Case Report

Missing Cells - A Rare Case of Persisting Thrombocytopenia in Pregnancy With Dengue and Role of Romiplostim in These Cases

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Abstract

Objective: Dengue cases in pregnancy have high morbidity and mortality. More so if it leads to immune thrombocytopenic purpura which causes a drastic decrease in platelet, increasing chances of bleeding and mortality and pregnancy itself being a state of hemodynamic instability.

Case report: Here, we present a case of dengue causing secondary immune thrombocytopenia. Managing these cases is challenging and need a multidisciplinary approach and should be done at a higher center. In previous reports, thrombocytopenia in such cases responded to steroids or IVIG. But in our case patient did not respond to either of them but to Romiplostim. There are only a few studies on the use of Romiplostim in dengue and dengue induced ITP and more study is required.

Conclusion: Dengue induced persistent thrombocytopenia is rare but should always be kept in mind in managing these cases.

Keywords: Dengue; Immune Thrombocytopenic Purpura; Romiplostim; Pregnancy; Thrombocytopenia; Steroids

Introduction

Viral infections are on a rise in recent years. Dengue infection is caused by four strains of the DENV virus and is transmitted by the bite of the Aedes aegypti mosquito. According to the ministry of health and family welfare in the year, 2015 total number of cases of dengue was ninety-nine thousand nine hundred and thirteen and the total number of deaths was two hundred and twenty, despite all measures of vector control India observed a rise in a number of cases since then and a total number of cases in 2021 were one lakh ninety-three thousand two hundred and forty- five, with total deaths being three hundred and six. However, as suggested by WHO reporting of cases might not be adequate due to covid pandemic. Dengue is endemic in many countries however Asian subcontinents have 70 % of the total caseload (1).

During pregnancy there are rapid hemodynamic changes that occur and dengue and dengue-like infection during this critical period doubles the risk of morbidity and mortality. The condition worsens if this is associated with other comorbidities. Despite the fact, there is little research material available, and management of these patients becomes very difficult and the need for more studies on the topic is desired. Here we report a challenging case of a pregnant

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female in whom a dengue-like infection leads to secondary immune thrombocytopenic purpura. Dengue infection leading to immune thrombocytopenic purpura is rarely reported and can be fatal as it leads to pronounced thrombocytopenia which can be life-threatening especially at the time of delivery so the diagnosis can be easily missed if the treating physician is not aware of the fact and so the importance of this case report.

Case report

On 3rd December 2021, while we were already struggling with the Covid pandemic we had this atypical case at Tata Main Hospital, Jamshedpur, Jharkhand. India. The patient was G2A1, previous 1 spontaneous miscarriage, admitted at 35 weeks of gestation with the report of Dengue NS 1 positive and thrombocytopenia (Platelet count: 43,000). She was asymptomatic 6 days back when she developed a high-grade fever associated with chills, joint, periorbital pain, and petechial rash. She went to a physician for the same and on investigation she was found to be dengue positive with thrombocytopenia and was referred to our hospital.

On examination, there was no pallor, icterus, or lymphadenopathy. Bilateral pedal edema was present. Upper limbs showed petechial rashes which did not blanch on pressure. Blood pressure (BP): 104/86 mmHg, pulse rate (PR): 104/min, Spo2: 97% and normal central nervous system, cardiovascular system and respiratory system. On per abdomen examination - fundal height was 34 weeks, fetal heart rate was present, and uterus was relaxed. No hepatosplenomegaly was present. There was no past or family history of bleeding disorder. Ultrasound showed a live intrauterine fetus.

On investigations, the platelet count was 32,000. Her dengue test for detection of NS1 antigen was positive but IgM and IgG were negative. As per CDC guidelines if NS1 is positive with symptoms suggestive of dengue infection diagnosis of dengue is confirmed and this region is not endemic to other flaviviruses. Table 1 shows the platelet trend. Peripheral smear showed thrombocytopenia with giant cells with no blast cells seen. Coombs's test, ANA, and an anti-double-stranded DNA test were negative. She received 6 units of RDP and Inj. Cefepime 1 gm iv 12 hourly, Tab Ursodeoxycholic acid 300 mg 8 hourly was started.

On day two, the platelet count decreased to 15,000 with a small ecchymotic patch over the anterior abdominal wall. Inj. Methylprednisolone 40 mg iv 12 hourly was started and continued for 5 days, and 1 SDP was given.

On day three, the platelet count further decreased to 9000. 2 SDP, and 6 RDP were given. On further investigation vit b12 was 144 (less than normal). So in spite of multiple platelet transfusions, her platelet count did not improve and remained critically low, so bone marrow aspiration was done which was suggestive of immune thrombocytopenia. Since there was no improvement with steroids, IgG 50 mg was given for 2 days.

