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Review

Computed tomographic and clinical features of pulmonary veno-occlusive disease: raising the radiologist's awareness

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Pulmonary veno-occlusive disease (PVOD) is a rare subtype of pulmonary arterial hypertension (PAH) characterised by preferential remodelling of the pulmonary venules. Differentiation from other subtypes of PAH is essential as the management can differ significantly; for example, initiation of vasodilator therapy may cause fatal pulmonary oedema in a patient with PVOD misdiagnosed with idiopathic PAH. PVOD also carries a substantially worse prognosis. Lung biopsy is required for definitive diagnosis, but this is hazardous, and ideally, should be avoided in pulmonary hypertension. Computed tomography (CT) may suggest the diagnosis, directing the patient towards specialist review. Potential distinguishing CT features between PVOD and other subtypes of PAH include interlobular septal thickening, mediastinal lymphadenopathy, and centrilobular ground-glass opacities. No evidence-based medical therapy exists for PVOD at present and lung transplantation remains the definitive treatment for eligible patients. Therefore, early radiological identification of this challenging diagnosis facilitates timely referral for transplant.

Introduction

The European Society of Cardiology and European Respiratory Society published guidelines in 2015 on the diagnosis and management of pulmonary hypertension (PH) dividing it into five categories according to aetiology (Table 1).[1–3] Group 1 consists of pulmonary arterial hypertension (PAH) and its subtypes, describing a group of patients with pre-capillary PH not due to other causes such as lung disease; group 2 is PH associated with left heart disease; group 3 is PH associated with lung disease and/or hypoxia; group 4 is PH due to chronic thromboembolic disease; and group 5 are miscellaneous conditions, such as sarcoidosis.

PVOD is classified as a sub-type within group 1, alongside pulmonary capillary haemangiomatosis (PCH). Once thought separate entities, PVOD and PCH are now considered varied expressions of the same disease process.[1] There is significant histological overlap[4] and clinicoradiological features are almost indistinguishable.[1,5–7] This paper

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Table 1
Clinical classification of pulmonary hypertension according to European Society of Cardiology/European Respiratory Society Guidelines.[3]

1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1'.1 Idiopathic
1'.2 Heritable
1'.2.1 EIF2AK4 mutation
1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
1'.4.1 Connective tissue disease
1'.4.2 HIV infection
1". Persistent pulmonary hypertension of the newborn hypertension due to left heart d
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumours
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders
5.4 Others: pulmonary tumoural thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

BMPR2, bone morphogenetic protein receptor, type 2; EIF2AK4, eukaryotic translation initiation factor 2 alpha kinase 4; HIV, human immunodeficiency virus.

reviews the aetiology, epidemiology, histopathology, clinical features, and prognosis of PVOD. Issues for the clinician and challenges for the radiologist in PVOD are then discussed. Finally, a potential imaging approach to making the diagnosis is proposed.

Aetiology

Traditionally, PVOD was felt to be an idiopathic process,[8] but multiple case reports and series have demonstrated congenital and acquired associations. Recently, a heritable form of the disease was discovered, caused by a bi-allelic mutation in the *EIF2AK4* (eukaryotic translation initiation factor 2 alpha kinase 4) gene.[9–11] One study demonstrated that compared to PAH patients without this mutation, EIF2AK4 mutants tend to be younger at diagnosis (29 versus 51) with a significantly higher frequency of mediastinal lymphadenopathy (27% versus 5%) and interlobular septal thickening (57% versus 0%) on computed tomography (CT).[12] There have also been reported associations of PVOD with BMPR-II gene mutations, classically associated with PAH.[13,14]

Multiple acquired risk factors for PVOD have been suggested. A viral aetiology has been proposed, including an association with human immunodeficiency virus (HIV) infection.[4,15,16] Several toxin-mediated associations have also been found.[13,17–22] Further associations with connective tissue disease have been made, particularly systemic sclerosis.[23–25] In this scenario, sometimes subtle CT findings can highlight the association.

Epidemiology

It has been difficult to establish a precise incidence and prevalence of PVOD due to vague clinical features, lack of non-invasive confirmatory tests, a lack of recognition of the disease process, and misdiagnosis of PVOD as PAH; however, data from a number of case series with histological tissue examination from patients labelled with idiopathic PAH show that 10% of these have histological features compatible with PVOD.[15] Through applying this percentage to a known incidence of idiopathic PAH, calculated from a French PAH registry of 456 patients, the incidence of PVOD can be estimated at between 0.1–0.2 cases per million.[13,26]

PVOD most commonly occurs in children and young adults, although reported age at diagnosis ranges from 8 weeks to the seventh decade.[1,4,27] Mean ages for all sporadic cases of PVOD are normally within the third decade.[4,27] The heritable form is more frequently encountered in a younger age group.[11] In addition, the sporadic form of PVOD is more likely to have a predilection for males, in contrast to PAH, which has a female bias.[1,4]

