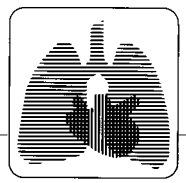

selected reports

Pulmonary Capillary Hemangiomatosis With Atypical Endotheliomatosis*

Successful Antiangiogenic Therapy With Doxycycline

Leo C. Ginns, MD, FCCP; David H. Roberts, MD, FCCP; Eugene J. Mark, MD; John L. Brusch, MD; and Jennifer J. Marler, MD

We report here our experience in achieving remission in a 20-year-old man with pulmonary capillary hemangiomatosis (PCH) with atypical endotheliomatosis following therapy with doxycycline. PCH is a rare disorder characterized by proliferating capillaries that invade the pulmonary interstitium and alveolar septae, and occlude the pulmonary vasculature. The patient's symptoms, lung function, and radiographic findings had worsened despite treatment with both prednisone and α-interferon. He was considered to be a candidate for transplantation. Given the elevated levels of basic fibroblast growth factor (bFGF) in urine and the capillary proliferation noted on biopsy specimens, we elected to treat the patient with doxycycline, a matrix metalloproteinase and angiogenesis inhibitor. Following several weeks of therapy, a gradual resolution of symptoms was noted, with normalization of pulmonary function test results and urine bFGF levels. After 18 months of therapy, the patient remains in complete remission.

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*From the Pulmonary and Critical Care Unit (Drs. Ginns and Roberts), General Medical Services, and the Department of Pathology (Dr. Mark), Massachusetts General Hospital, Boston, MA; the Department of Surgical Research (Dr. Marler), Children's Hospital Medical Center, Boston, MA; and the Department of Medicine (Dr. Brusch), Cambridge Hospital and Harvard Medical School, Boston, MA.

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Correspondence to: Leo C. Ginns, MD, FCCP, Pulmonary and Critical Care Unit, White 907, Massachusetts General Hospital, Boston, MA 02114; e-mail: lginns@partners.org

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Abbreviations: bFGF = basic fibroblast growth factor; MMP = matrix metalloproteinase; PCH = pulmonary capillary hemangiomatosis

Pulmonary capillary hemangiomatosis (PCH) is a rare disorder characterized by proliferating capillaries that invade the pulmonary interstitium and alveolar septae, and occlude the pulmonary vasculature.[1] While the etiology and inheritance pattern of PCH are unknown, one report[2] has suggested a familial cluster, and several patients were taking oral contraceptives when the condition was diagnosed.[3] The dysregulated angiogenesis seen in PCH patients possibly may result from either the neoplastic proliferation of capillaries or the sequelae of a prior pulmonary infection.[4]

Approximately 30 cases of PCH have been reported, primarily in young adults (age range, 6 to 71 years) without gender predominance. Presentations have included dyspnea, hemoptysis, and, in more advanced cases, manifestations of pulmonary hypertension.[1–15] Chest radiography usually shows basilar interstitial disease, and high-resolution chest CT scans may document nodules, increased interlobular septal markings, and ground-glass changes.[16] Spirometry has shown both restrictive and obstructive patterns, and the diffusing capacity of the lung for carbon monoxide is usually decreased.[1,6,9,10]

PCH is frequently misdiagnosed antemortem as pulmonary venoocclusive disease,[5,11] or pulmonary arterial hypertension due to arteriopathy,[4,7] multiple pulmonary thromboemboli,[1,5] or interstitial lung disease.[6,10] Occult PCH may be unmasked with pulmonary vasodilators, such as epoprostenol.[2,3,14] While untreated PCH is usually fatal, with death due to bleeding or respiratory failure, one report[17] has described incidental foci of PCH-like lesions found on routine autopsy.

The treatment of PCH with steroids and cyclophosphamide has not been successful. Therapy with α-interferon,[9] pneumonectomy (for unilateral disease),[8] heart-lung transplantation,[7] or single-lung transplantation[11] has been reported as being efficacious for the treatment of PCH. α-Interferon therapy for PCH remains unproven as a more advanced case was not responsive to this therapy.[15] PCH has not been reported to recur after transplantation.

We present our experience in administering doxycycline to a patient with PCH who was characterized by prominent atypical endothelial cell proliferation. The patient's symptoms, lung function, and radiography had worsened despite treatment with both prednisone and α-interferon. Doxycycline therapy was initiated because of its ability to interfere with matrix metalloproteinase (MMP) activity.[18]

We hypothesized that the increased MMP activity incited by dysregulated angiogenesis could be inhibited by doxycycline and could provide clinical benefit. After >18 months of doxycycline therapy, there has been sustained resolution of symptoms, pulmonary function test results, and radiographic abnormalities, as well as evidence for decreased angiogenic activity.

Case Report

Over 6 months, a previously healthy 20-year-old male college student developed hemoptysis, cough, hoarseness, and sore throat. Symptoms responded partially to therapy with oral ampicillin that was prescribed for possible sinusitis. Initially, the patient continued normal activities and denied any fatigue or dyspnea, but eventually minimal physical activity severely exhausted him, and his hemoptysis increased.

