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LETTER

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Normal mean platelet volume and thrombocytopenia: It may still be Wiskott–Aldrich syndrome

To the editor,

Wiskott–Aldrich syndrome (WAS) is a primary immunodeficiency characterized by an X-linked genetic inheritance, thrombocytopenia with small platelets size, eczema, recurrent infections, malignancy, and increased autoimmunity.[1,2] Thrombocytopenia in WAS has multifactorial causes. Although megakaryocytes are normal or increased in bone marrow, platelet turnover studies indicate ineffective thrombopoiesis in vivo. The patients diagnosed with WAS do not show increased levels of reticulated platelets and have low immature platelet fractions. Additionally, accelerated peripheral destruction contributes to thrombocytopenia. Normal platelet counts are achieved in most cases after splenectomy. Studies show increased ex vivo phagocytosis by macrophages in WAS patients, suggesting intrinsic defects in WAS platelets increase their phagocytosis by the reticuloendothelial system, reducing their survival.[1] While low mean platelet volume (MPV) (<7 fl) with severe thrombocytopenia is typical for WAS, normal MPV values can be observed in a small number of patients at the time of diagnosis. MPV values between 7 and 10.5 fl are generally considered normal.[3]

Upon re-evaluating our previously reported[4,5] patients and the two patients diagnosed within the last 3 years, we discovered that four patients (4/25, 16%) had normovolemic thrombocytopenia in consecutive complete blood counts (CBCs) during early infancy or prior to receiving any treatment. The MPV values ranged from 8.1 to 10.6 fl. The characteristics of these patients are shown in Table 1. The symptoms of the patients generally started during the infancy period. All patients presented with clinical features of classical WAS, with WAS severity scores of 4–5.[6]

The first patient (P1) presented with severe, atopic dermatitis that had been present since one month of age. The patient, whose testing revealed thrombocytopenia, had a normal MPV. He was referred to us with a preliminary diagnosis of immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome. A new mutation causing premature stop codon was detected in Exon 2 c.271C > T(p.Q91X) by targeted sequence analysis in P1. The second patient (P2) had petechiae and eczema on his body when he was 2 months old for the first time, and thrombocytopenia was detected in his CBC. He was referred to us because his maternal cousins were diagnosed with WAS. A previously reported mutation, exon 2 p. G291 > A; R86H missense, was detected in the targeted sequence analysis of the P2. The patient's thrombocytopenia continued in the control blood count, and the MPV value was normal. The third patient (P3) was diagnosed with immune thrombocytopenic purpura (ITP) with normovolemic thrombocytopenia at the hospital where he presented with petechiae, atopic dermatitis, and bloody stools since 1 month of age. IVIG and steroid therapies were given for ITP. His rectal bleeding was attributed to cow's milk protein allergy (CMPA). The patient consulted us with persistent thrombocytopenia. Targeted sequence analysis of the P3 identified a new mutation causing the c.1115delCp.Pro372Leufs Ter 73 change in Exon 10.P4's CBC on the first day of birth revealed normovolemic thrombocytopenia, which remained in subsequent two tests. The patient's older brother had been diagnosed with WAS and undergoing hematopoietic stem cell transplantation (HSCT) at our clinic. The family contacted us, and he was subsequently admitted to our hospital. WASp expression was measured only in P4 and was found normal. Targeted sequence analysis of his revealed a known nonsense mutation in exon 1 c.100C > T (p.R34*) (p.Arg34Ter).

HSCT were performed successfully on P1, P2, and P3 and was planned for P4. Normovolemic thrombocytopenia was detected in the first CBC performed in the newborn or early infancy in all four cases discussed. Although P1 and P3 showed microthrombocytopenic levels in the follow-up CBCs, we noticed the patients were still followed up and treated based on the diagnosis given by the physicians who first saw them. Before admission to our clinic, ITP was considered in one patient and IPEX syndrome in another. The two patients (P2 and P4) were referred to our hospital because of their family histories.

ITP is rarely observed in the early years of life. Some patients with WAS may be misdiagnosed with ITP.[7] Classically, microthrombocytopenia is expected in WAS but rarely, normal MPV values (>7–10.5 fl) may be observed. We found normal MPV values in 4 of 25 WAS patients who did not receive any platelet transfusion or treatment (IVIG, steroid) at the time of diagnosis. In the patients, there was no reduction in other cell lines suggestive of bone marrow failure (BMF) except for thrombocytopenia. Furthermore, no phenotypic findings associated with BMF were observed in any of the patients.

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TABLE 1 The clinical and laboratory characteristics of patients.

