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CASE REPORT

Successful resolution of severe hepatopulmonary syndrome following liver transplantation

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Summary

Hepatopulmonary syndrome (HPS) is a complication of portal hypertension, defined by the presence of liver disease, abnormal pulmonary gas exchange and evidence of intrapulmonary vascular dilatations producing a right-to-left intrapulmonary shunt. Liver transplantation (LT) is the treatment of choice; however, severe hypoxemia ($PaO_2 < 50$ mmHg on room air) is considered a contraindication to LT. This approach disadvantages some patients, particularly young patients with no intrinsic cardio-respiratory disease. We discuss one such patient who improved with LT despite having extremely severe HPS ($PaO_2 < 29$ mmHg)

Case details

A 17-year-old female Congolese refugee, presented to the emergency room with vaginal hemorrhage post incomplete abortion. She had immigrated to Canada 4 months before presentation. The duration of pregnancy was not clear, and she had a history of vaginal bleeding for the preceding 2 months. At the time of admission, she had dyspnea, orthodeoxia, cyanosis, digital clubbing and abnormal liver enzymes, with oxygen saturation of 77% on room air. She underwent emergency evacuation of retained products of conception; postoperative workup for hypoxia found hepatopulmonary syndrome (HPS). Complete work-up for the etiology of liver disease, including for schistosomiaisis were negative, and a liver biopsy showed non-specific bridging fibrosis, with no evidence of hepatitis. Abdominal imaging showed varices consistent with portal hypertension, with patent portal vessels with no evidence of previous thrombosis. A perfusion scan and bubble ECHO showed significant intrapulmonary right–left shunting (40%), and a contrast enhanced CT scan of the chest showed pulmonary vascular dilation. The patient was managed with home oxygen. A transjugular intrahepatic portosystemic shunt (TIPPS) placement was conducted, with a significant drop in the portal venous-systemic pressure gradient to 5 mmHg compared to 14 mmHg before the procedure. Her oxygen requirements decreased transiently from 12 to 8 l/min, but over several months, her oxygen requirement continued to escalate substantially in the face of well-preserved normal liver function, with a calculated MELD score of 6. She presented emergently a few months later with acute respiratory decompensation because of pneumonia. When extubated, the patient had a resting room air PaO_2 of 29 mmHg. She subsequently required ICU admission, mechanical ventilation, and tracheostomy. A repeat perfusion scan, using technetium labeled macro-aggregates of albumin showed right–left shunting of 84%, with cerebral uptake of 15%. Trans-esophageal echocardiogram revealed no evidence of intracardiac shunt, but shunting

from the right upper pulmonary vein. She underwent pulmonary arteriography to identify arteriovenous pulmonary fistulas for potential transcatheter coiling; however, no discrete lesions amenable to embolization could be identified and the mean PAP was 23 mmHg, with peripheral saturation consistently below 40% on room air. A trial of nitric oxide and methylene blue did not improve the PO_2, although her FiO_2 decreased to some degree once the lung infection resolved. We discussed different management options including dual-organ (liver–lung) transplantation, liver transplantation (LT) with extracorporeal membrane oxygenation, or liver transplant alone. A liver–lung transplant was excluded because of the absence of intrinsic lung disease and the added challenge of finding two appropriately size-matched organs for this small-sized recipient. We chose to proceed with a liver transplant alone (LT) because of age, absence of significant cardiac co-morbidity in the expectation that a functioning allograft would improve the oxygenation, and the remote chances of recovery without any intervention. She underwent an emergent liver transplant because of deteriorating respiratory function. At the time of surgery, her portal vein was patent with no evidence of previous thrombosis. The explanted liver showed fibrous expansion of most portal areas with the occasional portal-to-portal bridging fibrosis. Chronic inflammatory cellular infiltrate in the triads was seen, but with no evidence of granulomas. Special stains were all negative for organisms, including Schistosoma, and hepatitis B (HBV).

She had excellent graft function and markedly improved oxygenation, with near-complete resolution of the R–L shunt within 4 weeks (Fig. 1a, b), decreased oxygen requirement, (Fig. 2) and was discharged home on room air only, with normal oxygen saturation. She is currently 6 months post-LT and has been on room air for the last 5 months with normal activity levels for her age.

Discussion

The HPS is characterized as the triad of liver disease, pulmonary gas exchange abnormalities leading to arterial de-oxygenation and evidence of intrapulmonary vascular dilatations (IPVD) [1]. HPS affects 10–30% of the population awaiting LT, and is associated with poorer quality of life [2–4]. The prognosis associated with HPS is poor, and appears to be associated with the degree of hypoxemia [4–6]. IPVD especially in alveolar regions are the defining pathological hallmark of HPS and are thought to be responsible for hypoxemia [7]. Intravenous radio labeled technetium macro-aggregated albumin particles (^{99m}Tc-MAA) can be used to establish the presence of dilated pulmonary microvasculature, and the bio-distribution of intravenous ^{99m}Tc-MAA particles can be used to quantify right-to-left (R–L) shunts [8]. Greater than 90% of the particles are 10–90 μm in size (mean 20–40 μm). They mix homogeneously in blood pool and are trapped in pre-capillary arterioles. Following intravascular

