Immune Thrombocytopenia Due To Hepatitis A Virus: Case Report and Review of Literature

Abstract
Acute hepatitis due to hepatitis A virus (HAV) is usually a self-limiting disease among children. Hematological complications including immune thrombocytopenia (ITP) are rare. We report an 8-year female with massive upper gastrointestinal bleed and diagnosed to have ITP associated with acute HAV infection.

Keywords: Hepatitis A virus; Childhood; Immune thrombocytopenia

Abbreviations: HAV: Hepatitis A Virus; ITP: Immune Thrombocytopenia; GI: Gastrointestinal; aCL: Anticardiolipin; APLA: Antiphospholipid Antibodies; IVIG: Intravenous Immunoglobulin

Introduction
Hepatitis A virus (HAV) infection is the most common cause of infectious hepatitis among children in India [1, 2]. Hematological manifestations such as aplastic anemia, leucopenia, hemophagocytic syndrome, and immune thrombocytopenia (ITP) have been rarely described with HAV infection [3-12]. We report a child with ITP due to acute HAV infection who presented with upper gastrointestinal (GI) bleed.

Case Report
An 8-year old previously well female presented with history of fever and vomiting for 10 days; jaundice 7 days; and 3-4 episodes of hematemesis and melena in last 2 days with moderate to massive blood loss. There was no history of rash, myalgia, arthralgia, or drug intake. There was no history of jaundice in close contacts. At admission, she was in hypotensive shock due to massive GI blood loss which was managed with oxygen support, intravenous normal saline bolus and urgent blood transfusion. She continued to have GI bleed during the hospital stay for which she received packed red cell transfusion thrice and multiple platelet transfusion. For persistent thrombocytopenia (platelet count of 5,000/cumm), she underwent bone marrow examination on day 4 which revealed normocellular marrow spaces with megakaryocytic hyperplasia consistent with ITP. She was discharged after hospital stay of 10 days with hemoglobin of 8.1 gm/dl, platelet count of 36,000/mm$^3$, and decreasing liver enzymes. At 3 months after discharge, she was clinically well with platelet count of 2,47,000/mm$^3$.

Discussion
ITP is a self-limiting disorder presenting with a short history of mucocutaneous bleeding in children of either sex between age group of 2-10 years. The incidence is about 4/1,00,000 children/year. It may follow a viral infection or immunization and is caused by an inappropriate immune response [13,14]. Number of viruses has been implicated in the etiopathogenesis including: HIV, hepatitis C virus, hepatitis B virus, varicella-zoster virus, rubella, influenza, Epstein-Barr virus, parvovirus B19, and dengue virus [13-16]. Few cases of ITP associated with HAV infection has been reported in children [3-12] (Table 1).

Thrombocytopenia associated with viral infections may result from bone marrow depression; increased platelet consumption due to disseminated intravascular coagulopathy, hemophagocytosis, and hypersplenism; or immune-mediated peripheral destruction of platelets in reticuloendothelial system, particularly in spleen (principal mechanism) [5, 7, 13-15]. Thrombocytopenia occurring during the course of HAV may be due to presence of transient anticardiolipin (aCL) and antiphospholipid antibodies (APLA); anti-platelet antibodies; or non-specific deposition of immune anti-hepatitis E antibody, hepatitis B surface antigen and IgM anti-hepatitis C antibody were negative. Abdominal sonography revealed hepatosplenomegaly, mild bilateral pleural effusion, mild ascites, and thick gall bladder wall.

