Case Report

Dasatinib-induced chylothorax in a patient with chronic myeloid leukemia:
A Case Report

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SUMMARY
We report the case of a 51-year old man suffering from chronic myeloid leukemia for the past 20 years who presented in our department with a newly onset of cough and shortness of breathing. A chest X-ray revealed bilateral pleural effusions. A diagnostic thoracentesis under ultrasound guidance was performed and the fluid analysis revealed a high concentration of triglycerides both at the right (927 mg/dl) and left side (1,232 mg/dl). Based on Light's criteria the fluid was classified as an exudate with a predominance of lymphocytes at both sides. For the last 7 years, the patient was treated with dasatinib, an oral tyrosine kinase inhibitor which is associated with plenty of cases of chylotoraces in the literature. Dasatinib was stopped and the patient underwent strict dietary restrictions with oral fastening and parenteral nutrition. A new chest-X ray 2 months later revealed a fast completely remission of the effusions.
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INTRODUCTION

Chylothorax typically results from disruption of the normal lymphatic flow, such as insult to the thoracic duct, causing leakage of lymphatic fluid into the thoracic cavity. The etiology of chylothorax can be classified into two main categories, non-traumatic and traumatic chylothorax. Traumatic chylothorax, particularly postoperative chylothorax, accounts for more than 50% of all cases described in the literature[1]. Malignancy-induced thoracic duct obstruction is the leading cause of non-traumatic chylothorax, with most malignancies being lymphomas (70% of which are Hodgkin lymphomas)[2]. Treatment for chylothorax includes conservative measures (total parenteral nutrition, pleural drainage, and pleurodesis) and surgery (thoracic duct ligation). Conservative treatment aims to reduce chyle flow and to drain the pleural cavity in an effective manner[3].

CASE PRESENTATION

A 51- year-old man arrived at the Emergency Department complaining of a gradually worsening dry cough and shortness of breath for the past 2 weeks. The patient also reported anorexia, malaise and myalgia. He used to walk 2 to 3 km per day without any difficulty, however nowadays he would get short of breath walking less than 300m. He had been hospitalized for 7 days in a district hospital due to dry cough 3 days prior to this day. He had been diagnosed there with a lower respiratory tract infection and treated with antibiotics (2g ceftriaxone twice a day and 300 mg clindamycin once daily) and bronchodilators (500μg ipratropium bromide four times a day and 0.5 mg budesonide twice a day). The patient had been diagnosed with chronic myeloid leukemia (CML) 20 years ago. He has been on 70 mg dasatinib twice a day for the last 7 years, which he has tolerated well so far. He claimed to be a non-smoker.

During the physical examination, the patient was haemodynamically stable and his oxygen saturation was good (94% on breathing ambient air). He had a pulse rate of 80 beats per minute with a sinus rhythm on ECG, blood pressure of 110/60 mm Hg, temperature of 37° C and respiratory rate of about 28 breaths per minute. The findings of the lung auscultation were decreased breath sounds in the left base and diminished lung sounds in the right lower lobes. Physical examination on the other systems did not reveal any further problems.

The laboratory results showed white blood count of 12,350 cells/mm^3 (neutrophils=76.1%, lymphocytes=14.6%, monocytes=7.9%). CRP level was 1.6 mg/dl and ESR was 36mm. A chest X-ray was performed and revealed bilateral pleural effusion, more prominent on his right side. A subsequent chest Computed Tomography (CT) confirmed a large right pleural effusion and a small amount of pleural effusion at the left side, both causing atelectasis in the lower lobes. No mediastinal, hilar or axillary lymphadenopathy was discovered.

Furthermore, a diagnostic thoracentesis was performed with ultrasound guidance. The procedure revealed a thick milky pleural fluid from both sides. Pleural fluid analysis of the right side showed a cell count of 3,000 cells/μl with a predominance of lymphocytes, a lactate dehydrogenase level of 171 U/l, glucose of 107 mg/dl, protein of 4.66 g/dL, amylase of 48 U/L, triglycerides of 927 mg/dL, a pH of 7.4 and adenosine deaminase of 12 U/L. As for the left pleural effusion, the results of the thoracentesis were: cell count = 3,800 cells/μl with a predominance of lymphocytes, lactate dehydrogenase = 162 U/l, glucose = 109 mg/dl, protein = 4.37 g/dL, amylase = 40 U/L, triglycerides = 1232 mg/dL and pH 7.45. According to Light's criteria, the fluid from both sides was exudative.

The cultures of the fluid bilateral were negative for bacteria and fungus as well as the gram stain; tuberculosis was excluded. In addition, the cytology test of the pleural effusion found a small number of lymphocytes, macrophage and mesothelial cells. There was no evidence of malignancy.

Based on the clinical features, the pleural fluid's milky appearance and its high level of triglycerides, the diagnosis of chylothorax was reached. Following the patient's admission to the pulmonary department, a large bore catheter was placed in the right side for fluid drainage. Moreover, due to the advantages of reduced dietary intake on our patient's condition, parenteral nutrition was solely given. Finally, based on the suspicion that the cause of chylothorax was in fact dasatinib, it was immediately discontinued in consultation with the patient's leukemia treating physician.

