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ORIGINAL RESEARCH—CLINICAL

Hepatoportal Sclerosis—A Clinicopathologic Review of 28 Cases

Nazia Khatoon,[1] Andrew P. Keaveny,[2] Gian P. Carames,[1] Murli Krishna,[1] Jason Lewis,[1] and Raouf E. Nakhleh[1]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, Florida; and [2]Division of Gastroenterology and Hepatology, Department of Transplant Medicine, Mayo Clinic, Jacksonville, Florida

BACKGROUND AND AIMS: The aim of this study was to review a large series of cases with hepatoportal sclerosis (HPS) as a pathologically recognizable entity in liver tissue specimens and describe the associated clinical and radiographic manifestations, along with the outcomes of this entity. **METHODS:** Data were collected through a retrospective chart review. **RESULTS:** Twenty-eight patients were identified that had pathologically defined HPS. All patients had a significant past medical history and signs and symptoms of portal hypertension. The most consistent laboratory finding was an elevated alkaline phosphatase. Radiographically, 9 patients were mistakenly identified as having advanced fibrosis/cirrhosis. The initial histologic diagnosis was made on biopsy in 20 patients and after transplant in 8 patients. The severity of symptoms was variable and required transplantation in 11 patients, 3 were treated with transjugular intrahepatic portosystemic shunt, and the remaining patients were treated symptomatically. **CONCLUSION:** HPS is associated with past medical history that may be causal in nature. Signs and symptoms may be severe enough to require liver transplantation. A significant proportion of patients are radiographically misdiagnosed as cirrhosis. In this small series, overall outcomes for transplanted patients are acceptable.

Keywords: Portal Hypertension; Porto-Sinusoidal Vascular Disorder; Non-Cirrhotic Portal Hypertension; Transplantation

Porto-sinusoidal vascular disorder (PSVD) is the term that has recently been adopted to describe a broad range of clinical entities that encompass non-cirrhotic portal hypertension.[1] Many of these lesions are confusing and often referred to by multiple names (often based on clinical findings and not pathologic findings). One of these lesions is hepatoportal sclerosis (HPS). This is a condition that is localized to the pre-sinusoidal intrahepatic portion of the portal venous circulation and is characterized clinically by an increased portal pressure with patent portal and hepatic veins, without evidence of cirrhosis.[2,3] The primary hepatic lesions seen in HPS are varying degrees of fibrosis and sclerosis of the portal vein (PV) branches seen on microscopic examination (Figure).[4] The aim of this study was to review a large series of cases with HPS as a pathologically recognizable entity on liver tissue specimens and describe the associated clinical and radiographic manifestations, along with the outcomes of this entity.

Methods

We conducted a retrospective search for the diagnosis of HPS in our surgical pathology files at Mayo Clinic, Florida, from 2000 to 2020. Institutional review board approval was obtained for this minimal risk study. Cases were confirmed by an experienced liver pathologist. The presence of sclerotic PV branches was the main criterion for inclusion in this study. Patients with other liver disease were excluded from the study. A chart review was conducted for the clinical presentation, laboratory and radiographic studies, associated pathology findings, treatment, and outcome.

Results

There were 28 patients in our series (Table 1). Only 4 patients were referred with a diagnosis of HPS. The remaining patients had symptoms and signs of portal hypertension (PHT). Six patients had hepatic encephalopathy (HE) and 2 were diagnosed with hepatopulmonary syndrome. Past medical history was relevant in most cases: 7 (25%) patients had a history of malignancy, receiving various chemotherapeutic agents (Table 2); 14 (50%) patients had an extrahepatic autoimmune disease; 5 patients had congenital vascular anomalies, and 1 patient was infected with human immunodeficiency virus. Twelve of 15 patients who underwent hepatic venography had an elevated hepatic venous pressure gradient greater than 5 mmHg. Computerized tomography and magnetic resonance imaging studies were available in 25 patients. Findings of cirrhosis and advanced fibrosis were described in 8 and 1 case, respectfully. Caudate lobe hypertrophy was noted in 2 cases. One patient had a prior right lobe resection with left lobe hyperplasia. One patient demonstrated a

Abbreviations used in this paper: **HE, hepatic encephalopathy; HPS, hepatoportal sclerosis; LT, liver transplantation; NRH, nodular regenerative hyperplasia; PHT, portal hypertension; PSVD, porto-sinusoidal vascular disorder; PV, portal vein; SOS, sinusoidal obstruction syndrome; TIPS, Transjugular intrahepatic portosystemic shunt.**

