Dengue Fever Complicated with Thrombotic Thrombocytopenic Purpura: A Case Report and Literature Review

Muhammad Sohaib Asghar¹, Saira Anwar¹, Mohammed Akram², Maira Hassan², Behzad Rashid³, Muhammad Sohaib Khan³, Farzeen Wahab³, Iqra Iqbal Akbar³, Noor Jamil³, Rida Rehan³

¹Resident Physician of Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan
²Intern of Internal Medicine, Liaquat National Hospital & Medical College, Karachi, Pakistan
³Doctoral Student, Dow International Medical College (DIMC), Karachi, Pakistan

*Corresponding author: Muhammad Sohaib Asghar, Resident Physician of Internal Medicine at Dow University Hospital, Dow University of Health Sciences, Gulshan-e-Iqbal, Karachi, Pakistan, Tel: 00923343013947; E-mail: sohaib_asghar123@yahoo.com

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a hematological disorder with an incidence of around 6.5 cases per million every year. It is characterized by the clot formation in blood vessels and resulting thrombocytopenia due to widespread utilization in the process. Other clinical features include hemolytic anemia, neurological abnormalities, fever, and renal failure. The cause can be either congenital or acquired secondary to infections, the use of certain drugs, and autoimmune disorders. On the other hand, Dengue fever is a viral infection that can result in multiple systemic complications including disrupted coagulation, renal dysfunction, and inflammation in the liver, brain, and myocardial pathology. In this case report, we present a rare presentation of thrombotic thrombocytopenic purpura in a patient with dengue fever. The mortality rate, in untreated cases, has been reported by up to 90%. With timely diagnosis and management with
plasmapheresis, this can be reduced to 10-20%. Currently, it is important to control such an unknown outbreak of Dengue fever, as it is a serious health care issue of disease control and prevention in Pakistan.

**Keywords:** Dengue; Petechiae; Purpura; Fever; Rash

1. **Introduction**

Dengue is one of the potentially fatal and common arthropod-borne viral illnesses, mainly found in tropical and subtropical areas of the world. The number of cases per year has been estimated to be 390 million with clinically presenting cases making up around 96 million cases [1]. Dengue infection can result from one of the four stereotypes (DENV1-4) transmitted by mosquito Aedes [2]. The clinical presentation can range from mostly asymptomatic or mild infection to hemorrhagic shock and eventual death. Usual symptoms are fever, anorexia, nausea, vomiting, headaches, body aches and rashes. Furthermore, the patient may develop a shock-like state from hypotension, petechial rash, bleeding [3]. Moreover, the infection is characteristically associated with decrease count and altered function of platelets and associated with increased risk of death [4]. The mortality rate is less than 1% for dengue fever, and it is highly preventable by early diagnosis and efficient management of potential complications affecting vital organs [5]. Thrombotic thrombocytopenic purpura (TTP) is a life-threatening blood disorder involving multiple systems of the body, resulting in high mortality. It is characterized by a pentad of fever, renal and neurologic dysfunction, low platelet count, and decrease hemoglobin due to hemolysis. The diagnosis is usually made by laboratory studies, on a background of the classic clinical scenario. The mortality rate, in untreated cases, has been reported to be strikingly high i.e. up to 90%. With timely diagnosis and management with plasmapheresis, this can be reduced to 10-20%. This case is unique due to the co-occurrence of two potentially lethal diseases associated with decreased platelet count [6-8].

2. **Case Presentation**

A 62 years old female of Asian descent with a past history of diabetes mellitus and hepatitis B infection, presented with complaints of loose motions, nausea and vomiting, high-grade fever, generalized body aches and drowsiness for 5 days. It was followed by bilateral retrobulbar pain, bilateral lower limb edema, tachypnea, palpitations, and a deterioration in the level of consciousness. There was no associated hematemesis, hemoptysis, hematochezia, jaundice, or melena. The patient denied having any rash or joint pains. On physical examination, she was palor, normotensive with a basal body temperature of 102°F. Chest examination showed basal crepitations, up to the mid zones of lungs bilaterally on auscultation. Although she demonstrated no focal neurological deficit, she had a decreased GCS of 12/15. Multiple petechial rashes were appreciated in lower limbs. Differential diagnosis of viral hemorrhagic fever, complicated enteric fever, and cerebral malaria was made. Initially, she was started on injectable antiemetic and antipyretics for symptomatic treatment of vomiting and fever. In addition to that adequate hydration status was maintained. Laboratory investigations are given in Tables 1, 2, and 3. During the hospital course, the patient was repeatedly transfused with platelets, still, there was a persistent decremental response of the platelet count giving suspicion of hemolytic process, as was indicated by a peripheral smear of the blood picture. A provisional diagnosis of dengue hemorrhagic fever complicated by thrombotic thrombocytopenic purpura (TTP) was made and plasma ADAMTS13 activity level was sent which...
turned out to be less than 10%, further confirming the diagnosis. The patient was started on plasmapheresis after which resolution of symptoms and laboratory abnormalities was found on follow up.

