Pulmonary Vascular Occlusion and Fibrosing Mediastinitis*

Donald F. Berry, M.D.; David Buccigrossi, B.S.; John Peabody, M.D.; Kirk L. Peterson, M.D.; and Kenneth M. Moser, M.D., F.C.C.P.

Patients with fibrosing mediastinitis causing obstruction of pulmonary veins and arteries may present with many of the historic, physical, and laboratory findings of patients with pulmonary hypertension due to chronic thrombotic obstruction of major pulmonary arteries. Because the latter is subject to surgical correction, and the former is not, it is important to differentiate between the two and to be aware of the similarities in presentation. Three patients with pulmonary hypertension due to compression of pulmonary veins and the right pulmonary artery by fibrosing mediastinitis are presented who illustrate these points. A review of the literature documents other instances in which vascular involvement due to fibrosing mediastinitis has mimicked other types of pulmonary hypertension.

Patients with fibrosing and granulomatous mediastinitis commonly present a diagnostic challenge because of the variability of involvement of the different structures of the mediastinum. The spectrum of the disease varies from a benign condition with minor symptoms to severe pulmonary hypertension resulting in death. We have recently encountered three patients who have further broadened this spectrum. All were referred to us as potential candidates for pulmonary thromboendarterectomy with a presumptive diagnosis of pulmonary hypertension due to chronic thrombotic obstruction of major pulmonary arteries.

The findings in these three patients did, in fact, remarkably mimic those in patients with chronic, large vessel thrombotic obstruction. The history and physical findings, the results of perfusion and ventilation scanning, as well as pulmonary angiographic and certain findings on right heart catheterization all paralleled those which characterize chronic, major vessel thrombotic obstruction. However, all of the findings were explained by pulmonary arterial and/or venous obstruction due to fibrosing mediastinitis.

Because an attempted thromboendarterectomy in such patients would have had no positive—indeed, likely, quite adverse—effects, we feel it is important to describe this experience and to emphasize the differential diagnostic features between chronic thrombotic obstruction and this form of fibrosing mediastinitis.

*From the Departments of Pulmonary Medicine and Cardiology, UCSD Medical Center, San Diego.
Reprint requests: Dr. Moser, 285 Dickinson Street, San Diego 92103

CASE REPORTS

CASE 1

A 28-year-old white woman first noticed dyspnea on exertion in May 1982. Throughout the following months, she also noted mild intermittent cough productive of blood streaked sputum on several occasions. By May 1983, her dyspnea had progressed so that she was short of breath after one block of level walking.

Her medical history was significant only for her use of birth control pills. She denied any symptoms of deep venous thrombosis. She was a nonsmoker. She had lived in Tennessee for 23 years prior to moving to California.

In May 1983, she was evaluated at another hospital. Pulmonary ventilation and perfusion scans and right heart catheterization led to the diagnosis of probable chronic thrombotic obstruction of major pulmonary arteries. She was treated with coumadin and referred to UCSD Medical Center for possible thromboendarterectomy.

Physical examination showed unlabored respiration at rest with a rate of 16. The lungs were clear. Cardiac examination showed a sustained left parasternal lift, a split S2 that widened with inspiration, and an increased P2. There were no signs of right ventricular failure.

Chest x-ray films showed cardiomegaly with a right ventricular configuration, fullness of the left hilum, right pleural thickening, and possible Kerley B lines in both lower lobes. An area of possible subcarinal calcification was seen.

A perfusion scan showed near total absence of perfusion to the right lung, with only minimal perfusion to the right apex; on the left, there were several basilar subsegmental defects. Ventilation scan was normal (Fig 1).

Echocardiogram revealed an enlarged right atrium and ventricle, and a normal mitral valve and left ventricle. Impedance plethysmography was normal bilaterally.

At initial right heart catheterization, the pulmonary artery pressure was 87/45 (mean 60 mg Hg). The (Fick) cardiac output was 6.8 L/min. The pulmonary vascular resistance was elevated at 649 dynes/cm². The wedge pressure was not measured for technical reasons.

Pulmonary angiography showed abrupt cut-offs of the right lower...
and middle lobe arteries, and the right pulmonary artery was narrowed by 70 to 80 percent. On the left, there were questionable filling defects in the left lower lobe segmental vessels (Fig 2).

The CT scan of the chest demonstrated a large, calcified subcarinal mass displacing the left atrium and right pulmonary artery anteriorly (Fig 3). Calcified granulomas were seen in the liver and spleen.

A histoplasmin skin test was positive; PPD, negative. Results of serologic tests for histoplasmosis, blastomycosis, and coccidiomycosis were negative.

