CASE REPORT

A novel mutation in Wiskott-Aldrich gene manifesting as macrothrombocytopenia and neutropenia

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SUMMARY

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder, described as a clinical triad of microthrombocytopenia, eczema and recurrent infections. Different mutations in WAS gene have been identified, resulting in various phenotypes and a broad range of disease severity, ranging from classic WAS to X-linked thrombocytopenia and X-linked neutropenia. WAS in some cases can be fatal without haematopoietic stem cell transplantation early in life. In this particular case, we present a novel mutation with a unique presentation. An 18-year-old man incidentally found to have macrothrombocytopenia and neutropenia at 16 years of age later found to be hemizygous for c. 869T>C (p.Ile290Thr) mutation in WAS gene. The late presentation, absence of other manifestations of WAS and presence of macrothrombocytopenia, rather than microthrombocytopenia, which is usually a characteristic finding in WAS, misled the initial diagnosis. On review of literature, this mutation has not been reported as causing WAS.

BACKGROUND

Wiskott-Aldrich syndrome (WAS, MIM #301000) is a rare X-linked disorder, with an estimated incidence of less than 1 in 100 000 births. It was first described by Alfred Wiskott in 1937, and then by Robert Aldrich in 1954.¹ In 1994, the responsible gene for WAS was identified on the X chromosome (position Xp11.22-p11.23) by positional cloning.² The WAS gene consists of 12 exons encoding a 502 amino acid protein. Around 300 WAS mutations, spanning all 12 exons of the gene, have been identified,^{3,4} resulting in a broad range of disease severity, ranging from classic WAS to X-linked thrombocytopenia (XLT)⁵⁻⁷ and X-linked neutropenia (XLN).⁸ The lack of functional WAS protein (WASp) signalling impairs the function of the actin cytoskeleton in developing haematopoietic cells resulting in the inability of white blood cells to respond to infection, which is one of the leading causes of death in patients with WAS, along with bleeding and malignancy.⁹ The platelet (PLT) defect is characterised by both decrease in PLT number and size which increases bleeding tendency.

Classic WAS results from mutations that cause the absence of WASp, and is characterised by susceptibility to infection due to various immunodeficiencies, bleeding tendencies with microthrombocytopenia, severe eczema during infancy and increased risk for autoimmune disorders and

lymphoid malignancies in older patients.^{10,11} XLT results from mutations that cause decreased, rather than the absence of, protein expression, and is characterised by thrombocytopenia and can be associated with mild eczema and immunodeficiency.⁴⁻⁷ XLN results from activating mutations, and is characterised by neutropenia and myelodysplasia.⁸

We are reporting a novel mutation in Wiskott-Aldrich gene, associated with both thrombocytopenia and neutropenia. The presence of megakaryocytes, instead of small PLTs seen usually in WAS, and the presence of both thrombocytopenia and neutropenia, in an otherwise asymptomatic patient, misled the initial diagnosis.

CASE PRESENTATION

The patient is an 18-year-old young man, with a family history of macrothrombocytopenia in his mother and sister, both presumed to have immune thrombocytopenic purpura (ITP). He was incidentally found to have macrothrombocytopenia and neutropenia at age 16 during a preoperation evaluation for a traumatic shoulder injury. He otherwise had been healthy. He had no history of fatigue, fever, recurrent infections, bleeding tendency, eczema, malignancy or autoimmune diseases. His white cell count was found to be $2.5 \times 10^9/L$ ($4.5-13.0 \times 10^9/L$), haemoglobin 15.7 g/dL ($12.0-16.9$ g/dL), PLT $63 \times 10^9/L$ ($140-400 \times 10^9/L$), absolute neutrophil count 660 cells/ μL ($1800-8000$ cells/ μL) and mean platelet volume (MPV) ranging between 9.6 and 11.1 fL ($6.8-10.4$ fL). Peripheral blood smear demonstrated a normochromic, normocytic population of red cell counts without anisopoikilocytosis, polychromasia or schistocytes. WCC population was notable for paucity of neutrophils and the presence of atypical lymphocytes. PLT population was remarkable for many large PLTs. Closure time was normal. There was no significant abnormality in PLT aggregation studies. Antibodies against PLT glycoprotein (GP) Ia/IIa, GP Ib/IX and GP IIb/IIIa were found to be negative. Bone marrow aspiration and biopsy showed orderly trilineage haematopoiesis with no significant dyspoietic changes. Blasts appeared to be mildly increased. Megakaryocytes were present. Cell blood count (CBC) demonstrated thrombocytopenia. This extensive workup, which also included unremarkable autoimmune studies and inflammatory markers, failed to reveal any aetiology of his macrothrombocytopenia and neutropenia. Given the patient's familial macrothrombocytopenia, it was thought at that time his macrothrombocytopenia might be secondary to

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either a familial thrombocytopenia disorder, or autoimmune thrombocytopenia. However, his neutropenia was not congruent with these syndromes. He was thus diagnosed with chronic ITP and idiopathic neutropenia.

