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Case Report

A case report of Pulmonary Capillary Hemangiomatosis: Rapid Deterioration after Diagnosis with Unsuccessful Response to Doxycicline Therapy

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Abstract

Pulmonary capillary hemangiomatosis is an extremely rare cause of Pulmonary Arterial Hypertension. It is characterized by an uncontrolled proliferation of endothelial cells affecting thin walled micro vessels that invade lung parenchyma, the bronchial walls and the adventitia of larger vessels. This process leads to pulmonary arterial hypertension, hemoptysis and right heart failure, followed by death. Most cases have been confirmed with necropsy and the only effective treatment is bilateral lung transplant. We present a case of a young female patient affected by a rapidly progressive form of this disease. She did not respond to antiangiogenic therapy and required a bilateral lung and heart transplant.

Keywords: Antiangiogenic Therapy; Pulmonary Capillary Hemangiomatosis; Pulmonary Hypertension

Introduction

Pulmonary capillary hemangiomatosis (PCH) is an extremely rare cause of Pulmonary Hypertension. It shares pathologic, clinical and genetic characteristics with pulmonary veno-occlusive disease, being grouped as type 1' Pulmonary Arterial Hypertension (PAH) according to the updated clinical classification [1]. It is characterized by an uncontrolled proliferation of endothelial cells affecting thin walled micro vessels that invade lung parenchyma, the bronchial walls and the adventitia of larger vessels. This process leads to PAH, hemoptysis and right heart failure, followed by death [2]. No more than 50 cases have been reported and less than 25% of these patients had a pre-mortem definitive diagnosis made by lung biopsy. Most cases have been confirmed with necropsy [3]. The only effective treatment is bilateral lung transplant. We present a case of proven PCH affecting a young female patient.

Case Report

A 17-year-old female presents with a 2 year history of progressive dyspnea. Two months prior to her first medical consult she noticed an increase of fatigue and intermittent chest pain. Minimal physical activity exhausted her, but she did not complain of cough, hemoptysis, orthopnea or peripheral

edema. Physical examination revealed a good general appearance, normal blood pressure, SaO2 89%, perioral cyanosis, digital clubbing, no jugular venous distension, loud P2, clear lung sounds, no hepatosplenomegaly and no joint abnormalities.

The chest radiograph was normal (figure 1). The ECG showed right axis deviation and non-specific ST-T changes. The echocardiogram showed a dilated right ventricle with normal systolic function and moderate tricuspid regurgitation. The left ventricular systolic function and mitral valve were normal. The pulmonary artery systolic pressure estimated by Doppler was 50mmHg. A small early right to left pulmonary shunt was observed with agitated saline. There was no pericardial effusion.

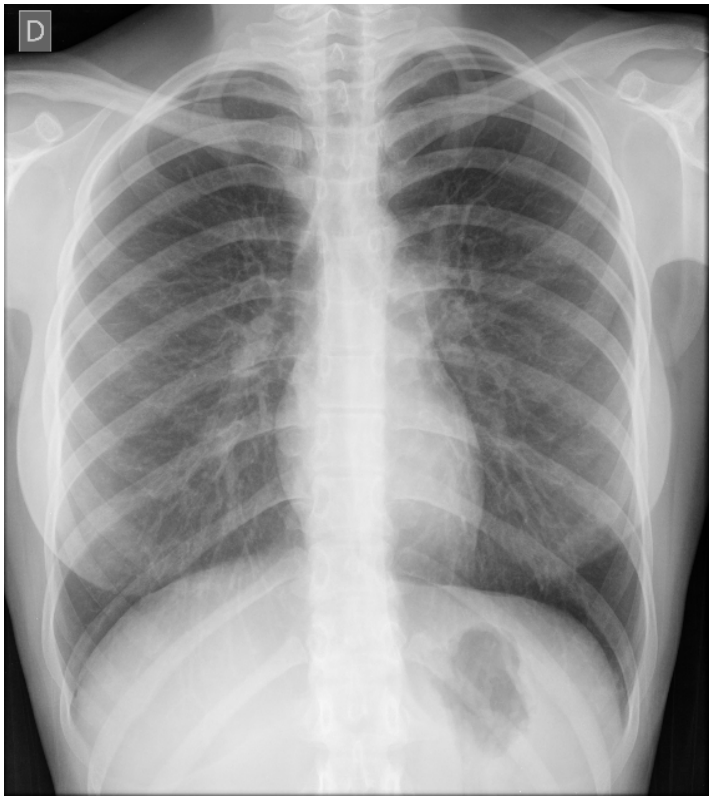

Figure 1. The patient had a normal chest radiograph at her first consult.