The vascular bed and histopathology

Fig 1a demonstrates a schematic diagram of the normal pulmonary vascular bed. Deoxygenated blood from the right ventricle passes via the pulmonary arteries to the vascular bed. It will then pass through the pulmonary arterioles, the capillaries (where gas exchange takes place)

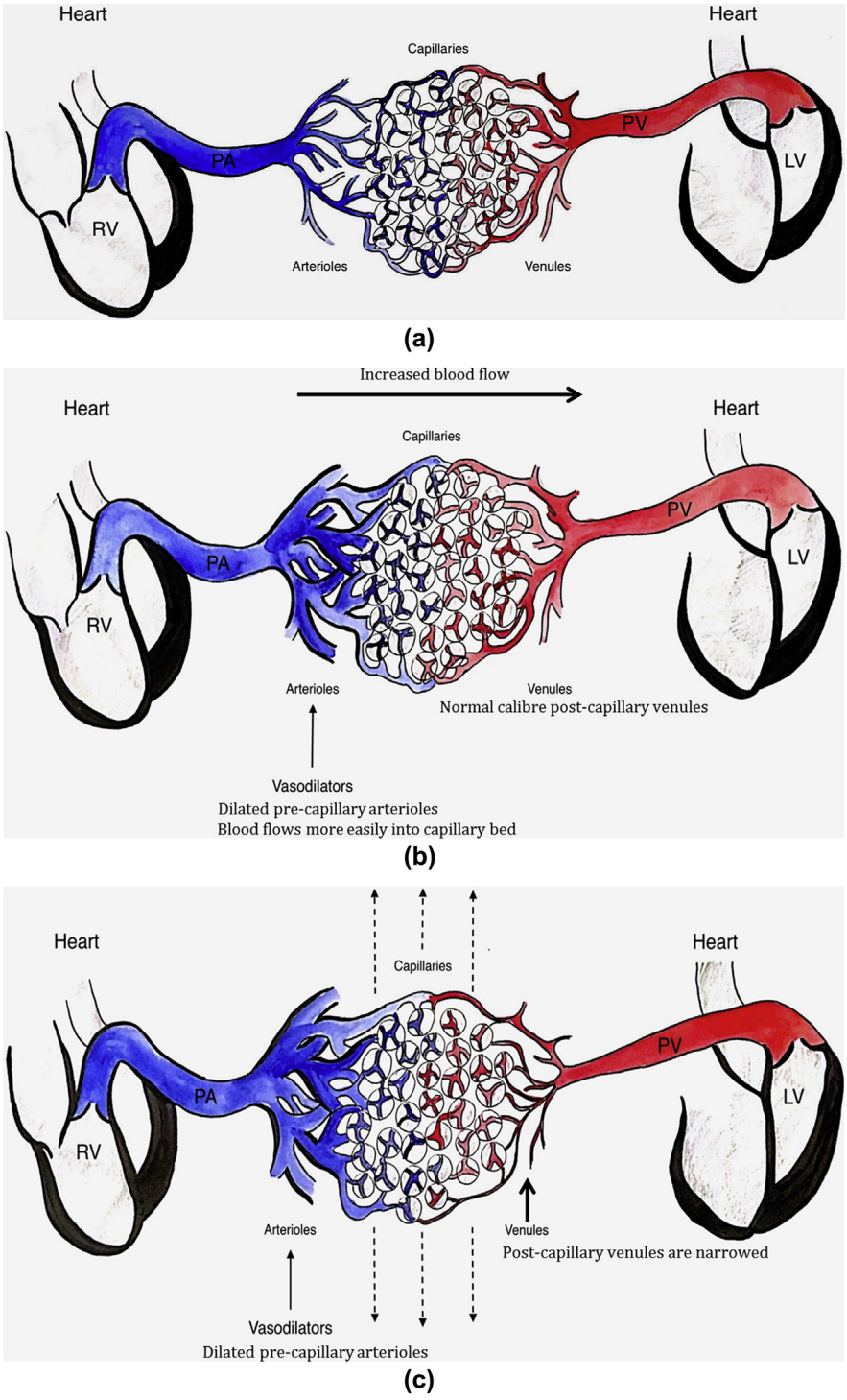

Figure 1 (a) Normal pulmonary vascular bed showing pre-capillary arterioles, capillaries, and post-capillary venules. (b) Pulmonary vascular bed. Potent vasodilators in traditional pulmonary hypertension therapy will target the pre-capillary arteriole causing dilatation. (c) Pulmonary vascular bed in PVOD. Dilated pre-capillary arterioles can result in an increase in hydrostatic pressure and pulmonary oedema due to the fixed, narrowed post-capillary venules.

and return to the left atrium via the post-capillary venules and pulmonary veins.

