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Letter to the Editor

Liver disease in cystic fibrosis presents as non-cirrhotic portal hypertension☆,☆☆

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Cystic fibrosis-related liver disease (CFLD) is allegedly caused by small bile duct obstruction leading to focal biliary fibrosis and eventually to cirrhosis with portal hypertension (PHT). However, CFLD patients typically present with PHT, without cholestasis and with preserved liver function. End-stage liver disease is exceptional. We previously suggested that CFLD-related PHT could be a vascular disease, more specifically non-cirrhotic PHT (NCPH) [1]. Indeed, other groups have also reported that cirrhosis is present in only 27% of patients with PHT, even when performing dual pass biopsies [2].

In the present work, we studied 8 patients with CFLD and PHT in detail. In 4 patients we performed transjugular hepatic venous portal gradient (HVPG) measurements and biopsies. Furthermore, we studied 5 CFLD explant livers. Details on the materials and methods: see online Supplementary materials.

In the 4 patients with HVPG measurements, PHT was diagnosed because of esophageal varices (with bleeding in 2 patients), splenomegaly, abdominal venous collaterals and/or ascites. None had hepatic encephalopathy and Model for End-Stage Liver Disease (MELD) scores were low (range 6–9), confirming the preserved liver function. All had normal bilirubin levels. In all 4 patients, HVPG was 4–9 mm Hg, clearly below the cut-off for clinically significant PHT. In the absence of a portal vein thrombosis, such low HVPG can only be explained by a presinusoidal type of portal hypertension [3]. On histology, none of them had cirrhosis, while vascular changes were found (Fig. 1; detailed results in online Supplementary Table 1). All of the above findings constitute NCPH [3,4].

Explant livers of 5 patients with PHT (MELD range 7–12) did not reveal cirrhosis either, only mild to moderate fibrosis (F2–F3) or incomplete septal cirrhosis (n = 2) (Fig. 1). The same vascular

Abbreviations: CF, cystic fibrosis; CFLD, cystic fibrosis-related liver disease; PHT, portal hypertension; NCPH, noncirrhotic portal hypertension; NRH, nodular regenerative hyperplasia; HVPG, hepatic venous pressure gradient.

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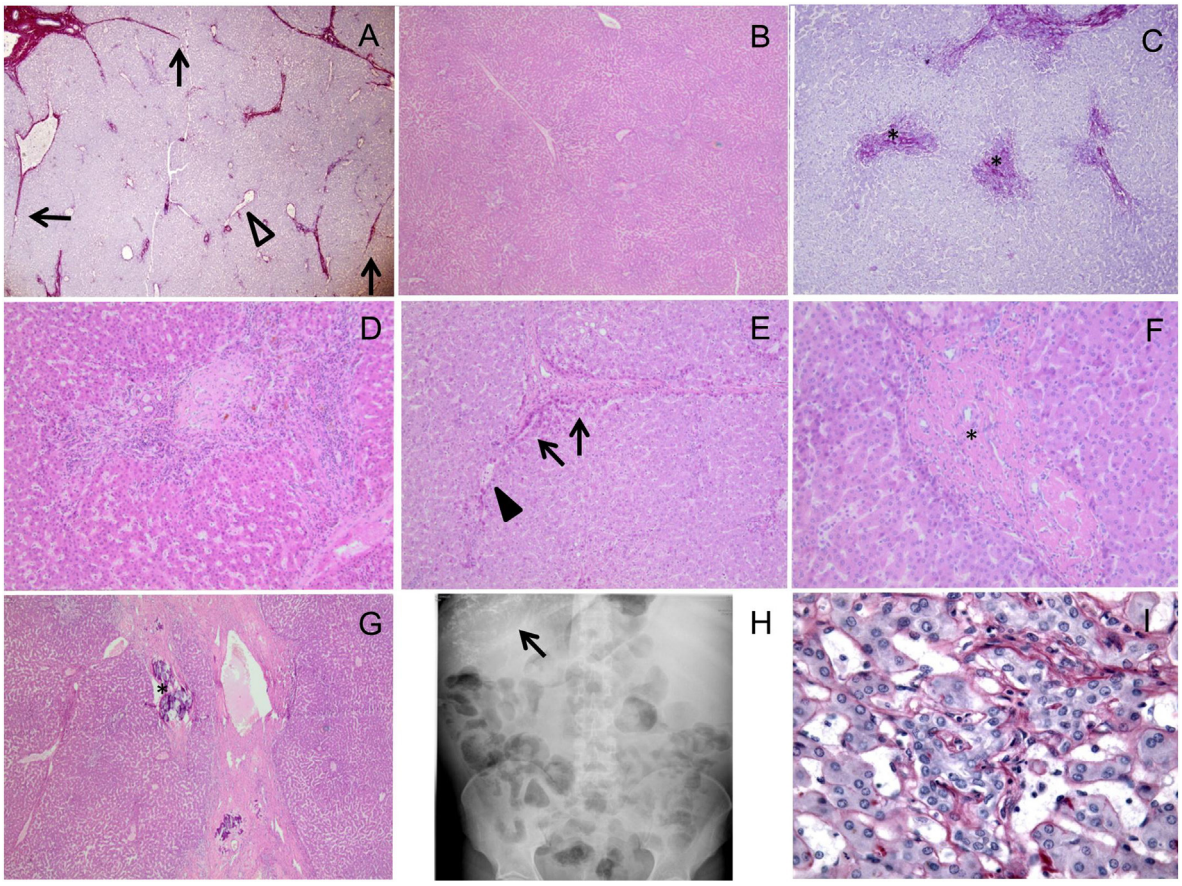

