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Case report

Pulmonary Hypertension Secondary to Dasatinib Use for the Treatment of Chronic Myeloid Leukemia

Kronik Miyeloid Lösemi Tedavisi için Dasatinib Kullanımına Sekonder Gelişen Pulmoner Hipertansiyon

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Abstract

A 20-year-old male patient under the treatment of Dasatinib for chronic myeloid leukemia was admitted with symptoms and signs of right heart failure. As a result of the transthoracic echocardiographic evaluation of the patient, severe enlargement of the right heart chambers was detected and systolic pulmonary arterial pressure was measured up to 105 mmHg. As a result of the other tests performed for pulmonary hypertension, it was thought that it might be secondary to the tyrosine kinase inhibitor Dasatinib with the exclusion of the other causes of pulmonary hypertension. Echocardiographic and symptomatic improvement was observed in the follow-up after Dasatinib treatment was changed to another tyrosine kinase inhibitor, Nilotinib.
Key words: chronic myeloid leukemia, dasatinib, nilotinib, pulmonary hypertension, right heart failure

ÖZ

Kronik miyeloid lösemi nedeniyle Dasatinib kullanan 20 yaşındaki erkek hasta sağ kalp yetersizliği semptom ve bulguları ile başvurdu. Hastanın ekokardiyografik değerlendirilmesi sonucunda sağ kalp boşluklarında ileri derece genişleme tespit edildi ve sistolik pulmoner arteryel basıncının da 105 mmHg' ya kadar yükselmiş olduğu saptandı. Pulmoner hipertansiyon açısından yapılan tetkikleri sonucunda diğer nedenler ekarte edildikten sonra kullanmış olduğu Dasatinib etken maddeli tirozin kinaz inhibitörüne sekonder olabileceği düşünüldü. Dasatinib tedavisi başka bir tirozin kinaz inhibitörü olan Nilotinib ile değiştirildikten sonraki takiplerinde ekokardiyografik ve semptomatik iyileşme gözlendi.
Anahtar kelimeler: kronik miyeloid lösemi, dasatinib, nilotinib, pulmoner hipertansiyon, sağ kalp yetersizliği

Highlights

- Dasatinib should be kept in mind as a factor in Drug-related PAH
- It is reasonable to screen routinely for PAH by echocardiography before commencing dasatinib treatment

Introduction

Pulmonary arterial hypertension (PAH) is a chronic and progressive cardio-pulmonary disease with a mean pulmonary artery pressure (mPAB) above 25 mmHg which hemodynamically meets the definition of precapillary pulmonary hypertension (1). As a result of many etiological reasons, disruption of mediator balance acting on the pulmonary arterial wall in the direction of proliferation and vasoconstriction leads to clinic of PAH (2). Drug-related PAH is an example of this. In this case report, we aim to present a patient with a history of pulmonary hypertension and recurrent pleural effusion caused by the use of Dasatinib, a tyrosine kinase inhibitor used for treatment of chronic myeloid leukemia (CML).

Presentation of the case

A 20 year old male patient was admitted to the cardiology outpatient clinic due to shortness of breath for 15 days. His general condition was good during application and his vital signs were found to be normal. He had no tachypnea. On physical examination, cardiac sounds were rhythmic, S2 was rigid, and systolic murmur was in tricuspid focus. The respiratory sounds were decreased in bilateral basals. The peripheral system examination was normal. He was on follow-up with CML for seven years and had been using Dasatinib. When he had a similar dyspnea a year ago, pleural effusion was detected in the outer center and Dasatinib was suspended for a while considering that it was drug-related. After pleural effusion regressed and the clinic recovered, Dasatinib was started again and the patient was continued to be followed up by hematology clinik.

