Case Report

A Rare Case of Late Presentation of Dasatinib-Induced Cardiopulmonary Toxicity

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Abstract

Tyrosine kinase inhibitors (TKI) (imatinib, dasatinib, and nilotinib) are used for the treatment and long-term control of chronic myeloid leukemia (CML). TKIs rarely cause systemic side effects with atypical presentations, and these must be borne in mind while prescribing these drugs over a prolonged period. Dasatinib-induced cardiopulmonary toxicity should be suspected in patients presenting with new-onset cardiac or pulmonary symptoms, with features of congestive cardiac failure and pulmonary infiltrates. We report a rare presentation of simultaneous occurrence of pleural effusion, interstitial pneumonitis, pulmonary hypertension, and heart failure in a CML patient on dasatinib for >6 years, which was successfully treated with discontinuation of the drug and oral steroids.

Keywords: Cardiopulmonary toxicity, chronic myeloid leukemia, tyrosine kinase inhibitors

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by reciprocal translocation t(9;22) (q34;q11) called the Philadelphia (Ph) chromosome, leading to constitutively elevated tyrosine kinase enzyme activity.^[1] In the 20th century, CML was treated primarily with radiotherapy, cytotoxic drugs, interferon, or allogeneic hematopoietic stem cell transplantation. Introduction of imatinib, a first-generation tyrosine kinase inhibitor (TKI) in 2001, revolutionized the treatment of CML. Subsequently, second-generation TKIs, dasatinib, and nilotinib, were approved for patients with imatinib intolerance or resistance and newly diagnosed CML.^[2]

TKIs are generally well tolerated, most side effects are mild, and patients rarely require interruption of treatment. Dasatinib rarely causes interstitial pneumonitis, pulmonary hypertension, and heart failure.^[3]

We present a case of CML who developed severe cardiac and pulmonary toxicity after 6 years of its use, which responded well to the withdrawal of dasatinib and oral steroids.

CASE REPORT

In 1998, a 33-year-old male patient, who presented with anemia, leukocytosis, massive splenomegaly, and presence

of Ph chromosome, was diagnosed as CML in chronic phase (CP). He received treatment sequentially with interferon, hydroxyurea, and cytarabine until 2003, without molecular monitoring. From 2008 to 2013, he received oral imatinib 400 mg once daily. On reassessment in 2013, he had persistent splenomegaly (4 cm), incomplete hematological response, and poor molecular response, with imatinib resistance mutation analysis revealing F317 L mutation suggestive of failure of response to imatinib.^[4] Given the lack of suitable donor for allogeneic hematopoietic stem cell transplantation, he was started on oral dasatinib 100 mg once daily.

In 2019, he (54 years old) presented with fever, dyspnea, and dry cough of 2-week duration. He had tachycardia, tachypnea, pallor, elevated jugular venous pressure, and pedal edema; splenomegaly; impaired percussion note; diminished breath sounds; and fine crackles in the bilateral infrascapular, infra-axillary, and interscapular areas. Pulse oximetry showed 93% saturation on room air with exercise-induced

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desaturation to 87% on 6-min walk test (6MWT) with distance covering 112 m. The differential diagnoses considered were infections (bacterial pneumonia or tuberculosis); CML in accelerated phase or blast crisis; and dasatinib-induced lung toxicity. His hemoglobin level was 10.6 g/dL, total leukocyte count was 12,700/mm³, and platelet count was 386,000/mm³. Erythrocyte sedimentation rate was 72 mm fall in the 1st h. The bone marrow was consistent with CML-CP, tuberculin test (10 TU) was negative, and sputum was negative for acid-fast bacilli (AFB). Chest radiograph [Figure 1] revealed bilateral pleural effusion with reticular infiltrates in the mid zones. High-resolution computed tomography chest [Figure 2] showed bilateral ground-glass opacities and patchy consolidation in the right lower lobe with bilateral pleural effusion. Spirometry showed severe restriction (forced vital capacity 1.2 L, 35% predicted) and moderately reduced diffusing capacity of the lungs for carbon monoxide (DLCO) (43% predicted). The pleural fluid analysis was exudative (lactate dehydrogenase 389 U/L, proteins 4.8 g/dL), lymphocyte predominant, and negative for malignant cells. Pleural fluid AFB, Gram stain, and *Mycobacterium tuberculosis*-polymerase chain reaction were negative, and adenosine deaminase was 20.4 U/L. Bronchoscopy and bronchoalveolar lavage (BAL) showed predominantly lymphocytes and were negative for malignant cells and AFB. Microbiological investigations for bacterial, mycobacterial, and fungal infection were negative on BAL. Transbronchial lung biopsy revealed fibroblastic plugs in the alveoli with interstitial fibrosis and moderate lymphoplasmacytic infiltration in the interstitium, suggestive of organizing pneumonia pattern [Figure 3]. The histopathological picture of organizing interstitial pneumonia and negative microbiological workup confirmed the diagnosis of dasatinib-induced interstitial pneumonitis and bilateral pleural effusion. Echocardiography revealed global hypokinesia with left ventricle ejection fraction of 35%, moderate tricuspid regurgitation, pulmonary hypertension with right ventricular systolic pressure (RVSP) of 60 mmHg, and no pericardial effusion.

