Autopsy Case Reports

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Pulmonary capillary hemangiomatosis: a lesson learned

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ABSTRACT

Pulmonary capillary hemangiomatosis (PCH) is a rare and controversial entity that is known to be a cause of pulmonary hypertension and is microscopically characterized by proliferation of dilated capillary-sized channels along and in the alveolar walls. Clinically, it is mostly seen in adults. Clinical features are characterized by nonspecific findings such as shortness of breath, cough, chest pain, and fatigue. It can be clinically indistinguishable from pre-capillary pulmonary arterial hypertension disorders such as primary pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension. However, the diagnostic distinction, which usually requires a multidisciplinary approach, is crucial in order to avoid inappropriate treatment with vasodilator medications usually used for PAH treatment. Prognosis of PCH remains poor with lung transplant being the only definitive treatment. We report an autopsy case of pulmonary capillary hemangiomatosis unmasked at autopsy that was treated with a prostacyclin analog, usually contraindicated in such patients. We emphasize that this entity should always be on the differential diagnosis in a patient with pulmonary hypertension and requires great vigilance on the part of the clinician, radiologist and pathologist to make the diagnosis and guide appropriate management.

Keywords
Pulmonary hypertension; Pulmonary veno-occlusive disease; pulmonary capillary hemangiomatosis; pulmonary heart disease

INTRODUCTION

Pulmonary capillary hemangiomatosis (PCH) is a rare entity in which patients typically present with pulmonary hypertension.[1-6] The disease does not have a sexual predilection. Unfortunately, the diagnosis of PCH is usually not made until an autopsy is performed.[1-6] It is microscopically characterized by an abnormal proliferation of thin-walled microvessels expanding the alveolar septum and encompassing bronchovascular bundles.[3] Imaging findings include widespread geographic regions of pulmonary ground glass attenuation and pulmonary hypertension. Familiarity with this entity is crucial as conventional therapies such as vasodilators utilized for treating pulmonary hypertension are contraindicated in PCH and can actually exacerbate the disease.[2] The overall prognosis remains poor with lung transplant being the sole definitive treatment.[2,4]

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CASE REPORT

We report a case of a 67-year-old female with a history of right heart failure, and COPD that presented for dyspnea, dizziness, and near syncope episodes. The patient had symptoms of dyspnea on exertion for many years prior and had been on 4 L oxygen by nasal cannula. She was referred for a cardiac consultation when it was revealed that she had proven pulmonary hypertension by echocardiogram and right heart catheterization. In particular, right heart catheterization demonstrated the mean pulmonary capillary wedge pressure and mean pulmonary artery pressure were 12 mmHg (reference range: 2-15 mmHg) and 54 mmHg (reference range: 8-20 mmHg), respectively, suggestive of severe pre-capillary pulmonary hypertension. Cardiac output (4.42L/min; reference range: 4-8L/min) and cardiac index (2.55; reference range: 2.5-4 L/min/m^2) were normal, indicative of preserved left heart function. The mean central venous pressure (14 mm Hg; reference range: 8-12 mmHg) and mean right atrial pressure (13 mmHg; reference range: 2-6 mmHg) were elevated and suggestive of right heart failure.

A chest computed tomography (CT) performed, at that time, demonstrated emphysema at the pulmonary apices and areas of dense ground glass opacifications without definite honeycombing, ruling out interstitial lung disease. However, imaging findings were consistent with pulmonary hypertension, although etiologies such as PCH were on the differential and could not be definitively excluded (Figures 1 and 2).

