Immune thrombocytopenic purpura during a dengue outbreak: A dynamic masquerader

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ABSTRACT

In this age of enhanced diagnostics and improved turnaround time, immune thrombocytopenic purpura (ITP), a disease primarily diagnosed by exclusion, is expected to be straightforward to diagnose. However, during a full-fledged dengue outbreak, the health-care system can be overwhelmed, and as a result, ITP can be underdiagnosed. The clinician should be aware of the various imitations that ITP can present with. Various clinical indicators have to be kept in mind while dealing with such an outbreak to avoid unnecessary health-care expenditure and prolonged hospital stays. In this case series, we present two patients diagnosed to have ITP during the dengue outbreak, each unique in its presentation and course, demonstrating the multiple patterns ITP can present itself.

Key words: *Dengue, Fever, Immune thrombocytopenic purpura, Thrombocytopenia*

Dengue virus runs rampant across Africa, Americas, Eastern Mediterranean, South-east Asia, and the Western Pacific with the South-east Asia and Asia-Pacific regions being the most seriously affected [1]. It transmits through vectors (*Aedes aegypti* mosquito) which thrive in many developing countries. The epidemiological season for dengue infection reaches its peak when vector growth ascends; normally during the monsoon season. Dengue outbreaks are very stereotypical in countries with cyclical monsoons.

In India, the World Health Organization and National Vector Borne Disease Control Programme quoted a figure of 99,913 dengue cases and 220 deaths in 2015 [2,3]. It is quite comprehensible that during these outbreaks, there is an underdiagnosis of other illnesses whose presentations involve thrombocytopenia. Immune thrombocytopenic purpura (ITP) is another such disease characterized by destruction of platelet cells in the peripheral blood. It can present both in a primary or secondary manner [4]. Dengue and ITP share a common immunological flaw that precedes a downswing in the platelet cell numbers. Dengue is known to induce and provoke an aberrant immune system response [5-8].

This case series provides an apt portrayal of how illnesses with similar presentation can be misread by unearthing ITP in a sea of dengue and the versatility of ITP in particular. A literature search linking an association between the two was unfeasible due to its scarcity. It also demonstrates the multiple patterns of presentation of ITP, i.e., primary and secondary.

CASE REPORTS

A case series was conducted in our tertiary center of Punjab, India, among two patients during a period encompassing a surge in the cases of dengue fever in this particular geographical area (midst of a dengue outbreak). All the patients were adults between the ages of 18 years and 67 years, admitted with an acute history of fever with or without bleeding manifestations along with laboratory evidence of a low or declining platelet count almost clinically suggestive of dengue fever. Of the 184 patients that presented to us over a period of 2 months (December 1, 2017–January 31, 2018), one was documented to have a primary ITP, and the other had secondary ITP.

The criteria and evaluation for ITP were followed as per the guidelines available [9]. In both cases, other myriad of conditions including other systemic illnesses (including systemic lupus erythematosus, hepatitis C infection, human immunodeficiency virus (HIV) infection, autoimmune thrombocytopenia, and liver disease) drug usage, and other primary hematologic disorders/malignancies, history of bleeding after previous surgery, dentistry, and trauma, recent blood transfusions, recent vaccinations, family history of thrombocytopenia or bleeding disorders were ruled out historically. The history and examination pertaining to the cases and other relevant details of each of them are mentioned below.

Case 1

A 56-year old female without any prior comorbidity presented to us with generalized weakness and thrombocytopenia. Her vitals were as follows pulse - 62/min, blood pressure - 134/72 mmHg, and respiratory rate - 20/min. She did not have any abnormal physical findings, any organomegaly and lymphadenopathy apart from a mucosal bleeding and hemorrhagic crusting over her soft palate. Her platelet counts were found to be 4000 cells/mm^3 with

the peripheral blood film confirming the same, dengue IgM and NS1 antigen were negative apart from an otherwise normal blood investigation. She was transfused random donor platelets and single donor platelets (SDP) following which she persisted to have a low platelet count (3000 cells/mm^3).

On day 3 of hospitalization, due to persistent thrombocytopenia refractory to donor platelet transfusions, an ITP was suspected. Bone marrow aspiration and biopsy were consistent with ITP (Increased megakaryopoiesis and other hematopoietic lineages being normal). She was started on oral corticosteroids (prednisolone) after which her platelet counts steadily rose to 74,000 cells/mm^3. She was diagnosed to have primary ITP and discharged on oral prednisolone. On follow-up a week later, she had platelet count of 230,000 cells/mm^3.

Case 2

A 22-year old man, without any prior comorbidity, presented with a history of fever for 3 days followed by a steady fall in platelet count. The physical examination did not reveal any organomegaly, lymphadenopathy, or any other abnormality. His vitals were as follows: Pulse - 84/min, blood pressure - 110/80 mmHg, and respiratory rate - 20/min. He was admitted and found to have a platelet count of 3000 cells/mm^3 (peripheral blood film confirming the same), dengue NS1 antigen and dengue IgM positive with the rest of the blood investigations being normal. He was diagnosed to have dengue fever without warning signs and was transfused 2 SDPs over the next 2 days (his platelet count rose to 23,000 cells/mm^3) after which there was a spontaneous, unprovoked rise in platelet count (up to 65,000/mm^3). He was discharged in an ambulatory condition.

