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REVERSIBLE PRE-CAPILLARY PULMONARY HYPERTENSION DUE TO DASATINIB

ABSTRACT:

Pulmonary arterial hypertension (PAH) and secondary pleural effusion have been reported in association with long-term therapy with the multi tyrosine kinase inhibitor dasatinib, approved for the treatment of chronic myeloid leukemia (CML). We present the case of a 50-year-old man diagnosed with CML in August 2003, who developed PAH after more than four years of treatment with dasatinib. The complete remission of PAH following dasatinib discontinuation suggests an etiological role of the drug in its development, although the administration of sildenafil may have played a therapeutic role.

KEYWORDS:

Pulmonary hypertension, chronic myeloid leukemia, long-term therapy, drug-induced.

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INTRODUCTION:

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a mean pulmonary artery pressure (*m*PAP) $\geq$ 25 mmHg and a progressive increase of pulmonary vascular resistance leading to right ventricle failure. The proposed causes of PAH range widely and one of these may be associated with the use of drugs.[1,2]

Dasatinib is a tyrosine kinase inhibitor (TKI) which also inhibits platelet-derived growth factor receptor (PDGFR)-b, Src, and c-KIT. It is approved for use in patients with chronic myeloid leukemia (CML) who have developed resistance, suboptimal response, or intolerance to prior imatinib.[3]

PAH in conjunction with pleural effusion secondary to dasatinib has been described in a few patients. This phenomenon was observed in patients after long-term treatment with dasatinib.[4,5] We present the following case of severe PAH associated with the use of this drug.

CASE REPORT:

In August 2003, a 50-year-old man, ex-smoker (20 pack-years) was diagnosed with CML, bcr/abl positive in chronic phase. He began treatment in October 2003 with imatinib, initially at a dose of 400 mg/day and subsequently increased to 800 mg/day, with good response. In June 2007, owing to the persistent loss of major molecular remission, this treatment was suspended and replaced by another TKI (dasatinib 100 mg/day). The patient began to suffer a range of symptoms including cramps, isolated episodes of diarrhea, somnolence and arthralgia, which caused problems in his working life but were considered insufficient to justify treatment interruption.

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In June 2011 he was admitted to the Respiratory Disease ward with a clinical history of dyspnea, which had progressively worsened over a period of two months, with repeated episodes of thoracic pain related to effort and accompanied by a hacking cough and wheezing sounds on auscultation. His physician prescribed bronchodilator treatment, with no improvement in his condition. The results of physical examination were: blood pressure 120/80 mmHg, temperature 36°C, respiratory rate 22 breaths/min, heart rate 83 beats/min; auscultation showed absence of normal breath sounds up to two thirds of the right hemithorax. Heart sounds, abdominal examination and extremities were all normal. Laboratory tests for glucose, urea, creatinine, ions, hepatic and lipid profiles, human immunodeficiency virus (HIV) serology, antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCAS) serology were all normal. An electrocardiogram showed sinus rhythm with right axis deviation and negative T waves in the right precordial leads. Chest X-ray showed right pleural effusion (Fig. 1). Pleural fluid from a diagnostic thoracentesis was compatible with lymphocytic exudate, negative on culture, with no flow cytometry evidence of hematolymphoid infiltration and no cytological evidence of malignancy. Pulmonary function tests showed normal spirometry results and a reduction in diffusing capacity of the lung for carbon monoxide (DLCO). On computerized tomographic (CT) angiogram an increase in the right atrium and ventricle was noted. The absence of perfusion alterations in the pulmonary arteries allowed pulmonary thromboembolism (PT) to be ruled out. Scintigraphy ventilation/perfusion lung scan showed hypoventilation and hypoperfusion of the right lung, a finding related to the presence of pleural effusion. There were no peripheral perfusion alterations suggestive of residual lesions after previous PT. Abdominal ultrasound did not identify signs suggesting portal hypertension.

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The result for N-terminal pro-brain natriuretic peptide (NTproBNP) was 7312 pg/l and the 6-minute walking test (6MWT) was 420m. The results of a transthoracic echocardiogram and right heart catheterization are shown in Table 1. Taking into consideration all these data, a diagnosis of severe pulmonary hypertension attributable to dasatinib was reached. During hospitalization, treatment with dasatinib was suspended and he began treatment with sildenafil 20mg/8h. Eleven days after the suspension of dasatinib, the pleural effusion had disappeared. In September 2011, treatment with second generation tyrosine kinase inhibitors (nilotinib 600 mg/day) for his CML was added and the dose of sildenafil was increased to 40mg/8h.