Fig. 1. A (patient TX2, Sirius Red stain (SR), Original magnification 40X) In two patients there was incomplete septal cirrhosis with slender blind ending septae extending into the liver parenchyma (arrows). Also note the paraportal shunt vessels (arrowhead). B (TX4, Hematoxylin and Eosin Stain (HE), 40X) Centrolobular sinusoidal dilatation giving rise to nodule formation in the liver. C (TX3, SR, 40X) The most common finding was absence of portal vein branches as seen in this posttransplant specimen of a patient with F3 fibrosis. There are no discernable portal vein branches in the portal tracts (asterix). D (TX5, HE, 100X) portal tracts with classical changes and neutrophilic infiltrate. There are no discernible portal vein branches. In some portal tracts there was a (compensatory) dilatation of the portal vein. E (TX2, HE, 100X) Portal tract with multiple small venous structures extending in the liver parenchyma (arrow) and the formation of a paraportal shunt vessel (arrowhead). F (TX4, HE, 200X) A prevalent feature was sclerosing of the portal vein branches. Portal tract with sclerosis of the portal vein with dense fibrogeneous material, no lumen can be seen (asterix). G (TX4, HE, 100X) In three patients there were calcifications. Calcification within the fibrogeneous material in the portal vein branch (asterix). H In two patients these were also visible on abdominal X-ray (arrows). tracts I (TX4, SR, 200X) In three patient who underwent a combined lung liver transplantation a centrolubular ductular reaction was seen with CK7 positivity of hepatocytes not in vicinity of the portal centrolobular pericellular fibrosis with ductular metaplasia.

changes as seen in the biopsies were present. Obliterative venopathy with dense fibrosis within portal vein branches or the disappearance of portal vein branches was evident in all tissue samples (Fig. 1; detailed results in online Supplementary Table 1). In three patients, calcifications in the larger portal vein branches were present. They were also visible on abdominal imaging (Fig. 1). This obliterative venopathy can indeed be held accountable for the PHT, as is typically seen in NCPH [4].

In our patient cohort, both haemodynamic (HVPG) measurements and histological findings are identical to those in NCPH. Hence, in at least a subset of CFLD patients, CFLD-related PHT is not due to the paradigmal "biliary" cirrhosis but corresponds to vascular damage as in NCPH. Although PHT clearly precedes the development of cirrhosis and end-stage liver failure in our patients, which percentage of PHT patients will go on to develop cirrhosis remains to be determined.

The underlying pathogenesis of NCPH and CFLD remains to be elucidated. Recently, an association between gut inflammation and CFLD has been demonstrated [5] and this could contribute to the development of NCPH [3].

These observations may have important consequences for the management of CFLD. The efficacy of ursodeoxycholic acid as treatment of CF-related "cholestasis" has been questioned repeatedly, and indeed may target the wrong pathophysiological mechanism. For more advanced stages of CFLD, porto-systemic shunting procedures to alleviate the PHT, might be preferable over transplantation given the absence of cirrhosis and the preserved liver function, similar to the situation in NCPH. The data presented here open new avenues for research into new therapies which are desperately needed.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2017.03.006.

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