Bosutinib-related pneumonitis

To the Editor:

We read with interest the recent correspondences from Hickey *et al.* [1] and Riou *et al.* [2] reporting bosutinib-associated pulmonary arterial hypertension (PAH) and pleural effusion. Tyrosine kinase inhibitors (TKIs) have revolutionised the treatment of chronic myeloid leukaemia (CML). However, TKIs are associated with potentially serious lung complications, which are particularly associated with dasatinib; the incidence of dasatinib-induced pleural effusion ranges from 15% to 35% [3, 4]. Dasatinib-related PAH has been reported in ∼0.45% of dasatinib-treated patients [5]. Bosutinib (developed by Pfizer (New York, NY, USA) in 2015) is a second-generation TKI approved for patients with CML that is resistant or intolerant to imatinib, nilotinib or dasatinib [6].

Here, we report the first case of bosutinib-related pneumonitis. The patient was a 70-year-old man with a 25-pack-year history of smoking. He had arterial hypertension treated with nicardipine and propranolol. He was diagnosed with CML in 2003. Following an initial, short treatment with hydroxycarbamide and then interferon, he was switched to imatinib 400 mg daily due to intolerance and obtained a major molecular response (MMR) (BCR-ABL1^{IS} ⩽0.1%). In 2010, the MMR was lost with no evidence of mutation and the patient was started on nilotinib 600 mg daily. MMR was regained but the patient developed coronary stenosis despite adequate therapy with statins after 3 years of therapy. Bosutinib 100 mg daily the first week, and then 200 mg daily was then introduced in 2013 and MMR was maintained. In September 2015, he became progressively breathless and experienced cough with sputum. A lung computed tomography (CT) scan showed bilateral subpleural consolidations and a left pleural effusion (figure 1a). The pleural effusion fluid was a sterile exudate with 95% lymphocytes. Fibreoptic bronchoscopy was performed. The airways were macroscopically normal and analysis of a bronchial aspirate revealed no pathogens. Bronchial biopsies showed no specific lesions. Echocardiography found both left ventricular ejection fraction and pulmonary arterial pressures within the normal ranges. He was then treated empirically with antibiotics with no improvement. 1 month later, the lung CT scan showed an increase in bilateral subpleural consolidations and a bilateral pleural effusion. A search for autoantibodies was negative. At this time, the patient underwent lung biopsies of both the upper and lower left lung lobes, as well as pleural biopsies, using video-assisted thoracoscopy. Lung biopsies showed granulation tissue plugs in the alveolar spaces with fibrinous exudate and interstitial eosinophilic infiltrate (figure 1c), as well as muscularisation of the arterioles and medial hypertrophy with intimal thickening of the small pulmonary arteries (figure 1d–f). The pleura was thickened with a dense fibrous tissue and infiltrated by a lymphoid infiltrate with rare lymphoid follicles. The diagnosis of bosutinib-related pneumonitis with pleural effusion was made and bosutinib was discontinued in January 2016 and no other CML-specific treatment was introduced. The patient's dyspnoea and cough subsequently resolved. In June 2016, the lung CT scan showed complete resolution of the pleural effusion and a decrease in the subpleural consolidations but also new consolidations and a reverse halo sign in the right upper lung lobe (figure 1b). No specific treatment was initiated. In November 2016, the lung CT scan showed complete resolution of the consolidation. In January 2017, the patient's CML remained in MMR without treatment and he had no respiratory symptoms.

The side-effects of TKIs have been shown to be dose-dependent and associated with age, being more frequent in older patients [7]. Although the most common side-effects of bosutinib are gastrointestinal, long-term bosutinib tolerability studies have noted some respiratory complications [7–9]. Respiratory infections have been reported in a long-term safety study of bosutinib in a Philadelphia chromosome-positive advanced leukaemia cohort [8]. Bosutinib-related pleural effusion has been reported in all stages of CML, with an overall incidence of 5–8% and up to 22% in patients >65 years old [7–9]. Together with the recent reported cases of PAH and the current case of pneumonitis, bosutinib may also be associated with a spectrum of lung complications previously described with dasatinib. Thus, the

