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Early View

Research letter

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First histopathological evidence of irreversible pulmonary vascular disease in dasatinib-induced pulmonary arterial hypertension

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To the Editor:

We read with interest the article by Weatherald *et al.* on the long-term outcomes of pulmonary arterial hypertension (PAH) induced by dasatinib [1]. The authors reported 21 incident cases of PAH confirmed by right heart catheterisation (RHC) and associated with dasatinib. Although a majority of patients improved after dasatinib discontinuation, PAH persisted in over one-third of cases during long-term follow-up and two additional patients had persistent exercise pulmonary hypertension despite normalisation of resting haemodynamic measures. Similarly, Shah *et al.* reported 41 cases of dasatinib-induced PAH confirmed by RHC with complete resolution of PAH in only 58% of patients, provided that follow-up RHC or echocardiography was most often not documented [2]. As mentioned by Weatherald and colleagues, these data suggest that dasatinib is likely to cause irreversible pulmonary vascular dysfunction and remodelling. An experimental model in rats and human pulmonary endothelial cells supports this hypothesis as it showed that dasatinib causes dose-dependent pulmonary endothelial dysfunction and apoptosis through the production of mitochondrial reactive oxygen species, a phenomenon that was not observed with imatinib [3]. To date, there is no published evidence of such pathological abnormalities on human lung. We report the case of a patient who developed dasatinib-induced severe PAH that progressed in spite of drug cessation and aggressive PAH-specific therapy and ultimately underwent lung transplantation.

A 32-year old male was diagnosed with chronic myeloid leukaemia (CML) BCR-ABL1+ which was treated sequentially with imatinib, nilotinib and dasatinib. Thirty-six months after dasatinib initiation, he developed pre-capillary pulmonary hypertension confirmed

by RHC with mean pulmonary arterial pressure (mPAP) of 57 mmHg, pulmonary artery wedge pressure (PAWP) of 9 mmHg, cardiac index of 1.4 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance (PVR) of 18.5 Wood units (WU), non-reactive to inhaled iloprost. Except for the above-mentioned tyrosine kinase inhibitors (TKIs), the patient had not been previously exposed to any chemotherapeutic agent or anorexigen drug. A comprehensive workup, including echocardiography, contrast-enhanced computed tomography (CT) of the chest, ventilation/perfusion lung scan, abdominal ultrasound, autoimmunity screening and HIV serology, excluded other causes of pulmonary hypertension, which thus was attributed to dasatinib. At the time of PAH diagnosis, the patient presented with New York Heart Association (NYHA) functional class III and 6-min walk distance (6MWD) was 340m. Chest CT and echocardiography showed significant bilateral pleural effusions and a minor pericardial effusion. Following discontinuation of dasatinib and the introduction of PAH treatment combining a phosphodiesterase type 5 (PDE-5) inhibitor and an endothelin receptor antagonist (ERA), NYHA functional class improved to class I/II and 6MWD increased to 610m within 12 months. A follow-up RHC performed 10 months after PAH diagnosis confirmed significant haemodynamic improvement with mPAP decrease to 38 mmHg, cardiac index increase to 5.8 L·min-1·m-2 and near-normalisation of PVR to 2.8 WU.

Owing to molecular relapse of CML, nilotinib was reintroduced at reduced dose (400 mg·day-1) by considering that it was less likely than dasatinib to induce PAH. During the three years following nilotinib resumption and despite further dose reduction to 200 mg·day-1, we observed a gradual clinical and functional worsening suggesting PAH progression. RHC was repeated and showed significant aggravation of PAH with an increase of mPAP to 70 mmHg, a drop of cardiac index to 2.2 L·min-1·m-2, a severe rise in PVR to 11.8 WU, as well as right atrial pressure above 14 mmHg and