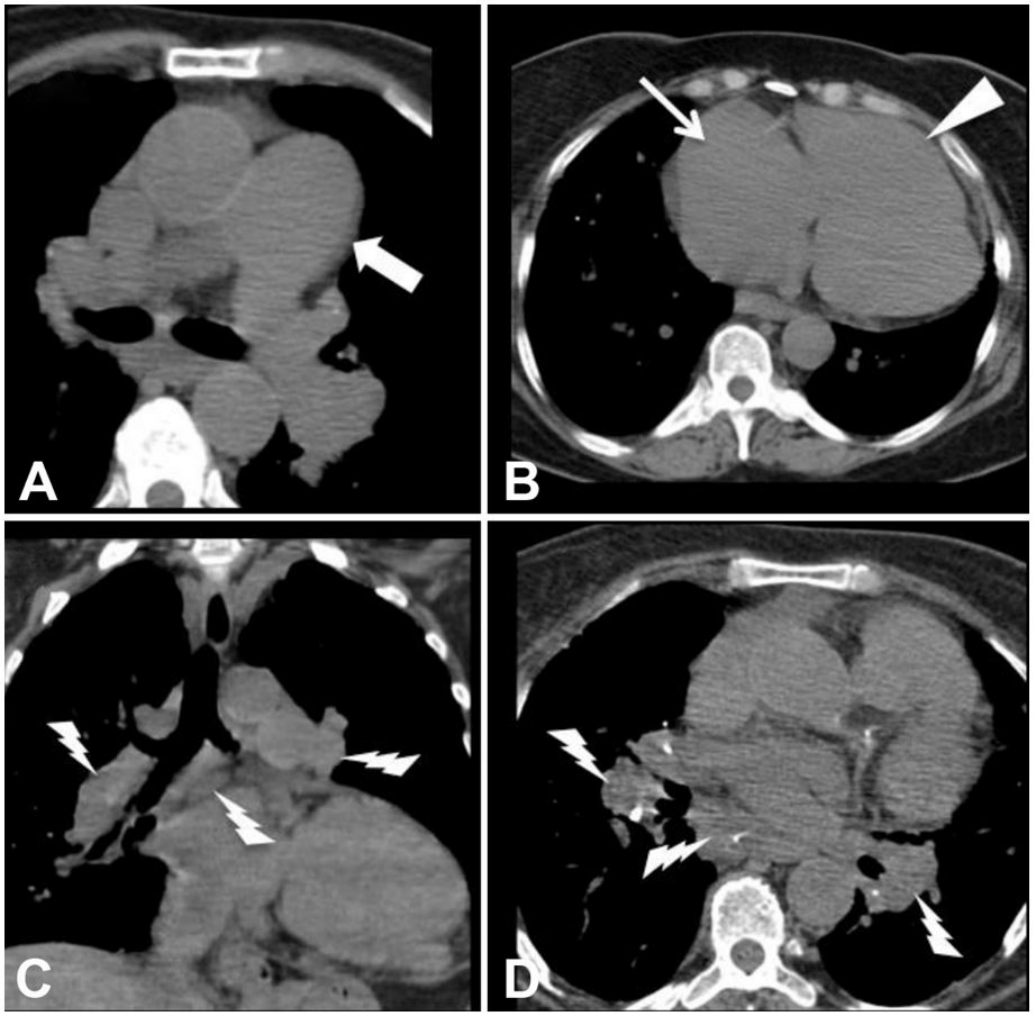

Figure 1. Imaging findings associated with PCH, as seen on non-contrasted chest CT in soft tissue windows. **A** and **B –** axial views demonstrate evidence of significant pulmonary hypertension manifested by enlargement of the main pulmonary artery (thick white arrow) which measured 3.6 cm, as well as marked enlargement of the right atrium (thin white arrow) and right ventricle (white arrowhead); **C** (coronal view) and **D** (axial view) show the enlarged mediastinal and hilar lymph nodes, nonspecific, but which in the setting of pulmonary hypertension can be associated with PCH.

