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Dengue-Induced Mucormycosis? Metamorphosis in the COVID-19 Age

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Abstract

Dengue-Induced Mucormycosis: Metamorphosis in the COVID-19 Age. COVID-induced immunosuppression resulted in an unprecedented outbreak of mucormycosis, a grave opportunistic infection by fungi. SARS-CoV-2 and dengue virus may coexist in tropical countries like India. They are studied to have converging clinical, pathophysiological and immunological properties, thereby resulting in potential interactions between them. Antibodies against SARS-CoV-2 may augment Dengue virus infection by utilizing ADE, a phenomenon in which antibodies produced in the body after infection or vaccination may enhance subsequent viral infections and secondary complications such as mucormycosis. Two such cases of mucormycosis in association with dengue are presented here. Hence, COVID-19 age may observe a metamorphosis in viral disease presentations as perhaps with Dengue virus.

Keywords: Dengue Virus; Mucormycosis; Fungi

Abbreviations: KOH: Potassium Hydroxide; CECT-PNS: Contrast Enhanced Computerised Tomography Paranasal Sinuses; CEMRI: Contrast-Enhanced Magnetic Resonance Imaging; ICU: Intensive Care Unit; PTCA: Post-Percutaneous Transluminal Coronary Angioplasty; SARSCoV2: Severe Acute Respiratory Syndrome Coronavirus2; TNF: Tumor Necrosis Factor; MIF: Macrophage Migration Inhibitory Factor; ADE: Antibody Dependant Enhancement.

Introduction

Dengue-endemic tropical countries have been double hit by COVID-19 alongside dengue. This has resulted in disarray in making the precise diagnosis as the two infections are indifferentiable in the early phase [1]. Patients with chronic diseases such as diabetes, hypertension, and cardiovascular disease are more likely to have severe illness and death in both COVID-19 and dengue [2].

A dramatic escalation in rhinorbital mucormycosis, a grave opportunistic fungal infection was seen as the second wave of COVID-19 was abating and was studied to result due to COVID induced immunosuppression. A new observation of post-dengue mucormycosis was first reported in a private Delhi hospital.

Through this case report we reflect on the dengue virus endemic in India as the likely cause resulting in a breeding ground for opportunistic fungal infections as grave as mucormycosis, including its potential interaction with the ubiquitous SARSCoV2, not only in at-risk patients having multiple comorbidities but also in apparently healthy patients.

Cases

Patient 1

A eighteen-year-old male, presented to our hospital as the second wave of COVID-19 was in a decrescendo, with complaints of left cheek swelling, left eye swelling, and bleeding from nose (Figure 1). He had been hospitalized for eight days in another hospital with complaints of fever, multiple episodes of loose stools and vomiting, and an episode of seizure. Thereafter, he was brought to our hospital for further management. Here, he tested positive for NS1 antigen and diagnosed with Dengue fever. He also tested positive to Reverse Transcriptase Polymerase Chain Reaction for COVID-19 testing. Absolute CD3+, CD4+, CD8+ counts were with in normal range. He had no significant past medical or surgical history.

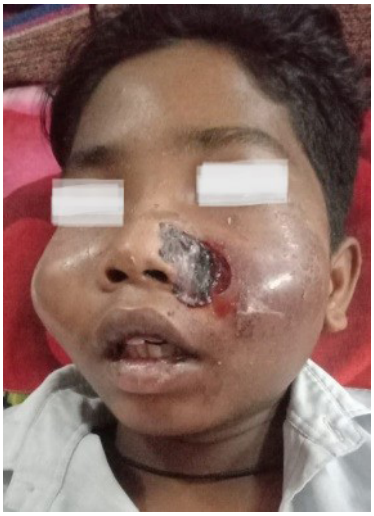

Figure 1: Rhinoorbital mucormycosis presenting as swelling in left eye and left cheek and bleeding per nose.

A potassium hydroxide (KOH) mount for fungal hyphae came positive for aseptate and septate hyphae. His Contrast Enhanced Computerised Tomography Paranasal sinuses (CECT-PNS) and Orbit were suggestive of invasive fungal sinusitis with orbital extension. His Contrast-Enhanced Magnetic Resonance Imaging (CEMRI) brain was suggestive of acute necrotizing encephalopathy secondary to dengue infection.

