

## Varicella-associated immune thrombocytopenic purpura in a child with bleeding manifestations with review of literature

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Received - 12 July 2017

Initial Review - 12 August 2017

Published Online - 17 October 2017

### ABSTRACT

Chickenpox is a benign and self-limiting viral exanthematous infection, but sometimes it may be associated with complications. Mild thrombocytopenia occurs in 1-2% of children with varicella, but severe immune-mediated thrombocytopenia associated with bleeding is a rare complication. Various other mechanisms for thrombocytopenia have been implicated-decreased bone marrow production of platelets, disseminated intravascular coagulation, virally-induced platelet aggregation followed by phagocytosis or lysis, direct viral invasion of platelet precursors and viral-derived neuraminidase causing enzymatic desialylation of platelets followed by removal of abnormal platelets by reticuloendothelial system. We report a case of severe thrombocytopenia, possibly immune-mediated with bleeding in the form of petechiae and epistaxis in a child recovering from chickenpox, who is successfully treated with steroids. This may at least in part guide clinicians to recognize this rare but potentially dangerous complication of chickenpox.

**Key words:** *Chickenpox, Epistaxis, Immune thrombocytopenic purpura, Petechiae*

Chickenpox is a benign and self-limiting viral exanthematous infection caused by varicella-zoster virus (VZV) but sometimes may associate with complications. Mild thrombocytopenia associated with chickenpox is well described in the pediatric population, but severe thrombocytopenia with bleeding is rare. Various mechanisms have been implicated in its pathogenesis. We report a case of severe thrombocytopenia, possibly immune-mediated with bleeding in the form of epistaxis in a child recovering from chickenpox, who is successfully treated with steroids.

### CASE REPORT

A 9-year-old male child was referred to us with increasing thrombocytopenia and bleeding from nose for 3 days (platelet counts  $<10 \times 10^9/L$  for past 3 days). The patient had a history of fever of 4 days followed by pleomorphic vesicular skin lesions of chickenpox 12 days back. There was no history of cough, vomiting, icterus, and bleeding from other sites. The patient was afebrile and was recovering from chickenpox. On examination, the patient was conscious and oriented, with pulse - 90/min, respiratory rate - 24/min, temperature  $37^\circ C$  by axilla, blood pressure 100/60 mmHg, and maintaining 99% oxygen saturation on room air. The patient had few dried scabbed lesions scattered over the body and numerous petechiae over both upper and lower extremities. The patient was having active bleeding in form of diffuse oozing from multiple sites of both nostrils, leading to

decline in previously documented hemoglobin (Hb) of 10 g/dL to 8.1 g/dL at the time of admission, which failed to stop with the initial local treatment (compression followed by plugging the nostrils with gauze soaked in topical decongestant), and so nasal packing was done along with platelets transfusion. There was no hepatosplenomegaly, lymphadenopathy, ecchymosis, bruises, bony tenderness, and no past and family history of transfusion of blood components.

Laboratory investigations were as follows. Hb 8.1 g/dL, hematocrit 24.8%, red blood cell (RBC) count  $4.28 \times 10^6/\mu L$ , mean corpuscular volume - 78.3 fL, mean corpuscular Hb - 25.23 pg, mean corpuscular Hb concentration - 32.24 g/dL, white blood cell (WBC) count  $12.3 \times 10^9/L$ , platelet count  $5 \times 10^9/L$ , reticulocyte count 1.8%, urea 21.74 mg/dL, creatinine 0.74 mg/dL, bilirubin total/direct - 0.56/0.29 mg/dL, serum glutamic pyruvic transaminase - 22.98 U/L, serum glutamic oxaloacetic transaminase - 26.52 U/L, and prothrombin time/activated partial thrombin time/INR - 14 s/31 s/1.16, respectively. Malaria parasite and dengue Ns1Ag/immunoglobulin M (IgM)/IgG were negative. Peripheral blood smear showed microcytic hypochromic RBCs with anisocytosis and polychromasia. WBC count was normal with lymphocytosis. Platelets were markedly reduced with few large size platelets, no clumps seen. There was no evidence of hemolysis and hemoparasites. Urinalysis was normal.

Coombs test (direct antiglobulin test) was negative. Human immunodeficiency virus and antinuclear antibody titer were negative. Varicella IgM index was  $>2.30$  (reference

value:  $\geq 1$  positive) and IgG index was 755.3 (reference value:  $\geq 150$  positive). Bone marrow examination revealed adequate cellularity. Erythropoiesis was predominantly normoblastic with micronormoblasts. M: E ratio was 3:1. Myelogram showed blasts 3%, promyelocytes 15%, myelocytes 18%, metamyelocytes 20%, neutrophils 39%, lymphocytes 16%, monocytes 2%, and eosinophils 1%. Megakaryocytes were increased in number. On the basis of history, clinical examination and investigations, a diagnosis of post-varicella immune thrombocytopenic purpura (ITP) was made. Short course of steroid was started along with supportive iron and multivitamin therapy. There was a rapid rise in platelet counts,  $154 \times 10^9/L$  on the 4<sup>th</sup> day of starting steroid with cessation of bleeding and no new hemorrhagic lesions, and the patient discharged. The patient had normal hemogram on follow-up examination, after 1 and 3 months of hospitalization.

