RadioGraphics

# From the Archives of the AFIP

## Pulmonary Veno-occlusive Disease and Pulmonary Capillary Hemangiomatosis[1]

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**CME FEATURE**

*See accompanying test at http://www.rsna.org/education/rg_cme.html*

**LEARNING OBJECTIVES FOR TEST 6**

*After reading this article and taking the test, the reader will be able to:*

- Discuss the clinical challenge of discerning PVOD and PCH from other causes of pulmonary arterial hypertension and the unique hemodynamics of these two diseases.
- Identify the radiologic manifestations of PVOD and PCH that strongly suggest their diagnosis.
- Describe the underlying histopathologic features of PVOD and PCH.

**TEACHING POINTS**

*See last page*

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are two unusual idiopathic disorders that almost uniformly manifest to the clinician as pulmonary arterial hypertension (PAH). Impressive clinical signs and symptoms often obscure the true underlying capillary or postcapillary disorder, thus severely compromising timely and appropriately directed therapy. The hemodynamics of PVOD and PCH are the consequence of a widespread vascular obstructive process that originates in either the alveolar capillary bed (in cases of PCH) or the pulmonary venules and small veins (in PVOD). Since the earliest descriptions of PVOD and PCH, there has been a debate as to whether these are two distinct diseases or varied expressions of a single disorder. The cause of PVOD or PCH has not yet been identified, although there are several reported associations. Without curative lung or heart-lung transplantation, patients with these conditions face inexorable clinical deterioration and death within months to a few short years of initial presentation. Surgical lung biopsy is the definitive diagnostic test, but it is a risky undertaking in such critically ill patients. The imaging manifestations of PVOD and PCH often reflect the underlying hemodynamic derangements, and these findings may assist the clinician in discerning PAH from an underlying capillary or postcapillary process with findings of septal lines, characteristic ground-glass opacities, and occasionally pleural effusion.

**Abbreviations:** PAH = pulmonary arterial hypertension, PCH = pulmonary capillary hemangiomatosis, PCWP = pulmonary capillary wedge pressure, PPH = primary pulmonary hypertension, PVOD = pulmonary veno-occlusive disease

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## Introduction

Veno-occlusive histopathologic changes were first described in 1934 as the cause of death in a 48-year-old German baker with progressive dyspnea, cyanosis, and pulmonary edema (1). In 1966, British pathologist Donald Heath and associates (2) were the first to assert that pulmonary veno-occlusive disease (PVOD) is a distinct entity rather than an incidental autopsy finding. Heath's exhaustive dissections revealed occlusive changes in up to 95% of the pulmonary veins and venules in a 37-year-old female patient and led him to propose that, "Whatever the etiology of this condition proves to be, there is no doubt that it should be separated from cases of classical primary pulmonary hypertension on the grounds of its histopathology with pronounced involvement of the pulmonary veins and alveolar walls" (3). A decade later, Dutch pathologist C. A. Wagenvoort (4) and his colleagues (5) proposed that PVOD is an acquired syndrome of devastating venous thrombosis induced by a wide spectrum of insults to the venous endothelium. Today, there is an estimated annual incidence of 0.1–0.2 cases of PVOD per million persons (1). PVOD affects patients with a wide range of ages, from 9 days to 60–70 years old, but it is chiefly reported in children and young adults (1,6). In the 30%–50% of patients who are less than 20 years of age, there is no sexual predilection, but among adult patients, men are affected twice as frequently as women (5,7–9). The duration of illness before death is usually 2 years from initial presentation; pediatric patients tend to experience a more rapid, relentless progression of disease, which leads to right-sided heart failure and death in only a few short months (7–11).

Pulmonary capillary hemangiomatosis (PCH) is reported much less frequently in the medical literature than PVOD. It was first recognized in 1978 by Wagenvoort and colleagues (12) in a 71-year-old woman with progressive dyspnea, hemoptysis, and hemorrhagic pleural effusions. They observed a distinctive "atypical proliferation of capillary-like channels" in the lung tissue that appeared to be an "angiomatous growth" (12). In PCH, the age range of affected patients is broad (2–71 years), with a mean age of 30 years, which is comparable to the age range of patients with PVOD. In contrast to PVOD, however, PCH occurs with equal frequency in both sexes in patients of any age (13–15). Median survival is 3 years from initial presentation, and, as in PVOD, death may occur only a few months after the onset of symptoms (13,15).

Both PVOD and PCH are considered idiopathic diseases, although a myriad of associated conditions is reported in the medical literature. An immune-mediated cause is suggested by the sporadic occurrence of PVOD in patients with underlying systemic lupus erythematosus, scleroderma, systemic sclerosis, human immunodeficiency virus infection, rheumatoid arthritis, Raynaud phenomenon, Hashimoto thyroiditis, Langerhans cell histiocytosis, or granulomatous venulitis (10,16–25). Similarly, PCH has developed in patients with systemic lupus erythematosus, scleroderma, Takayasu arteritis, Kartagener syndrome, or hypertrophic cardiomyopathy (15,19). A viral etiology has been proposed in several patients with PVOD who recounted a recent viral illness (1,10). Three pairs of siblings have died of PVOD, and an autosomal recessive hereditary form of PCH has been proposed, both instances prompting theories of a familial association (10,14,26). PVOD also occurs in cancer patients following radiation therapy, chemotherapy (including treatment with bleomycin, cisplatin, vincristine, carmustine, and mitomycin), peripheral blood stem cell transplantation, and autologous or allogeneic bone marrow transplantation (10,27–35). Antecedent malignancies in patients with PVOD have included neuroblastoma, lung cancer, multiple myeloma, leukemia, and Hodgkin lymphoma; there is one report of PCH in a patient with preexisting colon cancer (30,31, 33,36–39). Authors debate whether PVOD or PCH developed in these patients as a response to a toxic insult from their cancer treatment or as a complication of malignancy. Many of these questions remain unanswered.

## Deceptive Clinical Presentation

Progressive dyspnea and fatigue characterize the clinical manifestations of both PVOD and PCH, which are thus typically misdiagnosed as pulmonary arterial hypertension (PAH) (1,10,13–15). Patients may also have chronic cough (dry or pro-

ductive), chest pain, syncope, or digital clubbing (1,6,15). The only clinical features that may distinguish PCH from PVOD are the presence of hemoptysis (evident in 30% of patients with PCH but not reported in PVOD) and hemorrhagic pleural effusions (absent in PVOD but reported in up to 25% of patients with PCH) (12–15,40). As either PVOD or PCH progresses, right-sided heart failure may produce hypoxia, cyanosis, hypotension, peripheral edema, ascites, hepatomegaly, hepatojugular reflex, and right parasternal heave. Electrocardiography typically demonstrates right axis deviation and right ventricular hypertrophy. Echocardiography (M-mode, Doppler, and two-dimensional) reveals PAH and helps to exclude an underlying left-sided cardiac structural lesion (such as mitral stenosis or myxoma) or left ventricular dysfunction (7–10,16, 41,42). It is estimated that in 5%–25% of patients with PVOD, their condition is misdiagnosed as idiopathic pulmonary hypertension or pulmonary thromboembolic disease (1,7,8,10,11,41,43). In the great majority of patients with PCH, the condition is misdiagnosed before transplantation or death as primary pulmonary hypertension (PPH), PVOD, pulmonary fibrosis, sarcoidosis, pulmonary thromboembolism, or pulmonary hemosiderosis (15).