At repeat right heart catheterization, wedge pressures were measured in several areas: 26 mm Hg in the right lower lobe, 19 mm Hg in the right upper lobe, 26 mm Hg in the left lower lobe, and 21 mm Hg in the left upper lobe.

Selective pulmonary angiography on the right showed normal vasculature distal to the previously noted "cut-offs" (Fig 4). Left heart catheterization disclosed a mean left atrial pressure of 7 mm Hg, no mitral gradient, and normal left ventricular pressures. Selective injection of pulmonary veins clearly demonstrated obstruction near the entrance to the left atrium (Fig 5).

Because of severe cough, she was treated with a course of prednisone. Her cough markedly improved but the shortness of breath did not.
CASE 2

A 28-year-old woman was referred to UCSD Medical Center for pulmonary thromboendarterectomy. She was well until two years before when she had an episode of right pleuritic chest pain associated with shortness of breath and hemoptysis. She was treated as an outpatient with antibiotics. Three months later, she had similar symptoms and was again treated for pneumonia. After the second episode, dyspnea, a severe nonproductive cough, and wheezing persisted, despite treatment with bronchodilators.

Over the subsequent two years, dyspnea on exertion slowly increased. A third episode similar to the first two resulted in admission to another hospital in April 1983. Physical examination was remarkable for a right ventricular heave without evidence of right ventricular failure. Perfusion scan showed no flow to the right lung and defects in the left upper lobe. The angiogram reportedly showed stenotic main, right upper lobe and right lower pulmonary arteries, as well as cutoffs in the left upper lobe. There was an episode of greater than 100 ml of hemoptysis after angiography. Treatment with coumadin was initiated and a Greenfield filter was placed in the inferior vena cava.

In July 1983, there was another episode of severe hemoptysis that spontaneously resolved. Bronchoscopy revealed friability and increased vascularity of the mucosa of the major bronch on the right.

Her other medical history was significant for a history of birth control pill use.

At physical examination at UCSD, the jugular venous pressure was 8. There was a left parasternal lift. The P1was markedly increased and split. An S3, S4 and a 2/6 systolic murmur were present at the lower left sternal border.

Chest x-ray film revealed a small right lung and pulmonary artery. There were increased right interstitial markings. Old films showed the right lung and pulmonary artery were normal in 1980.

Right heart catheterization showed pulmonary artery pressures of 70/30 mm Hg with a mean of 45 mm Hg. The pulmonary artery wedge was 25 in LUL and LLL (cardiac output was 5.9 l/min; PVR 816 dynes s cm⁻⁵).

Angiography of the left lung revealed a large left PA with attenuated peripheral branches. The left upper lobe pulmonary veins appeared stenotic near their entry into the left atrium. The right PA could not be selectively catheterized, and angioscopy revealed no visible lumen (of the right PA).

The CT scan of the chest showed large calcified nodes involving the subcarinal and pretracheal regions and compromising the right pulmonary artery.

The histoplasmin skin test was positive.

After discharge, she moved to sea level with substantial resolution of signs and symptoms of pulmonary hypertension. During this time, she was also treated with a tapering course of prednisone.

CASE 3

This 68-year-old woman was admitted to University Hospital on Jan 2, 1985, for evaluation for possible pulmonary thromboendarterectomy. History disclosed recurrent respiratory illness dating to her childhood. She had "always" been mildly short of breath and could not keep up with her peers by adolescence. At least one episode of "pneumonia" required two weeks of hospitalization in 1942. In 1957, she had an excisional biopsy of cervical lymph nodes. No diagnosis was made.

In the mid 1960s, she was found to have a positive PPD and abnormal findings on chest x-ray film. She was treated for an unknown period for tuberculosis.

In 1971, she was presented with chest pain and shortness of breath and was presumed to have a pulmonary embolus. Neither perfusion scan or angiography was done. She was anticoagulated for six months. Apparently, several ECGs were suggestive of an acute myocardial infarction.

Over the next ten years, there was a slow increase in dyspnea on exertion. Recurrent episodes of cough and pleuritic chest pain continued.

She also described exertional chest pain relieved by nitroglycerin and rest. Two months before admission, evaluation elsewhere led to coronary angiography, which showed triple vessel disease, and pulmonary angiography, which disclosed total obstruction of the
right pulmonary artery. Chronic pulmonary thromboembolic disease was diagnosed. She denied any history of leg swelling or tenderness.

She had lived in St. Louis until 1942 when she moved to San Diego. Family members were thought to have had histoplasmosis.