Investigations at admission revealed hemoglobin 3.2 gm/dl, platelet count 14,000/mm$^3$, total leucocyte count 10,800/mm$^3$ (neutrophils 65%, lymphocytes 27%, monocytes 7%, and eosinophils 1%), and reticulocyte count of 2%. Liver function tests revealed total bilirubin 2.3 mg/dl (conjugated 0.91 mg/dl), aspartate transaminases 900 U/L (normal: 15-45 U/L), alanine transaminase 1125 U/L (normal: 15-35 U/L), alkaline phosphatase 230 U/L (normal: 100-320 U/L), total serum protein 6.1 gm/dl, and serum albumin 3.3 gm/dl. Prothrombin time was 20 seconds, prothrombin index 70%, activated partial thromboplastin time 34 second, international normalized ratio 1.5 seconds, fibrinogen 2 gm/dl, and negative d-dimers. Serum electrolytes and renal function tests were normal. Blood culture, peripheral smears for malarial parasite, dengue IgM and IgG, widal, leptospira serology, scrub typhus IgM ELISA, and HIV ELISA were negative. IgM anti-HAV antibody was positive. IgM anti-hepatitis E antibody, hepatitis B surface antigen and IgM anti-hepatitis C antibody were negative. Abdominal sonography revealed hepatosplenomegaly, mild bilateral pleural effusion, mild ascites, and thick gall bladder wall.
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complexes at the platelet surface [11,17-19]. Autoantibodies against glycoproteins over platelet surface (particularly IIb/IIIa) can be detected in 60–70% of cases, but are of no prognostic and diagnostic significance [13, 14].

Table 1: Clinico-laboratory profile, treatment and outcome of children with ITP due to HAV infection.

| S. No. | Author, year (reference) | n | Age, sex | Clinical presentation | Treatment | Outcome |
|--------|--------------------------|---|----------|----------------------|-----------|---------|
| 1      | Index case               | 1 | 8 years, female | Fever, vomiting, jaundice and upper GI bleed. Platelet count 5000/cumm, ALT 1125 U/L, AST 900 U/L, HAV-IgM positivity, bone marrow suggestive of ITP. | Anti-D | Improved |
| 2      | Leblebsatan et al. [3]   | 2 | 8 years, male | Diffuse ecchymosis on both extremities. Platelet count 10,000/cumm, ALT 350 U/L, AST 470 U/L, HAV-IgM positivity. | IVIG 1 gm/kg for 3 days | Improved |
| 3      | Leblebsatan et al. [3]   | 4 years, male | Skin bleeds. Platelet count 1000/cumm. ALT 1262 U/L, AST and 1143 U/L, HAV-IgM positivity, bone marrow suggestive of ITP. | IVIG 1 g/kg for 3 days followed by oral methyl-prednisolone 2 mg/kg | Improved |
| 4      | Samanta T et al. [4]     | 2 | Thrombocytopenia, bone marrow suggestive of ITP. | IVIG | Improved |
| 5      | Samanta T et al. [4]     | 2 | Isolated thrombocytopenia. | No treatment | Improved |
| 6      | Tanir G et al. [5]       | 1 | 4 years, male | Skin bleeds. Platelet count 2000/cumm, ALT 940 U/L, AST 1030 U/L, HAV-IgM positivity, bone marrow suggestive of ITP, and negative direct and indirect Coombs tests, antinuclear antibody, anti-ds-DNA, anti-cardiolipin and antiphospholipid antibodies. | IVIG 0.8 gm/kg for 1 day | Improved |
| 7      | Venkataravanamma P et al. [6] | 1 | 12 years, female | Hematemesis, menorrhagia, purpura, and hypotensive shock. Platelet count 5000/cumm, ALT 1837 U/L, AST 2116 U/L, HAV-IgM positivity, and normal bone marrow. | No treatment | Improved |
| 8      | Shenoy R et al. [7]      | 1 | 8 years, male | Generalized petechial rash and gum bleeding. Platelet count 5000/cumm, ALT 1116 U/L, HAV-IgM positivity, bone marrow suggestive of ITP, and negative Coombs test and antinuclear antibody. | No treatment | Improved |
| 9      | Sakha HS et al. [8]      | 1 | 6 years, male | Epistaxis, mouth bleeding, skin bleeds. Jaundice 10 days back. Platelet count <1000/cumm, ALT 171 U/L, AST 109 U/L, HAV-IgM positivity, and bone marrow suggestive of ITP, and negative antinuclear, anti-DNA and anti-smooth muscle antibodies. | IVIG 1 gm/kg followed by prednisolone 2 mg/kg/day | Improved |
| 10     | Scott JX et al. [9]      | 1 | 4½ years, female | Hematuria, hematemesis and skin bleeds. Platelet count 5000/cumm, AST 2070 U/L, ALT 2150 U/L, HAV-IgM positivity, bone marrow suggestive of ITP. | IVIG 1 gm/kg | Improved |
| 11     | Scott JX et al. [9]      | 1 | 4½ years, female | Generalized petechial rash and gum bleeding. Platelet count 5000/cumm, ALT 1116 U/L, HAV-IgM positivity, bone marrow suggestive of ITP, and negative antinuclear, anti-DNA and anti-smooth muscle antibodies. | IVIG 1 g/kg for 3 days | Improved |
| 12     | Scott JX et al. [9]      | 1 | 4½ years, female | Epistaxis, mouth bleeding, skin bleeds. Jaundice 10 days back. Platelet count <1000/cumm, ALT 171 U/L, AST 109 U/L, HAV-IgM positivity, and bone marrow suggestive of ITP, and negative antinuclear, anti-DNA and anti-smooth muscle antibodies. | IVIG 1 gm/kg for 3 days | Improved |
| 13     | Scott JX et al. [9]      | 1 | 4½ years, female | Hematuria, hematemesis and skin bleeds. Platelet count 5000/cumm, AST 2070 U/L, ALT 2150 U/L, HAV-IgM positivity, bone marrow suggestive of ITP. | Steroids | Improved |
| 14     | Scott JX et al. [9]      | 1 | 4½ years, female | Epistaxis, mouth bleeding, skin bleeds. Jaundice 6 weeks back when laboratory investigation revealed elevated bilirubin; ALT 1400 U/L, AST 1900 U/L, and HAV-IgM positivity. Presented with epistaxis and skin bleeds for 3 days. Platelet count 30000/cumm, bone marrow suggestive of ITP along with erythrocytopathy. | Oral methylprednisolone 2 mg/kg/day | Improved |
| 15     | Scott JX et al. [9]      | 1 | 4½ years, female | Skin bleeds. Platelet count 2000/cumm, ALT 923 U/L, AST 1053 U/L, HAV-IgM positivity, bone marrow suggestive of ITP, negative antinuclear, anti-ds-DNA, anti-cardiolipin and anti-liver-kidney microsomal antibodies, and elevated IgM antiphospholipid antibodies. | IVIG 1 gm/kg | Improved |