In PAH the pre-capillary arterioles become narrowed due to vascular remodelling, leading to a rise in pulmonary vascular resistance and hence right ventricular afterload. Modern PAH drug therapy targets and partially reverses these arteriolar changes, hence allowing blood to flow more easily into the capillary bed[28] (Fig 1b); however, in PVOD, it is the post-capillary venules that become narrowed by a similar vascular remodelling process.[29] If PVOD is

inadvertently treated with PAH therapy, the pre-capillary arterioles become inappropriately dilated whilst the post-capillary pulmonary veins remains narrowed. This can lead to an increase in trans-capillary hydrostatic pressure, resulting in pulmonary oedema[13] (Fig 1c).

In reality, it is likely that few patients exhibit "pure" PVOD changes affecting only the venous side of the pulmonary circulation, or "pure" PAH changes affecting only the arterial side. Instead, many PVOD patients most likely have a lesser degree of change within their arterial vascular bed.[27,30] Similarly, patients with PAH can also have an overlap, where disease is centred predominantly on the arterial side of the capillary bed, but there may be an additional post-capillary venous component. This variability can affect the patient's presentation, CT findings, and management, and in our experience is seen most commonly in the setting of systemic sclerosis associated PAH.

PCH is characterised by capillary proliferation within alveolar walls, causing secondary venous occlusion further downstream, and hence, a similar process to PVOD with intimal fibrosis and medial hypertrophy.[4]

Clinical features

Initially, patients with PVOD present similarly to patients with other forms of PH. The key presenting feature is exertional dyspnoea, which starts innocuously, but is progressive over time. As pulmonary arterial pressures rises other symptoms emerge, including: fluid retention, as the right ventricle (RV) fails; pre-syncope on extreme exertion as the RV becomes unable to increase cardiac output in response to demand; palpitations as the dilated heart becomes more susceptible to arrhythmias; and exertional angina as the hypertrophied RV's increasing metabolic requirements outstrip its supply. Superimposed on this, PVOD patients can also develop signs of pulmonary congestion, particularly if started on vasoactive PAH therapy (Fig 1c); these symptoms include worsening exertional dyspnoea, orthopnoea, and paroxysmal nocturnal dyspnoea.[13]

Prognosis

The prognosis for PVOD is poor and significantly worse than PAH.[13] Cases series have shown that the majority of patients diagnosed with PVOD will die within a year of diagnosis if they do not receive lung transplantation.[1,4,27] Willie *et al.* compared the outcomes for PVOD patients awaiting lung transplantation to those with PAH, and found that those with PVOD were twice as likely to die before a transplant became available, despite similar initial lung allocation scores aimed to prioritise the need for lung transplant.[31] Tejedor *et al.* examined a series of patients with a heritable form of PVOD, distinguishing two clinical phenotypes based on tolerance to pulmonary vasodilators. They found that those who were intolerant had a clinically and histologically more aggressive phenotype with a worse prognosis.[11]

Issues for the clinician

Clinicians should be alert to the possibility of PVOD in patients who present with debilitating breathlessness that seems disproportionate to the degree of pulmonary hypertension seen at echocardiography and/or right heart catheterisation. Unlike patients with "pure" PAH, these patients tend to have low transfer factor readings at lung function testing, desaturate and develop resting hypoxia. If initiated on vasoactive therapy, PVOD patients typically develop symptoms and signs of pulmonary oedema, usually presenting with orthopnoea and worsening hypoxia. PVOD patients can usually be distinguished from those with PH secondary to left heart disease through the absence of left heart pathology at echocardiography and by the presence of a normal post-capillary wedge pressure reading at right heart catheterisation.

Challenges for the radiologist

Radiologists may see patients with primary idiopathic "pure' PVOD; PVOD associated with connective tissue disease (especially systemic sclerosis); idiopathic PAH (IPAH) or PAH associated with connective tissue disease (CTD-PAH) where there is the suggestion of a "post-capillary venous component" to their disease (see below); and latent left heart disease deteriorating on PAH therapy.

Across all these scenarios, the imaging can range from subtle to overt, but shows consistent themes. It is important for the radiologist to be alert to these and suggest the potential diagnosis of either PVOD or a PVOD mimic. Although the radiologist may be able to suggest the possibility of PVOD, other investigations may support the diagnosis, as outlined in "issues for the clinician".

CTPA and HRCT: an approach for the radiologist (Fig 2)

Step 1

Initially, generic CT features of PH (common to all five PH sub-groups) should be assessed: dilated main pulmonary artery (MPA); RV enlargement and RV hypertrophy[32,33]; however, it is not uncommon for patients with PVOD to present with dyspnoea before pulmonary pressures become significantly elevated and these CT features may be absent.

