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Case Report

Wiskott Aldrich Syndrome having Atypical Presentation Like Evans Syndrome

Abhijit Anil Patil[1*] and Ashwath D[2]

[1]Child Neurocare Clinic, Jalgaon, Maharashtra, India; [2]Department of Paediatrics, Consultant Paediatrician and Neonatologist, Kovai Medical Center Hospital, Coimbatore, Tamil Nadu, India

ABSTRACT

Background: Wiskott Aldrich Syndrome (WAS) is an X-linked recessive condition characterized by thrombocytopenia and small dysfunctional platelets, recalcitrant eczematous dermatitis, and recurrent bacterial infections. In this report, we describe an unusual case of WAS in an Indian boy who presented with early onset thrombocytopenia and autoimmune haemolytic anemia.

Case presentation: 3 months male infant was evaluated for poor feeding and oral ulceration blood work up showed anemia and thrombocytopenia. He was treated with intravenous immunoglobulin. At 11 months of age he presented with yellowish discoloration of eyes, poor feeding, irritability, vomiting, generalised purpuric rashes. Blood investigations revealed anemia, thrombocytopenia, indirect hyperbilirubinemia, positive direct coombs test (4+). He was treated with steroids, intravenous immunoglobulin, to which he showed partial response. However 1 month later he presented with worsening thrombocytopenia and anemia, Mycophenolate Mofetil was initiated and continued for 4 months, due to unavailability of Mycophenolate Mofetil he was started on oral cyclosporine. He relapsed in 1 month, 6 doses of rituximab were given. He had refractory thrombocytopenia while his haemoglobin and white blood cell counts improved after rituximab therapy. He developed eczematous rashes all over face and neck regions. *WASp* Gene mutation screening showed splite site mutation (c.360+1G>T) in exon 3 intron 3 boundary in *WASp* gene. At 2 year of age child succumbed to *Staphylococcus aureus* sepsis.

Outcome: At 2 year of age child succumbed to *Staphylococcus aureus* sepsis.

Conclusion: Diagnosis of Wiskott Aldrich syndrome should be considered in any male infant who presents with early onset thrombocytopenia, eczema, and recurrent infections.

Keywords: Wiskott Aldrich syndrome; Evans syndrome; Intravenous immunoglobulin

INTRODUCTION

Wiskott Aldrich Syndrome (WAS) is an X-linked recessive condition characterized by thrombocytopenia and small dysfunctional platelets, recalcitrant eczematous dermatitis, and recurrent bacterial infections. It almost exclusively occurs in males with few reports of females affected [1]. WAS is secondary to loss-of-function mutations in the WAS protein (*WASp*) gene, which plays a role in lymphoid development and thereby affects both B and T lymphocyte function [2]. The WAS protein (*WASp*) is required to maintain the integrity of the actin cytoskeleton in multiple cell types. Thrombocytopenia occurs due to ineffective thrombopoiesis and increased platelet clearance [3]. Mutations in WAS can also lead to isolated micro-thrombocytopenia without syndromic associations [4] Mutations affecting the *WASp* interacting protein can also result in a phenotype resembling WAS that is inherited in an autosomal recessive fashion [5]. Owing to thrombocytopenia and platelet dysfunction from birth, patients often present initially with spontaneous bleeding, such as epistaxis or bloody stools. The dermatitis usually begins within the first few months of life and is indistinguishable from atopic dermatitis, but may be more generalized and/or severe. The face, scalp, and flexural areas are typically affected and secondary bacterial infections are common. Owing to the bleeding diathesis, excoriated areas are more likely to demonstrate serosanguinous crust, petechiae, purpura. Recurrent bacterial infections, especially with encapsulated organisms, begin in infancy as maternal antibodies wane. Most children with WAS also develop autoimmune or inflammatory disease over time.

