CASE REPORT

Pulmonary veno-occlusive disease: an uncommon cause of pulmonary hypertension

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SUMMARY

Pulmonary veno-occlusive disease (PVOD) is a rare and challenging cause of pulmonary hypertension. Clinical presentation is non-specific, including dyspnoea, cough and fatigue. Diagnosis of PVOD is typically based on high clinical suspicion with a definitive diagnosis confirmed by histology. Our case involves a healthy 21-year-old man who developed dyspnoea on exertion at an elevated altitude during deployment to Afghanistan. His work-up included an echocardiogram, a high-resolution CT scan, V/Q scan, pulmonary function tests with diffusion capacity, and a cardiac catheterisation with vasodilator challenge. Initially diagnosed with vasodilator responsive pulmonary arterial hypertension, an oral vasodilator was given with subsequent development of non-cardiogenic pulmonary oedema, thus confirming a clinical diagnosis of PVOD. He was medically stabilised with diuretic therapy, but developed progressive right-ventricular failure. For definitive treatment, he underwent a successful bilateral lung transplant. Explanted lung histology confirmed the diagnosis of PVOD.

BACKGROUND

Pulmonary veno-occlusive disease (PVOD) is characterised by diffuse occlusion of the pulmonary veins by fibrous tissue, pulmonary venous congestion and associated complications including severe pulmonary hypertension (pHTN), non-cardiogenic pulmonary oedema, hypoxia and right-ventricular failure. Clinical presentation is typically non-specific, including dyspnoea, fatigue and cough. Diagnosis of PVOD is based on high clinical suspicion with a definitive diagnosis based on histological confirmation. Work-up routinely includes high-resolution thoracic CT scan, pulmonary function testing with diffusing capacity, V/Q scanning, echocardiogram and cardiac catheterisation. Unfortunately, PVOD is typically diagnosed late in its clinical course and often misdiagnosed as idiopathic pulmonary arterial hypertension (WHO class I PAH) leading to inappropriate medical therapy with pulmonary arterial vasodilators. At present, there are no medical therapies that prevent disease progression, and lung transplant is the only effective intervention that impacts on mortality. Since first described in 1966, definitive guidelines for diagnosis and optimal therapy are yet to be defined, making diagnosis and management challenging.

CASE PRESENTATION

A 21-year-old active-duty Caucasian male soldier with no pertinent medical, social, or family history

presented with several months of abdominal discomfort and a non-productive cough. Initial work-up included a chest x-ray and a chest/abdominal CT scan. He was noted to have mild mediastinal and abdominal lymphadenopathy and subtle ground-glass opacity in the right lower lobe which prompted referral for pulmonary consultation. Repeat thoracic CT scan revealed stable lymphadenopathy and resolution of the right lower lobe opacity. The patient denied physical limitations, was able to pass his army physical fitness test, including a 2 mile run, and was clinically diagnosed with stage I sarcoidosis. He elected to delay biopsy and was allowed to deploy to Afghanistan. While at an altitude of 3000 ft for approximately 3 months, he developed progressive dyspnoea with chest pain and presented to medical attention where an oxygen saturation of 65% prompted medical evacuation.

INVESTIGATIONS

An echocardiogram performed in Germany revealed a right ventricular systolic pressure of 88 mm Hg (severe pHTN) with normal left ventricular function, and he was evacuated back to the USA for further evaluation. Pulmonary function testing yielded normal spirometry with a severe reduction in diffusing capacity of the lung for carbon monoxide (DLCO) (adjusted for haemoglobin) of 5.06 mmol/min/kPa (31.9% predicted). V/Q scan was performed to exclude acute or chronic thromboembolism and was normal. Thoracic CT revealed interlobular septal thickening suggestive of PVOD (figure 1). He was then taken for a right and left heart catheterisation confirming severe

Figure 1 Intralobular septal thickening seen in the setting of pulmonary veno-occlusive disease.

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elevation of pulmonary artery pressures, pulmonary vascular resistance, normal capillary wedge pressure and normal wedge saturation. A positive vasodilator response to inhaled nitric oxide was observed.

DIFFERENTIAL DIAGNOSIS

Diagnosis of pHTN with a differential including

- ▶ Idiopathic PAH (WHO class I)
- ▶ PVOD

Supporting evidence

- ▶ Mediastinal lymphadenopathy
- ▶ Normal lung volumes with decreased DLCO
- ▶ Normal V/Q scan
- ▶ Cardiac catheterisation findings (elevated pulmonary artery pressures, a normal wedge pressure and a normal wedge saturation)
- ▶ A positive response to inhaled nitric oxide

TREATMENT

In an intensive care unit (ICU) setting, the patient was treated with oxygen, anticoagulation and oral sildenafil after consultation with the regional transplant centre. After 1 dose of sildenafil, he developed severe non-cardiogenic pulmonary oedema, bilateral pleural effusions and worsening oxygenation. This response to pulmonary arterial vasodilation clinically confirmed the diagnosis of PVOD. Sildenafil was stopped immediately, escalating doses of loop diuretic were initiated, and the patient was transferred to a regional transplant centre for expedited evaluation.