Step 2

There should then be a review of the triad of ancillary PVOD findings: ground-glass nodules/opacities, lymphadenopathy, and smooth bilateral interlobular septal thickening. A study comparing cases of biopsy-proven PVOD with cases of biopsy-proven PAH demonstrated that this triad was present in 65% of the PVOD patients (Figs 3 and 4) and each feature was individually significantly more common in the PVOD group.[13] The study also demonstrated that the presence of two of these features

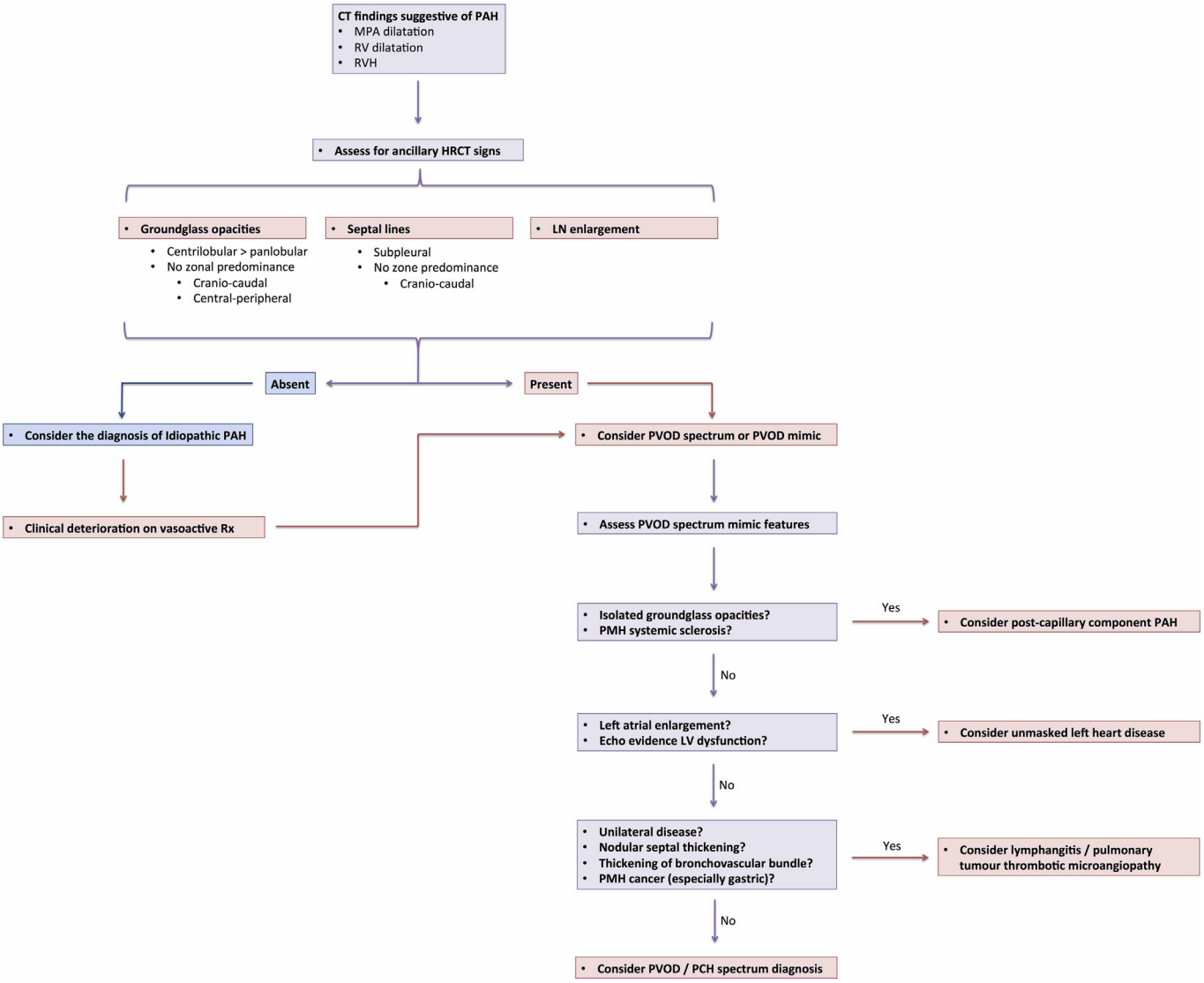

Figure 2 An approach to the CT findings of PVOD/PVOD spectrum.

demonstrated a 75% sensitivity and 85% specificity for PVOD. Another study revealed that a centrilobular (versus pan-lobular) distribution of ground-glass nodules was significantly associated with PVOD and the distribution of ground-glass opacities was random in both a craniocaudal and central–peripheral direction (73% and 80% respectively) in the majority of cases.[5] Ground-glass opacities are common in PAH in general, for example, one study reviewing cases referred to a PH centre demonstrated 41% of all patients with PAH had ground-glass opacities on CT, with the predominant pattern centrilobular.[34] Therefore, it is important to assess for the additional features of lymphadenopathy and septal thickening. Mediastinal lymphadenopathy is defined as lymph nodes with a short axis diameter >10 mm, aside from subcarinal nodes, which are enlarged if short axis is >12 mm.[35] When the triad of ancillary findings is present, PVOD or a PVOD mimic should be considered from the outset. Pleural and pericardial effusions are also sporadically reported in PVOD.[32,36,37] If the ancillary findings are absent, the patient may have IPAH; however, even then PVOD is not fully excluded and the diagnosis should be revisited in cases of apparent IPAH where there is a clinical deterioration after commencement of vasoactive treatment.

