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A case of severe respiratory distress in a patient with chronic myeloid leukemia receiving dasatinib

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Abstract

***Introduction*: Dasatinib is a multi-kinase inhibitor used primarily in the treatment of chronic myeloid leukemia (CML). The major reported side effects are pleural effusion, pulmonary hypertension, and severe infection. The most common infection among these patients is pneumonia. Here, we present a case of severe respiratory failure in a patient with CML who was taking dasatinib.**

***Case presentation*: A 75-year-old male with CML, hypertension, hyperlipidemia presented to the emergency department with progressively worsening shortness of breath and hemoptysis for one week. The patient's CML had been well controlled with dasatinib since his diagnosis two years ago, and the most recent BCR-ABL1 assay was undetectable. Computed tomography (CT) of the chest revealed diffuse ground glass opacity with superimposed interlobular septal thickening and intralobular lines ("crazy-paving pattern") and a moderate-sized right pleural effusion. Therapeutic thoracentesis yielded 1.8 l of lymphocyte predominant, exudative pleural effusion. Pneumocystis jirovecii polymerase chain reaction (PCR) of induced sputum was positive, which was consistent with the CT finding of "crazy-paving pattern." Dasatinib was held for the possibility of drug induced pneumonitis and pleural effusion, and the patient was successfully treated with trimethoprim-sulfamethoxazole for his pneumocystis jirovecii pneumonia (PCP).**

***Conclusion*: Our case suggests that a common tyrosine kinase inhibitor, dasatinib, cannot only act as an effective antileukemic agent, but also can cause several adverse effects including pleural effusion and immunosuppression. Physicians should consider opportunistic infections in their differential when patients on dasatinib present with respiratory insufficiency.**

Introduction

Dasatinib is a multi-kinase inhibitor (tyrosine kinase inhibitor [TKI]) used primarily in the treatment of chronic myeloid leukemia (CML). Compared to the first generation TKI, imatinib, dasatinib has shown superiority in chronic phase CML, but with a different toxicity profile. (1,2) The major side effects reported are pleural effusion, pulmonary hypertension, thrombocytopenia, and severe infection. One observational study showed an incidence rate of 25% for pleural effusion, and that age and dose were independent risk factors for developing an effusion. The majority of the cases (77%), however, were grade 1 (asymptomatic) or 2 (symptomatic requiring diuretics or limited therapeutic thoracentesis). In this study, 6% of patients had clinically significant infections, predominately respiratory tract infections. (2) There have been reports of an association between dasatinib and atypical infections, including pneumocystis jirovecii pneumonia (PCP) and Cytomegalovirus (CMV) reactivation, thought to be due to the drug's immunosuppressive effects on B cells, mast cells, T cells, and natural killer cells. (3) We here present a case of severe respiratory failure in a

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patient with CML due to multiple side effects of dasatinib, including pleural effusion and severe pneumocystis jirovecii pneumonia. This case illustrates the need for physicians to be aware of the tyrosine-kinase inhibitor's various side effects.

