Postnatal cytomegalovirus infection in an infant with congenital thrombocytopenia: how it can support or mislead the diagnosis of Wiskott-Aldrich syndrome

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SUMMARY

A male newborn developed a post-natal cytomegalovirus (CMV) infection, arising in the clinical setting of congenital thrombocytopenia, which was diagnosed as being alloimmune. The evidence of active CMV infection in an infant showing slow-resolution lower airways infection, persistent neonatal and low platelet volume thrombocytopenia, and diffuse eczema (associated to very high levels of serum immunoglobulin E) led to the diagnosis of Wiskott-Aldrich syndrome (WAS) before the third month of life, despite the presence of several confounding clinical factors. The correct interpretation of all clinical features supported the precocious diagnosis of WAS.

Keywords: thrombocytopenia, cytomegalovirus, Wiskott-Aldrich syndrome.

INTRODUCTION

Neonatal thrombocytopenia is often observed in preterm and/or low birth weight newborns, but it can be seen also in full-term neonates, showing a prevalence of 1%. Indeed, neonatal thrombocytopenia can recognize other causes than placental insufficiency and/or prematurity: 1) immune-mediated platelet consumption [e.g., allo-immune, auto-immune, drug-induced]; 2) mechanical platelet consumption [e.g., Kasabach-Merritt syndrome, disseminated intravascular coagulation]; 3) reduced platelet production [e.g., congenital and genetic platelet diseases, Wiskott-Aldrich syndrome, etc.]; 4) mixed mechanisms [e.g., congenital infections, sepsis, drug toxicity, perinatal asphyxia, etc.] [1].

Cytomegalovirus (CMV) is one of the most common infectious agents causing neonatal thrombocytopenia. Congenital CMV infection is symptomatic at birth in a minority of cases and several maternal factors, like CMV immune status, affect the incidence and the severity of such a disease. However, CMV infection can be acquired also after birth (through breast-feeding, saliva and blood transfusion) and the risk of symptomatic disease is usually limited to low birth weight and/or premature newborns. Both congenital and post-natal CMV infections can recognize thrombocytopenia as a dominant clinical finding [2].

The occurrence of post-natal symptomatic CMV disease in full-term infants with uncomplicated delivery can be seen in the clinical setting of primary immune deficiency diseases (PIDs). Here, we describe a case of post-natal CMV infection in a newborn diagnosed with Wiskott-Al-
drich Syndrome (WAS). Such a disease is caused by a X-linked genetic defect of the WAS protein (WASp), which is exclusively expressed in hematopoietic cells, playing a fundamental role in the cytoskeleton functioning. The classical phenotype of WAS includes immunodeficiency, thrombocytopenia (usually characterized with small volume platelets) and eczema of variable severity [3].

**CASE REPORT**

A 2-month old, male, full-term newborn was admitted to our pediatric ward because of the onset of mild to moderate respiratory distress, due to upper airways infection and bronchiolitis. Chest X-ray showed radiological findings being consistent with interstitial pneumonia. Since his arrival to the pediatric emergency room, the baby had received a careful clinical evaluation because his personal history was characterized with congenital and severe thrombocytopenia (34,000 mm$^3$). Indeed, after birth the newborn required Neonatal Intensive Care Unit (NICU) management: he received platelet transfusion and intra-venous immunoglobulin administration, and he was diagnosed with Neonatal Allo-Immune Thrombocytopenia (NAIT), through the demonstration of the incompatibility between the newborn and his mother for the Human Platelet Antigen 1 (HPA-1). Actually, his family history was negative for hematologic problems and hereditary diseases. At the admission, severe thrombocytopenia (46,000 mm$^3$) was confirmed, causing petechial skin rash. As regards the remaining parameters of blood cell count, moderate normocytic anemia (haemoglobin [Hb]: 7.4 g/dl; mean cell volume [MCV]: 82 fl) and mild leukocytosis (15,600/mm$^3$) were present. Blood biochemistry resulted to be normal, except for mild elevation of C-reactive protein (CRP: 17.05 mg/dl; normal values [n.v.] <5 mg/dl). Finally, the presence of human respiratory syncytial virus (RSV) was sought in the naso-secretions, but the result was negative. The overall clinical picture could be consistent with a viral illness in the setting of congenital thrombocytopenia: therefore, several serologic infectious tests were performed. Interestingly, specific CMV IgM was present (IgM = 72.7 U/ml, n.v. <18 U/ml; IgG = 42.7 U/ml, n.v. <12 U/ml). Actually, mother’s serology during pregnancy (third trimester) showed a protective immunity (IgM = 9.7 U/ml, n.v. <16 U/ml; IgG = 109 U/ml, n.v. <12 U/ml). In order to assess the presence of active CMV infection, urinary viral load and viremia were measured, resulting 315,000 copies/ml and 44,124 copies/ml, respectively. Moreover, the results of the analysis on the Guthrie card through nested polymerase chain reaction did not showed no presence of CMV genome in the blood spot at birth and after 15 days, confirming that CMV infection was acquired after birth. Finally, cerebral trans-cranial ultrasound showed mild enlargement of lateral ventricular spaces and, interestingly, two small calcifications were found in the corpus callosum, as it can be found in congenital or precocious CMV infections.