OUTCOME AND FOLLOW-UP

Upon arrival to the transplant centre and despite escalating doses of loop diuretics, the patient experienced rapidly progressive right-heart failure. He was admitted to the intensive care unit and stabilised with the addition of an inotropic support and continuous epoprostenol infusion therapy. The patient underwent successful bilateral lung transplantation. Explanted lung pathology confirmed the diagnosis of PVOD (figures 2–4). The patient tolerated the procedure well and has continued to recover.

DISCUSSION

PVOD is an often fatal disease frequently misdiagnosed as WHO class I PAH.¹ Proposed aetiologies include BMPR2 mutation, autoimmune disorders, exposure to chemotherapy, infection and thrombophilic disorders, but a definitive aetiology is

Figure 3 Vascular remodelling with pulmonary veno-occlusive disease: Fibrotic vein with duplication of the elastic lamina.

yet to be identified.² Clinical presentation is non-specific, including dyspnoea, fatigue and cough.³ Initial laboratory and radiological work-up is often non-specific or inappropriately suggestive of PAH.³ The diagnosis of PVOD is typically based on a high clinical suspicion, the presence of severe pulmonary hypertension, pulmonary venous congestion on high-resolution CT, mediastinal lymphadenopathy and haemodynamic findings on right-heart catheterisation (normal pulmonary artery occlusion pressure, normal wedge saturation and elevated mean pulmonary artery pressure and pulmonary vascular resistance).⁴ The presence of normal lung volumes with decreased diffusing capacity and the absence of a V/Q defect are also typical for PVOD.⁴ Definitive diagnosis is made by histological examination of either postmortem or explanted lung tissue (figures 2–4).³ The elevation in both pulmonary venous and arterial pressures makes the risk of life-threatening bleeding associated with bronchoscopic transbronchial lung biopsy excessive and is not recommended.³

PVOD treatment guidelines have not been defined. Smoking cessation should be strongly encouraged.⁵ Oxygen as well as avoiding exposure to high altitude will improve symptoms and reduce the likelihood of hypoxic-vasoconstriction.⁶ Therapeutic anticoagulation with Warfarin (goal International Normalised Ratio (INR) 1.5–2.5) is recommended to prevent venous thromboembolism as well as in situ pulmonary vascular thrombus formation.⁶ Diuretics are indicated for management of right-ventricular failure.⁴ Unfortunately, vasoreactivity testing is unable to predict the likelihood of developing pulmonary oedema following administration of pulmonary arterial

Figure 2 Vascular remodelling with pulmonary veno-occlusive disease: septal fibrosis vein fibrosis with occlusion of the native lumen.

Figure 4 Vascular remodelling with pulmonary veno-occlusive disease: Complete vein occlusion from intimal fibrosis.

vasodilators.⁷ Despite this concern, pulmonary arterial vasodilators (including sildenafil and epoprostenol) have been used successfully for the management of diuretic-refractory right-ventricular failure, and should be considered as a bridge to definitive management with lung transplantation.³

Without definitive treatment, the prognosis is poor for patients diagnosed with PVOD.⁵ The 1-year mortality is as high as 72% and the mean survival is estimated at 1–2 years.⁸ This short survival time is due to the relative rapid progressive nature of this disease, typical diagnosis late in its clinical course and a high frequency of misdiagnosis (PVOD accounting for 5–10% of cases initially believed to be PAH).⁴ Lung transplant is the only definitive therapy, and only those patients who are eligible for transplant and able to find a suitable donor have a reasonable chance of long-term survival.⁹

At this time, treatment options are limited and PVOD carries a poor prognosis with high 1-year mortality. Early diagnosis of PVOD and early referral for lung transplantation are critical in maximising the patient's survival.

Learning points

- ▶ Although rare, pulmonary veno-occlusive disease should be included in the differential diagnosis for pulmonary arterial hypertension.
- ▶ Prolonged exposure to high altitude and smoking may be precipitating factors.
- ▶ Vasodilators may cause pulmonary oedema and should be administered in a monitored setting.
- ▶ Lung transplant is the only definitive management option at this time and early identification with referral to a transplant centre is imperative.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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