## Distinctive Hemodynamics

Teaching Point

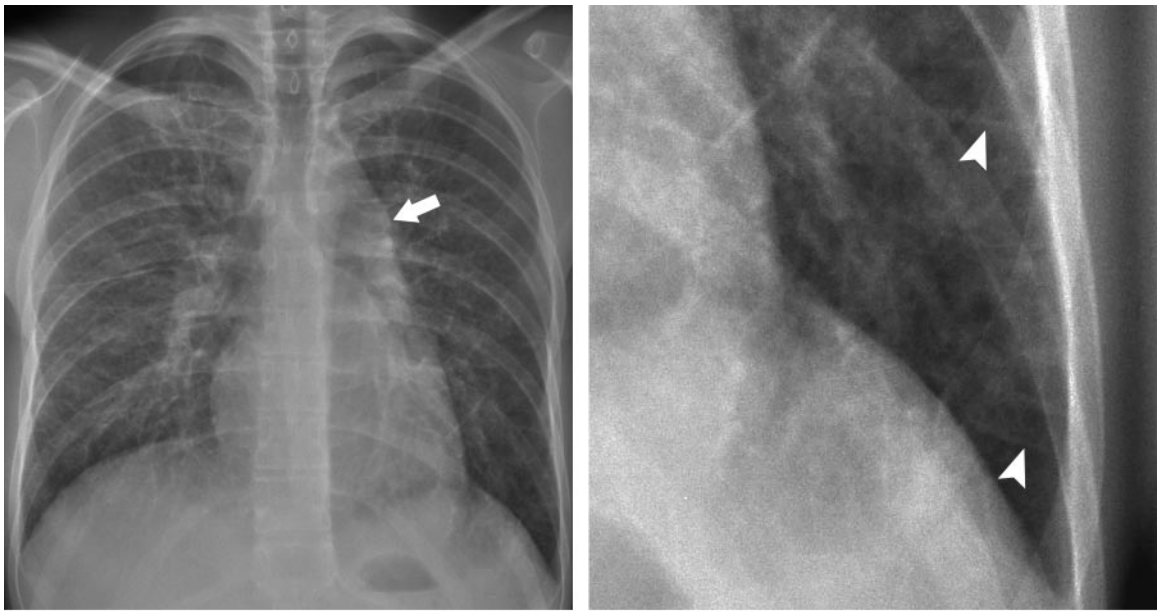
Two hemodynamic features characterize both PVOD and PCH: elevated pulmonary arterial pressures and normal or low pulmonary capillary wedge pressures (PCWP). Virtually all patients with PVOD and PCH have elevated pulmonary arterial pressures at right-sided heart catheterization, a finding that confirms the presence of PAH and potentially misleads clinicians in their diagnostic work-up (1,6–9,15,16,28,42,44–46). This PAH—which is further evidenced by medial hypertrophy of the pulmonary arterioles, dilatation of the main pulmonary artery, and right ventricular hypertrophy—is explained by the sustained reflection of pressure elevation in the pulmonary veins (as in PVOD) or capillary bed (as in PCH) (47).

The second characteristic hemodynamic finding is that of normal or low PCWP. The term *PCWP* is actually a misnomer since the pressure in the capillary bed is not assessed. The actual pressure being measured is distal to the wedged catheter tip and reaches beyond the venules and small veins to the largest pulmonary veins and left atrium; these structures are unaffected in both PVOD and PCH (1,6–8,16,46,48–51). The measurement of PCWP in most cases underestimates the pressure within the capillary bed itself (51). It is theorized that PVOD variably affects the venules and small veins, which allows some fraction of collateral bronchial veins and spared patent venous tributaries to provide perceived normal venous outflow into the larger veins and left atrium during PCWP measurement. The normal or even low values of PCWP observed in PVOD or PCH are helpful in the clinical differential diagnosis because they are in direct contrast to the elevated PCWPs obtained in patients with obstructed or stenotic larger pulmonary veins, left atrial myxoma, mitral stenosis, or left ventricular failure (52).

The hemodynamics of PVOD in particular may also lead the capillary hydrostatic pressure to exceed the osmotic pressure of blood. This state leads to transudation of fluid into the interstitium (ie, pulmonary edema) with consequent engorgement and dilatation of the subpleural and interlobular septal lymphatic channels. The clinical triad of findings—PAH, normal to low PCWP, and prominent radiologic septal lines—is well documented in PVOD, although in reality, many patients present with only one physical or radiologic finding suggestive of the diagnosis (1,6,53).

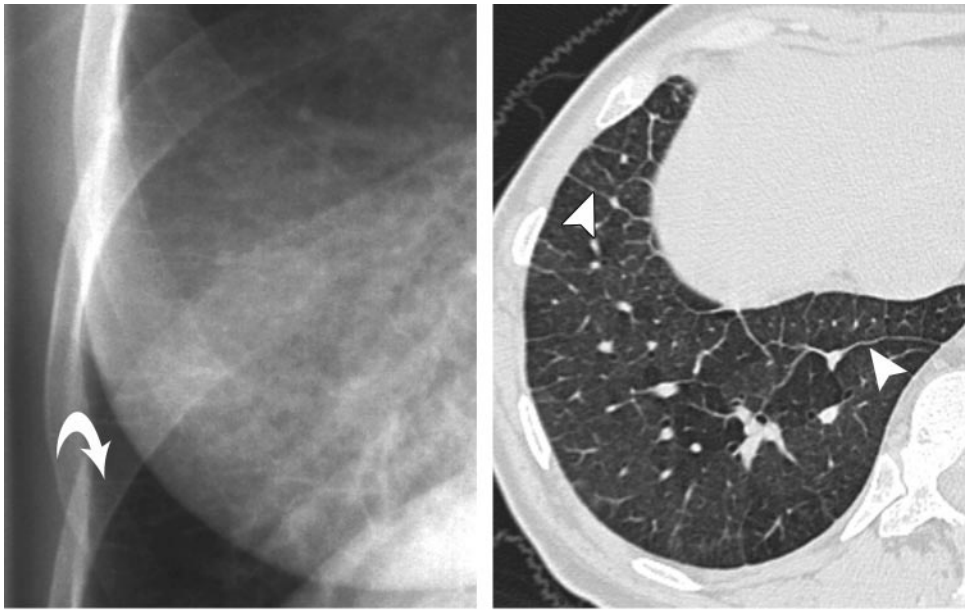
## Radiologic Manifestations of PVOD and PCH

The chest radiographic appearance of PVOD typically includes features of both PAH and of postcapillary congestion: Main pulmonary arterial enlargement and prominent septal (Kerley B) lines together reveal that the primary disorder lies beyond the pulmonary arterial circulation (Figs 1, 2a). Localization to the pulmonary veins is further suggested by evidence of normal-caliber pulmonary veins and normal left atrial and left ventricular contours. Pleural effusions may be present. Multifocal airspace consolidation occurs uncommonly and variably corresponds to parenchymal hemorrhage, pulmonary edema, or pulmonary infarction (6–9,11,16,28,41,43,44,48,52,54,55).



a. b.

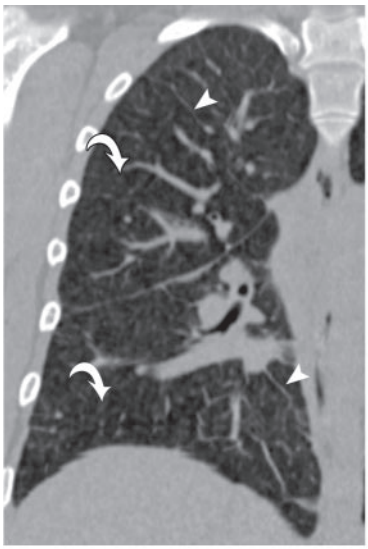
**Figure 1.** PVOD in a 20-year-old man. **(a)** Posteroanterior chest radiograph demonstrates a prominent main pulmonary artery (arrow), fissural thickening, and Kerley B lines. **(b)** Radiograph collimated to the left lower lobe helps confirm the presence of Kerley B lines (arrowheads).



a. b.

