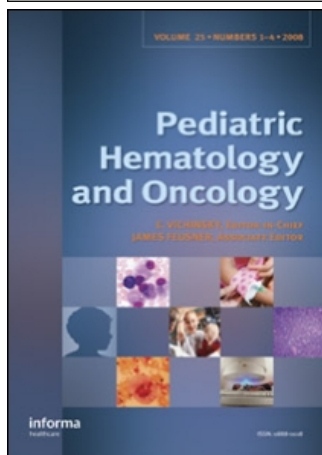


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THROMBOCYTOPENIA AFTER BACILLE CALMETTE-GUÉRIN IMMUNIZATION - POSSIBLY ON AN IMMUNE BASIS

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Letter to the Editor

THROMBOCYTOPENIA AFTER BACILLE CALMETTE-GUÉRIN IMMUNIZATION—POSSIBLY ON AN IMMUNE BASIS

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Autoimmune thrombocytopenic purpura (AITP) is one of the most common bleeding disorders in children [1]. Platelet-specific antibodies are generally observed 4–8 weeks following a viral illness or immunization. Autoantibodies, which bind both to platelets and to megakaryocytes, can cause platelet destruction and decreased platelet production. These occurrences are explained by interference with megakaryocyte proliferation and maturation [2, 3]. Numerous vaccines are related to the development of autoimmune phenomena or autoimmune diseases [4–6]. Although there are no conclusive records of AITP related to bacille Calmette-Guérin (BCG) immunization, some authors refer to the association between BCG immunization and autoimmunity [7, 8]. The exact mechanism of BCG-induced autoimmunity is not yet clear. The most likely explanation for this phenomena is molecular mimicry, when structural similarities exist between some mycobacterium tuberculosis and human antigens [4, 8].

Here we report a rare case of AITP in a 5-week-old male infant with IgM and IgG antiplatelet antibodies and an absence of megakaryocytes in the bone marrow. Although the etiology of the condition remains uncertain, the thrombocytopenia could have been a consequence of an inappropriate immune response to a BCG vaccination at birth.

A previously healthy 5-week-old boy was presented to the Children's Hospital in Zagreb 2 days after the occurrence of diffuse purpuric lesions.

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He was born at 39 weeks' gestation to a healthy mother, who had no relevant medical history and was not taking any medication. This was the mother's first pregnancy and she had never received any transfusion therapy. After a normal delivery of a full-term infant, with normal birth weight, a routine BCG vaccination was performed. The infant was discharged from the hospital 3 days later. The boy remained healthy until thrombocytopenic purpura appeared during the fifth week. After an initial physical examination, the patient showed to be afebrile with diffuse petechiae and ecchymoses, but with otherwise normal clinical status.

Significant laboratory data included the following: ESR 12 mm/h, WBC $6.2 \times 10^9/\text{L}$ (4% eosinophils, 1% basophils, 16% neutrophils, 64% lymphocytes, and 15% monocytes), RBC $3.14 \times 10^{12}/\text{L}$, Hb 104 g/dL, reticulocyte 1.3%, and platelets $3 \times 10^9/\text{L}$. The mean platelet volume (MPV) was 9.2 fL and the red blood cell type was A Rh (D) +. Direct and indirect Coombs' tests were negative. Flow-cytometry analysis revealed a significantly elevated number of platelet-associated immunoglobulins (IgM and IgG). All other routine laboratory results were within normal range. The boy's mother had a normal platelet count and no anti-platelet antibodies were detected. Monoclonal antibody-based tests showed a positive platelet antigen-1a (HPA-1a) status for both the patient and his parents. Cross-match testing between the maternal serum and paternal platelets was negative, as well as that between the maternal serum and the patient's platelets. Bone marrow cytomorphology analysis showed no megakaryocytes present and normal erythroid and myeloid precursors. Bone marrow cytogenetic analysis revealed a normal karyogram. Serologic tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), rubella, toxoplasma gondii, adenovirus, and parvo B-19 virus were non-reactive for IgM. Tests for human immunodeficiency virus (HIV) antibodies were negative, as were the serologic tests for hepatitis A, B, and C. Polymerase chain reaction (PCR) tests for CMV, EBV, and HSV all showed no indication of an infection.

