CASE REPORT

CO-INFECTION OF INFLUENZA AND DENGUE VIRUSES IN A PATIENT WITH GRAM-NEGATIVE BACTEREMIA- A CASE REPORT

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ABSTRACT

Co-infection with influenza and dengue virus is a rare occurrence, and when combined with gram-negative bacterial infection, can present a complex clinical picture. We present the case of a 68 years old male, with prostrate carcinoma and prior trans-urethral resection of the prostate 1-year ago, now presented with symptoms of profuse sweating and undocumented fever for 4 days. He was positive for both Influenza A and Dengue virus and developed Gram-negative bacteremia. The patient manifested pyrexia, chills, severe body aches, and laboratory investigations revealed thrombocytopenia and hemolytic anemia. Patient was managed with supportive care, intravenous antibiotics, and supplemental oxygen. After 2 weeks of hospital stay, patient was discharged. Early recognition and initiation of appropriate therapy can lead to a favorable outcome in such cases. Thus, co-infection with influenza, dengue, and gram-negative bacteria can present with a complex clinical picture and requires prompt diagnosis and management.

Keywords: Co-infection, Dengue virus, Hypoxia, Influenza, Thrombocytopenia.

BACKGROUND

Dengue fever is a common vector-transmitted disease in tropical regions. The vector in this disease is the mosquito *Aedes aegypti*. This constitutes a major burden on the health system with 400 million cases reported worldwide annually.[1] Dengue virus bears 04 serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. Clinically it presents as a minor viral infection in most patients.[2] Symptoms may include fever, malaise, rash, muscle and joint pains, severe headache, vomiting, nausea and lymphadenitis, lasting for 2-10 days.[3] The more severe manifestations of dengue hemorrhagic fever may be seen in about 1 out of 20 patients infected with the dengue virus. Caution signs are: abdominal pain, vomiting, fatigue, polypnoea, bleeding from orifices, agitation and altered mental status.[4] Patients with warning signs require hospital admission and close monitoring. Treatment for dengue infection is mainly supportive as it is a self-limiting disease bearing mortality rate >1%. With treatment, mortality associated with it ranges from 2-5%; however, if left untreated, mortality may be as high as 50%.[5]

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The virus detection was accomplished by Polymerase chain reaction (PCR), viral cultures, and non-structural protein or serologically through Enzyme-linked immunosorbent assay (ELISA) for IgM and IgG antibodies. The IgM are detectable after 1 week of infection until 3 months, while IgG may be detectable from day 7 for up to 3 years.[6]

Influenza is another common viral infection and is among the leading causes of mortality across the globe. Seasonal influenza results in 3-5 million infections and 250,000-500,000 annual mortality.[7] Its incubation period is 2 days on average. Treatment includes neuraminidase inhibitors (oseltamivir, zanamivir). Oseltamivir is effective in treatment of influenza A and B viruses if administered within 48 hours of the onset and duration of treatment is 5 days.[8] However, treatment should be instigated irrespective of the duration of symptoms in severe disease, hospitalized and immunocompromised patients. Annual influenza vaccine is recommended in dependent of the susceptibility status to prevent infection. Thus, a case of co-infection of dengue and influenza virus is presented below.

CASE REPORT

A 68 years old male, diagnosed case of prostate carcinoma with a previous history of trans-urethral resection of the prostate 1 year ago presented with symptoms of profuse sweating and undocumented fever for 4 days. At the time of presentation, he had a heart rate of 118 beats/min, blood pressure of 114/60 mm of Hg, a temperature of 36^{o}C and oxygen

saturation of 98% at room air. His random blood sugar was 283 mg/dl. Abdominal examination revealed mild tenderness in Right hypochondrium and a chest examination showed diminished right-sided breath sounds. The rest of the examination was unremarkable.

