Case Report

Pulmonary Veno-Occlusive Disease and Scleroderma Associated Pulmonary Hypertension

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ABSTRACT. Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension (PH). We describe a series of 4 patients with systemic sclerosis (SSc), concomitant PH, and biopsy-proven/presumed PVOD. We review the literature describing the association of PVOD and SSc and discuss diagnostic features and treatment implications. In our case series, treatment with an endothelin receptor antagonist did not confer a beneficial treatment effect. (First Release Sept 15 2006; J Rheumatol 2006;33:2347–50)

Key Indexing Terms:
PULMONARY VENO-OCCLUSIVE DISEASE PULMONARY ARTERIAL HYPERTENSION
SCLERODERMA SYSTEMIC SCLEROSIS ENDOTHELIN RECEPTOR ANTAGONIST

Pulmonary hypertension (PH) is the leading cause of death in Canadian patients with systemic sclerosis (SSc)[1]. PH in SSc is most commonly seen as a primary vasculopathy associated with the limited subtype[2] and the presence of anticentromere antibodies[3]. PH in African-American patients with SSc with anti-Scl-70 antibodies is usually secondary to pulmonary fibrosis[4]. Although obstructive vasculopathy and thrombotic arteriopathy are thought to be the most common pathophysiologic abnormalities[5], other causes of PH should be evaluated. Identification of the correct etiology can have important therapeutic and prognostic implications.

We discuss pulmonary veno-occlusive disease (PVOD) as an uncommon but important determinant of PH in patients with SSc.

CASE REPORTS

Case 1. A 64-year-old woman with limited SSc (manifesting as sclerodactyly, telangiectasias, Raynaud's phenomenon, and esophageal dysmotility) presented to hospital with a 2-year history of dyspnea and cough. There was no clinical or radiographic history of interstitial lung disease (ILD). She was anti-Scl-70 antibody-negative. On examination, she was hypoxic on pulse oximetry. Pulmonary function testing revealed forced expiratory volume (FEV1) 74%, forced vital capacity (FVC) 73%, and diffusion capacity for carbon monoxide (DLCO) 45% predicted. Echocardiogram revealed a right ventricular systolic pressure (RVSP) of 60 mm Hg with no abnormalities in right ventricular function. Right heart catheterization revealed a mean right atrial pressure of 2 mm Hg, while pulmonary artery pressure was 54/23 mm Hg with a mean pressure of 34 mm Hg. The pulmonary capillary wedge pressure was 12 mm Hg. Her cardiac output was preserved at 4.2 l/min. After nitric oxide challenge, her pulmonary pressure fell to 41/19 mm Hg with a mean of 28 mm Hg. Her wedge pressure also decreased to 7 mm Hg. High resolution computed tomography (CT) of the thorax (including a pulmonary embolism protocol) revealed multifocal peripheral pleuroparenchymal opacities, bilateral dependent pleural effusions, a small pericardial effusion, lymphadenopathy, and interlobular septal thickening. There was no evidence of acute or chronic pulmonary embolism on CT. A diagnosis of PVOD was proposed.

In the face of limited available therapies, bosentan and home oxygen was started. She developed progressively worsening dyspnea and syncope over a 3-month period. She was admitted to the intensive care unit with hypoxic respiratory failure. Due to progressive clinical deterioration on bosentan, a trial of inhaled nitric oxide and epoprostenol was made. Despite these interventions, she died. Autopsy revealed histologic features of PVOD. There was no evidence of arterial plexogenic lesions or thrombotic arteriopathy associated with pulmonary arterial hypertension (Figure 1).