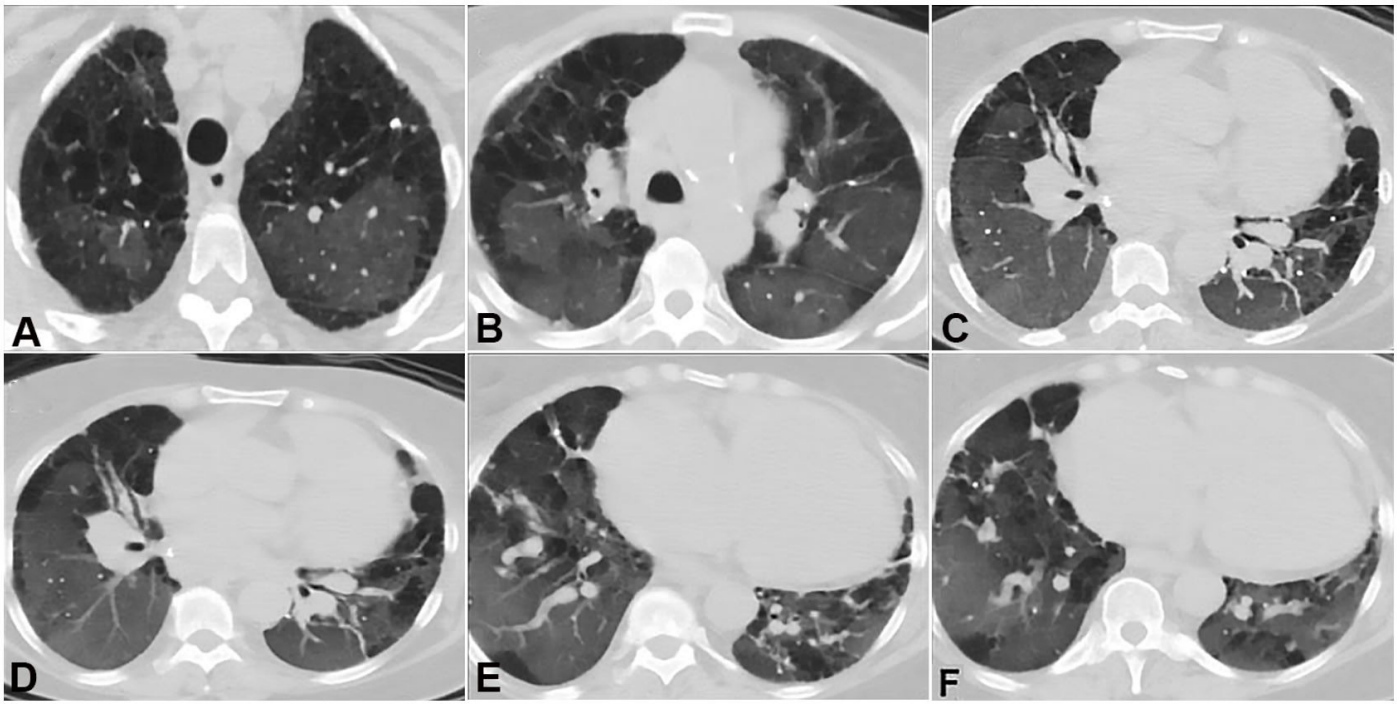

Figure 2. Imaging findings associated with PCH, as seen on non-contrasted chest CT in lung windows. **A** to **F –** sequential axial slices from the upper lung zones down to the lower lung zones demonstrate widespread geographic regions of pulmonary ground glass attenuation, which in the setting of pulmonary hypertension, raises the possibility of PCH. Although indistinguishable from PVOD on imaging alone, the relative paucity of septal thickening as compared to the degree of the ground-glass present may somewhat favor PCH over PVOD in the differential diagnostic consideration.

Subsequent pulmonary function tests revealed abnormalities that were consistent with her known history of pulmonary emphysema. After comprehensive evaluations, it was concluded that she had pulmonary hypertension that was likely secondary to multifactorial lung disease. She then began treatment for pulmonary hypertension and was also started on a high dose of corticosteroids and sildenafil, a prostacyclin analog.

Months later, she presented again with worsening respiratory distress and was hospitalized due to exacerbations of her heart failure. She had her oxygen supplementation increased to improve symptoms. Increased doses of medications offered little help. Her laboratory values continued to increase with a brain natriuretic peptide (BNP) of 3580 pg/mL (reference range [RR] < 100 pg/mL) and worsening kidney function. A chest X-ray revealed an enlarging cardiac silhouette with increased pulmonary vascular congestion relative to earlier imaging. On her last admission, she required 15 L of oxygen with BIPAP in order to maintain her oxygen saturation. Her chest CT at this time also showed evidence of worsening disease. After clinical consensus, the steroid was tapered off, and sildenafil was discontinued. She was started on comfort care treatment and made DNAR and expired soon thereafter. A lung only autopsy was performed.