The hemoglobin of patient was 7.4 g/dl, platelets of 63000 /Ul, total leucocyte count of 6400/Ul, creatinine of 1.24 mg/dl and lactate of 44.1 mg/dl. Liver function tests showed Alanine transaminase (ALT) 38 U/L (Ref range: 4-36 U/L), aspartate aminotransferase (AST) 30 U/L (8-33 U/L), gamma-glutamyl transferase (GGT) 72 U/L (5-40 U/L), bilirubin 1.17 mg/dl (<1 mg/dl), albumin 2.49 g/dl (3.4-5.4 g/dl). Further workup showed Malaria Parasite smear and COVID-19 (PCR) negative while Dengue IgM and Influenza A were positive. He was negative for Dengue NS1 antigen. He was started on oral oseltamivir 75mg twice daily for 5 days and was managed symptomatically for dengue fever.

His blood cultures showed growth of *Escherichia coli* sensitive to amikacin, chloramphenicol, ciprofloxacin, co-trimoxazole, and ertapenem. tetracycline, gentamicin, imipenem, levofloxacin, meropenem, piperacillin- tazobactam, tobramycin. Ultrasound abdomen revealed mild bilateral hydronephrosis. The patient was given piperacillin-tazobactam initially which was later switched to meropenem due to persistent fever spikes. His Hb dropped to 6.6 on day 4 of hospitalization, without any overt bleeding. The patient was transfused 1 packed red blood cell.

During the transfusion, his oxygen requirements gradually increased from room air to 2 liters to 10 liters/minute of supplemental Oxygen. The patient had distended neck veins and bilateral basal crepitations. Chest X-ray showed bilateral confluent perihilar infiltration suggestive of pulmonary edema. This was attributed to transfusion-related acute lung injury (TRALI) and underlying infections. He was managed in the intensive care unit with diuretics and non-invasive ventilation with 10 liters/minute of supplemental Oxygen for 2 days after which he was stepped down to high-dependency unit monitoring. His platelets over the subsequent week dropped to a nadir of 30 000 /Ul with no evidence of overt bleeding.

His clinical course remained static over the next few days with persistent fever spikes and minimal hypoxia requiring 2 liters/minute of supplemental oxygen. COVID-19 PCR was repeated twice and was negative. Computed Tomography chest, abdomen and pelvis (done on day 15 of admission) showed bilateral lung airspace changes with septal thickening. Bilateral moderate-volume pleural effusions were seen along with associated atelectasis.

Over the next few days, he reported lower backache for which Magnetic resonance imaging lumbosacral spine was performed that showed osteomyelitis and a 2.3 x 1.1 cm fluid collection in region of L5 to S1 in epidural space. CT guided drainage of fluid; aspirate cultures revealed growth of *Escherichia coli* (sensitive to amikacin, chloramphenicol, ciprofloxacin, cotrimoxazole, ertapenem, gentamicin, imipenem, levofloxacin, meropenem, piperacillin/tazobactam. Histopathology revealed vague necrotizing granulomas. Initial studies including Ziehl-Neelsen stain and MTB Gene Xpert were negative. Acid-fast bacilli cultures were reported negative at 6 weeks of incubation.

Over the next few days, the patient remained afebrile and his platelet counts improved to 86,000 /ul. He was discharged on intravenous ertapenem for 2 weeks due to single daily dosing with follow-up in the Infectious disease clinic with repeat imaging post-discharge. Repeat imaging was done after 4 weeks of antibiotics. Repeat MRI lumbar spine showed near complete resolution of abscesses. Currently, the patient is off antibiotics for more than 2 months and doing well.