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Index child was managed as ITP due to HAV infection and treated with anti-D immune globulin following which she had good clinical and hematological response. The treatment options for ITP include intravenous immunoglobulin (IVIG), oral steroids, and anti-D immunoglobulin. IVIG raises the platelet count rapidly (usually within 48 hours) and is therefore the treatment of choice for life threatening hemorrhage. Steroids are usually given at a dose of 1–2 mg/kg/day for up to 2 weeks. Anti-D immunoglobulin is effective in Rh (D) positive children with similar efficacy to IVIG and has advantage of being given as a rapid single injection and less cost [13, 14]. Treatment of ITP even in presence of very low platelet count may not be required because risk of serious bleeding is less and outcome is favorable even without treatment [13-15]. Currently, there is trend toward conservative management of children with ITP [19, 20].

Celik et al. [21] studied the efficacy, cost, and effects of anti-D immunoglobulin, methylprednisolone, and IVIG in children with newly diagnosed ITP and found no difference between platelet counts before treatment and on day 3 of treatment. However, platelet counts at day 7 were lower in the methylprednisolone group than in the IVIG group. They also noticed that the mean cost of IVIG was 7.4 times higher than anti-D and 10.9 times higher than methylprednisolone. Alioglu et al. [22] demonstrated that IVIG (400 mg/kg/day for 5 day) lead to a significant increase in platelet count at 24 hour, 48 hour, 72 hour, 7 day and 30 day when compared to anti-D (50 μg/kg and 75 μg/kg) among newly diagnosed ITP in children. Most of the case reports of children with ITP due to HAV have been treated with IVIG with or without steroids and have shown good clinical and hematological response (Table 1). In index patient, we preferred anti-D immunoglobulin 75 μg/kg over IVIG due to financial reasons. Steroids were deferred because of active GI bleeding.

We could not find any evidence of hemophagocytic syndrome or bone marrow suppression. However, increased erythroblasts and megaloblasts in bone marrow aspiration and the rapid response of the platelet counts to anti-D therapy suggested immune-mediated peripheral platelet destruction, though we could not measure aC1, APLA, or anti-platelet antibodies. Index case and other case reports (Table 1) suggest that ITP does not seems to be an indicator of hemophagocytic syndrome and emperipolesis in a patient with hepatitis A infection. Pediatr Hematol Oncol 19(1): 67-70.