**Figure 2.** PVOD in a 56-year-old woman. **(a)** Radiograph collimated to the right lower lobe demonstrates numerous Kerley B lines (arrow). **(b)** Axial computed tomographic (CT) image (lung window level) collimated to the right lower lobe helps confirm smoothly thickened interlobular septa (arrowheads) and geographic ground-glass opacities.

CT scans of PVOD depict the dilated central pulmonary arteries accompanied by widespread, smoothly thickened interlobular septa (Figs 2b, 3a, 4) and further reveal ground-glass opacity in diffuse, geographic, mosaic, perihilar, patchy, or centrilobular patterns (6,42,56–60) (Figs 2b, 3a). The central pulmonary artery is prominent, and the right chambers of the heart may be enlarged, findings compatible with cor pulmonale (56–58) (Figs 3c, 4). The left atrium and ventricle are normal in appearance. In a study of eight patients with PVOD, Swensen et al (57) observed that 50% or more of CT examinations demonstrated septal prominence, fissural thickening, enlarged central pulmonary arteries, normal-caliber pulmonary veins, bilateral pleural effu-



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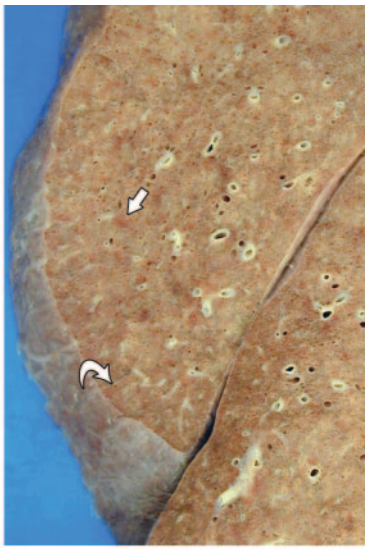

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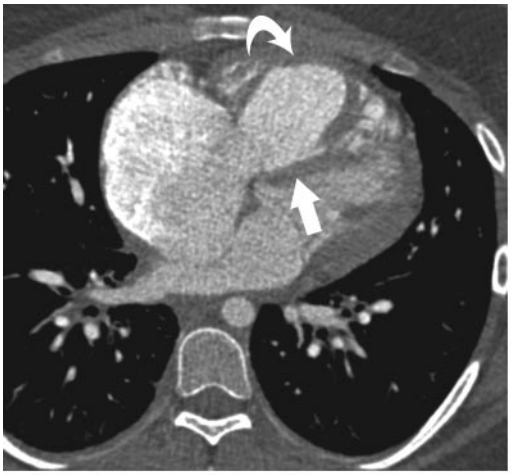

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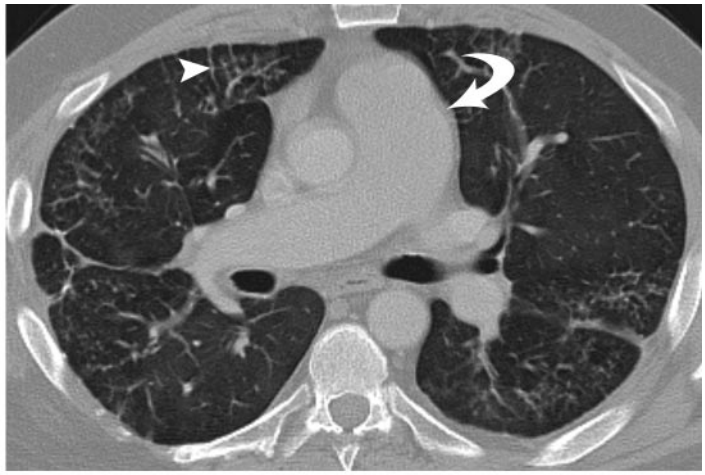


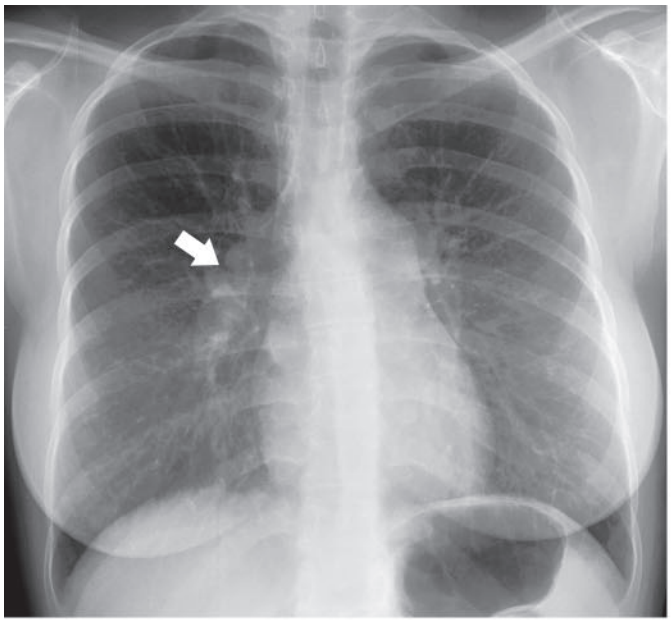
4.

**Figures 3, 4.** **(3)** PVOD in a 17-year-old girl. **(a)** Coronal reformatted CT scan (lung window level) reveals widespread septal lines (arrowheads) and diffuse, ill-defined ground-glass nodules (arrows). **(b)** Photograph of a cut coronal section of the right lung reveals septal prominence (curved arrow) and ill-defined reddish-tan parenchymal nodules (straight arrow). **(c)** Axial CT image (mediastinal window level) reveals a thickened anterior wall of the right ventricle (curved arrow), a straightened interventricular septum (straight arrow), and a dilated right atrium compatible with cor pulmonale. **(4)** PVOD in a 43-year-old man. Axial CT scan (lung window level) shows multiple septal lines (arrowhead) and a dilated central pulmonary artery (arrow).

sions, or mosaic lung attenuation. Resten et al (59) identified septal lines and poorly defined centrilobular ground-glass opacities as two of the most helpful CT findings in distinguishing between PVOD ($n = 15$) and PPH ($n = 15$). Although lymphadenopathy is reported with variable frequency in PVOD and has even been suggested as a helpful finding to distinguish PVOD from PPH, it may also be evident in chronic thromboembolic hypertension and left ventricular failure (6,57–60). Resten et al (59) reported no significant difference between PVOD and PPH in the frequency of either pleural or pericardial effusion.

Reports of pulmonary arteriographic findings in PVOD describe enlarged central pulmonary arteries, subtle narrowing of the distal arterial branches without arterial filling defects, a heterogeneous parenchymal phase "blush," and a prolonged circulation time through the lungs. The pulmonary veins may be normal or poorly visualized, and the left atrium characteristically appears normal or small, without evidence of a filling defect (11,28,41,43,48,49,61).

