JGH Open An open access journal of gastroenterology and hepatology Open Access

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12795

ORIGINAL ARTICLE

Identification and clinical significance of nodular regenerative hyperplasia in primary sclerosing cholangitis

Nazli Begum Ozturk, M.D.,* Maria Isabel Fiel, M.D.† and Thomas D. Schiano, M.D.*

*Division of Liver Diseases and Recanati-Miller Transplantation Institute and †Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Key words
nodular regenerative hyperplasia, obliterative portal venopathy, portal hypertension, primary sclerosing cholangitis.

Accepted for publication 4 July 2022.

Correspondence
Dr Thomas D Schiano, Division of Liver Diseases and Recanati-Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
Email: thomas.schiano@mountsinai.org

Declaration of conflict of interest: None.

Abstract

Background and Aim: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts. PSC is frequently associated with inflammatory bowel disease (IBD). Nodular regenerative hyperplasia (NRH) can occur in IBD with the use or even in the absence of thiopurine treatment. We aimed to study the significance of the presence of NRH and obliterative portal venopathy (OPV), both causes of non-cirrhotic portal hypertension (NCPH), in patients having PSC.

Methods: Patients with PSC and concurrent NRH on liver biopsy were identified from the digital pathology database covering the period 2003–2019. Evaluation of liver biopsy and the original diagnoses were confirmed on review based on standard histological features diagnostic for NRH and OPV. Clinical and laboratory data were obtained from electronic medical records.

Results: Thirty-one patients (21 male, 10 female; median age at biopsy 40.1 years) were included in the study. Twelve (38.7%) patients had OPV in addition to NRH on the liver biopsy. Nineteen (61.2%) patients had IBD including 11 with Crohn's disease (CD), 7 with ulcerative colitis (UC), and 1 with indeterminate colitis. Thirteen (41.9%) patients had evidence of portal hypertension, 10 (32.2%) with esophageal varices, 4 (12.9%) with history of variceal bleeding, 6 (19.3%) with ascites, and 14 (12.9%) with splenomegaly. Eleven (35.4%) patients had a cirrhotic-appearing liver on imaging. Twelve (38.7%) patients had a history of prior or current thiopurine use.

Conclusions: The current study suggests that NRH with or without OPV independently occurs in patients having PSC and may lead to NCPH, even in the absence of concurrent IBD and/or thiopurine therapy.

Introduction

Primary sclerosing cholangitis (PSC) is a chronic progressive liver disease characterized by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts.[1] The course of PSC is highly variable and carries the risk of progression to cirrhosis and the complications of portal hypertension.[2,3] The pathogenesis of PSC remains unclear, and liver transplantation (LT) is the only life-extending therapy for advanced cases.[4] Liver biopsy is often not required in patients with typical imaging findings and cholestatic serum tests, but may be necessary in patients not having such changes and/or to exclude overlap syndromes.[5]

Patients with PSC who progress to cirrhosis may have complications of portal hypertension.[6,7] Portal hypertension without cirrhosis, non-cirrhotic portal hypertension (NCPH), may be related to nodular regenerative hyperplasia (NRH) with or without obliterative portal venopathy (OPV), previously termed hepatoportal sclerosis.[8,9] NRH and OPV can be seen concurrently on the same liver biopsy.[9] Cross-sectional imaging in NRH may demonstrate morphological changes of cirrhosis and the gold standard for the diagnosis of NRH and OPV is liver biopsy.[7,10,11] NRH and OPV have similar etiologies including collagen vascular and hematological disorders, the post-LT setting, portal vein thrombosis, primary biliary cholangitis (PBC), and with the use of certain medications such as azathioprine (AZA), 6-mercaptopurine (6-MP), and didanosine.[7,11,12,13] The majority of cases however are idiopathic.

PSC is highly associated with the presence of inflammatory bowel disease (IBD).[14] Medications used in IBD treatment can have a number of hepatobiliary adverse effects. Thiopurines such as AZA and 6-MP may lead to cholestasis, peliosis hepatitis, veno-occlusive disease, and NRH.[15,16] We sought to assess the presence of NRH with or without concurrent OPV in liver biopsies of patients having PSC in order to assess whether the NRH/OPV could be related to concomitant IBD or rather could

be directly related to PSC, and what the clinical manifestations of these patients were.