Case 2. A 45-year-old woman with a 2-year history of limited SSc, (Raynaud's phenomenon, esophageal reflux and strictures, telangiectasias, antinuclear antibody titer of 1:320 with an anticentromere pattern, and no clinical or radiographic history of ILD) presented to hospital with acute onset retrosternal chest pain, dyspnea, palpitations, and presyncope while walking on a level plane. On examination, her oxygen saturation was 78% on room air by oximetry, and she required 40% oxygen supplementation by face mask. Echocardiogram revealed RVSP 104 mm Hg, large pericardial effusion, but normal right ventricular size and function. Chest radiograph revealed a right-side pleural effusion. CT of the thorax revealed pleural effusions, lymphadenopathy, and multifocal patchy opacities. Culture and sensitivity of pleural fluid was negative. There was no evidence of pulmonary emboli on ventilation-perfusion scan and high resolution CT of the thorax using a pulmonary embolism protocol. She was treated with prednisone 30 mg daily, bosentan 62.5 mg twice daily, and warfarin titrated to maintain an international normalized ratio of 2 to 3. She was not considered a candidate for lung transplant due to severity of her disease, high body mass index, and lack of social support. Four months later, she died without autopsy.

Case 3. A 55-year-old woman with a 20-year history of limited SSc (sclerodactyly, calcinosis, esophageal dysmotility, Raynaud's phenomenon, telang-

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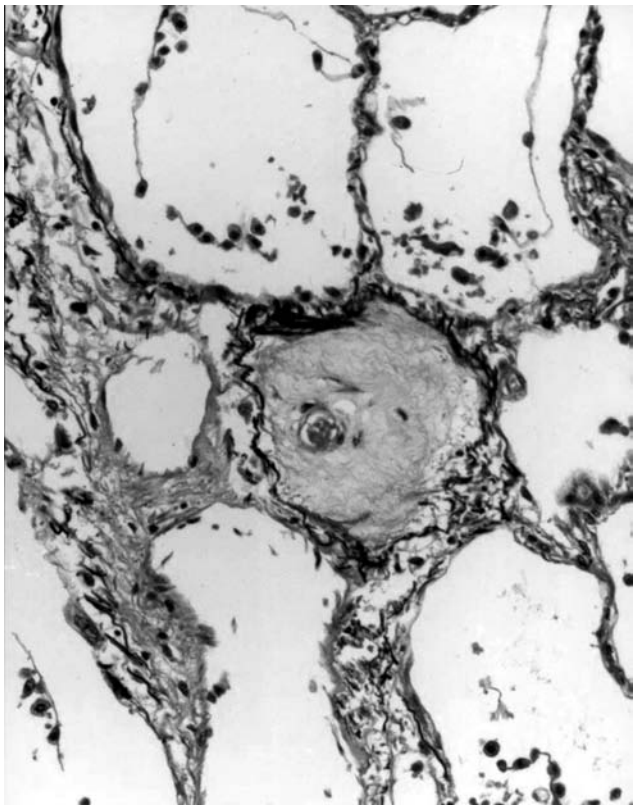

Figure 1. Small pulmonary venule with near occlusion of lumen by fibrous tissue (green) consistent with pulmonary veno-occlusive disease. Movat pentachrome stain; ×200.

