Noncirrhotic portal fibrosis: a rare cause of end-stage liver disease requiring liver transplantation

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Non-cirrhotic portal fibrosis (NCPF) is a disease of uncertain etiology characterized by periportal fibrosis and involvement of small and medium branches of the portal vein, resulting in the development of portal hypertension [1]. This has been reported from different parts of the world under a variety of names, such as idiopathic portal hypertension, hepatoportal sclerosis, and noncirrhotic intrahepatic portal hypertension, etc. In India, NCPF formed an important group of patients with portal hypertension, and accounted for 15–30% of all such patients in early nineties [2]. However, its incidence has considerably decreased over time and it is now believed to be a vanishing disease in the subcontinent [1]. Improvement in sanitary conditions and decrease in bacterial infections has lead to a decline in the incidence of the disease. Similar drop in the incidence of new cases has been reported from Japan and other countries [1, 3].

How NCPF differs from cirrhosis of liver has generated immense interest over the years, although at times it may not be possible to differentiate NCPF from Child A cirrhosis of liver. Majority of these patients present with features of portal hypertension and well-tolerated variceal bleeding and have good long-term prognosis [1, 4]. A long-term follow-up study of 59 patients with noncirrhotic intrahepatic portal hypertension in one hospital over 30-year period showed a 5-year survival of 90% and a 30-year survival of 55% [5]. However, a small proportion of patients do behave like end-stage liver disease and develop features of decompensation

in the form of ascites, jaundice and hepatic encephalopathy. This subgroup of NCPF with bad liver functions has been recognized and constitutes <10% of the patients, who have mild jaundice, mild ascites and low serum albumin [4, 6]. Nodular transformation of the liver with extensive subhepatic and portal fibrosis has been reported in these patients and the condition constitutes a late manifestation of NCPF. Incomplete septal cirrhosis and nodular regenerative hyperplasia may also be associated with NCPF or idiopathic portal hypertension and may be the late manifestation of this disorder [7–10]. These severe histological changes and abnormal liver function have been infrequently reported and require longer follow-up studies to look into this aspect.

There are no large studies that have looked at the subgroup of patients who undergo decompensation; however, in some patients with NCPH, the complications of portal hypertension are sufficiently severe to warrant liver transplantation [7, 11–16]. The study in this issue of *Hepatology International* shows that small fraction of patients (~5%) do develop ascites, jaundice, and hepatic encephalopathy making it difficult to differentiate it from cirrhosis of liver [17]. Another interesting observation of this study is the overlap NCPF group which has features of both NCPF and cirrhosis and was not reported earlier. This was seen in ten patients in which cause of chronic liver disease was hepatitis C in five, hepatitis B in one and nonalcoholic fatty liver disease (NAFLD) in four patients. All ten patients in this group had characteristic portal vein changes. This may be in continuum with the spectrum of NCPF not defined earlier due to absence of serological markers of hepatitis B and C and recent identification of NAFLD as a cause of significant liver disease; although nodular regenerative hyperplasia and incomplete septal cirrhosis have been reported earlier. The existence of two diseases in a single

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patient may portend a poor prognosis as progression to end-stage liver disease may be faster.

Pathologically, NCPF is characterized by small portal vein obliteration, aberrant vasculature, portal tract fibrosis which is rounded or streak and absence of significant hepatocellular injury and formation of regenerative nodules characteristic of cirrhosis [1]. This paper emphasizes the classical histopathological findings of NCPF with all ten patients showing obliterative portal venopathy and portal to portal fibrosis. Irregular coarse granularity and small nodules on the surface were seen in eight and seven patients respectively differentiating NCPF from cirrhosis of liver. In overlap NCPF the existence of two diseases has not been described earlier, this study gives insight into the probable different pathogenic mechanisms and coexistence of the two diseases with different pathological findings.

How does NCPF progresses to end-stage liver disease and liver failure is not known, although it has been postulated that as time progresses these patients develop progressive atrophy of liver owing to reduced blood supply to the periphery and subsequent manifestations of liver dysfunction [1].

This study has clearly demonstrated that the diagnosis of NCPF can easily be missed prior to the liver transplant and has had a pre-transplant diagnosis of cirrhosis of unknown or some known etiology. How could a pretransplant diagnosis of NCPF be arrived? NCPF should be suspected in cases of chronic liver disease with negative etiological work up, relatively preserved liver functions and a low MELD score. In this study seven objective and two subjective parameters showed significant differences between pure NCPF and NAFLD control groups, however, as proposed by the authors need further prospective validation. Should all patients with suspected NCPF or cryptogenic cirrhosis posted for liver transplantation subjected to liver biopsy? The biopsy in NCPF may be patchy and inconclusive as seen from explants liver histopathology. The hemodynamic changes in NCPF also differ from cirrhotics and demonstrate markedly elevated intrasplenic and portal vein pressures while the hepatic venous pressure gradient may be normal or slightly elevated because the site of resistance is predominantly presinusoidal [1]. The routine use of hepatic venous pressure gradient for differentiation of NCPF from cirrhosis is still underutilized and may prove to be a useful tool to differentiate sinusoidal from non-cirrhotic portal hypertension in this setting.

The indication for liver transplantation in NCPF still remains to be defined as no definite guidelines exist. MELD which is the strongest predictor of prognosis and post-transplant outcome and may not be applicable for organ allocation in NCPF due to fairly well preserved liver functions as seen in this study with all patients having low MELD scores and preserved liver functions. In this

situation, the indication for transplant is primarily based on complications of portal hypertension. The use of a new terminology of overlap NCPF as an indication for liver transplantation in this paper is clinically not relevant since it is a histopathological diagnosis and explant liver histology with careful examination is required.

The post-transplant outcome of the patients with NCPF is good and not different from other end-stage liver disease patients of different etiologies [18]. Recurrence of disease post-transplantation would not be an intriguing issue since it is a slowly progressive disease.

In summary, this study highlights NCPF as a rare cause of end-stage liver disease requiring liver transplantation. It does raise the interesting issue of chronic liver disease of other etiology, may supervene on preexistent NCPF and might have faster progression to end-stage liver disease. The diagnosis of NCPF can be easily missed prior to transplant and may become apparent only when explants liver is carefully examined. NCPF is a great mimicker of cirrhosis clinically and radiologically.

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