Obliterative Portal Venopathy is the Predominant Pathway of Liver Disease in Adult Cystic Fibrosis:
Retrospective Data from the Irish National Liver Transplant Unit

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INTRODUCTION

- Cystic fibrosis associated liver disease (CFLD) is the third most frequent cause of cystic fibrosis (CF) mortality[1], with an incidence of 32.2% by age 25[2], and represents 2-3% of CF mortality overall[3].
- It has long been held that CFLD arose in the setting of obstructive biliary disease due to abnormally thickened bile[4] resulting in cholestatic liver disease including biliary cirrhosis, similar to that seen in primary sclerosing cholangitis (PSC) or primary biliary cirrhosis (PBC), with portal hypertension (PHT) occurring as a late consequence of cirrhosis.
- The finding of absent cholestasis and early development of PHT in CFLD[5] raises the possibility of an alternative pathogenic pathway related to portal venopathy[6-9]. Histological correlates of resulting noncirrhotic presinusoidal portal hypertension (NCPH) include periportal shunt vessels, nodular regenerative hyperplasia (NRH), and portal branch obliterative venopathy (OPV) (absent, thickened or thrombosed portal veins)[6-10].
- Porto-sinusoidal vascular disease (PSVD) has been recently proposed as a histologically defined term encompassing NCPH, OPV and NRH without the need for PHT[11].

AIMS

- Evaluate the histological features of orthotopic liver transplant (OLT) explant specimens performed for CFLD in the Irish National Liver Transplantation Centre with clinical correlation and controlled against known cases of biliary cirrhosis (PBC and PSC).

METHODS

- The laboratory information system in St Vincent's University Hospital Department (SVUH) of Histopathology was interrogated for patients undergoing OLT for CFLD between 1993 and 2020 (n = 9) and recent OLT explant cases of PSC and PBC.
- Clinical data of liver function at time of transplant for above cases and controls were collected from the SVUH clinical record.
- Gross morphology for cases and controls was reviewed where available.
- Histological material was retrieved from archival storage and the following stains were examined in all cases: haematoxylin and eosin (H&E), CD31, ERG, CK7, shikata-orcein, reticulin, masson-trichrome and elastic-van-giesson.
- 15mm^2 areas of non-lesional liver were selected for total portal vein branch counts in both cases and controls. Counts on H&E sections were performed by JO'N and reviewed by NN.

RESULTS

Complete histological cirrhosis was not identified in any of the CF explants. There were significantly fewer portal venous branches identified in the CF patients compared to the biliary cirrhosis controls (mean/15mm^2 45.78 vs 81.90, p = 0.01523).

Morphological Marker	CFLD Cases (n = 9)	Biliary Cirrhosis Controls (n = 10, PSC = 7, PBC = 3)
Complete histological cirrhosis	0%	70%
Sclerotic portal tract nodules	100%	0%
Thrombosed portal vein branches	67%	40%
Paraportal shunt vessels	56%	10%
Nodular regenerative hyperplasia (NRH)	89%	0%
Copper associated protein (CAP)	75%	100%
Marginal ductular reaction	100%	100%
Phenotypic change	78%	100%
Clinical Marker	**CFLD Cases (n = 9)**	**Biliary Cirrhosis Controls (n = 10, PSC = 7, PBC = 3)**
Median age at transplantation	21 yr (range 16-30)	56yr (range 20-66)
Median MELD score at transplantation	16 (range 8-27)	11.5 (range 6-34)
Median bilirubin (µmol/L) at transplantation	49 (range 15-235)	37 (range 5-775)
Radiological splenomegaly (% of cases)	100%	90%
Radiological cirrhosis (% of cases)	100%	80%
Endoscopic upper GI varices (% of cases)	83% (n = 6)	86% (n = 7)
Ascites (% of cases)	67%	50%

Table 1 – Comparison of histomorphological and clinical markers between CFLD cases and biliary cirrhosis controls. Histological markers of portal venopathy/NCPH (NRH, shunt vessels, thrombosed PVBs) are compared to markers of cholestasis (CAP, ductular reaction and phenotypic change).

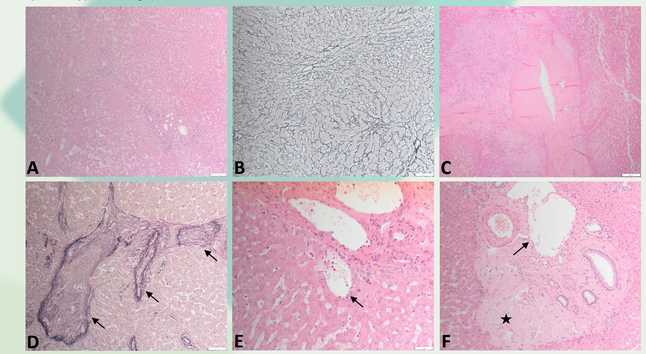

Figure 2 – Histological markers of noncirrhotic portal hypertension (NCPH) and portal branch venopathy in CFLD explants. (A&B) Nodular regenerative hyperplasia indicated by alternating compression and expansion of hepatic sinusoids, best appreciated on reticulin staining (B). (C) Phlebosclerosis with marked mural thickening of portal vein (centre). (D) Thrombosed portal vein branches (arrows) with elastic van giesson stain highlighting mural elastin. The largest branch shows recanalization. (E) Paraportal shunt vessel (arrow). (F)-Portal tract showing both portal vein dilation (arrow) of >3X bile duct size and a portal tract nodule (star)

