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Bone Marrow Transplantation as a Rare Cause of Pulmonary Arterial Hypertension

Pulmoner Arteriyel Hipertansiyonunun Nadir Bir Nedeni Olarak Kemik Iliği Nakli

ABSTRACT

The development of pulmonary arterial hypertension after bone marrow transplantation (BMT) is a rare but serious complication. In this case report, we presented the development of pulmonary arterial hypertension in a 22-year-old woman who underwent BMT due to aplastic anemia. Her symptoms on admission included shortness of breath, palpitations and fatigue. Pulmonary hypertension was classified with right heart catheterization as pulmonary arterial hypertension. The patient's laboratory, echocardiographic and hemodynamic findings improved with pulmonary arterial hypertension-specific treatment. Pulmonary arterial hypertension should be considered in the differential diagnosis of BMT patients with 'unexplained' hypoxemia or respiratory distress.

Keywords: Aplastic anemia, bone marrow transplantation, pulmonary arterial hypertension

ÖZET

Kemik iliği transplantasyonundan (KİT) sonra pulmoner arteriyel hipertansiyon gelişimi nadir fakat ciddi bir komplikasyondur. Bu olgu sunumunda aplastik anemi nedeniyle KİT yapılan 22 yaşında bir kadın hastada gelişen pulmoner arteriyel hipertansiyonu sunduk. Başvuru anındaki semptomları nefes darlığı, çarpıntı ve yorgunluktu. Pulmoner hipertansiyon, sağ kalp kateterizasyonu ile pulmoner arteriyel hipertansiyon olarak sınıflandırıldı. Pulmoner arteryel hipertansiyona özgü tedavi ile hastanın laboratuvar, ekokardiyografik ve hemodinamik bulguları düzeldi. 'Açıklanamayan' hipoksemi veya solunum sıkıntısı olan KİT hastalarının ayırıcı tanısında pulmoner arteriyel hipertansiyon düşünülmelidir.

Anahtar Kelimeler: Aplastik anemi, kemik iliği nakli, pulmoner arteriyel hipertansiyon

CASE REPORT
OLGU SUNUMU

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Bone marrow transplantation (BMT) has been developed as a treatment of last resort for many hematological diseases. It is utilized in hematological malignancies as well as in diseases such as hypocellular bone marrow and aplastic anemia that progresses with pancytopenia.[1] Many disease groups are included in the pulmonary hypertension subgroup classification; thus, their diagnosis and treatment are challenging. Pulmonary arterial hypertension (PAH) rarely develops after BMT, but when it does, there is a high risk of mortality.[2] In this context, a patient who underwent bone marrow transplantation due to aplastic anemia and was diagnosed with pulmonary arterial hypertension in the late postoperative period is presented.

Case Report

A 22-year-old female patient who was initially admitted to the hematology outpatient clinic was referred to the cardiology outpatient clinic due to dyspnea. She had complaints of shortness of breath, palpitations, and fatigue. Her complaints, which had been ongoing for 7 months, had exacerbated in the last 2 months. Blood pressure was measured as 135/80 mmHg. Additionally, heart rate was measured as 122 beats/min. Body mass index (BMI) was calculated as 19 kg/cm^2. Saturation was determined as 80% at room air. The heart was rhythmic, tachycardic, and S2 pulmonary component was stiff. She had undergone allogeneic BMT 10 months ago due to aplastic anemia. There was no feature in her family history. Electrocardiographic examination revealed sinus tachycardia and p pulmonale sign (Figure 1). No abnormality was detected in the