The catheter's placement resulted in improvement of the patient's dyspnea. About 1.5 L of milky chylous pleural fluid was drained and the chest drain could be removed after 3 days. In the meantime, he developed large pleural effusion on the left side as well. The patient remained under observation for 7 days, without perceiving any medication till a repeat chest X – ray showed a significant improvement in his pleural effusion bilaterally. Therefore, he was dismissed from the pulmonary department and

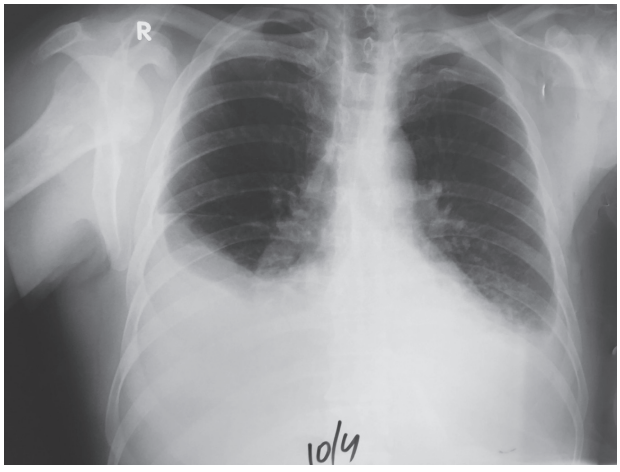

FIGURE 1. Initial chest X–ray demonstrates bilateral pleural effusion, more prominent at the right side.

was advised to follow a low – fat diet program.

A fast-complete remission of the pleural effusion bilaterally was noted at follow up (1 month and 2 months after hospitalization). The patient was also evaluated from his leukemia treating physician. Dasatinib was permanently discontinued and replaced by nilotinib. Currently, the patient continues to follow up with our pulmonary and oncology departments and reports no symptoms regarding his therapy.

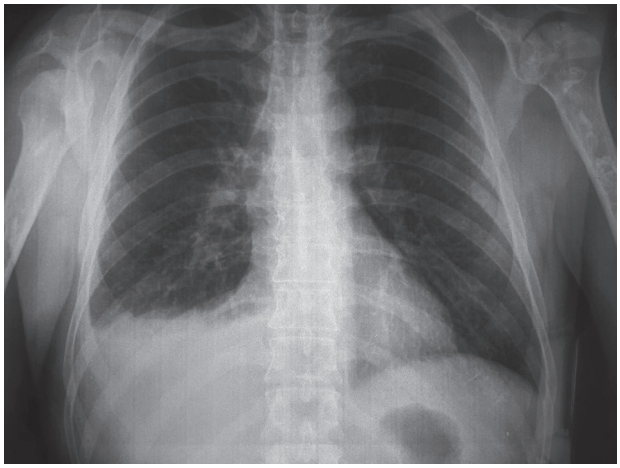

FIGURE 2. Chest X–ray at follow – up one month later reveals complete remission of the pleural effusion at the left side and a small amount of pleural effusion at the right side.

DISCUSSION

Here we present a rare case of dasatinib-induced chylothorax in a patient with CML. The patient's history and thorough workup, including a CT scan of the chest, did not suggest any other possible etiology. The chronic treatment with dasatinib was immediately interrupted after agreement with the patient's leukemia treating physician. A large bore catheter was inserted in the pleural cavity in order to drain the chylous effusion. In the meantime, special dietary modifications including fasting and systematically parenteral nutrition were applied. The patient was dismissed from our department clinically improved and went home with instructions to avoid oral food lipids intake. The reevaluation of the patient with a chest X-ray 1 and 2 months later revealed a fast complete remission of the effusion. To our knowledge, dasatinib is the only pharmaceutical agent that is associated with the induction of a chylothorax[5,6] Dasatinib is a second-generation potent and efficacious oral tyrosine kinase inhibitor, frequently used for *BCR-ABL*–positive chronic myeloid leukemia (CML) and for Philadelphia chromosome–positive acute lymphocytic leukemia[6]. Pulmonary