Step 3

Once PVOD is suspected, a systematic approach can help to distinguish specific aetiologies. As described above, the "PVOD spectrum" encompasses[1]: primary PVOD and PCH[2]; PVOD associated with CTD-PAH (especially systemic sclerosis), and[3] cases of IPAH or CTD-PAH where there is the suggestion of a post-capillary venous component to their PAH. The differentiation of connective tissue disease patients falling in to points[2] and[3] is essentially a spectrum of disease severity. The radiologist should consider any additional clinical history suggesting a concomitant connective tissue disease and evaluate the CT images for a dilated

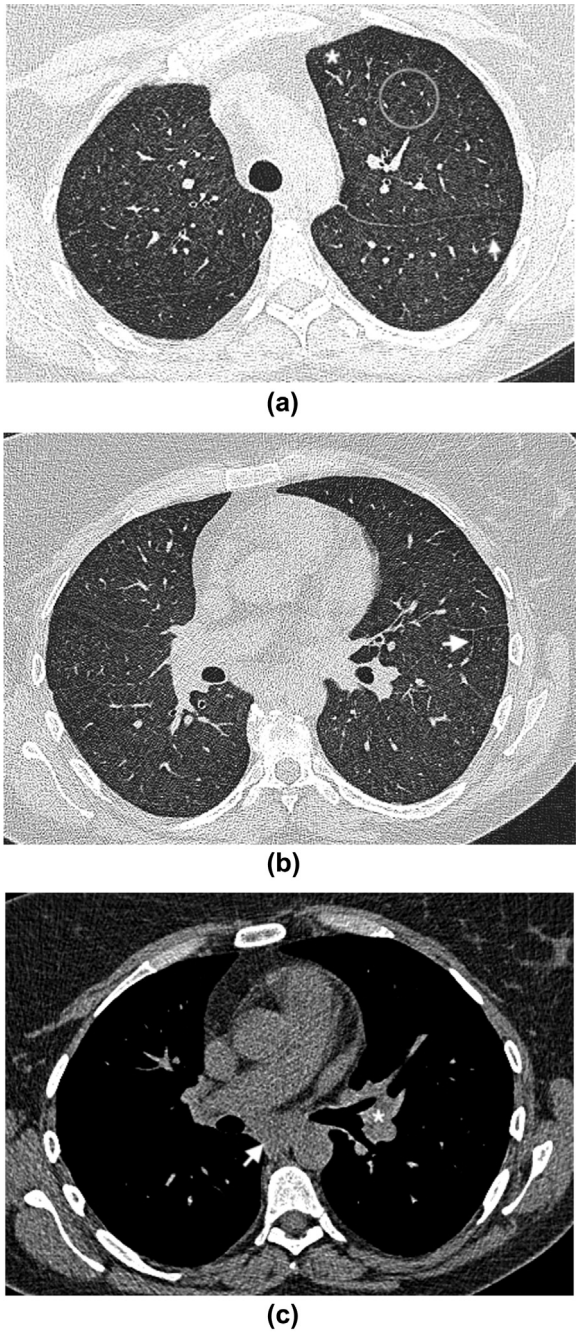

Figure 3 High-resolution CT images of a 44-year-old woman with PVOD. (a–b) Lung windows demonstrate relatively diffuse ground-glass nodules (encircled), compared with a relatively normal subpleural area of lung (asterisk), with several interlobular septa (arrows). (c) Mediastinal windows show an enlarged subcarinal lymph node (arrow) and mildly prominent left hilar nodes (asterisk).

oesophagus, commonly seen in systemic sclerosis. Like others, we have noticed that in PAH related to systemic sclerosis (and less commonly IPAH), the triad of CT features seen in PVOD may be present, most notably the ground-glass nodularity (Fig 5). In these cases, there has been no other reason for these opacities to develop (step 4 below). Anecdotally, these patients may have more severe disease

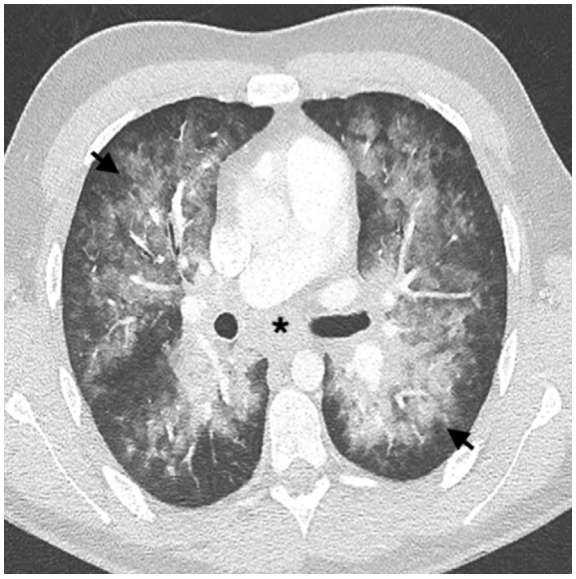

Figure 4 CTPA of biopsy-proven PCH. There is widespread ground-glass change (arrows) and lymphadenopathy (asterisk).

