Pulmonary Capillary Hemangiomatosis Associated with CREST Syndrome: A Case Report and Review of the Literature

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Established Facts

- Both CREST disease and pulmonary capillary hemangiomatosis (PCH) are uncommon disease states, but both clinical entities occurring together are a rarity.
- Patients with pulmonary hypertension may be treated with long-term epoprostenol to improve their symptoms.

Novel Insights

- Clinicians should suspect PCH in those patients with pulmonary hypertension failing an epoprostenol challenge.

Key Words

Arterial hypertension • Epoprostenol • Pulmonary artery abnormalities • Pulmonary capillary hemangiomatosis • Pulmonary vascular disease • Vascular disorders • Venooclusive disease

after administration of low-dose epoprostenol in the intensive care unit. An autopsy revealed the patient suffered from pulmonary capillary hemangiomatosis. We review our case and what is known about this rare disease.

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Abstract

This is a report of fatality immediately after administration of epoprostenol. The patient was previously diagnosed with CREST syndrome and associated interstitial lung disease. She developed worsening pulmonary hypertension and was clinically diagnosed with pulmonary veno-occlusive disease. The patient developed flash pulmonary edema and arrested

Introduction

Pulmonary hypertension is an uncommon but perplexing disease. It can present as a secondary process for a variety of chronic diseases. In the past decade, vast strides have been made to understand its pathophysiology and establish meaningful treatments. PCH is a rare

cause of pulmonary hypertension. It is an elusive diagnosis usually made at autopsy. We present a case of PCH and a review of the literature.

Case Report

The patient, a 52-year-old female with CREST syndrome, had experienced progressive dyspnea on exertion for about 1 year. An echocardiogram report showed mild left-ventricular hypertrophy and moderate tricuspid regurgitation with mild pulmonary hypertension. A computer tomography (CT) of the chest demonstrated an interstitial pattern in both lung fields and subcarinal adenopathy. She was started on 40 mg of prednisone which initially seemed to improve her dyspnea on exertion, but it worsened 1 month later. Subsequently, her dose was increased to 70 mg daily.

Within a few months, the patient was found to have progression of her symptoms and she was started on cyclophosphamide for suspected scleroderma-associated alveolitis; her steroid was tapered. Soon after, a CT scan of the chest revealed a diffuse ground-glass appearance. Pulmonary function tests showed a normal FVC (3.29 liters, 86% of predicted), normal FEV₁ (2.58 liters, 90% of predicted), and the FEV₁/FVC ratio was normal at 78%, but DLCO was decreased (8.44, 40% of predicted).

She underwent an outpatient right-heart catheterization to evaluate the pulmonary hypertension; she had elevated pulmonary-artery pressures of 72/39 mm Hg at baseline. After vasodilator challenge with epoprostenol her pulmonary-artery pressures improved marginally to a low of 60/31 mm Hg. However, the challenge had to be halted shortly after the dose was increased to 10 ng/kg/min due to dyspnea, anxiety, back pain, and hypoxia. Following a mixed venous blood gas and chest radiograph, she was diagnosed with flash pulmonary edema. She was treated with a diuretic and continuous positive airway pressure while her respiratory status improved within hours. Now the patient was felt to have diastolic dysfunction, coronary disease, and/or pulmonary veno-occlusive disease (PVOD). To evaluate her coronary arteries and assess diastolic function, the patient had a left-heart catheterization and coronary angiography. No stenosis was found and the end-diastolic left-ventricular pressure was 9 mm Hg.

Due to her response to the vasodilator and results from the cardiac catheterization it was determined that she had PVOD. Treatment was to be started with epoprostenol. The patient was admitted to the medical intensive care unit for initiation of therapy. She complained of back pain following the initiation of therapy, and after approximately 45 min of therapy the patient noticed increasing shortness of breath. The infusion was stopped but the patient quickly decompensated into respiratory failure and progressed to bradycardic arrest. Attempts to resuscitate her failed.

Discussion

PCH was first defined by Wagenvoort et al. [1] as caused by an uncontrollable proliferation of pulmonary capillaries infiltrating vascular, bronchial, and intersti-

tial pulmonary structures. Since the first case reported in 1978, about 40 cases of PCH have been described in the literature with only a single case of PVOD associated with CREST syndrome and a single case of PCH associated with scleroderma [2, 3]. Isolated pulmonary hypertension, without pulmonary fibrosis present, may occur in 10% of patients with CREST; typically, it is characterized by concentric fibrointimal proliferation with occlusion of small arteries and arterioles [2, 3].

