Case report

A 25-year clinical history of portopulmonary hypertension associated with latent myeloproliferative disorder

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Introduction

The presence of pulmonary hypertension together with portal hypertension, also termed “portopulmonary hypertension (PPH),” is a complication of chronic liver disease and occurs in 2%–3% of patients with portal hypertension.1–3 A variety of causes of pulmonary dysfunction in liver disease have been identified, including antiphospholipid syndrome; however, latent myeloproliferative disorder (latent MPD) followed by PPH has not been reported.

Portal hypertension is sometimes associated with chronic myeloproliferative disorder (CMPD). Pulmonary hypertension is also an occasional finding in CMPD patients. Latent myeloproliferative disorder, on the other hand does not fulfill the diagnostic criteria of classical CMPD and is characterized by younger age of onset, slow disease progression, a high risk of thrombosis, platelet dysfunction, and normal or increased platelet count in spite of the presence of splenomegaly. We report findings in a 50-year-old woman with portal hypertension for which there were three major etiological findings—increased splenic blood flow, infiltration of hematopoietic cells in the liver, and thrombosis in the portal or hepatic vein—over a 25-year clinical course, during which there was also reversible stenosis of the portal vein. Twenty-three years after her first admission, her condition was diagnosed as latent myeloproliferative disorder, and she developed pulmonary hypertension. Her clinical history and data indicated that the portopulmonary hypertension was due to the latent myeloproliferative disorder.

Key words: latent myeloproliferative disorder, portal hypertension, portal vein thrombosis, portopulmonary hypertension, splenomegaly

Pulmonary hypertension associated with increased pulmonary vascular resistance occurring in the setting of portal hypertension, referred to as “portopulmonary hypertension”, is a complication of chronic liver disease, and occurs in 2% to 3% of patients with portal hypertension. Portal hypertension is a relatively common finding in patients with chronic myeloproliferative disorder (CMPD). Pulmonary hypertension is also an occasional finding in CMPD patients. Latent myeloproliferative disorder, on the other hand does not fulfill the diagnostic criteria of classical CMPD and is characterized by younger age of onset, slow disease progression, a high risk of thrombosis, platelet dysfunction, and normal or increased platelet count in spite of the presence of splenomegaly. We report findings in a 50-year-old woman with portal hypertension for which there were three major etiological findings—increased splenic blood flow, infiltration of hematopoietic cells in the liver, and thrombosis in the portal or hepatic vein—over a 25-year clinical course, during which there was also reversible stenosis of the portal vein. Twenty-three years after her first admission, her condition was diagnosed as latent myeloproliferative disorder, and she developed pulmonary hypertension. Her clinical history and data indicated that the portopulmonary hypertension was due to the latent myeloproliferative disorder.

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Unclassified myeloproliferative disorder that did not fulfill the diagnostic criteria of classical CMPD has been termed an atypical form of chronic myeloproliferative disorder (atypical MPD) or latent MPD. It is characterized by younger age of onset, slower disease progression, a high risk of thrombosis, and normal or increased platelet count in spite of the presence of splenomegaly.6,11 Latent MPD is also reported to cause portal hypertension.6,8,11,12

Several mechanisms of the increased pulmonary arterial resistance in PPH have been proposed, including microthrombi in the pulmonary circulation, alterations in pulmonary vascular reactivity by vasoconstrictor substances originating in the gut and escaping liver deactivation, and a hyperkinetic systemic circulation.12,13 Pulmonary hypertension is also an occasional finding in MPD and may be due to pulmonary venous occlusion, pulmonary myeloid metaplasia, or interstitial pulmonary fibrosis.14,15
Here, we would like to report, for the first time, the rare association of portopulmonary hypertension with latent MPD, in a patient with a 25-year history of latent MPD.

**Case report**

In 1974, a 28-year-old Japanese woman was diagnosed with idiopathic splenomegaly after the discovery of a clinically enlarged spleen which was palpable 10 cm below the left costal margin. Physical examination on that admission did not reveal findings other than splenomegaly. At that time, the results of liver function tests, as well as the numbers of peripheral blood cells, were normal (red blood cells count, $4.38 \times 10^{12}$/l; white blood cell count, $6.3 \times 10^9$/l; platelet count, $311 \times 10^9$/l). Bone marrow aspiration revealed that the number of megakaryocytes was slightly increased.

In 1981, the spleen was enlarged to 15 cm below the left costal margin, which was confirmed on computed tomography (Fig. 1a). Arterial portal venography disclosed portal vein stenosis, spleno-renal shunt, and esophageal varices (Fig. 1b). The liver function test results were normal, except for total bilirubin (2.9 mg/dl; normal range, 0.2–1.2 mg/dl) and lactic dehydrogenase (LDH) levels (632 IU/l). The numbers of erythrocytes, leukocytes, and platelets were within normal limits ($4.75 \times 10^{12}$/l, $5.1 \times 10^9$/l, and $221 \times 10^9$/l, respectively).

In 1996, at the age of 50 years, she was admitted for a third time, and physical examination revealed icterus, splenomegaly which was palpable 15 cm below the left costal margin, and hepatomegaly which was palpable 3 cm below the right costal margin. Although the numbers of leukocytes and erythrocytes and the hemoglobin level were normal ($7.0 \times 10^9$/l, $3.98 \times 10^{12}$/l, and 1.18 g/l, respectively), the platelet count was slightly elevated, at $449 \times 10^9$/l. The liver function test results were normal, with the exception of total bilirubin, gamma-glutamyl transpeptidase, and LDH levels (2.8 mg/dl, 89 IU/l, and 1041 IU/l, respectively). The bleeding time, activated partial thromboplastin time, and anti-thrombin III values were normal; however, prothrombin time and plasminogen were decreased (61% and 64%, respectively). No protein C or S deficiency was found, and lupus anticoagulant was negative. Platelet adhesion ability and aggregation activity to epinephrine were markedly diminished, at 11% and 2%, respectively, and thromboelastogram showed hypercoagulability. Bone marrow biopsy showed hypercellularity of megakaryocytes, with morphological abnormality (Fig. 2a), and normal erythroid and myeloid components, but no fibrosis. Karyotype and complement were normal, and no autoantibodies, including antinuclear and antimitochondrial antibodies, were detected. Liver biopsy revealed hemopoietic cell infiltration in dilated sinusoids, without any signs of congestive liver fibrosis or cirrhosis (Fig. 2b). Computed tomography showed that the size of the spleen was almost same as that observed 15 years before (Fig. 3a). By endoscopic examination, esophageal varices were smaller than before. Arterial portal venography showed spleno-renal shunt and a small notch at the site of the previous stenosis in the portal vein (Fig. 3b). In the absence of hepatic cirrhosis, hepatic congestion, and autoimmune disease, a diagnosis of latent MPD was made.

![Fig. 1. a](image1)
![Fig. 1. b](image2)