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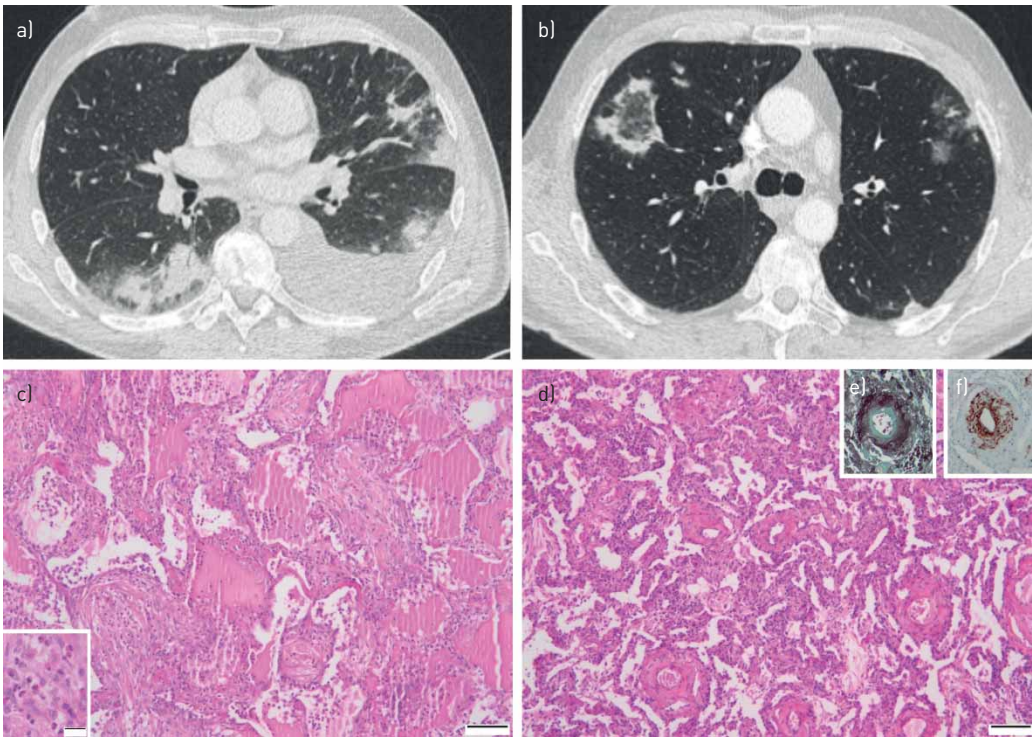

FIGURE 1 a) Lung computed tomography (CT) at diagnosis of bosutinib-associated pneumonitis with pleural effusion. b) Lung CT image 5 months after bosutinib was stopped showing a reverse halo sign. Lung biopsy showing c) granulation tissue plugs in the alveolar spaces (scale bar=100 µm) and interstitial eosinophilic infiltrate (inset; scale bar=20 µm) (haematoxylin and eosin staining (HES), 100× magnification) as well as d) muscularisation of arterioles (scale bar=100 µm; HES, 100× magnification); e) elastin staining (100× magnification); f) anti-smooth muscle actin immunostaining (100× magnification).

mechanism of bosutinib-related lung complications, similar to dasatinib, could be both oxidative and reticular endothelium stress [10], which is responsible for both endothelial and pulmonary epithelial apoptosis leading to an inflammatory environment. Both lung physicians and haematologists should be aware of the possibility of pneumonitis, pleural effusion and PAH in patients treated with bosutinib. When dyspnoea occurs in patients treated with TKIs, both chest imaging and transthoracic echocardiography should be performed. If drug-related pneumonitis is suspected, the drug should be discontinued and an infectious cause should be investigated. In cases of severe pneumonitis, corticosteroids should be discussed. Notably, the patient in our case still has a MMR for CML despite the discontinuation of bosutinib for 14 months. Thus, we did not reintroduce any TKIs [11]. Whether bosutinib could be reintroduced with caution, possibly at a lower dose after the lung manifestations have resolved, remains questionable. In cases where alternative treatments for CML are unavailable, a combination of bosutinib with low-dose steroids could be discussed.

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