Clinical Case Reports

Wiskott–Aldrich syndrome with possible congenital *Cytomegalovirus* infection: A diagnostic dilemma

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ABSTRACT

Wiskott–Aldrich syndrome (WAS) is an X-linked recessive disorder, characterized by thrombocytopenia, eczema and recurrent infections. We report a 4-month-old boy who presented with respiratory distress, petechiae, organomegaly and eczema. He was admitted to the paediatric intensive care unit because of severe respiratory distress due to *Cytomegalovirus* (CMV) infection. As peripheral blood smear showed microthrombocytopenia, Sanger gene sequencing was performed, which confirmed the diagnosis of WAS. This rare combination of possible congenital CMV infection in the background of WAS, misled the initial diagnosis.

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INTRODUCTION

Wiskott–Aldrich syndrome (WAS) occurs as a result of mutations in the *WAS* gene that affect the expression and/or activity of its protein product (WASp).[1] *WAS* is exclusively expressed in haematopoietic cells and is closely associated with the actin cytoskeleton in its active form. Through its effect on the oligomerization of actin monomers, the WASp regulates migration, assembly and adhesion of both myeloid and lymphoid cells, as well as intracellular signalling, phagocytosis and proliferation of these cells.[2] The ubiquitous expression of WASp in haematopoietic lineages is the reason underlying the heterogeneous phenotype with microthrombocytopenia, eczema, increased susceptibility to opportunistic infections, malignancies and autoimmunity.[3,4] The immunological phenotype consists of poor antibody response to polysaccharide antigens, reduced apoptosis of T cells in response to stimulation, prolonged antibody production, reduced number of regulatory B cells and T cells, dominance of Th2 response over Th1, low proportion of CD8+ T cells, reduced natural killer cell cytolytic activity and a characteristic immunoglobulin profile with low IgM, elevated to normal IgA, elevated IgE and normal to low IgG levels.[5]

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THE CASE

A 4-month-old boy, born of a consanguineous marriage, presented to us with respiratory distress, petechiae and eczema. On examination, the boy was cyanotic, had tachypnoea and subcostal and suprasternal retraction. He was febrile and his oxygen saturation on room air was 80%. He also had several pinpoint areas of haemorrhage on his back, upper chest and buttock, along with skin desquamation and redness with atopic distribution. He had a past history of thrombocytopenia, conjugated hyperbilirubinaemia and hepatomegaly since day 7 of his birth. This had not been properly followed up. He was immediately admitted to the paediatric intensive care unit (PICU). His investigations revealed diffuse mixed alveolar–interstitial infiltrations on chest computed tomography scan, compatible with viral pneumonia, along with hepatosplenomegaly. He was started on oxygen supplement and antibiotics.

His laboratory investigations showed a haemoglobin of 11.3 g/dl, total leucocyte count 11×10^3/µl (polymorphonuclear 52% and lymphocyte 48%), platelet count 18×10^3/µl, erythrocyte sedimentation rate 45 mm/1st hour, C-reactive protein 12.7 mg/L, aspartate aminotransferase 10^5 i.u./L, alanine transaminase 150 i.u./L, immunoglobulin (Ig) IgG 10.8 g/L, IgA 0.8 g/L, IgM 157 g/L and IgE 139 g/L. Peripheral blood smear revealed microthrombocytopenia and hypochromic and target red blood cells without microangiopathy. Congenital infections (i.e. TORCH) including *Cytomegalovirus* (CMV) infection, were suspected due to a constellation of thrombocytopenia, petechiae, hepatosplenomegaly with elevated liver enzymes, along with jaundice as early as day 7 after birth, and poor weight gain. A complete TORCH panel was done including a quantitative CMV DNA polymerase chain reaction (PCR) on the child's saliva, which was positive. He was started on ganciclovir with a diagnosis of possible congenital CMV infection. We also requested Sanger sequencing for the *WAS* gene as part of our immunological consult considering the presence of the triad of WAS with microthrombocytopenia, eczema and severe unexplained infections. The results showed a hemizygous single-nucleotide variant in the *WAS* gene (c.91G>A, E31K, ChrX:48542333G>A), giving rise to a missense mutation that is likely pathogenic. Sanger sequencing of *WAS* in the mother and healthy girl sibling of the patient was unremarkable, in line with a *de novo* mutation in the patient. Meanwhile, low cytosolic WASp expression was proved through flowcytometry analysis of peripheral blood mononuclear cells, confirming the diagnosis of WAS in the child.

