the mechanisms of HPS and portopulmonary hypertension overlap.

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Review

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The case study by Veitsman and colleagues describes two successful pregnancies in a patient with autoimmune hepatitis and hepatopulmonary syndrome (HPS).[1] Autoimmune hepatitis is a rare condition, and successful pregnancy has been reported in only a small number of cases in which disease activity is under control. Morbidity in the setting of autoimmune hepatitis and pregnancy is associated with prepartum flares at a rate of 21–47% and postpartum flares at a rate of 12–52%, typically in the first 3 months following delivery.[2] The most common adverse event associated with fetal mortality in pregnant autoimmune hepatitis patients is premature delivery, which is reported in up to 17% of cases.[3-4] Management of patients with autoimmune hepatitis-related cirrhosis who become pregnant is simple in theory; however, it involves the development of trust between doctor and patient, as well as compliance and frequent visits to a multidisciplinary care team for regular monitoring. The continuation of regular immunosuppression, typically azathioprine, does not carry an increased teratogenic risk, although breastfeeding is usually not advised due to the theoretical risks of breast milk carriage and bone marrow suppression in newborns.

The case by Veitsman and associates is noteworthy for many reasons. First, it highlights the fact that patients with stable autoimmune hepatitis-related cirrhosis may be capable of successful conception and completion of pregnancy. Second, it confirms that the continuation of standard immunosuppression, rather than an escalation in therapy, is generally sufficient to control disease activity. Throughout both pregnancies, the patient's disease was apparently stable, and with a total follow-up of 3 years so far, she has suffered no prepartum or postpartum complications in disease activity.

There is a close, recognized association between liver disease and the development of respiratory symptoms. In one reported series, over 50% of patients with cirrhosis complained of breathlessness.[5] This respiratory symptom can often be explained by the physiologic changes

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that develop in patients with cirrhosis including poor thoraco-abdominal compliance, diaphragmatic splinting in the setting of ascites, muscle weakness, previously undiagnosed lung or cardiac disease, and the development of pulmonary arteriovenous abnormalities and exertion-related dyspnea. Physical examination often provides clues to possible underlying respiratory abnormalities. The presence of large-volume, tense ascites, poor nutrition, muscle wasting, spider angioma, finger clubbing, and cyanosis are easily recognizable. The impairment of arterial oxygenation due to pulmonary vascular abnormalities and the association of chronic liver disease form the increasingly recognized triad of symptoms of HPS. The classic definition of HPS describes an elevated age-adjusted alveolar-arterial oxygen gradient ($AaPO_2$) in room air (>15 mm Hg or >20 mm Hg in patients >64 years of age), with or without hypoxemia, resulting from intrapulmonary vasodilatation in the presence of hepatic dysfunction or portal hypertension.[6] The previous exclusion of coexisting cardiovascular and respiratory disorders is no longer necessary, as HPS has been seen alongside these conditions.[7] It is these conditions that may provide a reversible element in HPS management. $AaPO_2$ varies with age, even in normal individuals; therefore, it is important to use age-adjusted levels.

Alveolar-arterial oxygen abnormalities are paramount in the diagnosis of HPS, as hypoxemia in itself is not required. The presence of resting hypoxia may provide a clue, if only for further evaluation and exclusion of a potential diagnosis. Routine assessment of patients with hypoxia includes chest radiograph and pulmonary function tests alongside arterial blood analysis. Measurement of peripheral oxygen saturations provides a cheap and simple outpatient screening tool rather than a diagnostic test. Measurement of arterial oxygen concentrations in room air by blood gas analysis is the gold standard of diagnosis and is necessary to establish the severity of disease.

The development of HPS is thought to result from local endothelial nitric oxide and carbon monoxide release, which leads to vascular dilatation and pulmonary diffusion-perfusion mismatch (arterial-alveolar gradient). Pulmonary vascular abnormalities can be determined either by transthoracic contrast bubble echocardiograph or macro-aggregated albumin lung scanning. The presence of contrast or bubbles in the left ventricle after 3 beats is a classic sign of shunting on a pulmonary level and is hence diagnostic of HPS.

The prevalence of HPS has been reported as ranging from 1.5% to 24% of cirrhotic patients but recently has also been found in certain noncirrhotic states.[8] The severity of underlying liver disease does not appear to influence the development of HPS, although there is a correlation between hypoxemia and Child-Pugh class. The cause of death in patients with HPS appears to result from portal hypertension or hepatic dysfunction and is not associated with hypoxia. However, HPS appears to influence the progression of liver disease and complications associated with portal hypertension, and is an independent predictor of survival.[9] This association also affects patient survival, as the 5-year median survival rate is only 23% in patients with HPS compared with 63% in cirrhotic controls without HPS.[10] Because of the close association of chronic liver disease and HPS, there is only one recognized definitive treatment: liver transplantation (LT). LT can result in total resolution or significant improvement in gas exchange in more than 85% of patients transplanted for HPS, although normalization may extend beyond 12 months.[6]

