Annals of Clinical Case Reports

Case Report
Published: 01 Aug, 2017

Chylothorax and Pulmonary Arterial Hypertension after Treatment with Dasatinib: A Case Report

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Abstract

Introduction: Dasatinib, a tyrosine kinase inhibitor, is first line treatment for patients with Chronic Myelogenous Leukemia (CML). PAH and chylothorax are rare complications of Dasatinib and have not been reported to occur simultaneously. We report a patient with chylothorax and PAH after 4 years of Dasatinib use.

Case Presentation: A 44 year old female complained of exertional dyspnea of 1 month, right chest discomfort, and nonproductive cough. Her exercise tolerance, unlimited 2 months prior, had declined to 1 block. She was treated for CML with Dasatinib 100mg once daily from 2012 to 2016 when she presented with dyspnea. Chest radiograph showed a large right pleural effusion, new since her last radiograph 8 months before. Computerized tomography with angiography showed large pleural effusion, parenchymal ground glass opacities, foci of septal wall thickening, no pulmonary embolism, and no hilar/mediastinal lymphadenopathy. Thoracentesis and transthoracic echocardiogram (TTE) were performed. Pleural fluid studies revealed a sterile chylous lymphocytic exudate and TTE showed basal right ventricular hypokinesis with tricuspid regurgitation jet max velocity estimated Pulmonary Artery Systolic Pressure (PASP) of 80 mm Hg (severe PAH), normal left ventricular function and normal left atrial pressure. Dasatinib was stopped. To relieve dyspnea, thoracentesis was repeated 13 and 27 days later. On day 169 imatinib was started and one month later (day 201), her chest radiograph revealed no infiltrates or effusions. On day 349 our patient's transthoracic echocardiogram demonstrated estimated PASP 30 mmHg.

Discussion: Exudative pleural effusion as a complication of Dasatinib typically occurs within the first 6-12 months of bi-daily use. Chylothorax and PAH are rare complications not previously described to occur simultaneously. Temporal recovery after Dasatinib discontinuation is not known.

Conclusions: Our patient's uniqueness derives from a) simultaneous development of chylous pleural effusion and PAH, b) after four years of c) once daily use dasatinib d) and her early recovery following dasatinib discontinuation. Within 6 months of dasatinib discontinuation, her pulmonary hypertension improved substantially, her pleural effusion resolved completely, and she is now symptom free.

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Received Date: *18 May 2017*
Accepted Date: *31 Jul 2017*
Published Date: *01 Aug 2017*

Citation:
Chua AT, Cleven KL, Wharton R, Appel DW. Chylothorax and Pulmonary Arterial Hypertension after Treatment with Dasatinib: A Case Report. Ann Clin Case Rep. 2017; 2: 1408.

ISSN: 2474-1655

Introduction

Dasatinib, a tyrosine kinase inhibitor, is first line treatment for patients with Chronic Myelogenous Leukemia (CML). Dasatinib is a break point cluster – ABL gene (BCR-ABL) inhibitor that has 325-fold higher potency in vitro compared with imatinib against engineered cell lines expressing non-mutant BCR-ABL, and inhibitory activity against the majority of imatinib-resistant BCR- ABL mutants. Pulmonary artery hypertension (PAH) and chylothorax are rare complications of dasatinib and have not been reported to occur simultaneously. We report a patient with chylothorax and PAH after 4 years of dasatinib use.

Case Presentation

A 44 year old woman complained of worsening exertional dyspnea over 1 month, right chest discomfort, and nonproductive cough. Her exercise tolerance, unlimited 2 months prior, was now limited to 1 block. She was treated for CML with dasatinib 100mg once daily from 2012 to 2016 when she presented with dyspnea. Her exam revealed dullness with egophony over the right lung from base to scapula. Chest radiograph showed a large right pleural effusion, new since her last radiograph 8 months before. Computerized tomography with angiography revealed large pleural effusion, parenchymal ground glass opacities, foci of septal wall thickening, no pulmonary embolism,

and no hilar or mediastinal lymphadenopathy. Thoracentesis and transthoracic echocardiogram (TTE) were performed. Pleural fluid studies revealed a sterile chylous lymphocytic exudate and TTE showed basal right ventricular hypokinesis with tricuspid regurgitation jet max velocity estimated Pulmonary Artery Systolic Pressure (PASP) of 80 mm Hg (severe PAH) (Table 1), normal left ventricular function and normal left atrial pressure.

Dasatinib was stopped.

Initially our patient's dyspnea improved, however, she returned with dyspnea and recurrent pleural effusion 11 days later. A repeat thoracentesis showed an exudative pleural effusion with decreasing triglyceride and lymphocyte concentrations. TTE at that time estimated PASP 60 mm Hg (moderate PAH). Twenty seven days after initial presentation she returned with dyspnea and a third thoracentesis was performed that demonstrated persistent exudative pleural effusion with further decline in triglyceride and lymphocyte concentrations. From the first day dasatinib was discontinued (day 1), she was monitored. Table 1 presents pertinent clinical features. Respectively, on days 97 and 120 the estimated PASP had declined to 39 mmHg and the chest radiograph revealed complete resolution of the pleural effusion. On day 169 imatinib was started and one month later (day 201), her chest radiograph revealed no infiltrates or effusions. On day 349 our patient's transthoracic echocardiogram demonstrated estimated PASP 30 mmHg.

