CASE REPORT

STEROID RESPONSIVE PROLONGED THROMBOCYTOPENIA IN DENGUE

ASHISH BHALLA, R. BAGGA¹, L. K. DHALIWAL¹, R. SHARMA², S. VARMA

ABSTRACT

Prolonged thrombocytopenia in a usual case of dengue virus infection is uncommon. Dengue-related thrombocytopenia is self-limiting and responds within 3-5 days. An underlying immunological disorder may be responsible for delayed return of platelet count to a normal level. We present a case of prolonged thrombocytopenia in a case of dengue hemorrhagic fever. The response to steroids suggests a possible immunological dysfunction.

Key words: Dengue, dengue hemorrhagic fever, thrombocytopenia, corticosteroids

INTRODUCTION

Infection with many flaviviruses is associated with transient suppression of hematopoiesis. The clinical syndrome of dengue-associated bone marrow suppression has been well documented in various studies.¹

Thrombocytopenia is an important hematological manifestation of dengue fever and platelet less than 10 × 10⁴/mm³ are seen in around 50% of the cases.² Three Thrombocytopenia may result from by destruction of peripheral platelet or bone marrow megakaryocytes by viruses which consequently reduce the platelet production.³

The disease presented as outbreaks in India in the year 2006. Serotypes 1, 2, and 4 have been reported from India earlier, but in this outbreak serotype 3 was suspected. We describe a patient with a primary dengue infection during this period. She presented with hemorrhagic manifestations and had a prolonged thrombocytopenia which responded to corticosteroids.

A 34-year-old female patient reported to a private hospital with history of pain abdomen and bleeding per vaginum. She was investigated and diagnosed as ruptured ectopic pregnancy with hemoperitoneum. She underwent surgery for this at a peripheral...
center and post procedure developed bleeding per vaginum and hematuria. She was also noted to have purpuric rashes all over the body and was referred to our institute. She was evaluated in the gynecology ward. Clinically, she was detected to have fever, purpuric rashes all over the body, severe pallor, and active bleeding per vaginum. She was catheterized and an ultrasound of pelvis revealed a large clot in the bladder for which she was started on bladder irrigation.

On reviewing the history, febrile illness of 3-4 days prior to development of abdominal pain was noted. There was no history of dyspnea, burning micturation, cough, itching, or jaundice. It was also noted that she had been amenorrhea since last 8 weeks. On examination, she was febrile, pulse was 108/min with a normal blood pressure (120/86 mm/Hg). She was pale, anicteric, did not have any palpable lymphnodes. Purpuric rash was noticed all over the body. She had a scar mark of surgery over her abdomen and minimal fluid in abdominal cavity. There was no organomegaly. Cardiovascular and respiratory systems were normal.

Routine investigations revealed a hemoglobin of 5 g/dl, TLC 5400/mm³ and platelet count of 6000/mm³. Her bilirubin and electrolytes were within the normal range and her renal functions were normal. Dengue serology was positive twice, repeated at the interval of 48 h. She was transfused 2 units of blood and 4 units of platelet rich plasma but her platelet count failed to rise beyond 7000 over the next 12 h and hematuria persisted. Her total leukocyte count fell to 3500/mm³ over next 48 h, but it subsequently rose to more than 7500/mm³. Empirically, antibiotics were given to cover for the risk of post operative infections. Over the next few days, she received repeated blood transfusions (total 6), 3 units of single donor apharesis and 12 units of platelet rich plasma, but the platelet counts failed to rise above 9000/mm³. Her fever subsided after 24 h. Blood cultures and urine culture were sterile. Coagulation parameters and work up for disseminated intravascular coagulation were negative. The platelet count failed to rise after repeated transfusions and more than 10 days had passed since she became symptomatic, a possibility of underlying autoimmune thrombocytopenia/idiopathic thrombocytopenia was considered. A bone marrow aspiration with a biopsy was done, which revealed normal cellularity with megakaryocytic hyperplasia. In the absence of active infection, a possibility of ITP/ATP was considered and it was decided to start the patient on steroids in the dose of 1 mg/kg body weight (60 mg). After 72 h, her platelet count was still below 10,000/mm³ but her hematuria had settled. Steroids were hiked up to 100 mg/day and her counts began to rise after 48 h. On discharge, her platelet count was 95,000/mm³, her bleeding had settled, purpuric rashes were subsiding, and her total count was normal.