The diagnosis of HPS carries significant morbidity and mortality. The severity of underlying liver disease itself may not warrant consideration for transplantation, but when combined with HPS, the associated mortality is significant enough to consider LT. Indeed, prioritization for transplantation is widely accepted for HPS cases with significant hypoxemia. The 5-year transplant survival rate in patients with HPS (including severe HPS) who undergo transplantation is equal to the survival rate of patients without HPS.[7] Therefore, liver transplantation is the only available therapeutic intervention that appears to influence long-term mortality. This appears to hold even for patients with severe hypoxemia. Patients previously excluded from transplantation would therefore benefit, even though recent evidence suggests that postoperative mortality is higher in the first 3 months following transplant in this group.[10] A classification system for HPS based on arterial oxygen tension (PaO_2) has been proposed: PaO_2 less than 50 mm Hg indicates very severe HPS and is excluded from transplantation; PaO_2 between 50–60 mm Hg indicates severe HPS; and PaO_2 between 60–80 mm Hg indicates moderate HPS.

Consideration for LT in this patient would solely be due to the diagnosis and severity of HPS, rather than to underlying liver disease. The difficulty is in establishing the diagnosis and then stratifying severity from the available data. Resting or baseline PaO_2 is crucial and would provide an important marker of disease severity. HPS may indeed be an indication for LT, but the determination of severity allows for informed consent and assessment of postoperative mortality. This would be significant if the O_2 saturations of 84% did not improve postpartum. The presence of pulmonary shunts diagnosed on transthoracic contrast echocardiograph is a classic sign for HPS, but formal assessment of the arterial-alveolar gradient should have been undertaken prior to pregnancy. Current PaO_2 measurements would be extrapolated from documented arterial saturations, rather than direct PaO_2 measure-

ments. Arterial saturations ranged from 84% to 94% in this patient, approximating PaO_2 to between 55 and 80 mm Hg. These extremes would stratify HPS between severe and moderate. Transient changes in physiology may be important in this case and may need to be taken into consideration, as improvement postpartum is normally likely to occur.

The physiologic changes that occur in pregnancy are also well recognized. The systemic vasodilatation that occurs in the first trimester may exacerbate pulmonary vascular abnormalities and increase pulmonary shunting. This would worsen hypoxia, albeit only transiently, placing greater strain on the right side of the heart. It is unsurprising in this case that arterial saturations were seen to deteriorate during this time period. Changes after the first trimester are associated with the pooling of blood, with decreased venous return being the main cause of hemodynamic compromise. Thus, pulmonary shunting would theoretically improve in the later stages of pregnancy. There are no reported cases in the literature describing the development of spontaneous pulmonary vascular abnormalities occurring as a direct result of pregnancy.

The use of supplemental oxygen in patients with severe HPS or exertion-induced hypoxemia is well recognized. Data are somewhat limited regarding efficacy or the relationship to reduction in morbidity, although improvements in exercise tolerance and quality of life may justify the use of supplemental oxygen. The presence of a reduced diffusion capacity of carbon monoxide is recognized in HPS but also in other conditions such as pneumonitis, interstitial lung disease, and anemia. The presence of underlying lung disease or anemia would explain the relative hypoxia and also the lack of progression over the documented 3-year period.

In view of both the development and progression of symptoms, it is critical to reassess this case further. It would thus be appropriate to repeat baseline investigations and to determine the possibility of underlying lung disease in addition to establishing a resting PaO_2 value. The development of pulmonary hypertension further clouds the diagnosis. Indeed, there appears to be increasing recognition of the overlap of these conditions, even extending into the posttransplant period. A recent case report described the possible overlap between HPS and portopulmonary hypertension (PPHTN) in one patient,[11] and in our own practice, we have identified a handful of cases with apparent overlap between these entities.

PPHTN is characterized by pulmonary vasoconstriction through vasoactive mediators, the most important of which is endothelin-1, resulting in pulmonary hypertension. The development of PPHTN does not exclude candidates from transplantation with mild or moderate disease, but consideration for transplantation should be undertaken as soon as possible because coexistent disease and right ventricular dysfunction would render the likelihood of survival to be low. A possible hypothesis is that the development of PPHTN in the setting of HPS or indeed interstitial lung disease provides transient improvement in gas exchange and symptoms, but would eventually lead to pulmonary hypertension and right-sided heart failure.

In conclusion, although HPS is an indication for transplantation independent of the severity of liver disease, there should be investigations that include arterial blood gas analysis and transthoracic contrast echocardiograph. Although early posttransplant survival depends on the severity of disease, the 5-year survival rate for HPS patients equals that of patients without HPS. The clinical entities of HPS and PPHTN may in fact represent extremes of a spectrum in respiratory complications associated with liver disease.

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