By the 2nd week of treatment with ganciclovir, the viral load of CMV reduced from the initial 169 938 copies/µl to 1972 copies/µl, and ultrasound showed no organomegaly. Ganciclovir was continued for another 2 weeks. Unfortunately, neuroimaging of the infant revealed multiple foci of calcification in the periventricular white matter in T1 MRI. The auditory brainstem

response test was abnormal, whereas fundoscopic examination revealed no retinitis or scars. The boy was a candidate for early haematopoietic cell transplantation. We also advised the parents about the necessity of PCR direct mutation testing for the mother, and its importance for their future children, but they were reluctant to undergo this test. Informed written consent was received from the family to publish relevant clinical information.

DISCUSSION

Our patient showed characteristic clinical features of WAS with petechiae due to microthrombocytopenia, eczema and severe pneumonia, possibly due to CMV infection, which is an unusual cause of viral pneumonia in infants. The diagnosis of possible congenital CMV infection was made based on the presence of typical laboratory and clinical findings under 3 weeks of age and virologically proven CMV after 3 weeks.[6] Thrombocytopenia and rash overlapped with the classic triad of WAS in the patient, leading to a protracted course of diagnosis. Our patient had hemizygous single-nucleotide variant in the *WAS* gene (c.91G>A, E31K, ChrX:48542333G>A), giving rise to a missense mutation that is likely pathogenic and has been previously reported in 13 patients with WAS.[7–13]

CMV is a worldwide prevalent herpesvirus, transmitted through close person-to-person contact via saliva, genital secretions, urine or breast milk. Seroprevalence of CMV IgG has been estimated to be 92% among Iranian adult blood donors,[14] slightly higher than estimates within the USA.[15] Congenital CMV infection occurs as a result of transplacental transmission of a reactivated latent infection or a primary CMV infection. The likelihood of transmission is higher and prognosis is poor following a primary infection in the mother, as up to 40% of women with seroconversion during pregnancy transmit the infection to their foetus.[16] There are heterogeneous reports on the seroprevalence of CMV IgM in pregnant Iranian women, estimated between 2.5% and 12.2% of all normal deliveries.[17–19] Unfortunately, the prevalence of primary maternal CMV infection is estimated to be higher in women in developing countries, compared to most western countries.[15]

Between 11% and 12.7% of neonates with congenital CMV eventually become symptomatic.[16] Conjugated hyperbilirubinaemia starting within the first 24 hours of birth and direct bilirubin levels above 2 mg/dl is the most common initial finding (~80%) and a diagnostic alert for all TORCH infections.[6] Petechiae, elevated liver enzymes and thrombocytopenia are next in prevalence, reiterating the importance of the diagnostic dilemma between WAS and congenital CMV infection.[15] Postnatal CMV infection was another possibility in our patient, considering that CMV virology in saliva and serology were not performed under 3 weeks of age.[6] The profound cellular immunodeficiency in WAS results in increased vulnerability of these patients to severe viral infections, including CMV. However, due to the small number of studies investigating limited number of patients, the exact prevalence of CMV seropositivity in WAS is not known.[20–24] Postnatal acquisition of CMV has little clinical importance and is rarely associated with serious long-term complications in term, non-immunocompromised infants. Nonetheless, in low birth-weight, premature or immunocompromised infants, acquired CMV presents with sepsis-like symptoms, pneumonia, thrombocytopenia and poor outcomes, similar to the congenital form.[25] Therefore, the discrimination between congenital and acquired CMV infection in this patient cannot be solely made based on the clinical presentation or timing of symptoms.

The WAS: C.91G>A mutation identified in this patient is a single-nucleotide variant resulting in a missense codon on exon 1 of the transcript. The change in glutamic acid to lysine (E31K) happens in the critical Ena-VASP homology domain (EVH1) of the protein, resulting in disruption of the secondary protein structure and folding.[26] The EVH1, also known as WH1, serves as a binding site for the WASP-interacting protein, which in turn stabilizes the intracellular WAS in its inactive form and protects it from calpain and proteasomal degradation.[2] The ensuing increase in intracellular WASp degradation results in reduced to absent cytosolic WASp expression in patients carrying the c.91G>A single-nucleotide variant (rs1557006239),[11,12] typically below 5% of the control sample.[4]

There are two other reports in the literature of congenital or postnatal CMV infection, initially misleading the diagnosis of WAS.[27,28] The fatal outcome of recurrent CMV infections, namely CMV pneumonitis, in patients with WAS, as well as shared haematological and systemic manifestations of congenital CMV and WAS, mandates a careful diagnostic work-up for timely identification of either condition.

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Conflicts of interest. None declared

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