No	Age of Diagnosis	Age of symptom	Initial symptoms	Initial diagnosis	Clinical findings	Thrombocyte (mm^3) (min-max)	MPV (fL) (min–max)	WASp expression	Mutations	WAS score
P1	5 months	Neonatal period	Dermatitis, diarrhea	IPEX	CMV viremia, pneumonia, AIHA, HSM, LAP	33,000–67,200	7.6–10	N/A	Exon 2 c.271C>T(p.Q91X)	5
P2	2 months	Neonatal period	Dermatitis, petechiae	His cousins diagnosed with WAS	P.jirovecii pneumonia, Metapneumovirus pneumonia	40,000–55,000	7.2–8.1	N/A	Exon 2 p. G291>A; R86H missense mutation	4
P3	6 months	Neonatal period	Rectal bleeding, petechiae, ecchymosis	ITP CMPA	Severe mucosal and subcutaneous bleeding	19,000–80,000	7.1–10.7	N/A	Exon 10 c.1115delC p.Pro372Leufs Ter 73 (novel mutation)	4
P4	Newborn	Neonatal period	Bloody defecation, eczema, petechiae	His brother was diagnosed with WAS	Severe rectal bleeding, recurrent respiratory tract infections	35,000–68,000	7.3–8.5	Normal	Exon 1 c.100C>T (p.R34*) (p.Arg34Ter) nonsense mutation	4

Abbreviations: AIHA, Autoimmune hemolytic anemia; CMPA, Cow's milk protein allergy; CMV, Cytomegalovirus; HSM, Hepatosplenomegaly; ITP, Immune thrombocytopenic purpura; LAP, Lymphadenopathy; N/A, Not applicable.

Patel et al.[8] reported an infant with thrombocytopenia in the neonatal period who was treated with IVIG, but no response was obtained. While MPV values (mean 8.8 fl ±0.57) were normal in CBCs, MPV was found to be low (7.1 fl) in the last count. Flow cytometry analysis demonstrated decreased expression of WAS protein (WASp). Genetic analysis revealed a hemizygous mutation of the WAS gene, and he diagnosed as WAS (nonsense mutation, c.862A>T (K288X)). In a case presented by Cunha Carneiro et al., a 3-year-old male patient followed up for acute otitis media sepsis due to H. influenzae was diagnosed with ITP in the first postnatal month. The patient, whose thrombocytopenia did not improve and who presented with normal MPV, underwent splenectomy due to refractory thrombocytopenia. The thrombocytopenia did not improve until the age of 4. After splenectomy, the patient's MPV values continued to be normal. Genetic analysis revealed a mutation in the WAS gene (Exon 3, c. 295C>T:p.(Gln99*)).[9] It has been reported in the literature that there is an increase in platelet count and MPV values following splenectomy. Nevertheless, it is important to note that splenectomy may potentially result in fatal infections in patients with WAS or in thrombocytopenic patients with an unknown diagnosis. Splenectomy should be avoided in WAS, a combined immunodeficiency disease.[4]

The case report by Mawalla et al. presented a 10-month-old boy with thrombocytopenia, recurrent skin infections, and bloody stools. At his presentation, the blood count revealed leukopenia, microcytic anemia, and thrombocytopenia with normal MPV. Bone marrow aspiration performed due to pancytopenia was normal. Because of normal MPV, it was thought to be one of the hereditary thrombocytopenias. Despite receiving supportive therapies and regular follow-up, the patient passed away 4 months after presentation. The authors highlighted that the diagnosis of WAS, a rare genetic disease, may be overlooked, particularly when MPV is normal and access to genetic testing is limited. Genetic analysis revealed a mutation in the WAS gene (c.360+1G>A).[10] In a case report published by Baharin et al., a 9-month-old Malay infant was diagnosed as having persistent thrombocytopenia from birth. The patient's platelet count increased from 43,000/mm^3 to 68,000/mm^3 after treatment for suspected sepsis due to borderline prematurity. The patient was admitted at 3 months due to petechiae and bloody stools. The patient's platelet counts increased after receiving IVIG, but remained low during subsequent hospital admissions. Although platelet values tended to increase after IVIG treatment, no comment was made in this article about the change in MPV values. A mutation analysis of this patient revealed a c.1264G>T mutation in exon 10 of the WAS gene, which led to a change in the 422nd amino acid from alanine to serine.[11] Ouchi-Uchiyama et al. from Japan have published the results of genetic analyses of 32 patients with small- or normal-sized platelets. They identified a genetic defect causing hereditary thrombocytopenia in 12 of the patients who had a family history of early-onset thrombocytopenia. A 6-year-old boy was diagnosed as ITP when he presented with bleeding and normovolemic thrombocytopenia. Subsequently, genetic evaluation revealed a diagnosis of WAS.[12]

