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Simultaneously occurred pleural and pericardial effusion related to dasatinib treatment: A case report

Dasatinib tedavisine bağlı eşzamanlı gelişen plevral ve perikardiyal efüzyon: Olgu sunumu

Burak Bursalı [1], Serhat Sayın [1], Ramazan Gökdemir [1]

[1] Department of Internal Medicine, Aksaray University, Aksaray Education and Research Hospital, Aksaray, Turkey

Abstract

Dasatinib is a proven potent tyrosine kinase inhibitor which is used in the newly diagnosed Philadelphia Chromosome (Ph1) positive chronic myeloid leukemia (CML) treatment when there is no hematological and/or cytogenetic response to imatinib treatment. Pleural and pericardial effusions due to dasatinib therapy may be seen 5 to 30 weeks after the onset of the treatment, but may also develop at any time interval. Pleural effusions are frequently bilateral and exudative, and lymphocyte cell dominance is often observed. It has been observed that when dasatinib treatment is stopped, the side effects which occurred with the treatment are greatly regressed. In this article, we present a case with New York Heart Association (NYHA) functional class III dyspnea under the treatment of dasatinib and developed simultaneous pleural and pericardial effusion, which is rare in the literature. Our aim of presenting this case is to emphasize once again the rarity of simultaneous pleural and pericardial effusion development in dasatinib therapy, and the importance of intermittent cardiopulmonary evaluation before and during the treatment of CML patients.

Keywords: Dasatinib, Pleural effusion, Pericardial effusion, Chronic myeloid leukemia

Öz

Dasatinib, imatinib tedavisine hematolojik ve/veya sitogenetik yanıt alınamayan yeni tanı almış Philadelphia Kromozomu (Ph1) pozitif kronik miyeloid lösemi (KML) tedavisinde kanıtlanmış potent bir tirozin kinaz inhibitörüdür. Dasatinib tedavisine bağlı plevral ve perikardiyal efüzyonlar ilacın başlanmasından genellikle 5-30 hafta sonra görülebilmekle beraber, herhangi bir zaman aralığında da gelişebilir. Plevral efüzyonlar sıklıkla bilateral ve eksüda karakterinde olup lenfosit hücre hakimiyeti çoğunlukla gözlenmektedir. Dasatinib tedavisine devam edilmemesi durumunda ortaya çıkan yan etkilerin büyük oranda gerilediği gözlemlenmiştir. Bu yazıda, dasatinib tedavisi altında New York Heart Association (NYHA) fonksiyonel klas III dispne ile başvuran, eş zamanlı plevral ve perikardiyal efüzyon gelişen, literatürde nadir gözlemlenen bir vaka sunuldu. Bu olguyu sunma amacımız, Dasatinib tedavisinde eşzamanlı plevral ve perikardiyal efüzyon gelişiminin nadir görülmesi, tedavi öncesi ve süresince yapılacak aralıklı kardiyopulmoner değerlendirmenin KML hastalarının takibindeki önemini bir kez daha vurgulamaktır.

Anahtar kelimeler: Dasatinib, Plevral efüzyon, Perikardiyal efüzyon, Kronik miyeloid lösemi

Introduction

Chronic myeloid leukemia (CML) and myeloproliferative diseases are clonal malignancies of the hematopoietic stem cell. The Philadelphia (Ph1) chromosome, an important chromosome in CML which was discovered more than 30 years ago, is the chromosome 9-22 translocation of Abelson proto-oncogene (t9: 22). Recently, tyrosine kinase inhibitors (TKI) are being successfully used as a new treatment option as well as isoallogenic bone marrow transplantation and alpha-interferon treatment in the medical treatment of Ph1 positive CML disease [1].

Dasatinib is a second generation TKI and is used in the treatment of patients who does not respond to imatinib treatment and/or cannot tolerate it [2]. Although dasatinib is known to be a well-tolerated agent, side effects such as pleural, pericardial effusion and dyspnea have been frequently observed as a consequence of fluid retention in a number of clinical trials [3].

Corresponding author / Sorumlu yazar:
Burak Bursalı
Address / Adres: Cumhuriyet Bulvarı, Bahçeşehir Sitesi, 1.Etap 5.Blok Daire:3, Aksaray, Türkiye
e-Mail: dr.burakbursali@hotmail.com

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Pulmonary complications, especially pleural effusions, are being encountered as a non-hematologic adverse effect in dasatinib treatment [4]. Recent publications have documented potential and serious cardiac side effects such as pericardial effusion, QT prolongation, arrhythmia, congestive heart failure, myocardial ischemia and myocardial infarction in patients treated with dasatinib [5].

