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Case Report

Case Report: Pleural Effusion During Tyrosine-Kinase Inhibitor Treatment in Chronic Myeloid Leukemia

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Abstract

The spectrum of TKI-related adverse events (AEs) is variable. Pleural effusion (PE) is a frequent AE attributable to dasatinib treatment. The pathogenetic mechanism leading to PE during Dasatinib therapy is still unknown and its management has not yet been defined. To the best of our knowledge, only a limited number of similar case reports have already been reported in the literature so far. Here, we describe the case of a 34-year-old CML patient who developed PE during first-line Dasatinib, successfully treated with Dasatinib permanent discontinuation and shifting to Nilotinib. We highlight the differences among our patient and the others, proposing therapeutic strategies to solve this rare but still possible AE, of which physicians should be aware.

Introduction

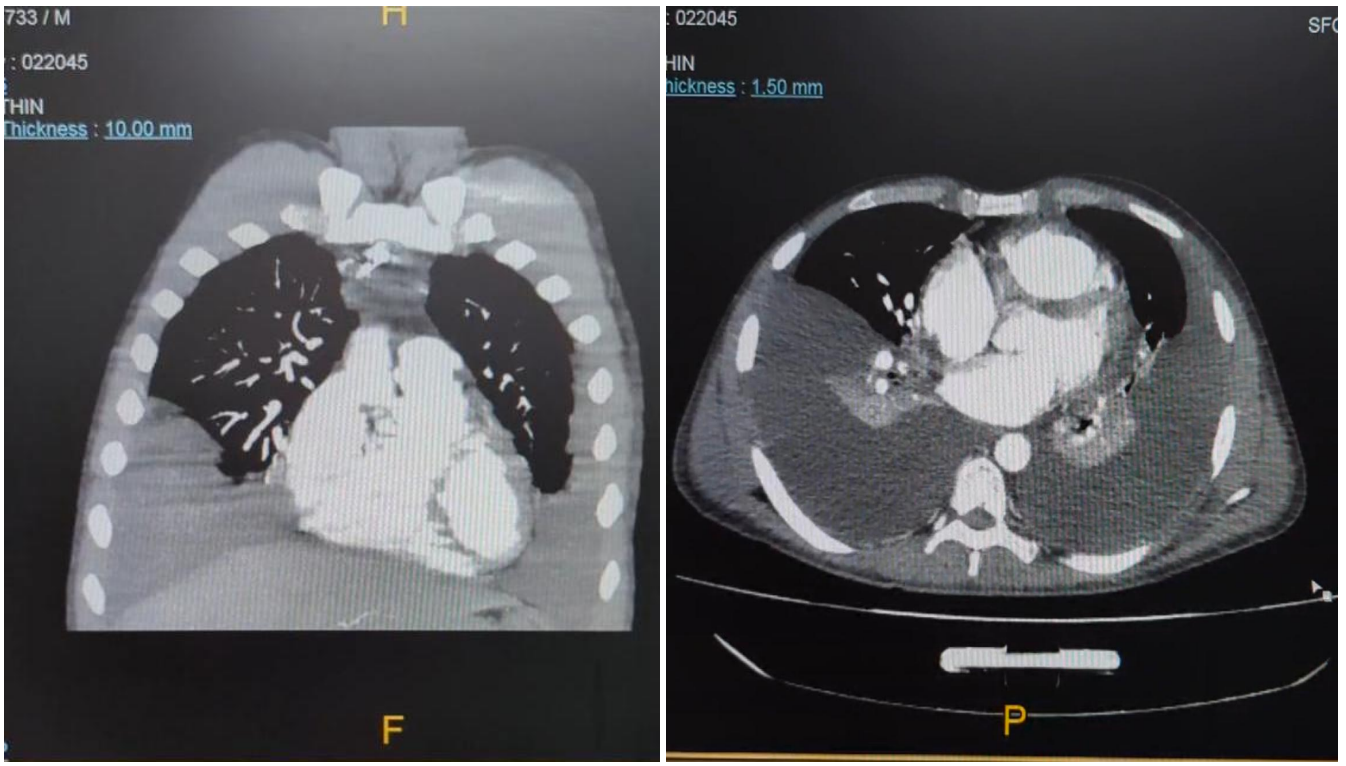
BCR::ABL1-positive chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1-2 cases per 100.000 adults, which represents approximately 15% of newly diagnosed cases of leukemia in adults. This disease is characterized by a single reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia (Ph) chromosome. BCR::ABL1 fusion gene encodes a p210 protein (BCR::ABL1) with deregulated tyrosine kinase activity. Knowledge of this translocation was the basis for the development of drugs known as small molecule tyrosine-kinase inhibitors (TKIs) (1).