Correspondence to: Dr. Abhijit Anil Patil, Fellow Paediatric Neurology, Child Neurocare Clinic, Jalgaon-425001, Maharashtra, India, Tel: +919003300957; E-mail: abhineurology87@gmail.com

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Hemolytic anemia is the most common, but other conditions reported in patients with WAS include autoimmune neutropenia, painful cutaneous small vessel vasculitis, arthritis, cerebral vasculitis, inflammatory bowel disease, and renal disease [6]. In 1 study, nearly 25% of WAS patients developed malignancies including lymphoma and myelodysplasia [7]. The platelet phenotype consists of small platelets with normal granularity. Treatment is based on supportive care for infection, including prevention of infection using antibiotics and immunoglobulin therapy. Splenectomy has been shown to improve platelet counts [8]; however, it significantly increases infectious risk in these already immunocompromised patients. Allogeneic stem cell transplantation with reduced intensity conditioning is curative and retroviral-based gene therapy is under investigation [9].

CASE PRESENTATION

3 months male infant with normal antenatal and perinatal history, was evaluated at local hospital at 2 month 9 days of age for poor feeding of 2 days with oral ulceration, no history of fever, rashes, bleeding manifestations, respiratory distress, he was alert, active, good hydration, heart rate was 130 per minute, respiratory rate was 30 per minute, no organomegaly on per abdomen examination, cardiac, respiratory, central nervous system examinations were normal, his haemoglobin was 6.9 g%, total leucocyte count 10,800, polymorph 36%, lymphocyte 48%, monocyte 14%, eosinophil 1%, platelets count was 75000/cumm, repeat blood counts after 4 days showed platelet count 6000/cumm, bone marrow examination showed solidly cellular fragments with relatively poor cell trails, mild lymphocytosis and scattered atypical lymphoid cells? reactive lymphocytes, prothrombin time was 11.8 seconds, international normalised ratio was 1.08, he was given trial of intravenous immunoglobulin in view of low platelet counts without benefit as platelet count remained on lower side post intravenous immunoglobulin. At 3 months of age he was readmitted for loose stool with passage of blood in stool of 1 day, on examination he was active, afebrile, no signs of dehydration, pallor was present, he had ejection systolic murmur, no signs of cardiac failure haemoglobin was 8.3 g%, platelet count was 79000, total leucocyte count was 18,100 cell/cumm, erythrocyte sedimentation rate was 8 mm/hour, c reactive protein was 16.8 mg%, he was managened with oral antibiotic and zinc. At 11 months of age first time he was brought to our hospital with complaints of yellowish discoloration of eyes, poor feeding, irritability, vomiting, generalized rashes, on examination he was conscious, irritable, pale, icteric, petechial rashes over trunk, back, eczematous rashes all over body, right sided hydrocele, scar mark over right lumbar region, weight 9 kilogram, length 74 cm, head circumference 44 cm, no organomegaly on per abdomen examination, other system examination was normal, he was admitted in intensive care unit, blood investigations showed haemoglobin 4 g/dL, platelet count 5000 cell/uL, total leucocyte count 14900 cell/cumm, total serum bilirubin 5.04 mg/dL, indirect bilirubin 4.32 mg/dL, positive direct coombs test (4+), peripheral smear showed marked anisocytosis with macrocytes and spherocytes, autoagglutination, polychromasia and nucleated red cells with megaloblastic changes, severe thrombocytopenia and reactive lymphocytosis, picture suggestive of immune haemolytic anemia with severe thrombocytopenia. Possibility of evans syndrome was considered in view of combination of autoimmune haemolytic anemia, thrombocytopenia. He was initialy treated with steroids (intravenous dexamethasone 4 mg OD for 4 days) and intravenous immunoglobulin (2 g per kg over 2 days), to which he showed partial response. However 1 month later he presented with fever of 10 days, loose stools with passage of blood and mucus, blood reports showed worsening thrombocytopenia and anemia so second line agent Mycophenolate Mofetil was started at 1000 mg/m^2 dosage, flowcytometry of peripheral blood lymphocytes was negative for double negative T lymphocytes so autoimmune lymphoproliferative syndrome was ruled out. Hemoglobin stabilized but he continued to have severe symptomatic thrombocytopenia. Mycophenolate Mofetil was continued for 4 more months, due to unavailability of Mycophenolate Mofetil he was started on oral cyclosporine. He relapsed in 1 month and was admitted twice with fever of 3 weeks duration, lab reports showed severe anemia, thrombocytopenia. He was transfused with least incompatible packed red cells at 10 mL/kg. Treatment options were limited so 6 doses of rituximab were given at weekly interval. He had refractory thrombocytopenia while his haemoglobin and white blood cell counts improved after rituximab therapy. He developed eczematous rashes over the face and neck region. Considering this presentation in a male child, with eczema, recurrent infection, refractory thrombocytopenia, possibility of Wiskott Aldrich syndrome was thought and *WASp* Gene mutation screening was done, which showed splite site mutation (c.360+1G>T) in exon 3 intron 3 boundary in *WASp* gene, family was explained in detail about course, prognosis and available treatment options. Child developed *Staphylococcus aureus* sepsis and succumbed to his illness at around 2 years of age (Figure 1).