AUTOPSY PRESENTATION

On gross examination, both lungs demonstrated patchy emphysematous changes and areas of consolidation (Figure 3).

Histopathologically, focal areas of passive congestion were identified with increased septal capillary densities, capillary proliferation and associated pulmonary hypertension (Figure 4). Special stains of such areas demonstrated aberrant capillary proliferation and layering, with immunohistochemical stains of endothelial markers confirming this impression (Figure 5). A diagnosis of pulmonary capillary hemangiomatosis was rendered.

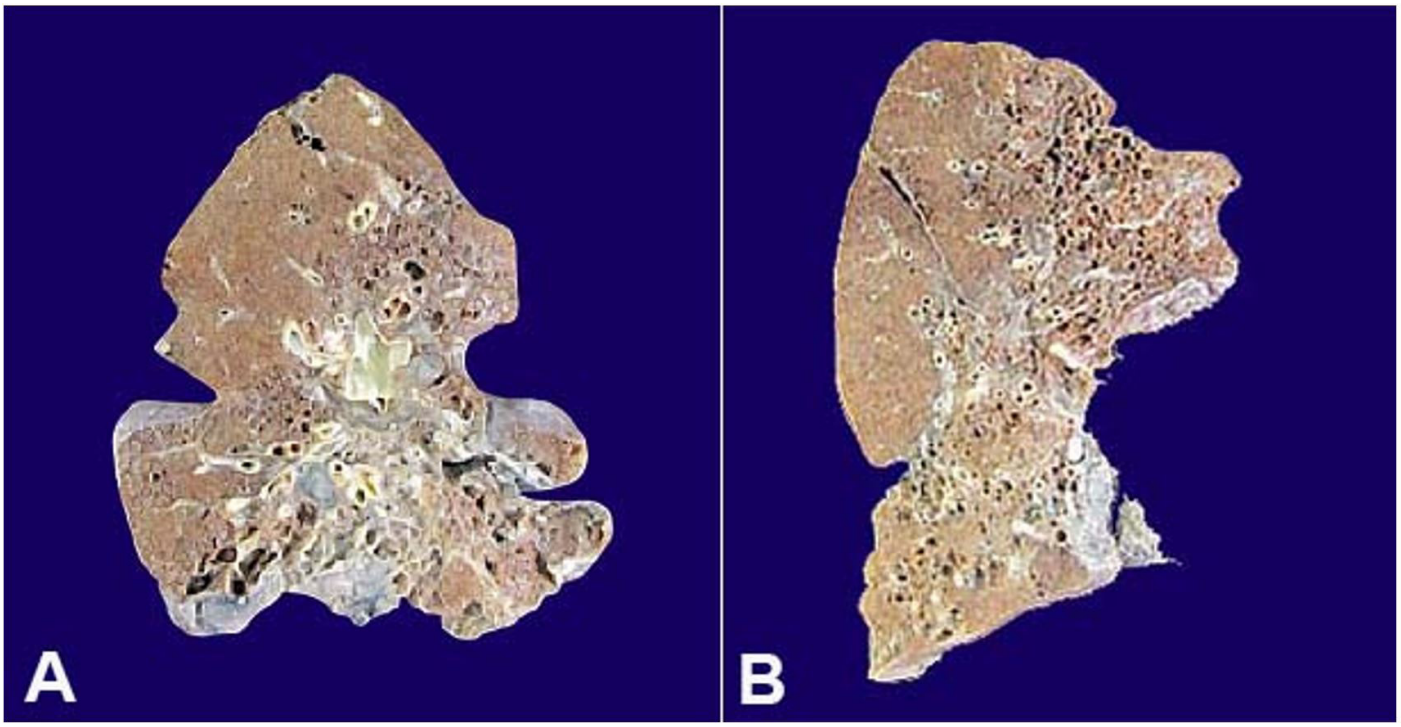

Figure 3. Gross findings of the lungs at autopsy (post-formalin fixation). **A –** Right; **B –** Left lung parenchyma revealing emphysematous changes and areas of consolidation with firm pulmonary parenchyma.