DISCUSSION

Co-infection of dengue and influenza virus is an unusual occurrence with limited reports in literature. We report a case of Dengue Virus and Influenza A co-infection with *Escherichia coli* bacteremia and multiple spinal abscesses. A case series from Brazil included 4 patients with fatal dengue and influenza co-infection. Histopathological and necropsy findings revealed peripheral cyanosis, bilateral pleural effusion, pericardial effusion, heart enlargement, hepatomegaly and congested kidneys. Microscopy showed cerebral edema, congestive heart and edema, hypertrophy of myocardial fibers and dilation of the chambers. Lung hyaline membranes were thick and had interstitial pneumonitis and intra-alveolar edema. Kidneys had acute tubular necrosis and liver showed cholestasis. A study found four patients with fatal influenza A (H1N1) pdm09 and dengue virus coinfections, similar to our case report. Clinical, necropsy, and histopathologic findings in all cases were indicative of influenza-dengue coinfections, and all cases, including

ours, had laboratory confirmation of both infections. Four cases of laboratory-confirmed coinfection of deadly influenza A(H1N1) pdm09 with DENV occurred during the dengue and influenza season in 2012 and 2013 in Ceará. The study concluded that the influenza and dengue seasons coincide in Ceará, which led to diagnostic difficulties [9]. The lung fragments were positive for Influenza A (H1N1) virus by real-time RT-PCR, and liver fragments were positive for dengue viruses (DENV) by immune histochemistry. Our patient however has no evidence of heart failure or liver involvement. One case report from India of a 27-year-old male who presented with fever, headache, myalgia, dry cough and runny nose tested positive for dengue NS1 and IgM. Another corroborating study conducted on a 27-year-old male presented with fever, headache, myalgia, dry cough, running nose, sore throat, and increasing breathlessness with his vital signs showed low blood pressure, rapid pulse, and decreased oxygen saturation was reported. Laboratory investigations revealed low platelet count and elevated hematocrit. Dengue virus infection was confirmed through positive NS1 and IgM dengue ELISA tests, as well as positive real-time polymerase chain reaction (RT PCR) for dengue serotype DEN1. Chest X-ray showed left pleural effusion, and subsequent evaluation identified H1N1 pneumonia. With supportive management and oseltamavir his condition gradually improved and he was discharged after 20 days.[10]

Animal models have demonstrated high DNV titers in spleen, lungs and liver tissue that increase risk of pneumonia by impairing monocyte function in dengue and influenza co-infection.[11-12] Poor outcomes associated with influenza and dengue virus co-infection in a pregnant woman presented with fever, headache and myalgia, were reported.[13] Her initial workup showed thrombocytopenia and proteinuria and she was managed along the lines of pre-eclampsia. Later, her dengue IgM was positive. Chest X-ray showed bilateral pleural effusion. The patient was shifted to ICU and later died. Post-autopsy lung tissue showed microangiopathic changes similar to that seen in dengue, while lung tissue staining and PCR revealed influenza infection.[11-12] Our patient was shifted to ICU. However, early diagnosis and prompt treatment resulted in early improvement and step down from the ICU, and later discharge from the hospital. Our findings were supported by a report that thrombocytopenia was found in both dengue and gram-negative sepsis.[14] A peripheral blood smear provided the evidence of hemolytic anemia by showing characteristic findings such as schistocytes (fragmented red blood cells), spherocytes (spherical-shaped RBCs), polychromasia (increased reticulocytes), increased unconjugated bilirubin, and anisocytosis/poikilocytosis (variation in size and shape of RBCs). These findings, along with clinical symptoms and other laboratory parameters, can aid in the diagnosis of hemolytic anemia. However, in the presence of hemolytic anemia and fragmented erythrocytes, the diagnosis of thrombotic thrombocytopenic purpura should be considered, because it is rare but life-threatening condition presented as a complication of both influenza and dengue infection.[15]

CONCLUSION

In conclusion, co-infection with influenza, dengue, and gram-negative bacteria can present a complex clinical picture and requires prompt diagnosis and management. Early recognition and initiation of appropriate therapy can lead to a favorable outcome.

CONFLICT OF INTEREST

There is no conflict of interest to declare by any authors.

AUTHOR CONTRIBUTION

Rabia Islam Abbasi: Manuscript writing, Literature search, concept

Salma Muhammad Abbas: Literature search, proofread and finalization of report

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