Pulmonary hypertension associated with primary biliary cirrhosis in the absence of portal hypertension: a case report

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Abstract

Pulmonary hypertension is well described in association with portal hypertension of any cause including end stage primary biliary cirrhosis (PBC). The essential feature of this association is the presence of portosystemic shunting, including surgically created shunts. A patient with primary pulmonary hypertension and PBC without portal hypertension is reported. This suggests that primary pulmonary hypertension may be associated with PBC in the absence of portal hypertension. Decisions regarding appropriate organ transplantation may depend on whether pulmonary hypertension is primary or secondary to portal hypertension.

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Primary biliary cirrhosis (PBC) is a chronic disorder where inflammation and fibrosis of intrahepatic bile ducts leads to cirrhosis and liver failure. PBC has been associated with numerous diseases of an autoimmune nature, most notably, thyroiditis and various rheumatological manifestations.¹ Pulmonary involvement in PBC includes interstitial lung disease and airways obstruction.^{2,3} Pulmonary hypertension (PHT) has been described only with end stage PBC⁴ as well as portal hypertension of any cause. We present a patient with PHT and PBC in the absence of demonstrable portal hypertension, suggesting that primary pulmonary hypertension may be independently associated with PBC.

Case history

A 44 year old white woman was initially found to have raised alkaline phosphatase, an anti-mitochondrial antibody titre of 1:160, and hypothyroidism with high anti-microsomal and anti-tyroglobulin titres. Except for myalgia, which quickly resolved with appropriate thyroid replacement, she was entirely asymptomatic. Abdominal ultrasonography showed cholelithiasis and she had a cholecystectomy. The serum aspartate amino transferase was 33 U/l (normal range=10-47 U/l), alkaline phosphatase 217 U/l (11-189 U/l), and total bilirubin 11 µmol/l (7-26 µmol/l). An intraoperative liver biopsy was consistent with a diagnosis of PBC.

Over the next five years, the patient had gradually progressive exertional dyspnoea and a vague non-pleuritic central chest discomfort. She was otherwise asymptomatic and did not have any symptoms suggestive of a rheumatological disorder including Raynaud's phenomenon. There was no recurrence of myalgia.

The past medical history was otherwise unremarkable. The patient was a non-smoker and did not consume alcohol.

Physical examination showed an obese woman. There were no abnormalities in the head and neck region; rheumatological, dermatological, and neurological examinations were unremarkable. Examination of the chest was unremarkable with no evidence of hyperinflation and clear auscultation. Cardiovascular examination showed mild dependent peripheral oedema. Jugulovenous distension and a hepatojugular reflux was present. Auscultation of the precordium detected a loud fixed split second heart sound in the left upper parasternal area and a II/VI diastolic decrescendo murmur. Splenomegaly, ascites, and extrahepatic symptoms of chronic liver disease were notably absent.

An electrocardiogram showed right heart strain. Radiographs of the chest showed enlargement of the right heart with prominence of the pulmonary outflow tract. A ventilation perfusion scan was non-diagnostic, however, pulmonary angiography did not show pulmonary thromboemboli. The pulmonary artery pressure was raised at 99-108/20-25 mm Hg systolic/diastolic.

Pulmonary hypertension was diagnosed and the patient referred for consideration of a lung transplant. Laboratory data showed normal haematological parameters, serum electrolytes, and creatinine. The serum aspartate aminotransferase was 30 U/l, alkaline phosphatase 200 U/l, total bilirubin 29 µmol/l, albumin 36 g/l, international normalised ratio 1.14 partial thromboplastintine (PTT) 33.1 s, and erythrocyte sedimentation rate 2 mm in the first hour. Assay for antinuclear antibody, extractable nuclear antigens, anticentromere antibodies, and cryoglobulins were negative. Pulmonary function studies showed a very mild restrictive pattern consistent with obesity and were otherwise normal. An echocardiogram showed dilatation of the pulmonary artery and tricuspid regurgitation. Cardiac catheterisation showed moderate mitral regurgitation with a pulmonary capillary wedge pressure of 14 mm Hg. The pulmonary artery pressure was 104/42/65 mm Hg (systolic/diastolic/mean), the right ventricular pressure 103/14 mm Hg, and mean right atrial pressure 14 mm Hg.

Repeat abdominal ultrasonography was normal with spleen length 10 cm and no evidence of ascites, collateral vessels, or varices. Transfemoral liver biopsy showed portal fibrosis consistent with stage III PBC.¹ Hepatic vein catheterisation showed a hepatic vein wedge pressure of 12-14 mm Hg and inferior vena caval mean pressure of 12-13 mm Hg. The hepatic

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vein wedge pressure-inferior vena caval mean pressure gradient was 1–2 mm Hg (normal <6 mm Hg)⁵ suggesting no portal hypertension.

One year after the initial diagnosis of PHT, the patient shows no evidence of portal hypertension. Upper gastrointestinal endoscopy did not show any varices. Upper gastrointestinal radiology was likewise normal. A technetium sulphur colloid liver spleen scan was normal with no evidence of portal hypertension or cirrhosis. Repeat abdominal ultrasonography remains normal. The patient awaits heart and lung transplantation.