Table 1: Investigations and progress of platelets counts during the course of illness

	3/12/2022	4/12/2022	5/12/22	15/12/22
Haemoglobin	11.6			
TLC	9800			
DLC				
CRP	5.11			
PLTC	32,000(6unit RDP)	15000(1 SDP)	9000(2 SDP)	22,000
INR	1.03			
S. Creatinine	0.61			
S. Na/k/cl	115/3.9/88			
LFT				
Billirubin	0.84			2.01 (D- 1.24)
AST	731			455
ALT	252			288
ALP	242			144
Anti HAV, Anti HEV antibody	Negative			
Dengue antigen / antibody	NS1 Positive			
Paracheck	Negative			
BSMP	Negative			
S. Fibrinogen				300

The fetus on CTG showed signs of compromise but understanding the risk of bleeding during LSCS joint decision along with the husband to avoid a cesarean section was taken. Risk of IUD was explained. On 9 December patient had 2 episodes of generalized tonic-clonic seizures and the patient was transferred to HDU due to poor GCS and patient was intubated and antiepileptic levetiracetam was started. Suspecting intracranial bleed NCCT brain was done but there was no evidence of intracranial bleed.

As shown in table 1 patient`s condition improved but she had intrauterine fetal death. She went into spontaneous labor and delivered a stillborn fetus. It was 2 weeks since the onset of the fever and her platelet count was still not improving .On 14/12/21 she had hematuria for which she was given multiple transfusions of platelets, still it was between 8000 - 10,000 /cu mm. So need to change plan of management was felt and she was started on oral prednisolone at 1g/kg body weight and TPO receptor agonist Inj. Romiplostim 250 mcg SC was given on 16/12/21 and her platelet count increased (22,000 on day 15/12/21 and 50,000 on 19/12/21). So there no spontaneous rescue as is usually seen in dengue patients and Romiplostim was helpful in increasing platelet count.

Discussion

Immune thrombocytopenic purpura is identified as a low platelet count (<100,000/microL) due to impaired platelet production and increased destruction. It is a diagnosis of exclusion, and the reported incidence is 2 to 5 per 100,000 people (2). It can be a primary isolated event or a secondary one. Secondary ITP is defined as ITP with an underlying cause or disorder, which includes drug-induced or systemic illness-induced (eg. SLE, HIV, etc) (3). ITP secondary to dengue-like infection in pregnancy is rarely reported. Bleeding resulting from even severe thrombocytopenia is unpredictable ranging from minor bleeding manifestations like bruising and petechiae to severe manifestations like menorrhagia, epistaxis, gastrointestinal haemorrhage, haematuria and even intracranial haemorrhage (4, 5, 6).

In secondary thrombocytopenia, the inciting event is usually a viral, bacterial infection or immune alteration. The antibodies formed against them cross-reacts with platelet membrane glycoprotein 2b /3a complex, 1b/2a or GP 6 antigen due to molecular mimicry (7). This causes platelet destruction. The most common viral infections include HIV, Hepatitis C, Cytomegalovirus, and Varicella Zoster (7). Secondary ITP is relatively more common in children.

Dengue has rarely been reported as causing secondary ITP. Antibodies against NS1 antigen cross-react with platelet glycoprotein. In dengue, infection thrombocytopenia reaches its nadir in the critical phase i.e., the phase of plasma leakage which lasts for 24 - 48 hrs and comes after the febrile phase and this thrombocytopenia resolve by itself. Thrombocytopenia persisting beyond 2 weeks is rarely seen in dengue fever until complicated by immune thrombocytopenia.

In previously reported cases various modalities were used to treat thrombocytopenia. The initial treatment modality for rapid response in ITP is oral or intravenous steroids, Guidelines suggest using either prednisone (0.5-2 mg/kg/day) or dexamethasone (40 mg/kg/day for four days) as corticosteroids of choice (2). In cases not responding to steroids, intravenous immunoglobulin (IVIg) or anti D immunoglobulin is started to increase platelet count temporarily and in our case, there was a slight increase in platelet count seen, before ruling out secondary causes of thrombocytopenia, bone marrow examination to rule out malignancy or bone marrow failure and switching over to the secondary line of treatment. According to 2019 guidelines of the American Society of Haematology ITP guideline, second line modalities include TPO receptor agonist (Romiplostim) or Rituximab or splenectomy in cases who have severe bleeding manifestation or cases not responding to steroids. In our case patient had severe bleeding manifestation and was not responding to steroids so Romiplostim was started, and she responded well to it. However, for second-line therapy, TPO-RAs are favoured over rituximab or splenectomy, and rituximab is recommended as third-line therapy after failure of TPO-RAs (8).

Romiplostim is a TPO agonist started when the patient is willing for long-term treatment and wants to avoid splenectomy. Romiplostim binds to and activates the TPO receptor on megakaryocyte precursors, thus promoting cell proliferation and viability, resulting in increased platelet production (9). While adverse effect includes rebound thrombocytopenia, marrow fibrosis and myelodysplasia.

Only few previous case reports have reported ITP due to dengue fever. Study by Y.L Boo reported the mortality of a 14 yearr child with this condition due to intracranial haemorrhage (10). Another case report with patients in the paediatric age group responded to

steroids but developed chronic ITP (11). In another case report by Prabhat Kumar done in RML Delhi also did not respond to steroids and responded to IVIg (12). Romiplostim is used in only a few case reports and has shown promising results in dengue-induced thrombocytopenia (13).

Conclusion

Dengue illness-induced ITP is a rare condition and this should be kept in differential diagnosis while dealing with dengue with thrombocytopenia with no spontaneous remission even after 2 weeks. Hence follow-up of dengue and dengue-like diseases patients is essential. Romiplostim proved highly effective as in our case and more studies are required in this regard.

Conflict of Interests

Authors declare no conflict of interests.

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