Pulmonary Veno-occlusive Disease: A Sinister Cause of Heart Failure

Jeffrey Chun-Yin Lee, MBBS (HK), MRCP (UK), FHKCP, FHKAM
Cardiac Medical Unit, Grantham Hospital, Hong Kong

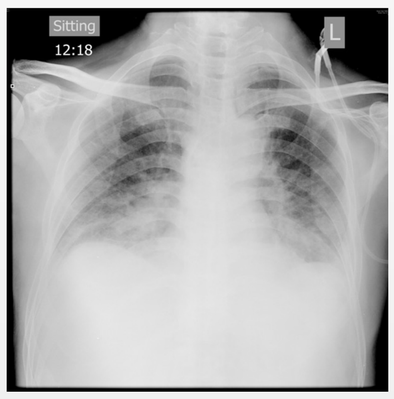
Introduction

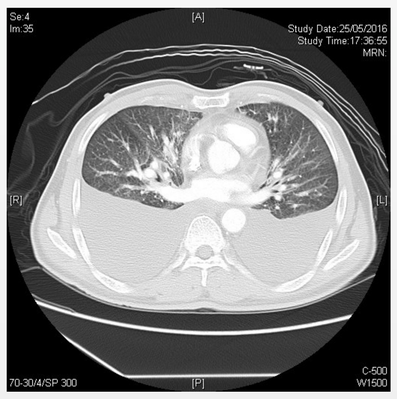
Pulmonary hypertension is a disease entity that is gaining more and more attention in recent decades, particularly with the development of new drug therapies. However, pulmonary veno-occlusive disease (PVOD) still remains an obscure diagnosis, due to the rarity of the condition, diagnostic difficulty and the lack of treatment options. We would like to report an encounter with a PVOD patient, the initial investigative challenges we faced, and the eventual awareness, diagnosis and treatment for this disease.

Case History

Our patient was a 58 years old man with a history of chronic myeloid leukaemia. He was treated with haemopoietic stem cell transplant (HSCT), and was given a pre-conditioning chemotherapy regimen of fludarabine and busulphan. His first procedure was unsuccessful and required a second HSCT (with another round of chemotherapy plus anti-thymocyte globulin) to achieve remission.