The routine blood investigations including blood sugar levels were in the normal range during the current hospital admission. Health records from the previous hospital admission were unavailable. He received ten cycles of Amphotericin B and was posted for debridement surgery. The trachea of patient was intubated using awake fibreoptic intubation under conscious sedation with intravenous dexmedetomidine as he had limited mouth opening secondary to mucormycosis involvement of the face. He underwent subtotal maxillectomy with left orbital decompression which resulted in major blood loss of approximately 45 percent of his blood volume which was adequately replaced with crystalloids, colloids, and blood products and maintained hemodynamically stable. The patient was not reversed, and his trachea was not extubated in view of the nature and extent of surgery and the presence of a difficult airway and was shifted to the intensive care unit (ICU) for further care. His trachea was extubated next day using an airway exchange catheter. The debridement surgery was extensive and mutilating. The histopathological examination of the excised tissue was consistent with mucormycosis. He made an uneventful recovery and discharged home.

The patient was followed up over the next few months and readmitted 8 months later, for receiving Platelet Rich Plasma injection at the local site to stimulate bone growth (Figure 2).

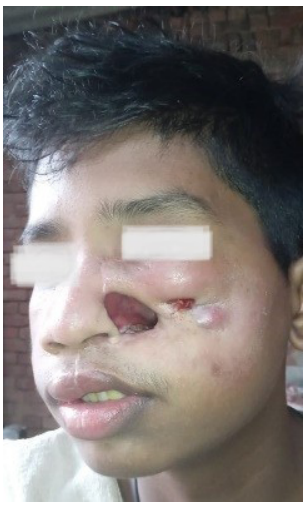

Figure 2: Post Debridement Surgery Which was Mutilating and Left Major Bone and Soft Tissue Defects.

Patient 2

A 69 year old male, presented with headache and nasal obstruction for fifteen days. Patient had a history of dengue fever twenty-five days prior, and also gave a history of COVID-19 one year back. He had multiple comorbidities namely chronic interstitial lung disease, hypothyroidism on oral levothyroxine supplement, chronic type two Diabetes Mellitus on oral hypoglycaemic agents, coronary artery disease and post- percutaneous transluminal coronary angioplasty (PTCA) on dual antiplatelets, chronic hypertension. Blood sugars were uncontrolled with fasting value of 166 milligrams per decilitre and postprandial value of 203, and glycated hemoglobin HbA1C was 10.9.

KOH mount showed septate and aseptate hyphae. CECT PNS, head, and orbit study were normal. The patient was planned for surgery, but he left against medical advice and was lost to follow-up.

Discussion

Infection with tropical pathogens like dengue virus (DENV), especially in the absence of respiratory involvement may be confused with early COVID-19 caused by Severe acute respiratory syndrome coronavirus2 (SARSCoV2) due to overlapping clinical manifestations like fever, skin rash, and nonspecific symptoms and laboratory investigations like leukopenia, and thrombocytopenia [1,3].

SARS-CoV-2 and DENV also 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) [4].

SARS-CoV-2 infection may also result in a false positive test for Dengue virus IgM.3 Furthermore, contributing to the conundrum early symptoms such as nasal bleeding in mucormycosis, may also be confused to be due to dengue infection [5].

This poses significant implications for infection prevention and control, as unsuspected cases of COVID-19 masquerading as undifferentiated fever may initially be managed without isolation, thereby eluding its containment and causing healthcare-associated transmission [6]. On the flip side, a necessary consideration is that isolation may lead to delayed recognition and management of plasma leakage in coexisting severe dengue.

Therefore, patients with viral prodromes should be routinely screened during a dual outbreak of COVID-19 and dengue, also because the two infections may coexist [7]. A similar pandemonium was encountered in the evaluation of patients presenting with undifferentiated fever, during the SARS outbreak in 2003 [8].

The situation is worsened owing to the resource-limited health infrastructure of the tropics which is further stretched by the overlapping outbreaks. This thereby contributes to increased disease complications and worse outcomes.

When cases of mucormycosis were noted in association with DENV infection, it emerged as a new phenomenon. DENV has been studied to cause profound bone marrow suppression that affects all three cell lineages, showing recovery as virus and virus-infected cells are eliminated by the immune system [9].