Methods

This is a descriptive, retrospective observational study that aims to investigate the presence of concurrent NRH and OPV in the setting of PSC. A total of 108 patients were identified by combining PSC and NRH search terms in the Mount Sinai Medical Center Department of Pathology database covering the years 2003–2019 (Fig. 1). Clinical data were collected from the electronic medical record (EMR). Demographic data were obtained along with careful documentation of IBD treatment and natural history. Liver biopsies were reviewed independently by an experienced liver pathologist (MIF) to confirm the histological changes of both PSC and NRH and OPV. Histological diagnosis of PSC was based on the typical bile duct lesions including periductal onion-skin fibrosis, bile ducts that are dilated or have diminished caliber, ductular reaction, and bile duct scars. A reticulin stain was used to reach a definitive diagnosis of NRH and was based on the presence of vague nodules composed of hyperplastic zone 1 hepatocytes and bordered by atrophic zone 3 hepatocytes. OPV is characterized by portal veins with diminished or obliterated luminal caliber, dystrophic or herniated veins, and paraportal shunt vessels. Those patients with no clinical information on EMR, missing more than two laboratory data, and having liver histology other than PSC and concurrent NRH or OPV on liver biopsy, including secondary sclerosing cholangitis, PBC, PSC, and autoimmune hepatitis overlap, vanishing bile duct syndrome, and sarcoidosis were excluded. Patients with PSC without NRH or NRH without evidence of PSC on liver biopsy were also excluded. Patients having conditions associated with NRH including prior LT, common variable immunodeficiency, end-stage renal disease, portal vein thrombosis, and Turner's syndrome were excluded. The patient cohort consisted of those who had undergone liver biopsy for diagnostics reasons (imaging suggestive of cirrhosis in the setting of normal or mildly elevated liver tests, and clinical signs of portal hypertension in the absence of advanced PSC). Liver explant samples were not included.

Presence and/or complications of portal hypertension, imaging findings, IBD history and medications, laboratory data, and liver biopsy slides were reviewed. Portal hypertension was defined as the presence of varices, ascites, splenomegaly, hypersplenism-associated cytopenias, or portosystemic collaterals, with the exclusion of other potential causes. Clinical characteristics and biochemical tests were presented as absolute