Case presentation

A 75-year-old male with well controlled CML, hypertension, and hyperlipidemia presented to the emergency department with progressively worsening shortness of breath and hemoptysis for one week. The patient's CML had been successfully treated with dasatinib since his diagnosis two years ago, and the most recent BCR-ABL1 assay was undetectable. The initial vital signs showed blood pressure 118/59 mmHg, heart rate 92 beats per minute, respiratory rate 28 breaths per minute, oxygen saturation 87% on room air, body temperature 36.8 °C. Physical exam revealed the patient in mild acute distress with decreased breath sounds over the right base and rhonchi diffusely. The laboratory findings were: white blood cell count $17.1x10^3/\mu l$ (segments 83%, bands 2%, lymphocytes 2%), hemoglobin 9.2 g/dl, platelets $857x10^3/\mu l$, blood urea nitrogen 67 mg/dl, creatinine 2.4 mg/dl, lactate dehydrogenase 325 IU/l, erythrocyte sedimentation rate 99 mm/hr, and lactic acid 1.6 mmol/l. Arterial blood gas (on 3 l nasal cannula) was: pH 7.34, pO2 46, pCO2 37, HCO3 20. Chest radiograph reported diffuse bilateral opacities, left greater than the right **(Figure 1)**. Subsequent computed tomography (CT) of the chest showed diffuse ground glass opacity with superimposed interlobular septal thickening and intralobular lines ("crazy-paving pattern") mainly in the bilateral upper lobes and left lower lobe. There was also air space disease with air bronchograms adjacent to a moderate right pleural effusion (**Figure 2**). The patient was admitted to the Intensive Care Unit for respiratory support with high flow nasal cannula. Therapeutic thoracentesis yielded 1.8 l of clear yellow, lymphocyte predominant exudative pleural effusion, and the patient's respiratory status subsequently improved. Given his immunosuppressed state from CML and dasatinib therapy, extensive workup was performed including serial cultures (bacterial, fungal, acid-fast bacillus), influenza polymerase chain reaction (PCR), serum CMV immunoglobulin M, serum human immunodeficiency viral antibody, Pneumocystis jirovecii PCR from induced sputum, anti nuclear antibody, complement 3, complement 4, anti-Sjögren's-syndrome-related antigen A (Ro), anti-Sjögren's-syndrome-related antigen B (La) antibody, antineutrophil cytoplasmic antibodies titers, and anti-glomerular basement membrane antibody. All the tests resulted negative except for Pseudomonas aeruginosa and Pneumocystis jirovecii PCR from induced sputum. Empiric antibiotic therapy with piperacillin/tazobactam, vancomycin, and trimethoprim-sulfamethoxazole was initiated. Dasatinib was held for the possibility of drug induced pneumonitis and pleural effusion. The patient's respiratory status improved gradually, and he was discharged on day 12. The patient was followed as an outpatient and completed his 21 day course of PCP treatment with atovaquone. Repeat CT scan in one month showed residual small right pleural effusion but improvement of the overall crazy paving pattern.

Discussion

Dasatinib is a potent antileukemic agent successfully used in the treatment of CML. It has also been described, however, to produce several adverse side effects. The most common adverse effect is exudative, lymphocyte predominant pleural effusion, which occurred in 25% of patients on dasatinib. Some studies reported grade II and higher pleural effusions occurring in 75% of these patients. (2,3) Our patient had a grade 4 (moderate-sized) pleural effusion with typical characteristics of dasatinib-associated effusion (exudative, lymphocyte predominant). Previous studies reported advanced age and higher dose as risk factors for developing a pleural effusion, consistent with our patient's presentation (age 75 years or older, dasatinib dose 140 mg/day).

Studies have also demonstrated dasatinib binds to key kinases of the immune system and blocks the activation of T cells, B cells, and basophils, placing the patient at risk of opportunistic infection, especially with the dose of 140 mg/day. (3) There is limited but increasing evidence suggesting that other classes of tyrosine kinase inhibitor (ibrutinib) (4) and phosphatidylinositol 3-kinase inhibitors (idelalisib, duvelisib) used for chronic lymphocytic leukemia are associated with invasive fungal infections, including PCP, and prophylaxis is recommended by the manufacturer in patients receiving idelalisib or develisib. (5-7) Although there is lack of evidence about PCP infection in patients receiving dasatinib, it may be reasonable to consider prophylactic antimicrobial therapy in high dose dasatinib-treated patients who have other risk factors for developing infections (e.g. neutropenia, other comorbidities, history of atypical infection).

Various infections may occur among patients receiving dasatinib. A previous cohort study investigated the prevalence of infections in dasatinib-treated patients and found a variety of such infec-

tions. Among them, bacterial was the most common, and the most common infected site was the lung. Viral infection occurred in 7% of the patients. Atypical infection, including opportunistic infection, was relatively rare but present, but PCP was not observed in this study. (8) Other data suggests CMV reactivation to be the most commonly reported opportunistic infection associated with dasatinib. Nevertheless, three cases of PCP have been previously reported in the literature. (9) In two of those cases, the patients were on systemic steroids for other reasons; the effect of which cannot be excluded. In our case, the patient was not treated with steroids prior to the onset of infection, and the patient's CML was in remission, which increases the likelihood dasatinib's immunosuppressive effect lead to opportunistic infection.