A physical examination revealed a pale, chronically ill-appearing individual without adenopathy, clubbing, rash, oral lesions, or joint abnormalities. His chest was clear to percussion and auscultation, and there was no hepatosplenomegaly. Chest radiograph showed diffuse interstitial disease without lymphadenopathy. WBC count and differential count were normal. Hematocrit was 19.6%, with microcytic and hypochromic RBC indexes. Serum lactate dehydrogenase levels and arterial blood gas levels obtained with the patient breathing room air were normal. A chest CT scan revealed multiple faint bilateral nodules (Fig 1, *top left*). Three sputum smears were negative for acid-fast bacilli, but one sputum culture grew *Neisseria meningitidis*. A sinus CT scan revealed diffuse sinusitis, for which an additional course of ampicillin therapy was administered. HIV serology was negative, the antinuclear antibodies result was positive at 1:80 (speckled pattern), and the results of other rheumatologic and serologic testing, including for antineutrophil cytoplasmic antibodies, were negative. There was no pulmonary hypertension found by transthoracic echocardiogram. A lung biopsy was performed using video-assisted thoracoscopic surgery. While the results were pending, therapy with prednisone (60 mg daily), trimethoprim-sulfamethoxazole for Pneumocystis prophylaxis, and a fluticasone metered-dose inhaler was initiated.

The biopsy showed diffuse pulmonary hemorrhage and hemosiderin with proliferation of capillaries, which in part surrounded veins. These findings were initially interpreted as being consistent with pulmonary venoocclusive disease. Little improvement occurred with prednisone therapy, and the patient was referred to Massachusetts General Hospital for further evaluation. A secondary review of the original biopsy specimen emphasized highly atypical cells in capillaries and venules, as well as excessive numbers of capillaries. The differential diagnosis included epithelioid hemangioendotheliomatosis, PCH, and bacillary angiomatosis.

Additional biopsy specimens were obtained by video-assisted thoracoscopic surgery in order to provide further information. These showed diffuse proliferation of highly atypical endothelial cells with abundant cytoplasm, which gave the cells epithelioid features. Nuclei in certain areas were moderately pleomorphic. The endothelial cells caused diffuse interstitial thickening of the alveolar walls (Fig 2), formed nodules beneath the pleura (Fig 3) and around bronchovascular bundles (Fig 4), and narrowed small arteries and veins. The atypical endothelial cells stained for factor VIII, Ulex, CD 31 antigen, and CD 34 antigen, and did not stain for keratin, desmin, muscle actin, or smooth muscle actin. These results are characteristic of endothelial cells. The excessive numbers of capillaries with impingement on small airways and blood vessels define PCH, while the atypical endothelial cells can be described as endotheliomatosis superimposed on the PCH. This combination is highly unusual but has been described before.[4]

Given the poor prognosis associated with PCH, the patient was listed for lung transplantation. Because of reported efficacy in PCH, therapy with subcutaneous α-interferon (initially 1 million units/m^2 three times per week) was begun. The dose was

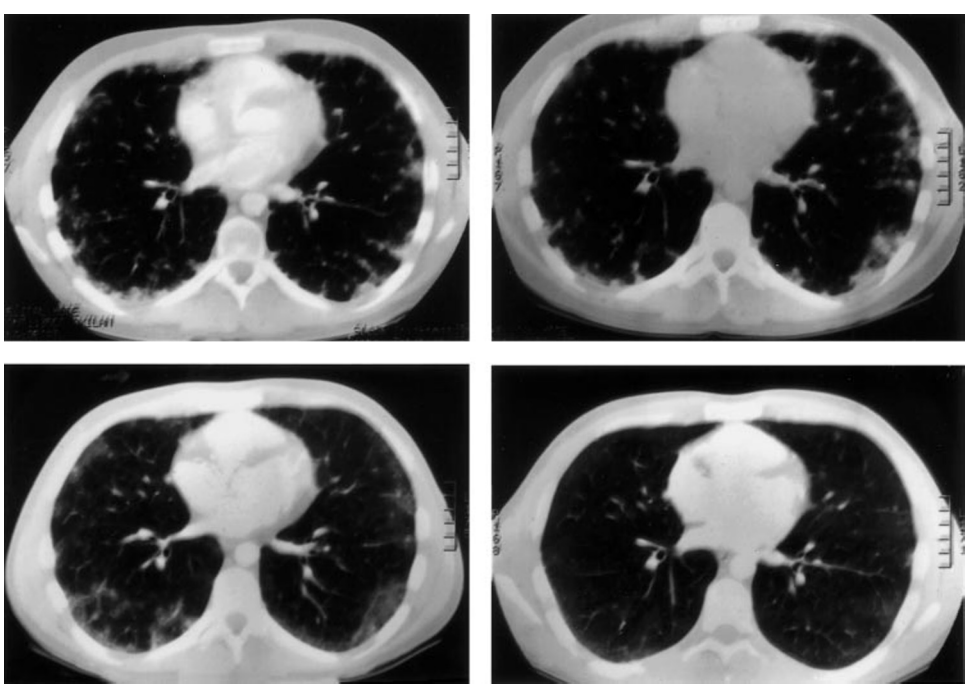

Figure 1. Chest CT scans at the time of presentation (*top left*), 9 months after presentation (*top right*), 18 months after presentation (*bottom left*), and 21 months after presentation (*bottom right*).