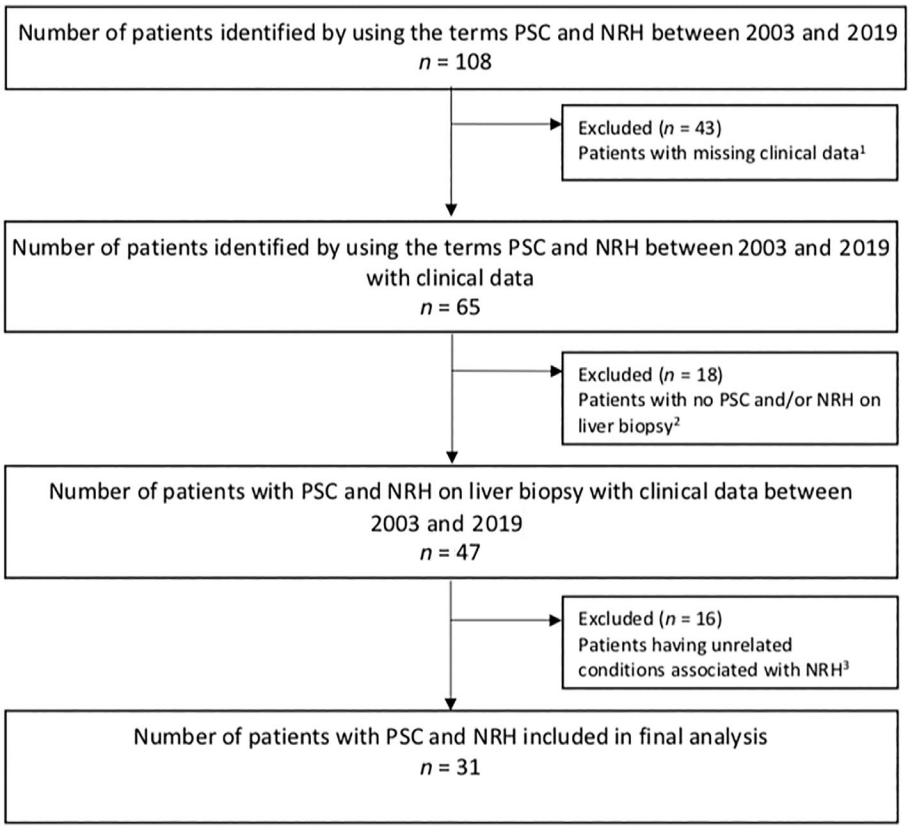

Figure 1 [1]Reasons for exclusion including no chart access, missing clinical or laboratory data. [2]Patients with secondary sclerosing cholangitis ($n = 6$), primary biliary cholangitis ($n = 3$), overlap of autoimmune hepatitis ($n = 2$), vanishing bile duct syndrome ($n = 1$), and sarcoidosis ($n = 1$) on liver biopsy were excluded. Patients having PSC without NRH ($n = 3$) and NRH without PSC ($n = 2$) were excluded. [3]Conditions associated with NRH including prior liver transplantation ($n = 5$), portal vein thrombosis ($n = 4$), end-stage renal disease ($n = 3$), common variable immune deficiency ($n = 2$), and Turner's syndrome ($n = 2$) were excluded.

numbers with percentages or median with range. The study was approved by the Mount Sinai Institutional Review Board.

Results

Thirty-one patients having PSC and concurrent NRH (21 male, 10 female; median age at the time of biopsy 40.1 years, range 14–72 years) on liver biopsy were included in the study. Patient characteristics are shown in Table 1. Twelve of 31 (38.7%) patients had OPV in addition to NRH on liver biopsy (Fig. 2). Laboratory data are shown in Table 1.

Thirteen (41.9%) patients had evidence of portal hypertension, 10 (32.2%) with esophageal varices, 4 (12.9%) had a history of variceal bleeding, 6 patients (19.3%) with ascites, and 14 (12.9%) patients with splenomegaly. Thrombocytopenia was present in 10 (32.2%) cases with a median platelet count of 92.5 $\times$ 10^9/L and a range of 43–144 $\times$ 10^9/L. Four (30.7%) of 13 patients with portal hypertension had normal platelet counts. Eighteen (58.0%) patients had clinical imaging findings of PSC on cholangiography and 11 (35.4%) had cirrhotic morphology on imaging (Table 2).

Seventeen (54.8%) patients had cholestatic liver chemistry tests, while 10 (32.2%) had normal liver tests, 3 (9.6%) had a mixed pattern, and 1 (3.2%) had a hepatocellular pattern of abnormal liver tests at the time of liver biopsy. Nineteen (61.2%) patients had IBD including 11 with CD, 7 with UC, and 1 with indeterminate colitis. Twelve (38.7%) patients had no IBD (Table 1). Eight of 11 (72.2%) patients with CD had colonic involvement. A total of 12 (38.7%) patients had a history of prior or current thiopurine use, while 19 (61.2%) patients had no history of thiopurine use. Eight CD patients (72.7%) had thiopurine

Table 1 Patient characteristics and laboratory data

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Gender	
Male	21/31 (67.7%)
Female	10/31 (32.2%)
IBD	19/31 (61.2%)
Crohn's disease	11/31 (35.4%)
Ulcerative colitis	7/31 (22.5%)
Indeterminate colitis	1/31 (3.2%)
No IBD	12/31 (38.7%)

	Median	Range	*n*	Reference ranges
Hemoglobin	13.1	8.4–15.4	30	12–16 g/dL (F) 14–17 g/dL (M)
Platelets	202.5	43–478	30	150–350 $\times$ 10^9/L
INR	1.1	0.9–1.4	24	0.8–1.2
Total serum bilirubin	0.9	0.2–27.4	31	0.2–1.0 mg/dL
ALT	48	12–214	31	0–40 U/L
AST	51	13–305	31	0–40 U/L
ALP	143	45–687	31	40–125 U/L
GGT	157	17–1530	17	10–55 U/L
Creatinine	0.79	0.53–1.33	30	0.7–1.2 mg/dL

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; GGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; INR, international normalized ratio; M, male.