During the first two months after discharge, echocardiographic signs of right ventricular failure persisted. At six months there was clear improvement in clinical symptoms, NTproBNP, DLCO, echocardiograms and 6MWT. A year after the diagnosis, normalization of all the hemodynamic parameters was observed on right cardiac catheterization and echocardiography (Table 1), and the dose of sildenafil was therefore reduced to 20mg/8h. In the final follow up at 21 month of diagnosis the patient was stable, with results indicating good prognosis: NTproBNP 80 ng/l and New York Heart Association (NYHA) functional class I-II. The final right heart catheterization performed in March, 2013 (Table 1) confirmed complete resolution of PAH. Repeat pulmonary function test after the resolution of PAH showed increased DLCO from 63% to 91%.

DISCUSSION

Pulmonary hypertension (PH) is defined hemodynamically as a $mPAP \geq 25$ mmHg.[1] The first category of the clinical classification termed PAH includes: idiopathic PAH, hereditable PAH and PAH related to risk factors or associated conditions,[2] such as

connective tissue diseases, congenital heart diseases, portal hypertension, HIV infection and exposure to drugs and toxins.[6]

Dasatinib is a multi TKI approved for first and second line therapy of CML.[7] Accumulated evidence indicates that receptor tyrosine kinases (RTKs) play an important role in the pathogenesis of PAH, and inhibition of some specific RTK signaling may represent an attractive option for treatment of the disease. A 24-week randomized, double-blind, placebo-controlled pilot study showed that imatinib was associated with significant hemodynamic improvement, although not with any significant change in the primary end point (6MWT).[8]

The association between PAH and dasatinib is paradoxical because the drug also acts as a potent RTK inhibitor. In contrast to imatinib, dasatinib is a potent inhibitor of additional important families of RTKs, including Src and Eph receptors/ephrin kinases. It may therefore be speculated that Src inhibition plays a role in the development of dasatinib-associated PAH. It has recently been reported that dasatinib inhibits PDGF-induced proliferation and migration of vascular smooth muscle cells via inhibition of both PDGFR activity and PDGF-dependent Src activation downstream of the PDGFR, which would in theory be beneficial in PAH.[4,9]

Severe cardiovascular and respiratory adverse effects are infrequent in CML patients treated with dasatinib at the recommended dose of 100 mg/day. PAH and pleural effusion were not observed in patients enrolled in a phase-III clinical trial and assigned to receive dasatinib 100 mg/day. On the contrary, this dosage significantly minimized the occurrence of key adverse events. This regimen does not affect short- or long-term efficacy and, at these low doses, only a few cases of PAH have been reported.[3,10] However, the occurrence of late onset symptomatic PAH (48 months after starting dasatinib in our case), may reflect a chronic pathological mechanism which, after an

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insidious onset, might become clinically significant while on long-term therapy with TKIs. These drugs are typically life-long therapies[5,7] and information on long-term adverse effects is therefore of considerable clinical interest. In the French pulmonary hypertension registry, the lowest estimate of incidence of PAH in patients exposed to dasatinib was 0.45%.[8]

The incidence of pleural effusion in patients receiving dasatinib was 17% (grades 3–4 in 4%). In a recent report by Quintás - Cardama et al., pleural effusion occurred in 48 (35%) of 138 patients treated with dasatinib. Most pleural effusions were exudate, arguing against primary cardiac impairment as the mechanism of pleural fluid accumulation.[11,12]

In our case, other conditions associated with PAH, such as pulmonary embolism or parenchymal lung disease, were ruled out by chest CT scan with contrast, CT angiogram and scintigraphy ventilation/perfusion lung scan. Hepatic ultrasound excluded portopulmonary hypertension and bubble contrast echocardiogram excluded congenital heart disease, which may be associated with PAH. Furthermore, laboratory screening tests for HIV and systemic rheumatic diseases, including antinuclear antibodies, were negative. There was no clinical evidence of PAH when dasatinib was initiated and the echocardiogram, performed 1 year before starting dasatinib, was normal. All these findings support the diagnosis of PAH associated with dasatinib.

Dasatinib was discontinued on suspicion of its involvement in PAH. During follow up, we performed right heart catheterization on two occasions: at one year, it showed normalization of all hemodynamic parameters, which coincided with complete resolution of breathlessness and the dose of sildenafil was therefore reduced to 20mg/8h. At final follow up 21 months after diagnosis, right heart catheterization showed no evidence of recurrent PAH, but the targeted PAH therapy with sildenafil was

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not discontinued until months later to avoid the possible consequences of abrupt discontinuation.

