

## CASE STUDY

# Pulmonary veno-occlusive disease in myeloproliferative disorder

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**ABSTRACT:** The present study reports a case of biopsy-proven pulmonary veno-occlusive disease as a cause of severe pulmonary hypertension in a patient suffering from a chronic myeloproliferative disorder. The pulmonary disease evolved favourably under treatment with defibrotide, a pro-fibrinolytic medication used in hepatic veno-occlusive disease.

**KEYWORDS:** Anagrelide, chronic myeloproliferative disorder, defibrotide, pulmonary hypertension, pulmonary veno-occlusive disease

A 66-yr-old female was admitted to the intensive care unit (ICU) for severe dyspnoea at rest and minor exertion (New York Heart Association (NYHA) class IV). Her past medical history was marked by a myeloproliferative and myelodysplastic syndrome, which was treated with hydroxyurea for 4 yrs. There was no clinical or radiographical evidence of a pre-existing pulmonary disease. Anagrelide, a selective inhibitor of megacaryocyte maturation, was introduced (4 mg·day<sup>-1</sup>) 6 weeks prior to admission because of refractory thrombocytopenia and hydroxyurea-induced neutropenia. After several weeks, the patient experienced a progressive worsening of dyspnoea resulting in orthopnoea. The patient also presented with a nonproductive cough, without fever.

On admission to the ICU, oxygen saturation on air was 75% and increased to 99% upon oxygen supply. Bibasilar rales were present on lung auscultation. A chest radiograph showed bilateral pulmonary infiltrates suggestive of pulmonary oedema. Helical angio-computed tomography (CT), ventilation-perfusion scans and echo-Doppler examination of the lower limb veins showed no pulmonary embolism or deep venous thrombosis. A bronchioloalveolar lavage demonstrated the absence of pathogenic organisms. Transthoracic echocardiography displayed a markedly dilated and hypocontractile right ventricle with paradoxical septal motion and an estimated pulmonary artery systolic pressure of >60 mmHg. There was no left sided myocardial (systolic and diastolic) dysfunction or valvular disease. High-resolution CT of the thorax showed dilatation of central pulmonary arteries, septal

thickening, diffuse ground-glass opacities and bilateral pleural effusion (fig. 1a). According to the clinical, echocardiographic and CT findings, pulmonary veno-occlusive disease (PVOD) was diagnosed. Right heart catheterisation confirmed pulmonary hypertension (pulmonary artery pressure: 69/31 mmHg; mean: 48 mmHg), and the pulmonary arterial occlusion pressure was 10 mmHg. The cardiac output was 3.9 L·min<sup>-1</sup> and the pulmonary vascular resistance was 779 dynes·s·cm<sup>-5</sup>. While well tolerated, inhaled nitric oxide failed to reverse pulmonary hypertension. Treatment with high doses of *i.v.* methylprednisolone (2 mg·kg<sup>-1</sup> *b.i.d.*), subcutaneous enoxaparin (40 mg *b.i.d.*), aspirin (100 mg *q.d.*) and *i.v.* defibrotide 60 mg·kg<sup>-1</sup> was initiated; anagrelide was replaced by hydroxyurea. After a 15-day course of treatment, this therapy resulted in clinical (NYHA class II), echocardiographic (decrease in right ventricular enlargement and septal dyskinesia) and radiological improvement (fig. 1b). Estimated systolic pulmonary artery pressure was 42 mmHg. Defibrotide was discontinued while enoxaparin (40 mg *q.d.*) and oral methylprednisolone (in tapered doses) were continued and the patient was discharged from hospital.

The clinical symptoms relapsed 2 months later and the patient was readmitted to the ICU because of severe pulmonary oedema requiring noninvasive ventilation. Chest radiographs showed severe diffuse pulmonary infiltrates. Echocardiography and thoracic CT scans demonstrated the recurrence of right ventricular dysfunction, pulmonary hypertension and pulmonary abnormalities, highly suggestive of PVOD.

