Pulmonary Capillary Hemangiomatosis With Atypical Endotheliomatosis*

Successful Antiangiogenic Therapy With Doxycycline

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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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Key words: α-interferon; angiogenesis; antiangiogenic therapy; basic fibroblast growth factor; matrix metalloproteinases; pulmonary capillary hemangiomatosis

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 report2 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.5–15 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 report17 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 transplantation11 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 trans-thoracic 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 hemangioendotheliatosis, 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.

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/m² three times per week) was begun. The dose was...
gradually increased to 9 million units daily. The prednisone dose was tapered to 15 mg per day over 6 months. Despite incomplete improvement in daily hemoptysis, spirometry declined and the radiographic appearance of the patient’s lungs did not improve (Fig 1, top right). He was unable to resume a normal level of activity and remained cushingoid. He experienced severe myalgias and depressive symptoms that were attributed to the α-interferon therapy. A thigh abscess at the injection site required hospitalization and repeated debridement.

The therapeutic regimen was deemed to be ineffective, which was associated with complications that decreased compliance. A decision to initiate treatment with doxycycline (100 mg orally twice daily) was made based on the rationale that an MMP inhibitor might modulate the increased MMP activity associated with dysregulated angiogenesis.

**Results**

Within weeks of initiating doxycycline therapy, the patient reported a substantial increase in exercise tolerance and a decrease in hemoptysis. The prednisone dose was decreased, and the patient was weaned approximately 4 months after starting therapy. After 6 months of doxycycline therapy, the α-interferon dose was decreased. The patient stopped taking the α-interferon on his own 2 months later. Nine months after starting doxycycline therapy, the patient was symptom-free. Improvement was seen on both the chest CT scan images (Fig 1, bottom left) and in the pulmonary function test results (Fig 5, top). The patient’s status on the lung transplant list was converted to inactive.

While receiving doxycycline therapy, the patient has remained without symptoms of hemoptysis or dyspnea. His chest CT scan reveals near-complete resolution of the prior ground-glass and nodular changes (Fig 1, bottom right), and his pulmonary function test results are normal. Currently, 24 months since presentation, he is attending college, working at a part-time job, and playing both soccer and basketball without limitation.

**Angiogenic Growth Factors**

During his course, the patient’s urine was assayed serially by enzyme-linked immunosorbent assay (R&D

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**Figure 2.** Lung biopsy performed at the Massachusetts General Hospital shows diffuse thickening of the alveolar walls and expansion of the alveoli by blood (hematoxylin-eosin, original × 4).

**Figure 3.** Nodule of atypical endothelial cells in an interlobular septum beneath the pleura (top [hematoxylin-eosin, original × 20]). The endothelial cells contain brown granules of hemosiderin.
Systems; Minneapolis, MN) for the angiogenic growth factors, basic fibroblast growth factor (bFGF), vascular endothelial growth factor, and interleukin-8. The urinary bFGF level peaked at 32,000 pg/L (normal, 4,000 pg/L) 9 months after presentation, correlating with the patient’s most severe illness. After doxycycline therapy was initiated, and α-interferon and prednisone therapy were discontinued, the patient’s urinary bFGF level decreased dramatically (Fig 5, bottom). The urinary bFGF level has remained within the normal range (temporally paralleling the patient’s clinical improvement). Vascular endothelial growth factor was detectable at normal levels, and no detectable level of interleukin-8 was found. Following therapy, urine was assayed for MMPs using gelatin zymography (the test was not available prior to therapy). There were no urinary MMPs detectable.

**DISCUSSION**

To our knowledge, this case of PCH with atypical endotheliomatosis is the first case of PCH, or any other vascular malformation or neoplasm, that may have been treated successfully with doxycycline. This is one of only two well-documented cases in which a patient has responded to medical therapy. In the earlier case, α-interferon therapy was discontinued after 5 years without disease recurrence (GW White; personal communication; October 10, 2000). While α-interferon therapy has been shown in vitro to decrease bFGF messenger RNA expression, its efficacy or mechanism of action in PCH patients remains unknown. In this case, escalating α-interferon doses were unsuccessful in decreasing symptoms and caused intolerable adverse effects.

