

Wiskott-Aldrich Syndrome With Normal-Sized Platelets in an Eighteen-Month-Old Boy: A Rare Mutation

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Introduction: Wiskott-Aldrich syndrome (WAS) is an X-linked recessive disorder characterized by thrombocytopenia, eczema, and recurrent infections. The disease is usually associated with small defective platelets.

Case Presentation: We described an 18-month-old boy who presented with lower gastrointestinal bleeding, eczema, and recurrent infections. There was pancytopenia with normal-sized platelets. In addition, the CD4 count was significantly low and serum IgA and IgE levels were increased. The diagnosis of WAS was confirmed by detecting a mutation of WAS gene, which was due to a deletion mutation resulting in frameshift (c.177DeIT).

Conclusions: Usually microplatelets with mean platelet volume of 4-5 fl are seen in WAS, but in this case, the patient had normal-sized platelets with a rare mutation of WAS gene. Therefore, high index of clinical suspicion is needed to diagnose WAS.

Keywords: Wiskott-Aldrich Syndrome; Eczema; Thrombocytopenia

1. Introduction

Wiskott-Aldrich syndrome (WAS), an X-linked recessive syndrome, is characterized by atopic dermatitis, thrombocytopenic purpura with small defective platelets, and undue susceptibility to infection (1). Patients usually have bloody diarrhea during infancy. Atopic dermatitis and recurrent infections usually develop during the first year of life. *Streptococcus pneumoniae* and other bacteria with polysaccharide capsules cause otitis media, pneumonia, meningitis, and sepsis. Later infections with agents such as *Pneumocystis jiroveci* and the herpes virus become more frequent. Patients rarely survive beyond their teens. Infections and Epstein-Barr virus-associated malignancies are the major causes of death (1).

The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal IgG. Percentages of T cells are moderately reduced and lymphocyte responses to mitogens are variably depressed. The abnormal gene, on the proximal arm of the X chromosome at Xp 11.22-11.23 near the centromere, encodes a 501-amino acid proline-rich cytoplasmic protein restricted in its expression to hematopoietic cell lineages (1). We presented a child suspected of WAS with a unique feature of normal-sized platelets in whom the diagnosis was confirmed by mutation analysis of WAS gene in peripheral blood leucocytes. It is a rare finding indicating the need for high index of clinical suspicion for diagnosing WAS.

2. Case Presentation

An 18-month-old boy presented with respiratory dis-

stress, eczema of the whole body and scalp, and altered sensorium. On examination, respiratory rate was 55 per minute and blood pressure was 90/60 mm Hg. Routine laboratory tests revealed pancytopenia (hemoglobin, 54 g/L; total leucocyte count, 2.5×10^9 cells/L; and platelets, 60×10^9 cells/L); urea, creatinine, sodium, potassium, liver function tests results were within normal limit. On taking detailed history, it was revealed that child had bloody diarrhea since he was seven day old with dermatitis of whole body since one month of age along with recurrent lower respiratory tract infection. Colonoscopy of the patient done at one year of age showed multiple ulceration in a continuous and symmetric fashion. Histopathologic examination showed nonspecific proctocolitis with eosinophils in the lamina propria. Skin lesions were diagnosed as atopic dermatitis by a dermatologist and were treated with corticosteroid cream, antihistamines, and emollients. The child was a product of non-consanguineous marriage and there was no family history of any congenital or acquired immunodeficiency disease.

After admission to our hospital, as the child had pancytopenia with gradually decreasing sensorium, treatment was initiated with intravenous ceftriaxone and vancomycin, fluid resuscitation, nebulization with bronchodilators, and injection of fluconazole; later, the antibiotic regimen was changed to intravenous meropenem and vancomycin. The results of HIV screening of the child and his parents were negative.