On physical examination, she was an afebrile elderly woman coughing frequently. She was not dyspneic at rest. Chest examination revealed bilateral lower lung field crackles more prominent on the right. The jugular venous pressure was 8 to 9 cm. Cardiac examination was normal.

Chest x-ray film showed biventricular cardiac enlargement, right lung volume loss, right pleural thickening, subtle bilateral Kerley B lines, and a right lower lung field infiltrate. The ABG showed a pH of 7.46, PaO₂ of 65, and a PaCO₂ of 36 on room air. Impedance plethysmography was normal in both legs. Skin tests for histoplasmosis and PPD were positive.

A perfusion lung scan showed no perfusion to the right lung with scattered subsegmental defects in the left lung. The ventilation scan was normal.

A CT scan of the chest disclosed a large calcified subcarinal mass, right of the midline. The mass was seen to compress the right lower pulmonary vein and the right pulmonary artery.

Repeat cardiac catheterization revealed RA pressure of 8 to 10, RV pressure of 70/8, and PA pressure of 70/24. The mean wedge pressure was 20 in both the LUL and LLL. The P(A-a) O₂ difference was 5.1 volumes percent; the O₂ consumption 130 ml/min/m². The cardiac index (Fick) was 2.6 L/min/m². The calculated pulmonary vascular resistance was 408 dynes·s·cm⁻⁵. The mean left atrial pressure was 12. The LA injection showed no filling of the right pulmonary veins.

As in case 1, cough was a major problem. Prednisone was instituted with substantial relief.

**DISCUSSION**

These three patients presented with many of the historic, physical, and laboratory features we have found to be associated with chronic thrombotic obstruction of major pulmonary arteries. However, as documented, each proved to have pulmonary arterial and venous obstruction due to fibrosing mediastinitis.

Like patients with chronic thromboembolic obstruction, they had a history of progressive dyspnea on exertion of obscure origin. As in many patients with thromboembolic obstruction, a clear cut history of venous thromboembolism was lacking. However, hemoptysis, pleuritic chest pain, and dyspnea suggested that possibility, and all three had been treated for embolism.

Physical findings of pulmonary hypertension were present in two patients. None had evidence of lower extremity venous thrombosis; but many patients with proven thrombotic obstruction lack such findings.

Laboratory findings were also, in the main, remarkably similar to those in chronic thrombotic obstruction. Electrocardiographic findings were not distinctive, nor were the results of pulmonary spirometric or rest and exercise studies.

The first differential clue was provided by the chest roentgenogram. All three patients demonstrated Kerley B lines, a finding present (and less marked) in only two of our more than 30 patients with chronic thrombotic obstruction. Clearly, the presence of Kerley B lines should raise suspicion about the diagnosis of chronic thromboembolic pulmonary hypertension. Noteworthy, however, is the fact that subcarinal calcification was seen on the standard roentgenogram in only one patient; and, even in that instance, was "suggestive" (even in retrospect).

Very deceptive, in this context, were the perfusion scan results. All disclosed large perfusion defects which, on ventilation scan, were normally ventilated. Such large "mismatched" defects are not seen in primary pulmonary hypertension, but are characteristic in thromboembolic hypertension. However, in these patients with fibrosing mediastinitis, they proved to be due to regional decrements in pulmonary arterial flow secondary either to fibrotic obstruction of the pulmonary arteries or of major pulmonary veins. That this was the case was documented by angiographic studies. However, even pulmonary angiograms may mimic thrombotic obstruction. An occluded pulmonary artery may represent thrombus or periarterial fibrosis, as demonstrated in case 3. Furthermore, apparent thromboembolic "cutoffs" in these patients can result from regional pulmonary venous pressure differences, as in case 1.

Right heart catheterization should have been the definitive procedure documenting, at the least, that the pulmonary arterial hypertension was due to some "downstream" process that had elevated pulmonary venous pressure. However, in patients with large right atria and ventricles and pulmonary hypertension, technical difficulties are often encountered in obtaining satisfactory pulmonary "wedge pressures," and that was the case in these patients. Two had been catheterized previously without "wedge" pressures obtained. Indeed, when this differential is entertained, not only is a "wedge" pressure essential, but such pressures should be obtained in several regions. Pulmonary venous obstruction is not uniform, resulting in variable degrees of pulmonary venous hypertension in regions drained by different pulmonary veins.

Once the presence of pulmonary venous hypertension is established, the differential must include all the known causes, including fibrosing mediastinitis. Thus, left heart catheterization and angiographic studies of the type described here are indicated.