and be more resistant to treatment. As these CT findings are seen in PVOD, it raises the possibility of a "post-capillary venous component" to their PAH. This is supported by the fact that Gunther and Connolly have shown that the presence of ground-glass nodules in scleroderma was associated with pulmonary oedema on therapy and a trend towards worse survival, likely a manifestation of a post-capillary venular vasculopathy.[38,39] Other authors suggest that these CT findings are a manifestation of more severe PH.[33] One study has demonstrated that ground-glass opacities in scleroderma patients with PH have a higher frequency of a central rather than peripheral distribution than other subtypes.[34] The exact aetiology of the ground-glass nodules in PAH is poorly understood with reports suggesting they are cholesterol granulomas, plexiform arterial lesions, or foci of recurrent haemorrhage.[40–43]

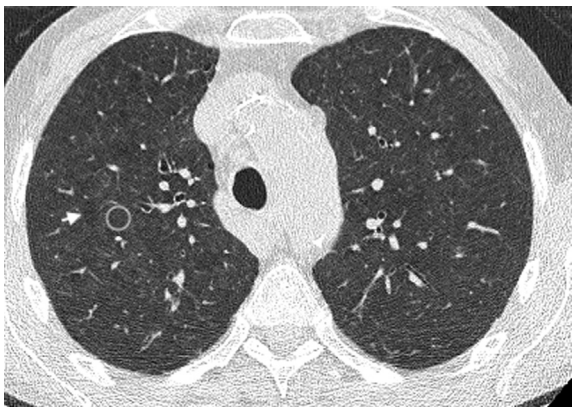

Figure 5 High-resolution CT of a 68-year-old woman with known scleroderma demonstrates scattered areas of ground-glass opacity (encircled) adjacent to normal lucent lung parenchyma (arrow).

The importance of the CT findings is crucial for the radiologist to appreciate for several reasons. Firstly, as they are seen in IPAH and CTD-PAH, the age range at presentation may be wider than seen in "pure" PVOD; secondly, in CTD-PAH these ground-glass changes can be mistaken for early interstitial lung disease, such as non-specific interstitial pneumonia (NSIP). Finally, the suggestion that there may be a post-capillary venous component is crucial for treatment. Although PAH therapy may be tried (it is a relative not absolute contraindication), it will be done so more cautiously to avoid exacerbating the disease (Fig 6) or inducing pulmonary oedema.

Step 4

Clinical deterioration on vasoactive PH treatment can be a result of post-capillary venous component of disease as mentioned in step 3; however, another consideration is latent left heart disease (a PVOD mimic) where elevated left atrial pressure and pulmonary venous hypertension may be unmasked by inadvertently administering PAH therapy. This causes an increase in trans-capillary hydrostatic pressure and pulmonary oedema. There may be direct evidence of left heart disease even on non-electrocardiography (ECG)-gated CT, such as left atrial dilatation, left ventricular dilatation, and heavy coronary artery calcification, as well as indirect evidence such as bilateral pleural effusions. All patients with PH should have had an echocardiogram. If available, reviewing the report and/or images can help confirm or refute this mimic.

Step 5

Additional PVOD mimics to consider include lymphangitis carcinomatosis and pulmonary tumour thrombotic microangiopathy (PTTM; Fig 7). Unilateral findings should alert the radiologist to the possibility of lymphangitis. Scrutinising the septal line prominence for nodularity and assessing the bronchovascular bundle for thickening may also suggest lymphangitis. CT features in PTTM can be strikingly similar to PVOD and is most commonly seen in gastric cancer, but also in several other malignancies including lung, breast, and colon.

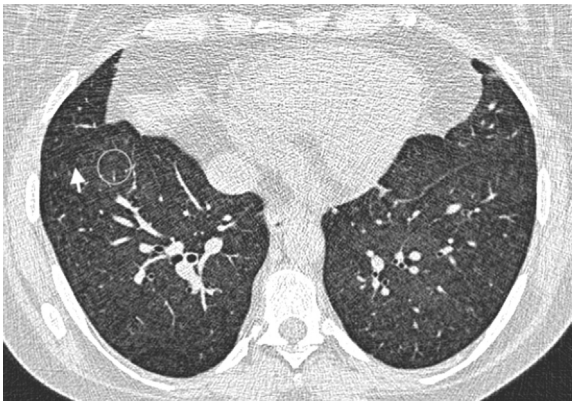

Figure 6 A 44-year-old woman with PVOD and scleroderma. Initial high-resolution CT (not shown) was near normal, with only a few scattered septa and an initial diagnosis of IPAH was made. Six months post-treatment, the patient's symptoms deteriorated, and repeat high-resolution CT showed the development of widespread nodular ground-glass change. An abnormal area of ground glass is shown (encircled) next to an adjacent normal lucent area of lung (arrow).