OUTCOME AND FOLLOW-UP

The patient presented at age 18 for routine follow-up. He remained asymptomatic with persistent macrothrombocytopenia and neutropenia, total IgG 764 mg/dL (723–1685 mg/dL). On reviewing his family history, it was found that his nephew at birth had thrombocytopenia and bleeding tendency, without neutropenia and was recently diagnosed with WAS. His nephew was found to be hemizygous for a c. 869T>C mutation in the WAS gene. The patient's sister, who also had macrothrombocytopenia without neutropenia, was found to be heterozygous for the same mutation. This new family history led to consider the diagnosis of WAS in our patient despite the lack of other manifestations of WAS syndromes. Targeted testing via WAS gene sequencing was obtained which showed that he is hemizygous for the same mutation c. 869T>C (p.Ile290Thr).

DISCUSSION

After review of the current literature, c. 869T>C (p.Ile290Thr) has not been reported previously as a known mutation in WAS gene. It is of unknown clinical significance. Thrombocytopenia with small PLTs is a cardinal finding in WAS.¹² The presence of large PLTs and family history of ITP are thought to have misled the initial providers to believe the patient had ITP, which typically manifests with few but large PLTs. WASp is thought to be absent or decreased in the PLTs of patients with WAS.⁴ Different theories have been suggested to explain the role of WASp in PLTs physiology.¹³ Some authors identified the role of WASp in PLTs development and biogenesis by inhibiting proplatelet formation through the collagen I receptor.^{14–15} The role of WASp has been also described in PLT function; however, the results are contradictory and inconclusive. While some described a normal activation, aggregation and α -granule secretion in WAS, the others identified defects in these functions.^{4–16–19} An increase in MPV post splenectomy led other authors to suggest an important role of the spleen in determining low MPV in WAS.²⁰ These phenomena were explained by different theories, such as immunological changes and altered splenic function; however, this remains unclear.²¹ The aetiology of the macrothrombocytopenia in our patient is unclear. It could be explained by the presence of antibodies, concomitant ITP or the result of the novel mutation manifesting with a unique phenotype. The presence of normal PLT size^{21–24} and megakaryocytes^{25–26} has been reported in a few other cases.

WAS has been described in children, whereas our patient was diagnosed at the age of 18. We highlight the importance of considering the diagnosis of WAS in young adults who are presenting with thrombocytopenia with or without neutropenia especially when they have a family history of thrombocytopenia with or without neutropenia. It was challenging to diagnose our patient and differentiate his presentation from ITP, but yet important. The diagnosis did not alter our patient's current therapeutic management given the absence of symptoms. The decision was made to continue to closely monitor the patient for the development of any symptoms that could be related to this newly diagnosed mutation. Genetic counselling was recommended to other family members. Further investigations might be warranted to assess how the diagnosis would alter the therapeutic management in the future. This is especially important

given the accompanied high risk of developing autoimmune disorders and myeloid malignancies in older ages as seen in WAS. It is unknown if this mutation would also lead to an increase in myeloid malignancies as seen with other known mutations.

Learning points

- ▶ c. 869T>C (p.Ile290Thr) is a novel mutation in the Wiskott-Aldrich gene. Further characterisation of c. 869T>C (p.Ile290Thr) and its clinical significance should be done to understand its role in possibly causing Wiskott-Aldrich syndrome (WAS) and the phenotype of WAS caused by it.
- ▶ Inherited thrombocytopenia can be discovered in late childhood, and in some cases in adult life, leading to misdiagnosis with immune thrombocytopenic purpura.²⁷ Mutations in the Wiskott-Aldrich gene such as c. 869T>C (p.Ile290Thr) should be in the differential diagnosis of adult patients presenting with thrombocytopenia, with or without neutropenia, as in our patient.
- ▶ Although microthrombocytopenia has been described as a consistent finding in WAS, the presence of normal platelets size and megakaryocytes has been reported in few cases of WAS. It is possible that c. 869T>C (p.Ile290Thr) mutation in the WAS gene also results in macrothrombocytopenia. Further studies might help clarify this association.
- ▶ WAS has variant clinical presentations and phenotypes which makes its diagnosis challenging, but important to reach, especially given the increased incidence of autoimmune diseases and malignancies leading to early death in patients with WAS if not identified and treated appropriately.

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