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## STATEMENT OF INTEREST

A statement of interest for this study can be found at [www.erj.ersjournals.com/misc/statements.shtml](http://www.erj.ersjournals.com/misc/statements.shtml)

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A surgical lung biopsy was then performed. Histopathological examination disclosed a diffuse involvement of small and medium-sized veins by obliterative fibrosis. The walls of the veinules also showed medial thickening with duplication of the elastic lamina, resulting in the so-called arterialisatation phenomenon. Pulmonary arterioles exhibited moderate hypertrophy. There was irregular fibrosis of the lung parenchyma and abundant deposits of haemosiderin in the interstitium, as well as in alveolar macrophages (fig. 2). The diagnosis of PVOD was thereby definitely confirmed. After improvement with *i.v.* defibrotide and in the absence of proven medical treatment, it was decided to continue with oral administration of defibrotide (400 mg *b.i.d.*), concomitantly with aspirin (100 mg daily) and hydroxyurea (1,500 mg daily).

After 12 months of follow-up, the patient remained relatively asymptomatic (NYHA class II) and active in daily life; defibrotide therapy was then discontinued. Unfortunately, the pulmonary symptoms relapsed and the patient died 3 months later from refractory respiratory failure.

## DISCUSSION

PVOD is a rare, but probably under diagnosed, condition characterised by extensive occlusion of small pulmonary veins resulting in pulmonary hypertension and interstitial oedema in lobular septa [1]. PVOD is increasingly recognised as a cause of pulmonary hypertension occurring during the course of cytotoxic chemotherapy and haematopoietic stem cell transplantation [1, 2]. The prognosis is poor, with no currently effective medical treatment and most patients die a few months following diagnosis [2].

The major symptom is severe exertion dyspnoea. Chest radiographs suggests pulmonary oedema. A CT scan of the thorax typically shows interstitial oedema, ground-glass mosaic-attenuation pattern, interlobular septal thickening, enlarged central pulmonary arteries and normal calibre of pulmonary veins. Echocardiography highlights an enlarged right ventricle with moderate dysfunction and severe pulmonary hypertension in the absence of left-sided myocardial and valvular disease [2]. While clinical and radiographical findings often provide useful clues to the diagnosis [2], the definite confirmation of PVOD can only be

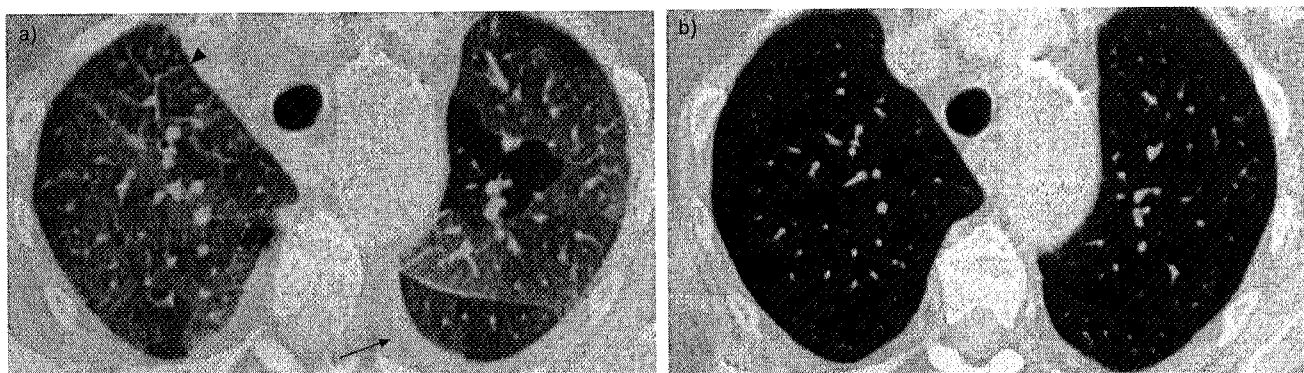
reliably made by lung biopsy. The prominent finding of PVOD is the obstruction of pulmonary veins and venules by fibrous tissue and secondary arteriolar media hypertrophy. Alveolar haemorrhage and haemosiderosis may also be present [1].

A study from the USA [3] suggested a surprisingly high incidence of severe unexplained pulmonary hypertension in patients with chronic myeloproliferative disorders. Indeed, the 26 cases reported in the referred population far exceed the 0.53 new cases expected in the entire USA population during the 13-yr observation period [3]. In the study by REISNER *et al.* [4], 13% of the patients with myeloproliferative disorders presented with pulmonary hypertension unrelated to cardiac disease. In most instances, the aetiology of pulmonary hypertension remained undetermined and aggressive treatment of the underlying haematological disease did not modify the course of pulmonary hypertension [3].

