CASE REPORT

NON-CIRRHOTIC PORTAL FIBROSIS ASSOCIATED WITH PULMONARY ARTERIOVENOUS COMMUNICATION AND PULMONARY ARTERIAL HYPERTENSION

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Abstract. A case of non-cirrhotic portal fibrosis associated with pulmonary arteriovenous communication and pulmonary arterial hypertension is reported. The patient was a 7-year old boy who presented with hematemesis, cyanosis, hypoxemia and orthodeoxia. His liver pathology was compatible with non-cirrhotic portal fibrosis. His pulmonary angiography showed arteriovenous shunting and pulmonary arterial hypertension (mean pulmonary artery pressure 34 mmHg). His sister also had non-cirrhotic portal fibrosis with neither hypoxemia nor orthodeoxia. This report raises the possibility of non-cirrhotic portal fibrosis having a genetic etiology.

Non-cirrhotic portal fibrosis (NCPF) is characterized by presinusoidal portal hypertension in the absence of cirrhosis, primary hematologic disease, parasites, or occlusion of the main portal, splenic or hepatic veins (Basu *et al*, 1967; Okuda *et al*, 1984). There are other terms for this disease describing the same clinical syndrome, such as idiopathic portal hypertension, hepatoportal sclerosis and Banti's disease. This disease has been reported with a high prevalence in developing countries, such as India. However, there have also been reports from developed countries like Japan. The coexistence of portal hypertension and pulmonary arterial hypertension (PAH) has been documented based on clinical and autopsy data (McDonnell *et al*, 1983), as well as hemodynamic studies (Hadengue *et al*, 1991). The liver disease most commonly reported associated with PAH was cirrhosis. Non-cirrhotic portal hypertension such as extrahepatic portal venous obstruction, nodular regenerative hyperplasia, multiple nodular hyperplasia and schistosomiasis have been demonstrated to occur along with PAH. Likewise, the occurrence of pulmonary arteriovenous communication in non-cirrhotic portal hypertension has been shown (Castro and Krowka, 1996).

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This report aims at describing a case of NCPF with pulmonary arteriovenous communication and PAH. The patient also had a sister who was diagnosed with NCPF but without hypoxemia or orthodeoxia.

A 7-year-old boy was first seen by us in 1997. He presented with recurrent hematemesis and cyanosis having persisted for 3 years. He had a 4-year-old sister who developed hematemesis and mild hepatomegaly. Her liver biopsy showed non-cirrhotic portal fibrosis and the esophagogastroduodenoscopy revealed esophageal varices. Neither child had a past history of neonatal umbilical sepsis, malarial infection or exposure to chemicals or toxins. They lived in the same agricultural environment. His pedigree is shown in Fig 1. He was found to have hepatomegaly (span 10 cm), impalpable spleen, digital clubbing and central cyanosis. The complete blood count was Hb 14.6 gm%, Hct 45%, wbc 34,900/mm^3 (N 84%, M3%, L10%, AL 3%) platelets 208,000/mm^3. The results of the liver function test were TB 0.78 mg/dl, DB 0.16 mg/dl, AP 950 U/l, SGOT 67 U/l, SGPT 63 U/l, albumin 2.9 gm/dl, globulin 3.2 gm/dl. The prothrombin time and partial thromboplastin time were 14.1 (control 12) and 31.9 (control 40.9) seconds, respectively. His PaO_2 was 44.3 mm Hg in

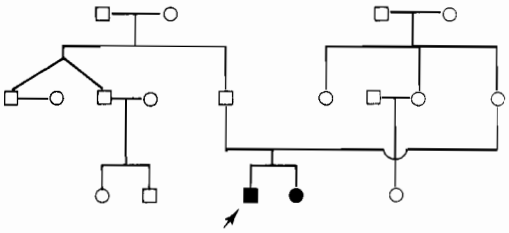

Fig 1–The pedigree of the patient.

room air and it increased to 140.5 mm Hg after providing O_2 10 l/minute via face mask with bag (26% shunt). He also had orthodeoxia.

The echocardiogram was normal. The ultrasonography and Doppler study of the upper abdomen revealed diffusely increased parenchymal echo of the liver without space taking lesion, normal direction and spectral wave form of the portal vein, hepatic artery, splenic vein, and superior mesenteric artery. The CT scan of the chest showed diffuse interstitial thickening and prominent pulmonary vessels of both lungs (Fig 2). The pulmonary angiogram demonstrated a mean main pulmonary artery pressure of 34 mm Hg, no capillary phase between arterial and venous phase. The celiac and superior mesenteric angiogram showed no A-V shunting, patent portal and splenic vein with normal caliber, no collateral vessels. The liver pathology showed non-cirrhotic liver tissue with dilated sinusoids and mild portal fibrosis (Fig 3).