The electrocardiogram (ECG) of the patient had right axle deviation and was comatible with right ventricular hypertrophy **(Figure 1).**

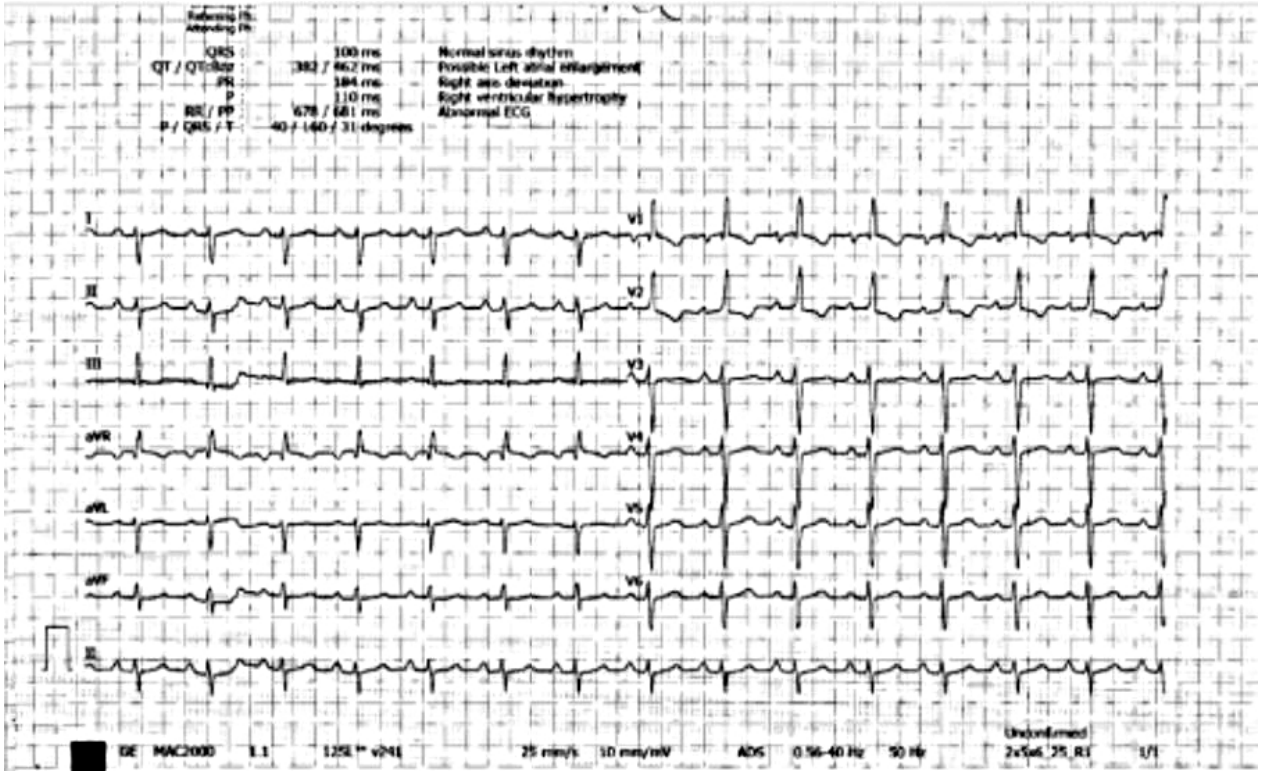

Figure 1: ECG; Right axle deviation and right ventricular hypertrophy

Transthoracic echocardiography showed normal left ventricle ejection fraction but wide right cavities, decreased right ventricular systolic functions, severe tricuspid regurgitation and the systolic PAB (sPAB) calculated on maximum TY velocity were 105 mmHg **(Figure 2).** The patient was hospitalized to the cardiology department due to decompensated heart failure. The volume of the patient was decreased with intravenous diuretic therapy and sPAP was still high on the control echocardiography. Other tests for the etiology of pulmonary hypertension were normal and the pulmonary hypertension of patient was thought to be related to Dasatinib which was then discontinued. Consulting with hematology for the treatment of CML, Dasatinib was changed with Nilotinib, which is another tyrosine kinase inhibitor. The patient was discharged and at 3 week follow-up, his complaints were significantly decreased. On echocardiography, the right cavities were wide, but the severity of tricuspid regurgitation decreased. sPAB was measured as 76 mmHg **(Figure 2).**