Table 2 Clinical and imaging characteristics of the study patients

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Portal hypertension	13/31 (41.9%)
Esophageal varices	10/31 (32.2%)
Variceal bleeding history	4/31 (12.9%)
Ascites	6/31 (19.3%)
Splenomegaly	14/31 (45.1%)
Thrombocytopenia	10/31 (32.2%)
Previous episode of cholangitis	6/31 (19.3%)
Spontaneous bacterial peritonitis	1/31 (3.2%)
Portosystemic encephalopathy	1/31 (3.2%)
PSC on imaging	18/31 (58.0%)
Cirrhosis on imaging	11/31 (35.4%)

PSC, primary sclerosing cholangitis.

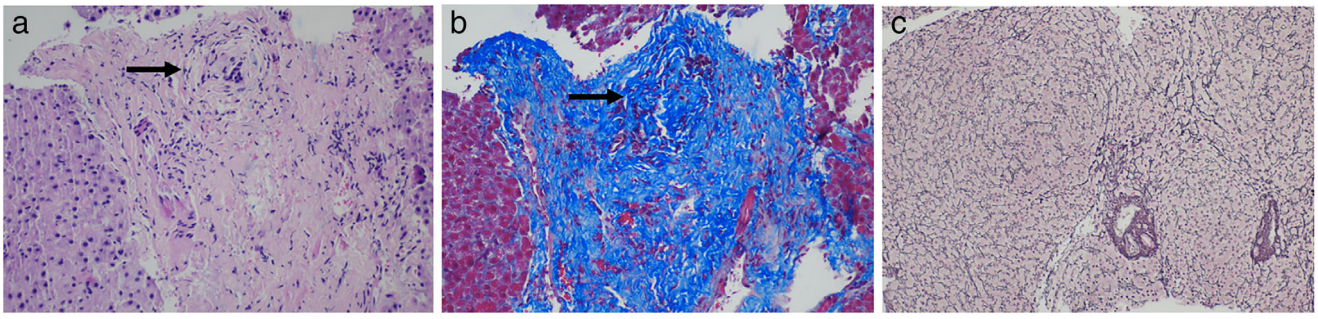

Figure 2 (a) A medium-sized portal tract shows an interlobular bile duct being surrounded by layers of fibrous tissue resulting in near-total collapse of the bile duct (arrow) (H&E, original magnification ×20). (b) The same portal tract seen in (a) shows that the bile duct is almost totally replaced by fibrosis (bile duct scar). Also highlighted is a fibrous expansion of the portal tract (arrow) (Masson-trichrome stain, original magnification ×20). (c) Reticulin stain demonstrates distinct nodules with nodules comprised of hyperplastic hepatocytes as highlighted by reticulin stain showing thickening of the hepatocyte plates while the periphery of the nodules is comprised of atrophic hepatocytes as demonstrated by thinner hepatocyte plates (reticulin stain, original magnification ×10).

exposure (6-MP [$n = 6$], AZA [$n = 2$]), 2 UC (28.5%) patients (6-MP [$n = 1$], AZA [$n = 1$]), and 2 (16.6%) patients without IBD had AZA exposure. Medications used other than thiopurines included prednisone, sulfasalazine, mesalamine, methotrexate, adalimumab, infliximab, vedolizumab, and tofacitinib. Eleven (35.4%) patients had no exposure to any IBD medications.

Median duration of the initiation of thiopurine use to diagnosis of PSC and concurrent NRH in patients with CD was 9.2 years, in the range of 2.5–23 years. In patients with UC, the median time of thiopurine use to the liver biopsy was 3.5 years, with 2 and 5 years for AZA and 6-MP, respectively. Patients without IBD, but a history of AZA use for other indications ($n = 2$, misdiagnosed autoimmune hepatitis cases), were diagnosed after 7 and 13 years of medication use.

There was no difference in morphological presentation of NRH on liver histology in patients with and without IBD. Both groups had typical histology of NRH, which included hyperplastic hepatocytes without surrounding fibrosis and with atrophic hepatocyte plates.

Discussion

PSC is highly associated with IBD, with UC being the most frequent type.[1,14,17,18] In our patient cohort, IBD was present in 61.2% of cases, with CD being the most common type.