Although clinical signs and symptoms may suggest PCH, rarely is the disease diagnosed antemortem. Our patient's initial presentation was that of worsening dyspnea on exertion which is the most common manifestation of PCH. Although this nonspecific symptom is a clinical manifestation of PCH, it is also found with inflammatory alveolitis caused by the CREST syndrome, which was also included in our differential diagnosis. In the setting of primary pulmonary hypertension, the presence of hemoptysis, pleural effusion, elevated number of iron-laden bronchoalveolar macrophages, and an interstitial radiological pattern suggest PCH [2, 4–6], though there has been at least one report in which pulmonary hypertension was absent in the presence of PCH [6], adding to the difficulty in diagnosing this rare disease. Retrospective analysis of a report by Humbert et al. [4] demonstrated that the clinical presentation of PCH is indistinguishable from that of classic hypertensive pulmonary arteriopathy. Pathological diagnosis requires surgical biopsy, but the compromised condition of the patient makes this hazardous. Even with a tissue sample, discerning between PCH and PVOD is difficult.

At autopsy, our patient's lungs contained numerous punctate erythematous lesions throughout all lobes with no gross evidence of interstitial fibrosis. Microscopically, these lesions consisted of thickened alveolar septae containing at least double layers of capillaries (fig. 1). Aggregates of capillaries, sometimes encroaching onto adjacent venules, were also found (fig. 2). These findings are characteristic of PCH [7]. It has been suggested that PCH may be a secondary angioproliferative process caused by post-capillary obstruction in patients with PVOD [8]. Our patient, however, showed a markedly predominant pattern of PCH with no evidence of interstitial fibrosis and only rare occlusion of venules.

In almost all reported cases of PCH in which epoprostenol infusion was initiated, like our patient, pulmonary edema ensued. The mechanism of epoprostenol-induced pulmonary edema is at best speculative. It is believed that prostaglandins induce pulmonary edema in the setting of PVOD. This presumably occurs by increasing pulmonary

Fig. 1. Verhoeff-van Gieson stain of the lung, low power view. Sections of the lung demonstrated panlobular discrete lesions showing capillary proliferation within alveolar septae. The intervening lung parenchyma was unremarkable.

Fig. 2. Verhoeff-van Gieson stain of the lung, high power view. This section shows a nodule of proliferating, cytologically benign capillary-sized vessels situated within the pulmonary interstitial tissue.

capillary hydrostatic pressure [4]. Humbert et al. [4] suggest that epoprostenol therapy should not be used in patients with severe pulmonary hypertension secondary to PCH. We believed that our patient had pulmonary hypertension secondary to scleroderma which is why we re-challenged her with epoprostenol. During the second trial of epoprostenol infusion our patient expired, similar to the first case of scleroderma and PCH reported [2]. One retrospective review, by Resten et al. [9], suggests doing thin-section CT to help predict who will fail epoprostenol therapy in the treatment of pulmonary hypertension. Findings such as a centrilobular pattern of ground-glass opacities, septal lines, pleural effusion, pericardial effusion, and/or adenopathy were found in the group of patients who subsequently died. Postmortem lung examinations of patients who experienced treatment failure revealed a postcapillary occlusive vasculopathy pattern. Our patient had a CT performed demonstrating an interstitial pattern bilaterally and subcarinal adenopathy; a later scan revealed a diffuse ground-glass pattern bilaterally. Therefore, our patient's scan corresponded with the pattern associated with treatment failure.

Presently, few treatment options exist for PCH. Lung transplantation seems to be the most effective long-term treatment. However, there is a shortage of organ donors indicating a need for bridge therapies until transplant [4, 10, 11]. Some success has been noticed with continuous inhaled nitric oxide in primary pulmonary hypertension,

and in a study by Humbert et al. [4] neither of their patients with PCH clinically deteriorated with acute inhalation of nitric oxide. Interferon α -2a has demonstrated some success but the mechanism of action is not well understood [12, 13]. A more recent case report describes successful treatment using doxycycline [14]. Unsuccessful treatments have included angiotensin-converting enzyme inhibitors, diuretics, oxygen, corticosteroids, and warfarin [12].

Conclusion

PCH is a rare disease that can be associated with scleroderma. It is difficult to diagnose due to the debilitating pulmonary hypertension and the need for pathologic confirmation. Intolerance of an epoprostenol challenge should prompt consideration of the diagnosis. A thin-section CT of the chest may help in determining the safety of epoprostenol. Treatment options are limited but promising. A clinical history suggesting the diagnosis may be sufficient for referral to a transplantation center.

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