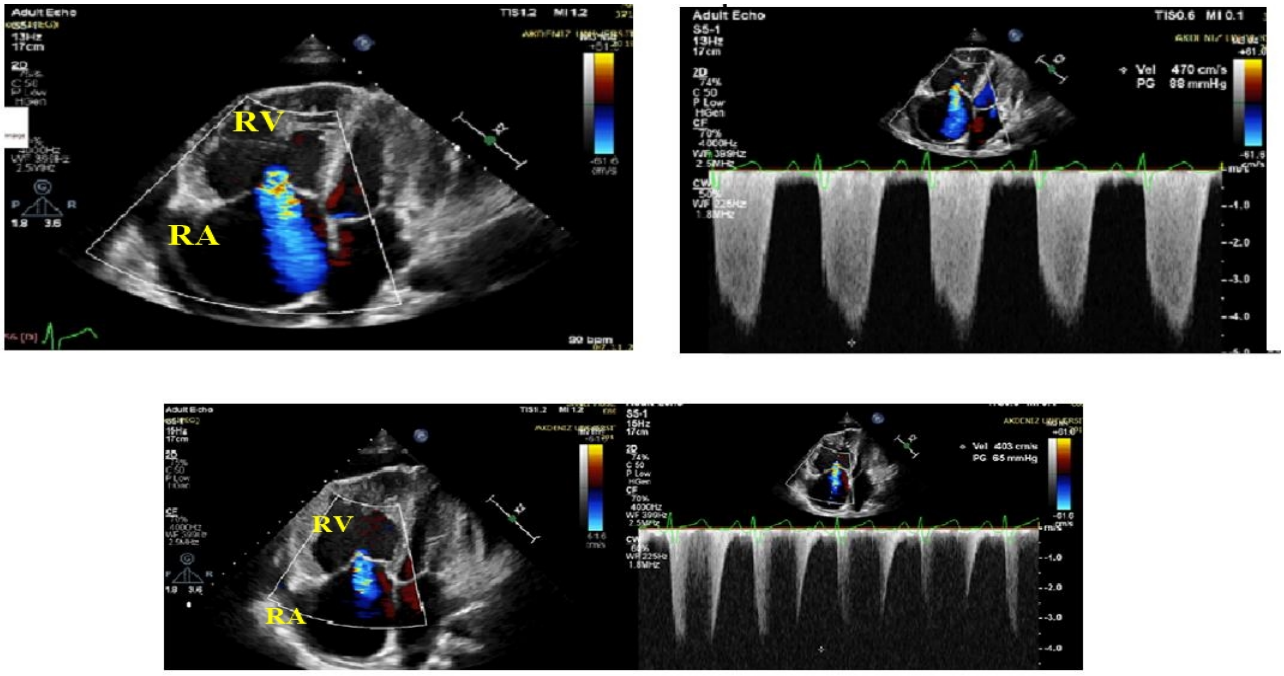

Figure 2: Comparative view with second echocardiography: moderate tricuspid regurgitation and PAB; calculated over maximum TY velocity; following drug discontinuation and clinical improvement.

TAPSE and S' values showed right ventricular systolic functions elevated from 13 to 20 and from 9 to 14 respectively. sPAP decreased to 65 mmHg at the follow-up after 3 months, and decreased to 45 mmHg at the 6-month follow-up **(Figure 3).**