The mediastinal CAT scan provided the most striking evidence of the structural problem in each patient. Large calcific masses were readily identified, even though routine roentgenography did not disclose them.

It is also worth noting that none of these patients had lived in an area endemic for histoplasmosis for some years. Yet all had lived in such areas during childhood and all had positive skin reactions to histoplasmin antigen (though serologic tests were negative).

Thus, the clues suggesting the diagnosis of pulmo-
monary arterial and/or venous obstruction due to fibrosing mediastinitis—rather than chronic thromboembolism—were present in each patient. Yet, those of us involved were impressed with how easily one might have bypassed the clues, made the diagnosis of chronic thrombotic obstruction, and proceeded to attempt thromboendarterectomy.

Fibrosing mediastinitis is a rather uncommon condition, a factor which further obscures ready diagnosis. The fibrotic process is thought to be a sequel of active granulomatous diseases, especially histoplasmosis. Immunogenic material is thought to leak from caseous nodes and cause an intense fibrotic reaction. Alternatively, an abnormal host response, in this case elaborating large amounts of collagen, has been suggested to be the problem. If organisms are seen, they are likely to be suggestive of Histoplasma capsulatum. However, in lesions with thick capsules, organisms rarely grow from the lesions.

The disease has the capacity to affect almost all mediastinal structures. The common symptoms and signs include superior vena cava (SVC) syndrome, cough, hemoptysis, dyspnea, wheezing, and dysphagia.

Among the most common complications is involvement of the tracheobronchial tree. Collagenous tissue actually invades bronchial walls and may grow into the airway lumen causing obstruction. It is this process which often is responsible for recurrent hemoptysis, cough, and dyspnea. Care needs to be taken at bronchoscopy as endobronchial tissue is friable and tends to bleed. There is at least one reported death from massive hemoptysis induced at bronchoscopy.

Most authors note, however, that mortality and morbidity are most likely in patients with pulmonary artery or vein involvement. Pulmonary hypertension previously has been reported from obstruction of arteries, veins, or both. Pulmonary venous obstruction occurred in three of 64 patients with fibrosing mediastinitis in the series of Schowengerdt et al., zero of seven in the series of Prager et al., two of 31 of Dines et al., and six of 38 of Goodwin et al. Two more recent cases have been reported, who presented with dyspnea and hemoptysis. There are a few cases in the literature in which this disease closely mimicked mitral stenosis. Left atrial myxoma has also been considered in the differential diagnosis.

Whether any effective medical therapy exists for fibrosing mediastinitis and mediastinal granuloma is not clear. Because of the small number of cases, no controlled trials are available. Amphotericin B has not proven to be effective. This is not surprising given that fibrosing mediastinitis does not seem to be associated with active infection. Steroids have been advocated, but there is little evidence demonstrating efficacy. Davis and Andrus treated two of their patients for a three month course and neither showed improvement. Hicks treated his patient for hemoptysis with only ten mg QOD of prednisone, with rapid resolution of symptoms; however, the patient had a surgical procedure at the same time making the possible benefit of steroids impossible to evaluate.

Surgical resection of advanced cases such as ours is said to be technically very difficult. However, there have been reports of some success when surgery is employed to control severe hemoptysis. Dye et al and Hicks separately reported patients with severe hemoptysis and dyspnea who underwent right middle and lower lobe resection with improvement of dyspnea and resolution of hemoptysis. Perhaps these good outcomes were made possible by the fact that both patients had focal pulmonary venous obstruction.

Most other reported patients in whom surgery was attempted proved unresectable.

Our three patients have been treated with corticosteroids with some improvement. Two had marked improvement of cough. The other had relief of dyspnea, but her steroid treatment coincided with moving from an altitude of 5,000 feet to sea level. Anti-coagulant therapy was discontinued in those patients in whom it had been initiated. The substantial incidence of hemoptysis from bronchial mucosa or venous obstruction would appear to place those patients at particular risk of anti-coagulant-induced pulmonary hemorrhage.

**References**

5. CPC. Johns Hop Hosp Bull 1966; 118:73-84
19 Botticelli JT, Schlueter DP, Lange RL. Pulmonary venous and arterial hypertension due to chronic fibrous mediastinitis. Circulation 1966; 33:962-71
26 Hicks C. Fibrosing mediastinitis causing pulmonary artery and vein obstruction with hemoptysis. NY State J Med 1983; 83:242-44
34 Cosio FG, Gobel FL, Harrington DP, Sako Y. Pulmonary arterial stenosis with wide splitting of the second heart sound due to mediastinal fibrosis. Am J Cardiol 1973; 31:372-76