We also assessed arterial blood gas that showed pH of

7.48, PCO₂ of 39.7 mm Hg, HCO₃ of 29.7 mmol/L, PO₂ 100 mm Hg, sodium of 132 mmol/L, potassium of 3.9 mmol/L, and calcium of 2.2 mmol/L. Blood culture report showed growth of *Candida* (non-*albicans*) sensitive to amphotericin B and cerebrospinal fluid culture showed no growth. Intravenous amphotericin B started and urea, creatinine, and electrolytes were measured every other day. Complete blood count was measured on several occasions and all of the results revealed pancytopenia and marked thrombocytopenia with normal mean platelet volume (MPV). Examination of peripheral smear showed normal and occasional macroplatelets. During the first admission, the MPV was 8.1 fL and platelet distribution

width (PDW) was 14.1 fL. Bone marrow aspiration cytology showed non-specific changes. The serum levels of IgA and IgE were raised to 156 and 87.6 IU/mL, respectively, with markedly diminished CD4 count to 0.44 × 10⁹ cells/L. A provisional diagnosis of primary T-cell immunodeficiency was made and blood was sent for molecular diagnosis with a high index of clinical suspicion for WAS. The report came to be positive for mutation of WAS gene (c.177-177delT) (Figure 1). The patient was discharged with multivitamin, iron, and trimethoprim/sulfamethoxazole prophylaxis, and IVIG therapy at in monthly follow-up visits. Due to financial constraints, the family of the patient could not afford other modes of therapy.

