中文題目：晚期膽道癌病人所表現之肝肺症候群 - 病例報告

英文題目：Hepatopulmonary syndrome in late-stage intrahepatic cholangiocarcinoma：A Case Report

作　　者：[1]林子容，[2]蘇冠名，[2]陳育萱，[3]郭雨庭，[4]許嘉林

服務單位：[1]台灣大學附設醫院內科部，[2]國立台灣大學醫學院附設醫院雲林分院胸腔內科，[3]國立台灣大學醫學院附設醫院綜合診療部內視鏡科，[4]國立台灣大學醫學院附設醫院內科部胸腔內科

Introduction:

Shortness of breath is one of common chief complaints in our clinical practice. However, one of the important differential diagnosis, shunting,[1] is rarely recognized, let alone the etiology of intra-cardiac/intra-pulmonary shunting.

Hepatopulmonary syndrome (HPS) is a pulmonary complication of late-stage liver disease, characterized by a defect in arterial oxygenation induced by pulmonary vascular dilatation. Overproduction of gaseous vasodilators and angiogenesis seem to be the pathogenic hallmark. The triad of HPS consists of: (1) Presence of liver disease and/or portal hypertension (2) $PaO_2 < 80$ mmHg or A-a gradient ≥ 15 mmHg (or > 20 mmHg for patients > 65-years-old) while breathing ambient air (3) Documented intrapulmonary vascular dilatation.[2-4]

Classically, patients of HPS present with dyspnea and hypoxemia. Platypnea-orthodeoxia syndrome (POS) lead by shunt, is the characteristic finding in HPS patients, as demonstrated in our case.

Herein, we illustrate a case of elder woman with late-stage cholangiocarcinoma who developed acute respiratory failure. Depending on strong clinical suspicion, the patient was thereby confirmed with the diagnosis of hepatopulmonary syndrome.

Case Presentation:

A 76-year-old woman with medical history of late-stage intra-hepatic cholangiocarcinoma (progress with obstructive jaundice and received endoscopic retrograde biliary drainage (ERBD) placement), coronary artery disease, hepatitis B carrier (currently HBsAg negative with undetectable HBV viral load), diabetes mellitus, hyperlipidemia and hypertension. Initially, the patient presented to our emergency

department with fever and shortness of breath. Fever with a body temperature over 38.3 degree Celsius and desaturation (SpO_2 92% when breathing ambient air) were recorded. On physical examination, the patient had jaundice and otherwise unremarkable finding. Laboratory investigations showed hyperbilirubinemia with total bilirubin 6.76 mg/dL and direct bilirubin 4.77 mg/dL. Both computerized tomography (CT) scan and abdomen sonography showed bilateral intrahepatic ducts dilatation with suspicion of ERBD dysfunction.

Hence, the patient was admitted and received ERBD revision. Her symptoms improved after the procedure and administration of antibiotics. On the third day after ERBD revision, the patient had sudden onset respiratory distress. The patient was afebrile and the blood pressure was stable. On physical examination, the jaundice was still present, but her breathing sound was clear and no heart murmur was recorded. Her blood-work showed normal range of white cell count (4.45 k/μL) and hemoglobin (11.4 g/dL); partial resolving hyperbilirubinemia (total bilirubin 4.45 mg/dL, direct bilirubin 2.45 mg/dL). When she was breathing through simple mask oxygen at a flow rate of 10L/min (FiO_2 80%), her arterial blood gas showed PaO_2 147.4 mmHg (80–100 mmHg), PCO_2 35.8 mmHg (35–45 mmHg), and pH 7.484 (7.35–7.45). Her A-a gradient was 378.3 mmHg. Chest X-ray showed clear lung fields. An uncommon phenomenon was noticed later. We found that the patient felt more dyspneic while sitting in upright position. Her saturation was SpO_2 98% when sitting straight but the SpO_2 dropped to 87% when lying down. A platypnea-orthodeoxia syndrome was established, which raised our clinical suspicion of a hepatopulmonary syndrome. A diagnostic contrast-enhanced echocardiogram was performed. Agitated saline was infused during the exam and saline bubbles were found in her left atrium at the second heart beat after right atrium opacification. A right to left shunt was confirmed. Reviewing her previous echocardiogram, no congenital heart disease or other structural abnormalities had ever been documented. Together with her underlying late-stage liver disease, a diagnosis of hepatopulmonary syndrome causing hypoxia was made.

Unfortunately, she was not a candidate for liver transplantation due to advanced cancer status. She was discharged with home oxygen supplement and home hospice care was provided.

Discussion:

Hepatopulmonary syndrome is defined by the triad of chronic liver disease, pulmonary gas exchange abnormalities and documented intrapulmonary vascular dilatations.[2-4] Our patient met all three of the cardinal findings. Also, she had classical platypnea-orthodeoxia syndrome.[5] In one prospective study, platypnea was presented in 65.5% of the HPS group vs 6.2% in the non-HPS group.[6]

There are several techniques to evaluate the presence of intrapulmonary vasodilatation, including contrast-enhanced echocardiography, macroaggregated albumin lung perfusion and pulmonary angiography. A contrast enhanced echocardiography with agitated saline is the diagnostic gold standard. Our patient had a positive finding of saline bubbles in the left atrium at the second heart beat. Regarding the timing of left heart contrast appearance, a "three-beat rule" was proposed by a single Mayo Clinic case report in 1976 to distinguish between intracardiac and extracardiac shunts.[7] However, the concept was challenged by other studies. In one case report, a 40-year-old man had frequent transient ischemic attacks and neither transthoracic echocardiogram (TTE) nor transesophageal echocardiogram (TEE) demonstrated any congenital heart diseases. He received agitated saline contrast study and more than 20 bubbles appeared in the left atrium (LA) at the third cardiac cycle following opacification of the right atrium. Instead of having intracardiac shunts, his final diagnosis was hereditary hemorrhagic telangiectasia with associated large pulmonary arteriovenous malformation(PAVM).[8] In addition, in a cohort study with 64 eligible patients, which also suggesting that early appearance of saline bubbles in the left atrium may occur in patients with large intrapulmonary shunts and high-output state.[9] In our case, TEE was inappropriate due to her critical status and the patient declined any invasive procedures.

Currently, no effective pharmaceutical interventions for HPS are available. Supplemental oxygen therapy is offered in hypoxemic patients with HPS, but no studies have evaluated its survival benefit. Inhaled nitric oxide (NO), somatostatin, aspirin, norfloxacin, quercetin and mycophenolate mofetil (MMF) have all been studied in patients with HPS, but seemingly without clear benefit.[10-15] Liver transplantation is the only effective therapy for patients with HPS.[16-19]

The presence of HPS markedly contribute to increased mortality and worse quality of life in affected patients. A retrospective analysis reported 41% mortality over an approximate 2.5 year period in 22 patients with HPS. Furthermore, some reports suggesting no differences in post-transplantation morbidity between patients with and without HPS. No association was found between the severity of baseline hypoxia and survival after transplantation, either.[20]

Conclusion:

Hepatopulmonary syndrome should be considered in patient with chronic liver diseases present with dyspnea. Further diagnostic workup can be made once we have a clinical suspicion.

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