

Plexogenic pulmonary arteriopathy and liver cirrhosis

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ABSTRACT Primary pulmonary hypertension with plexiform vascular changes in the lungs and liver cirrhosis is a rare combination of unclear pathogenesis. Until now, the real prevalence has not been known. The diagnosis of this association is usually made retrospectively. The criteria are morphological—that is, right ventricular hypertrophy and the characteristic pulmonary arterial lesions, as well as clinical—based on ECG and chest radiography. Between 1970 and 1977, two such cases have been found among a total of 11 998 necropsies performed on adults. In the same necropsy series, 765 cases of liver cirrhosis were found. The prevalence of this combination is 0.26% of the cirrhosis and 0.016% of all necropsies of adults. This low prevalence raises serious doubts as to whether the association is more than coincidental.

There has been a growing interest in recent years in discovering non-haemodynamic causes of pulmonary hypertension. Of particular interest is the possibility that vasoactive agents may bypass the liver and damage the pulmonary vasculature.¹ Although the association between chronic liver injury and pulmonary hypertension has been known for the past 30 years,² there are no data to indicate whether this association is real or coincidental.

Since the epidemic of pulmonary hypertension in Switzerland, Austria, and Germany,³ we have paid particular attention to the occurrence of unexplained right ventricular hypertrophy and plexogenic pulmonary arteriopathy. We report here on the association between cor pulmonale, plexogenic arteriopathy, and liver cirrhosis in a large unselected series of necropsies, in order to provide the basis for future clinico-epidemiological studies on the pathogenesis of primary pulmonary hypertension.

Methods

Among 11 998 necropsies of adults (older than 20 years) performed between 1970 and 1977 at the Institute of Pathology of the University Hospital of Zurich (95% of all hospital deaths), there were

765 cases of liver cirrhosis (6.3%). Two of these cases were associated with unexplained cor pulmonale and pulmonary plexiform arteriopathy.

Until 1975, right ventricular hypertrophy was diagnosed on the basis of macroscopic evaluation and measurement of myocardial thickness.⁴ Since 1975, the diagnosis has been made by calculating the ratio of the weight of the left ventricle and septum to that of the right ventricle⁵; a ratio of 2 or less is diagnostic of cor pulmonale.

Plexogenic pulmonary arteriopathy was characterised histologically by focal dilatation of muscular pulmonary arteries, 100–200 μ m in diameter, proliferation of endothelial cells with formation of anastomosing channels inside the vascular lumen, and concentric intimal fibrosis.^{6–8}

Case reports

CASE 1

A 65-year-old man with a history of chronic alcoholism (one litre of wine a day) and decompensated liver cirrhosis was admitted to hospital with jaundice. He died a few days later because of massive gastrointestinal bleeding.

Necropsy (AZ 97–71)

Macroscopic examination revealed hepatic cirrhosis with small and large nodules (1550 g), oesophageal varices, erosive gastritis with massive

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haemorrhage, jaundice, right ventricular hypertrophy (heart weight: 450 g), and focal bronchopneumonia.

Microscopically, the diagnosis of nodular cirrhosis with proliferation of bile ducts was confirmed. The most striking findings were in the pulmonary vessels. They consisted of two types of lesions: (1) muscular medial hypertrophy of the small arteries and concentric intimal thickening; (2) plexiform lesions (2–3 per cm²). No thromboembolism was identified in the lung.

CASE 2

A 62-year-old man was admitted to hospital because of liver cirrhosis, oesophageal bleeding, and ascites. He had a history of heavy alcohol intake, but no history of drug ingestion. Seven years before admission, he underwent splenectomy and cholecystectomy for hypersplenism. A liver biopsy (HZ 17577–70) at that time revealed annular cirrhosis with fatty changes and siderosis. At the time of admission, a chest radiograph showed two 2 cm round nodules in the left lung, cardiac enlargement and increased hilar markings.

Electrocardiogram revealed right ventricular hypertrophy and right bundle block. Laboratory findings disclosed pronounced anaemia, thrombocytopenia, raised LDH, and a positive serum α -fetoprotein. The patient died three weeks later. The clinical diagnosis was metastatic hepatoma and cor pulmonale. Heart catheterisation studies had not been performed.

Necropsy (AZ 660–77)

There was a large, partially necrotic tumour, 17 cm in diameter, in the left lobe of a cirrhotic liver, with invasion of the portal vein and metastases in the right hepatic lobe. There were haemorrhagic ascites (four litres), jaundice, and oesophageal varices with gastrointestinal haemorrhage. The heart weighed 540 g. There was marked right ventricular hypertrophy. The weight ratio between left and right ventricles was 1.4. Metastases were found in the lung.

Microscopic sections of the liver revealed hepatocellular carcinoma and cirrhosis. Sections of the lung demonstrated in the small pulmonary arteries below 200 μ m all types of hypertensive changes, from muscular medial hypertrophy to intimal fibrosis, as well as plexiform lesions (fig). In some instances, tumour emboli were present. However, the plexogenic pulmonary arteriopathic changes were four times as frequent as the emboli.