A CT pulmonary angiogram ruled out embolism. It showed dilated central pulmonary arteries and multiple bilateral nodules of ground-glass opacity. There was no prominent interlobar septal thickening, pleural effusion or mediastinal lymphadenopathy. These findings suggested the diagnosis of PCH (figure 2).

Complete blood count, serum chemistry panel and rheumatologic testing were normal. Arterial blood gas level breathing room air was PaO2 53mmHg.

A right heart catheterization was performed confirming pre-capillary pulmonary hypertension (mean pulmonary artery pressure 31mmHg, PCWP 10mmHg, pulmonary vascular resistance 7U Wood, Cardiac output 2.9lt/min).

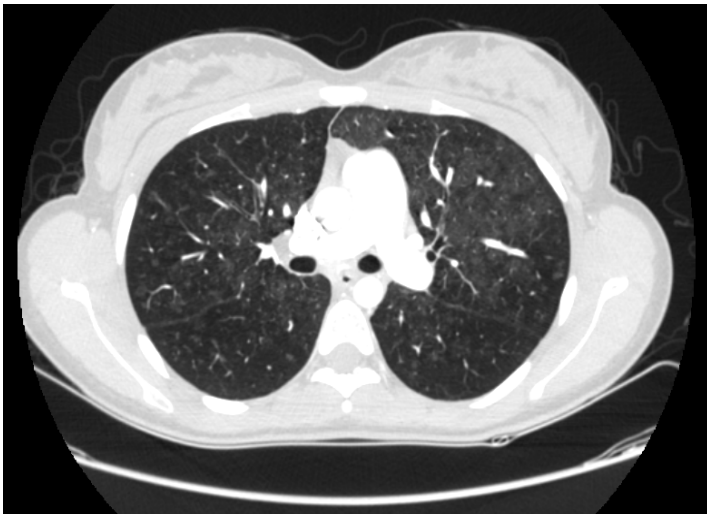

Figure 2. The CT pulmonary angiogram showed dilated central pulmonary arteries, multiple bilateral nodules of ground-glass opacity.

Lung function tests revealed a severe decrease of carbon monoxide diffusing capacity, normal alveolar volume and normal spirometry. The patient could not complete the six-minute walk test despite 3lt/min oxygen supplementation. She walked 226 meters, stopping after two and a half minutes with moderate dyspnea, SaO2 76% and increase of resting tachycardia.

A lung biopsy of the right inferior lobe was performed using video-assisted thoracoscopic surgery. No complications occurred by the procedure. The biopsy showed multiple microscopic foci of mild alveolar septal thickening with capillary vessels that protruded into the alveolar lumen and pronounced hyperaemia. There was no inflammation and no evidence of malignancy. These findings were consistent with PCH (figure 3). After diagnostic confirmation the patient was enlisted for bilateral lung transplant. While waiting for the transplant she was started on antiangiogenic therapy with doxycycline and used permanent oxygen supplementation. She rejected the suggested use of alpha-Interferon.

One month after the biopsy the patient had a rapid deterioration, with increasing resting dyspnea and right upper quadrant abdominal pain. She was admitted to an intensive care unit. A CT pulmonary and abdomen angiogram was performed. It revealed signs of pulmonary hypertension with dilated right heart and liver congestion, persistence of multiple bilateral nodules of ground-glass opacity, signs of peribroncovascular edema and interstitial edema. There was no evidence of pulmonary embolism or complications secondary to the lung biopsy (figure 4).

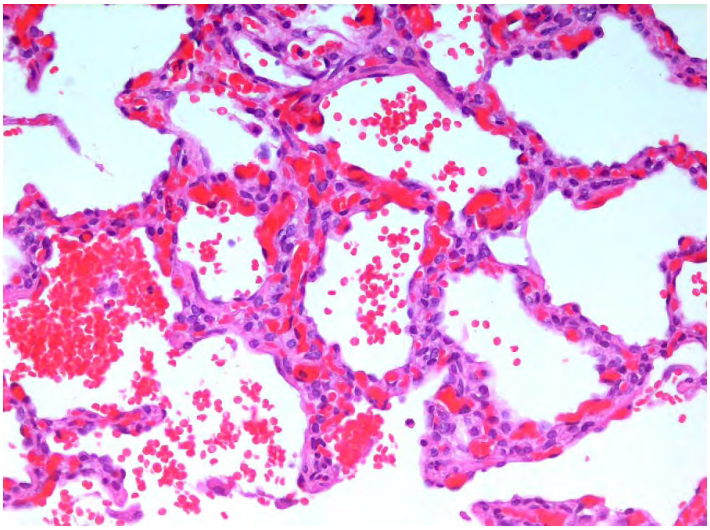

Figure 3. The lung biopsy showed multiple microscopic foci of mild alveolar septal thickening with capillary vessels that protruded into the alveolar lumen and pronounced hyperemia.