This article is presented due to the sudden and simultaneous development of pleural and pericardial effusion which are serious and important adverse effect that should always be kept in mind in a patient with CML who has been receiving dasatinib therapy for 4 months, also the situation is rarely seen in the literature.

Case presentation

A 50-year-old male patient presented with complaints of significant shortness of breath, dry cough and right sided pain to the emergency department. When the complaints of the patient were questioned, it was learnt that the shortness of breath and its intensity had increased within the last 10 days. The side pain was especially noticeable in the lying position and decreased with sitting and leaning forward. In the history of the patient, he had been diagnosed with CML 3 years ago and received imatinib mesylate treatment for about 2.5 years. Dasatinib 100 mg/day was initiated 18 weeks ago due to the development of resistance and insufficient response to this treatment.

In the physical examination, patient was conscious and general condition was moderate. The patient was agitated and could not lie flat. There was no fever but he was in tachycardia (105/min, rhythmic), hypotension (95/55 mm/Hg) and tachypnea (26/min). In the examination of the cardiovascular system, heart sounds were deep and jugular venous distension was present. In the examination of the lung, respiratory sounds were absent the right middle and right lower zones and they were significantly decreased in the left lower zone. The spleen was 1 cm below the ribs and the traube space was closed in the abdominal examination. Hepatomegaly and peripheral lymphadenomegaly were not detected.

In the laboratory review; leukocyte count was 11500/mm3, hemoglobin was 10.9 g/dL, hematocrit was %33.5, C-reactive protein (CRP) was 23.3 mg/dL (normal range 0-3) and lactate dehydrogenase (LDH) was 291 U/L and troponin I was 0.53 ng/ml. The urine analysis was normal. On the P-A chest X-ray, bilateral pleural effusion, more at the right side compared to th e left side and cardiomegaly were detected (Figure 1).

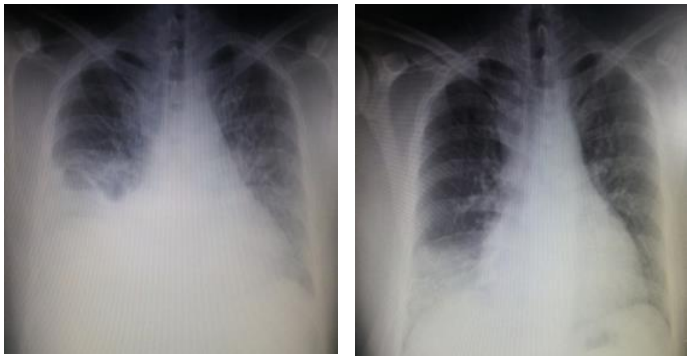

Figure 1: Chest X-ray images of the patient on the 1st day (left image) and after the treatment; on the 12th day (right image)

Bilateral pleural effusion was confirmed by ultrasonography evaluation. Thorax CT revealed a massive pleural effusion extending to the upper quadrant of the right hemithorax and an appearance of effusion reaching a thickness of 3 cm in the intrapericardial space adjacent to the right ventricle. Also, a small amount of pleural effusion was seen in the basal section of the left lung (Figure 2).

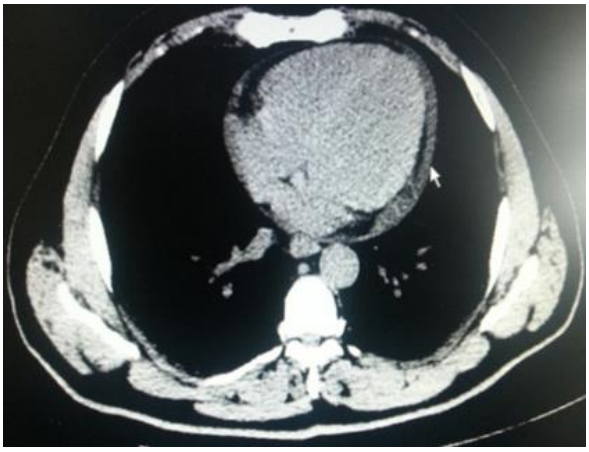

Figure 2**:** Computed tomography of thorax. Appearance of effusion reaching a thickness of 3 cm in the intrapericardial space adjacent to the right ventricle

There was a voltage drop in the electrocardiography of the patient whose troponin I levels were found to be high. There was no evidence of ischemia or arrhythmia. On the 2nd day of the hospitalization, transthoracic echocardiography showed: EF: 55%, pericardial effusion (posterior 14mm, right ventricle 15mm, lateral 11mm) and floating heart appearance without tamponade finding. There was no cardiac valve anomaly. Diagnostic thoracentesis was performed on the right with ultrasound guidance. Pleural effusion fluid obtained via thoracentesis analyzed biochemically. Effusion was found to be exudative according to the Light criteria and lymphocyte dominancy was observed in the microscopic examination (Table 1).