As an additional clinical finding, the baby resulted to be affected with extensive eczema involving head, limbs and trunk. Thus, he received an accurate allergy evaluation, revealing very high elevation of total serum IgE (>3000 UI/ml) and, particularly, of cow milk proteins specific IgE (α-albumin: 47.7 kUA/l; β-albumin: 13.2 kUA/l; casein: 23.8 kUA/l). As a consequence, the baby was fed by soy formula, and a significant improvement of skin lesions was achieved. However, despite the evidence of cow milk allergy, the history of NAIT and the ongoing CMV infection, actually the association of congenital/severe thrombocytopenia and eczema made focus the attention on the reduced platelet volume (6,1-6,8 fl), which was confirmed by the microscopic analysis of the blood smear. Indeed, this association of clinical manifestations raised the suspicion of a rare primary immunodeficiency, namely Wiskott-Aldrich syndrome (WAS). Therefore, a blood sample was drawn in order to analyze the leukocyte intra-cellular expression of WAS-related protein (WASp), which resulted to be severely deficient. That confirmed the diagnosis of WAS.

**DISCUSSION**

CMV is a widespread pathogen and, thus, presents a high adult rate of positive serology worldwide. It is a well-known cause of congenital infections and a large spectrum of clinical manifestations can occur in symptomatic cases...
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at birth, including thrombocytopenia and, as a consequence, petechial rashes. However, perinatal CMV infection can be acquired after birth too and, if so, breast milk is considered the most common transmission, although the mother resulted to be positive for CMV specific IgG. Alternatively, newborns could acquire CMV because of respiratory environmental transmission and that occurrence was supposed in our clinical case [2, 4]. Indeed, the patient was formula-fed since his birth and, moreover, the research of CMV genome in the blood spot of the Guthrie card resulted to be negative in all available controls (until 15 days of life), namely even after he received platelets transfusion and intra-venous immunoglobulin administration.

Post-natal CMV infection is almost always asymptomatic in full-term newborns; when this infection becomes symptomatic, the clinical manifestations include sepsis-like syndrome, pneumonia, enteritis, hepatitis or thrombocytopenia, and are usually seen in pre-term and low birth weight infants [2]. Hematological manifestations, including thrombocytopenia, anemia and leukocytosis or leukopenia, are common during perinatal CMV infection, even in immune-competent infants, but are usually transient [5]. Therefore, persistent and/or symptomatic hematological findings and the occurrence of extra-hematological manifestations focused the suspicion on the immune status of the subject. The immune protection against viral infections is largely T cell-mediated. Both CD4+ and CD8+ specific cells play a fundamental role in CMV infection and, recently, also γ/δ lymphocytes and natural killer cells have been shown to be critically involved in this task [6]. Therefore, all clinical settings where the cellular immunity is impaired, including several primary immunodeficiency diseases (PIDs), are prone to the occurrence of symptomatic CMV infections. In fact, WAS is a PID, where the impairment of the cytoskeletal rearrangement (caused by WASp mutation) produces pleiotropic consequences on several immune system components, including T cell functioning, starting from the antigenic activation to the effector mechanisms [7]. Indeed, CMV infection resulted to be among the main cause of mortality in patients affected with WAS and pneumonia was the most frequent CMV-related disease [8]. In addition to respiratory diseases, few case reports described WAS-affected infants developing hemorrhagic gastritis or enteritis, complicated uveitis or retinitis, and hepatitis [4,9-12]. Therefore, the evidence of symptomatic CMV infection in a thrombocytopenic male newborn or infant must promote - and not stop - a careful diagnostic work-up: although this virus can be responsible of several hematologic abnormalities, actually those could recognize other concomitant causes, as we showed. Therefore, further investigations could unveil WAS, whose typical clinical expression is characterized with micro-thrombocytopenia and severe eczema. A precocious diagnosis and treatment of CMV infection in an infant affected with WAS is mandatory, as its superimposition on a basal thrombocytopenic setting might lead to fatal hemorrhagic events and might affect adversely the outcome of the hematopoietic stem cell transplantation used to cure such a disease.

Declaration of interest: The authors report no conflict of interest.

REFERENCES


