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Letter to the Editor / Editöre Mektup

Donor-related EDTA dependent pseudothrombocytopenia after allogeneic stem cell transplantation. Can it be real?

Allojeneik Kök Hücre Nakli Sonrası Gelişen Donör Kaynaklı EDTA'ya Bağlı Pseudotrombositopeni. Gerçek olabilir mi?

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Abstract: Hematopoietic stem cell transplantation (HSCT) may take place in the form of an autologous or allogeneic transplant depending on the indication for transplantation. Because of the myeloablative conditioning regimens preceding HSCT, deep thrombocytopenia is experienced by most of the stem cell recipients in whom replenishment of leukocytes and platelets is expected within the first month following the transplantation. Prolonged thrombocytopenia, on the other hand, usually develops as a delayed complication of allogeneic stem cell transplantation (allo-SCT) and is associated to the source of stem cells, quantity of the infused CD34+ cells, graft-versus-host-disease (GVHD), insufficient engraftment, relapse of the malignancy, microangiopathy, alloimmunisation, medications, or viral infections. In an attempt to explain pathogenesis leading to post-HSCT thrombocytopenia, two main theories have been proposed. First one is the peripheral destruction caused by anti-platelet antibodies, splenic sequestration, or other factors. The latter blames insufficient platelet generation due to impaired thrombopoiesis. Nevertheless, most of the clinical conditions arise with overlapping of both mechanisms.Here we present a pseudothrombocytopenia case induced by donor-related ethylene-diamine-tetra-acetic acid (EDTA) as an unanticipated cause of thrombocytopenia to which most recipients of allo-SCT are prone to.
Keywords: EDTA, Allogeneic Stem Cell Transplantation

Özet: Hematopoietik kök hücre nakli (HKHN) endikasyona göre otolog veya allojeneik yapılabilir. Derin trombositopeniler, myeloablatif hazırlama rejimlerine bağlı olarak genellikle tüm hastalarda görülür. Lökositlerin ve trombositlerin yenilenmesi nakilden sonraki ilk ay içinde beklenir.. Uzun süreli trombositopeni, genellikle allojeneik kök hücre nakli sonrası hastalarda geç komplikasyon olarak görülür. Bu durum, kök hücre kaynağına, infüze edilen CD34+ hücrelerin miktarına, graft versus host hastalığına, engrafman yetmezliğine, altta yatan malignitenin nüksüne, mikroanjiyopatiye, alloimmünizasyona, ilaçlara veya viral enfeksiyonlara bağlanmaktadır. HKHN sonrası trombositopeninin patogenezi için iki ana teori ileri sürülmüştür, ilki anti-trombosit otoantikorları, splenik sekestrasyon veya diğer faktörler nedeniyle periferik yıkım; ikincisi ise, trombosit üretiminin, bozulmuş trombopoez nedeniyle yetersiz olmasıdır. Bununla birlikte, çoğu klinik durum, iki mekanizmanın üst üste çakışması ile karşımıza çıkar.Bu yazıda alloKHN sonrası beklenen bir durum olan trombositopeninin beklenmeyen bir nedeni olarak 'donör kaynaklı EDTA'ya bağlı pseudotrombositopeni' vakası sunulmuştur.
Anahtar Kelimeler: EDTA, Allojeneik kök hücre nakli

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1. To the editor

Hematopoietic stem cell transplantation (HSCT) may take place in the form of an autologous or allogeneic transplant depending on the indication for transplantation. Because of the myeloablative conditioning regimens preceding HSCT, deep thrombocytopenia is experienced by most of the stem cell recipients in whom replenishment of leukocytes and platelets is expected within the first month following the transplantation. Prolonged thrombocytopenia, on the other hand, usually develops as a delayed complication of allogeneic stem cell transplantation (allo-SCT) and is associated to the source of stem cells, quantity of the infused CD34+ cells, graft-versus-host-disease (GVHD), insufficient engraftment, relapse of the malignancy, microangiopathy, alloimmunisation, medications, or viral infections. In an attempt to explain pathogenesis leading to post-HSCT thrombocytopenia, two main theories have been proposed. First one is the peripheral destruction caused by anti-platelet antibodies, splenic sequestration, or other factors. The latter blames insufficient platelet generation due to impaired thrombopoiesis. Nevertheless, most of the clinical conditions arise with overlapping of both mechanisms (1-3).

Here we present a pseudothrombocytopenia case induced by donor-related ethylene-diamine-tetra-acetic acid (EDTA) as an unanticipated cause of thrombocytopenia to which most recipients of allo-SCT are prone to.

