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Case Report

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Emerging peril of post–dengue mucormycosis: A case report

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ABSTRACT

Rationale: Dengue fever is a leading cause of death in tropical and subtropical countries. Although most patients have a self-limited febrile illness, the viral infection can induce virus-mediated host changes, making immunocompetent persons susceptible to deadly fungal infections. However, there are only a few reports of such an association. Here we present a case of this deadly co-infection.

Patient's Concern: A 17-year-old male patient was diagnosed with dengue fever. He presented to us with facial swelling, periorbital edema, and black discoloration over the palate during the second week of his illness.

Diagnosis: Diagnostic tests confirmed the presence of fungal hyphae. A diagnosis of post-dengue mucormycosis was made. No other comorbidity or underlying immune deficit was detected.

Interventions: The patient underwent surgical debridement and antifungal treatment.

Outcomes: The patient recovered and showed signs of palatal healing with an advancing mucosal edge.

Lessons: Dengue virus and mucor co-infection has brought to light a new pathogenic paradigm. Clinicians need to be aware of this emerging medical condition and maintain a high index of suspicion for mucor co-infections while treating dengue patients.

KEYWORDS: Dengue virus; Mucormycosis; DENV; Post-dengue mucormycosis; Post dengue mucor

1. Introduction

Dengue virus (DENV) is one of the leading causes of mortality in tropical and subtropical countries. Despite the frequent cyclical outbreaks of classical dengue fever in these regions, no effective antiviral drugs or vaccines have been developed against this virus[1]. Co-infections with other pathogens may lead to permanent damage. The recent explosion of COVID-associated-mucormycosis has highlighted the role of virus-mediated host changes that may increase susceptibility to deadly fungal infections in previously immunocompetent patients. Isolated news items have reported post-dengue mucormycosis (PDM)[2-4]. We report a case of this novel affliction and explore the immunopathogenic mechanisms to hypothesize a likely explanation for this clinical scenario.

2. Case report

The patient and his guardian provided their informed consent for the publication of this case report.

A 17-year-old male was diagnosed with a case of dengue viral fever based on a positive test report for dengue IgG antibodies and NS1 antigen. Though the fever subsided within a week, the patient started developing facial swelling and black discoloration over the palate over the next ten days. He was referred to our hospital during the second week of illness for the suspicion of mucormycosis.

At the time of admission to our hospital, the patient had extensive

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Table 1. Summary of laboratory tests.

Parameters	Normal references	Results
Neutrophils, /μL	4300-10000	3000
Thrombocytes, /dL	150000-450000	39000
PT, s	30-40	16.0
APTT, s	60-70	37.5
INR	0.8-1.1	0.9
SGOT, IU/L	5-40	2210
SGPT, IU/L	7-56	1680
Absolute CD3+ T-helper lymphocytes, /μL	1007-2479	1204
Absolute CD4+ T-helper lymphocytes, /μL	371-1217	648
Absolute CD8+ T suppressor lymphocytes, /μL	355-1171	652
CD4/CD8 ratio	0.72-2.10	0.99

PT: Prothrombin time; APTT: Activated thromboplastin time; INR: International normalized ratio; SGPT: Serum glutamic-pyruvic transaminase; SGOT: Serum glutamic oxaloacetictransaminase

facial edema, a black necrotic scar over hard palate, and left nasolabial region and periorbital region. The disease spread progressed rapidly extending to the opposite side with bilateral facial edema (Figure 1A). There was no history of COVID-19 infection, no diabetes mellitus, or any other immunocompromising conditions.

The diagnosis of PDM was made based on clinical, laboratory, and radiological tests (Table 1). Diagnostic nasal endoscopy showed black crusts which filled the nasal cavity bilaterally and an edematous middle turbinate with black eschar which was seen on the left side. Left nasal cavity floor was necrotic with black eschar extending from level of vestibule to posterior end of inferior turbinate. Contrast-enhanced computed tomography showed soft tissue density in the left nasal cavity and bilateral maxillary sinus (L>R); obliteration of left ostiomeatal complex; rarefaction and thinning of nasal turbinates with evidence of extraconal and intraconal fat stranding. Magnetic resonance imaging with contrast confirmed the computed tomography findings and also showed extensive edema on the left side of the face and the left pre-maxillary region extending onto the right side; diffuse periorbital soft tissue edema predominantly in infra orbital region on T2 images. There was rarefaction and thinning of nasal turbinates with evidence of extraconal and intraconal fat stranding (Figures 1B-1F). Patient was positive for DENV serology (NS1 antigen) and negative for human