On the second day after his admission to the hospital, the patient's hemoglobin level fell to 72 g/L and the platelet count decreased to $1 \times 10^9/\text{L}$. Hematuria and gastrointestinal bleeding were evident. The patient received a transfusion of packed, leukopore-filtered, and irradiated red blood cells and platelets. In an attempt to stop the bleeding, he was also given a single dose of recombinant activated factor VII (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) 200 $\mu\text{g}/\text{kg}$. The latter proved to be successful. After the diagnosis of an immune thrombocytopenia, the patient was put on intravenous immunoglobulins (IVIG) 1 g/kg daily for 2 days. The third day after completing IVIG therapy, there was still no improvement in the platelet count or in the result of bone marrow aspiration. Bone marrow was still amegakaryocytic. We assumed the amegakaryocytic bone marrow to be immune-mediated so additional immunosuppressive therapy was

given. Intravenous methylprednisolone 30 mg/kg daily was administered for 3 days. That therapy resulted in an increase of platelet count after the first 24 h. Ten days after additional immunosuppressive therapy, the platelet count was within the normal range and the patient was in good health without any signs of bleeding. He was subsequently discharged from the hospital. Bone marrow examination and all other clinical and laboratory tests performed 4 weeks after discharge were within normal parameters. The patient's condition was monitored for 1 year up to the time of writing, when he was a healthy 14-month-old toddler.

We have described a very severe case of an acute autoimmune thrombocytopenia in a previously healthy male infant. All other types of thrombocytopenias were excluded and no viral etiology was established in our patient. The only vaccination our patient received was a neonatal BCG vaccine. This led us to suspect that the vaccine might have been the trigger for AITP, although there are no reports in the literature describing this sort of a reaction to BCG vaccine. Our patient had amegakaryocytic bone marrow and the initial prognosis appeared to be very poor, but the amegakaryocytic thrombocytopenia had a good outcome after corticosteroid treatment and the patient currently does not require any immunosuppressive therapy. The loss of antiplatelet antibodies and bone marrow megakaryocyte regeneration after a corticosteroid therapy suggested an immune-mediated disease. BCG is known to stimulate the immune system to trigger autoimmune diseases [7, 8]. Systemic immune responses and autoimmune manifestations have been documented after intravesical instillation of BCG [8]. Nonetheless, there is no literature available talking about BCG vaccine triggering an immune thrombocytopenic purpura, especially in young infants.

Mycobacteria have been proven to be immunogenic [9] and a high frequency of autoantibodies has been found in blood of patients infected with mycobacteria [10]. So the possibility of cross-antigenicity between mycobacterial antigens and host (human) antigens has been examined [11]. The results indicated that infecting mycobacteria share some antigens with human tissue, which accounts for some production of autoantibodies during a mycobacterial infection [8].

There are only a few case reports about tuberculosis presenting as immune thrombocytopenic purpura [12–14]. Al-Majed et al. found that 1% of active tuberculosis presented itself with AITP [13]. Thrombocytopenia in this case is thought to be the effect of cytotoxic antibodies directed against platelets and is usually seen in disseminated tuberculosis [14]. The significant increase in the platelet count after antituberculous treatment was considered a convincing proof of tuberculosis as the cause of thrombocytopenia [12]. Perhaps molecular mimicry (cross-antigenicity between mycobacterium tuberculosis and human platelet antigens) might be an explanation for AITP during tuberculosis infection and after a BCG vaccination.

Our patient has responded well to high-doses of methylprednisolone, but we must bear in mind that if there was a transient bone marrow suppression due to BCG vaccine or a minor intercurrent viral infection, thrombocytopenia and reduced megakaryocytes in the bone marrow could have recovered with time, irrespective of the administration of immunoglobulins or steroids.

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