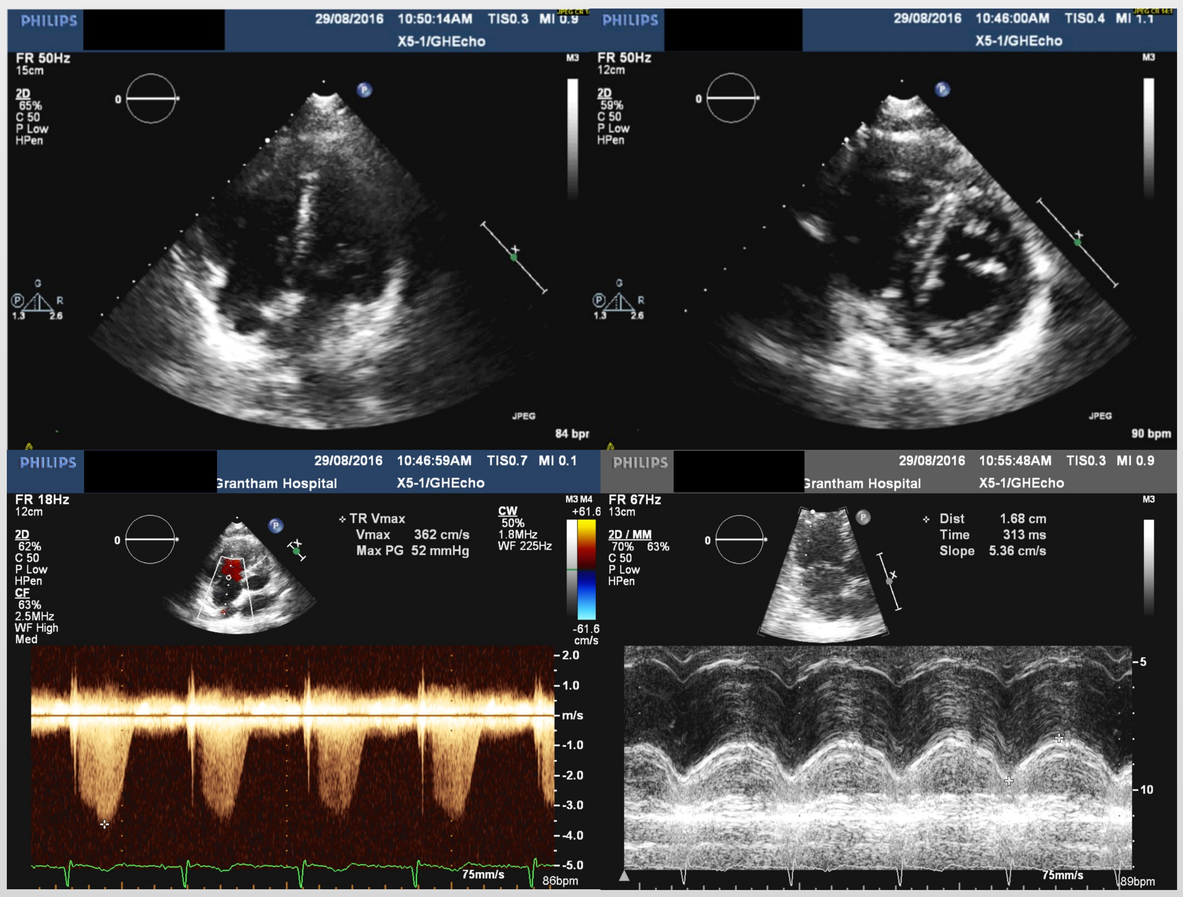
3 months later, he was admitted to another hospital for shortness of breath and acute pulmonary oedema (Figure 1). He was given intravenous diuretics with marked improvement in his symptoms. Echocardiogram was done, which showed a normal left ventricular (LV) ejection fraction, normal valves and mild diastolic dysfunction. He was hence labelled to have heart failure with preserved ejection fraction (HFpEF), and was discharged soon after. However, he was readmitted twice more in the next few weeks for shortness of breath. Further investigations were done including a contrast CT scan of the thorax (Figure 2). It only revealed non-specific findings, including a pleural effusion, diffuse ground glass opacities (GGOs) and prominent mediastinal lymph nodes. A bronchoscopy and biopsy of the lymph nodes were done, which revealed haemosiderin-laden macrophages and no malignant cells. Seeing that no specific findings were obtained, his diagnosis remained as HFpEF and he was referred to our centre for further evaluation of 'advanced heart failure'.





Figures 1 and 2: CXR showing congestion on presentation. CT thorax showing pleural effusion, pericardial effusion and GGOs.

On reassessment echo, which was performed three months after his initial presentation, we noted several interesting features (Figures 3-6). There was a dilated right ventricle (RV) with a D-shaped septum. M-mode and Doppler exam revealed a normal RV systolic function (TAPSE 1.7cm) and an elevated RV systolic pressure (RVSP) of 60mmHg. There was in fact a normal LV diastolic function by tissue doppler interrogation (average E/e' ratio = 5). Given the new echo findings, we began to question the diagnosis of HFpEF, and proceeded with a right heart catheterisation (RHC).



Figures 3-6: Echo findings showing a dilated RV on apical 4-chamber view and a flattened interventricular septum on short axis view. Doppler and M-mode showed an increased TR V_{max} of 3.6m/s, and a TAPSE of 1.7cm.