The cumulative risk for the development of NRH in patients with IBD treated with AZA was found in one study to be 0.5% at 5 years and 1.25% at 10 years.[19] Another study found the cumulative incidence of NRH to be 1.28% at 10 years.[20] In our study, the diagnosis of NRH was made within a median year and a range of 7.7 (5–13) and 7 (2–23) for AZA and 6-MP, respectively. NRH has been reported to occur in 6% of thiopurine-naive patients with IBD.[21] In another study, a total of 82 thiopurine-naive IBD patients undergoing IBD-related surgical operations were evaluated for the presence of NRH by intraoperative liver biopsy and NRH was found in five (6%) biopsies.[22] Comparing this study with a large autopsy study including 2500 liver specimens without IBD,[23] in which NRH was found in 2.6% of the samples, IBD itself was considered as a risk factor for the NRH.

The current study shows that NRH with or without OPV may lead to NCPH in patients with PSC, even in the absence of IBD and/or thiopurine therapy. In this study, 12 of 31 (38.7%) patients with PSC had no IBD, and of those, 10 (83.3%) patients had no exposure to any medication or had a condition associated with NRH. Portal hypertension was reported in 71% of patients in this cohort.[24] In one study investigating 26 patients who underwent LT for chronic biliary disease including PSC ($n = 18$), PBC ($n = 5$), autoimmune cholangitis (2), and secondary sclerosing cholangitis ($n = 1$), 46.1% of patients had NRH and 30.7% had OPV on histology. Sixty-nine percent of these patients had some evidence of at least one sign of portal hypertension, suggesting the histologic changes of the NRH can precede clinical signs of portal hypertension.[8] The current study shows that at the time of the diagnosis, 13 of 31 (41.9%) patients had clinical evidence of portal hypertension. A low platelet count is frequently seen in portal hypertension, and although the majority of patients in the current study were thrombocytopenic, 4 of 13 (30.7%) had normal platelet counts.

On imaging, the nodular appearance of the liver caused by the NRH may lead to the misdiagnosis of cirrhosis.[10] This is particularly important in the setting of chronic liver diseases such as PSC. We found that 11 of 31 (35.4%) patients in our study had a cirrhotic morphology on imaging, without having histologically proven cirrhosis. NRH was the cause of the nodularity seen on imaging in these patients. NRH and OPV may be more common than originally thought in patients having PSC. This is because liver biopsy is not routinely performed once the PSC diagnosis is established unless there is a concern for an alternate diagnosis or for an overlap syndrome.

NRH-like changes have been reported in NCPH patients before, and one of the hypotheses for the development of OPV/NRH is thought to be a heterogeneous distribution of blood flow within the liver with obliterative changes involving small portal vein branches.[9,25] It is plausible that in PSC there could be shared pathophysiologic mechanisms playing a role in the development of OPV/NRH. A shared pathogenesis with PSC may result from altered blood flow to the biliary plexus with interrupted or perturbed blood flow regionally within the liver leading to the NRH. This could explain the concurrence of PSC and NRH in our cohort, which is demonstrated in the absence of IBD/AZA therapy.

Our study has a few limitations. The study was performed in a single center, and because of the retrospective design selection bias may be present. In addition, lack of a significant number of patients with hepatic venous pressure gradient measurements prevented the correlation of the clinical and histopathological presentations. Since liver biopsy is not required in all patients with PSC the presence of concurrent NRH may be underestimated, especially in the absence of portal hypertension. Some patients with signs of portal hypertension on imaging had normal platelet counts. Thus, NRH might be present in PSC in the absence of thrombocytopenia. This supports the recommendation to perform surveillance endoscopy for the detection of gastroesophageal varices in patients with cholestatic liver disease who appear to have cirrhosis at a higher platelet count as compared with other patients with cirrhosis.[26] Strengths of our study include a relatively large number of cases of PSC diagnosed on needle liver biopsy and all of the biopsies being reviewed by a single experienced liver pathologist.

In conclusion, NRH and/or OPV can occur concurrently with PSC on liver biopsy. NRH should be included in the differential diagnosis of PSC cases with preserved liver synthetic function and portal hypertension and/or cirrhosis on imaging even in the absence of IBD. NRH with or without OPV may occur with PSC in the absence of concurrent IBD and is a cause of NCPH. Histology showing cholestatic changes in the setting of NRH and/or OPV could alert the clinician to the diagnosis of PSC, especially if accompanied by cholestatic liver tests. Although NRH can occur in conjunction with IBD and with the use of thiopurines used to treat IBD, it also appears to occur in patients having PSC in the absence of IBD. It is unclear whether this occurs related to a shared pathophysiology or to what extent the association exists, but is worthy of further study.

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