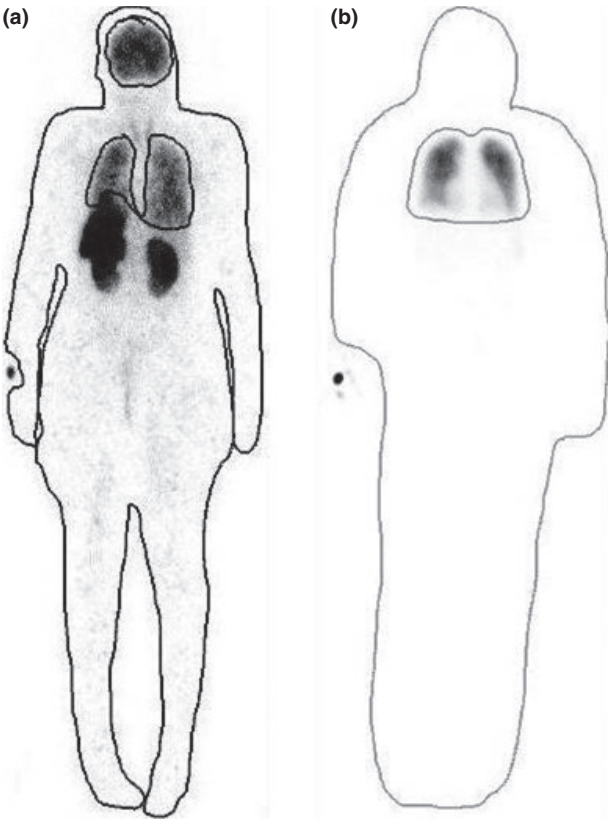

Figure 1 (a) Pre-transplant ^{99m}Tc-MAA scan showing extensive systemic L–R shunt with uptake in the cerebral cortex, liver and kidneys. (b) Scan 4 weeks post-LT, showing near complete resolution of the shunt and activity limited to the pulmonary region.

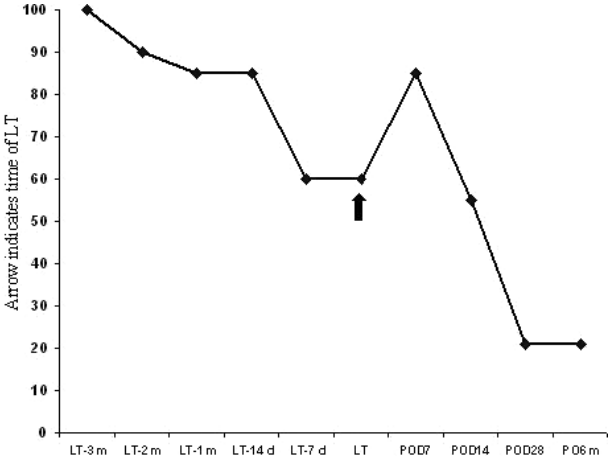

Figure 2 Oxygen requirements over time.

injection, the bio-distribution of ^{99m}Tc-MAA particles can be used to quantify relative organ/tissue blood perfusion accurately. After systemic venous injection, only about 3% or less of the administered activity is seen outside the lungs because of small particle size (5–10 μm), and *in vivo* biodegradation of ^{99m}Tc-MAA particles. In the presence of a R–L shunt, labeled MAA particles will bypass pulmonary arterial capillary bed and lodge in pre-capillary arterioles of systemic organs, and the percentage of total systemic venous return (i.e., cardiac output) bypassing the pulmonary capillary bed can be quantified. After systemic venous injection, <3% activity is seen outside the lungs because of small particle size; In this case, the shunt fraction was 84% with extensive uptake of tracer in the brain and the kidneys (Fig. 1a); there was 15% cerebral uptake as compared to <5% in normal studies [9].

In this case, the etiology of the liver disease was not clear even on explant; an initial suspicion of schistosomiasis was not supported by explant biopsy or serology. HPS in schistosomia-associated liver disease has been reported, and the degree of portal hypertension appears to be an important factor in its development [10]. Pregnancy can also worsen symptoms of HPS, but this usually occurs in the second trimester; an exact duration of the pregnancy could not be ascertained in this case [11].

Therapeutic options for HPS include the use of nitric oxide, methylene blue, pentoxifylline, iloprost and more recently, bosentan [12–15]. A reduction in portal pressure appears to be beneficial in HPS; this patient had only a transient improvement in oxygenation with the use of TIPPS, after which the PO_2 deteriorated steadily. Other studies using TIPPS have not shown overall sustained change in arterial blood gas profile [16]. Alternatively coil embolization of prominent pulmonary arteriovenous fistulae, if present, may offer some benefit before or after LT [17].

Liver transplantation offers the only therapeutic option for HPS, but carries high risk in patients with severe hypoxia. The degree of hypoxemia is often used as a prognostic indicator and a $PaO_2 < 50$ mmHg on room air is considered a contraindication to LT [4,6]. This approach disadvantages some patients, particularly young patients with no intrinsic cardio-respiratory disease. Extracorporeal membrane oxygenation (ECMO) has been used for life-threatening hypoxia following liver transplantation, but carried substantial risk of bleeding in the postoperative period, and can only be sustained for a relatively limited period [18]. Fortunately for this patient, she improved dramatically and rapidly following LT without requiring ECMO, with near-complete resolution of the R–L shunt within 4 weeks, and was discharged home on room air.

This case represents a successful outcome in the most severe case of HPS reported in literature and underscores the need to consider LT as a potential therapeutic option even in extreme cases. Accurate diagnosis and careful patient selection are critical.

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