Dasatinib was stopped, and he was treated with oral steroid (tablet prednisolone 30 mg once daily) for 6 weeks followed by gradual tapering over the next 6 weeks. The patient had a remarkable recovery; the opacities cleared on the repeat chest radiograph [Figure 4] and the pleural effusion resolved. Follow-up echocardiography done after 3 months showed regression of pulmonary hypertension (RVSP 30 mmHg) and improvement in ejection fraction to 55%. He was initiated on oral nilotinib 300 mg twice daily, which was well tolerated, and the hematological parameters remained stable.

DISCUSSION

Dasatinib-induced interstitial pneumonitis is a rare entity. The presentation may mimic atypical pneumonia, with bilateral pulmonary opacities, septal thickening, and ground-glass opacities on imaging.^[5] Pneumonitis reported with dasatinib

Figure 1: Chest radiograph posteroanterior view at admission: bilateral middle and lower zone nodular infiltrates with pleural effusion

Figure 2: High-resolution computed tomography thorax showing ground-glass opacity and patchy consolidation in the right lower lobe with bilateral pleural effusion

Figure 3: Transbronchial lung biopsy (histopathological examination) showing interstitial pneumonitis (organizing pneumonia, x300)

Figure 4: Chest radiograph posteroanterior view after 6 weeks of treatment showing the complete clearing of pulmonary infiltrates and effusions

occurred at a median period of 229 days (range, 20–510 days) after initiation of treatment^[5] Lymphocytes were predominant in pleural and BAL fluid. The mechanism of systemic toxicity of dasatinib is proposed to be due to off-target tyrosine kinase inhibition or immune-mediated damage in the lung. In the study done by Bergeron *A et al.* None of the patients underwent bronchoscopic biopsy and pleural biopsy was done in a few patients. The pleuro-pulmonary manifestations subsided after dasatinib was stopped in the majority and only one of the nine cases required steroids. No recurrence was seen in 75% of patients after reintroduction at a lower dose of 40 mg twice daily.^[5] Our patient was on 100 mg once daily for 6 years, which is the longest time in literature review for developing this complication of interstitial pneumonitis. Moreover, bronchoscopic lung biopsy showed organizing pneumonia, which is one of the characteristic patterns of drug-induced lung injury, and the lesions resolved with oral steroids.^[5,6]

The 6MWT is a good index of physical function and therapeutic response in patients with chronic lung disease. Healthy controls can typically walk 400–700 m. The magnitude of desaturation and timing of heart rate recovery have been associated with clinical outcome. In this case also, the patient had desaturation on room air with reduction in distance walked.

Dasatinib-induced pleural effusion is relatively common, with an incidence of 35% noted in a series by Quintás *et al.*^[7] The median time to onset was 5–28 weeks, however it can occur even years after exposure to the drug. Increased incidence was also associated with higher doses (140 mg daily) and a twice-daily dosing schedule. Management must be based on the severity of pleural effusion, with Grade 1 (asymptomatic) effusion, detected by routine chest radiograph, requiring only close monitoring. In patients with Grade 2–3 pleural effusion (involving 11%–50% of the thorax on chest radiograph), dasatinib therapy must be discontinued and a short course of diuretics with oral steroids is required. In patients with massive or recurrent effusions, thoracentesis and indwelling thoracostomy catheter may be necessary.^[7] In our patient, there was mild-to-moderate

bilateral pleural effusion which responded well to the withdrawal of the culprit drug.

Dasatinib-induced pulmonary hypertension is a rare complication. Its incidence was found to be <0.45% and usually occurs as a late complication after 8–48 months of exposure.^[8,9] The majority of patients had improved after the withdrawal of dasatinib, however some had persistent symptomatic pulmonary hypertension even several months later. Re-challenge with dasatinib must be avoided in patients who develop pulmonary hypertension and nilotinib is considered safe for such patients.^[5]

Other rare adverse effects of dasatinib include arrhythmias, pericardial effusion, and congestive cardiac failure, which are seen in <1%.^[10] Our patient had global hypokinesia with moderate left ventricular dysfunction, which recovered after stopping the drug, indicating direct cardiac toxicity of dasatinib in addition to reversible pulmonary hypertension.^[9] In patients who do develop heart failure, the management of heart failure status should not be guided by the patient's cancer status.

The majority of adverse events occur initially early in the course of treatment, however the onset of some toxicities, including significant cardiopulmonary toxicity, may be delayed months or years after the initiation of therapy.^[9,10] In this case report, the patient presented with all the adverse effects after a prolonged period of 6 years, which makes the case unique. Simultaneous presentation of pulmonary hypertension, pleural effusion with pulmonary infiltrates, and worsening left ventricular dysfunction is not described in the literature. Each TKI has a distinct toxicity profile with specific cardiovascular, pulmonary, and metabolic adverse effects, and it is, therefore, important to evaluate baseline risk factors for certain adverse effects before treatment initiation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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