Introduction

Hepatopulmonary syndrome is a clinical triad: arterial blood deoxygenation, intrapulmonary vasodilation, and liver disease. Both acute and chronic cases of this syndrome have been reported, and the most common cause is cirrhosis. The principle disease mechanism is dilation of the pulmonary blood vessels causing alterations in gas exchange. Increased pulmonary production of nitric acid has been implicated as the primary pathogenic mechanism of vasodilation although it has also been associated with imbalance between vasodilators and vasoconstrictors. We describe the case of a patient with hepatopulmonary syndrome and adenocarcinoma of the colon with metastases to a previously healthy liver.

Key words: Hepatopulmonary syndrome, Pulmonary vasodilation, Liver disease, Adenocarcinoma of the colon.

Case Description

The patient was a 60-year-old retired office worker and nonsmoker with a history of hyperuricemia, high blood pressure, and polymyalgia rheumatica that had been diagnosed 2 years earlier. Fifteen months prior to diagnosis, the patient had been evaluated for liver enzyme abnormalities secondary to taking antiinflammatory drugs. There was no evidence of chronic liver disease at that time.

Hepatopulmonary syndrome in a Patient With Adenocarcinoma of the Colon Metastatic to the Liver and No Apparent Chronic Liver Disease

Brian Vila Auli,a Diego Pérez García,a Conrado Fernández Rodríguez,b Pilar Bañuls Polo,a and Julio Marín Pardo

1Servicio de Neumología, Hospital Clínico Universitario de Valencia, Valencia, Spain.
2Servicio de Medicina Interna, Hospital Clínico Universitario de Valencia, Valencia, Spain.
and γ-glutamyl transpeptidase was 165 U/L (normal, 10 to 49 U/L). Hepatitis serology was negative for hepatitis B surface antigen, hepatitis B core antibodies, hepatitis B antibodies (0.0 U/L), hepatitis C antibodies, and hepatitis A immunoglobulin M antibodies. Liver sonogram images and indocyanine green clearance were normal. After withdrawal of medication, drug-induced alterations returned to normal. The patient came to our emergency department after a month of asthenia, anorexia, weight loss of 6 kg, abnormal intestinal activity, progressive dyspnea to the point of fatigue at moderate exercise (walking 20 m), dry cough, and occasional fever. Arterial blood gas analysis (fraction of inspired oxygen, 0.21) revealed a pH of 7.49, PaO2 of 57 mm Hg, PaCO2 of 27 mm Hg, and bicarbonate (HCO3^−) of 20.6 mmol/L. The patient was referred to our outpatient clinic, where a computed tomography (CT) scan of the chest and upper abdomen was requested. Twenty-five days later, he returned for the CT scan, after which he made a second visit to the emergency department complaining of increased dyspnea that limited his ability to drink a glass of water. He was admitted for partial respiratory failure and multiple hypodense lesions in both lobes of the liver indicative of diffuse metastatic infiltration (Figure 1); arterial blood gas analysis (inspired oxygen fraction, 0.21) revealed a pH of 7.50, PaO2 of 45 mm Hg, PaCO2 of 26 mm Hg, and HCO3^− of 20 mmol/L. Physical examination showed a temperature of 37°C, blood pressure of 110/50 mm Hg, respiratory rate of 28 breaths/min, with no platypnea, and heart rate of 110 beats/min. Thorough cardiopulmonary auscultation detected no abnormalities. Telangiectasia was observed on the patient’s face, torso, and upper limbs and was especially apparent on the palms (Figure 2) and chest. Liver function tests were carried out. Plasma biochemistry showed an aminotransferase level of 57 U/L; alanine amino transferase, 42 U/L; γ-glutamyl transpeptidase, 252 U/L; lactate dehydrogenase, 1428 U/L (normal, 240-480); total proteins, 7 g/dL; albumin, 3.4 g/dL; total bilirubin, 1.1 mg/dL; urea, 37 mg/dL; creatinine, 1.0 mg/dL; carcinoembryonic antigen, of 4645 ng/mL (normal, 0-6); and carbohydrate antigen 19.9, less than 5000 U/mL (normal, 0-37). Coagulation tests showed a prothrombin time of 16 seconds, a Quick index of 65%, and a fibrinogen level of 9.9 g/L. A hemogram showed total leukocytes of 10200 cells/µL; 73.3% were polymorphonuclear cells, 17.2% were lymphocytes, and 9% were monocytes. Colonoscopy revealed a mass 30 cm from the anus. A biopsy was performed and the mass was identified as infiltrating adenocarcinoma. Fine needle aspiration of the hepatic lesions was performed and cytologic evaluation indicated they were adenocarcinoma metastases. Assessment of the hypoxemia was concluded with a ventilation-perfusion scintigram, which showed a pattern suggesting low probability of pulmonary thromboembolism, and a high resolution spiral CT scan, which revealed small bronchiectases in both lung bases. Lung function test results were normal: forced vital capacity was 3.04 L (82.4%), forced expiratory volume in 1 second was 2.61 L (92.7% of predicted), the ratio of these parameters was 0.85, and the ratio of carbon monoxide diffusing capacity to alveolar volume was 1.24 mmol/min/kPa (99.5%). Arterial blood gas values measured in supine decubitus and sitting positions showed a decrease of 10% in PaO2. Contrast-enhanced transthoracic echocardiography revealed microbubbles in the left heart chambers appearing between the third and fourth beats after they were visualized in the right chambers. Magnetic resonance angiography produced normal images. The patient’s condition deteriorated. Gas exchange worsened and systolic blood pressure progressively decreased to 86 mm Hg despite cessation of antihypertensive treatment. Moreover, carcinoembryonic antigen levels rose to 14 533 ng/mL.