Dysregulated angiogenesis, analogous to that found in other forms of hemangiomatosis, appears to contribute prominently to the pathogenesis of PCH. The central mechanisms of pathologic angiogenesis include the loss of normal apoptosis in vascular endothelial cells, as well as the overexpression of angiogenic growth factors (such as bFGF) and MMPs involved in extracellular matrix remodeling. Evidence has pointed to a loss of normal apoptotic pathways in the pathophysiology of other pulmonary vascular diseases, such as familial primary pulmonary hypertension and hereditary hemorrhagic telangiectasia. In both diseases, genetic errors in the transforming growth factor-β receptor family (ie, BMPR2, in primary pulmonary hypertension, and endoglin, in hereditary hemorrhagic telangiectasia) result in the inhibition of normal apoptosis and uncontrolled cellular proliferation within the pulmonary vasculature. In this case, pathologic angiogenesis was suggested by both direct evidence from the biopsy specimens, showing proliferating capillaries, and from indirect evidence through the detection of markedly elevated levels of urinary bFGF.

When overexpressed, bFGF may influence several pathologic processes, such as uncontrolled tumor growth and neoplastic angiogenesis. These effects may be due to the inhibition of apoptosis or up-regulation of MMP activity. Up-regulated MMP activity also may exert positive feedback on the production of angiogenic growth factors, such as bFGF. Abnormally elevated bFGF levels could account for several of the features of this case, including proliferating capillaries that invade the pulmonary interstitium and alveolar septae with resultant cough, dyspnea, and hemoptysis.

While the initial stimulus for dysregulated angiogenesis remains unknown, the potential sources of up-regulated bFGF in this case include the atypical endothelial cells themselves, injured epithelial cells, activated polymorphonuclear neutrophils or tissue macrophages, or ischemic cells within the extracellular matrix. We hypothesized that many of the manifestations of increased bFGF levels were the sequelae of increased MMP activity. When stimulated by angiogenic growth factors such as bFGF, MMPs facilitate significant changes in the extracellular matrix. These changes allow for blood vessel growth and tissue invasion. In this case, the neoplastic-like atypical endothelial cells may have been both the source of the angiogenic factors and the site of increased MMP activity.

The main limitation of this study is that the evidence suggesting a causal relationship among doxycycline ther-
apy, decreased urinary bFGF levels, and clinical improvement is circumstantial. While we cannot rule out an antibiotic effect of doxycycline in this case, no organism was identified by culture of sputum, BAL fluid, or lung biopsy specimen. Similarly, we cannot exclude that doxycycline enhanced any beneficial effect of α-interferon. Finally, we are not able to exclude entirely a delayed effect on bFGF levels or clinical outcome by steroids, α-interferon, or combination therapy. In fact, the clinical course raises the possibility that lower doses of prednisone may be more effective than higher doses for PCH. Nonetheless, the temporal association between the initiation of doxycycline and the improvement noted is compelling and suggests the need for future study. Whether or not the monitoring of urinary bFGF levels may be a useful tool for adjusting the dose and extent of therapies for PCH, as in cases of infantile hemangiomatosis, also remains to be determined.

This case of PCH is notable for its rapid diagnosis shortly after presentation with hemoptysis and dyspnea, no evidence of familial disease, and improvement with medical therapy obviating the need for lung transplantation. This patient had several adverse effects as a result of α-interferon therapy. In contradistinction, oral doxycycline therapy has been well-tolerated for nearly 2 years. This report also underscores the difficulty of differentiating PCH from other pulmonary vascular disorders. In this case, a definitive diagnosis required a second lung biopsy.
The elevated urinary bFGF level that was measured in association with PCH in this report is a novel finding. In addition, the atypical endotheliomatosis found in this patient may have been a clue to pathologic angiogenesis with loss of normal apoptosis and, hence, to the potential efficacy of an MMP inhibitor. We do not know the results of doxycycline therapy in PCH patients without endotheliomatosis. Nonetheless, the data support the concept that doxycycline may successfully modify the course of PCH with atypical endothelial proliferation. We speculate that MMP inhibition plays a role, as suggested by studies of other pulmonary vascular and parenchymal disorders.29–31 The complete clinical remission seen in this patient, together with the normalization of abnormal bFGF levels and the lack of toxicity, strongly suggest that doxycycline should be evaluated further for the treatment of patients with PCH. This case represents, to our knowledge, the first case of a vascular neoplasm that has been successfully treated with doxycycline.

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