Diagnosis and Treatment

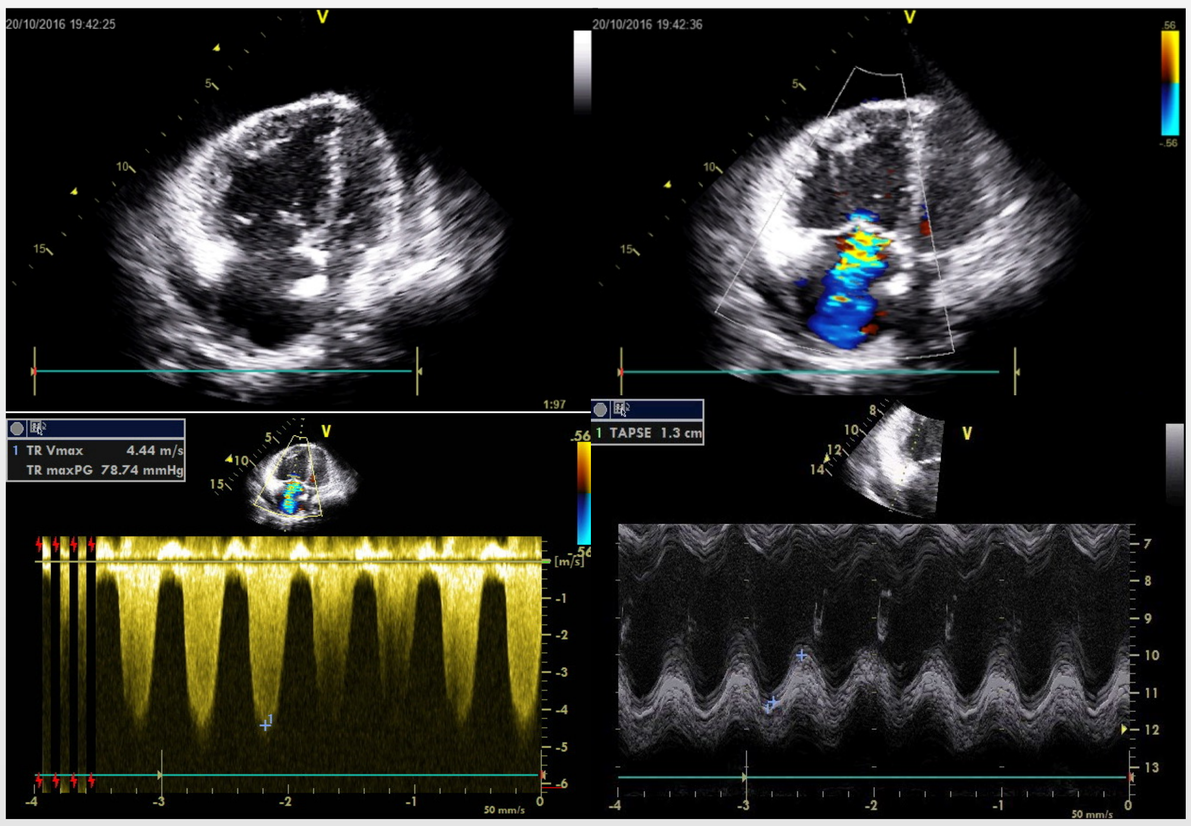
The RHC (Figure 7) showed an elevated mean pulmonary artery pressure (mPAP) of 37, normal capillary wedge pressure (PCWP) of 4 and an elevated pulmonary vascular resistance (PVR) of 7.7: i.e. haemodynamic findings compatible with Group 1 pulmonary hypertension (PH). There was no evidence of an intracardiac shunt. While the most straightforward diagnosis was seemingly pulmonary arterial hypertension (PAH), we felt that it could not fully explain the patient's clinical picture. When taking into account his age, symptoms, history of HSCT and other investigations (i.e. CT thorax and bronchoscopy findings), we came to the conclusion that PVOD was the most likely diagnosis.

	Baseline 2LO2	100% O2	100% O2 + NO 10ppm	100% O2 + NO 20ppm
RA (a/v/m)	3/2/1	-	-	-
RV (s/d/m)	57/0/5	-	-	-
PA (s/d/m)	58/21/37	42/19/29	32/24/23	34/11/22
PCWP (a/v/m)	6/6/4	5/4/4	6/4/4	6/5/4
Cardiac Output by Thermodilution(L/min)	4.3	3.77	3.9	4.0
Pulmonary Vascular Resistance (Wu)	7.7	6.6	4.9	4.5

Figure 7: Right heart catheterisation findings.

Subsequently, we started the patient on treatment with low dose sildenafil cautiously. Initially he showed poor tolerance to vasodilator therapy and developed pulmonary oedema, which also served as indirect evidence to support the diagnosis of PVOD. Gradually, he became more stabilised with the addition of oxygen and diuretics. At the same time, we also referred him to our lung transplant team for assessment.