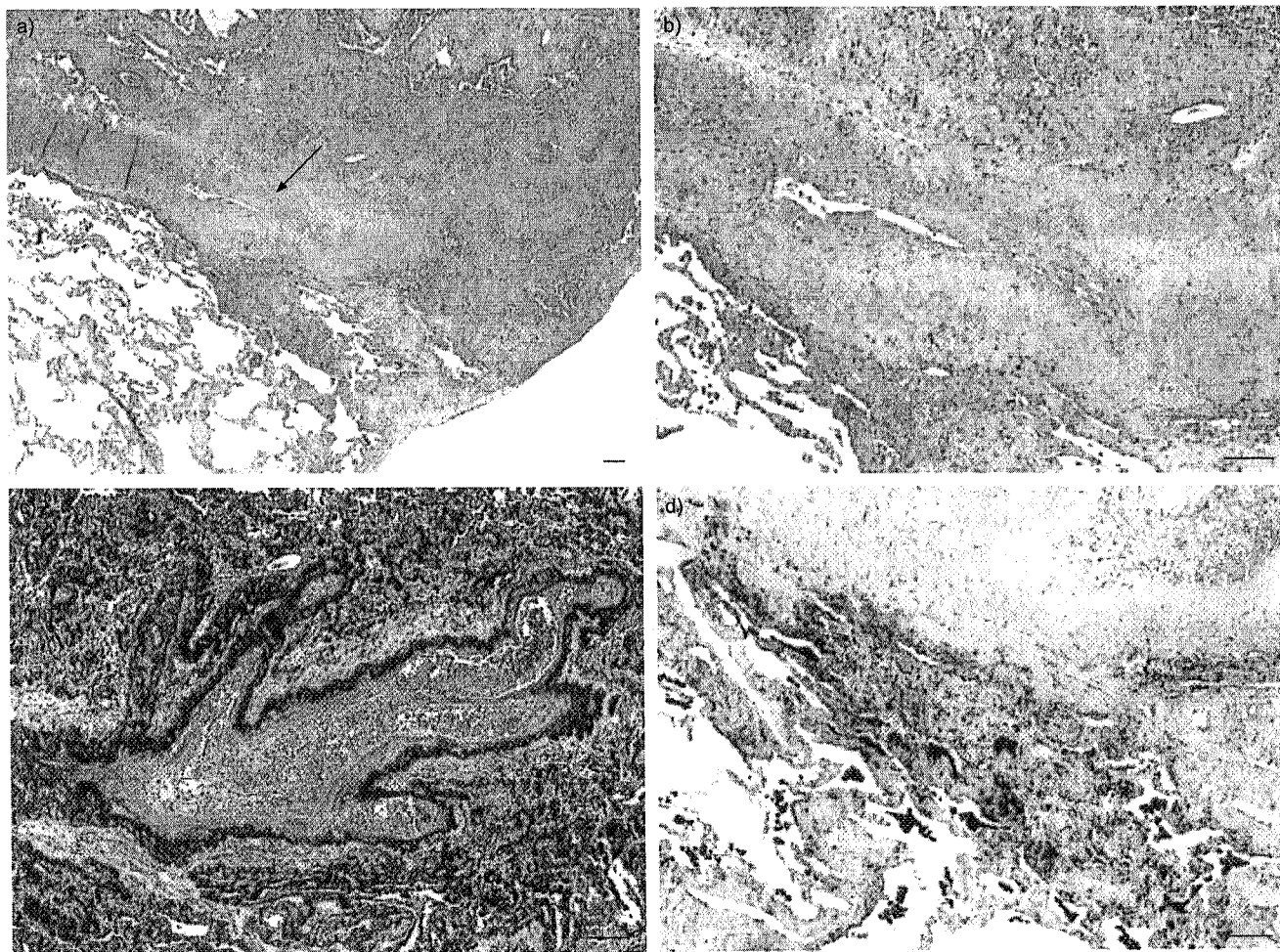
Although suspected, the presence of PVOD was, until now, not formally confirmed in patients with chronic myeloproliferative disorder in the absence of haematopoietic stem cell transplantation. Although a fortuitous association cannot be formally excluded, the case reported herein strongly suggests that PVOD should be considered in the differential diagnosis of pulmonary hypertension in patients with a chronic myeloproliferative disorder.