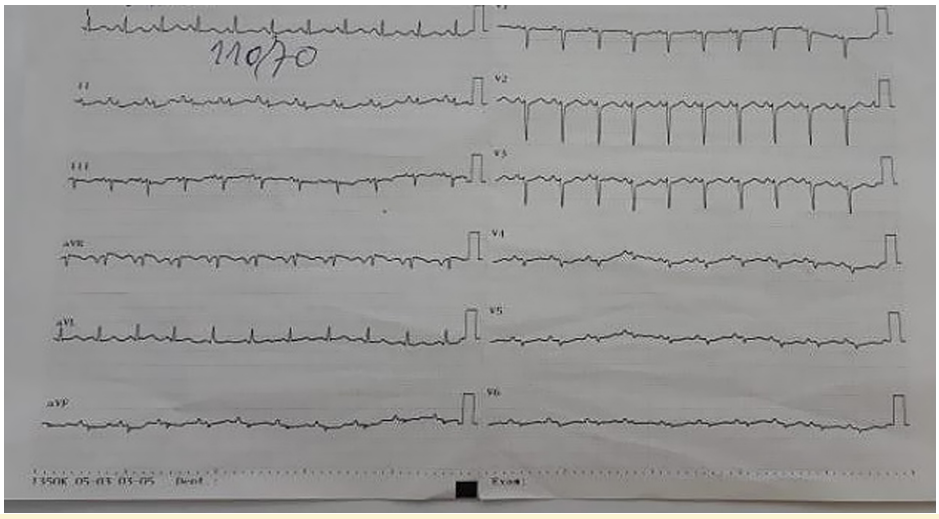

Figure 1. Echocardiography shows sinus tachycardia and p pulmonale signs.

left ventricular functions on transthoracic echocardiography. The ejection fraction was 65%. Diastolic functions were normal. No valve disease was detected. The pulmonary artery was dilated in the parasternal short axis view (Figure 2A). The right side of the heart was dilated, the left ventricle was D-shaped, and there was moderate tricuspid regurgitation (Figure 2B and C). Tricuspid regurgitation velocity was measured as 4.3 m/s, whereas estimated systolic pulmonary artery pressure (sPAP) was measured as 90 mmHg (Figure 2D). In addition, the right ventricle was hypertrophic, and pericardial effusion was detected. The patient was hospitalized to investigate the etiology of pulmonary hypertension (PH). No defect or shunt was detected in the transesophageal echocardiography performed after hospitalization. The results of patient's laboratory tests were as follows: hemoglobin (Hb): 11.7 g/dL, hematocrit (Hct): 35.3%, glucose: 82 mg/dL, creatinine: 1.2 mg/dL, N-terminal pro-B-type natriuretic peptide (NT proBNP): 3754 pg/mL, aspartate aminotransferase (AST): 22 U/L, and alanine transaminase (ALT): 8 U/L. The results of thyroid function and D-dimer tests were within the normal range, and human immunodeficiency virus and hepatitis markers were negative. The rheumatological autoantibody tests were normal. In arterial blood gas, pH was 7.43, PaO_2 was 49.6 mmHg, $PaCO_2$ was 20.5 mmHg, and oxygen saturation was 84.5%. The pulmonary function test revealed a restrictive pattern. The results of the test were as follows: forced vital capacity (FVC): 48%, forced expiratory volume (FEV1): 51%, and FEV1/FVC: 109%. The diffusion test revealed that diffusing capacity for carbon monoxide was 25%, which is quite low. The chest x-ray revealed a prominent pulmonary conus and elevated cardiothoracic index. In computed tomography (CT) pulmonary angiography, there was no filling defect compatible with embolism in the pulmonary artery and the branches thereof. The main pulmonary artery was