In PVOD, ventilation-perfusion scans produce a wide spectrum of manifestations, from normal to "diffuse irregularity . . . with no discrete defects" to multiple segmental perfusion mismatched defects (6,7,16,31,42,44,62). One unusual case produced a "segmental contour pattern" that outlined the bronchopulmonary segments without true perfusion defects (55). When



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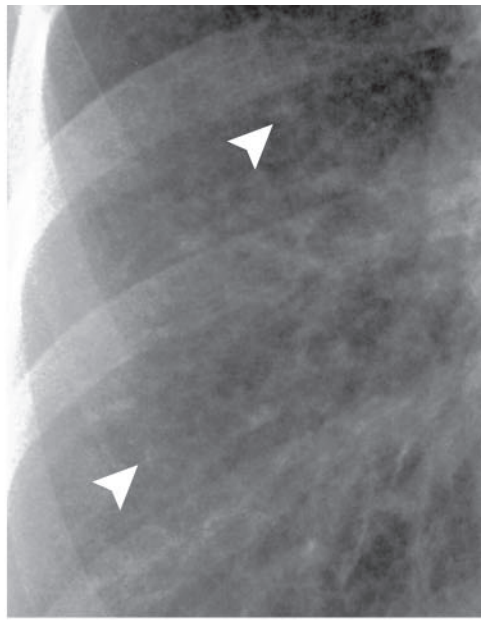

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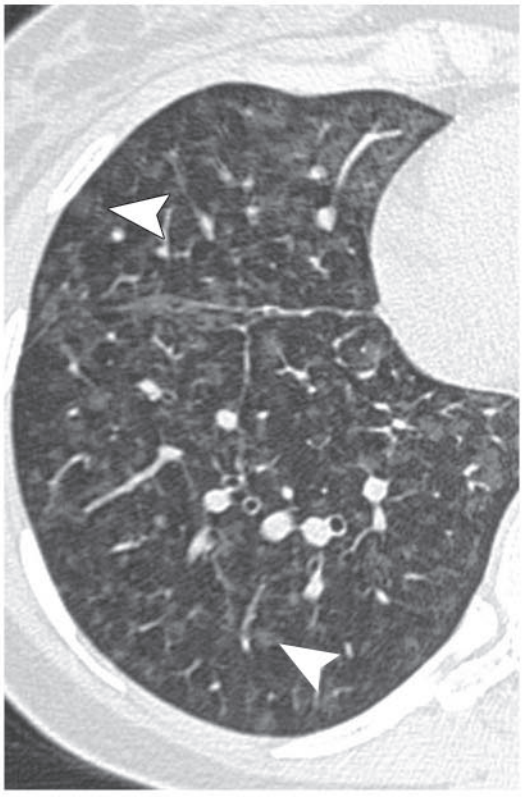

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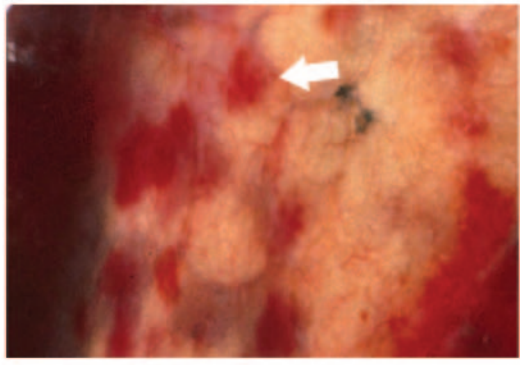

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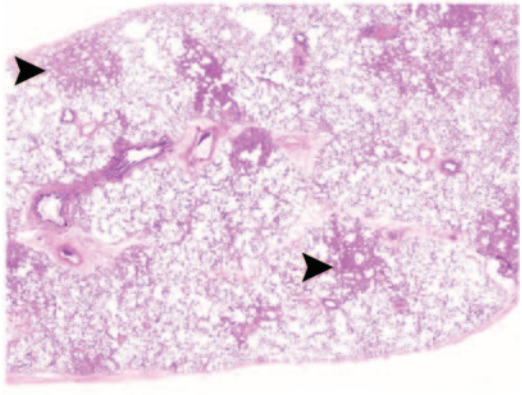

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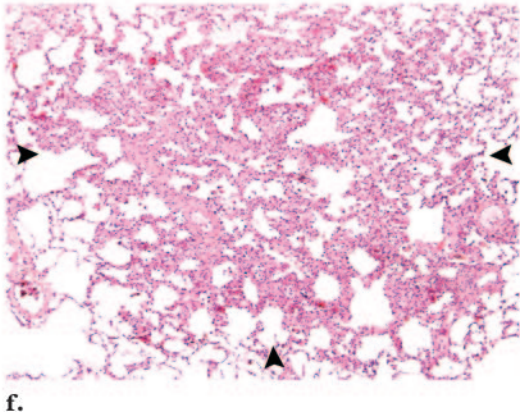

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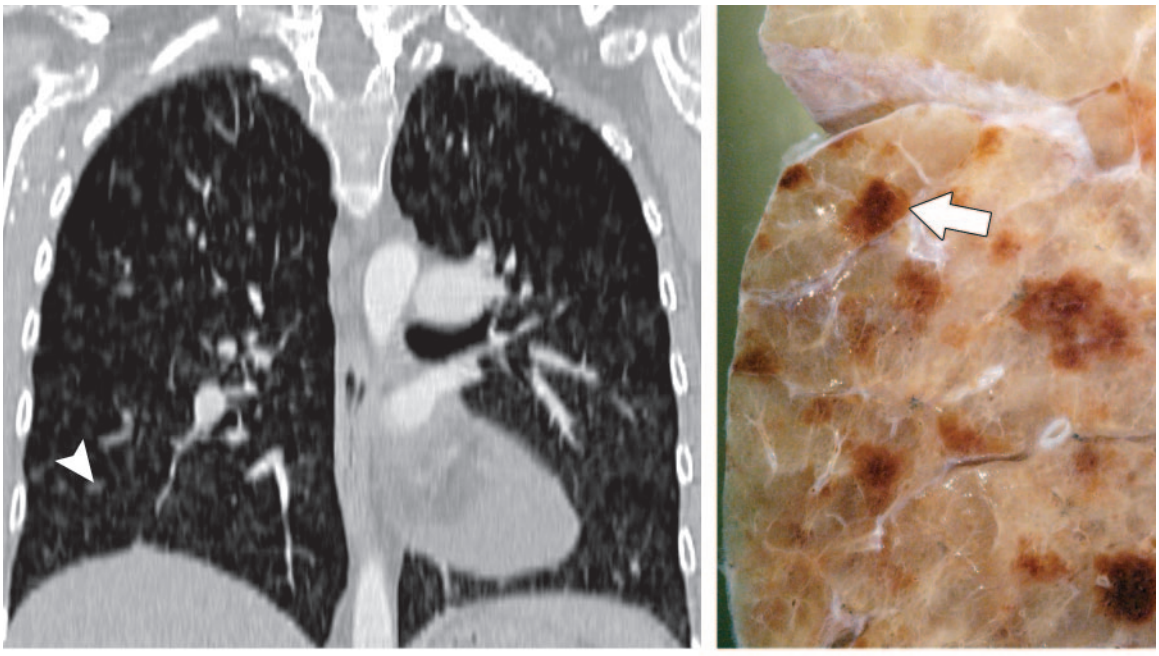


a. b.

**Figure 6.** PCH in a 27-year-old woman. **(a)** Coronal reformatted CT scan (lung window level) shows diffuse, ill-defined, ground-glass nodules (arrowhead) and no evidence of interlobular septal thickening. **(b)** Photograph of a cut coronal section of the lung reveals multiple parenchymal nodules that appear hemorrhagic (arrow).

a ventilation-perfusion scan obtained in a patient with PVOD is understandably interpreted as "high probability," this interpretation may lead to a misdiagnosis of chronic thromboembolic disease; therefore, ventilation-perfusion scans are regarded as nonspecific for PVOD (1,6,7,28,49).