Discussion

Pulmonary hypertension is present when the pulmonary artery pressure exceeds 30 mm Hg systolic and a mean of 20 mm Hg.⁶ In the absence of secondary causes including primary lung disease, primary left sided heart and valvular disease or systemic diseases affecting the pulmonary vasculature, PHT is considered primary.⁷ An autoimmune basis has been suggested as PHT can be associated with rheumatological conditions including systemic lupus,^{8,9} scleroderma, and its CREST variant,¹⁰ mixed connective tissue disease,^{11,12} primary Sjogren's disease,¹³ and rheumatoid arthritis.⁷ PBC has been associated with the same rheumatological diseases.¹⁴ The association of primary Raynaud's phenomenon with primary PHT and the finding of cold induced pulmonary vasospasm in healthy subjects with primary Raynaud's syndrome¹⁵ suggest an underlying vasoconstrictive disorder. Pulmonary endothelial injury affecting endothelial derived mediators of smooth muscle has been suggested as a mechanism of primary PHT.¹⁶

The association of liver disease and PHT is well recognised.^{17–23} It seems that portal hypertension is the essential feature of this association. The underlying liver disease, which results in portal hypertension, may be of any cause as extrahepatic causes of portal hypertension have been associated with PHT.^{21,24,25} The prevalence of PHT in portal hypertension has been reported by McDonnell *et al* as 0.73% in a series of 17 901 unselected necropsies (*v* 0.13% for primary PHT) and 0.61% in a clinical series of 2549 patients with cirrhosis confirmed by biopsy.⁸ Recently Hadengue *et al* reported a higher prevalence of 2% in 507 patients with portal hypertension.²⁰ The histological features of portal hypertension associated pulmonary hypertension (portopulmonary hypertension) are identical to the plexogenic changes of primary PHT medial hypertrophy, concentric intimal fibrosis, and plexiform lesions of small pulmonary arteries.^{8,16,17–25}

The most widely accepted hypothesis for portopulmonary hypertension is the shunting of vasoactive substances, usually inactivated in the liver, into the pulmonary vasculature, resulting in pulmonary vasoconstriction and chronic arterial changes. Organised thrombi have been noted in some patients in association with plexiform lesions²³ suggesting chronic thromboemboli as the cause. This hypothesis is not widely accepted as the clinical evidence generally is not

supportive.^{17,19,21,24,25} The thrombi are considered to be secondary to local injury, stasis²³ or cor-pulmonale.²⁴

Our patient with PBC and PHT had no evidence of a primary pulmonary or cardiac disease. Clinically there was no evidence of portal hypertension. Investigations did not show varices or ascites. Furthermore, the hepatic vein wedge pressure-inferior vena caval mean pressure gradient was normal. Although the inferior vena caval mean pressure and absolute hepatic vein wedge pressure were high this reflected high right sided filling pressures secondary to cor-pulmonale as the right atrial pressure was similar to the inferior vena caval mean pressure.²⁶ This gradient reflects sinusoidal pressure and is an indirect measure of portal pressure. In 21 to 43% of patients with presinusoidal portal hypertension, however, this method may underestimate portal pressure.^{27,28} In the early stages of PBC there may be a component of presinusoidal portal hypertension. Our patient, however, was found to have stage III PBC on biopsy examination. It has been reported that in stages III and IV of PBC, portal hypertension if present reflects sinusoidal pressure.²⁹ Our patient thus failed to show evidence of portal hypertension. Patients described in published works with portopulmonary hypertension have all had clinically obvious portal hypertension.

Although the rheumatological conditions associated with PBC are also associated with PHT, our patient had no clinical or laboratory evidence of a rheumatological disorder. The only manifestation of PBC associated autoimmune disease was hypothyroidism and there have been no patients described in English language publications with PHT and thyroiditis. One patient reported in Japanese studies with PHT had coincident chronic thyroiditis and chronic hepatitis³⁰; no further details are available. Our patient thus had no primary systemic disorder, other than PBC, that would have resulted in PHT.

We therefore conclude that our patient with PBC had true primary PHT. Although the possibility remains that there may have been some undetectable degree of portosystemic shunting, our patient did not have clinically evident portal hypertension. As mentioned previously, all cases of portopulmonary hypertension reported have had obvious portal hypertension. Morrison *et al*³¹ did describe a 52 year old woman with a weakly positive antimitochondrial antibody and Raynaud's disease, treated with immunosuppressive agents, who died secondary to PHT. There was no pathological examination of the liver, however, and no mention of the presence or absence of portal hypertension, and no definitive diagnosis given. Therefore, there have been no definite cases of PBC associated PHT described in published works without evident portal hypertension. Our case is thus the first to be described.

Because PBC is felt to reflect immune dysfunction¹⁴ and autoimmunity has been suggested as a possible cause of primary PHT,⁷ it is possible that the two conditions are causally associated. Given that the recognition of the significance of portal hypertension in portopulmonary hyper-

tension is recent, it is possible that other cases of PBC associated primary PHT have been dismissed as merely associated with liver disease. This has important therapeutic implications. We have reported that PHT can recur in portopulmonary hypertension if transplanted with a lung only.³² Transplantation with either a combined liver and lung (heart)⁴ or in certain situations a liver alone,^{32,33} however, offers the possibility of longterm relief of PHT. Patients with PBC and PHT cannot be assumed to have portal hypertension without investigation as primary PHT may be associated with PBC without portal hypertension.

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