Discussion

Between June 2006- December 2010 Bristol-Myers Squibb identified 51 cases of pulmonary artery hypertension (PAH) (right heart catheterization confirmed) after initiation of dasatinib therapy [1]. Exudative pleural effusion has been reported as a complication of dasatinib [2]. Chylothorax rarely has been a complication of dasatinib use [3]. We are unaware of chylothorax and pulmonary artery hypertension occurring simultaneously in a patient taking dasatinib. Importantly, temporal recovery of chylothorax and PAH after dasatinib discontinuation has not been carefully described. There are no reports of recovery occurring sooner than 15 months. The description of our patient's serial recovery following dasatinib discontinuation and her recovery sooner than 15 months are features that previously have not been reported.

CML itself has also been cited as a cause of PAH [4]. Because our patient seemingly developed PAH only after dasatinib use, chest computed tomography angiogram revealed no pulmonary emboli, and the severity of PAH declined after dasatinib was discontinued, we believe her PAH resulted from dasatinib use and not from CML or pulmonary emboli.

The exact mechanism of dasatinib associated pleural effusion development is unknown. Brixey et al. [5] reported a review of all incident dasatinib associated pleural effusions published from 2006-2010. They found these effusions were lymphocyte predominant exudates, suggesting an immune-mediated mechanism and rendering cardiac or renal dysfunction of less likely etiology. Typically, these effusions occurred within 6-12 months of bi-daily use of dasatinib. While our patient's pleural effusion was a lymphocyte predominant exudate, she differed from previous cases in that she developed a chylous exudate after four years of once daily use of dasatinib.

A chylous pleural effusion is diagnosed by the presence of chylomicrons, and suggested by a triglyceride concentration of >110mg/dL. Chyle leak results from microscopic disruptions in the lymphatic network. Dasatinib, a tyrosine kinase inhibitor, has activity against platelet derived growth factor (PDGFR). Off-target kinase inhibition has been posited as a possible mechanism for dasatinib related pleural fluid development given its PDGFR-beta receptor effect on postnatal angiogenesis, lymphangiogenesis, and interstitial fluid pressure regulation [6]. Thus, chylothorax associated with dasatinib use may be related to microvasculopathy associated with a protein leak.

From 2006-2010, the French Pulmonary Hypertension Registry showed among all patients with CML treated with tyrosine kinase inhibitor (TKI), only those treated with dasatinib developed PAH (N=9). Pulmonary Artery Hypertension occurred after 8-48 months of dasatinib use [7]. The cases from the French registry of dasatinib associated PAH were characterized by rapid clinical, hemodynamic, and functional improvements in 8 patients within 4 months of discontinuing dasatinib. The mechanism of the association has not yet been determined. Guignabert et al. [8] recently published a study in rodents demonstrating that chronic dasatinib therapy can induce direct endothelial toxicity. The same study also found that dasatinib-induced apoptosis in cultured human endothelial cells causing endothelial dysfunction and vascular damage. They posit that dasatinib causes pulmonary vascular damage which may lead to increased susceptibility to pulmonary hypertension development. Further studies are needed, however, to validate this concept and to elucidate how much pulmonary vascular injury leads to PAH. The above literature review instructs us that mechanistically dasatinib-induced chylothorax and PAH typically develop independently. Part of our patient's uniqueness relates to her having both these disorders simultaneously. Perhaps Guignabert et al. [8] and Goldblatt et al. [6] work should be viewed as complementary. While Guignabert et al. [8] did not report chylous pleural effusions in their rodent studies, their observations still may be pertinent to our patient. Dasatinib may have-induced simultaneous apoptotic injury to both pulmonary vessels and lymphatics resulting in PAH and chylous pleural effusion. The development of pleural effusion with regional lung hypoxemia may have facilitated the development of PAH. Quintás-Cardama et al. [9] reported 48 patients with dasatinib-induced pleural effusions. Eighteen of these had TTE measurements that showed mild PAH (median 42 mmHg) that seemingly developed with the onset of the effusion. Both pleural effusion and PAH resolved with discontinuation of dasatinib. They did not report the nature of the effusion among those that developed PAH. In our patient, the effusion was chylous, the PAH was severe, and both resolved with dasatinib discontinuation.

The management of chylous pleural effusions and pulmonary hypertension in patients with these dasatinib-associated adverse effects has included reduction or complete cessation of the drug. Brixey et al. [5] have proposed a management algorithm for dasatinib related pleural effusions based on severity of pleural effusions as defined by National Cancer Institute (NCI) guidelines. However, the appropriateness of their recommendations focused on management of the dasatinib-induced pleural effusions, may apply only to those with pleural effusion who lack PAH. Our patient instructs us that diagnosis of dasatinib related chylous pleural effusions merits assessment for PAH, which, if present, would warrant discontinuation of the drug.

Our patient's uniqueness derives from a) simultaneous development of chylous pleural effusion and PAH, b) after four

years of c) once daily use dasatinib d) and her early recovery following dasatinib discontinuation. While after initial thoracentesis her dyspnea-producing pleural effusion reaccumulated rapidly over the next 3 weeks, pleural fluid lymphocyte and triglyceride concentrations and PASP had already started to decline. Within 6 months of dasatinib discontinuation, her pulmonary hypertension improved substantially, her pleural effusion resolved completely, and she is now symptom free.

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