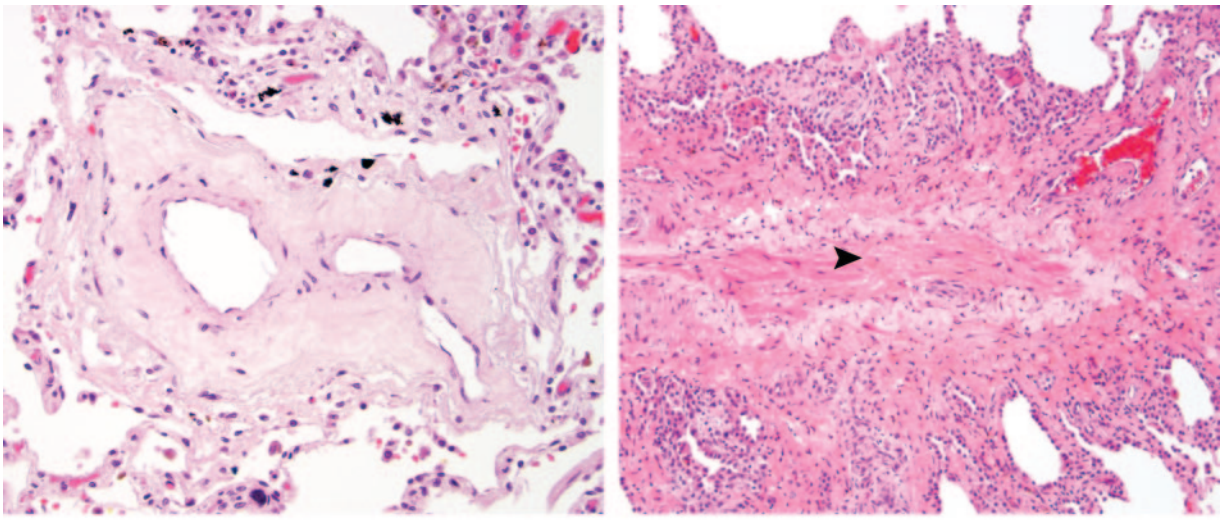
In PCH, chest radiography demonstrates PAH (enlarged central pulmonary arteries and right-sided prominence of the heart), accompanied by diffuse or bibasilar reticulonodular or micronodular areas of opacity uncharacteristic of PVOD (Fig 5a, 5b). In further contrast to PVOD, septal lines or pleural effusions are unusual (13–15,40, 45,61,63–66) (Figs 5c, 6a). Mediastinal lymphadenopathy is reported occasionally at chest radiography (14,64).

At CT, main pulmonary arterial enlargement and widespread ill-defined centrilobular nodules of ground-glass opacity are consistently described in PCH, often mixed with lobular ground-glass opacities (13,15,58,65–67) (Figs 5c, 6a). The left atrium is normal or small in outline. Sporadically reported findings include septal thickening, lymphadenopathy, pleural effusion, enlargement of the right chambers of the heart, and pericardial effusion (15,58,67).

Pulmonary arteriograms usually appear normal in PCH, although there are isolated interpretations of pulmonary embolism or "nonspecific vascular abnormalities" (15).

As in PVOD, a ventilation-perfusion examination is not helpful for confirming the diagnosis of PCH. There is a wide spectrum of reported manifestations, including normal results, small perfusion mismatch defects (considered "low probability"), perfusion mismatch defects large enough to be considered "high probability," multiple matched defects, and diffusely increased bibasilar perfusion (13–15,19,63,65).

◀ **Figure 5.** PCH in a 22-year-old woman. **(a)** Posteroanterior chest radiograph shows a prominent central pulmonary artery (arrow) and faint nodular opacities, best seen in the lung bases. **(b)** Radiograph collimated to the right lower lobe reveals widespread, poorly circumscribed nodular opacities (arrowheads). **(c)** Axial CT image (lung window level) collimated to the right lower lobe shows well-circumscribed ground-glass nodules (arrowheads) and no septal lines. **(d)** Photograph of the visceral pleural surface reveals multiple petechial-appearing nodules (arrow), just visible beneath the pleura, that actually represent the angiomatous lesions of PCH. **(e)** Low-power photomicrograph (original magnification, ×1; hematoxylin-eosin [H-E] stain) shows multiple discrete parenchymal nodules (arrowheads). **(f)** Low-power photomicrograph (original magnification, ×4; H-E stain) shows a discrete parenchymal nodule (arrowheads) abutting the visceral pleura.



a. b.

**Figure 7.** Microscopic features of PVOD. **(a)** Medium-power photomicrograph (original magnification, ×20; H-E stain) of a parenchymal vein demonstrates narrowing of the lumen by loose, edematous intimal fibrous tissue that has been recanalized to form three channels. **(b)** Medium-power photomicrograph (original magnification, ×10; H-E stain) demonstrates a fibrotic interlobular septum containing a vein whose lumen is occluded by dense, collagen-rich fibrous tissue (arrowhead).

## Pathologic Characteristics of PVOD and PCH

Teaching Point

PVOD is histologically characterized by intimal fibrosis that narrows and occludes the pulmonary veins (3,5,52,68). Pulmonary veins of all sizes, from large interlobular vessels to venules of immediate postcapillary size, may be involved. Large numbers of veins may be affected, or the process may be patchy, so that a spectrum of normal to occluded veins is observed. The intimal fibrous tissue that narrows and occludes the pulmonary veins ranges from loose, edematous, and hypocellular (Fig 7a) to dense and collagen-rich (Fig 7b). Recanalization of intimal fibrosis is common and results in the development of channels separated by intravascular septa (Fig 7a).

Venous lesions in PVOD are accompanied by a variety of changes in the interlobular septa, lung parenchyma, and pulmonary arteries. Interlobular septa are typically edematous and contain dilated lymphatic spaces (Fig 8a). Infarcts (so-called venous infarcts) can occur adjacent to interlobular septa containing affected veins. Upstream from narrowed and occluded veins, patchy areas of alveolar capillary dilatation are present in the lung parenchyma (Fig 8b). In these areas, there is often interstitial fibrosis, hemorrhage, and intraalveolar hemosiderin-ladened macrophages, which are thought to occur secondary to chronic passive congestion (64). Vascular and interstitial elastic fibers may become coated with iron (so-called endogenous pneumoconiosis), in situ fibrosis, and a granulomatous giant-cell reaction. Arterioles in the lung parenchyma become muscularized (Fig 8c), and muscular pulmonary arteries show medial hypertrophy (Fig 8d) secondary to postcapillary obstruction of venous drainage (10). Note that muscularized arterioles are rounded in configuration, which helps to distinguish them histologically from the more flaccid morphology of venules.

The most distinctive histologic feature of PCH is proliferation of capillary channels within alveolar walls (12,40,63,64,67,69). When scanning magnification is used, PCH shows well-demarcated parenchymal lesions with relatively unremarkable intervening lung tissue (Fig 5e). Early

