Invasive Fungal Infections in Dengue Recovered Patients: A New Phenomenon in the Covid-19 Era

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Abstract Invasive fungal rhinosinusitis was seen to rise to epidemic levels after the 2nd wave of ongoing Covid pandemic, especially in tropical countries, maximally in India. A similar trend is being observed for cases who have recently recovered from dengue virus infection. Post dengue invasive fungal infection is a new presentation and any associations between it and Covid pandemic need to be studied in detail to help prepare for any complications. 3 patients presented to the out-patient department of E.N.T at a tertiary level teaching hospital in East India with complains similar to rhinosinusitis. These patients were then evaluated and diagnosed to be infected from Mucormycosis and Aspergillosis fungal sinusitis after which they were managed with surgical debridement and systemic antifungal therapy. All had a recent history of recovery from Dengue virus infection and a possible association could be suspected. 3 patients presented with complains of pain over upper jaw with orbital swelling and loss of vision developing over a period of 24 days. Two of them had ulceration of hard palate. They were then subjected to Contrast MRI along with CT scan of the Paranasal sinuses which depicted pansinus involvement with intracranial extension in two patients. These were then planned for diagnostic nasal endoscopies along with biopsies which turned out to be Invasive fungal sinusitis in the form of Aspergillosis and Mucormycosis. All the 3 patients had recent history of recovery from Dengue virus infection and did not have any other co-morbidities. Covid Associated Mucormycosis (CAM) is a well-known entity now but no reports of Dengue associated Invasive fungal sinusitis are yet reported. Whether this new phenomenon has anything to do with the interactions between dengue virus and coronavirus is not known at present and needs to be studied in detail so appropriate management protocols can be formulated.

Keywords COVID19 · Mucormycosis · Post dengue · New phenomenon

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Received: 14 February 2022 / Accepted: 25 August 2022 / Published online: 4 September 2022

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**Introduction**

WHO declared COVID-19 as a global pandemic on 11th March 2020 and has completed almost 2 years of human circulation now. After the initial case reports of acute respiratory distress syndrome (later proved to be caused by SARS CoV-2) on December 31, 2019 in the city of Wuhan, China, the outbreak spread significantly affecting all the countries around the world (1). Since then, all the continents across the globe have been facing the brunt of pandemic in terms of overwhelming health care systems, lack of health care workers and significant economic and psychological burden as well. Millions of people were infected and expired in the past two years owing to COVID-19 infection (2) (Table 1).

Coronavirus disease has a wide range of spectrum from being asymptomatic to severe pneumonia and about 5% of patients require ventilator support. Various studies and research papers have shown the pathophysiology of covid19 as: cytokine surge, markedly increased pro inflammatory CD4 and CD8 toxic granules, hyper coagulable state, altered iron metabolism and increased iron overload which result in hypoxia and multisystem failure [3, 4,]. All these factors lead to immune system dysfunction and are proposed to be the major causes of the emergence of acute invasive fungal infections of head and neck region in post covid patients (5).

In the pre covid era mucormycosis was a rare entity with an incidence of 0.0051.7 per million population. However, the Indian subcontinent has witnessed a marked rise in mucormycosis cases especially during the 2nd wave of covid 19 pandemic. The incidence of CAM was cited as 0.14/1000 diabetic patients which is 80 times higher than that reported in other parts of the world. This became a major public health burden in India (5, 6) and was declared as an epidemic. The possible etiological factors of CAM include Diabetes Mellitus (which in itself is a pandemic and an independent risk factor for mucormycosis) as the underlying disease in up to 5476% cases, and other factors like Diabetic ketoacidosis, cytokine storm and corticosteroid therapy to treat severe covid pneumonia cases (7). However, the true incidence and etiology of rhino-orbital mucormycosis in post covid patients is still unknown.

