

A Case Report of Uncommon Cause of Cyanosis in a Child

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Abstract

Pulmonary complications may occur as a result of end-stage liver disease, probably due to decreased hepatic clearance or increased hepatic production of circulating cytokines and other vascular growth mediators. We report a case of a female Egyptian patient 15-year-old that presented with cyanosis who was investigated for a long time for being a cardiac patient as she showed no symptoms suggestive of liver affection but eventually she was diagnosed to have hepatopulmonary syndrome. We aim to highlight pulmonary affection secondary to hepatic disease that although rare can lead to significant morbidity in patients with liver cirrhosis.

Keywords: Hepatopulmonary syndrome; Liver cirrhosis; Intrapulmonary shunts; Cyanosis

Introduction

Advanced liver disease and portal hypertension produce various intrathoracic complications that involve the pleural space, the lung parenchyma, and the pulmonary circulation

[1]. These complications include hepatopulmonary syndrome (HPS), portopulmonary hypertension (POPH) and hepatic hydrothorax [2]. Additionally, mechanical factors may lead to thoracic complications, such as cephalic displacement of the diaphragm by increased abdominal pressure and ascites with resultant dyspnea, and passage of ascites from the peritoneal space to the pleural space through diaphragmatic defects resulting in hepatic hydrothorax [3].

HPS is defined clinically as the triad of chronic liver disease, abnormal pulmonary gas exchange with an increased alveolar-arterial oxygen gradient, and evidence of pulmonary vascular dilatations [4]. HPS is primarily a gas exchange problem characterized by arterial hypoxemia [5]. The prevalence of HPS in the setting of cirrhosis ranges between 4% - 30% [6]. The European Respiratory Society has proposed a classification system that uses arterial oxygen tension (PaO₂) to stage the severity of HPS, as a means of predicting survival and determining the timing and risks of orthotopic liver transplantation. According to this system, a PaO₂ < 50 mmHg indicates very severe HPS, a PaO₂ in between 50 to 60 mmHg suggests moderate HPS and a PaO₂ in between 60 and 80 mmHg corresponds with mild HPS [7].

POPH, on the other hand, is best defined as pulmonary artery hypertension (PAH) associated with portal hypertension, whether or not that portal hypertension is secondary to underlying liver disease, and its diagnosis is traditionally based on hemodynamic data from right heart catheterization [8]. POPH is primarily a hemodynamic problem which can result in right heart failure and death [5]. Recent work using hemodynamic studies have estimated the prevalence of POPH to be between 2% and 5%. The prevalence in patients undergoing liver transplantation (LT) is probably higher, with one study showing a prevalence of 8.5 % [8].

Case Report

A 15 year old girl presented to the Out-Patient clinic of the Children's Hospital, Ain Shams University with cyanosis and shortness of breath of 4 years duration. Her condition started 5 years prior to presentation with abdominal enlargement; hepatomegaly and lymphadenopathy. Malignancy was

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suspected and a surgical biopsy was taken from the intra-abdominal lymph nodes. The pathological examination excluded malignancy but raised the possibility of tuberculosis, with subsequent antituberculous treatment for 2 years.

Abdominal distension did not persist after the open biopsy. However the mother noticed that her child developed progressive cyanosis, with dyspnea, tachypnea, easy fatigability and deterioration in her general condition. The child did not complain of any symptoms suggestive of liver disease. She was not jaundiced, and there had been no change in the color of urine, no hematemesis and no abdominal distension at that time.

Echocardiography was done repeatedly and showed a structurally normal heart with a patent foramen oval (4 mm) shunting from left to right, and mild tricuspid regurgitation with an estimated peak right ventricular systolic pressure of 26 mmHg. Cardiac catheterization showed normal pulmonary artery pressure of 25/10 mmHg, right ventricular systolic pressure of 28 mmHg and end diastolic pressure of 8 mmHg. Oxygen saturation was 74% in the aorta, 61% in the right ventricle and 63% in the pulmonary artery. Angiography showed no evidence of fistulous communications to the pulmonary artery and normal pulmonary venous drainage. Multislice CT angiography was done 2 months later and showed confluent sizable PA branches with no evidence of pulmonary arteriovenous fistulae or aortopulmonary window. The lungs showed no evidence of interstitial lung fibrosis. During that time she was only on O₂ therapy with no appreciable improvement.

When the child presented to our hospital a year later she was severely cyanosed, with third degree clubbing and mild jaundice. Her weight was 34 Kg and height was 145 cm, both below the 5th centile for age. The heart rate was 87 beats/min, her respiratory rate was 35 breaths/min, and her blood pressure was 110/70 mmHg. She was markedly dyspneic with shallow breathing and she preferred to lie flat (platypnoea).

Cardiac examination revealed an accentuated second heart sound with an audible ejection systolic murmur (grade 2/6) over the pulmonary area. Chest examination was unremarkable. Abdominal examination revealed the paraumbilical scar of the previous biopsy. The right lobe of the liver was 5 cm below right costal margin in the midclavicular line and was firm in consistency with a sharp border. The spleen was palpable 4 cm below left costal margin.

Arterial blood gases in room air demonstrated a pH of 7.42, PaCO₂ of 28.0 mmHg, PaO₂ of 20 mmHg, HCO₃ of 18.1 mM/L, and saturation of 35%, which did not improve significantly on 100% O₂ inhalation.