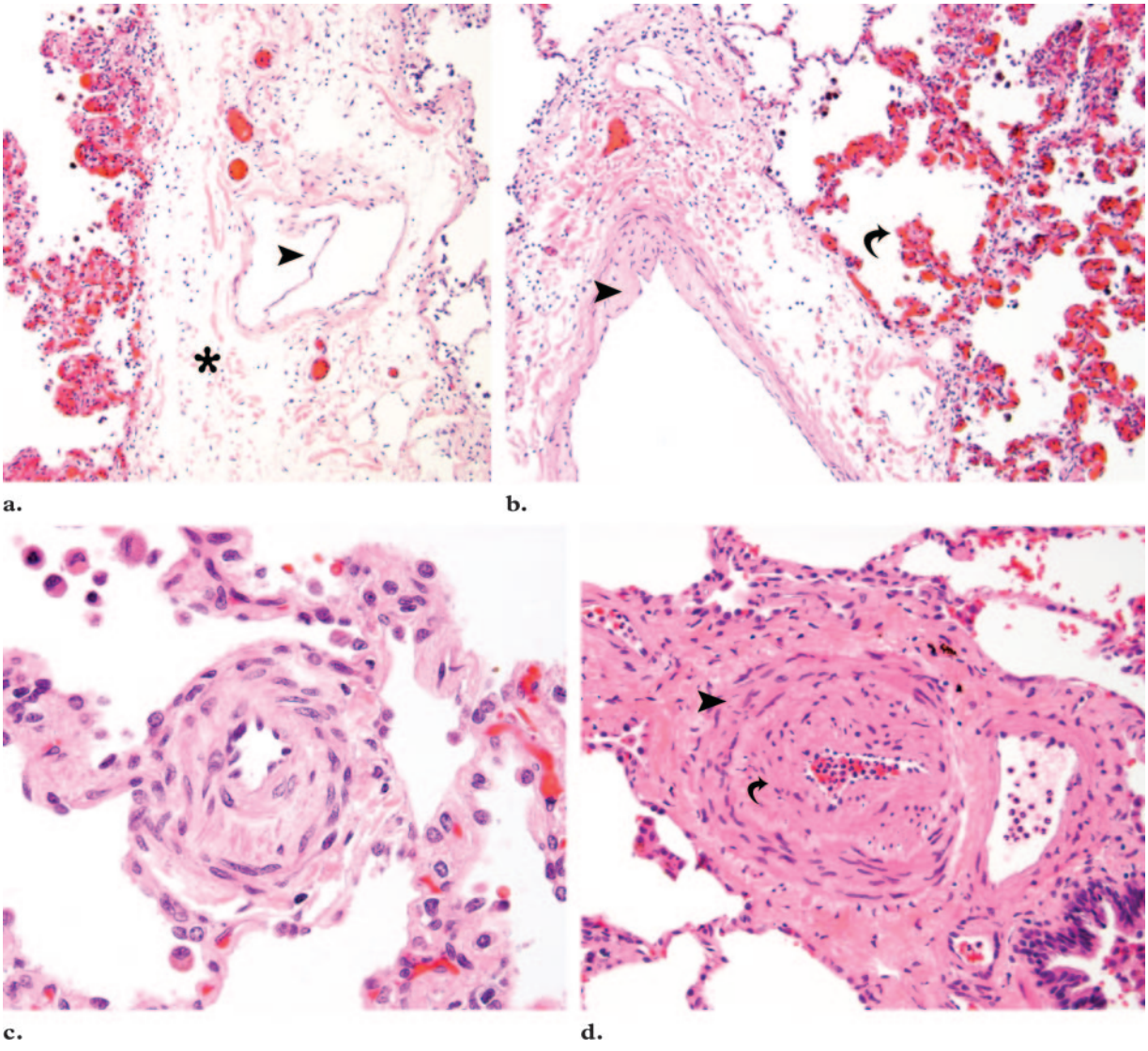
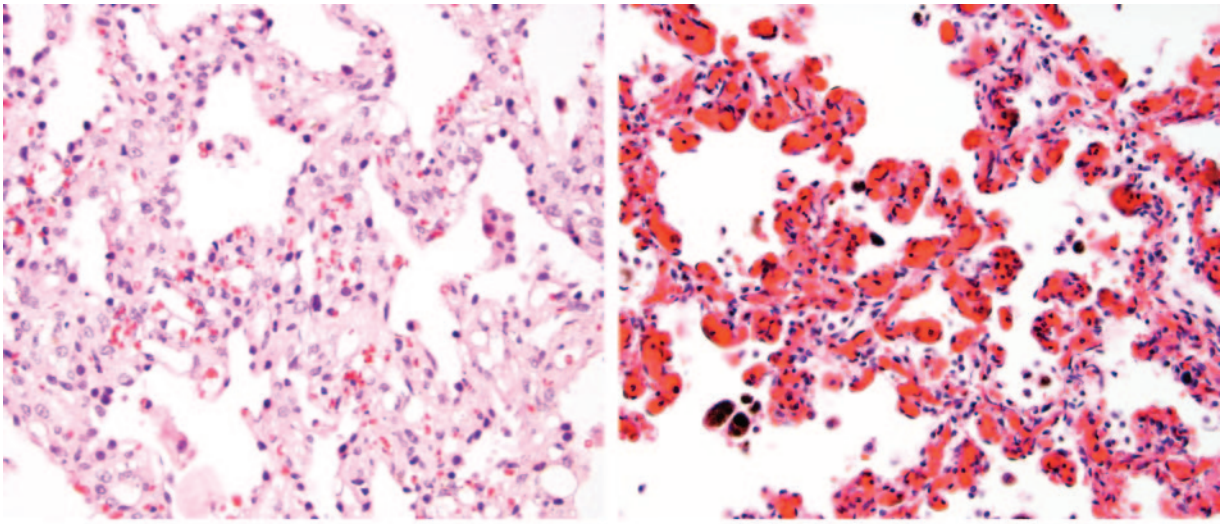



**Figure 8.** Microscopic features of PVOD. **(a)** Medium-power photomicrograph (original magnification, ×10; H-E stain) demonstrates an edematous interlobular septum (*) that contains a dilated lymphatic, the latter of which is identified by the presence of valves (arrowhead). **(b)** Medium-power photomicrograph (original magnification, ×10; H-E stain) shows loop-like alveolar capillary dilatation (arrow) upstream from a narrowed vein (arrowhead). **(c)** High-power photomicrograph (original magnification, ×40; H-E stain) demonstrates a muscularized arteriole composed of concentric layers of spindle-shaped smooth muscle cells that give the vessel a distinctly rounded configuration; typically, arterioles lack smooth muscle. **(d)** Medium-power photomicrograph (original magnification, ×20; H-E stain) of a muscular pulmonary artery reveals medial hypertrophy (arrowhead) and, in this case, also intimal thickening (arrow).

lesions demonstrate several rows of capillaries along alveolar walls; this feature progresses to nodules and sheets of back-to-back capillaries in advanced lesions (64). These proliferative changes lead to the histologic appearance of densely cellular alveolar walls, which are in contrast to the distended capillary loops seen in



a. b.

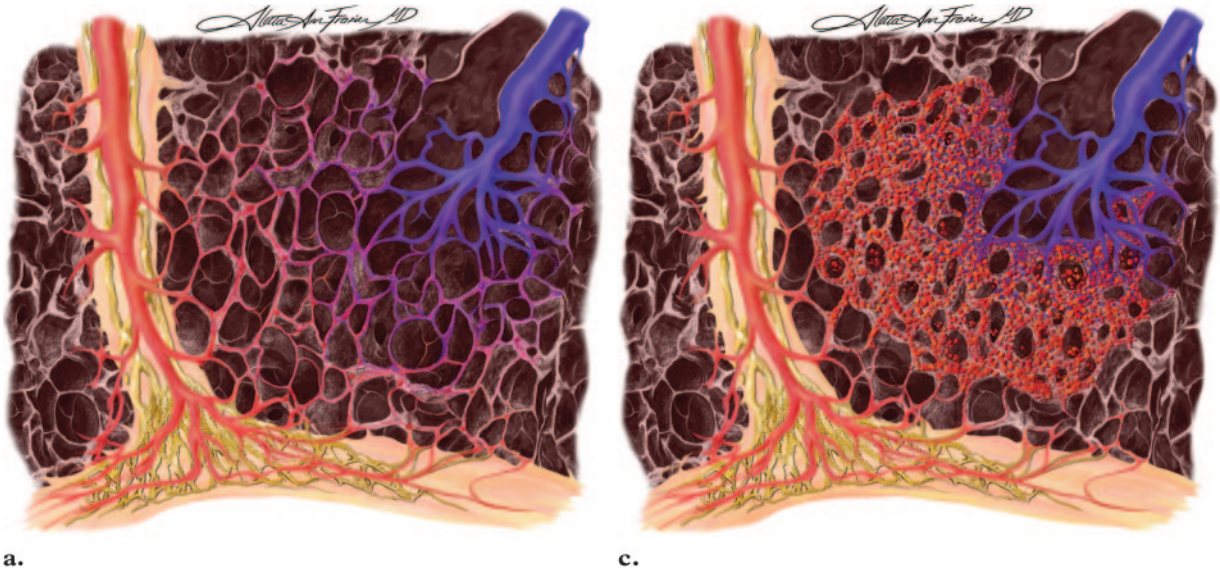
**Figure 9.** Microscopic features of PCH. **(a)** Medium-power photomicrograph (original magnification, ×20; H-E stain) demonstrates thickened and cellular alveolar walls due to capillary proliferation in PCH. **(b)** In contrast, this medium-power photomicrograph (original magnification, ×20; H-E stain) shows the loop-like dilatation of capillaries in PVOD.

