Hepatopulmonary Syndrome with Noncirrhotic Portal Hypertension Diagnosed Following Acute SAR-CoV-2 Infection

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Abstract

Discussed is the case of a 13-year-old male with no significant past medical history, who presented to the hospital for evaluation of multisystem inflammatory syndrome in children (MIS-C). He arrived with findings of conjunctivitis, strawberry tongue, tachycardia at rest, and hypoxemia with oxygen saturation of 85%. The patient was recently hospitalized 1 week prior for viral pneumonia and hypoxemia due to SARS-CoV-2. During his inpatient stay he received combination therapy of remdesivir and dexamethasone. Following, he weaned to room air and his pulse oximetry (SaO2) order was switched to intermittent with floor vitals prior to his discharge.

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To the Editor,

Discussed is the case of a 13-year-old male with no significant past medical history, who presented to the hospital for evaluation of multisystem inflammatory syndrome in children (MIS-C). He arrived with findings of conjunctivitis, strawberry tongue, tachycardia at rest, and hypoxemia with oxygen saturation of 85%. The patient was recently hospitalized 1 week prior for viral pneumonia and hypoxemia due to SARS-CoV-2. During his inpatient stay he received combination therapy of remdesivir and dexamethasone. Following, he weaned to room air and his pulse oximetry (SaO2) order was switched to intermittent with floor vitals prior to his discharge.

Upon this re-admission, the patient re-developed a supplemental oxygen (O2) requirement of 3 liters via nasal canula to maintain saturation above 90%. Pulmonary was involved following a negative workup for MIS-C, which included inflammatory markers, electrocardiogram, and chest X-ray. Initial recommendations included 5 days of azithromycin (1 day 500 mg, 4 days 250 mg) for anti-inflammatory effects and 5 days of prednisone 60 mg daily with hypoxemia believed to be due ventilation/perfusion (V/Q) mismatch.

The patient remained unable to wean supplemental oxygen and even with support, he was only able to SaO2 of 92%. Corticosteroids were extended for a total of 7 days, added ipratropium bromide every 6 hours for a total of 4 treatments, and broadened our differential diagnosis for causes of hypoxemia to include diffusion defects and veno-arterial shunting. An echocardiogram was performed to evaluate for pulmonary hypertension and left ventricular dysfunction that were previously observed in SAR-CoV-2 infections; the study revealed normal heart function. Computerized tomography angiogram (CTA) was completed and showed occasional scattered patchy opacities without evidence of pulmonary embolism.

As care continued, it was noted that the patient had developed progressive polycythemia over a two-week time frame with elevations in hemoglobin to a max of 18.6 g/dL (Reference Range [RR]: 12.5-16.4 g/dL) and

hematocrit to 53.7 % (RR: 37.0-49.0%). Resolving 4 days after initiation of supplemental oxygen, suggesting chronic hypoxemia. At this time, the patient began mometasone/formoterol 100 mcg 2 puffs twice a day. He remained stable and was discharged home with supplemental oxygen of 1.5 L/min with an increase to 4 L/min with activity.

Shortly afterwards, he was readmitted for worsening hypoxemia at home. Given that he remained clinically well, other than inability to wean to room air, a CT chest without contrast was obtained. Pulmonary findings were unremarkable with no signs of arteriovenous malformations. However, abnormal vasculature was seen in the upper abdominal omentum, the perisplenic and perigastric regions concerning for varices and collateral vasculature (Figure 1). This raised concerns for portal hypertension. A follow up abdominal ultrasound with Doppler did show normal portal venous flow, as well as heterogeneous echotexture of the liver consistent with diffuse hepatocellular disease.

Due to growing concern for intrapulmonary shunting, an echocardiogram with contrast was conducted and showed agitated saline bubbles appearing in the left atrium after 4 beats, suggesting a right-to-left shunt. This finding was consistent with the results of a 6-minute walk test where the patient had desaturations as low a 78% while on room air with no significant improvement noted on 6 L/min. Pulmonary function testing (PFT) was completed with evaluation of diffusion capacity for carbon monoxide (DLCO) moderately impaired at 55% predicted for his age and height (RR: 75-140%).