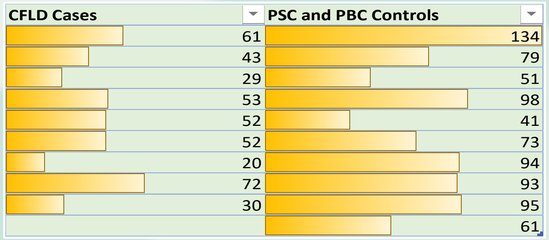

Table 2 – Portal venous branch counts per 15mm^2, each case and control. The numbers of portal veins in CF cases (M = 45.78, SD = 16.78, n = 9) were hypothesised to be less than portal vein numbers in controls (M = 81.90, SD = 27.01, n = 10). This difference was significant, t (17) = 1.73, **p = 0.001523** (1 tail).

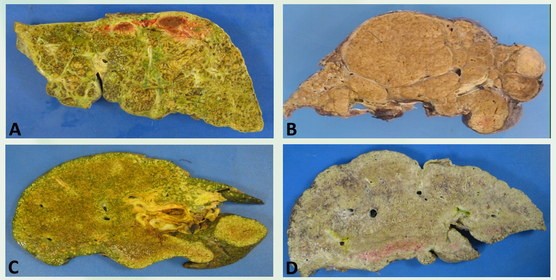

Figure 1 – Comparison of gross morphology of CFLD (A, B) with PSC (C) and PBC (D) explants. CFLD explants show coarse nodularity with thick fibrous bands encompassing regenerative parenchyma without cirrhotic nodules. PSC and PBC explants show fine nodularity with well established cirrhotic nodules.

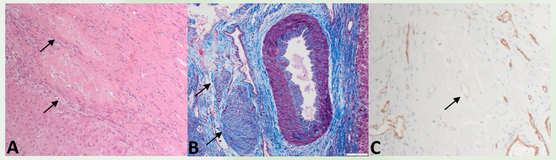

Figure 3 – Portal based hyaline sclerotic nodules. All CFLD explants showed portal-based nodules (A&B arrows) with a homogenous appearance on H&E (A), often without nearby portal vein branches (A&B). Dense sclerosis is highlighted on special histochemical stains, masson trichrome shown here (B). Residual vascular lumen within a nodule identified on CD31 immunohistochemistry (C).

DISCUSSION

- This is the first study examining the clinicopathological features of CFLD controlled against cases of known biliary cirrhosis.
- Our findings support OPV as playing a central pathogenic role in CFLD. NRH (Fig 2A&B) is strongly associated with portal venopathy[10] and was a common (89%) feature in CFLD cases and absent in controls. Importantly, a significant (p = 0.0015) reduction in portal vein branches when compared to controls was identified (Table 2) (Fig 3A&B), in keeping with OPV. Other associations with OPV: paraportal shunt vessels (Fig 2E) and thrombosed portal vein branches (Fig 2D), were more common in CFLD cases (Table 1).
- CFLD explant cases showed a differing quality of fibrosis compared to biliary cirrhosis controls. CFLD cases showed coarse nodularity associated with thick fibrous bands imparting a regenerative appearance without discrete cirrhotic nodules (Fig 1A&B). Controls showed typical features of biliary cirrhosis with defined cirrhotic nodules (Fig 1C&D). We believe this differing CFLD morphology reflects nodular regeneration secondary to blood inflow alteration (OPV and PHT) in NCPH.
- Portal hyaline sclerotic nodules (Fig 2F and Fig 3A-C) were universally associated with CFLD, and absent in controls. These rounded or linear areas are best appreciated on H&E, shikata orcein and masson trichrome stains (Fig 3B). We suspect this morphology to be a marker of CFLD and postulate they represent scars of obliterated portal vein branches, i.e. extreme phlebosclerosis[12](Fig 2C). Indeed, a residual endothelial lining was identified within one such nodule (Fig 3C).
- Clinical markers of PHT (ascites, varices, splenomegaly) were equally frequent in cases and controls, reflecting common endpoints of advanced liver disease prior to transplantation. Importantly, these PHT markers were very common in CFLD cases in the absence of histological cirrhosis, in keeping with NCPH.
- In contrast to other studies[9], features of biliary obstruction (CAP, marginal ductular reaction, phenotypic change, biliary concretions) were present in CFLD cases, albeit less pronounced than in controls, and again likely represent end stage changes prior to transplantation.

CONCLUSION

- The presence of an NCPH/OPV pathway in CFLD has important clinical consequences with the possibility of effective early portosystemic shunting, in addition to explaining the lack evidence for efficacy of ursodeoxycholic acid therapy in CFLD[2].
- Further study is required to elucidate pathological changes at an earlier stage in the disease course to eliminate confounders present in end stage disease.

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