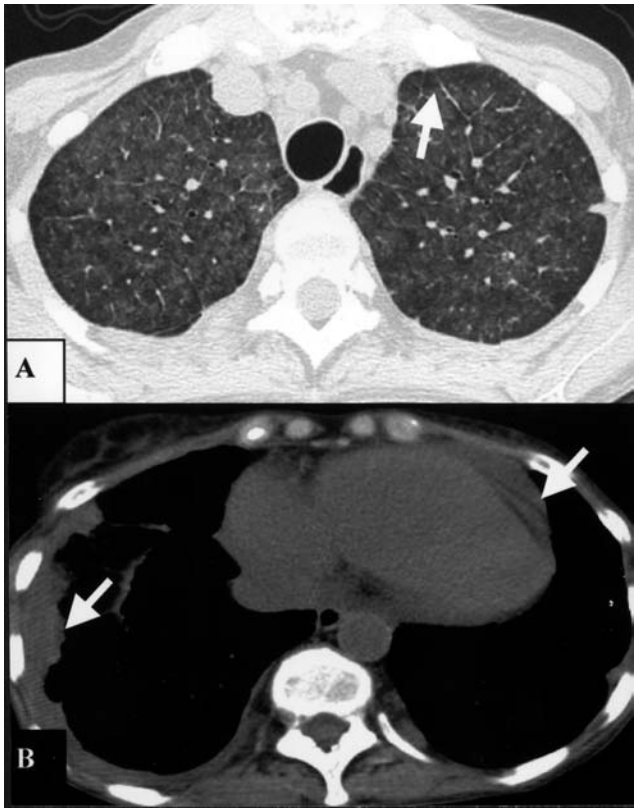

Figure 2. A. High resolution CT of the thorax shows smooth interlobular septal thickening (arrow) and intralobular ground glass opacities. B. CT of the thorax shows right pleural and pericardial effusion (arrows) and incidental left subpleural lymph node.

iectasias, and no ILD) presented to clinic with a one-year history of dyspnea, cough, and hypoxia requiring home oxygen. Echocardiogram revealed right atrial and ventricular dilation and RVSP 60 mm Hg. CT of the thorax revealed a dilated main pulmonary artery, a right-side pleural effusion, a small pericardial effusion, prevascular and paratracheal lymphadenopathy, diffuse ground glass opacities, and smooth interlobular septal thickening (Figures 2A, 2B).

Despite treatment with bosentan 125 mg twice daily, her clinical symptoms and indices did not improve, and she was listed for lung transplant. While awaiting transplant, she died. Autopsy results are not available.

Case 4. A 48-year-old woman with limited SSc (sclerodactyly, Raynaud's phenomenon, digital ulceration, telangiectasias, calcinosis, esophageal dysmotility, no history of ILD) presented with a history of worsening dyspnea, edema, and abdominal fullness. Examination was consistent with decompensated right heart failure. CT of the thorax showed a dilated main pulmonary artery, diffuse heterogeneity of the lung parenchyma throughout with fine ground glass nodules, fine septal thickening, and mediastinal lymph node enlargement. There was no evidence of acute or chronic thromboembolism. Pulmonary function testing revealed FVC 3.0 l (100% predicted), FEV1 2.4 l (106% predicted), FEV1/FVC ratio of 80 (105% predicted), and DLCO 25% of predicted. Pulmonary artery catheterization revealed pulmonary artery pressure 65/25 mm Hg, mean pressure 45 mm Hg, and cardiac index 2.1. On catheterization, her cardiac index and pulmonary vascular resistance improved with epoprostenol and sildenafil, but showed worsening hemodynamics with nifedipine. She was treated with epoprostenol, warfarin, furosemide, and spironolactone. Despite initial improvement in clinical symptoms, she progressively deteriorated. She was evaluated for lung transplant, but was declined secondary to renal impairment. Three months after initiation of therapy, she died at home. Autopsy results are not available.

DISCUSSION

Pulmonary arterial hypertension (PAH) is a well described complication of SSc, with recent prevalence estimates ranging from 19% to 26%[4,6], and is the leading cause of death in this population[1]. It occurs more frequently in patients of African ancestry and is often associated with elevations in anti-topoisomerase II antibodies, erythrocyte sedimentation rate[7], immunoglobulin G[7], digital pitting, ulceration, and genetic markers HLA-DRW6[8] and HLA-DRW52[8,9]. If untreated, Canadian patients with SSc with PAH have a median survival of 12 months[10].