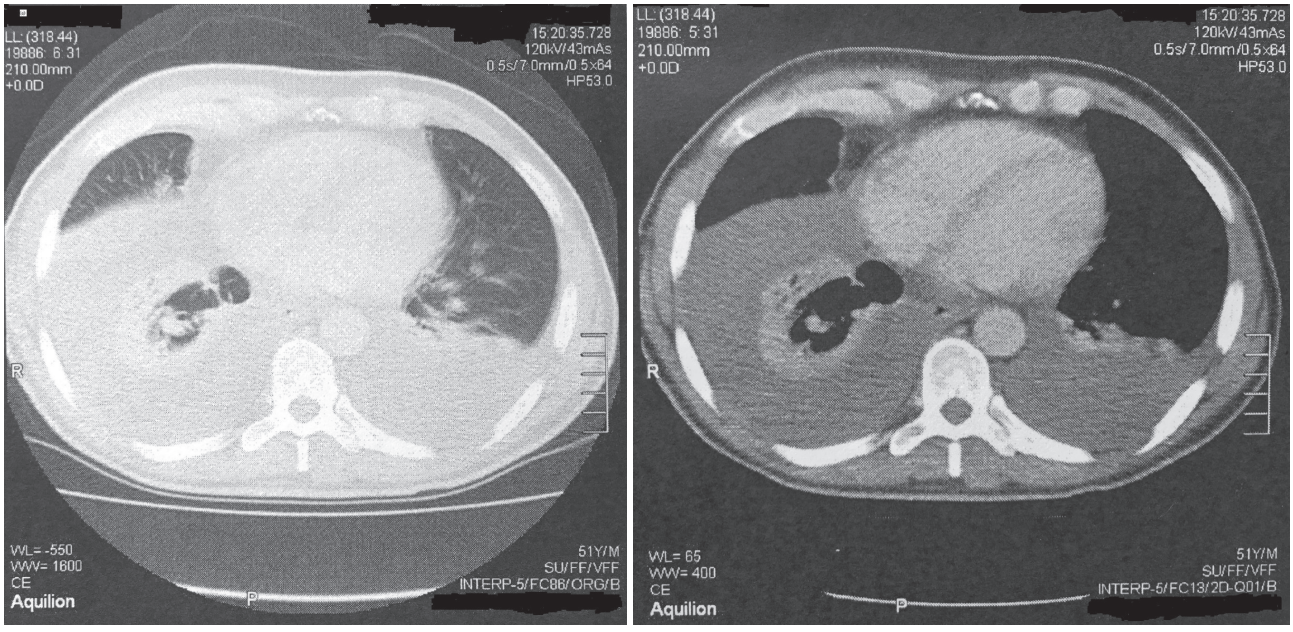

FIGURE 3. Chest CT demonstrates a large right pleural effusion and a small amount of pleural effusion at the left side, both causing atelectasis in the lower lobes.

adverse events are reported in about 35% of patients. The most common pulmonary abnormalities associated with dasatinib include pleural effusion, pulmonary hypertension, and parenchymal opacities. Dasatinib-related chylothorax is an uncommon pulmonary adverse event and the mechanism via which chylothorax is provoked is not fully understood[5]. Various factors have been associated with the appearance of dasatinib-associated chylothorax. The prescription of a single dose (140 mg) per day is associated with a significantly lower number of chylothoraces and pleural effusions generally than those who receive 70 mg twice a day[7]. Initial efforts should be focused on treating the chylothorax by attempting dose reduction as opposed to discontinuing dasatinib altogether. In addition, the use of short-term steroids and diuretics has also been shown to be helpful[8]. There are no firm guidelines to establish when to switch from one kind of treatment to another.

ΠΕΡΙΛΗΨΗ

Χυλοθώρακας οφειλόμενος στη λήψη dasatinib σε ασθενή με Χρόνια Μυελογενή Λευχαιμία: Παρουσίαση περιστατικού

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Παρουσιάζουμε την περίπτωση ενός 51χρονου άνδρα που πάσχει από χρόνια μυελογενή λευχαιμία κατά τα τελευταία 20 χρόνια και προσήλθε στο τμήμα μας λόγω βήχα και αισθήματος δύσπνοιας από ημερών. Η ακτινογραφία θώρακα ανέδειξε υπεζωκοτική συλλογή αμφοτερόπλευρα. Διεξήχθη διαγνωστική παρακέντηση του υπεζωκοτικού υγρού με υπερηχογραφική καθοδήγηση και η βιοχημική ανάλυση του πλευριτικού υγρού αποκάλυψε υψηλή συγκέντρωση τριγλυκεριδίων τόσο δεξιά (927 mg/dl) όσο και αριστερά (1232 mg/dl). Με βάση τα κριτήρια του Light το υγρό ταξινομήθηκε ως εξίδρωμα λεμφοκυτταρικού τύπου αμφοτερόπλευρα. Κατά τα τελευταία 7 χρόνια ο ασθενής λάμβανε θεραπεία με dasatinib, έναν από του στόματος αναστολέα της τυροσινικής κινάσης που έχει συσχετιστεί με μεγάλο αριθμό περιπτώσεων χυλοθώρακα. Η λήψη dasatinib διακόπηκε και ο ασθενής τέθηκε σε αυστηρούς διαιτητικούς περιορισμούς με διακοπή σίτισης per os και παρεντερική διατροφή. Μια νέα ακτινογραφία θώρακα 2 μήνες αργότερα ανέδειξε ταχεία πλήρη υποχώρηση των πλευριτικών συλλογών.

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Λέξεις - Κλειδιά: *Χυλοθώρακας, dasatinib, Χρόνια Μυελογενής Λευχαιμία*

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