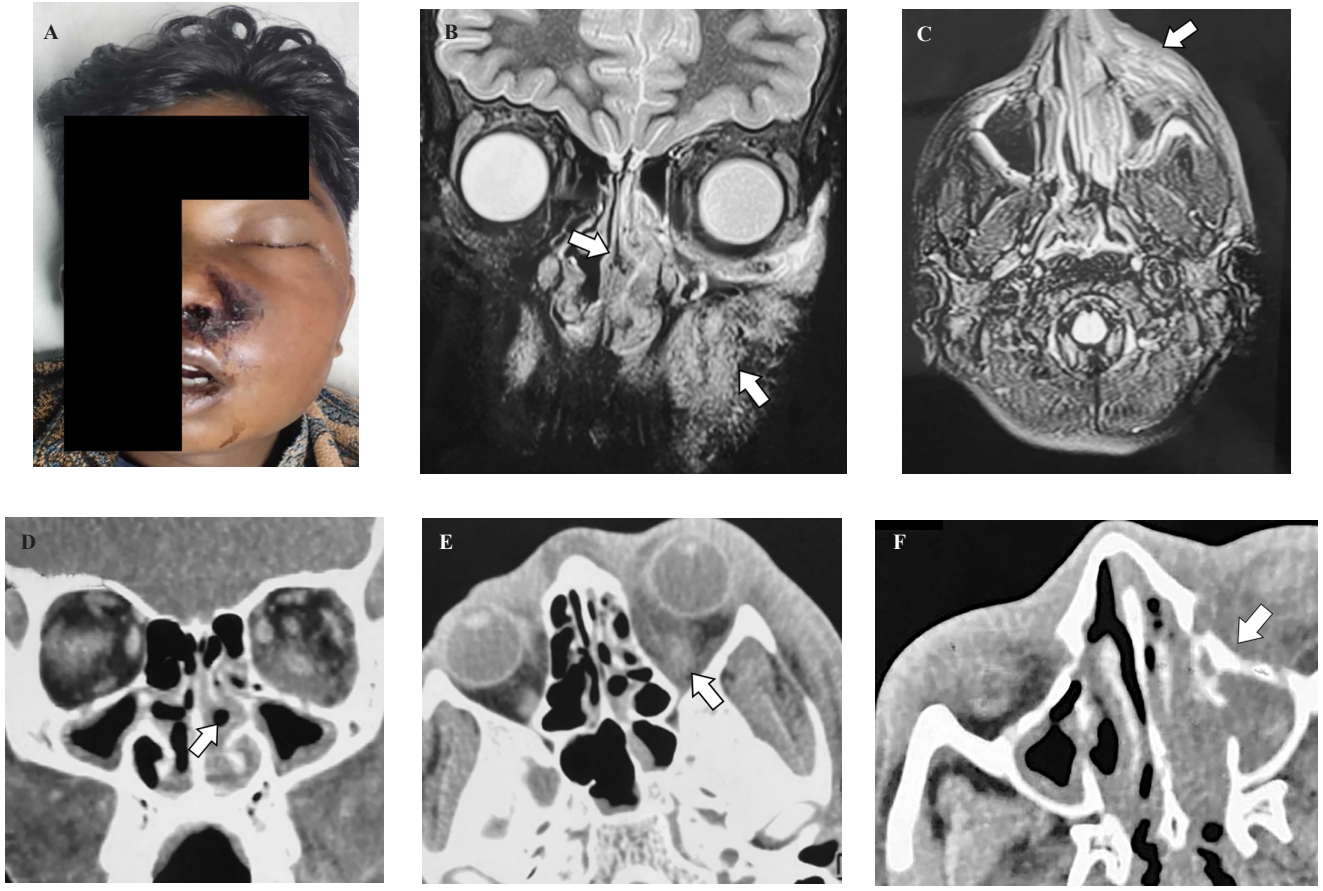

Figure 1. Image of a 17-year-old patient in the pre-operative period showing extensive bilateral facial swelling, left periorbital edema and black eschar over the left perialar and nasomaxillary region extending into the left nasal cavity and left upper perioral region (A). MRI scan coronal image showing diffuse periorbital soft tissue edema predominantly in infra orbital region and thickened hyperintense nasal mucosa over the left inferior and the middle turbinate (arrows) (B) and MRI scan axial image showing extensive edema and inflammation in the left premaxillary region (arrow) (C). Contrast enhanced CT scan coronal section showing soft tissue density in the left nasal cavity, bilateral maxillary sinus (L>R), blocked left ostiomeatal complex with rarefaction and thinning of nasal turbinates (arrow) (D). Contrast enhanced CT scan axial section showing extraconal and intraconal fat stranding in the left eye along with soft tissue densities in the anterior and posterior ethmoid sinuses (arrow) (E) and destruction of walls of the maxillary sinus (arrow) (F).

immunodeficiency virus, hepatitis B surface antigen, anti-hepatitis C and fibrinogen degradation products. Potassium hydroxide mount reported aseptate fungal hyphae.

