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Case Report

Clinical Diagnosis of Wiskott–Aldrich Syndrome Without Molecular Testing: Two Pediatric Cases from Ethiopia

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Abstract:
Wiskott-Aldrich syndrome is an uncommon X-linked recessive disorder characterized by a triad of symptoms: micro thrombocytopenia/bleeding, eczema, and recurrent infections. This syndrome presents diagnostic challenges due to its diverse clinical manifestations and limited diagnostic capabilities in resource-constrained settings. The report highlights two cases exhibiting similar triad symptoms, albeit with varying degrees of organ-specific expressions and severity. The diagnosis was made by leveraging clinical syndrome as a basis for heightened suspicion, coupled with clinical diagnostic criteria. Thus, prompt identification in low-resource settings can be achieved by combining a high index of suspicion with the diagnostic criteria in male children exhibiting the clinical syndrome.

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Introduction

Since its first description by Dr. Alfred Wiskott in 1937 (1) , our understanding of Wiskott-Aldrich syndrome (WAS), a rare X-linked recessive disorder, has improved with advanced diagnostic tools like genetic sequence analysis. However, detecting cases remains challenging in resource-limited settings (2,3). WAS is classically defined by a triad of micro- thrombocytopenia/bleeding, eczema, and recurrent infections that occur exclusively in boys. The incidence varies by region but ranges from 1-10 cases per million live births (1,4).

The diagnosis is confirmed by genetic sequence analysis and identification of WAS gene mutation which is responsible for WAS protein expression (2,3). Three well defined genotypic variants exist that correspond well to the phenotypic clinical presentation: classic WAS, X-linked thrombocytopenia, and X-linked Neutropenia (4). Allogeneic hematopoietic stem cell transplantation is currently the only definitive therapy for WAS (4).

There is a general pattern of similarity in the clinical presentation of children with Wiskott-Aldrich syndrome, though some variability in the degree of severity is possible. Understanding this general pattern of similarity is vital, especially in low-resource settings where the non-availability of advanced diagnostic investigations is common (3–6).

WAS is often diagnosed late, and fatality is its hallmark. Here, we present two cases with a similar symptom triad but variations in organ-specific manifestations. The clinical diagnosis of WAS was made by using the ESID (European Society for Immunodeficiency) registry, working definition of primary immunodeficiency (7) . The ESID criteria were developed for those with no genetic diagnosis, and their proper utility ensures physicians and scientists use the same definitions while diagnosing their patients, as well as in their research studies (7,8).

Based on the ESID/PAGID criteria a probable diagnosis of WAS can be made in a male patient with a minimum of two measurements of thrombocytopenia having small platelets (MPV< 7.5Fl) and atleast one of the clinical presentation consistent with WAS; eczema, recurrent bacterial or viral infections, autoimmune diseases, malignancy, reduced WASP expression in a fresh blood sample, abnormal antibody response to polysaccharide antigens and/or low isohemagglutinins (7,8). By utilizing the clinical syndrome as a basis for

suspicion and following diagnostic criteria from the Pan-American Group for Immunodeficiency (PAGID) and European Society for Immunodeficiency (ESID), we were able to make a clinical diagnosis in our resource limited setting.

Case 1

This case involves a 9-month-old male infant who presented to Worabe buchComprehensive Specialized Hospital with a complaint of high-grade intermittent fever, vomiting of ingested matter, watery diarrhea with episodes of intermittent bloody diarrhea worsening over the past three days. He also has an associated cough of five days duration. Similar episodes of bloody diarrhea and cough, which lasted for two weeks, were also reported when he was five months old. And since then, he had three hospital admissions: at 6 months for severe pneumonia, at 7.5 months for acute gastroenteritis with severe dehydration and pneumonia, and at 8 months for hospital-acquired pneumonia. There was also a recurrent skin rash over his back, arms, and legs that comes and goes, leaving marks and making him irritable, and he continuously rubs his feet together. He has been given a variety of oral and intravenous medications, which bring temporary relief before the symptoms reappear after a few days.