Currently, five TKIs are approved for CML treatment: original/generic imatinib, nilotinib, dasatinib, and bosutinib are recommended for both first and second or later lines, and ponatinib for second or subsequent lines, representing at the moment the only TKI that can be effectively used also in the case of the T315I point mutation. Each TKI has a distinct toxicity profile with most adverse effects (AEs) expressing 'off-target' toxicity of TKIs such as in the case of pleural effusion (PE). This AE is reported only rarely during treatment with imatinib (1-2%) or bosutinib: considering in particular the latter TKI, PE has been reported in both the first and second or subsequent lines of treatment, with an incidence rate which varies from 1.9% to 6.1%. On the contrary, PE is a typical dasatinib-related AE with a higher incidence in patients showing baseline risk factors such as older age, history of pulmonary and/or hearth diseases, uncontrolled hypertension, hypercholesterolemia and/or autoimmune disorders. In the DASISION trial, the incidence of PE at 5 years of follow-up was 28% in the dasatinib arm compared to 1% in the imatinib arm. A similar incidence of PE during

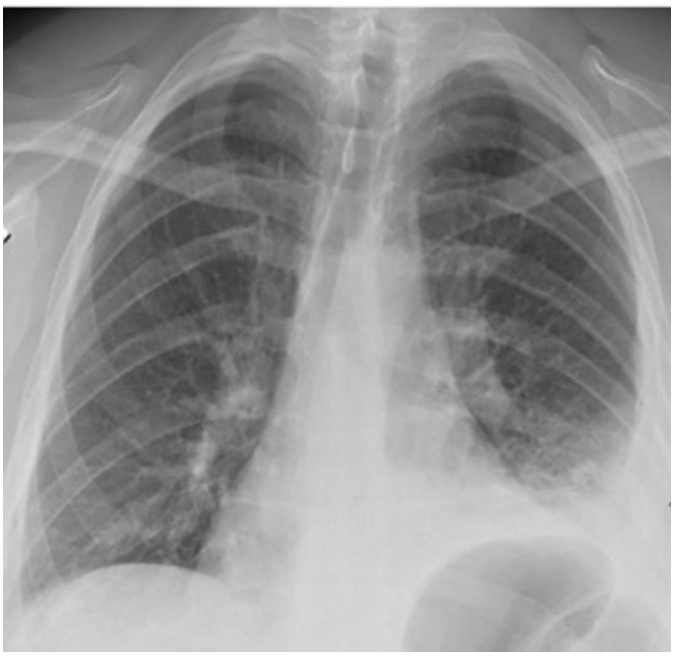
dasatinib treatment was reported in real-life experiences, with a recurrence rate of 59.4%. In the ELN recommendations for the management of TKI-related AEs, recurrence of PE occurs in approximately 70% of the cases, thus representing the leading cause of dasatinib discontinuation (12).

Case Description

A 34-year-old man presented to our department with exertional dyspnea, accompanied by intermittent cough, edema, fatigue, abdominal distension. He had a 2-months history of exertional dyspnea that had worsened over the previous 15 days. He had been diagnosed with CML at the age of 26, for which 6MP and Methotrexate, second-generation TKI, dasatinib (75 mg Twice daily), was prescribed as his first-line therapy. After 6 months of therapy, he came to our center with presentation of exertional progressive breathlessness, non productive cough. At that time, initial workup was done in the department including chest radiograph showing bilateral massive pleural effusion. Patient was then conservatively managed. About 2 litres of pleural fluid was aspirated which was hemorrhagic and sent for chemical examination, routine microscopy and cyto pathology which revealed TLC – 1100, polymorphs – 20%, lymphocytes – 80%, mesothelial and red blood cells were present. Chemical examination revealed ph – 7.5, protein – 5.37, sugar – 141, LDH – 240, ADA – 21. Cyto pathology was negative for malignant cells. Therapeutic pleural fluid aspiration was done followed which patient was discharged. Patient came to our department again with same complaints of shortness of breath. Chest radiograph showed bilateral pleural effusion.



A. Chest radiograph showing bilateral pleural effusion



B. Chest radiograph showing mild pleural effusion on left side (on follow up)

Discussion

The most common non-hematological AEs of dasatinib are already well-known, including peripheral arterial occlusive diseases, followed by QTc interval prolongation, pancreatic enzymes, bilirubin and glucose blood levels elevation, gastrointestinal symptoms, pruritus, rash, headache, fatigue, arthralgia, nasopharyngitis, fever and night sweats; on the contrary, dasatinib has a peculiar pulmonary toxicity with a high incidence of PE estimated between 14% and 30% (17).