## DISCUSSION

Mild thrombocytopenia occurs in 1-2% of children with varicella, but severe immune-mediated thrombocytopenia (ITP) associated with bleeding is rare [1]. In a retrospective study by Amir et al., the incidence of post-varicella ITP was 1.9% among children diagnosed with ITP and 1.1% among children hospitalized for varicella. The male-to-female ratio was 1.5:1. ITP was diagnosed, on average, 8.5 days after the onset of the varicella rash with an average minimal platelet count of  $9500/mm^3$ . Post-varicella ITP had an acute course in 80% of cases and a chronic course in the remaining 20%. The infection caused a relapse in 71% of the patients with chronic ITP but had no apparent effect on the platelet count of the children with acute ITP. Post-varicella ITP has similar clinical features and course to non-varicella associated ITP. The calculated risk of ITP as a complication after varicella infection was approximately 1:25,000 [2].

In the study of Rivest et al., frequency of thrombocytopenia associated with chickenpox in children was 22.5% [3]. Ware et al. described chronic thrombocytopenia in association with varicella in three girls [4]. Mantadakis et al. also reported chickenpox-associated ITP [5]. Amir et al. describe bleeding complication in three patients with post-varicella ITP [2]. Tobin and Tobin and Ten Bensele, and Marcus et al. reported cases of varicella with thrombocytopenia causing fatal intracranial hemorrhage [6,7]. Various mechanisms have been implicated in its pathogenesis, including decreased bone marrow production of platelets, disseminated intravascular coagulation, viral-induced platelet aggregation followed by phagocytosis or lysis, direct viral invasion of platelet precursors, viral-derived neuraminidase causing enzymatic desialylation of platelets followed by removal of abnormal platelets by reticuloendothelial system, and immune-mediated platelet destruction [5,8-10].

Platelet-specific IgM antibody against various platelet surface glycoproteins (GP), namely, GPIb, GPIIb, GPIIIa, and GPV were found in patients with varicella-associated thrombocytopenia by immunoblotting technique [8,11]. In our case, the child has thrombocytopenia when he was recovering from the illness. RBC

and WBC counts and coagulation profile were within normal limits range. The child has active bleeding from both nostrils, causing a decline in Hb level and leading to anemia, a potential life-threatening situation, which needed nasal packing and platelet transfusion to control it.

Bone marrow examination is not indicated in acute ITP with typical features, which includes, Hb level of  $>10$  g/dL (6-12 months of age) or  $>11$  g/dL (older than 1 year), total WBC count of  $>5 \times 10^9/L$  (6-60 months of age) or  $>4 \times 10^9/L$  ( $>6$  years), neutrophil count of  $>1.5 \times 10^9/L$  (6 months-6 years) or  $>2 \times 10^9/L$  ( $>6$  years), and a platelet count of  $<50 \times 10^9/L$  [12]. Children who did not meet the above criteria are categorized as atypical ITP, as in our case having Hb level of 8.1 g/dL, and may need bone marrow examination. Diagnosis of ITP is based on findings of clinical examination and peripheral blood smear in all cases, and bone marrow aspiration in some. Even with state-of-the-art tests including anti-platelet antibodies, thrombopoietin, glycofalin, and platelet reticulocyte counts, immune thrombocytopenia cannot be distinguished from other thrombocytopenias and diagnosis is established by ruling out the other systemic processes [13]. Diagnosis of varicella is usually made clinically. However, when clinical diagnosis is a challenge, laboratory test is helpful, which includes varicella antibody titer in serum and detecting VZV in skin lesion with polymerase chain reaction.

Winiarski et al. quantified platelet-associated (PA) Igs and complement factors (C3, C4) and found that PA Igs were elevated in 98% patients of acute and chronic idiopathic thrombocytopenic purpura. PA IgG was elevated in 95%, PA IgA in 82%, and PA IgM in 74% of the patients. PAC3 and PAC4 were elevated in 86% and 57% of the patients, respectively. In acute ITP, PAC3 was strongly correlated with PA IgG than PAC4; while in chronic ITP, PAC4 correlated strongly with PA IgG than PAC3 [14]. In another study, percentage of elevated PAC3 values was found higher in thrombocytopenic patients than in non-thrombocytopenic patients. However, no statistically significant correlation was found between platelet counts and PAC3 levels [15]. In our case, we are not able to do PA Igs and complement levels.

Rapid improvement in thrombocytopenia with corticosteroid treatment along with bone marrow findings of normal myeloid and erythroid series with an increased number of megakaryocytes are suggestive of immune mediated mechanism of thrombocytopenia in our case. Both corticosteroids and intravenous Igs can be used to treat varicella-induced thrombocytopenia. Corticosteroids during the incubation period of varicella can lead to the development of visceral varicella, so they should be used in recovery phase past the incubation period [5]. Although fatal intracranial hemorrhage is reported with some cases of varicella-induced thrombocytopenic purpura, most of the reports describe quick recovery, showing excellent prognosis.

## CONCLUSION

Thrombocytopenia is commonly reported with varicella having various immune and non-immune mechanisms with an overall

excellent prognosis, but it can also lead to life-threatening bleeding complications.

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*Funding: None; Conflict of Interest: None Stated.*

**How to cite this article:** Kumar M. Varicella-associated immune thrombocytopenic purpura in a child with bleeding manifestations with review of literature. *Indian J Child Health*. 2017; 4(4):641-643.