PVOD (Fig 9). Cytologic atypia and mitoses are absent. Proliferating capillaries surround and compress walls of pulmonary venules and veins, causing intimal fibrosis and secondary veno-occlusion (64). As in PVOD, these characteristics result in compensatory muscularization of arterioles and medial hypertrophy of muscular pulmonary arteries (67).

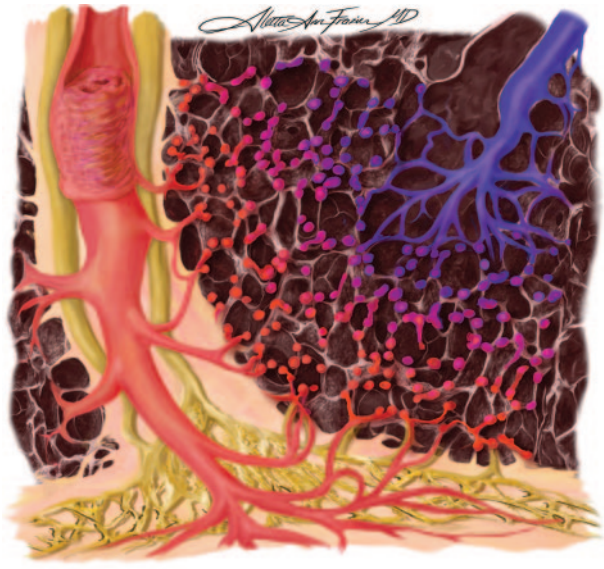
In the setting of unexplained PAH, the clinical and radiologic diagnosis of PVOD and PCH can be very difficult, and histologic examination is regarded as the most reliable means to establish the diagnosis. Typically, PVOD manifests with obstructive venous lesions within edematous interlobular septa, accompanied by loop-like dilatation of the capillary bed and secondary arterial changes (Fig 10a, 10b). Classic PCH manifests with well-circumscribed, proliferative capillary lesions that also produce secondary arterial changes (Fig 10c). However, PCH is easily misdiagnosed pathologically as PVOD—and, less commonly, PVOD as PCH—because of their histologic similarities. For example, it may be difficult to distinguish loop-like capillary engorgement from capillary proliferation. Special histologic studies to highlight reticular and elastic fibers (such as those in which reticulin, Movat pentachrome, or Verhoeff–van Gieson stains are used) demonstrate the difference between loop lesions in PVOD, which are composed of single dilated capillaries between the alveolar epithelial layers, and the proliferative rows of capillaries that expand the alveolar walls in PCH. A second histologic pitfall is that the pulmonary arterial changes may be so striking in PVOD that the case is misdiagnosed as PAH or PCH. Finally, inadequate biopsy material, particularly specimens without interlobular septa, may also lead to missed diagnosis of either PVOD or PCH. It has been recommended that a minimum of five blocks from a surgical lung biopsy is required for adequate evaluation of pulmonary vasculopathies (70).

## Therapeutic Agents and the Importance of Radiology

No randomized clinical trials have been developed to examine the safety and efficacy of pharmacologic agents in treating patients with either PVOD or PCH; most of the data concerning treatment is available only in case reports (1,6, 71,72). Lung or heart-lung transplantation is the only curative therapeutic option; consequently,



a.



b.



c.

**Figure 10.** Drawings of microscopic lung anatomy at the level of the secondary pulmonary lobule and an interlobular septum. **(a)** In normal hemodynamics, the centrilobular pulmonary artery (blue) enters the broad capillary network within the alveolar walls. The oxygenated blood then flows into interlobular septal veins (red). There is a lymphatic network (yellow) in both the pleura and interlobular septum. **(b)** In PVOD, the interlobular septal veins are occluded, the capillary network is secondarily dilated in a configuration of multiple vascular loops, the lymphatic channels are engorged, and the interlobular septum is edematous. **(c)** In PCH, a discrete area of capillary proliferation is present, typically without evidence of changes within the pulmonary veins or interlobular septum.

pharmacologic agents serve only as supportive care and a bridge to transplantation (1,6,13–15, 73–75). Clinicians use conventional medical therapies to decrease pulmonary vascular resistance, increase cardiac output, and reduce volume overload; the medications include diuretics, anticholinesterase (ACE) inhibitors, anticoagulants (warfarin), cardiac glycosides (digoxin), and oxygen supplementation (1,15). Additional agents employed include pulmonary vasodilators (calcium channel antagonists, prostacyclin therapies) and immunosuppressive agents (glucocorticoids) (1). Experimental therapies include regimens of α-interferon and angiogenesis inhibitors (15,72,75,76).

Although many of these agents have scientific data that support their role in the treatment of PPH, their benefit in the treatment of PVOD or PCH remains questionable (15,19,75,77). A selective pulmonary vasodilator medication used in PAH, oral sildenafil (a phosphodiesterase-5

inhibitor), has been shown to improve hemodynamics and the clinical course in some patients with PVOD (78,79). In many cases, however, clinical experience has shown that potent vasodilators (including continuous intravenous prostacyclin and calcium channel blockers) induce florid and even fatal pulmonary edema in patients with either PVOD or PCH. This deleterious outcome is explained as follows: If the pulmonary muscular arteries and arterioles are dilated and yet the pulmonary vein resistance remains fixed, the increased transcapillary hydrostatic pressure leads to massive transudation of fluid into the lung parenchyma (15,19,58,75,80). Radiologists play an important role in this situation: To exclude unsuspected radiologic evidence of PVOD or PCH, it is currently recommended that patients with presumed PPH should undergo a high-resolution CT examination before initiation of vasodilator therapy (75,81).

Teaching Point

Unfortunately, the average time frame to receive an organ transplant often exceeds the life expectancy of both PVOD and PCH patients (1). In one patient who underwent single-lung transplantation for PVOD, high-resolution CT performed 3 months after the surgery demonstrated normalization of the previously dilated right chambers of the heart as well as nearly complete resolution of ground-glass opacities and septal lines in the native lung (56). The ventilation-perfusion scan showed 80% perfusion to the transplanted lung, a finding that suggests that the radiologic changes of PVOD are at least partially related to hemodynamic factors rather than fixed anatomic changes (56). Another case report described PVOD that recurred in a patient 3 months after heart-lung transplantation, although the diagnosis in this case was based on clinical and radiologic features without lung biopsy confirmation (82).

## Cases at the AFIP

Eleven cases of PVOD ($n = 7$) and PCH ($n = 4$) at the AFIP were reviewed by two radiologists (A.A.F., J.R.G.) and two pathologists (T.J.F., I.H.O.) (Table). The age of patients with PVOD ranged from 17 to 56 years (mean, 38 years) with a male-to-female ratio of 2:5. The age range of patients with PCH was 12–52 years (mean, 28 years) with a male-to-female ratio of 1:3. Chest radiographs were available only in three cases of PVOD; all three cases had central pulmonary artery prominence, two had Kerley B lines, and the third showed pleural effusion. In the single case of PCH for which chest radiographs were available, the images demonstrated main pulmonary artery prominence and widespread, small, subcentimeter pulmonary nodules. The majority of PVOD patients (six of seven) and half of the PCH patients (two of four) demonstrated impressive CT findings compatible with PAH, including a dilated main pulmonary artery (>3 cm in diameter), enlarged right-sided heart chambers, reflux of intravenous contrast material into the inferior vena cava, or pericardial effusion. On CT scans (with lung window levels), all seven cases of PVOD manifested with smoothly thickened interlobular septa, which ranged from a few septa in three cases to numerous septa in four cases. CT scans of all four PCH cases also demonstrated smoothly thickened interlobular septa, but in every case, the septa were uniformly sparse and few in number. Ground-glass opacities, either geographic or nodular, were evident in all cases of PVOD and PCH and were predominantly diffuse in distribution. The nodules of ground-glass opacity appeared either ill defined (two of four PCH cases; three of seven PVOD cases) or well defined (two of four PCH cases; no PVOD cases). Geographic ground-glass opacities were evident in four of seven cases of PVOD but were not seen in the PCH cases. Pleural effusions were identified in three of seven PVOD cases, and lymphadenopathy was present in only one case of PVOD. In two cases, a radiologic diagnosis of PCH based on the appearance of ground-glass nodules was incorrect, and the diagnosis was ultimately confirmed as PVOD at histopathologic examination.

