continued for 5 days with dose of 2 g/kg. While on treatment, patient showed no significant improvement. He developed respiratory muscle involvement, and was put on invasive mechanical ventilation. He also developed autonomic dysfunction. He went into cardiac arrest and couldn't be revived and was declared dead on August 1, 2021.

DISCUSSION

COVID-19 is predominantly a respiratory illness, but extrapulmonary manifestations are also seen in this disease. It may be associated with mucormycosis. Our patient first developed rhino-orbital mucormycosis and then developed extrapulmonary manifestation in the form of GBS.

In a study conducted by Singh et al,[3] 101 cases of mucormycosis in COVID-19 patients were reported. Of these, 82 cases were from India and the remaining 19 from other parts of the world. Mucormycosis was more commonly seen in males (78.9%), both in individuals who were active (59.4%) or had recovered (40.6%) from COVID-19. Pre-existing diabetes was reported in 80% of cases, and concomitant DKA was evident in 14.9% cases. Corticosteroid intake for COVID-19 treatment was reported in 76.3% of cases. Mucormycosis involving nose and sinuses (88.9%) was most frequently seen, followed by rhino-orbital mucormycosis (56.7%). Mortality was noted in 30.7%. We also reported a male patient who was a known case of diabetes mellitus, and presented with DKA along with COVID-19 for which

Table 1. Brighton Criteria for Diagnosis of Guillain-Barré Syndrome

Level 1 of diagnostic certainty	Bilateral, flaccid limb weakness *plus* Reduced or absent deep tendon reflexes in weak limbs *plus* Monophasic illness with interval between onset and nadir of weakness of 12 hours to 28 days; subsequent clinical plateau *plus* Electrophysiological findings conforming with GBS *plus* Cytoalbuminologic dissociation (Raised CSF protein above laboratory normal value with CSF total white cell count <50 cells/µL) *plus* No detectable alternative diagnosis for weakness
Level 2 of diagnostic certainty	Bilateral, flaccid limb weakness *plus* Reduced or absent deep tendon reflexes in weak limbs *plus* Monophasic illness with interval between onset and nadir of weakness of 12 hours to 28 days; subsequent clinical plateau *plus* CSF total white cell count <50 cells/µL (with or without raised CSF protein above laboratory normal value) OR Electrophysiological studies conforming with GBS (If CSF not collected or results not available) *plus* No detectable alternative diagnosis for weakness
Level 3 of diagnostic certainty	Bilateral, flaccid limb weakness *plus* Reduced or absent deep tendon reflexes in weak limbs *plus* Monophasic illness with interval between onset and nadir of weakness of 12 hours to 28 days; subsequent clinical plateau *plus* No detectable alternative diagnosis for weakness

corticosteroid treatment was given. He developed rhino-orbital mucormycosis while having active COVID-19.

The first case of COVID-19–associated GBS was reported from Wuhan, as a suspected parainfectious disease, where the patient developed symptoms of COVID-19 seven days after the onset of GBS symptoms.[4] But, this was not seen in our patient as our patient presented with GBS as post-COVID complication, 2 months after COVID-19.

Diagnosis of GBS is based on Brighton criteria which was developed by Brighton collaboration in 2011 (Table 1).[5] Our patient fulfilled Brighton's criteria with level 1 of diagnostic certainty.

GBS can be treated with IVIG (2 g/kg body weight divided in 5 daily doses) or plasmapheresis.

Mortality rate is <5% in optimal settings, prognosis is poor with advanced age, a fulminant or severe attack, delay in onset of treatment and if patient presents with AMSAN variant.[6]

Our patient was middle-aged, and was started on IVIG on Day 3 of onset of weakness and there was no undue delay in treatment. As the outcome of patient was death, severe attack of AMSAN variety with respiratory involvement and dysautonomia may be the cause of poor prognosis in the patient.

CONCLUSION

GBS and mucormycosis are likely to be complications of post-COVID-19. They should always be considered if a COVID-19 patient, during the infection or in recovery phase, develops progressive areflexic paralysis. The patient should be diagnosed and treated as early as possible to reduce morbidity and mortality. Thus, our case report aims to raise awareness among healthcare providers for this type of association, i.e., possibility of GBS and mucormycosis both in association with COVID-19. In our knowledge, this is one of the first cases with this association. COVID-19 may be a cause or a mere coincidence, needs further study.

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Male Sex, Older Age Linked with Risk of Antibiotic Failure in Pneumonia

According to a secondary analysis of a randomized trial, two factors have been found to be associated with a greater risk for antibiotic failure in clinically stable patients hospitalized with community-acquired pneumonia (CAP). These factors include age and sex.

In around 300 CAP patients who were stable after 3 days of beta-lactam treatment, the rate of treatment failure was 26.8% at 15 days. Multivariable analysis after adjustment for Pneumonia Severity Index (PSI) scoring and baseline urea level revealed that male sex (odds ratio [OR] 1.92, 95% confidence interval [CI] 1.08-3.49) and age (OR 1.02 per year, 95% CI 1.00-1.05) were predictors of treatment failure, and were independent of duration of antibiotic therapy or biomarkers, such as CRP and procalcitonin. The results were published in *JAMA Network Open*… (*Source: Medpage Today*)