Hepatology was consulted and the patient underwent a liver biopsy. The histopathology showed subtle abnormalities in the liver parenchyma: patchy mild portal chronic inflammation, focal lobular inflammation, and focal minimal peri-central sinusoidal dilatation. No fibrosis, cholestasis or steatosis was seen (Figure 1). Hepatic venogram performed with a second liver biopsy, resulting in a normal portosystemic gradient of 5 mmHg. Subsequently, direct portography with portal pressure measurements and splenic venogram with splenic pulp pressure measurements were performed. These were consistent with non-cirrhotic portal hypertension. An arterial blood gas (ABG) was obtained to calculate the Alveolar-arterial (A-a) gradient. His blood gas showed a pH of 7.35 (RR: 7.35-7.45), partial pressure of carbon dioxide 52 mmHg (RR: 36-46 mmHg), partial pressure of oxygen (PaO2) 62 mmHg (RR: 80-105 mmHg), and a base excess of 2.4 mmol/L. His PaO2 represented moderate hypoxemia, with the severe range measuring at 60 mmHg or lower. Expected A-a gradient for his age was 7.3 mmHg and calculated was 47.7 mmHg, representing significant V/Q mismatch.

Without evidence of primary parenchymal lung disease on extensive evaluation, the best unifying diagnosis to explain his persistent hypoxemia was idiopathic noncirrhotic portal hypertension (NCPH) with hepatopulmonary syndrome (HPS). The patient was listed and successfully underwent a liver transplant with significant improvement in his symptoms. A year out from initial diagnosis, the patient was weaned off supplemental oxygen outside of strenuous activity and only required 0.2 liters per minute with activity.

This unique case highlights a rare condition that is even rarer in the pediatric population, particularly outside of associated cirrhosis. HPS is a condition first described in 1977 [1], but not formally named until 1990[2]. The hallmark is the presence of the triad including: intrapulmonary vascular dilation (IPVD) and abnormal arterial oxygenation in the setting of advanced liver disease, portal hypertension, or congenital portosystemic shunts (CPSS)[3]. Prevalence of this condition occurs between 9%-20% of children with end-stage liver disease, with the prognosis once diagnosed being poor[4]. Presentation can be severe with an insidious onset that often extends the time from presentation to diagnosis.

Clinically, HPS is characterized by the presence of increased A-a gradient on room air, with or without hypoxemia[3]. Most cases are seen with associated cirrhosis (up to 40%) and a liver biopsy may be beneficial. HPS may develop in noncirrhotic portal hypertension, congenital portosystemic shunt (CPSS), and ischemic hepatitis[3,4]. A previously reported case report of HPS caused by NCPH showed similar findings on histologic review of liver biopsy including dilated sinusoids and portal spaces[5].

Although exact pathogenesis is not fully understood, there are three postulated mechanisms that may play a key role in impaired oxygenation: They are V/Q mismatch, intrapulmonary shunting, and limi-

tation of oxygen diffusion[3]. Patients may be asymptomatic during the early stages of the disease, but typical symptoms include: dyspnea on excretion or at rest, growth retardation, cyanosis, and digital clubbing. Dyspnea is the most frequent symptom of progression and when it occurs upon standing, it is known as platypnea; hypoxemia exacerbated in the upright position is known as orthodeoxia, which is seen in 20-80% of patients[1,3].

Chest radiography and PFT tend to be nonspecific; however, abnormal DLCO is frequently observed[1]. It is essential to confirm the presence of hypoxemia by blood gas analysis and to demonstrate IPVD, which can be done via a contrast-enhanced transthoracic echocardiogram[3]. Confirming the diagnose HPS, also requires impaired oxygenation be shown[4]. An ABG are the most sensitive and recommended diagnostic modality[1]. An elevated A-a gradient $>$ 20 mm Hg is pathologic and important in HPS diagnosis[5]. However, due to the invasive nature of ABG measurements, they are often – particularly in pediatric patients – substituted with simple pulse oximetry which does have a reasonable sensitivity and specificity for diagnosing HPS[6]

At present, liver transplantation is the only curative and life-saving therapy, by reversing the intrapulmonary vascular shunting and hypoxemia. It has also been shown to provide complete resolution of gas exchange abnormalities in the vast majority of patients[3].

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