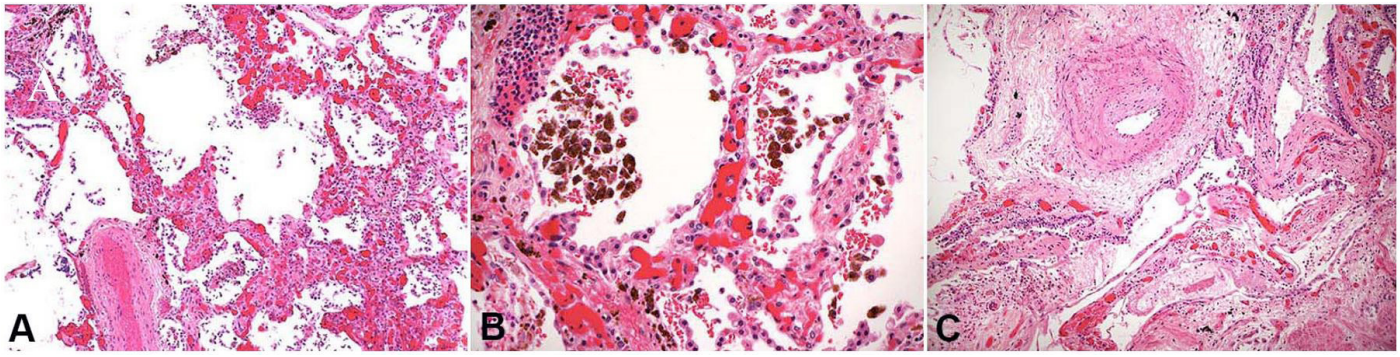

Figure 4. Photomicrographs of the lung. **A –** thickened alveolar walls with increased capillary density and passive congestion; **B –** increased capillary density and congestion in the alveolar walls with hemosiderin-laden macrophages in the alveolar spaces; **C –** Muscularized arteriole within the alveolar septa with intimal thickening and medial hypertrophy characteristic of pulmonary hypertension (H&E, A 40X, B 100X, C 100X).

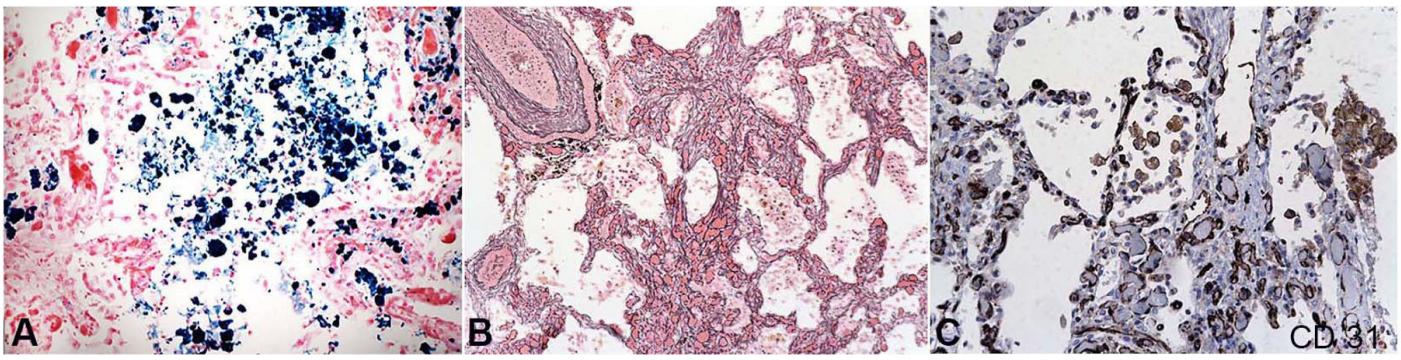

Figure 5. Photomicrographs of the lung. **A –** Iron staining highlights hemosiderin in alveolar walls and in the alveolar spaces (Perls Prussian blue stain, 100X); **B –** reticulin stain revealing the increased number of capillary walls in alveolar walls (Verhoeff van Gieson stain, 100X); **C –** CD31 stain revealing increase vessel proliferation in alveolar walls (100X).