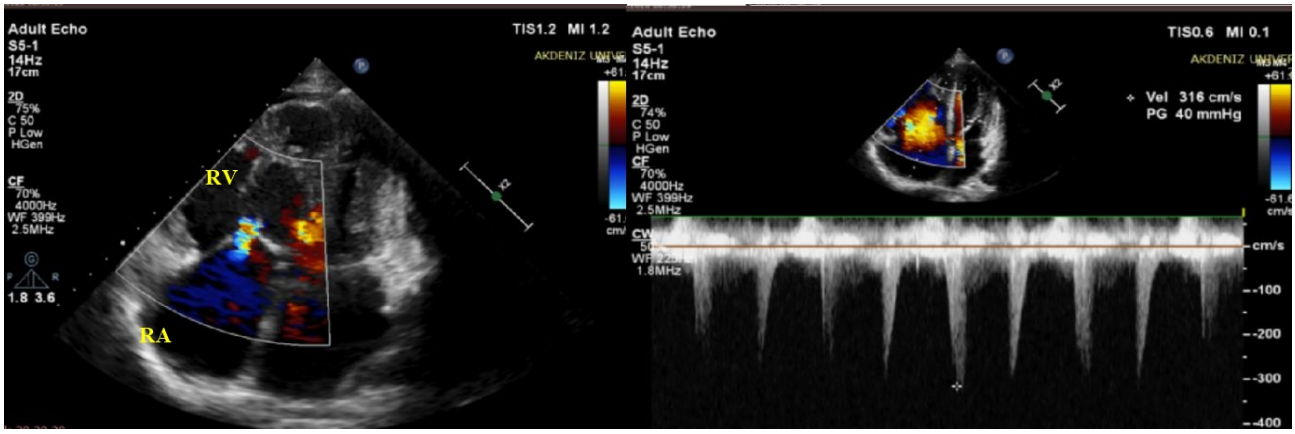

Figure 3: On echocardiography performed at the 3rd month following discharge, mild tricuspid regurgitation and measurement of PAB as 65 mmHg.

Discussion

Dasatinib is one of the second generation tyrosine kinase inhibitors which is preferred in early chronic phase treatment of CML in case of the first-line imatinib treatment failure, insufficient response, intolerance or resistance (3). Although the most common side effects are myelosuppression, nausea, vomiting, diarrhea and skin rash, it may also have serious side effects such as cardiac fluid retention, pleural and pericardial effusion, cardiac dysrhythmia, dysfunction, and pulmonary hypertension. The most common pulmonary toxic adverse effect is pleural effusion, but it usually creates a reversible clinical picture following drug discontinuation (4).

PAH is a chronic and progressive cardio-pulmonary disease that can result from many etiological reasons such as connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis, hereditary causes like BMPR 2 mutation, drug-toxin-related and idiopatic. According to WHO's Updated Clinical Pulmonary Hypertension Classification, these patients are included in group 1 of pulmonary hypertension (5). Hemodynamically it meets the definition of precapillary pulmonary hypertension; mean pulmonary artery pressure (mPAB) above 25 mmHg and PVR is >3 Woods, PCWP and cardiac output are normal (6).

The underlying reason for the development of PAH is the disruption of the mediator balance on the pulmonary arterial wall in the direction of proliferation and vasoconstriction. The activity of serotonin, endothelin-1 and thromboxane increases. They lead to vasoconstrictive and proliferative effects. Since the activity of prostacyclin and nitric oxide decreases, vasodilator and antiproliferative effects decrease. Proliferation develops in intima and adventitia layers of vascular wall, hypertrophy and plexiform structures develop in smooth muscles. Consequently PVR and PAB increases due to in situ thrombosis (2). Because of the specific treatment for these underlying causes, Group 1 PAH patients have the best prognosis as reported in recent studies (7). Although the mechanism of drug-induced PAH remains unclear, it was thought that serotonin might play a role in the generation of this phenomenon (8).

A study in 138 dasatinib-treated patients found increased right ventricular systolic pressure in 18 of them from a median of 29 mmHg at baseline to 42 mmHg, with a return to baseline levels after the discontinuation of the drug (9). Then, in 2012, a study was published 9 case series reporting dasatinib-induced PAH from the French Registry Network. The median delay between initiation of dasatinib and PAH diagnosis was 34 month, suggesting that PAH may be a late complication of dasatinib. The positive mechanism of dasatinib-induced PAH may be hypoxic pulmonar vasoconstruction responses and endotelial cell disfunciton via increased production of reactive oxidants (10).

Conclusion

We reported a case of PAH and heart failure symptoms and signs with dasatinib use. The first-line treatment in drug-related pulmonary hypertension is discontinuation of the drug like our case. PAP may decrease and clinical improvement can be achieved. Spesific treatment methods, such as endothelin receptor blockers may be preferred to accelerate the process at this point. In our case, we stopped the dasatinib drug. The patient did not need specific PHT treatment in the follow-ups. However, it should be kept in mind that in some cases which causes Dasatinib pulmonary hypertension, the situation is irreversible (11). It is reasonable to screen

routinely for PAH by echocardiography before commencing dasatinib treatment, especially in patients with underlying cardiopulmonary disease.

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