low mixed venous oxygen saturation as factors of poor prognosis. PAH therapy was intensified with continuous intravenous treprostinil infusion up to 40 ng·kg-1·min-1, in addition to maximal oral doses of PDE-5 inhibitor (sildenafil) and ERA (ambrisentan). However, PAH further progressed and over the following 6 months, the patient developed symptomatic right heart failure with NYHA functional class IV, exertional presyncopes, refractory hydrosodic retention and severe hypoxemia that ultimately necessitated continuous intravenous diuretics, recurrent thoracenteses, high flow oxygen therapy and haemodynamic support with noradrenaline and levosimendan infusions. In view of an immediately life-threatening situation due to PAH and given the favourable prognosis of CML on long-term TKI, it was decided, after multidisciplinary discussion, to perform bilateral lung transplantation which was successfully achieved under perioperative veno-arterial extracorporeal membrane oxygenation support, after 20 days on the waiting list. The patient was rapidly weaned off the hemodynamic support and extubated after three days. A transoesophageal echocardiography performed 24 hours after surgery showed normalisation of PAP and resolution of right ventricular dilatation with only minor residual dysfunction. After satisfactory cicatrisation of bronchial anastomoses and in the absence of imatinib resistance, imatinib 400 mg·day-1 was reintroduced. Six months after lung transplantation, CML is currently controlled on imatinib with undetectable BCR-ABL transcript level (major molecular response). No mutation in the BMPR2 gene was found.

The analysis of the explanted lungs showed atherosclerosis and typical histopathological features of chronic PAH [4]. Pulmonary arteriopathy was characterised by major vascular wall remodelling with medial hypertrophy and

concentric laminar intimal thickening, as well as plexiform lesions (Figure 1), without evidence of pulmonary veno-occlusive or thromboembolic disease.

In our opinion, this case deserves attention as it suggests a possible severe evolution of dasatinib-induced PAH despite transition to nilotinib and maximal PAH-specific therapy. To our knowledge, there are no published data regarding lung transplantation in such a context. Moreover, this is the first case providing evidence of dasatinib-induced characteristic pulmonary arterial remodelling in humans, as seen in other causes of PAH. It appears to confirm the hypothesis raised by Weatherald and colleagues of irreversible pulmonary vascular disease in patients with persistent PAH in spite of dasatinib discontinuation. It could also explain why, even though clinical and functional improvement is most often observed upon treatment discontinuation, abnormal haemodynamic can persist. In our case, it is interesting to note that PAH initially improved after dasatinib cessation and with dual PAH therapy, with near-normalisation of PVR, and worsened only after nilotinib reintroduction, raising questions about the role of nilotinib in PAH progression. However, except for one case of suspected nilotinib-induced PAH without confirmation of diagnosis by RHC [5], there is currently no confirmed case of incident PAH caused by nilotinib, nor reported case of PAH worsening or relapse following replacement of dasatinib by nilotinib, although nilotinib is the most frequently used TKI after dasatinib withdrawal [6]. On the other hand, there have been published cases of incident or worsening PAH related to ponatinib or bosutinib in patients with previously documented dasatinib-induced pleural effusions or PAH [7-9]. Consequently, we cannot exclude that nilotinib, similarly to ponatinib and bosutinib, played some role in PAH progression and perpetuated pulmonary vascular toxicity following previous injury by dasatinib. Alternatively, the

disease might have inevitably progressed, as seen in other forms of PAH, despite dasatinib withdrawal and after transient improvement on PAH therapy.

The risk of PAH recurrence after lung transplantation and reintroduction of TKIs is unknown but seems unlikely as, on the one hand, it now depends on the predisposition of the pulmonary graft to PAH, and on the other hand, treatment with imatinib is not known to cause PAH and has even showed some beneficial effects in patients with PAH [10]. In case of resistance or intolerance to imatinib, rechallenge with dasatinib would be contraindicated. In the absence of previous graft exposure to dasatinib, the replacement of imatinib by nilotinib could be an option to be considered cautiously and with close monitoring.

In conclusion, this extreme case illustrates the possible occurrence of irreversible pulmonary vascular remodelling and suggests that dasatinib induced PAH. It is difficult to implicate dasatinib conclusively as the sole agent responsible for the development of PAH in this case or in patients in the other reports. However, given the number of cases associated with dasatinib, it should be considered as a major factor in the development of PAH in CML patients.

