CASE REPORT

Dengue Fever Mimicking as Granulomatosis with Polyangiitis: An Unsolved Diagnostic Dilemma

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Abstract

Hemorrhagic manifestations are well documented with dengue fever (DF) but thrombotic/thromboembolic events complicating acute dengue illness are only scarcely reported in the literature. Here we present a case of a DF complicated by multiple brain infarcts along with pulmonary hemorrhage. The simultaneous occurrence of hemorrhagic and embolic phenomena in presence of thrombocytopenia provoked us to rule out the differential diagnosis of an underlying vasculitic disorder which would then have altogether diverse management.

Keywords: Dengue, Granulomatosis with polyangiitis, Vasculitis.

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Introduction

Dengue fever (DF) is an arthropod-borne illness. Infection may be asymptomatic or have a broad spectrum of clinical manifestations ranging from isolated fever to life-threatening multiple organ involvement and shock.[1] The neurological manifestations in DF are not well defined.[2] Furthermore, pulmonary hemorrhage and hemoptysis have scarcely been reported in the literature.[3] Tropical fevers, for instance, DF with uncommon presentations may closely mimic vasculitis such as granulomatosis with polyangiitis (GPA), which is a life-threatening, small-vessel necrotizing granulomatous vasculitis predominantly affecting the lungs and kidneys. The management of DF is conservative, whereas GPA requires adequate immunosuppression for disease remission. We present a case of DF with multiple cerebral embolic infarcts, pulmonary hemorrhage, hemoptysis, and subglottic stenosis, which are all uncommon presentations of the illness.

Case Description

A 52-year-old woman presented with fever followed by multiple episodes of seizures and altered sensorium. The patient had stable vitals and a Glasgow Coma Scale (GCS) score of 9. There were no signs of meningeal irritation, nor did she have any rash or petechiae. Abdominal examination revealed hepato-splenomegaly. The cardiovascular and respiratory examination was normal. The patient had no history of hypertension, diabetes mellitus, cardiac disease, epilepsy, fetal loss, illicit drug use, or oral contraceptive pill use. There was also no history suggestive of hypercoagulable states or vasculitic phenomena.

The initial laboratory workup revealed thrombocytopenia and transaminitis along with a positive dengue serology. The patient was given antiepileptics, antibiotics, antiplatelets, and intravenous fluids to which she responded and her GCS improved to a score of 15. A contrast-enhanced magnetic resonance imaging (CEMRI) of the brain undertaken in view of seizure episodes revealed multiple, variable-sized, relatively well-defined, rounded T2/FLAIR (T2-weighted-Fluid-Attenuated Inversion Recovery) heterogeneously hyperintense lesions along with grey-white matter interface in bilateral cerebral hemispheres with mild surrounding edema. Similar lesions were also seen in the left putamen, the posterior part of the body of the corpus callosum, and in the right cerebellar hemisphere. The largest lesion measured approximately 1.2 cm in the left frontal lobe and 1.4 cm in the right cerebellar hemisphere. No significant postcontrast enhancement was seen. Marked diffusion restriction was seen with no blooming on Fast Field Echo images. On Magnetic Resonance Spectroscopy, the lesions showed a reduced choline/N-acetylaspartate peak and a positive creatinine peak. No lipid lactate peak was observed. These findings suggested multiple acute embolic infarcts. To determine the source of emboli, a bilateral carotid artery doppler, 2-Dimensional echocardiography, and angiography (arch of the aorta and its branches) were performed and were all found to be grossly normal. On day 6 of hospital admission, the patient had an episode of hemoptysis. The hemogram done on the same day revealed a fall in hemoglobin level but a normal platelet count. Chest radiograph revealed diffuse infiltrates in the bilateral lung parenchyma. Contrast-enhanced computerized tomography (CECT) Scan of the chest revealed relatively symmetrical areas of dense ground-glass opacities with few areas of early consolidation predominantly involving bilateral perihilar lung fields, suggestive of possible pulmonary edema or hemorrhage (in view of the history of hemoptysis). The aforesaid atypical manifestations prompted us to consider the alternative diagnosis of a vasculitic disorder.

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Although the patient's erythrocyte sedimentation rate was elevated at 99 mm in the first hour, the antinuclear antibody, antineutrophil cytoplasmic antibodies (ANCA), anti-beta-2-glycoprotein antibodies, anticardiolipin antibodies, and lupus anticoagulants were negative. Mild renal involvement is seen on day 10 of the illness resolved with hydration.

Based on the patient's clinical features and laboratory workup, a diagnosis of tropical fever with thrombocytopenia complicated as multiple cerebral embolic infarcts and pulmonary hemorrhage secondary to DF was made. She was managed and discharged in a fully conscious state performing all her daily activities independently. A review CECT chest performed on day 10 follow-up revealed significant resolution of the lung parenchymal changes.