Discussion

Hepatopulmonary syndrome is associated with acute9 as well as chronic liver disease. In some cases—for example, in noncirrhotic portal hypertension—the hepatic parenchyma may not be involved. Altered metabolism or clearance of vasoactive substances secondary to liver failure or portal hypertension may produce a decrease in vasoconstrictor substances and an increase in vasodilator substances. The most important mechanism in pulmonary vasodilation is believed to be increased levels of nitric oxide synthetase in the endothelium of pulmonary vessels. Other vasoconstrictor substances that potentially may be involved are atrial natriuretic peptide, platelet activating factor, vasoactive intestinal peptide, estrogens, glucagon, and prostaglandins. Levels of vasoconstrictor substances, such as endothelin I and serotonin, may decrease, thus contributing to vasodilation of pulmonary microcirculation. The difficulty in diagnosing this syndrome lies in the nonspecific nature of its symptoms. The most frequent symptom is dyspnea—with cyanosis, clubbing, and spider angioma. Although the most characteristic symptom is platypnea.
(dyspnea on standing up from a recumbent position), it does not manifest in all patients. Exertional dyspnea appears during the natural course of cirrhosis, but only in certain cases is it associated with hepatopulmonary syndrome. However, platypnea and orthodeoxia (decrease in PaO$_2$ ≥5% or ≥4 mm Hg upon standing up from a recumbent position) are common observations in patients with hepatopulmonary syndrome and indicate a greater shunt in the lung bases, which become more perfused when the individual is standing. Hypoxemia with respiratory alkalosis demonstrated by arterial blood gas analysis should arouse suspicion of this syndrome. In cirrhosis this is a common finding, such that calculation of the alveolar-arterial oxygen partial pressure gradient and testing for the presence of orthodeoxia are essential. Lung function test results are usually normal, with the exception of reduced diffusing capacity. Dilation causes accelerated blood flow through the pulmonary capillaries, leaving insufficient time for gas exchange; therefore diffusing capacity is diminished even though there are no changes in the alveolointerstitial membrane. Transthoracic echocardiography with agitated saline or indocyanine green contrast enhancement, a noninvasive technique that enables detection of intrapulmonary vascular dilatations, is the most sensitive technique for detecting pulmonary vasodilation. Microbubbles can be visualized in the left heart chambers between the third and sixth beats after they have been observed in the right chambers. This technique can determine from exactly which pulmonary vein the bubbles are issuing. If the bubbles are seen before the third beat, diagnoses of cardiac disease and large thoracic vessel disease characterized by right-to-left shunt must be ruled out. The microbubbles that pass through normal pulmonary circulation are so small (8-15 μm) that they are trapped and dissolved before entering the left heart chambers. It should be noted that a considerable number of cirrhosis patients have positive echocardiograms but normal blood gas findings; the prognosis for such patients is unknown. Another diagnostic technique is ventilation-perfusion scintigraphy performed with technetium 99m macroaggregated albumin; uptake is observed if there is a right-to-left shunt in the brain, kidneys, liver, bone, or spleen. However, cardiac and pulmonary shunts cannot be distinguished with this technique and it is less sensitive than transthoracic echocardiography. Pulmonary angiography, now in disuse, will detect pulmonary vasodilation, although no abnormalities may be present. Severity of liver dysfunction, esophageal varices, and spider angioma is believed to be associated with the hemodynamic alterations characteristic of liver cirrhosis, but not with ascities or liver encephalopathy.