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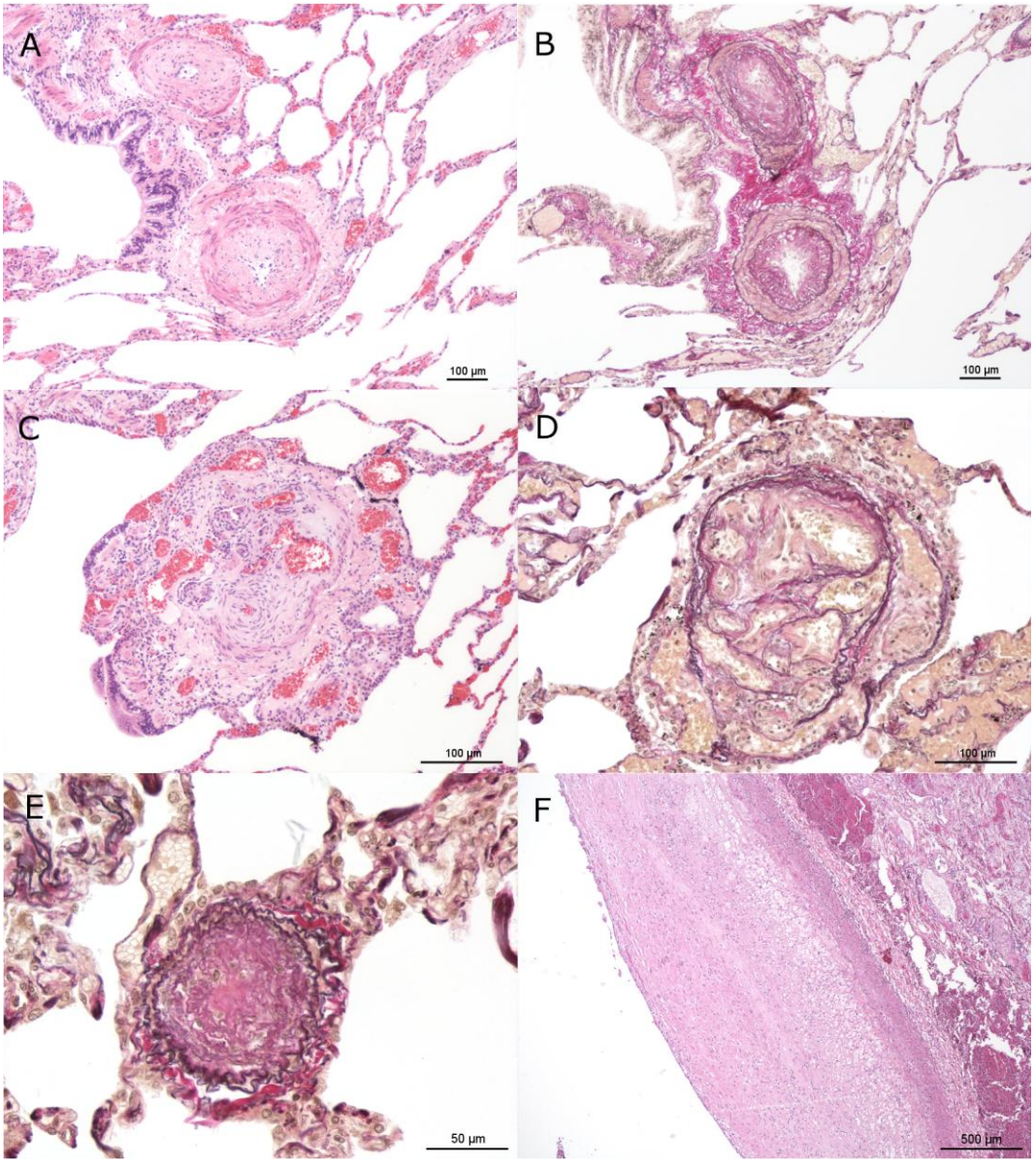
Legend to figures:

FIGURE 1 Histopathological features of dasatinib-induced pulmonary arteriopathy observed on explanted lungs: A) Small pulmonary artery with medial hypertrophy and concentric non-laminar intimal thickening, Hematoxylin Eosin (HE) stain, x100. B) Same lesion as A with van Gieson Elastin (VGE) stain for elastin highlighting the internal and external elastic laminae of the arterial wall, x100. C) Plexiform lesion corresponding to a complex vascular structure originating from remodelled pulmonary arteries and formed by focal proliferation of endothelial cells, HE stain, x200. D) Same lesion as C with VGE stain showing disruption of the elastic laminae associated with partial destruction and remodelling of the arterial walls, x200. E) Pulmonary arteriole beneath 70 µm showing complete obliteration through mainly intimal thickening, VGE stain, x400. Note: changes in small arterioles were heterogeneously distributed throughout the lung. F) Proximal pulmonary artery showing important atherosclerosis, HE stain, x40. Note: neither bronchial artery remodelling (hypertrophy/dilatation) nor pulmonary veins remodeling (smooth muscle hyperplasia and/or intimal fibrosis) were observed.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