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Secondary immune thrombocytopenia: post-transfusion thrombocytopenia in a patient with acute lymphoblastic leukemia

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Immune thrombocytopenia results from the presence of antiplatelet antibodies, the destruction of platelets by T-lymphocytes, and decreased platelet production in the bone marrow. The interaction between platelets and antigen-presenting cells and lymphocytes plays an important role in the pathomechanism of the disease.

Antiplatelet antibodies are detected in c.60–70% of cases, mostly IgG class that are directed against platelet glycoproteins IIb/IIIa, Ib-IX-V, Ia/IIa, V and IV and other membrane antigens. In the same way, antibodies simultaneously react with megakaryocytes, reducing platelet production. The site of production of antibodies is primarily the spleen, followed by the bone marrow [1, 2]. The destruction of antibody-coated platelets that have undergone phagocytosis by macrophages occurs mainly in the spleen. Another mechanism of thrombocytopenia can be the breakdown of platelets under the influence of cytotoxic T-lymphocytes (CD3+CD8+), which can also damage megakaryocytes. Reduced platelet production then results from an abnormal maturation pattern and increased apoptosis of megakaryocytes. The concentration of thrombopoietin in a patient with immune thrombocytopenia is close to normal, and significantly lower than in the case of thrombocytopenia associated with bone marrow damage after chemotherapy.

Post-transfusion thrombocytopenia, with a not entirely clear pathology, is associated with the presence of alloantibodies against HPA-1a antigen. Thrombocytopenia occurs suddenly 5–10 days after transfusion of a material containing platelet antigens. The number of platelets usually does not exceed 10 G/L.

The most common symptoms are: bleeding from the mucous membranes, gastrointestinal tract and/or urinary tract, and resistance to platelet transfusions. Intracranial hemorrhage leading to death can occur. Older populations with underlying conditions such as coagulopathy, arrhythmias, leukemia or transplantation are at increased risk of the disease. The number of units of platelets transfused to a patient has also been shown to have an effect on the occurrence of the disease. The treatment of choice is intravenous immunoglobulin [1].

Patient: an 8-year-old boy suspected for leukemia was admitted to the hospital. On physical examination upon admission he had: numerous diffuse ecchymoses, tachycardia, and hepatosplenomegaly. In laboratory tests: white blood cell (WBC) count — 97.91 G/L, hemoglobin (Hb) — 5.5 g/dL, platelets (PLT) — 9 G/L. After transfusion of red blood cell (RBC) count and PLT concentrates, he obtained Hb — 8.9 g/dL, and PLT — 40 G/L. He was diagnosed with acute lymphoblastic leukemia (pre-B-ALL). Therapy according to the AIEOP-BFM-2017-POLAND protocol was started. On the ninth day, spontaneous bleeding from the subcutaneous tunnel of the implanted Broviac catheter occurred. The platelet count was 2–3 G/L. Ineffective transfusions of platelet concentrations were used many times. Due to the suspected immunological background of the disorders, respective diagnostics were extended. Antiplatelet antibodies with specificity anti-HPA-1a, directed to the platelet glycoprotein (GP) IIb/IIIa, anti-human leukocyte antigen (HLA) class I antibodies, poly-specific lymphocytotoxic antibodies were detected in the patient's serum, while a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 13 (ADAMTS13) deficiency was excluded. Allele-specific probes, the FluoGene HPA NX assay determined platelet antigen genotype

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Table I. Differential diagnoses of thrombocytopenia

	Patient	Post-transfusion thrombocytopenia (PTT)	Immune thrombocytopenic purpura (ITP)	Drug-induced thrombocytopenia (DIT)	Thrombotic thrombocytopenic purpura (TTP)	Heparin-induced thrombocytopenia (HIT)
Onset	9 days after first transfusion	5–10 days after transfusion	Infection, altered immune homeostasis	7–14 days after starting treatment	Idiopathic onset	5–10 days after heparin
Intensity	Severe <10 G/L	Severe <10 G/L	Variable	Variable	Severe	Mild 50–60 G/L
Bleeding	Mild	Can be severe	Variable severity	Variable severity	Petechiae, bruising, hematuria, microvascular thrombosis	Bleeding uncommon, high risk of thrombosis
Platelet antibody testing	HPA-specific, HLA antibodies	HPA-specific antibodies with possible HLA antibodies present	Pan-reactive antibodies	Reactivity with normal platelets in presence of offending drug	Negative reactivity unless previously immunized	Positive heparin/PF4 antibody testing
Other diagnostic tools	HPA genotyping	HPA genotyping	Coagulation tests, PBS (large platelets)	Drug history	ADAMTS13 activity/inhibitor PBS with schistocytes	Serotonin release assay
Treatments	TPO-RA	IVIG, steroids	Steroids, IVIG, splenectomy, rituximab, TPO-RA	Drug cessation, transfusion for bleeding, steroids	PLEX, rituximab	Heparin cessation, non-heparin anticoagulants

ADAMTS13 — a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 13; HLA — human leukocyte antigen; HPA — human platelet antigen; IVIG — intravenous immunoglobulins; PBS — peripheral blood smear; PF4 — platelet factor 4; PLEX — plasma exchange; TPO-RA —thrombopoietin receptor agonist

and HLA class I antigens locus A and B for donor selection based on HPA-1 platelet antigen and HLA antigen compatibility. The treatment included intravenous immunoglobulins 1 g/kg, but with no expected effect. Treatment with a thrombopoietin receptor agonist, eltrombopag, at a dose of 50 mg/day was started. After 10 days of therapy, the platelet count normalized (>200 G/L). During further chemotherapy, the patient did not require any more platelet transfusions.

In this case, diagnosis of transfusion-related secondary immune thrombocytopenia in the course of cancer treatment was based on laboratory tests (Table I). Intravascular coagulation syndrome was excluded. The diagnosis was made after the use of steroid therapy and one dose of vincristine and daunorubicin, which could affect the picture of the blood.

The treatment of choice in post-transfusion thrombocytopenia is intravenous infusion of immunoglobulins 0.4 g/kg for five consecutive days or 1–2 g/kg for 2–5 days. Response to treatment is recorded in 90% of cases, usually after two days of treatment. Steroids are also often used in the treatment, but their effectiveness has not yet been proven. Platelet transfusions are rarely effective, but are recommended for life-threatening bleeding [1, 3].

Based on the presented case, the use of a thrombopoietin receptor agonist also seems to be a good therapeutic alternative [4], although the long-term effects of such treatment are not yet known.

Thrombocytopenia in the course of leukemias, lymphomas with bone marrow involvement and in metastases of solid tumors to the bone marrow are usually caused by the displacement of the platelet-forming system from the bone marrow by the proliferative process. Due to the complexity of the disease and treatment process, it can also take on a different character. Since the definition of post-transfusion thrombocytopenia in 1961, it has been only a rarely reported post-transfusion complication [1]. In a case of post-transfusion thrombocytopenia, it is recommended to extend the diagnostics:

- determination of platelet antigens from HPA-1 system using molecular biology methods;
- determination of HLA class I antigens locus A and B for selection of platelet concentrate;
- expanding diagnostics by testing anti-HLA antibodies in lymphocytotoxic test in order to determine/modify method of selecting platelet concentrate donors.
- Transfusion recommendations:
- transfused platelets from donors from registry selected on basis of compatibility in platelet antigens in HPA-1a system and HLA class I antigens locus A and B between donor and recipient;
- transfuse leukocyte-depleted blood components [5].

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ED — sole author.

Conflict of interest

The author declares no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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