When the Main Symptom is Missing

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Abstract
The authors in this paper point to the difficulty of diagnosing a child with primary immunodeficiency. Most primary immunodeficiencies are among rare diseases with an incidence of less than 1: 100,000. There are currently no primary screening methods for primary immune deficiencies, and a significant part of the diagnosis consists of basic examination procedures, namely medical history, clinical picture, laboratory and diagnostic imaging examinations. No all of the symptoms may be present in the newborn and early infant. Case report is a patient with early and severe clinical manifestation of Wiskott-Aldrich syndrome without the presence of typical microthrombocytopenia in neonatal age.

Keywords: Thrombocytopenia; Primary Immunodeficiency; Infections; Juvenile Myelomonocytic Leukemia; Neonatal Alloimmune Thrombocytopenia; Wiskott-Aldrich Syndrome

Abbreviations
CMV: Cytomegalovirus; CNS: Central Nervous System; HLA: Major Histocompatibility System Antigens; ITP: Idiopathic (Immune) Thrombocytopenic Purpura; JML: Juvenile Myelomonocytic Leukemia; LAD: Leukocyte Adhesion Deficiency; MPV: Mean Platelet Volume = SVTr - Mean Platelet Volume; NK Cells: Natural Killers - Lymphocyte Subclass; RSV: Respiratory Syncytial Virus; WAS: Wiskott-Aldrich Syndrome WAPS protein of Wiskott-Aldrich syndrome

Introduction
The authors deal with the differential diagnosis of thrombocytopenia in neonatal and infant age [1,4,10,12]. Thrombocytopenia with skin and mucosal manifestations of bleeding manifests in a child without other co-morbidities in an acute respiratory infection, therefore differential-diagnostic considerations are directed initially from the most commonly occurring thrombocytopenias such as: fetal/neonatal thrombocytopenia, or idiopathic (immune) thrombocytopenic purpura of ITP, up to the rarely occurring [2,6]. Due to the non-response to initial high-dose intravenous immunoglobulin therapy and the further course of accumulation of severe infections in multiple systems, differential diagnosis is widespread. There is a gradual failure of the immune system, looking for rare causes of thrombocytopenia in connection with immunodeficiency.

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Case Report

The 13-day-born neonate of the Roma ethnic group was admitted for respiratory insufficiency due to RSV bronchiolitis with petechial manifestations of bleeding into the skin around the navel and the mucosa of the harsh climate. In the forerunner 3 dni had a lasting irritating cough. The boy was free of perinatal and peripartal pathology, eutrophic (4050 g/53cm) born in term, spontaneously in the head. He was the third child of his parents, still had two older sisters. The family history was unremarkable, the parents negated consanguinity, but there was a generational difference of 18 years between them.

In addition to finding a small number of platelets of appropriate size, moncytosis appears in the peripheral blood count, along with various stages of development of granulocytes - leftward shift to the blasts.

![Image](image-url)

**Figure 1:** Initial blood count and differential blood count with microscopic coating.

The child does not respond to ITP treatment or to blocking treatment of fetal/neonatal alloimmune thrombocytopenia. (IVIG: 2 g/kg) [2]. To avoid bleeding in mucous membranes and bleeding in the CNS, it requires repeated substitutions with platelets.

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For persistent abnormal findings in peripheral blood counts typical of juvenile myelomonocytic leukemia: leukocytosis $14 \times 10^9/\text{l}$, monocytosis $4.29 \times 10^9/\text{l}$, thrombocytopenia $22 \times 10^9/\text{l}$, presence of erythroblasts, presence of immature myeloblasts in differential blood count: 1%, promyelocyte 1%, myelocyte neutrophil 1%, non-segmented metamyelocyte 9% are re-examined by bone marrow. Bone marrow morphological examinations, or ancillary examinations (without fetal hemoglobin elevation) or genetic examinations - exclusion of monosomy 7 do not confirm the juvenile myelomonocytic leukemia considered [3, 7, 11].

**Figure 2:** Persistence of thrombocytopenia and repeated thrombocyte concentrate replacement therapy in clinical manifestations of bleeding.

**Figure 3:** Diagnostic criteria for juvenile myelomonocytic leukemia (JMML), according to Clinical Trial Protocol, EWOG-MDS 2006.
Explanatory notes: PB- peripheral blood count, BM- bone marrow bone marrow, NF1- neurofibromatosis 1, GM-CSF- granulocyte and macrophage colony-stimulating factor.

In addition, serious infections of bacterial and viral nature are associated, and initially a 4 kg baby is stagnant in weight. Several systems are affected initially from respiratory insufficiency due to RSV, a week of enteritis with enterorrhagia in enteropathogenic *E. coli*. At 1.5 months of age, he fights with severe, swollen skin affections in the capillaries and on the face imitating seborrheic dermatitis secondary to *Klebsiella pneumoniae*. At 2 months, medial otitis caused by *Streptococcus pneumoniae* is resolved as it struggles with CMV pneumonitis for 3 months.

![Figure 4: Patient X-ray documentation.](image)

Its immune profile, which is largely influenced by treatment and infections, shows signs of lack of function. There is a gradual increase in gammaglobulinemia A, after repeated supportive treatment with intravenous immunoglobulins, hypergammaglobulinemia G is also found. E.

After repeated transfusions, formation of alloantibodies against both platelets and leukocytes occurs and the efficacy of platelet concentrates decreases. Commonly available treatment options are exhausted, and efforts to restore the loss of haemopoietic organ functions to provide immune homeostasis lead to stem cell transplantation. Pre-transplant examinations of parents where surprising finding of HLA identity of mother with child (finding in common population found among siblings) and HLA haploidentity between father and mother (finding in common population found between parent and child) are surprisingly found. in the family. From the point of view of donation and graft acceptance, a relative HLA identity is ideal.