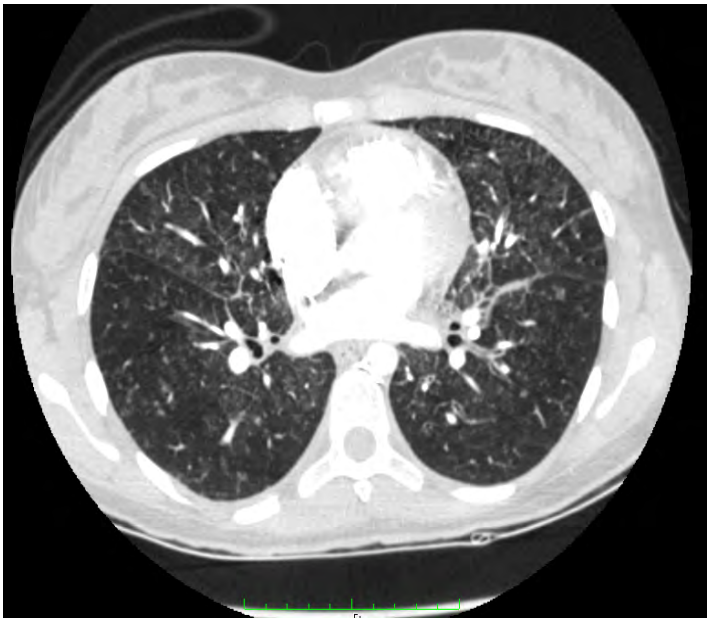

Figure 4. The second CT angiogram revealed signs of pulmonary hypertension, progression of multiple bilateral nodules of ground-glass opacity, signs of peribroncovascular edema and interstitial edema.

During the first day of admission she developed hypotension and severe hypoxemia. A new echocardiogram showed dilated right ventricle with decreased systolic function (TAPSE 6mm), severe tricuspid regurgitation and an estimated pulmonary artery systolic pressure of 100mmHg. The patient was treated with intravenous milrinone and oxygen therapy without positive results. While waiting for surgery her clinical status became worse and two days later she was supported with a right ventricle assistance device. After 16 days she finally received a heart and bilateral lung transplant without success, dying in the early postoperative period.

Discussion

PCH is a diffuse proliferation of capillaries that can form glomeruloid nodules and invade pulmonary veins, arteries, interstitium and airways. It usually affects young adults, being more common in women. Manifestations of the disease include dyspnea, cough, fatigue, hemoptysis, weight loss, altered pulmonary function tests and pulmonary hypertension with right heart failure. The median survival after making the diagnosis is 3 years [3].

PCH behaves as a low-grade vascular neoplasm. The main histopathological finding is proliferation of cytologically normal capillary channels within alveolar walls [4]. Pathologic characteristics frequently overlap with pulmonary veno-occlusive disease [5].

PCH is a rare cause of pulmonary arterial hypertension, associated with significant venous or capillary involvement. Remodelling and narrowing of pulmonary arteries associated with a mechanical obstruction of blood flow due to invasion of venules and veins is believed to increase the pulmonary resistance. Invasion of the alveolar septa and bronchioles alters gas exchange by reducing the surface area and diffusion capacity of the lung. These changes result in recurrent pulmonary haemorrhage, scar formation, thrombosis and pronounced vascular obliteration. Pulmonary hypertension, chronic hypoxia and restrictive remodelling of the lung tend to develop and progress.

High-resolution CT scans show a diffuse bilateral thickening of the interlobar septa and small centrolobular, poorly circumscribed opacities. Ground-glass pattern can also be seen [6]. The CT scan performed on our patient had these findings.

Differential diagnosis that should be considered include pulmonary veno-occlusive disease, pulmonary arterial hypertension (Type I) [1], cavernous hemangiomatosis or pulmonary angiomatosis (which involves larger calibre vessels), interstitial pneumonitis, recurrent pulmonary thromboembolism, and idiopathic pulmonary hemosiderosis.

Lung biopsy using video-assisted thoracic surgery showing proliferation of two layers of normal capillary channels within alveolar walls is the gold standard of the diagnosis [7]. This is consistent with our patient's findings. There has been some discussion on the safety of performing a lung biopsy in these cases because of an increased concern for bleeding. This can impact on the time of confirmation of the disease, which may contribute to making it most frequently a post mortem diagnosis by necropsy. The biopsy performed on our patient proved to be safe, with no complications following the procedure. Because of this safety issue, it has been proposed that the diagnosis can be established with a high probability without a lung biopsy, based on clinical suspicion, physical examination and radiological findings [8].