He was born at full term through spontaneous vaginal delivery at a local health center to non- consanguineous parents. The exact birth weight and Apgar score are unknown, but the child cried immediately after birth. Six hours later, the child was discharged home without any reported complications. The Mother reported that the umbilical stump sloughed off around one week of age. Immunization records were up to date, and the child's developmental milestones were appropriate for his age.

He is the fourth child in the family, and his 8-year-old brother is in good health. The mother previously experienced early male neonatal death, where the baby passed away at one week of age after experiencing fever, failure to breastfeed and fast breathing which lasted for one day. The mother did not seek medical attention, leaving the cause of death unknown.

On examination, the child appeared sick and was irritable. He had pale conjunctivae. He had a respiratory rate of 56/min, pulse rate of 112/min, axillary temperature of 37.9°c, and his peripheral oxygen saturation (SaO_2) was 86%. His weight was 7.5kg, which is underweight for his age. However, his linear growth was not affected.

Abdominal examination revealed a palpable spleen of 2cm below the left costal margin along the line of growth. The skin displayed petechial rashes on the face, hypo pigmented rashes and erythematous papules on the abdomen and extremities (Fig.1 A)

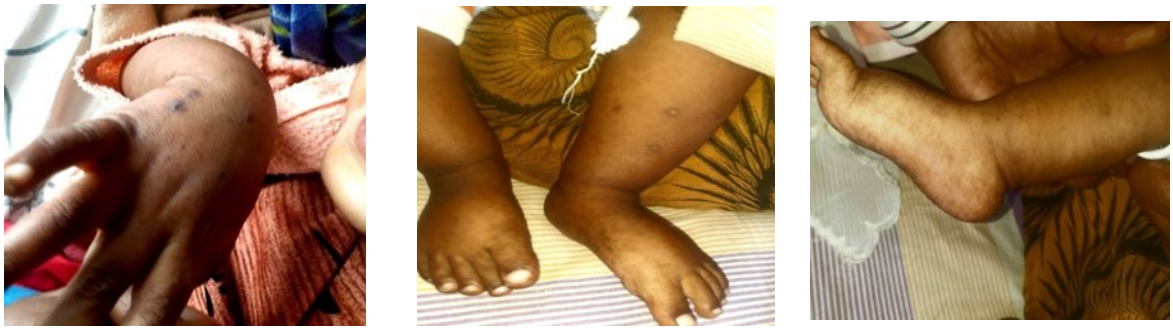

Figure 1A : Erythematous papules and petechial rashes over the feet and hands

Laboratory result showed a total White blood cell (WBC) count of 7.17×103/mm3 (normal for his age 6000-14000/mm3), his absolute neutrophil count being 2460/mm3 (normal for age, 3000-5800/mm3), and absolute lymphocyte count of 4440/mm3 (normal for age, 1500-3000/mm3). His platelet count was 12,000/mm3 (normal for his age, 150,000-400,000/mm3) with a mean platelet volume (MPV) of 6.9 fL (normal 9-12 fL). His C-reactive protein was elevated (80mg/l), his direct Coombs test and maternal HIV serology test were negative. His abdominal ultrasound was normal. Peripheral smear examination revealed a significant decrease in platelet count (Fig.1 B).

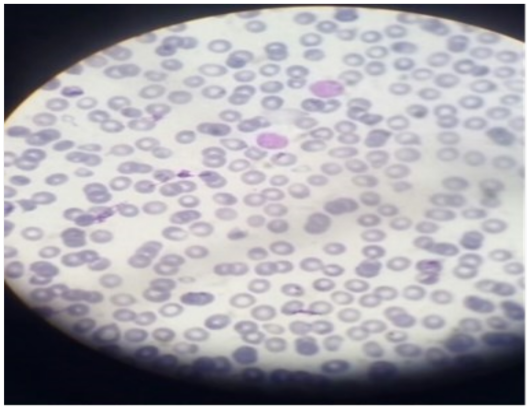

Figure 1B: Peripheral blood smear showing scanty platelets, normocytic normochromic red blood cells, and frequent microcytes.