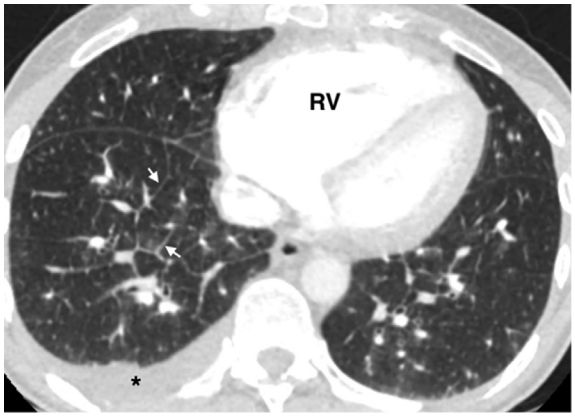

Figure 7 A 39-year-old woman presenting with presumed IPAH. CT pulmonary angiography demonstrates large RV, right pleural effusion (asterisk), and septal lines (arrows). The left atrium was normal sized and PVOD was considered. The patient subsequently died and histology showed micro-tumour emboli.

Step 6

Once the systematic algorithm has been worked through and potential mimics are excluded or considered unlikely (and especially if two or more of the PVOD CT triad are present), then the diagnosis of PVOD/PCH should be entertained and urgent specialist referral suggested in the radiological report.

Conclusion

PVOD is a disease predominantly affecting young adults and the outcome is invariably fatal if it is not diagnosed promptly and referred for the only definitive treatment of lung transplantation. Key differentiators found on CT between PAH and PVOD are centrilobular ground-glass nodules/opacities, septal lines, and lymphadenopathy; however, patients with IPAH and PAH associated with connective tissue disease may also present with some (or all) of this CT triad and the radiologist is in a key position to raise the possibility of a "post-capillary venous component" to the disease process or associated PVOD, both of which will affect treatment decisions.

Conflict of interest

The authors declare no conflict of interest.