Such a high incidence of previously rare invasive fungal infection is a surprise thing in covid recovered patients, but what is more surprising is the emergence of mucormycosis cases in dengue recovered patients. This is because SARS CoV-2 being a novel infection, its exact pathophysiology and consequences are not completely understood at present, but dengue virus infection has been an endemic disease and a major public health concern throughout tropical and subtropical countries like India for many decades (8). Dengue virus is a single stranded RNA virus and has four serotypes from DEN 1 to DEN 4. All these serotypes are antigenically similar, yet they differ enough to elicit cross protection only for a few months after infection from any one of them (9). To the best of our knowledge, invasive fungal infections were never seen as a complication in dengue recovered patients before the covid pandemic. Should we worry about this new phenomenon in the covid era?

**Case Series**

Three patients of post dengue rhinoorbitocerebral mucormycosis presented in our tertiary care center, details of which are described below:

**Case 1.**

A 43 years old female presented to us with complaints of left sided jaw pain, left periorbital swelling and loss of vision. On examination, the patient was conscious and oriented with negative perception of light in left eye and palatal erosion over left side of hard palate. There was gum abscess on the right side also (Fig. 1a). On the basis of clinical suspicion, the diagnosis of mucormycosis was made and injection liposomal Amphotericin B started at a dose of 5 mg/kg/day. Patient was not a known case of diabetes mellitus and no past history of covid infection or steroid use was present. However, she suffered from dengue 10–12 days before mucormycosis and was found to be hyperglycaemic at the time of admission to hospital. Contrast enhanced MRI with fat suppressed images of paranasal sinuses (PNS), orbit and brain was performed for further evaluation (Fig. 1b). Contrast enhanced CT scans were obtained to look for bony erosions of maxilla, orbit and skull base. Endoscopic biopsies were taken and sent for KOH mount, histopathological examination and fungal culture. Ophthalmological opinion was obtained. All routine investigations were done including complete blood counts, blood sugar, HbA1c, renal function tests, liver function tests, quantitative C reactive protein and d-dimer. Preanesthetic evaluation was done and patient planned for surgical debridement with left total maxillectomy, right infrastructural maxillectomy and left orbital clearance under general anaesthesia. Blood sugar was regularly monitored and controlled. Liposomal Amphotericin B injection (5 mg/kg/day) was continued for three weeks postsurgery. Then she was started on tab posaconazole 300 mg/day for six months. She was on monthly follow up for endoscopic crust removal for three months.

**Case 2.**

This is a case of a 26 years old male student who suffered from moderately severe dengue. 5 days following recovery he developed a sudden onset of left eye proptosis, chemosis, loss of vision, headache and slurred speech (Fig. 2a). He was in a state of confusion and irritability at the time of...
presentation. There was no history of covid infection, diabetes mellitus or steroid use. Endoscopy revealed grossly necrosed left nasal mucosa and turbinates. Oral cavity examination was normal. Biopsy specimen sent for KOH mount, HPE and fungal culture. Inj. Liposomal Amphotericin B started at a dose of 5 mg/kg/day. Gadolinium enhanced MRI with fat suppressed images of PNS, orbit and brain showed hypointense mucosa in bilateral nasal cavity, left maxillary, ethmoid, sphenoid and frontal sinuses, left orbital cellulitis and left temporal lobe abscess of 19 × 17 × 21mm size (Fig. 2b). Neurology and ophthalmology opinion obtained and tablet levetiracetam 500 mg was given twice daily along with injection mannitol 1.5 g/kg IV infusion. All routine blood investigations done similar to case 1. Transient hyperglycaemia was noted at the time of admission which was controlled. He was planned for bilateral sinonasal debridement with left orbital exenteration under GA. Post operative lip Amp B injection (5 mg/kg/day) continued for 4 weeks followed by tab posaconazole 300 mg daily for six months. Follow up was similar to case 1.

Case 3.