The striking finding of consistent thrombocytopenia in all the samples, together with a low MPV in the presence of early infantile onset recurrent pulmonary infections, pruritic rash, and recurrent bloody diarrhea, together with previous early male neonatal death, makes the diagnosis of Wiskott-Aldrich syndrome a top consideration.

Immunologic assays and gene analysis could not be done due to unavailability. The patient was treated with intravenous ceftriaxone, transfused twice with whole blood (his hemoglobin was 6g/dl with persistent respiratory distress and desaturation), and received only one unit of platelet concentrate (platelet concentrate is not readily available in the setup). The platelet counts later rose to 30,000 and did not increase any further. He was also started on co-trimoxazole prophylaxis.

Case 2

A 6-month-old male infant, born to newly married, non-consanguineous parents, presented with a high-grade fever, cough, fast breathing and grunting of five days duration. He also had purulent discharge from the ear. He later became increasingly irritable and had decreased breastfeeding. The child had a similar history of recurrent ear discharge since the age of two months, necessitating repeated visits to the outpatient clinic. Although treatment provided temporary relief, the discharge consistently recurred within a few days. He also had a history of treatment for recurrent skin rash at the dermatology outpatient unit and took a variety of treatments, but the condition persisted. The rash is pruritic and extensive, involving the face, trunk, and extremities, leading the child to continuously rub his feet together, crying for hours and refusing breastfeeding. Since his first medical attention at the age of two months, he was admitted five times, including the current one, with severe pneumonia being the principal diagnosis.

He is the first and only child for his parents and his perinatal history was uneventful. His birth weight was 2800 g and 5th 5th-minute Apgar score was 7. His mother reported that the umbilical stump sloughed off a few days after delivery. He is immunized for his age. He cannot sit alone, but he started rolling over.

On examination, the child appeared sick, in respiratory distress and was irritable. He had pale conjunctivae. His respiratory rate was 66/min, with a pulse rate of 124/min, an axillary temperature of 38.1°C, and an SaO_2 of 84%. The skin displayed generalized areas of erythematous papules, multiple excoriation marks, and areas of lichenification, hyperpigmentation, and dark brown discoloration of the forehead and abdomen (Fig..2A).

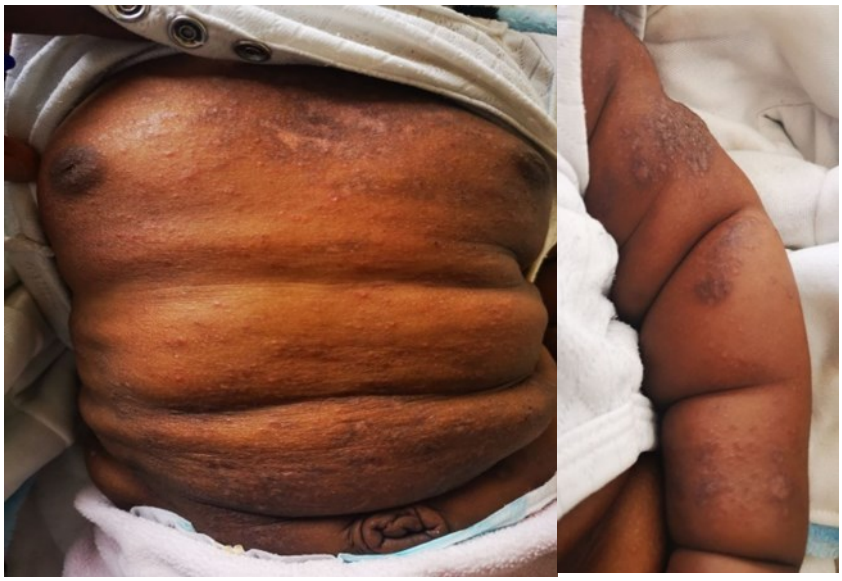

Figure 2A: Eczematous lichenification, excoriation and dark brown hyperpigmentation of the skin around chest, arm, abdomen and face