References

1. Montani D, Lau EM, Dorfmüller P, *et al.* Pulmonary veno-occlusive disease. *Eur Respir J* 2016;**47**(5):1518–34.

2. Galiè N, Humbert M, Vachiery J-L, *et al*. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016;**37**(1):67–119.
3. Galiè N, Humbert M, Vachiery J-L, *et al*. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015;**46**(4):903–75.
4. Lantuejoul S, Sheppard MN, Corrin B, *et al*. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: a clinicopathologic study of 35 cases. *Am J Surg Pathol* 2006;**30**(7):850–7.
5. Resten A, Maitre S, Humbert M, *et al*. Pulmonary hypertension: CT of the chest in pulmonary venoocclusive disease. *AJR Am J Roentgenol* 2004;**183**(1):65–70.
6. Best DH, Sumner KL, Austin ED, *et al*. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. *Chest* 2014;**145**(2):231–6.
7. Huertas A, Girerd B, Dorfmuller P, *et al*. Pulmonary veno-occlusive disease: advances in clinical management and treatments. *Expert Rev Respir Med* 2011;**5**(2):217–31.
8. Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension: a pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation* 1970;**42**(6):1163–84.
9. Eyries M, Montani D, Girerd B, *et al*. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet* 2014;**46**(1):65–9.
10. Tenorio J, Navas P, Barrios E, *et al*. A founder EIF2AK4 mutation causes an aggressive form of pulmonary arterial hypertension in Iberian Gypsies. *Clin Genet* 2015;**88**(6):579–83.
11. Navas Tejedor P, Palomino Doza J, Tenorio Castaño JA, *et al*. Variable expressivity of a founder mutation in the EIF2AK4 gene in hereditary pulmonary veno-occlusive disease and its impact on survival. *Rev Española Cardiol (English Ed)* 2018 Feb;**71**(2):86–94.
12. Hadinnapola C, Bleda M, Haimel M, *et al*. Phenotypic characterization of EIF2AK4 mutation carriers in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. *Circulation* 2017;**136**(21):2022–33.
13. Montani D, Achouh L, Dorfmüller P, *et al*. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine (Baltimore)* 2008;**87**(4):220–33.
14. Runo JR, Vnencak-jones CL, Prince M, *et al*. Case report pulmonary veno-occlusive disease caused by an inherited mutation in bone morphogenetic protein receptor II. *Am J Respir Crit Care Med* 2003;**167**:889–94.
15. Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. *Am J Respir Crit Care Med* 2000;**162**(5):1964–73.
16. Escamilla R, Hermant C, Berjaud J, *et al*. Pulmonary veno-occlusive disease in a HIV-infected intravenous drug abuser. *Eur Respir J* 1995;**8**(11):1982–4.
17. Ranchoux B, Günther S, Quarck R, *et al*. Chemotherapy-induced pulmonary hypertension. *Am J Pathol* 2015;**185**(2):356–71.
18. Gagnadoux F, Capron F, Lebeau B. Pulmonary veno-occlusive disease after neoadjuvant mitomycin chemotherapy and surgery for lung carcinoma. *Lung Cancer* 2002;**36**(2):213–5.
19. Perros F, Günther S, Ranchoux B, *et al*. Mitomycin-induced pulmonary veno-occlusive disease. *Circulation* 2015;**132**(9):834.
20. Montani D, Lau EM, Descatha A, *et al*. Occupational exposure to organic solvents: a risk factor for pulmonary veno-occlusive disease. *Eur Respir J* 2015;**46**(6):1721.
21. Kramer MR, Estenne M, Berkman N, *et al*. Radiation-induced pulmonary veno-occlusive disease. *Chest* 1993;**104**(4):1282–4.
22. Townend JN, Roberts DH, Jones EL, *et al*. Fatal pulmonary venoocclusive disease after use of oral contraceptives. *Am Heart J* 1992;**124**(6):1643–4.
23. Günther S, Jaïs X, Maitre S, *et al*. Computed tomography findings of pulmonary veno-occlusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheum* 2012;**64**(9):2995–3005.
24. Dorfmüller P, Humbert M, Perros F, *et al*. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. *Hum Pathol* 2007;**38**(6):893–902.
25. Zhang L, Visscher D, Rihal C, *et al*. Pulmonary veno-occlusive disease as a primary cause of pulmonary hypertension in a patient with mixed connective tissue disease. *Rheumatol Int* 2007;**27**(12):1163–5.
26. Grosse C, Grosse A. CT findings in diseases associated with pulmonary hypertension: a current review. *RadioGraphics* 2010;**30**(7):1753–77.
27. Barry Jr W, Loyd JE, Ely W, *et al*. Pulmonary veno-occlusive disease. *Chest* 2000;**118**(6). 1671–1671.
28. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004. Sep 30;**351**(14):1425–36.
29. Pietra GG, Capron F, Stewart S, *et al*. Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol* 2004;**43**. S25–32.
30. Jonigk D, Golpon H, Bockmeyer CL, *et al*. Plexiform lesions in pulmonary arterial hypertension: composition, architecture, and microenvironment. *Am J Pathol* 2011;**179**(1):167–79.
31. Wille KM, Sharma NS, Kulkarni T, *et al*. Characteristics of patients with pulmonary venoocclusive disease awaiting transplantation. *Ann Am Thorac Soc* 2014 Nov;**11**(9):1411–8.
32. Frazier AA, Franks TJ, Mohammed T-LH, *et al*. From the Archives of the AFIP: pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. *RadioGraphics* 2007;**27**:867–82.
33. Aluja Jaramillo F, Gutierrez FR, Díaz Telli FG, *et al*. Approach to pulmonary hypertension: from CT to clinical diagnosis. *RadioGraphics* 2018;**38**(2):357–73.
34. Rajaram S, Swift AJ, Condliffe R, *et al*. CT features of pulmonary arterial hypertension and its major subtypes: a systematic CT evaluation of 292 patients from the ASPIRE Registry. *Thorax* 2015;**70**(4):382–7.
35. Kay C, Roberts A, Guthrie A, *et al*. *Recommendations for cross-sectional imaging in cancer management. Lymph nodes*. Second edition. 2014. p. 1–7 Available at:. https://www.rcr.ac.uk/system/files/publication/field_publication_files/BFCR%2814%292_4_Lymph.pdf. accessed 25.2.19.
36. Swensen SJ, Tashjian JH, Myers JL, *et al*. Pulmonary venoocclusive disease: CT findings in eight patients. *AJR Am J Roentgenol* 1996;**167**(4):937–40.
37. Dufour B, Maître S, Humbert M, *et al*. High-resolution CT of the chest in four patients with pulmonary capillary hemangiomatosis or pulmonary venoocclusive disease. *AJR Am J Roentgenol* 1998;**171**(5):1321–4.
38. Günther S, Jaïs X, Maitre S, *et al*. Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheum* 2012;**64**(9):2995–3005.
39. Connolly MJ, Abdullah S, Ridout DA, *et al*. Prognostic significance of computed tomography criteria for pulmonary veno-occlusive disease in systemic sclerosis–pulmonary arterial hypertension. *Rheumatology (Oxford)* 2017;**56**(12):2197–203.
40. Sheehan R, Perloff JK, Fishbein MC, *et al*. Pulmonary neovascularity: a distinctive radiographic finding in Eisenmenger syndrome. *Circulation* 2005;**112**(18):2778–85.
41. Resten A, Maître S, Humbert M, *et al*. Pulmonary arterial hypertension: thin-section CT predictors of epoprostenol therapy failure. *Radiology* 2002;**222**(3):782–8.
42. Nolan RL, McAdams HP, Sporn TA, *et al*. Pulmonary cholesterol granulomas in patients with pulmonary artery hypertension: chest radiographic and CT findings. *AJR Am J Roentgenol* 1999;**172**(5):1317–9.
43. Horton MR, Tuder RM. Primary pulmonary arterial hypertension presenting as diffuse micronodules on CT. *Crit Rev Comput Tomogr* 2004;**45**(5–6):335–41.