A 61 years old male came to us with sudden onset bilateral periorbital edema (R > L) and vision loss in both eyes which developed 10 days after dengue infection (Fig. 3). There was no prior history of covid infection, diabetes mellitus or steroid use. Bilateral upper jaw ache, numbness and palatal erosion was present. Endoscopic biopsy, imaging and routine investigations were carried out similar to case 1 and 2. Liposomal Amphotericin B injection (5 mg/kg/day) started and continued for four weeks after surgery. Patient underwent bilateral sinonasal debridement with bilateral infrastructural maxillectomy and orbital clearance.

Discussion

The fungi causing mucormycosis is ubiquitous in nature and is acquired mainly by inhalation of spores, less commonly via infected wounds and ingestion of spores. It is a highly fatal angioinvasive disease that causes tissue necrosis.
Human infections are mainly caused by the species of genera Rhizopus, Mucor and Rhizomucor (10). The etiological agent in majority of the cases of CAM were rhizopus sp. And unspecified mucorales. Aspergillus and candida infections were also seen (11). This is contradictory to our study as in two cases aspergillus sp was identified predominantly on histopathological examination and fungal culture both.

According to the site of involvement, mucormycosis can be classified as rhino-orbito-cerebral, pulmonary, cutaneous and gastrointestinal forms. Rhino-orbito-cerebral invasion was most common among CAM patients followed by pulmonary and cutaneous mucormycosis (12, 13).

SARS-CoV-2 infection is found to be associated with impairment of beta cell function of pancreas. Due to this reason, previously euglycemic patients were found to develop hyperglycemia during the course of COVID 19. Hence, it may be concluded that, covid 19 infection may trigger development of diabetes mellitus with or without ketoacidosis which may persist weeks or months after recovery [14, 15]. This helps relating to the fact that although there was no history of covid infection in none of our patients yet transient hyperglycemia was noticed at the time of admission to the hospital.

On reviewing the literature for determining SARS-CoV-2 infection as an independent risk factor for development of mucormycosis, it is observed that covid 19 infection increases the synthesis of GRP78 protein, which is a specific receptor on host endothelium that facilitates fungal endocytosis [10, 16]. GRP78 being a stress related protein, is also enhanced with elevated blood glucose and ketone bodies. Furthermore, increase in S. iron, ferritin and heme in
covid infection results in free radical injury and predisposes to endothelial damage which further add to thrombosis and angioinvasive property of mucorales [17–19]. Why India has the highest number of mucormycosis cases during covid pandemic requires in depth research.

The fungal infection associated with dengue in our cases is similar to that of post covid mucormycosis in terms of presentation, clinical signs and symptoms, MRI/CT findings and management. The notable difference between the two entities is seen in terms of sudden loss of vision in all cases as the first presenting symptom.

Recently, a few research papers have mentioned the interaction of dengue virus and SARS CoV 2 in terms of Antibody Dependent Enhancement and cross reactivity between antibodies against the two viruses. Both these viruses share some pathophysiological similarities such as capillary leakage, thrombocytopenia, coagulopathy and cytokine storm mediated by tumor necrosis factor (TNF), interleukin 6, interferon gamma and chemokines like macrophage migration inhibitory factor (MIF) (20, 21, 22, 23). Further detailed studies are required to explain the interaction between dengue virus and SARS CoV 2 and whether this interaction plays any role in the emergence of invasive fungal infections as a post dengue sequelaes.

### Conclusion

Invasive fungal infections like mucormycosis which were rarely seen in pre covid times are reported to occur in large numbers in 2nd wave of covid 19, maximally in India. Dengue is an endemic disease in tropical countries since many decades and mucormycosis is seen as a complication of dengue for the first time. Possibility of interaction between the two viruses and pathophysiology of SARS CoV 2 needs to be studied in detail. This will help in predicting the possible complications that can be encountered during pandemic as
no one is sure how long the virus is going to remain in the community.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr. PS. The first draft of the manuscript was written by AR and SS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

Declarations

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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