PVOD is a less commonly recognized cause of PH in patients with SSc. PVOD is characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules, occasionally extending to the arteriolar bed. Pulmonary venous obstruction may lead to hydrostatic pulmonary edema characterized by features of heart failure on chest radiography but normal indices of left ventricular end-diastolic pressure. We have described 4 patients with SSc followed at the University of Toronto Pulmonary Hypertension Program who developed PH with concomitant biopsy-proven/presumed PVOD. Established in 1998, our multidisciplinary program actively follows 350 patients with PH, about 20% of whom have an underlying connective tissue disease. To our knowl-

edge, there are only 3 other cases of PVOD and SSc-associated PH in the literature[11-13]. Clinical features suggestive of idiopathic PVOD include severe hypoxia and pleural effusions. Although described in isolation, cumulatively these features are not typically seen among patients with limited SSc who develop PAH. Indeed, in our experience, resting hypoxia is an uncommon manifestation of SSc-associated PAH unless there is coexisting ILD, an intracardiac shunt, or severe mismatch between pulmonary ventilation and perfusion, magnified by low cardiac output. Pleuropericardial effusions have been described in SSc patients[14]. Although pleural effusion is uncommon, it is associated with a poor prognosis. None of the patients in our series had features suggestive of coexisting lupus, overlap syndrome, infection, or thromboembolic disease.

The most common CT findings in idiopathic PVOD include smooth interlobular septal thickening, centrilobular ground glass opacities, pleural effusions, enlarged pulmonary arteries, small or normal size pulmonary veins, and adenopathy[15]. In our case series, all the patients had radiographic features consistent with PVOD. Right heart catheterization may be of great diagnostic value in cases such as these. Catheterization not only provides a more accurate measure of pulmonary pressure than echocardiography, but also allows evaluation of concomitant PVOD through a vasodilator challenge. A supervised setting is required as vasodilators can precipitate worsening oxygenation, acute pulmonary edema, or respiratory failure. Although surgical lung biopsy is the only definitive means of establishing the diagnosis, most PAH physicians would not biopsy these patients, owing to the high morbidity and mortality associated with this procedure in adults with PAH (Channick R, personal communication).

Treatment options are limited for patients with idiopathic PVOD. There are conflicting reports on the efficacy of vasodilator therapy. Some authors advocate the use of epoprostenol as a bridge to transplantation[16]. Others have described precipitous pulmonary edema and respiratory failure with initiation of epoprostenol, and thus advise caution in patients with known PVOD[17]. Most PAH specialists feel that epoprostenol use is contraindicated in patients with PVOD. Lung transplant remains the only alternative for most patients with PVOD. In SSc, however, benefits of transplantation are not usually realized as many centers do not transplant patients with SSc or they succumb prior to transplantation because of progressive disease.

Our case series suggests that endothelin receptor antagonism does not confer a beneficial treatment effect in the treatment of PH secondary to PVOD and SSc. Case 4 was not treated with an endothelin receptor antagonist and suffered a poor outcome, illustrating the rapidly progressive course of PVOD in SSc. Although a randomized trial would be ideal to evaluate the efficacy of these treatment modalities, it would be implausible due to the rarity of these conditions. Future investigators may overcome this barrier by considering innovative methodologic approaches, such as the randomized placebo phase design or multiple N-of-1 studies using Bayesian metaanalysis to study the efficacy of therapies in rare disease[18].

Clinical and radiographic features (severe hypoxia, pleural effusions, poorly defined opacities, lymphadenopathy, and septal lines on CT of the thorax) in a patient with SSc presenting with new-onset PH without known ILD may suggest a diagnosis of PVOD. Cardiac catheterization should be considered in these patients. Clinicians should exercise caution when instituting vasodilator therapy in this population as it may precipitate worsening oxygenation, acute pulmonary edema, or respiratory failure. Our case series suggests that endothelin receptor antagonism does not confer a beneficial treatment effect in these patients.

PVOD should be considered in the differential diagnosis of PH in SSc, and our report illustrates that bosentan is not effective therapy for all patients with SSc, perhaps especially for those with certain radiographic findings. Further research into the efficacy of endothelin receptor antagonists, prostacyclin I_2, and lung transplant for SSc-related PH and PVOD is needed.

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