The close temporal relationship between the introduction of anagrelide and the development of the symptoms could suggest that this drug might be, at least partially, involved in the pathogenesis of the disorder in the patient. Indeed, the coexistence of a chronic myeloproliferative disorder and pulmonary hypertension has been reported previously in patients receiving anagrelide [3]. However, a clear temporal relationship between the introduction of the drug and the development of pulmonary symptoms was not evidenced by the authors [3]. Furthermore, while pulmonary infiltrates and pulmonary hypertension have already been reported in patients treated with anagrelide, a definite histological diagnosis of PVOD was not established [5].

There are few therapeutic options in PVOD and the patients usually respond poorly to the treatment [1, 6]. Vasodilator therapy can lead to disastrous outcomes; lung transplantation



**FIGURE 1.** a) Cross-sectional high-resolution computed tomography (HRCT) demonstrating mosaic-type, ground-glass opacity of both lungs, which is associated with interlobular septal thickening (arrowheads). The arrow indicates the presence of a small pleural effusion bilaterally. The central pulmonary veins and left atrium are normal (not shown). The findings are highly suggestive of pulmonary veno-occlusive disease. b) An HRCT image obtained at the same level as in a) following treatment with *i.v.* defibrotide, which shows complete resolution of ground-glass opacities, thickened interlobular septa and pleural effusion.



**FIGURE 2.** Histological staining of lung biopsy in pulmonary veno-occlusive disease. a) Low-power view showing thickening and partial luminal obliteration of a medium-sized vein in an interlobular septum (arrow), and partial fibrous obliteration of the surrounding lung parenchyma (haematoxylin–eosin stain). b) Higher-power view of the obliterated vein (haematoxylin–eosin stain). c) Elastin stain showing duplication of the elastic lamina, indicative of arteriolisation of the vein (orcein stain). d) Perl's iron stain showing coarse iron deposits in the pulmonary interstitium, as well as in alveolar macrophages. a–d) Scale bars=100 µm.

remains the only proven treatment [2]. As inflammatory and haemostasis disorders appear to be involved in veno-occlusive disease (VOD), steroids and low-molecular weight heparin have been advocated as empirical therapy in VOD. However, there is no evidence that they are effective [7]. Defibrotide, a deoxyribonucleic derivat, is an investigational drug that has been used successfully in hepatic VOD. Defibrotide has been defined as an orphan drug by the US Food and Drug Administration and by the European Commission to treat VOD. In a cohort study of 88 patients presenting with severe hepatic VOD after stem cell transplantation, a favourable response to defibrotide (median duration of treatment 15 days) was observed in 36% of the patients with 35% survival at 3 months of follow-up [8]. A phase III clinical trial is currently underway [9]. Defibrotide appears to be able to increase the fibrinolytic capacity and to reduce the pro-coagulant activity (antithrombotic effect) of the endothelial cells [10]. These actions are probably due to the drug's ability to selectively increase prostaglandin I<sub>2</sub> and E<sub>2</sub> levels and to increase tissue plasminogen activator and decrease plasminogen activator

inhibitor function [11]. To the best of the current authors' knowledge, defibrotide has never been used in PVOD. It cannot be claimed that the clinical improvement of the patient was exclusively due to defibrotide therapy because the patient was initially concurrently treated with enoxaparin, aspirin and tapered doses of methylprednisolone. However, this therapeutic combination resulted in the rapid resolution of clinical, echocardiographic and radiographic abnormalities. It should be emphasised that, contrary to defibrotide, neither low-molecular weight heparin nor steroids have demonstrated a favourable effect in VOD in large trials. Moreover, chronic oral administration of defibrotide (in association with aspirin) appeared to be effective in preventing the recurrence of symptoms, while discontinuation of defibrotide therapy was associated with clinical relapse.

In conclusion, pulmonary veno-occlusive disease should be considered as a potential cause of unexplained pulmonary hypertension in patients with chronic myeloproliferative disorder. A potential beneficial effect from defibrotide therapy has been suggested but requires further investigation.

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