This was followed by a second visit to the emergency with sudden-onset shortness of breath and stridor a few days later. Oral examination was normal but laryngeal crepitus was present. Laryngoscopy revealed a stenotic segment measuring 1.8 cm in the subglottic region. The patient underwent an elective tracheostomy. Histopathological examination revealed a section lined with pseudostratified columnar epithelium. The subepithelium showed congested blood vessels, and mucinous glands with mild lymphomononuclear cell infiltrate in the intervening areas. Repeat investigations revealed a normal hemogram, renal function tests, and a negative antiproteinase-3 ANCA (c-ANCA). Urine microscopy was negative for dysmorphic red blood cells or casts. The patient underwent successful decannulation after 2 months. The patient declined the renal biopsy consent. A written and informed consent was retrieved from the patient for publication of this case report.

Discussion

WHO guidelines (2011), classified dengue into DF, dengue hemorrhagic fever (DHF), dengue shock syndrome, and expanded dengue syndrome (EDS). The new entity EDS incorporates unusual systemic presentations including hepatic, renal, neurological, gastrointestinal, and pulmonary involvement.[4] This syndrome can closely mimic various vasculitic conditions which too have multisystem involvement as occurred in our case. GPA is one such distinct entity characterized by granulomatous vasculitis of the respiratory tract along with glomerulonephritis.

Our patient presented with fever and multiple episodes of seizures followed by a postictal state. CEMRI brain was suggestive of multiple acute embolic infarcts which have been never reported in dengue before. Cardioembolic and arterial embolic phenomena were ruled out by relevant investigations. Hypercoagulable states like Antiphospholipid syndrome and vasculitic disorders were excluded by clinical history and laboratory parameters.

The multiple cerebral and cerebellar infarcts in this patient with no source of external embolus can be explained by the local inflammatory reactions due to the dengue virus. The relationship between DHF and atypical neurological manifestations was described earliest in 1976.[2] The exact incidence of various neurological complications is uncertain. As per the review of literature, they are known to complicate as many as 0.5–6% of the cases of DF.[5] Previously considered to be non-neurotropic, there is increasing evidence to prove direct neurotropism and neurovirulence of dengue virus by assessing viral proteins, ribonucleic acids and immunoglobulins in the central nervous system (CNS).[6]

Various mediators are released in dengue infection such as cytokines and chemokines. The secreted glycoprotein, the nonstructural 1 antigen, functions as a cofactor for viral RNA replication and triggers cytokine cascade. There is the activation of the natural killer cells and T-helper cells which is central to the pathogenesis of neurological manifestations in DF.[7] These immune-mediated mechanisms are responsible for the various findings in peripheral blood and the brain of the infected patients. They cause the breakdown of the blood-brain barrier, leukocyte infiltration, and local inflammation, followed by vasoconstriction, thromboembolism, cerebral edema, ischemia, and hemorrhage.[8,9] These vasoactive and procoagulant effects are also responsible for thrombocytopenia, disseminated intravascular coagulation, and vasculitis which may also result in a stroke.[10] CNS involvement in GPA is uncommon and has been seen in approximately 8% of the patients.[11]

Our differential diagnosis of GPA gained more strength as the patient developed complications in form of hemoptysis and subglottic stenosis. Pulmonary complications in form of pleural effusion, pneumonitis, noncardiogenic pulmonary edema, and acute respiratory distress syndrome are seen in a small number of patients. Hemoptysis has been reported in only 1.4% of patients with dengue and pulmonary hemorrhage is, even more, rare.[12] No association of DF with subtracheal stenosis could be seen in the literature review in a patient who was never intubated.

Early diagnostic confirmation of either tropical illness like DF or vasculitic condition is essential to prevent complications, morbidity, and mortality because the management of each is entirely on different lines. Dengue is diagnosed with a demonstration of NS1 Ag in the sera in the first 5 days and IgM dengue antibodies with rising titer from day 5 till 2–3 months. DF patients are managed symptomatically with no specific treatment options.

On the other hand, approximately, 90% of patients with active GPA have a positive c–ANCA. In the absence of active disease, its sensitivity drops to 60–70% and up to 20% may lack ANCA.[13] Definitive diagnosis of GPA is made on tissue biopsy showing necrotizing granulomatous vasculitis. Pulmonary tissue biopsy offers the highest diagnostic yield.[13] Renal biopsy can also confirm the diagnosis. Biopsy from the subglottic area may confirm the diagnosis but the positive result is usually infrequent.[14] Management involves immunosuppressants to induce remission followed by maintenance therapy. Treatment of disease complicated by subglottic stenosis is not straightforward and includes medical therapy along with surgical intervention in form of elective tracheostomy followed by decannulation.

Conclusion

It is evident that DF can present with a wide spectrum of unusual systemic manifestations. Dengue should be a diagnostic possibility in patients presenting with fever and thrombocytopenia along with neurological or pulmonary findings as in our case. However, mimickers like GPA should also be kept in differential diagnosis and patients should be closely followed up after discharge. Prompt diagnosis and appropriate supportive care help to reduce the patient fatality due to these atypical multisystemic complications.

Informed Consent

The author certifies that they have obtained the appropriate patient consent forms. The patient has given her consent for clinical information to be reported in the journal. The patient understands

that her name and initials will not be published and due efforts will be made to conceal her identity.

Author Contributions

We verify and confirm that each author contributed to every stage of this manuscript equally.

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