Discussion

Plexiform pulmonary arteriopathy has been considered the hallmark of primary pulmonary hypertension.⁹ Although very characteristic for primary pulmonary hypertension, these anatomical changes are not pathognomonic and have been observed in pulmonary hypertension of known causes such as congenital cardiac left-right shunts, lung sequestration with arterial supply from the aorta, and schistosomiasis. The association of

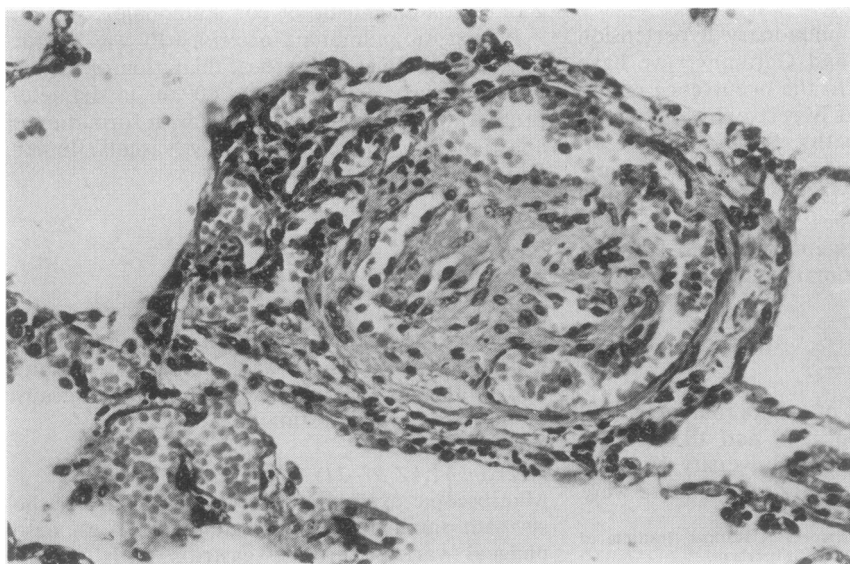


Figure Small pulmonary artery with plexiform lesions in case 2 ($\times 250$).

plexiform lesions and cirrhosis of the liver is often cited in papers dealing with primary pulmonary hypertension.^{10,11} The few pathological reports^{7,12-15} do not give the incidence of this association. In 50 cases of cirrhosis studied in Liverpool, however, no pulmonary hypertension was found.¹⁶ Plexiform lesions may occur in patients with portal hypertension from portal thrombosis only, without concomitant cirrhosis.¹⁷

In our large necropsy series, only two cases of plexiform pulmonary arterial changes and right ventricular hypertrophy were found among 765 cases of liver cirrhosis (a prevalence of 0.26%). In the same series, nine cases of plexiform pulmonary arteriopathy and cor pulmonale were observed. In eight cases, the disease was associated with the intake of an appetite-reducing drug. All nine patients with cryptogenic or drug-associated plexogenic arteriopathy were women (between 37 and 78 years).

In contrast, both cases of liver cirrhosis and pulmonary plexogenic arteriopathy were men (over 60 years). Both patients were alcoholics, had pronounced portal hypertension with oesophageal and gastric haemorrhage, and jaundice. In both cases, right ventricular hypertrophy was found at necropsy; in one, it was diagnosed before death. The plexiform lesions were not easily missed, since they were found in multiple areas of the lungs and did not differ from those encountered in congenital cardiac shunts.⁶ Signs of recurrent pulmonary thromboembolism were not present. The tumour emboli in case 2 were recent and represented terminal events; they could have accounted for the cardiac hypertrophy.

The mechanism of pulmonary hypertension associated with liver cirrhosis is poorly understood. Various pathogenic processes have been invoked. Naeye¹² suggested that, in most of the cases, the changes in the pulmonary vascular bed were the result of thromboemboli arising from the portal vein. Porta-pulmonary anastomoses have been demonstrated by Calabresi and Abelman¹⁸ through perigastric, perioesophageal, and mediastinal veins penetrating the pleura and draining lung capillaries, thus permitting microemboli to enter the lung. However, this does not explain the development of plexiform lesions in patients with liver cirrhosis but without portal thrombosis. Even in Naeye's material,¹² portal thromboses were found in three cases only. Moreover, thromboemboli in pulmonary arteries can be distinguished microscopically from plexiform lesions.⁷

Haemodynamic disturbances, such as increased cardiac output and pulmonary blood flow in cirr-

hosis, have been suggested but not proved as sufficient pathogenic factors.^{16,17} Lunseth *et al*¹⁹ demonstrated the lack of relationship between the severity of cirrhosis and the tendency to develop cor pulmonale in animal experiments as well as in humans. It was therefore suggested that the portal hypertension, rather than the cirrhosis *per se*, is of importance.¹⁷

In accordance with the experience in primary pulmonary hypertension, vasoconstriction of the small pulmonary arteries has been considered to be the initiating cause of pulmonary hypertension in liver cirrhosis. Wagenvoort and Wagenvoort^{7,20} believe that vasoconstriction leads to local endothelial lesions followed by thrombosis and finally organisation of the thrombi, which in turn lead to plexiform lesions. In this respect, dietary factors may be of importance. Metabolites escaping hepatic inactivation caused by cirrhosis may be responsible for the changes in lung vessels.¹⁷ Fishman¹ favours the theory that plexiform lesions are the result of extreme bursts of pulmonary arterial hypertension, possibly induced by attacks of metabolically induced vasoconstriction.

Another mechanism is the possible effect of ingested substances normally inactivated by the liver. Pulmonary hypertension has been produced experimentally by feeding or injecting pyrrolizidine alkaloids.²¹⁻²⁵ Whether genetic influences contribute to acquiring pulmonary hypertension in liver cirrhosis remains open. In children, our necropsy material over the last eight years has not shown any association between cirrhosis and pulmonary hypertension.

It is evident from our study that the combination of liver cirrhosis and pulmonary hypertension is exceptionally rare. It is, therefore, too early to exclude a coincidental association. Prospective clinicopathological investigations may prove helpful in elucidating this unsolved problem.

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