The case we report is uncommon because it involved detection by contrast-enhanced transthoracic echocardiography of intrapulmonary vasodilation associated with metastases from an adenocarcinoma of the colon to a previously healthy liver. Lee and Lepler reported the case of a female patient with metastatic carcinoma affecting the liver and associated with vasoactive substances secreted by the carcinoid tumor. Teramoto et al hypothesized an association of nitric oxide with pulmonary vasodilation. The case we describe presents both pulmonary and systemic vasodilation—reflected by expression of spider angioma and a decrease in arterial blood pressure despite the withdrawal of medication. The clinical picture suggested generalized vasodilation and hyperdynamic circulation. These symptoms could be caused by a vasodilator substance secreted by the tumor or by a vasodilator-vasoconstrictor imbalance associated with the extensive metastatic involvement of the liver.

**REFERENCES**

18. Terramoto S, Matsuse T, Ouchi Y. Carcinoid-related intrapulmonary vascular dilatations (decrease in PaO$_2$ ≥5% or ≥4 mm Hg upon standing up from a recumbent position) are common observations in patients with hepatopulmonary syndrome and indicate a greater shunt in the lung bases, which become more perfused when the individual is standing. Hypoxemia with respiratory alkalosis demonstrated by arterial blood gas analysis should arouse suspicion of this syndrome. In cirrhosis this is a common finding, such that calculation of the alveolar-arterial oxygen partial pressure gradient and testing for the presence of orthodeoxia are essential. Lung function test results are usually normal, with the exception of reduced diffusing capacity. Dilation causes accelerated blood flow through the pulmonary capillaries, leaving insufficient time for gas exchange; therefore diffusing capacity is diminished even though there are no changes in the alveolointerstitial membrane. Transthoracic echocardiography with agitated saline or indocyanine green contrast enhancement, a noninvasive technique that enables detection of intrapulmonary vascular dilatations, is the most sensitive technique for detecting pulmonary vasodilation. Microbubbles can be visualized in the left heart chambers between the third and sixth beats after they have been observed in the right chambers. This technique can determine from exactly which pulmonary vein the bubbles are issuing. If the bubbles are seen before the third beat, diagnoses of cardiac disease and large thoracic vessel disease characterized by right-to-left shunt must be ruled out. The microbubbles that pass through normal pulmonary circulation are so small (8-15 μm) that they are trapped and dissolved before entering the left heart chambers. It should be noted that a considerable number of cirrhosis patients have positive echocardiograms but normal blood gas findings; the prognosis for such patients is unknown. Another diagnostic technique is ventilation-perfusion scintigraphy performed with technetium 99m macroaggregated albumin; uptake is observed if there is a right-to-left shunt in the brain, kidneys, liver, bone, or spleen. However, cardiac and pulmonary shunts cannot be distinguished with this technique and it is less sensitive than transthoracic echocardiography.

Pulmonary angiography, now in disuse, will detect pulmonary vasodilation, although no abnormalities may be present. Severity of liver dysfunction, esophageal varices, and spider angioma is believed to be associated with the hemodynamic alterations characteristic of liver cirrhosis, but not with ascities or liver encephalopathy. The case we report is uncommon because it involved detection by contrast-enhanced transthoracic echocardiography of intrapulmonary vasodilation associated with metastases from an adenocarcinoma of the colon to a previously healthy liver. Lee and Lepler reported the case of a female patient with metastatic carcinoma affecting the liver and associated with vasoactive substances secreted by the carcinoid tumor. Teramoto et al hypothesized an association of nitric oxide with pulmonary vasodilation. The case we describe presents both pulmonary and systemic vasodilation—reflected by expression of spider angioma and a decrease in arterial blood pressure despite the withdrawal of medication. The clinical picture suggested generalized vasodilation and hyperdynamic circulation. These symptoms could be caused by a vasodilator substance secreted by the tumor or by a vasodilator-vasoconstrictor imbalance associated with the extensive metastatic involvement of the liver.