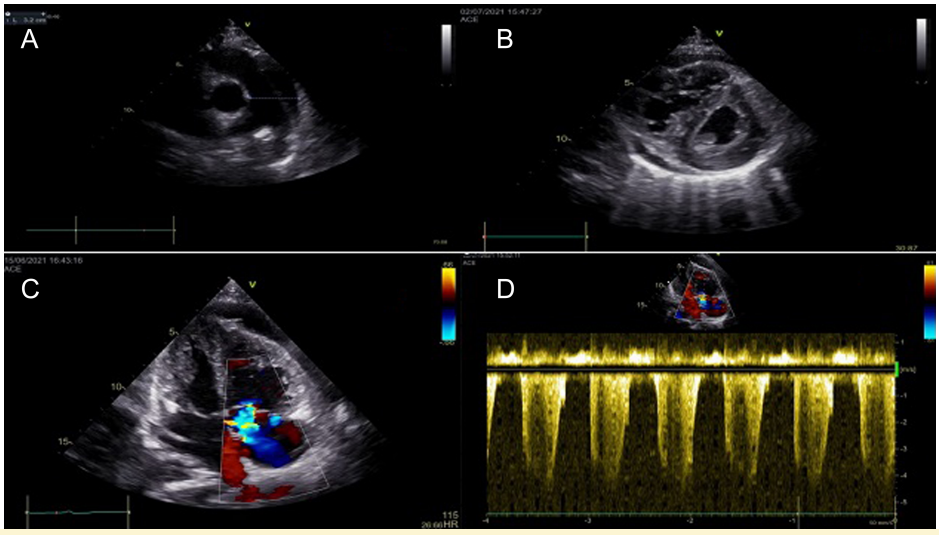

Figure 2. (A) Transthoracic echocardiography shows dilated pulmonary artery in parasternal short axis view. (B) Transthoracic echocardiography shows that the right ventricle is dilated and the interventricular septum is flattened, and the left ventricle takes a D shape in the parasternal short axis view. (C) In the apical 4-chamber view, dilated right ventricle and moderate tricuspid regurgitation with color Doppler and also pericardial effusion are seen. (D) Estimated systolic pulmonary artery pressure measured over the tricuspid regurgitation jet.

34 mm in diameter and was dilated. No significant pathology was found in the chest x-ray and tomography, except for the slight ground-glass density in the parenchyma.

High-resolution CT indicated an increase in the diffuse interlobular septal thickness and ground-glass densities in all segments of both lungs. The results of the lung ventilation perfusion scintigraphy were normal. Right heart catheterization was planned for the patient. Mean PAP and pulmonary capillary wedge pressure (PAWP) were measured as 48 mmHg, and 8 mmHg, respectively. Pulmonary vascular resistance (PVR) was measured as 8.55 WU (Woods unit). Cardiac index was 2.96 L/min/m^2. The result of the vasoreactivity test conducted with nitric oxide was negative. The patient was assessed in the cardiology, pulmonology, and hematology council, where lung biopsy was recommended to exclude the differential diagnosis of chronic graft versus host disease (GVHD) and pulmonary veno-occlusive disease (PVOD). However, the patient refused the lung biopsy due to the associated risks. Follow up with medical treatment was planned. Bosentan 62.5 mg twice a day and furosemide 40 mg once a day were started. Nevertheless, her complaints had not regressed by her follow-up visit approximately 1 month later. The NT ProBNP value had increased to 6441 pg/mL, whereas there was no significant worsening in other laboratory values. Control thorax CT did not reveal any significant change except for a mild increase in the ground glass density. Based on these findings, she was started on intravenous furosemide and methylprednisolone, and the dose of bosentan was increased to 125 mg twice a day. In addition, an iloprost inhaler was added to the treatment 6 times a day. With the recommendation of chest diseases, methylpred-nisolone 80 mg IV was started once a day during her hospitalization. The dose was gradually reduced, and methylpredisolone treatment was discontinued approximately 1 month later. One week later, her NT proBNP value decreased to 640 pg/mL, and she was able to walk 195 meters in the 6-minute walking test. The patient's symptoms had regressed by the third-month follow-up. In terms of the New York Heart Association, the class was II-III. The saturation was measured as 88%-90% at room air. The results of arterial blood gas analysis were as follows: PaO_2: 55.2 mmHg, $PaCO_2$: 26.3 mmHg, and oxygen saturation: 90.3%. The 6-minute walking test had increased to 240 meters. Her NT proBNP was 304 pg/mL. Control echocardiography revealed the following results: ejection fraction: 60%, tricuspid regurgitation velocity: 3.4 m/s, sPAP: 60 mmHg, pericardial effusion: minimal, vena cava inferior: 16 mm, and inspiratory collapse: >50%. Right heart catheterization was performed to evaluate the response to treatment. Mean PAP, PVR, and cardiac index were measured as 38 mmHg, 4.78 WU, and 3.31 L/min/m^2, respectively. Accordingly, the medical treatment of the patient, whose condition was determined to have improved based on the laboratory, echocardiographic, and hemodynamic assessments, was continued.