These AEs may be due to "off-target" effects; in particular, dasatinib-induced PE may be secondary to potent PDGFR-β inhibition in association with other possible mechanisms such as SRC inhibition (18). Indeed, it should be emphasized that PDGFR-β inhibition alone cannot cause serosal inflammation: for example, this AE is not associated with sorafenib which, however, also targets PDGFR-β.

One possible explanation is that dasatinib-related PE may be secondary to the cytotoxic T and NK cells expansion or to the action of other kinases (18). Indeed, PE is usually associated with dasatinib-induced non-malignant inflammatory lymphocytosis, which is often of NK type. The drug inhibits key kinases involved in the maturation of T and B lymphocytes, sometimes causing clonal expansion of large granular lymphocytes (LGL); the latter mainly involve NK or cytotoxic T cells, which can be detected in both PB and pleural fluid. This immunomodulatory effect, with lymphocytosis and clonal expansion of LGL, which are positively correlated with the onset of PE, has also been shown to be associated with a better response to treatment (19–21). As expected, patients with autoimmune diseases or previous immune-mediated AEs related to other TKIs are at increased risk of PE during dasatinib therapy (20, 21).

Regarding bosutinib, an orally active dual SRC and ABL1 TKI with minimal activity against PDGFR or c-KIT (22, 23), it has been more rarely associated with PE (24), both in real-life experiences (25) and in randomized clinical trials: more specifically, the incidence rate of PE ranged from 1.9% in the phase III BELA trial (26) to 6.1% in the phase IV BYOND study (4). Also considering the most recent BFORE trial, which compared bosutinib vs. imatinib for patients with newly diagnosed CP-CML, PE occurred in 5.2% of bosutinib-treated subjects, with the most promising risk factors for this AE, in addition to bosutinib treatment, represented by advanced age, smoking habit, and history of pulmonary events (5). The mechanism of action for bosutinib is unclear; however, major immunological changes during treatment do not seem to be the predominant factor (27).

Although the pathogenesis of dasatinib-induced PE has already been elucidated, the etiology of this AE during treatment with nilotinib has not yet been described (16).

Unlike dasatinib, nilotinib is a weaker PDGFR inhibitor, thus leading to a PE incidence of less than 1% in this setting (2), while inhibiting DDR1 phosphorylation expressed on bronchial epithelial cells in the same way as dasatinib (21, 28).

Consequently, as CML patients receiving TKIs can be expected to have a near-normal life expectancy and quality of life (QoL), individual characteristics of CML subjects, including comorbidities, lifestyle preferences, and TKI compliance, along with distinct 'off-target' TKI toxicities (which can lead to drug-related long-term morbidities) and molecular BCR::ABL1 profile, are among the critical factors to consider when choosing the proper TKI, either as first, second or subsequent lines of therapy (2, 32–34).

All this considered, returning to our patient, it was decided not to restart dasatinib, even at half the standard dose, but to introduce nilotinib for multiple reasons: In support of this observation, Teke et al. resumed nilotinib at a reduced dose of 200 mg BID, then increased to 400 mg BID (30); on the contrary, Satoh et al. modified CML treatment in ponatinib (31).

Conclusions

In this case report, dasatinib was found to be the only possible cause of PE, after excluding other etiologies. However, unlike previous experiences, due to the severity of this rare AE and also considering the optimal response that the patient had already obtained, with the aim of preventing future PE recurrences, dasatinib was permanently discontinued with no new episodes during subsequent TKIs. In addition, some differences from other cases should be noted: firstly, this AE occurred during first-line therapy without concomitant medications. Overall, considering these experiences, it is not possible to hypothesize clear risk factors for dasatinib-induced PE with the sole exception of male sex. Indeed, differently from gender, older age does not seem to be prognostically relevant. The same was true for comorbidities: the first patient reported had coronary artery disease and hypertension, among others. The remaining patients, including the one described in this case report, had no significant comorbidities. Duration of treatment also does not appear to have an impact on PE risk as patients developed this AE within 2-3 months to 5 years of starting dasatinib. An unmet clinical need may be the best management of this AE: apart from supportive care, i.e., steroids and diuretics, the real indication for switching from dasatinib to another TKI after a single episode of PE is still unclear. In our case, due to the severity of the clinical presentation of this rare AE and the progressive reduction in BCR::ABL1 transcript level, in order to avoid new drug suspensions due to recurrences of PE, it was decided not to restart dasatinib, not even at a lower dosage, but to change the TKI by starting nilotinib in the light of its safer toxicity profile.

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