Non-cirrhotic portal fibrosis has mostly been reported from India, the mean age of patients varied from 25-35 years (Sarin, 1989). The etiology of NCPF remains poorly understood. Some reports relate this disease to chronic exposure to arsenic or vinyl chloride (Morris *et al*, 1974; Thomas *et al*, 1975). Intra-abdominal infections or infections affecting the portal venous system might correlate with this disease based on the experimental portal fibrosis induced by intraportal bacterial injection in animal models (Kono *et al*, 1983). There was one report of NCPF following neonatal infection by cytomegalovirus where this patient, the youngest to date, presented with hematomesis at the age of 16 months (Dresler and Linder, 1978). Sarin *et al* (1987) suggested a genetic background of NCPF. He found four families with more than one member afflicted with this disease and of those, six out of seven (85.5%) were HLA-DR 3 positive. Our patient and his sister presented with ruptured esophageal varices at a much younger age (4 years)

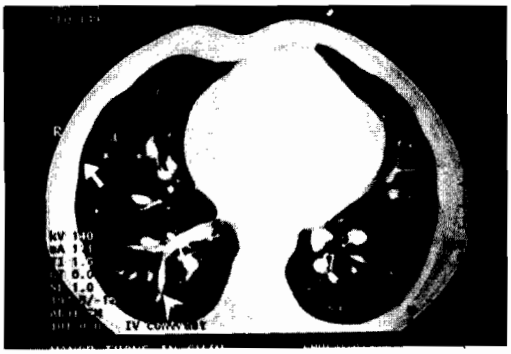

Fig 2–High resolution CT scan (lung window) revealed dilated lung vessels extending to pleura (arrow) and an abnormally large number of visible terminal branches (arrowhead).

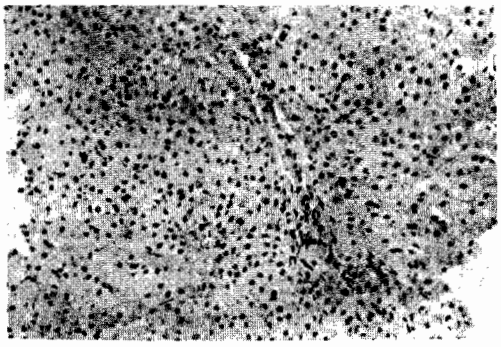

Fig 3–Mild portal fibrosis was seen. No histologic evidence of cirrhosis was present. (Hematoxylin and eosin stain, × 400).

than those reported in the world literature. He also had pulmonary hypertension and hepatopulmonary syndrome. The hepatopulmonary syndrome was first suggested by Kennedy and Knudson (1977). This syndrome consists of a triad comprising liver dysfunction, intrapulmonary vascular dilatation and hypoxemia (Krowka and Cortese, 1994). The angiographic pattern of hepa-topulmonary syndrome type I is rather diffuse, whereas that of type II shows focal involvement (Castro and Krowka, 1996). Pulmonary angiography of our patient resembled the minimal type I pattern which ranges from normal to a finely diffuse spidery vascular abnormality on the arterial phase. In contrast, the advanced type I pattern shows a diffuse, spongy or blotchy appearance and the type II pattern reveals focal arteriovenous malformation. Our patient also had pulmonary hypertension which is defined as a rest-

ing mean pulmonary artery pressure of more than 25 mm Hg (Mandell and Groves, 1996). Very few cases of non-cirrhotic portal fibrosis associated with pulmonary AV fistulae or PAH have been reported in the literature (Amarapurkar *et al*, 1989; Goenka *et al*, 1992; Kothari *et al*, 1992).

The mechanisms of hypoxemia in hepatopulmonary syndrome have been the subject of ongoing intense investigation. Intrapulmonary vascular dilatations are proposed to be the major cause of severe hypoxemia in this syndrome (Krowka and Cortese, 1990). The oxygen molecules from adjacent alveoli cannot diffuse to the center of the dilated vessels to oxygenate the midstream erythrocytes of the venous blood, thus leading to the condition of so-called diffusion-perfusion impairment or alveolar-capillary oxygen disequilibrium. Other debated mechanisms of hypoxemia in this syndrome include a displacement of the oxygen-hemoglobin dissociation curve to the right which is caused by increased intracellular 2,3-diphosphoglycerate (Keys and Snell, 1983), intrapulmonary (Rydell and Hoffbauer, 1956) and portopulmonary shunt (Krowka and Cortese, 1994). Many hypotheses have been proposed to explain the mechanisms of intrapulmonary vascular dilatations such as an imbalance between pulmonary vasodilators and vasoconstrictors, abnormal sensitivity of the pulmonary vascular bed to a vasodilatory factor, and angiodysplasia. There have been studies suggesting that nitric oxide contributes to the vasodilatation in hepatopulmonary syndrome (Whittle and Moncada, 1992).

The cause of pulmonary hypertension in patients with portal hypertension is still unknown. Previous authors postulated that thromboembolies, arising in the portal system, might reach the pulmonary arteries via portopulmonary anastomosis (Senior *et al*, 1968). This hypothesis was not confirmed by histopathology since the pulmonary hypertension in patients with portal hypertension was rather due to pulmonary arteriopathy with plexiform lesions than to thrombotic pulmonary arteriopathy (Schraufnagel and Kay, 1996). The second hypothesis was high cardiac output with hemodynamic disturbance in portal hypertension leading to increased pulmonary blood flow and thus to pulmonary hypertension (Boot *et al*, 1987). Recent prospective studies failed to correlate collateral flow with pulmonary pressure (Hadengue *et al*, 1991). The third one suggested that vasoactive agents from the portal vein having escaped hepatic metabolism entered the pulmonary circulation through the collateral flow, resulting in vasoconstriction (Levine *et al*, 1973).

In conclusion, the presence of pulmonary arteriovenous communication and pulmonary arterial hypertension in this patient confirms portal hypertension rather than cirrhosis in particular as the prerequisite for the development of these pulmonary conditions. This observation also suggests a possible genetic etiology of NCPF.

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