A 39-year-old male patient visited emergency care on March 2018 complaining of chest pain and high fever lasting for the last 3 days. On his physical examination, pale conjunctivas and tachycardia was noted. Cardiac enzymes were tested due to chest pain of the patient which revealed increased troponin-T and CK-MB levels. Therefore, the patient was hospitalized at the ward of cardiology upon diagnosis of acute coronary syndrome and myocarditis. On admission, his test results were hemoglobin: 13.1 g/dL, leukocyte: 13800/mm3, absolute neutrophile count (ANC): 10900/mm3, platelet: 64000/mm3, C-reactive protein: 100 mg/dL, and erythrocyte sedimentation rate (ESR): 117 mm/h. Echocardiography showed EF: 60%, minimal mitral regurgitation, with a normal coronary angiography. Colchicine and ibuprofen were initiated for the patient based on diagnosis of myocarditis and then he was discharged to home. During his follow-ups conducted by the cardiology outpatient department, the patient was referred to the outpatient department of hematology as he developed anemia and deepening thrombocytopenia. Peripheral blood smear of the patient showed myeloblasts featuring with Auer rods. Preliminary diagnosis of acute leukemia was considered, and bone marrow aspiration/biopsy was performed. Bone marrow aspirate of the patient was composed of 25% myeloblasts with Auer rods. The diagnosis of acute myeloid leukemia (AML)-M2 was then established and thereupon 7+3 regimen of remission-induction chemotherapy was applied. A post-treatment bone morrow exam was performed to check the patient's response to the first course of chemotherapy which indicated a blast ratio of 8%. As complete remission was not achieved, second course of 7+3 regimen was applied. Complete remission was attained through the second 7+3 regimen. After complete remission, the patient underwent allogeneic stem cell transplantation from a fully compatible sibling in July 2018 because of primary resistance and variable t (8; 21) positivity. At post-transplant Day 100, the patient's test results were hemoglobin: 13.4 g/dL, leukocyte: 7800/mm3, ANC: 4200/mm3, and platelet: 165000/mm3. Bone marrow exam was negative for t(8;21) abnormality, and cytogenetic analysis was normal. In February 2019, 8 months after allo-SCT, his test results were hemoglobin: 14.3 g/dL, leukocyte: 8410/mm3, ANC: 3260/mm3, and platelet: 23000/mm3. At that time, patient had a negative medical history for any other herbal or medical treatment. Blood smear of the patient was prepared, showing clumped platelets. Complete blood count of the patient's donor resulted as hemoglobin: 16.7 g/dL, leukocyte: 5300/mm3, ANC: 2600/mm, platelet: 22000/mm3, and query in his past medical history elicited known EDTA-induced pseudothrombocytopenia.

Consequently, EDTA-induced pseudothrombocytopenia of the patient subsequent to allo-SCT was considered to be donor-derived (peripheral blood smear findings of the patient and donor were given in Figure). A retrospective analysis of the patient's former investigations figured out health checkup tests done in 2009. At that time, his hemoglobin: 15.3 g/dL, leukocyte: 10000/mm3, ANC: 6800/mm3, platelet: 196000/mm3, and peripheral blood smear was normal.

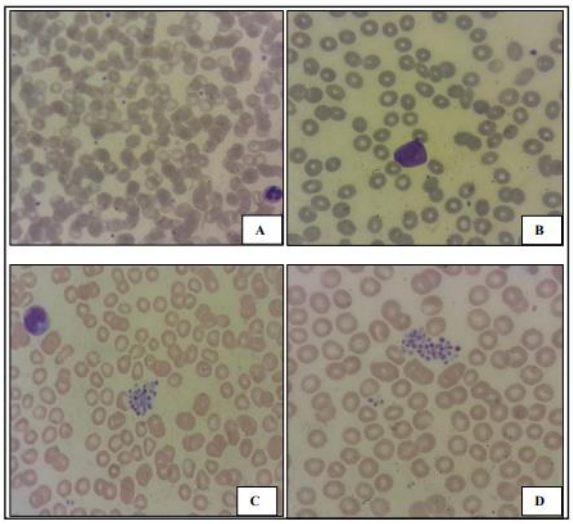

Figure. The patient's peripheral smear results by time **A.** Peripheral smear from a routine checkup in 2009, with normal results **B.** Peripheral smear of blasts in March 2018 when AML was diagnosed **C.** Peripheral smear of pseudothrombocytopenia due to donor-related EDTA 8 months after allogeneic stem cell transplantation. **D.** The donor's peripheral smear, EDTA-induced pseudothrombocytopenia

Prolonged thrombocytopenia following HSCT usually develops as a delayed complication of allo-SCT (1). EDTA-induced pseudothrombocytopenia is not a likely cause of thrombocytopenia following allo-SCT and may very rarely occur in association with medication (2). When our patient was evaluated for thrombocytopenia developed in the 8th month of post-transplant, it was found that he did not take any medicine in her interrogation. Peripheral blood smear was evaluated for relapse which was the preliminary diagnosis. No relaps was detected, clumped platelets were seen. The cause of thrombocytopenia was pseudothrombocytopenia due to EDTA. When the patient was further assessed to address the reason causing EDTA-induced pseudothrombocytopenia, no secondary cause was identified. On the other hand, his donor had experienced EDTA-induced pseudothrombocytopenia leading to the conclusion that the patient's clinical picture was originating from his donor.

As a result, this is the first case of donor-related EDTA-induced pseudothrombocytopenia in the literature. Donor-related EDTA-induced pseudothrombocytopenia should be listed as a rare etiological cause of thrombocytopenia occurring following allo-SCT.

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Ethics

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