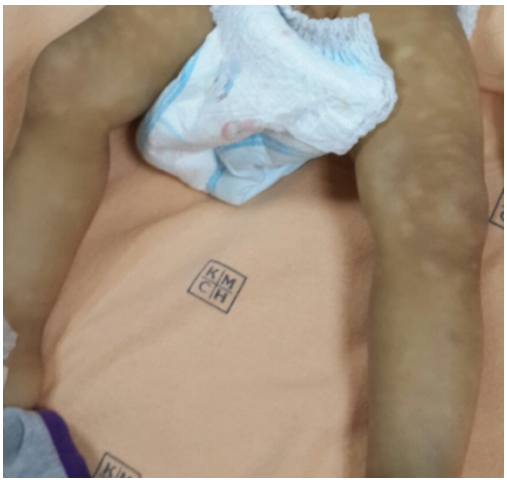

Figure 1: Clinical image showing hypopigmented skin patches.

DISCUSSION

In this report, we describe a case of a patient with WAS who presented with poor feeding, oral ulceration, thrombocytopenia and anemia at early infantile age. The unusual feature of this report is thrombocytopenia with immune hemolysis, one of the characteristic feature of WAS. Our patient demonstrated a splite site mutation (c.360+1G>T) in *WASp* gene. The clinical manifestation of thrombocytopenia in WAS is heterogeneous. In a study involving 154 patients with WAS, the most common bleeding manifestation was either petechiae or purpura, which was seen in 78% of patients [10]. Bleeding from the gastrointestinal tract, as seen in our patient, only occurred in 28% of the cases [10]. The WAS scoring system is used to categorize patients according to disease severity [11]. A score of 1 indicates that the patient has only thrombocytopenia, a score of 2 is given when the patient has thrombocytopenia with additional findings of mild/transient eczema or minor infections. Patients with a score of 1 and 2 are designated as having XLT. Those

with treatment-resistant eczema and recurrent infections in spite of optimal treatment receive a score of 3 (mild WAS) or 4 (severe WAS). A score of 5 is given to patients with autoimmune disease or malignancy, regardless of the original score. Using this system, our patient had a score of 5. The identification of a mutation in our patient enabled us to counsel family. An early diagnosis by means of prenatal diagnosis or blood investigations taken in the first few days of life in affected families will enable early arrangement of stem cell transplantation. Allogeneic stem cell transplantation with reduced intensity conditioning is curative and retroviral-based gene therapy is under investigation [9].

CONCLUSION

Diagnosis of Wiskott Aldrich syndrome should be considered in any male infant who presents with early onset thrombocytopenia, eczema, and recurrent infections. Bone marrow or cord blood transplantation is the treatment of choice and is usually curative.

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