Teaching Point

## Summary

PVOD and PCH are clinically indistinguishable from a primary PAH disorder such as PPH or chronic thromboembolic pulmonary hypertension. This distinction, however, is essential for appropriate pharmacologic intervention as well as for timely evaluation for lung transplantation. Indeed, if a patient with PVOD or PCH is treated presumptively for PPH with standard vasodilators such as continuous intravenous prostacyclin or calcium channel blockers, the treatment may result in a critical and potentially fatal pulmonary edema. The radiologist may be the first to discern an unsuspected capillary or postcapillary disorder that is otherwise obscured by impressive clinical

Teaching Point

**PVOD and PCH Cases from the AFIP: Radiologic Manifestations**

| Sex/Age (y) | Chest Radiographic Findings | Chest CT | | | | Diagnosis | |
|---|---|---|---|---|---|---|---|
| | | Image Type | Features of PAH* | Parenchymal Findings and Distribution | Other Findings | Radiologic | Pathologic |
| M/20 | Large central PA, pleural effusion, prominent septal lines | HRCT | Dilated PA | Few septal lines, GGO, geographic; diffuse distribution | Pleural effusion | PVOD | PVOD |
| F/39 | Large central PA, pleural effusion | CT w/o contrast | Dilated PA, RA, and RV; pericardial effusion | Few septal lines, GGO nodules, ill-defined; diffuse distribution | Pleural effusion | PCH | PVOD |
| F/56 | Large central PA, prominent septal lines | CT w/o contrast, HRCT | Dilated PA, RA, and RV; pericardial effusion | Few septal lines, GGO nodules, ill-defined; diffuse distribution | None | PCH | PVOD |
| F/17 | Not available | CT w contrast, HRCT | Dilated PA, RA, and RV; IVC reflux; pericardial effusion | Numerous septal lines, GGO nodules, ill-defined; diffuse distribution | None | PVOD | PVOD |
| F/54 | Not available | CT w/o contrast, HRCT | Dilated PA, pericardial effusion | Numerous septal lines, GGO, geographic; lower lobe distribution | Lymphadenopathy | PVOD | PVOD |
| M/43 | Not available | CT w contrast | Dilated PA and RA | Numerous septal lines, GGO, geographic; diffuse distribution | None | PVOD | PVOD |
| F/39 | Not available | CT w/o contrast | None | Numerous septal lines, GGO, geographic and peribronchiolar; diffuse distribution | Pleural effusion | PVOD | PVOD |
| M/12 | Not available | CT w contrast | None | Few septal lines, GGO nodules, well-defined; diffuse distribution | None | PCH | PCH |
| F/52 | Not available | CT w/o contrast, HRCT | Dilated PA, pericardial effusion | Few septal lines, GGO nodules, ill-defined; diffuse distribution | None | PCH | PCH |
| F/22 | Large central PA, prominent nodules | HRCT | None | Few septal lines, GGO nodules, well-defined; diffuse distribution | None | PCH | PCH |
| F/27 | Not available | CT w contrast | Dilated PA, RA, and RV; IVC reflux; pericardial effusion | Few septal lines, GGO nodules, ill-defined; diffuse distribution | None | PCH | PCH |

Note.—GGO = ground-glass opacity, HRCT = high-resolution CT, IVC = inferior vena cava, PA = pulmonary artery, RA = right atrium, RV = right ventricle.
*Dilated PA = transverse main pulmonary artery diameter > 3 cm.

features of PAH, and high-resolution CT is currently recommended as the optimal means of radiologic evaluation in these patients.

Radiologic manifestations that help to distinguish PVOD and PCH from PAH are the presence of smooth septal lines, geographic or nodular ground-glass opacities, and pleural effusion. Precapillary conditions such as PPH and chronic thromboembolic pulmonary hypertension do not produce thickening of the interlobular septa, which is caused by elevated pressures in the capillary or postcapillary circulation. PPH leads to oligemia in the lung periphery, and chronic thromboembolic pulmonary hypertension may appear with mosaic lung attenuation and vascular pruning, but neither manifest with septal lines. Diseases that are characterized radiographically by smooth septal thickening and ground-glass opacities include mediastinal fibrosis (constricting pulmonary venous drainage), left atrial myxoma, cor triatriatum, mitral stenosis, and left ventricular failure (48,49,57–60). In these conditions, however, CT may reveal pulmonary venous dilatation as well as other distinctive features such as mediastinal calcifications, mitral valvular calcifications, a left atrial filling defect, or left ventricular chamber enlargement.

In our review of 11 cases of PVOD and PCH at the AFIP, we further sought any radiologic features that might allow PVOD to be distinguished from PCH. It is clear that the CT manifestations of PVOD and PCH broadly overlap; thus, both PVOD and PCH should be mentioned in the differential diagnosis of PAH features accompanied by smooth septal lines, ground-glass opacities, and occasionally pleural effusion. Although septal lines are present in both PVOD and PCH, we found that more numerous (vs scarce) septal lines strongly suggest the diagnosis of PVOD over PCH. In addition, if ground-glass nodules are present and appear more well circumscribed, it seems reasonable to suggest the diagnosis of PCH over PVOD, particularly if septal lines are scarce or absent.

**Acknowledgments:** Because the diseases discussed herein are rare and the medications used in these patients are indicated (and approved by the Food and Drug Administration) for more common clinical conditions including congestive heart failure and PPH, the authors must discuss the application of pharmaceuticals that are not officially approved by the U.S. Food and Drug Administration for treatment of either PVOD or PCH. The authors extend their deep gratitude to Dr Tan-Lucien Mohammed for the generous contribution of three cases to the Archives of the AFIP from his busy practice at the Cleveland Clinic. The authors also extend their sincere thanks to all radiology residents who have made case contributions to the Thompson Archives in the Department of Radiologic Pathology at the AFIP. Finally, we acknowledge Ingrid Jenkins and Anika Torruella for their gracious assistance in manuscript preparation.

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# Pulmonary Veno-occlusive Disease and Pulmonary Capillary Hemangiomatosis

*Aletta Ann Frazier, MD et al*

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**Page 869**
Two hemodynamic features characterize both PVOD and PCH: elevated pulmonary arterial pressures and normal or low pulmonary capillary wedge pressures (PCWP).

**Page 874**
PVOD is histologically characterized by intimal fibrosis that narrows and occludes the pulmonary veins (3,5,52,68).... Venous lesions in PVOD are accompanied by a variety of changes in the interlobular septa, lung parenchyma, and pulmonary arteries. Interlobular septa are typically edematous and contain dilated lymphatic spaces (Fig 8a). Infarcts (so-called venous infarcts) can occur adjacent to interlobular septa containing affected veins.... The most distinctive histologic feature of PCH is proliferation of capillary channels within alveolar walls (12,40,63,64,67,69).

**Page 878**
Clinical experience has shown that potent vasodilators (including continuous intravenous prostacyclin and calcium channel blockers) induce florid and even fatal pulmonary edema in patients with either PVOD or PCH..... To exclude unsuspected radiologic evidence of PVOD or PCH, it is currently recommended that patients with presumed PPH should undergo a high-resolution CT examination before initiation of vasodilator therapy (75,81).

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