Concerning the role of nilotinib in resolving PAH, initiated 1 month after diagnosis in our patient, we cannot affirm or deny its therapeutic value. Zakrzewski et al. presented the first case report of pulmonary hypertension in a patient treated with nilotinib for CML. They found that the change in pulmonary artery pressure was dose dependent and that the decrease occurred after discontinuation of nilotinib. [13] However, a clinical trial is currently investigating the efficacy, safety, tolerability and pharmacokinetics of nilotinib in pulmonary arterial hypertension, the results of which may help clarify its therapeutic usefulness.

In our patient, complete resolution of pulmonary arterial hypertension was noted several months after discontinuation of dasatinib and, after the introduction of sildenafil therapy, with *mPAP* levels within the normal range to date.

This is remarkable because complete remission and normalization of pulmonary hemodynamics is not usually achieved in PAH by medical treatment. However, in our case, resolution was achieved not only by discontinuation of dasatinib but also after therapy with sildenafil. Similarly, in a case reported by Dumitrescu et al, the development of severe PAH was associated with dasatinib treatment for CML which completely resolved after TKI withdrawal and the administration of targeted PAH therapy (6 months) with sildenafil.[4]

In conclusion, we here report a case of severe PAH fulfilling the criteria of drug-induced PAH after complete invasive hemodynamic evaluation, which suggests a direct and specific effect of dasatinib on the pulmonary vasculature. Physicians need to be aware of this possible adverse effect of dasatinib in order to appropriately monitor and manage these patients.

Conflict of interest: The authors have no conflict of interest to declare.

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Table 1 Right heart catheterization, transthoracic echocardiography, 6MWT and NT proBNP parameters at baseline and after dasatinib discontinuation.

	June 2011	**August 2012**	**March 2013**
WHO/NYHA FC	IV	II	I
Right heart catheterization			
RVSP (mmHg)	82	36	44
PAP mean (mmHg)	52	19	20
PVR (WU)	16	2	1
PCWP (mmHg)	11	3	12
RAP (mmHg)	10	2	2
CO (l/min)	2.6	6.7	6.1
CI (l/min/m^2)	1.2	3.2	2.9
Transthoracic echocardiography			
PASP (mmHg)	60	34	NA
TAPSE (mm)	16	24	NA
Systolic function	Reduced	Normal	NA
6 MWT (m)	420	540	480
NTproBNP (ng/l)	7312	28	80

Abbreviations: WHO/NYHA FC: World Health Organization/New York Heart Association functional class; RVSP: right ventricular systolic pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistances; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; CO: cardiac output; CI: cardiac index. PASP: Pulmonary artery systolic pressure TAPSE: tricuspid annular plane systolic excursion, NTproBNP: brain natriuretic peptide propeptide; 6MWT: 6-minute walk test. NA: not available.

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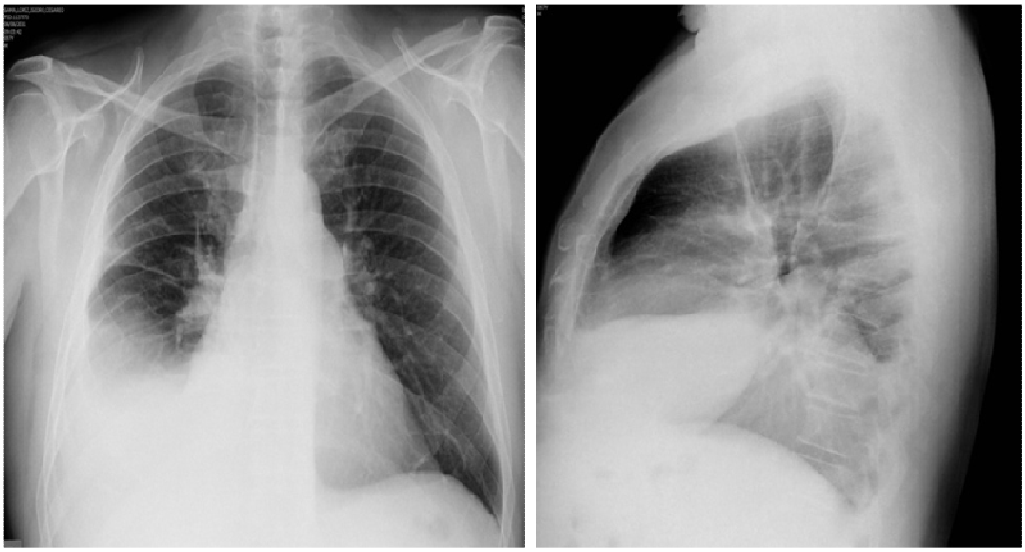

Figure 1: Chest X-ray PA and lateral: Right pleural effusion with atelectasis. ICT limit.