DISCUSSION

Pulmonary capillary hemangiomatosis is a rare cause of pulmonary hypertension that is typically seen in younger adults but can occur in an age range from 2 years to 72 years.

The etiology of PCH remains unknown, and its prognosis is invariably unfavorable with death occurring within 3-5 years from the diagnosis. Patients typically present with progressive dyspnea as their major complaint but can also have hemoptysis, chest pain, cough, and fatigue.[1-6] Their pulmonary function tests are usually normal.[2] Right heart catheterization reveals markedly pulmonary hypertension.[2,3]

Therapeutically, PCH patients do not respond to conventional therapy for pulmonary hypertension such as diuretics, ACE-inhibitors, warfarin, and steroids.[2] Noteworthy, the addition of prostacyclin analog to the therapeutic regimen of these patients have been reported to have a disastrous outcome such as sudden-onset of respiratory distress. Therefore, the use of prostacyclin analogs is not indicated.[2] The only definitive treatment is lung transplantation, although a case of recurrence in this setting has been reported. [2,4]

Pulmonary capillary hemangiomatosis (PCH) (and its closely related condition Pulmonary Veno-occlusive Disease-PVOD) can be clinically indistinguishable from pre-capillary pulmonary arterial hypertension disorders such as primary pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension. However, the diagnostic distinction is crucial to avoid inappropriate treatment with vasodilator medications usually used for PAH treatment (i.e., prostacyclin agonists, endothelin antagonists, calcium channel blockers, phosphodiesterase-5 inhibitors), as these agents can cause pulmonary edema for PCH/PVOD patients. The diagnostic distinction is also important to prompt timely evaluation for possible lung transplantation, given the rapid progression to end-stage disease and death. Although imaging features can remain nonspecific, the radiologist may raise the question of an otherwise unsuspected capillary/postcapillary disorder suggestive of PCH/PVOD, with high-resolution CT as the preferred modality for optimal radiological evaluation.

Imaging characteristics of PCH involve, in general, the presence of pulmonary artery hypertension, such as enlarged pulmonary arteries. Also, as pulmonary artery hypertension progresses, evidence of secondary right heart dysfunction can be seen with typical CT imaging findings of right ventricular hypertrophy, leftward bowing of the interventricular septum, right atrial enlargement, and reflux of IV contrast into the inferior vena cava and hepatic veins.

More specific findings that can help to distinguish PCH/PVOD from pre-capillary causes of pulmonary arterial hypertension (such primary pulmonary hypertension and chronic thromboembolic pulmonary hypertension) include the presence of pulmonary smooth interstitial/interlobular septal thickening, geographic or nodular ground-glass opacities, and pleural effusion, which can be caused by elevated capillary (or postcapillary) pressure. These findings, particularly interlobular septal thickening, are therefore less typical of precapillary causes of pulmonary artery hypertension.[7] Downstream postcapillary causes of pulmonary hypertension (such as mitral stenosis, left ventricular failure, or left atrial myxoma) may also demonstrate these manifestations, but will often demonstrate pulmonary venous dilation (absent in PCH/PVOD) as well as other more specific findings consistent with their respective conditions, such as mitral valve calcifications, left atrial filling defect, and left ventricular enlargement. Additionally, lymphadenopathy is more commonly associated with PCH/PVOD than with other pre-capillary causes of pulmonary hypertension, probably secondary to venous congestion and veno-lymphatic shunts in PCH/PVOD.[8,9]

In the context of pulmonary hypertension, when smooth septal thickening and ground glass opacities are seen or when enlarged mediastinal lymph nodes are present, both PCH and PVOD should be considered in the imaging differential diagnosis.[7,9] Further distinguishing these two conditions radiologically can be difficult as they share many imaging features. However, relatively more conspicuous or widespread centrilobular and lobular ground-glass opacities, and relative paucity of septal thickening, may favor PCH over PVOD; and vice versa, relatively more conspicuous septal thickening with absent or less centrilobular ground glass nodules may favor PVOD over PCH.[7] Additionally, mediastinal lymphadenopathy may be present with PCH more likely than with PVOD.[2]