A full blood count revealed hemoglobin of 12.6 gm/dl, a hematocrit of 42.6%, White blood cell count of $4.7 \times 10^3/\mu\text{L}$, and a platelet count of $177 \times 10^3/\mu\text{L}$. Her total bilirubin was 3.6 mg/dl, with a direct bilirubin of 1.5 mg/dl. Her serum albumin was 2.6 g/dl, ALT was 28 U/L, AST 37 U/L and her

INR was 1.25. Blood urea was 27 mg/dl and creatinine 0.6 mg/dl.

An anteroposterior chest x ray showed normal cardiac size and increased vascular markings of the lungs. Repeat echocardiography done at our institution showed normal cardiac structure, trivial tricuspid regurgitation with estimated peak RVSP 40 mmHg, and some turbulence across the RVOT into pulmonary artery. Contrast echocardiography with agitated saline demonstrated the appearance of bubbles in the left atrium after 4 beats, suggestive of intrapulmonary shunting.

Abdominal ultrasonography with Duplex study revealed hepatosplenomegaly with parenchymatous affection, enlarged portal vein (14 mm in diameter) with hepatofugal flow and an average velocity of 15cm/sec, and congested lieno-renal collaterals. There was mild ascites, chronic calculous cholecystitis and multiple portahepatis and para-aortic lymph nodes.

The patient was diagnosed as having hepatopulmonary syndrome and placed on the liver transplantation list. Unfortunately the child collapsed at home and was admitted to the nearest hospital where she was admitted to PICU but arrested with failed resuscitation.

Discussion

In 1884 Fluckiger first described a woman with liver cirrhosis, cyanosis, and digital clubbing [9]. The term 'hepatopulmonary syndrome', the triad of liver disease, an increased alveolar-arterial gradient while breathing room air, and evidence of intrapulmonary vascular dilatations, was coined in 1977 by Kennedy and Knudson [10].

Hepatopulmonary syndrome manifests clinically as progressive dyspnea, cyanosis, and clubbing in a patient with cirrhosis. The insidious onset of dyspnoea, particularly on exertion, is the most common complaint but is non-specific. Platypnoea (shortness of breath exacerbated by sitting up and improved by lying supine) is a usual symptom [11].

Our patient demonstrated marked cyanosis and clubbing which was initially confusing as she was not known to be a hepatic patient and did not report any symptoms suggestive of hepatic affection.

Ruth and Wolfe 1994 [7] reported the case of an 11-year old boy with severe liver disease that started on the 2nd day of life. He was noted to have digital clubbing at the age of 9 years and over the next 2 years he developed dyspnea and cyanosis. His oxygen saturation was 68% and he had ejection systolic murmur grade II/VI over the left midsternal border. All the reported cases describe dyspnea and cyanosis and clubbing in well known hepatic patients after years of follow up either in children or adults [12].

It is generally assumed that the mechanism of hepatopulmonary syndrome is excessive vascular production of

vasodilators, particularly nitric oxide, underlying the vasodilatation. At pathologic analysis, intrapulmonary vascular dilatations represent dilated precapillaries, direct arteriovenous communications, and dilated pleural vessels [13].

Contrast enhanced echocardiography is the preferred screening test for HPS. Differentiation between intracardiac and intrapulmonary shunting is based on the timing of when these bubbles are found in the left side chamber of the heart. In intracardiac right-to-left shunts, these bubbles appear in the left chamber of the heart within 3 heart beats of their appearance in the right chamber of the heart. In intrapulmonary shunts, these bubbles appear within 4 - 6th heartbeats [14].

Our patient demonstrated intrapulmonary shunting as evidenced by the appearance of agitated saline bubbles in the left atrium after 4 heart beats of their appearance in the right atrium during contrast echocardiography.

Since patients with advanced liver disease usually hyperventilate, hypocapnia ($\text{PaCO}_2 < 35$ mmHg) and respiratory alkalosis are common [15]. Orthodeoxia, defined as arterial deoxygenation accentuated in the upright position as opposed to the supine position is also reported [7] and this finding was present in our patient.

According to the European Respiratory Society classification system for HPS, our patient would have been classified as very severe since her O_2 saturation was 35%. Hansoti, and Sharma 1989 [16] also reported cases of similar severity in India. They reported 20 cases over a 20-year period with arterial desaturation due to liver cirrhosis that was so severe so as to simulate congenital cyanotic heart disease. They reported the predominant occurrence of this condition in a younger age group and the invariable presence of an ejection systolic murmur at the pulmonary area, which further increases the resemblance to congenital cyanotic heart disease. This systolic murmur is almost certainly due to the hyperkinetic circulation. Hepatic and splenic enlargement is usual and point to the liver pathology [16].

Our patient highlights the importance of extensive history taking and clinical examination particularly in cyanotic patients in whom extensive investigations for cardiac, pulmonary and hematological causes are repeatedly negative. Additionally, although rare, patients with unexplained cyanosis should be assessed for long standing liver disease, especially children. Finally, contrast echocardiography with agitated saline is very simple, safe and cost-effective investigation to differentiate intra and extracardiac right to left shunts in patients with cyanosis and structurally normal hearts.

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Conflict of Interest

The authors have read and approved the manuscript.

List of Abbreviations

HPS: hepatopulmonary syndrome; POPH: portopulmonary hypertension.

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