Laboratory results showed leukocytosis (WBC= 16000/mm3 with 70% neutrophil), hemoglobin of 8.2 g/dl (normal range, 10.5-14g/dl). Initial platelet count was 46,000/mm3 (normal range 150×103-450×103 /mm3), MPV was normal with 9.1fL (normal 9 -12fL). While in the hospital, his platelet count dropped subsequently to 25,000/mm3, 32,000/mm3, and 18,000/mm3 with the average MPV of 7.2fL. In addition, a review of previous CBC panel showed persistent thrombocytopenia with the maximum platelet count of 71,000/mm3 during his last follow-up visit, a month before the current admission. In addition, he had elevated CRP (130mg/l) and diffuse areas of airspace opacity on chest x-ray. Otherwise, the maternal HIV serology test was negative. His cerebrospinal fluid analysis, urinalysis, and abdominal ultrasound were all normal. Measurement of immunoglobulin levels and genetic analysis were not possible due to unavailability.

He was put on supportive management, received empiric intravenous antibiotics, and discharged after ten days with co-trimoxazole prophylaxis. His parents were counseled on the probable diagnosis and informed of the need for genetic analysis. Unfortunately, he passed away a month later at home after a brief episode of bloody diarrhea, accompanied by cough and shortness of breath. Due to the presence of early infantile onset severe eczema, recurrent purulent otitis media, and recurrent pneumonia, along with persistent thrombocytopenia with low MPV, we considered Wiskott-Aldrich syndrome as a possible diagnosis.

Discussion

While there may be variations in the expression of symptoms, there is a general pattern of similarity in how patients with WAS present clinically (4,9). The first defining characteristic is thrombocytopenia. Thrombocytopenia is a universal finding in WAS, and most patients (70-80%) experience associated bleeding complications (10). However, there have been rare cases where patients with confirmed WAS had normal platelet counts at the time of presentation (2,5).

Another classic feature of WAS is the presence of small platelets, referred to as microthrombocytopenia. However, there have been instances where the MPV was normal in children with confirmed WAS (4,5), emphasizing the need for repeated analysis of platelet number and MPV, as well as a high index of suspicion.

Different WAS gene mutation variants correspond to the phenotypic variability in clinical presentation. One simplified clinical scoring method can be utilized in resource-limited settings to differentiate classic WAS from X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN), where a score of 4 and 5 implies classic WAS (11).

The age at onset of symptoms is typically around three months, with a median age at diagnosis of two years (12). However, in resource-limited settings, there can be delays in diagnosis, as observed in two cases in Ethiopia, where the diagnosis was made at four years and 12 years of age, respectively

(3,6).While the classic triad of thrombocytopenia, eczema, and recurrent infections is commonly seen in WAS patients, it may not be present in all confirmed cases, as demonstrated in a study where only 15.7% of cases displayed this triad at the time of presentation (4). The severity and specific organ involvement associated with thrombocytopenia and eczema can also vary among patients, which was also observed in our cases.

As Wiskott-Aldrich syndrome is an inherited X-linked recessive condition, a positive family history of affected males is usually evident. However, it is not uncommon to find confirmed cases without an affected family member (3). Similarly, our second patient has no family history.

In conclusion, in resource-limited settings, the expeditious recognition of Wiskott-Aldrich syndrome, in a male child exhibiting the clinical syndrome, can be accomplished by combining a heightened level of suspicion with the application of PAGID/ESID diagnostic criteria.

Acknowledgment
We express our deepest gratitude for the parents, for their invaluable contribution and for allowing us to write a comprehensive report on their child's case. Their consent and willingness to share their child's medical journey was instrumental for advancing our knowledge and hope will help fellow healthcare professionals provide better care to other children of similar cases.

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Authors contributions
Zelalem; Original draft preparation
Iman; Chart review
Tinsae; Review and editing.

Conflict of interest
The author (s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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