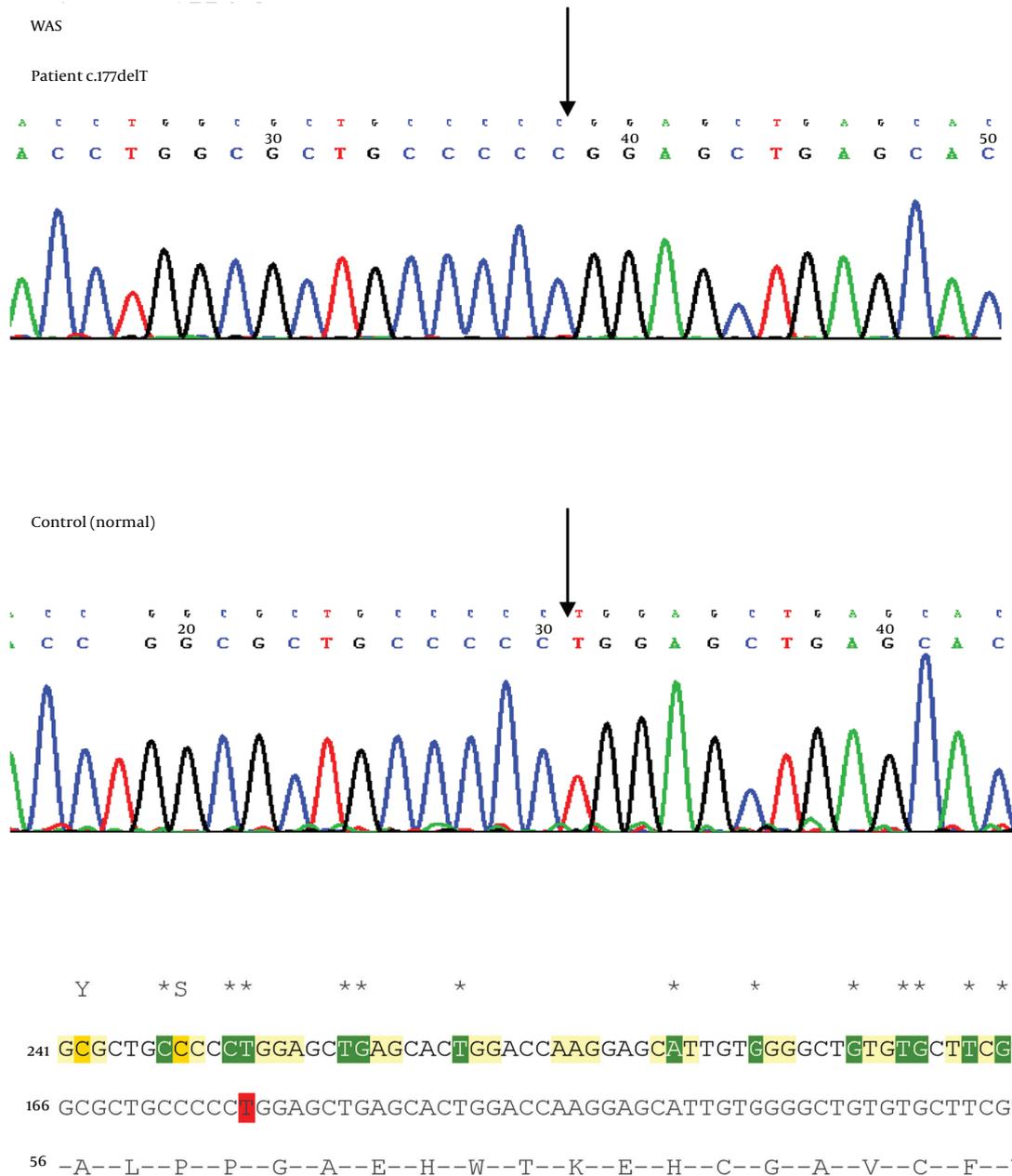


Figure 1. Genetic Sequencing and the Mutation of WAS Gene in Patient

3. Discussion and Review of Literature

The WAS affects one to ten of every one million male newborns and their life expectancy is approximately 15 years. The protein encoded by the WAS gene (WASP) is a hematopoietic-specific regulator of actin nucleation in response to signals arising at the cell membrane (2, 3).

Among clinical manifestations of WAS, hemorrhages are the most frequent ones (80%) and can present from non-life-threatening conditions such as epistaxis, petechiae, purpura, and oral bleeding, to severe manifestations such as intestinal and intracranial bleeding. In 21% of patients with WAS, death is caused by hemorrhages (4). Bleeding is the result of severe thrombocytopenia with reduced platelet size (4 - 5 microns), which is the most common finding in patients with WAS and X-linked thrombocytopenia (XLT) (incidence of 100%). Thrombocytopenia occurs irrespective of the mutation severity and is possibly caused by instability of mutated WASP in platelets (5). Megakaryocyte numbers are reported to be normal in the majority of patients with WAS, whereas platelet abnormalities could be due to a defect in proplatelet formation or in megakaryocyte (MK) migration (6). The accelerated destruction could be caused by an intrinsic defect of WASP-deficient platelets, showing an increased surface exposure of phosphatidylserine, or could be mediated by autoimmune reaction due to the presence of antiplatelet antibodies as was reported in patients and in the murine knockout model (7). The typical skin lesions in patients with WAS resembles acute or chronic eczema in appearance and distribution. Eczema develops in 80% of the patients and is heterogeneous in severity and persistence. Currently, the causes of eczema in patients with WAS are unknown. Patients with WAS often have elevated IgE levels and develop allergies, which suggests an atopic origin (8). Recently, an imbalance in cytokine production toward the Th2 type has been described in T-cell lines of patients with WAS, which might contribute to the pathogenesis of eczema and allergy (9). The WAS-associated autoimmune complications are frequently observed.

Many different mutations in WAS gene can cause WAS although several mutational hotspots have been identified. Certain types of mutations at particular locations are more likely to cause XLT than classic WAS. The analysis of affected members of 270 unrelated families with WAS from three large referral centers (the United States, Italy, and Japan) revealed 158 unique WAS gene mutations (8). The most common types were missense mutations, followed by splice-site mutations, short deletions, and nonsense mutations. Insertions, complex mutations, and large deletions were less frequent. Most deletions and insertions involved fewer than ten nucleotides, resulting in frameshift and early termination of transcription. Amino acid substitutions are typically located in exons 1 through 4.

In our case, there was a frameshift deletion mutation

in the 177 base pair, resulting in normal-sized platelets, but the exact mechanism is unknown and this particular mutation has not been reported in medical literature yet, which definitely makes our case unique.

Normally microplatelets present with thrombocytopenia in WAS, but WAS with normal MPV is a rare finding. There are very few case reports up to now (10). There are also case reports of WAS with macroplatelets (11).

Our patient was managed conservatively with blood, platelets, corticosteroids, and antibiotics. Intravenous immunoglobulins were administered for thrombocytopenia and regularly every four weeks to prevent infection. Although both regimens showed good outcome, it was only temporary improvement and the ultimate cure can be achieved by bone marrow transplantation.

In summary, WAS is a rare condition that needs a high index of suspicion for early diagnosis and should be suspected in any male newborn with unexplained rectal bleeding or any infant with recurrent infection, eczema, and thrombocytopenia. Thus, WAS with normal MPV is a rare entity.

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Authors' Contributions

All the contribution belongs to the authors regarding the management of the case and sending samples for molecular diagnosis.

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