A wide range of platelet sizes can be observed in the peripheral blood smears of patients with WAS. In some patients, particularly

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those with lower platelet counts, CBC devices are unable to measure MPV values. In children with thrombocytopenia, the ratio of immature platelet fraction to mature platelet count should be calculated before further investigations.[13]

Misdiagnosis WAS patients may lead to incorrect treatment and delay in treatment, as seen in our patients. In a disease such as WAS in which the immune system is severely affected and predisposes to infections, treatments such as steroid use and splenectomy may contribute to immunodeficiency and worsen the clinical condition.[13,14] In a study conducted by Socolic et al. in 2015, a formula was developed to evaluate the relationship between immature platelet count and mature platelet count in order to prevent diagnostic confusion between WAS and ITP. Eighteen patients with WAS and 38 patients with ITP were included in the study. The IPF/PLT rule states that the sum of the platelet count (expressed in thousands of platelets per microliter) and 75 times the IPF being less than 500 suggests the diagnosis of WAS as opposed to ITP. It has been reported that subjects with WAS have a low IPF, which is consistent with the notion that a platelet production defect contributes to the thrombocytopenia of WAS. The formula in question can be used as a preliminary tool for distinguishing between WAS and ITP. It offers a cost-effective means of identifying these conditions, although it is essential to employ genetic testing for a definitive diagnosis.[13] Regrettably, our CBC device does not provide the requisite calculations for these values. Nevertheless, when we evaluated the CBC of the patients before their apply to us and without any treatment, we found that the platelet-large cell ratio (P-LCR) was below the normal age reference intervals in three patients and the platelet-large cell concentration (P-LCC) was low in one patient. If these parameters have been studied in thrombocytopenic patients, their evaluation may facilitate the diagnosis. CBC and P-LCC values of the patients before admission to our center was given in Table S1 (Reference source 15 was used for the reference ranges of laboratory values in the supplemental table.).

Patients with WAS presenting with eczema and bloody stools may be misdiagnosed as having CMPA at initial examination.[5] In a case report published by Yoonessi et al, a male patient in good health presented with bloody stool and thrombocytopenia, with normal MPV (33,000/mm^3, 7.9 fl), normal growth parameters, and erythematous diaper rash at 6 weeks. The deformed crypts in his colonic tissue and an increase in eosinophils in the rectal biopsy material were consistent with alterations related to CMPA. At 3 months, he was hospitalized for a croup-like illness, with persistent thrombocytopenia and irritability. During hospitalization, he recovered from leukocytoclastic vasculitis. The genetic analysis revealed a hemizygous WAS mutation (hemizygous for c.1125_1129delTGGAC mutation in the *WAS* gene).[16] It is also possible that patients with WAS may have CMPA and eczema. CMPA should not mask the diagnosis and should be investigated to clarify the cause of thrombocytopenia. Conversely, in male patients presenting with eczema and CMPA, it is advisable to perform a CBC to screen for thrombocytopenia, as this may identify patients with WAS. WAS should be considered in cases of rectal bleeding that does not improve after the removal of CMP from the diet.

Our findings indicated that the MPV values of our patients were within the normal range in at least three consecutive CBCs. In contrast to other case reports in the literature, our data are presented longitudinally rather than cross-sectionally in normothrombocytopenic WAS patients. The CBC results of the patients before they were admitted to our center and before they received any treatment are provided in Table S1.

In conclusion, infants with WAS may present with thrombocytopenia with normal MPV values on blood counts in the neonatal period and the first months of life. As a result, the diagnosis of WAS may be overlooked, particularly in patients without a family history. Physicians who first see patients with normal MPV usually consider them to have ITP, sepsis-associated thrombocytopenia, or hereditary thrombocytopenia. WAS is typically not considered. In fact, it is important to highlight that the diagnosis of WAS may be overlooked in infants presenting with rectal bleeding and eczema, particularly when CMPA is a consideration. WAS should be considered as a potential diagnosis in the case of persistent thrombocytopenia in a boy, regardless of the presence or absence of additional features such as atopic dermatitis, infections, or autoimmunity.

AUTHOR CONTRIBUTIONS

Şule Haskoloğlu: Conceptualization; methodology; data curation; supervision; investigation; writing – review and editing. **Gökcan Öztürk:** Conceptualization; investigation; writing – original draft; writing – review and editing; methodology. **Kübra Baskın:** Conceptualization; investigation; visualization; data curation. **Candan İslamoğlu:** Data curation; supervision; conceptualization; visualization. **Figen Doğu:** Conceptualization; investigation; methodology; supervision. **Aydan İkincioğulları:** Supervision; data curation; methodology; conceptualization; investigation.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest between the authors.

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