It would be advisable to send the patient to a stem cell transplantation of known diagnosis based on the normal platelet size (reference mean SVTr/MPV 7.2 - 11.1 fl platelet volume).

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Fetal/neonatal alloimmune thrombocytopenia or idiopathic thrombocytopenic purpura would respond to treatment with high dose intravenous immunoglobulins [2,6]. The diagnosis of Wiskott-Aldrich syndrome lacks the cardiac symptom - macrothrombocytopenia, characterized by small platelets with SVTr/MPV < 7fl, most commonly SVTr/MPV (3.8 - 5fl) [5,6,8-10]. For phagocytosis disorder with impaired leukocyte adhesion (LAD syndrome), there are no signs of extreme leukocytosis and significantly low oxidative burst of neutrophils - (the patient had marginally lower values) [1,4]. Di-George's syndrome for pre-detected hypocalcaemia was also considered, in which vitamin D deficiency was confirmed and calcium was corrected after its substitution [1,4]. Typical skeletal changes were lacking for infantile osteopetrosis. Due to the increased destruction of platelets in the spleen in the presence of free and bound antithrombocyte antibodies, their absence at the beginning was not indicative. Congenital CMV infection would have a platelet response in response to causal ganciclovir treatment. For juvenile myelomonocytic leukemia lacked the positivity of morphological examinations from bone marrow and genetic examinations [3,7,11].

The diagnosis was made only after complete clinical manifestation of Wiskott-Aldrich syndrome (microthrombocytopenia, eczema, hyper IgA, hyper IgE, immunodeficiency) with unmasking of microthrombocytopenia. After a secondary review of all blood count findings, 7.0 fl platelets appeared for the first time at 1.5 months of age [14,15]. They then appear intermittently (after platelet survival from platelet concentrates) with a minimum platelet size of MPV 6.6fl. Molecular genetic examination confirmed the X-linked recessive form of inheritance- WASp mutation, Xp11.22-23, mother was a carrier.

**Discussion**

Wiskott-Aldrich syndrome is a primary immunodeficiency with a rare incidence of 2 - 8.8%, with an incidence of 4.1 per 1,000,000 live births. It is diagnosed in neonatal or childhood [1,4,10,12]. Inheritance is most often X-linked recessive (boys affected), but can also be autosomal dominant, autosomal recessive, or unspecified. WAS is caused by a mutation of the WAS gene for the WAS protein. (WASp Xp11.22-23). The WAS gene is expressed exclusively in hemopoietic cells. Its exact function is not yet fully understood [4].
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The product of the WAS gene is the WASP protein, which is required for many functions in lymphoid and myeloid immune cells [9]. It is part of the cytoskeleton of cells, affecting the polymerization of new branched actin microfilaments. Its deficiency or lack can lead to immune deficiency at all levels. From impaired antigen recognition by the receptor, through impaired migration and chemotaxis of neutrophils and T-lymphocytes. In addition, a disorder of phagocytic function of dendritic cells and macrophages is present. Impaired formation of podosomes, phagosome, cytokine secretion, integrin function, impaired cell polarization. In neutrophils, integrin-mediated adhesion and migration fail, granule release from neutrophils is impaired, oxidative enzymatic reactions are reduced. Lymphocytes are incapable of generating an immune synapse for impaired signaling functions and cytokine production. Immune sympathetic disorders also affect NK cells, T cells and B cells. These changes lead to the development of an immunodeficient state with insufficient cooperation between immuno competent cells [9].

WAS is clinically characterized by a triad of symptoms: microthrombocytopenia (θ1.8 μm, SVTr/MVP 3.8-5fl), primary immunodeficiency and eczema. In laboratory tests, heterogeneity may be decreased IgM, hyper IgA, hyper IgE, decreased isohemagglutinin concentrations, or total lack thereof. The disorder is also in cellular immunity - decreased number and function of T lymphocytes, decreased oxidative burst of neutrophils [1]. In 70% of cases, autoimmune disease may develop, in 10 - 20% of cases hematological malignancies occur [4].

WAS requires consistent and comprehensive care. Patients may be asymptomatic, have recurrent infections - where prophylactic antibiotic and immunoglobulin replacement therapy is indicated, or severe. They are suitable preventive measures - vaccination against pneumococci and polysaccharide antigens. In bleeding manifestations, they require platelet concentrate replacement therapy. In patients with severe course of treatment, curative treatment is important as soon as possible after diagnosis. Treatment consists of stem cell transplantation [4,10]. In some European centers (Great Ormond Street Hospital-London, Necker Children’s Hospital-Paris), prospective studies have started using gene therapy with the implantation of recombinant WAS gene using Lentiviruses into stem cells [4,5,13].

Figure 6: Typical clinical manifestation of Wiskott-Aldrich syndrome (adapted to Focosi D. Inherited monogenic immune disorders, Copyright © 2001-2014).
Conclusion

As the case study suggests, not all symptoms are fully expressed at the same time. Microtrombocytopenia, a symptom considered to be a pathognomonic sign, may be masked at infant age by infection and leaching of younger (larger) forms of platelets from the bone marrow, which may lead to diagnostic delay [14,15].

The patient underwent a stem cell transplantation at the Bone Marrow Transplant Unit in DFNsP Bratislava, where a definitive diagnosis was made. The first transplantation was performed from an HLA identical mother to minimize antigen loading. For graft rejection, he underwent retransplantation from an HLA identical unrelated donor. He developed full chimerism, is regularly monitored for TJKD and enjoys good health.

Bibliography


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