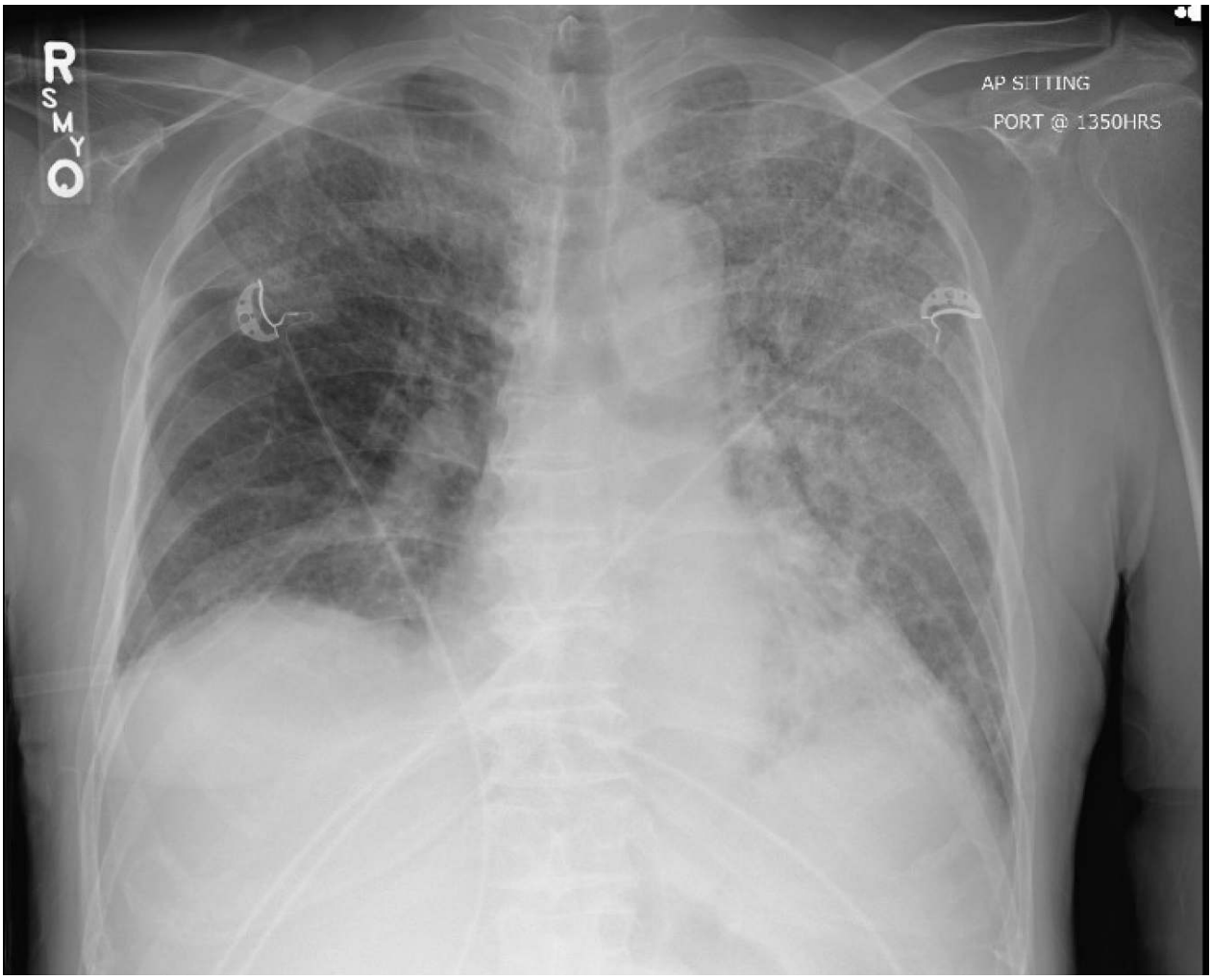
Leukemia itself may have contributed to the patient's susceptibility to opportunistic infections, however, in all previous cases, as well as ours, patients developed PCP during CML remission, not at the time of initial diagnosis. There are no reported cases of PCP that developed upon the initial manifestation of CML, and this supports our hypothesis that PCP is more closely associated with dasatinib therapy rather than leukemia itself.