Dengue virus results in endothelial barrier damage and induces endothelial cell apoptosis. It leads to the rupture of skin integrity and consequent infection facilitation [10]. DENV infection has been demonstrated to induce suppression of humoral immunity, as well as cell-mediated immune responses. This may consequently create flourishing grounds for opportunistic infections, especially in patients with an already weakened immune system. Opportunistic fungal infections in association with DENV have been rare in pre-COVID times.

An increase in this rare occurrence was noted post the second wave of COVID-19. The possible explanations for it are put forward here. The potential for interaction between SARS-CoV-2 and DENV may not only coexist in a host but may undergo a potential interaction. The possible cross-reactivity between the two viruses may result in Antibody Dependent Enhancement (ADE).

Antibody-dependent enhancement (ADE) is a phenomenon in which antibodies produced in the body after infection or vaccination may enhance subsequent viral infections. This is thought to be due to the production of antibodies with low neutralizing activity that bind to the virus and facilitate viral entry, or antigen–antibody complexes that cause inflammation [11].

In contrast to the theory of ADE favoring severe disease causation, there has been evidence conveying that DENV antibodies are not involved in ADE of SARS-CoV-2 and may instead reduce the severity by cross-reacting with SARS CoV-2 Abs. It is not established whether SARS-CoV-2 antibodies impede DENV infection by binding to DENV particles or augment DENV infection by utilizing antibody dependent enhancement [3].

The first such case reported was a 49-year-old male who presented with a sudden loss of vision in one eye, 15 days after his recovery from the vector-borne disease [12] diagnosed as post-dengue mucormycosis.

Singhal, et al. [13] reported three patients with the diagnosis of severe invasive mucormycosis who had a history of recovery from dengue infection. They concluded that there is a possibility of interaction between the DENV and SARS-CoV-2 in decreasing the immunity and providing grounds for fungal growth [13].

There have been rare reports of post-dengue mucormycosis in the past. Therefore, the role of DENV resulting in a state

of immunosuppression only by itself seems to be of lesser consequence. COVID-19 is an evolving systemic disease and has been unfolding its diverse manifestations. It is well established that COVID-19 causes a prolonged period of immune dysregulation by involving both innate and adaptive immunity after SARS-CoV-2 infection.

This indicates the likely possibility of undiagnosed COVID disease coexisting with dengue infection which had resulted in immunosuppression and mucormycosis infection in our patients. Although, uncontrolled diabetes in the second patient may have also been abetted in causing mucormycosis [14]. Comorbidities, in particular, diabetes and cardiovascular disease as in our second patient have been observed to be risk factors for severe disease outcomes [2].

Further detailed studies are required to explain the interaction between DENV and SARS-CoV-2 and whether this interaction plays any role in the emergence of invasive fungal infections as post-dengue sequelae.

There are no reported cases of mucormycosis this season, though patients are still presenting with dengue as well as COVID-19, with overlapping outbreaks. Now, since the SARS-COV-2 virus is mutating to less virulent strains, it may be causing lesser immunosuppression and entailing opportunistic infections. The clinical presentation of mucormycosis in the case in point was like that in COVID-associated mucormycosis (CAMCR).

Studies carried out to predict the virulence of emerging viruses suggest an evolutionary trade-off between virulence and transmissibility that the virus evolves to become less infectious and more transmissible in a successful attempt to improve its survival [15].

The SARS-COV-2 virus seems to have evolved to a mitigated virulent form having a milder clinical manifestation which could be explained by Cross-reactivity along with the viral mutations and population herd immunity achieved with natural infections and vaccinations. This may explain the milder onslaught brought on by the latest covid variants [15]. The benign variant may cause lesser immunosuppression in comparison to the virulent variants.

That said, some argue that the abating of the pandemic may only be a coincidence and ongoing rapid antigenic evolution may produce variants that may escape immunity and be more severe [15].

Consequently, from the available research, it is difficult to derive a predictable pathway for Dengue-associated mucormycosis in COVID times.

Conclusion

In our two patients with Dengue infection, Dengue virus may have resulted in a significant immunosuppression, increasingly so in a potential interaction with SARSCoV2, thereby facilitating a grave opportunistic infection like mucormycosis. Hence, COVID-19 age may observe a metamorphosis in viral presentations as perhaps with Dengue virus.

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