On follow-up a week later, he was clinically found to be normal but had a platelet count of 36,000 cells/mm^3. A week later, his platelet count was 23,000 cells/mm^3. Each of these times, his peripheral blood films confirmed the thrombocytopenia. He underwent a bone marrow aspiration and biopsy which was consistent with ITP (increased megakaryopoiesis and other hematopoietic lineages being normal). He was started on oral prednisolone after which his platelet counts steadily rose to 186,000/mm^3. He was diagnosed to have secondary ITP following a dengue fever and continues to be on regular follow-up. All other known secondary causes of ITP were ruled out.

In both the above-mentioned cases, other bone marrow dyscrasias were ruled out by a meticulous bone marrow examination. Peripheral blood count and peripheral blood smear (to rule out pseudo-thrombocytopenia), *Helicobacter pylori*, HIV, and HCV testing were also performed and found to be negative.

DISCUSSION

During a dengue endemic, ITP can go unnoticed. It is up to the clinician to have a high index of suspicion and identify patients who do not follow the usual course of dengue fever. An ITP can easily imitate and confound the diagnosis of a fever and thrombocytopenia syndrome. Therefore, a possibility of ITP must be entertained if thrombocytopenia persists beyond the expected period of platelet count turnaround. The age-old classification of ITP holds true here and illustrates the complexity of the disease. Hence, as in the first case, primary ITP was at first deceptively diagnosed as a classic case of dengue, while in the second case, the dengue infection triggered an immunological breakdown following which a secondary ITP ensued.

ITP is an autoimmune disorder characterized by low platelet counts and bleeding. ITP being a diagnosis of exclusion does not do justice to the threatening virulence it carries. Antibodies against platelets are responsible for most cases of ITP. Although most cases are asymptomatic, very low platelet counts can lead to a bleeding diathesis. Mucocutaneous bleeds such as petechiae, purpura, and easy bruising are expected in ITP. Older patients have more severe hemorrhagic manifestations ranging from gastrointestinal bleeds to intracranial bleeds [10]. The nature of the bleeding usually corresponds to the platelet count. It is known that ITP can be divided between primary or secondary as well as acute or chronic. In adults, ITP is primary, chronic and idiopathic. Acute, secondary ITP is usually seen in children after a viral infection and is self-limiting. The causes of ITP are given in Table 1. The mechanisms involved in the resulting thrombocytopenia are given in Table 2 [11].

Clinical indicators hinting at ITP are refractory, persistent, prolonged thrombocytopenia, and poor response to donor platelet transfusions. At present, there are no scientific recommendations or evidence available to predict the development of secondary

Table 1: Causes of immune thrombocytopenic purpura

Primary
Antibody mediated
Idiopathic
Secondary
Postinfectious
HIV
Hepatitis C
Helicobacter pylori
Other viral infections like CMV, EBV, dengue
Drug dependent
Quinine
Heparin
Lymphoproliferative disorders
Leukemia
Associated with vasculitis/autoimmune disorders
SLE
Rheumatoid arthritis
Antiphospholipid syndrome
Evans syndrome
Others
Postmeasles-mumps-rubella vaccination
Cirrhosis

EBV: Epstein–Barr virus, CMV: Cytomegalovirus, HIV: Human immunodeficiency virus, SLE: Systemic lupus erythematosus

Table 2: Mechanisms of thrombocytopenia in immune thrombocytopenic purpura

Mechanisms of thrombocytopenia in ITP
Increased platelet destruction
Breakdown in central and peripheral immune tolerance of T cells and B cells
Antiplatelet antibodies against glycoprotein IIb/IIIa, resulting in its destruction
Drug or inactivated/live pathogen binds to platelet surface recruiting antibodies, thereby triggering a temporary immune response to platelets
Foreign antigens cross-react with platelet antigens (molecular mimicry)
Development of anti-platelet antibodies
Decreased platelet production
Anti-platelet antibodies also target megakaryocytes
Impaired function of megakaryocytes
Foreign antigen/virus induced bone marrow suppression
Insufficient thrombopoietin levels

ITP: Immune thrombocytopenic purpura

ITP. Nor are there any specific criteria available to formulate a diagnosis of ITP. Currently, the diagnostic approach is based essentially on a process of exclusion [12]. A failure of platelet count to rise well after the illness should rouse the thought of an ITP. Unfortunately, as it may hold true for most diseases, a high index of suspicion and a search for certain clinical indicators may be the only approach to diagnosing such a predicament. To the best of our knowledge, only a few authors in the past have reported an association with dengue and ITP, all having a dramatic response with corticosteroids [13-16].

CONCLUSION

Primary and secondary ITP can be a masquerader as well as an offspring of dengue fever. An ITP can mimic and go undetected and unnoticed during a dengue endemic. The physician should intently be on the lookout for certain telltale signs and features and signs that indicate an ITP in a patient presenting with a fever and thrombocytopenia syndrome, particularly during a dengue outbreak. Although an initial misdiagnosis can rarely lead to mortality, it can certainly stretch healthcare costs. Early detection and a prompt initiation of treatment need no clarification of its benefits. A careful assessment for clinical indicators of an ITP especially during a dengue endemic is vital to timely diagnosis.

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