Patients on dasatinib can develop multiple adverse effects during their treatment course, and this is likely due to the drug's potency. It is important to acknowledge this fact and keep the differential broad when patients on dasatinib are presenting with respiratory failure.

Conclusion

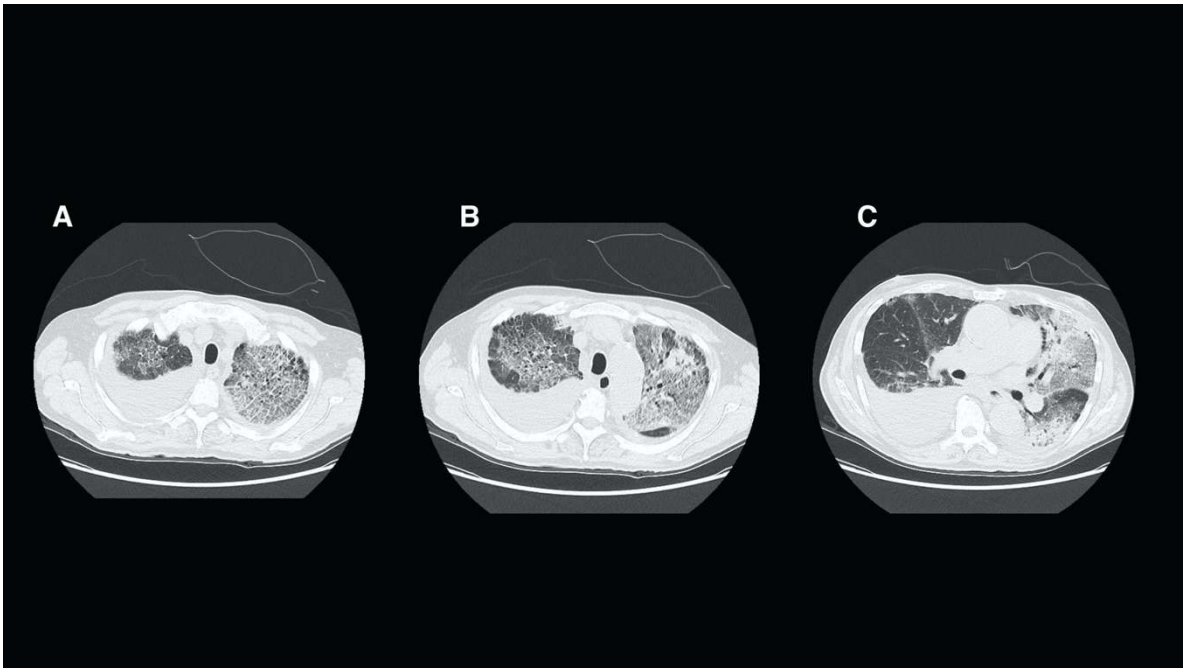
Our case suggests that a common tyrosine kinase inhibitor, dasatinib, cannot only act as effective antileukemic agent, but also can adversely affect respiratory status. The most common adverse effect is pleural effusion, but it can also trigger opportunistic infection by affecting the T cell, B cell, and basophilic activity. Physicians should consider these atypical infections, including PCP, in their differential when patients on dasatinib present with respiratory insufficiency.

Figure 1. Chest X ray on the day of admission



Legend: There is diffuse bilateral opacities, left greater than the right.

Figure 2. CT chest on day of admission



Legend: CT=computed tomography. Diffuse ground glass opacity with superimposed interlobular septal thickening and intralobular lines ("crazy-paving pattern") mainly in the bilateral upper lobe and left lower lobe (A and B). There was also air space disease with air bronchograms adjacent to a moderate right pleural effusion (C).

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