On follow up after 7 days, her counts had normalized and she was advised to continue steroids for three more weeks before tapering over 3 weeks.

**DISCUSSION**

In majority of patients, dengue fever and thrombocytopenia present in three phases of illness. In the first phase, there is proteinuria and hypoalbuminemia. The second phase of
illness is characterized by maximal cytopenia and in the third phase, bradycardia and liver enzyme elevation are noted.\[4\]

The maximal thrombocytopenia is seen within the fifth day and eighth day from the onset of constitutional symptoms and more than 70% of patients show recovery of their platelet count after that.\[3-5\] In the natural history of illness, by the 9th to 11th days, all the patients show convalescence and platelet count recover to the pre-illness level.\[5\] In our patient, the platelet count failed to rise by day 10 even after repeated platelet transfusion. We suspected an immunological platelet dysfunction which responded to oral steroids.

Bone marrow suppression in dengue hemorrhagic fever evolves rapidly through several phases: (1) onset of marrow suppression starts within 3-4 days of infection; (2) host inflammatory responses in the marrow and of fever start shortly thereafter; (3) occurrence of a neutrophil nadir occurs on the fourth to fifth day after onset of fever; (4) simultaneously, immune activation sufficient to neutralize viraemia and accelerate elimination of infected cells starts; (5) remission of symptoms is followed by (6) resolution of cytopenias.\[1\]

Bone marrow studies show mild hypocellularity in the acute stage (less than 1 week) and normal cellularity in the convalescent stage (greater than 1 week). Megakaryocytic hyperplasia is seen in 60% of cases on the 6th-10th days of illness. After the first week of illness, megakaryocytes increase in number, with various stages of mature megakaryocytes appearing marrow. Nuclear vacuolization of megakaryocytes is also commonly seen.\[5\] In a study, bone marrow CFU-GM when performed within 1 week of illness showed no growth or low colony count, and reverted to normal after 1 week of onset of fever.\[3\]

One of the proposed hypotheses is a transitory alteration in the humoral regulation of thrombopoiesis, which possibly may be the consequence of the lymphoid tissue damage, provoked by dengue viruses. This results in extended thrombocytopenic state and contributes to the appearance of hemorrhagic complications (G, VI). Normally, the Tpo level rise with falling platelet levels due to illness but in dengue hemorrhagic fever, it has been noted that the Tpo levels do not increase in spite of low platelet counts in early phase. A rapid increase in Tpo levels from the sixth to seventh day is followed by a rise in the platelet counts subsequently.\[5\]

Another hypothesis proposes that down-regulation of hematopoiesis is probably a protective mechanism of the microenvironment that limits injury to the marrow stem/progenitor cell compartment during the subsequent process of elimination of infected cells.\[1\]

To add to this, most patients with DF or DHF, even without overt hemorrhage, have consumptive coagulopathy but the hemorrhage in dengue, without circulatory collapse, is most likely due to activation of platelets rather than coagulopathy.\[6\] In these patients, lower platelet count can be a predictor of mortality, with death six times greater among those platelet count < 50,000/µl.\[7\]

In our patient, the appearance of megakary-
ocytes in bone marrow could suggest either convalescence or ATP/ITP which could have resulted in prolonged thrombocytopenia.

There have been a few case reports of similar kinds with patients having prolonged thrombocytopenia.[2,8] The mechanism in these is presumed to be immunological and they responded dramatically to steroids, just as our patient did.[2] After complete recovery, these patients should be evaluated for an underlying disorder like autoimmune thrombocytopenia, which could result in prolongation of thrombocytopenia in dengue fever and could result in serious adverse outcomes. Such patients should be properly advised as to the possibility that common dengue fever may substantially enhance their risk for hemorrhagic complications.[8]

CONCLUSION

Prolonged thrombocytopenia in a patient with dengue fever should alert the physician to look for an underlying immunological disorder resulting in prolonged thrombocytopenia. A dramatic response to steroids further strengthens the possibility of a coexisting immunological cause in these patients. Such patients are to be carefully followed up since subsequent exposure to dengue virus may result in severe prolonged thrombocytopenic state in them.

REFERENCES