| WBC (K/ul x1000) | 4.2 |
|------------------|-----|
| RBC (million/ml) | 2.57|
| Packed cell volume (%) | 51 |
| Hemoglobin (g/dl) | 8.1 |
| Platelets (K/ul) | 11 |
| Reticulocytes | 4% |
| Serum sodium (mmol/L) | 137 |
| Serum potassium (mmol/L) | 4.1 |
| Blood urea nitrogen (mg/dl) | 32 |
| Creatinine (mg/dl) | 1.62 |
| Prothrombin time (seconds) | 20 |
| INR (international normalization ratio) | 1.5 |
| Activated partial thromboplastin time (seconds) | 40 |
| Total bilirubin (mg/dl) | 15.25 |
| Direct bilirubin (mg/dl) | 4.05 |
| Indirect bilirubin (mg/dl) | 11.2 |
| Serum Lactate Dehydrogenase (IU/L) | 1374 |
| Serum Haptoglobin (mg/dl) | 4.0 |
| Urine Detailed Report | RBCs 10-12/hpf without proteinuria |
| Peripheral blood smear | Schistocytes, burr cells, and spherocytes |

**Table 1:** Initial Laboratory values at presentation.

| CMV IgG and CMV IgG | Negative |
|---------------------|----------|
| EBV IgG and EBV IgG | Negative |
| Parvovirus IgG and Parvovirus IgG | Negative |
| HIV 1 / HIV 2 screening EIA | Non-reactive |
| Dengue virus-specific IgM | Reactive |
| Dengue virus-specific IgG | Reactive |
| Hepatitis B s Ab | Non-reactive |
| Hepatitis B s Ag | Non-reactive |
| Hepatitis B c Ab | Non-reactive |
| ESR (mm/hr) | 73 |
### Table 2: Serological Studies.

| Test                                | Result     |
|-------------------------------------|------------|
| CRP (nmol/L)                        | 11.2       |
| Direct Coombs antibodies            | Negative   |
| ICT malaria immunochromatographic test | Negative |
| Rapid viral panel                  | Negative   |
| Flu swab                           | Negative   |
| Blood cultures                     | No growth  |
| Sputum cultures                    | No growth  |
| Urine cultures                     | No growth  |
| D-dimer (µg/mL)                     | Less than 0.5 |
| Fibrinogen (mg/dL)                 | 257        |
| ANA                                 | 1:320      |
| Cardiolipin antibody               | Negative   |
| dsDNA (IU/ml)                      | <12        |
| Anti-smith antibody (AI)            | <0.2       |
| ANCA                               | Negative   |
| C3 (mg/dl)                         | 117        |
| C4 (mg/dl)                         | 14         |
| Blood for flow cytometry           | Negative for malignant cells |

### Table 3: Further labs during Hospital course.

3. **Discussions**

Dengue virus infection presents with a wide range of clinical pictures, where it may manifest itself as a mild viral illness, at times it is associated with grave complications related to organ failure and fatal consequences [6]. Of multiple complications and associations, very few cases of thrombotic thrombocytopenic purpura have been reported during dengue infection [7, 8]. One of the reasons for not having enough data on the subject is that the condition often goes unnoticed because of the incomplete investigation profile [9]. The pathophysiology of Thrombotic thrombocytopenic purpura (TTP) is related to inefficient ADAMTS13, which functions to cleave von Willebrand factor (vWF) multimers. This deficiency results in the circulating uncleaved multimers of vWF, as a result, cause the extensive microthrombi formation, utilizing platelets resulting in the decreased count. Inherited mutations in ADAMTS13 genes are responsible for the congenital disease, while they can be acquired due to antibody-mediated destruction or decreased production of ADAMTS13 [10]. Viral infections, malignant, and autoimmune diseases, pregnancy, and certain drugs have been associated with the development of acquired TTP [3]. The classic pentad of symptoms is only found in 50% of cases, so
the laboratory evidence of microangiopathic hemolytic anemia, as shown by increased unconjugated bilirubin, lactate dehydrogenase, decreased haptoglobin, and schistocytes on peripheral smear, along with thrombocytopenia is essential for diagnosis [11], it is further confirmed by the decreased ADAMTS13 activity level. A significant response to plasmapheresis is also supportive of TTP diagnosis. Our patient fulfilled the clinical pentad of symptoms and the diagnosis was supported by laboratory abnormalities, characteristic of TTP. Further investigations to rule out other similar conditions like Disseminated Intravascular Coagulation (DIC) and Hemolytic Uremic Syndrome (HUS) was done. The presence of neurological abnormalities inclined the diagnosis towards TTP and not HUS, in which neurological deficits are not very common [12]. This distinction is important as the treatment protocols of these different disorders are entirely distinguished. The mainstay of treatment of TTP is plasmapheresis with immunosuppressive therapy, while patient refractory to this treatment is given rituximab [13]. Long term effects after recovery include depression, mild cognitive impairment, and decreased survival [14]. In the discussed case, ADAMTS13 was sent and immediate plasmapheresis was started. The patient made a gradual recovery with an improvement of renal function and resolution of schistocytes in peripheral smear.

4. Conclusions

Dengue fever has multiple complications and long-term sequelae that need to be identified early and promptly to decrease the mortality associated with it. Very few cases of dengue have presented with concurring thrombotic thrombocytopenic purpura, and this may suggest a possible correlation, which needs to be identified. This case was described in order to enlighten the fact that these two conditions may present in a manner to mask each other’s classic clinical picture. Currently, it is important to control such a drastic outbreak of Dengue fever, as it is a serious health care issue of disease control and prevention in Pakistan [15, 16].

Conflict of Interest

The authors declare no conflicts of interest with this article's content.

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Ethical Approval

Ethical consent to participate has been taken from the patient in the form of written informed consent.

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