The patient was started on intravenous amphotericin B and was stabilized and worked up for surgical sinonasal debridement. The patient underwent bilateral subtotal maxillectomy with left orbital decompression under general anesthesia. There was extensive involvement of the hard palate and premaxilla. The necrosed hard palate mucosa was stripped, and necrosed incisor teeth were removed. To prevent hemodynamic instability and reduce post-op functional morbidity, palate was removed partially to remove only the most affected region of palate and stage the resection for a second surgery.

The patient continued to receive intravenous amphotericin B and tablet posaconazole for missed amphotericin days (due to electrolyte disturbance/drug intolerance). Repeated nasal endoscopies and regular debridement over premaxilla were followed. Despite clinical improvement, he developed a fever on the ninth day secondary to osteomyelitis of exposed palatal bone. Injectable linezolid and rigorous oral hygiene were added to treatment and the patient became afebrile within the next 48 hours.

After treatment, the patient was recovering and showing signs of palatal healing with an advancing mucosal edge. He continued to receive oral posaconazole over the next 2 months and was referred to the maxillofacial department for palatal debridement and dental rehabilitation. He continues to follow-up and will be scheduled for flap reconstruction.

3. Discussion

Fungal infections are traditionally seen in patients with a pre-existing cause of immunodeficiency. However, since the onset of the SARS-CoV-2 pandemic, the medical community witnessed an unusually high caseload of mucormycosis in post-COVID-19 patients. The recent association of mucormycosis with DENV only adds to the void in our understanding of the viruses. This co-infection so far was unreported and has further bolstered the need to explore the underlying mechanisms of these pathogens to develop effective prevention and treatment strategies.

The frontline defense mechanism of the human body against fungal infections is “innate immunity,” which includes macrophages, neutrophils, and dendritic cells. Mouse models and human autopsy studies show that DENV infection also affects the same cells[1,5]. The DENV infection of these cells occurs early on in the disease process and usually within six days from inoculation, altering the host immune system[5].

Several investigators have reported neutropenia in dengue-infected patients[6]. Though not severe, the clinical significance of this phenomenon remains uncertain. The role of neutrophils in DENV infection is an area of interest since, in addition to a reduction in the absolute count, there may be an associated functional deficit in the DENV-infected neutrophils.

Researchers have shown elevated cytokine levels in DENV patients with a manifold increase in the blood concentrations of soluble mediators such as IFN-α, INF-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, interferon-gamma induced protein, monocyte chemoattractant protein-1, TNF-α and regulated on activation, and normal T cell expressed and secreted (RANTES)[1]. This “cytokine storm” leads to lymphocytopenia by promoting apoptosis of the lymphocytes and atrophy of the lymphoid tissue.

Several studies have shown that DENV causes endothelial damage either by direct infection or indirectly through cytokine-induced damage. Due to high IL-8 levels, the resulting thrombocytopenia alters the clotting mechanisms and leads to venous thrombosis and subsequent endothelial damage. IL-8 also causes degranulation of neutrophils, leading to increased plasma elastase levels, which activates the complement, fibrinolytic systems, and coagulation pathways. This deranged clotting homeostasis contributes to the breach of the endothelial barrier allowing angioinvasion and dissemination of the fungal elements.

Decker *et al*. demonstrated high plasma levels of soluble intercellular adhesion molecule (sICAM)-1, thrombospondin-1, and vinculin in patients with invasive fungal infections[7]. These adhesion molecules are also elevated in dengue patients, promoting fungal attachment and permeation of vascular channels.

A state of haemophagocytic lymphohistiocytosis is seen in dengue infections secondary to the cytokine storm leading to hyperferritinemia[8]. Ferritin is essential for iron metabolism in fungi[9]. Dengue patients’ persistently high serum ferritin levels may promote fungal growth and replication.

There remain several other possible mechanisms of pathogenesis for PDM which may contribute individually or collectively towards suppressing the host immune system, thereby predisposing the patient towards opportunist fungal infections. Apart from the agent-host factors, the changes in the environment need to be studied to understand the pathogenesis of this post-dengue mucormycosis fully. We suggest further studies at the population level and *in vitro* and *in vivo* models to explore the pathogenesis of mucor-dengue co-infection.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

All authors contributed equally to the writing of this article.

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