In the imaging workup of PCH, the CT is the preferred modality for optimal characterization of its imaging features. Nuclear imaging VQ-scanning

is sometimes done as part of the imaging workup, particularly when chronic pulmonary thromboembolism is in the differential diagnosis for pulmonary artery hypertension, however VQ scanning is not helpful for either confirming or excluding PCH; VQ scan findings in PCH include the entire spectrum from normal to small or large perfusion mismatched defects possible.[10]

Upon a gross exam, the lungs will typically appear congested and have an edematous and firm appearance without significant fibrosis. Histopathologically, at low power, areas of the lung involved by PCH demonstrate passive congestion.[3] At higher power, an abnormal proliferation of thin-walled microvessels expanding the alveolar septum and encompassing bronchovascular bundles can be characteristically identified.[3] These proliferations can infiltrate small pulmonary arteries and interlobular veins, causing an obstruction and resultant PAH.[3] Such proliferations are also prone to bleeding which results in hemorrhage and hemosiderin-laden macrophages in the alveolar spaces. In order to make the diagnosis of PCH, there must be at least 2 layers of aberrant capillaries that are seen within the alveolar wall.[2,3] The typical characteristics of pulmonary hypertension will also be seen, which include intimal thickening and medial hypertrophy of the small muscular arterioles, but in contrast to other forms of pulmonary hypertension, the presence of plexiform lesions will not be observed.[3] Special stains and immunohistochemistry are not necessary to diagnose but are helpful for the diagnosis of pulmonary capillary hemangiomatosis.[2,3] Endothelial markers such as CD31, or CD34 will highlight the proliferation of septal capillary endothelial cells.[2,3]

Common misdiagnoses include PVOD and pulmonary arteriopathy.[1,5] However, in both entities the capillary proliferation lacks.[1-3] A Trichrome, or a Movat Pentachrome stain can highlight the supporting collagen of the loop lesion and occluded veins seen in PVOD but not in PCH. However, PCH like findings and PVOD like findings have been documented in both entities interchangeably, raising the possibility that these distinct entities may represent spectrums of the same disease.[3] Interestingly, such findings have also been reported in patients who do not have pulmonary hypertension[3].

CONCLUSION(S)

Overall, in our patient's case, the pulmonary artery hypertension presumably involved multiple contributing factors, including a contributing element from chronic obstructive pulmonary disease (COPD) in addition to her PCH. Additionally it is possible the PCH developed as a reactive process due to hypoxia and chronic congestion, rather than a primary/idiopathic etiology, in this patient with multiple additional conditions that could contribute to pulmonary hypertension.[11] However, regardless of the primary or secondary etiology, considering the presence of PCH remains diagnostically important since it still has important unique clinical consequences, specifically, avoiding typical vasodilatory therapy and early potential transplant planning.

This autopsy case highlights the importance of due vigilance in pulmonary hypertension patients and the multidisciplinary approach required to establish a diagnosis of pulmonary capillary hemangiomatosis and appropriately guide management. Although the clinical symptoms are non-specific, findings suggestive of PCH can be radiologically suspected, which can indicate a subsequent biopsy. However, histology remains the sole reliable means to make the diagnosis when the lungs have been adequately sampled. Most of the time, the diagnosis is not suspected or masked by coexisting lung disease, adequate lung tissue is not sampled, or the patient is inappropriately treated, and thus, most cases of PCH are unmasked at autopsy. Lesson learned, recognition of this rare entity is imperative to convey accurate prognosis and appropriately guide patient management, avoiding treatment with prostacyclin analogs (conventionally used to treat pulmonary hypertension) which may end up actually exacerbating the disease process in these patients.

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The authors retain an informed consent signed by the patient's next-to-kin authorizing the usage of the pertinent scientific findings gathered from performing the autopsy for educational purposes, medical research and/or quality purposes.

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