4. Samanta T, Das AK, Ganguly S (2010) Profile of hepatitis A infection with atypical manifestations in children. Indian J Gastroenterol 29(1): 31-33.

5. Tanir G, Aydemir C, Tuygun N, Kaya O, Yarali N (2005) Immune thrombocytopenic purpura as sole manifestation in a case of acute hepatitis A. Turk J Gastroenterol 16(4): 217-219.

6. Venkataramanama P, Rau AT (2004) Severe thrombocytopenia in association with hepatitis A. Indian Pediatr 41: 1178-1179.

7. Shenoy R, Nair S, Kamath N (2004) Thrombocytopenia in hepatitis A--an atypical presentation. J Trop Pediatr 50(4): 241-242.

8. Hosainpour Salha S, Gharbarec R, Sari Sorkhabi R (2004) Immune thrombocytopenia associated with hepatitis A infection in children. Iran J Med Sci 29: 148-149.

9. Scott JX, Gnananayagam EJ, Gupta S, Simon A, Mukhopadhyya A (2003) Thrombocytopenic purpura as initial presentation of acute hepatitis A. Indian J Gastroenterol 22(5): 192-193.

10. Avci Z, Turutlu, Cilat E, Olgu S, Baykan A, et al. (2002) Thrombocytopenia and emperipolesis in a patient with hepatitis A infection. Pediatr Hematol Oncol 19(1): 67-70.

11. Ertem D, Acar Y, Pehlivanoglu E (2001) Autoimmune complications associated with hepatitis A virus infection in children. Pediatr Infect Dis J 20(8): 809-811.

12. Ertem D, Ozguven E, Acar Y, Alper G, Pehlivanoglu E (1999) Thromboembolic complications in children with Crohn’s disease. J Pediatr Gastroenterol Nutr 28(5): 540-541.

13. Bolton-Maggs PH (2000) Idiopathic thrombocytopenic purpura. Arch Dis Child 83(3): 220-222.

14. Labarque V, Van Geet C (2014) Clinical practice: immune thrombocytopenia in paediatrics. Eur J Pediatr 173(2): 163-172.

15. Cines DB, Blanchette VS (2002) Immune thrombocytopenic purpura. N Engl J Med 346(13): 995-1008.

16. Kumar S, Khadwal A, Verma S, Singh SC (2013) Immune thrombocytopenic purpura due to mixed viral infections. Indian J Pediatr 80(5): 421-422.

17. Ertem D, Acar Y, Arat C, Pehlivanoglu E (1999) Thrombotic and thrombocytopenic complications secondary to hepatitis A infection in children. Am J Gastroenterol 94(12): 3653-3655.

18. Ibarra H, Zapata C, Inostroza J, Mezzano S, Riedemann S (1986) Immune thrombocytopenic purpura associated with hepatitis A Blut 52(6): 371-375.

19. Gnaining JD, Rees JL, Reeves M, Bolton-Maggs PH (2012) Changing trends in the UK management of childhood ITP. Arch Dis Child 97(1): 8-11.

20. Schultz CL, Mitra N, Schapira MM, Lambert MP (2014) Influence of the American Society of Hematology guidelines on the management of newly diagnosed childhood immune thrombocytopenia. JAMA Pediatr 168(10): e142214.

21. Celik M, Bulbul IA, Aydogan G, Tugcu D, Can E, et al. (2013) Comparison of anti-D immunoglobulin, methylprednisolone, or intravenous immunoglobulin therapy in newly diagnosed pediatric immune thrombocytopenic purpura. J Thromb Thrombolysis 35(2): 229-233.

22. Alioglu B, Ercan S, Tapci AE, Zengin T, Yazarli E, et al. (2013) A comparison of intravenous immunoglobulin, methylprednisolone, or intravenous immunoglobulin therapy in newly diagnosed pediatric immune thrombocytopenic purpura: Ankara hospital experience. Blood Coagul Fibrinolysis 24(5): 505-509.