Most cases are sporadic. Up to this patient's death, she had two asymptomatic siblings. Familial occurrence has been reported as autosomal recessive trait secondary to bi-allelic mutations in EIF2AK4. The detection of these mutations can be sufficient to establish the diagnosis in heritable cases [9]. PCH has also been described in association with autoimmune diseases such as Lupus erythematosus and scleroderma, suggesting an immune-mediated cause [10].

Because of the low incidence of this disease and its poor prognosis, evidence is lacking to recommend pharmacological treatment. Our only knowledge of treatment regimens comes from case reports. The best outcomes to date are in patients treated with bilateral lung transplant, which can be curative. One case report described de-novo PCH in a transplanted lung after 3 months [11].

Because of this, pharmacological treatment should be considered supportive until transplantation, if lung transplantation is an option. Since an immune mediated cause has been suggested, immunosuppression with alpha-Interferon has been used in a few cases with successful results [12]. Matrix proteases MMP-2 and MMP-9 play an important roll in endothelial cell invasion and angiogenesis. Doxycicline is an MMP inhibitor and has been used as antiangiogenic therapy in one case to treat PCH with promising results [13]. Prostacyclin and calcium channel blockers, typically used in pulmonary arterial hypertension, can cause pulmonary edema in patients with pulmonary postcapillary vasculopathies such as PCH and pulmonary veno-occlusive disease. They are relatively contraindicated in this setting [14].

We believe that this is the first case of confirmed PCH in our country. The patient developed a rapidly progressive form of PCH, with severe pulmonary hypertension and right heart failure. Antiangiogenic therapy with doxycicline has shown promising results in some cases, but our patient failed to respond. Since a rapid deterioration and fatal outcome is expected in these cases, these patients should probably have priority for a bilateral lung transplant. The cause of this fatal disease is poorly understood and there is no established pharmacological treatment. Because of this cause transplant surgery should not be delayed.

References

1. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C et al. Updated Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol. 2013, 62 (25Suppl): D34–41.

2. Rich S. Pulmonary hypertension, pulmonary capillary hemangiomatosis. In: Braunwald's Heart disease: a textbook of cardiovascular medicine (2012), 9th edn. Saunders, Philadelphia, 1696–1718.

3. Almagro P, Julià J, Sanjaume M, Gonzalez G, Casalots J et al. Pulmonary capillary hemangiomatosis associated with primary pulmonary hypertension: report of 2 new cases and review of 35 cases from the literature. Medicine(Baltimore). 2002, 81(6): 417-424.

4. Tron W, Magee F, Wright JL, Colby T, Churg A. Pulmonary capillary hemangiomatosis. Hum Pathol. 1986, 17(11): 1144–1150.

5. Lantuejoul S, Sheppard MN, Corrin B, Burke MM, Nicholson AG. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: a clinicopathologic study of 35 cases. Am J Surg Pathol. 2006, 30(7): 850–857.

6. Dufour B, Maitre S, Humbert M, Capron F, Simonneau G et al. High-resolution CT of the chest in four patients with pulmonary capillary hemangiomatosis or pulmonary venoocclusive disease. Am J Roentgenol. 1998, 171(5): 1321-1324.

7. Havlik DM, Massie LW, Williams WL, Crooks LA. Pulmonary capillary hemangiomatosis-like foci. An autopsy study of 8 cases. Am J Clin Pathol. 2000, 113(5): 655–662.

8. Montani D, Achouh L, Dorfmuller P, Le Pavec J, Sztrymf B 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): 220–233.

9. Best DH, Sumner KL, Austin ED, Chung WK, Brown LM et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. Chest. 2014, 145(2): 231–236.

10. FernandezAlonso J, Zulueta T, ReyesRamirez JR, Castillo-Palma MJ, Sanchez-Román J. Pulmonary capillary hemangiomatosis as cause of pulmonary hypertension in a young woman with systemic lupus erythematosus. J Rheumatol. 1999, 26(1): 231–233.

11. de Perrot M, Waddell TK, Chamberlain D, Hutcheon M, Keshavjee S. De novo pulmonary capillary hemangiomatosis occurring rapidly after bilateral lung transplantation. J Heart Lung Transplant. 2003, 22(6): 698–700.

12. White C, Sondheimer H, Crouch E, Wilson H, Fan LL. Treatment of Pulmonary Hemangiomatosis with recombinant interferon Alfa-2a. N Engl J Med. 1989, 320(18): 1197-1200.

13. Ginns LC, Roberts DH, Mark EJ, Brusch JL, Marler JJ. Pulmonary capillary hemangiomatosis with atypical endotheliomatosis: successful antiangiogenic therapy with doxycicline. Chest. 2003, 124(5): 2017–2022.

14. Humbert M, Maitre S, Capron F, Rain B, Musset D. Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. Am J Respir Crit Care Med. 1998, 157: 1681–1685.