Discussion

Pulmonary arterial hypertension is hemodynamically defined under the precapillary PH group. It is characterized by mean mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR >2 WU.[3] Pulmonary arterial hypertension rarely develops after BMT, but when it does, there is a high risk of mortality. There is only a limited number of studies on the incidence, etiology, and risk factors of PAH that develop after BMT in the literature.[4] In one of these studies, Jodele et al[2,5]. reported that the incidence and mortality of PAH after BMT were 2.4% and 80%, respectively. Respiratory signs and symptoms associated with PAH after BMT are nonspecific and may be attributed to infection, bronchiolitis, interstitial pneumonia, and other complications related to BMT as well. Therefore, such respiratory signs and symptoms are often misleading and lead to a delay in diagnosis, especially during the period when the pulmonary pressure is only mildly increased.[4,6] Although the relevant etiology and pathophysiology are not known, some of the bone marrow cells have been shown to play a role in the remodeling of small pulmonary arteries and perivascular infiltration.[4] On the other hand, it has been speculated that underlying conditions such as myeloproliferative diseases that require BMT may predispose to the development of PH.[1] The frequent occurrence of infection after BMT, respiratory distress, hypoxia, and the drugs used to prepare the patient for BMT cause endothelial dysfunction in the pulmonary vascular structure.[7] It has been reported that complement activation and transplant-associated microangiopathy also lead to endothelial dysfunction.[5] The related mechanism is not clear, yet an immunological process is probably involved. A transient vasculopathy occurs with the development of autoantibodies after BMT. However, this process is different from the immune reaction mediated by donor T lymphocytes in GVHD.[8,9] Levy et al[4] reported cellular proliferation in the pulmonary artery wall of 3 patients who developed PH after BMT based on the histological examination findings but did not detect intimal fibrosis in these patients. Consequentially, they attributed these findings to an acute and potentially reversible process.[4] The fact that the pulmonary pressure got back to normal after aggressive treatment is consistent with this hypothesis. In another study, Limsuwan et al[7] reported 2 patients who developed PH 4 and 10 months after BMT and recovered with PAH-specific treatment.

In our case, the patient was given cyclophosphamide treatment to prepare for BMT. Cyclophosphamide is considered one of the drugs that may cause PAH. In addition, PVOD may develop due to pulmonary vascular endothelial damage after BMT because of conditioning regimens.[10] It has also been reported that GVHD may also lead to PAH in the late period after BMT.[6] Hence, a lung biopsy may be required to rule out these diseases in the differential diagnosis. Then again, lung biopsy is an invasive procedure that poses a high risk for this patient group. In parallel, open or thoracoscopic lung biopsy is not recommended in patients with PAH.[3] For this reason, the case presented herein refused to have a lung biopsy. Thus, it has been difficult to rule out drug-related PAH. However, PAH has also been reported in cases who did not receive a conditioning regimen prior to BMT.[4] Pulmonary arterial hypertension persisted in the case presented herein even almost a year after the discontinuation of the drug as opposed to the drug-related PAH cases reported in the literature in whom the process has been said to be reversible. The patient responded positively to the PAH-specific treatment, that the results of her genetic tests (BMPR2, EIF2AK4 mutation) came out normal, that PVOD is commonly seen in the early postoperative period after BMT, and that chronic GVHD mostly affects the skin, mouth, liver, and eyes but not much the gastrointestinal tract, lungs and joints,

made it possible to rule out the diagnosis of PVOD and chronic GVHD. Consequentially, the patient was started on medical treatment with the diagnosis of PAH after BMT.

To conclude, this case report suggests that patients undergoing BMT are at risk of developing PAH regardless of the pathogenesis. Therefore, PAH may be considered in patients who develop cardiorespiratory symptoms after transplantation. Furthermore, PAH may be considered in the differential diagnosis of BMT patients with "unexplained" hypoxemia or respiratory distress without significant radiological lung abnormalities or infections. The mortality of PAH after BMT is quite high; however, the rate of response to PAH-specific treatment is also high. For this reason, it is of utmost importance to start treatment as soon as a diagnosis is made.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Declaration of Interests: The authors declare that they have no competing interest.

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