Cytological analysis of the fluid did not reveal malignant cells. ADA level was studied in terms of differential diagnosis of tuberculosis and PCR was performed to reveal Mycobacterium tuberculosis. PCR was negative and ADA level was normal. The levels of ANA, Anti-dsDN, Anti-ssA, Anti-ssB, c-ANCA, p-ANCA, Anti-Cardiolipin IgM and IgG, Anti-RNP, C3 and C4 were also found to be within normal limits for differential diagnosis of collagen connective tissue diseases.

Table 1: Biochemical analysis of the pleural fluid according to light criteria

	Glucose (mg/dl)	LDH (u/l)	Total protein (g/dl)	Albumin (g/dl)
Pleural fluid analysis	177	181	4.1	2.9
Analysis of serum	114	281	7.3	4.1

LDH: Lactate dehydrogenase

The patient's clinical condition was considered to be due to the side effect of dasatinib treatment which is a second-generation tyrosine kinase inhibitor and was administered 18 weeks ago. Dasatinib treatment which was in progress was stopped. Furosemide 80 mg/day and indomethacin capsule 3x25 mg treatments were started. After the treatment started, the patient's symptoms such as shortness of breath and side pain

quickly recovered. On the 12th day of treatment, control chest X-ray showed a significant regression in pleural effusion on the right side (Figure 1). Control echocardiography performed on the 7th day of treatment showed an EF of 48% and hypokinesia with mild mitral and tricuspid insufficiency on apical sections of anteroseptum. The pericardial effusion with a diameter of 0.5 cm in front of the right atrium and ventricle was detected and the effusion decreased severely when compared with the previous ECO findings. The patient who was treated for 14 days and had a rapidly improved clinical condition was discharged with the suggestion of polyclinic control.

Discussion

CML is a disease characterized by Philedelphia chromosome which is a result of translocation on chromosomes 9 and 22. The resulting BCR-ABL fusion gene plays an important role in the pathogenesis of the disease by encoding the tyrosine kinase. Dasatinib is an effective tyrosine kinase inhibitor and has been successfully used at all stages of CML therapy and in the treatment of Ph positive acute lymphoblastic leukemia (ALL) [6].

Dasatinib is a multi-targeted tyrosine kinase inhibitor with effects on many receptors besides BCR-ABL, including platelet-derived growth factor receptor (PDGFR), Src, discoidin domain receptor and c-kit. Studies have shown that ABL inhibition is about 300 times stronger when compared to imatinib [2].

Pleural effusions are detected in about 10-20% of patients under dasatinib therapy, but mostly in 5-28th weeks of the treatment. Particularly at higher doses (140 mg/day) and in patients receiving twice-a-day dosing, significantly higher rates were observed. Several risk factors such as advanced age, acute or blastic phase of the disease, long-term therapy, arterial hypertension, hypercholesterolemia and accompanying autoimmune diseases are also known to be responsible in the development of pleural effusion [7,8].

Dasatinib-related pleural effusions are bilateral in 79% of patients and are usually exudative. Lymphocyte cell dominance is seen in fluid analysis, bronchoalveolar lavage and pleural biopsies. In the majority of these cases, pulmonary symptoms were regressed within 1 week after the drug withdrawal and did not recur after starting on low dose dasatinib therapy in 3 out of 4 cases [9,10].

In a case study involving 13 CML patients who received low dose (50-100 mg / day) dasatinib treatment, 4 patients developed pleural and/or pericardial effusion and fluid accumulation of the two was in the level of life-threatening grade III/IV. In addition, those four patients had no history of any cardiac or pulmonary [11].

In this case we reported, Dasatinib 100 mg/day treatment, started due to inadequate response to high dose imatinib treatment. The patient had no history of heart and/or lung diseases. The patient underwent routine blood tests with short periods while under Dasatinib treatment and monthly evaluated with chest x-rays and ECG's. However, our patient was admitted to our hospital with dyspnea and clinical deterioration on the 18th week after the onset of treatment. Dasatinib treatment was stopped. Tuberculosis, malignancy and collagen connective tissue diseases were considered to be preliminary in terms of differential diagnosis. These diseases were excluded as a result of the performed clinical evaluations. Pleurodesis was not considered as an option because the patient responded to treatment and fluid collection decreased rapidly.

In conclusion, since dasatinib is an effective treatment option that has an increased usage day by day in the treatment of CML, the side effect profile should be well known especially by the clinician following the patient. The cases should be well analyzed in terms of comorbid factors and potential risks before treatment and should be followed closely with periodic cardiac and pulmonary examinations during treatment.

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