Unfortunately, the patient deteriorated rapidly over the next few months. Serial echocardiogram showed a worsening RV function (TAPSE 1.3cm) and an RVSP of 100mmHg (Figures 8-11). There was also an enlarging pericardial effusion, severe tricuspid regurgitation and a compressed LV. A timely lung transplant could not be done and the patient succumbed soon after. A post-mortem examination confirmed the diagnosis of PVOD.



Figures 8-11: Serial echocardiogram showed worsening of the pericardial effusion and tricuspid regurgitation. The TR V_{max} is now increased to 4.4m/s, with a reduced TAPSE of 1.3cm.

Discussion

Our case illustrates that PVOD is a deadly and rapidly progressive disease. It has been known to be notoriously elusive, and is often misdiagnosed as PAH. While the true incidence remains unknown, some studies have estimated an annual incidence of 0.1-0.2 cases per million persons in the general population[1]. Typical risk factors include a history of chemotherapy exposure and HSCT, both of which were present in our patient[2]. In addition, PVOD tends to affect both sexes equally, and has a bimodal age distribution. Recognition of these characteristics may have been helpful in prompting an earlier diagnosis in our case.

Testing for PVOD is also challenging. A definitive diagnosis requires histological proof, i.e., a surgical lung biopsy. However, in reality, that is often difficult to arrange, and the underlying pulmonary hypertension confers a high risk of pulmonary haemorrhage. Non-invasive investigations may provide circumstantial evidence, but no one test is sensitive or specific enough to make the diagnosis. Common adjunctive tests include CT thorax and bronchoscopy. Classical CT findings include pleural effusion, GGOs and interlobular septal thickening; while bronchoscopy would often find haemosiderin-laden macrophages reflective of occult alveolar haemorrhage[3]. Lung function testing, if done, would show hypoxaemia and a low diffusing capacity of lungs for carbon monoxide (DLCO). RHC usually reveals Group 1 PH haemodynamics. Unfortunately, it cannot further differentiate between PAH and PVOD, as our current catheterisation techniques does not allow us to measure the pressure in the small pulmonary venules where PVOD occurs[4]. Despite the many supportive investigations that can be done, one still must have a very high index of suspicion in order to come to a unifying diagnosis of PVOD.

Lastly, regarding the treatment for PVOD, there are currently limited options. Lung transplant is the only curative treatment, but of course that is not easily available. PAH-specific drug therapies may be tried; however, it comes with the caveat that pulmonary oedema may develop. This is due to a preferential arteriolar vasodilation resulting in an increased transcapillary hydrostatic pressure into the alveolar space[5]. Hence, early recognition and early referral to a lung transplant unit is essential to improve patient outcomes.

In summary, this case illustrates the difficulties in diagnosing and treating PVOD. A high index of suspicion in a patient with typical risk factors is important to avoid a delay in diagnosis. Once diagnosed, PAH-specific drug therapies may be tried cautiously, and referral for lung transplant consideration is needed.

Acknowledgements & References

- **Prof. Guang-Ming Tan, Department of Medicine and Therapeutics, The Chinese University of Hong Kong**
- **Dr. Lap Tin Lam, Cardiac Medical Unit, Grantham Hospital, Hong Kong**

We have no conflict of interest to report

1. Rubin LJ. Primary pulmonary hypertension. N Engl J Med. 1997 Jan 9;336(2):111-7.
2. Ranchoux B. et al. Chemotherapy-induced pulmonary hypertension: role of alkylating agents. Am J Pathol. 2015 Feb;185(2):356-71.
3. Pérez Núñez M et al. Radiological Findings in Multidetector Computed Tomography (MDCT) of Hereditary and Sporadic Pulmonary Veno-Occlusive Disease: Certainties and Uncertainties. Diagnostics (Basel). 2021 Jan 19;11(1):141.
4. Weed HG. Pulmonary "capillary" wedge pressure not the pressure in the pulmonary capillaries. Chest. 1991 Oct;100(4):1138-40.
5. Montani D et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. Eur Heart J. 2010 Aug;31(15):1898-907.