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Table 1. Clinical and Pathologic Findings in 28 Patients With Hepatoportal Sclerosis

Clinical and pathologic findings	Number of cases	Percentage of all cases
Gender		
Male	17	60.7%
Female	11	39.3%
Presentation		
Established diagnosis	4	14.2%
No signs or symptoms	3	10.8%
Signs of portal hypertension	23	82.1%
Hepatic encephalopathy	6	21.4%
Abnormal AST/ALT/TBIL	5	17.8%
Past history		
Non-hepatic autoimmune disorders	14	50%
Malignancy treated with chemotherapy	7	25%
Congenital vascular anomalies	5	17.8%
Infectious disease (HIV)	1	3.6%
Additional workup		
Elevated alkaline phosphatase (range, 138–417 U/L)	13	46.4%
Elevated hepatic venous pressure gradient	12 (n = 15)	80%
Indication of advanced fibrosis not correlated with pathology by CT/MR/ elastography	9 (n = 25)	36%
Additional detected hepatic or vascular alterations	5 (n = 25)	20%
Histologic diagnosis		
On biopsy	20	71.5%
On explant	8	28.5%
Additional histologic findings		
Mild portal fibrosis	25	89.2%
Steatohepatitis	1	3.5%
Nodular regenerative hyperplasia	1	3.5%
Treatment		
Liver transplantation	11	39%
TIPS placement	3	10.8%
Symptomatic	13	46.4%
Follow-up		
Alive & well	18 (n-28)	64.2%
Alive & well post-transplant	8 (n-12)	28.6%
Died post-transplant	4 (n-12)	14.2%
Alive & well following TIPS	3 (n = 3)	10.7%
Total lost to follow-up	4	14.2%

ALT, alanine transaminase; AST, aspartate transaminase; CT, computerized tomography; HIV, human immunodeficiency virus; MR, magnetic resonance; TBIL, total bilirubin; TIPS, transjugular intrahepatic portosystemic shunt.

Table 2. Cancer Diagnoses and Types of Chemotherapy Administered

Cancer	Number of patients	Chemotherapy
Acute lymphatic leukemia	1	Details not available
Colorectal carcinoma	3	5-Fluorouracil Leucovorin Oxaliplatin Capecitabine Irinotecan Bevacizumab
Breast cancer	1	Adriamycin Cyclophosphamide Paclitaxel Capecitabine Eribulin Irinotecan Carboplatin Nab-paclitaxel
Non-Hodgkin's lymphoma	1	Rituximab Bendamustine
Follicular lymphoma	1	Rituximab Bendamustine Ibritumomab

nonocclusive thrombus in the main PV with occlusion of the right PV. Another patient demonstrated attenuation and delayed filling of the PV branches. In 1 patient, there was absence of the PV with splenic and superior mesenteric veins draining into a hepatic venous confluence along the medial border of the liver.

Histologic diagnosis was made on biopsy in 20 patients. The initial diagnosis was made on the explanted livers in the remaining 8 cases (4 with prior biopsies). Treatment and outcome are listed in Table 1.

Three patients underwent transjugular intrahepatic portosystemic shunt (TIPS) placement to manage complications of PHT. Another patient had a TIPS placed prior to a bowel resection for Crohn's disease given the presence of significant PHT. Eleven patients proceeded to liver transplantation (LT)—the indications for transplant were HE refractory to medical therapy (5 patients, 2 of whom were post-TIPS), heptopulmonary syndrome (2 patients), progressive spastic paresis post-TIPS and progressive liver dysfunction (1 patient each). Other indications for LT included malnutrition (2) and pulmonary hypertension (2). Some patients had more than 1 indication for LT. One patient underwent simultaneous liver and kidney transplant for refractory HE and end-stage renal disease, respectively. The mean biological model for end-stage liver disease score at the time of LT was 15 (range, 7–38); 1 patient was on warfarin at the time of LT. Four patients had been awarded model for end-stage liver disease exception scores given their presentation to expedite transplantation. Four of the LT recipients died postoperatively, one at the time of surgery, the other 3 surviving for a mean of 5 years (range, 4–6 years); 1 patient required retransplantation 6 days after the first LT for hepatic artery thrombosis. The remaining 7 patients were alive at a median of 3 years post-LT (range, 2 months–17 years). Two of the 3 patients who had a TIPS were alive while the third patient was lost to follow-up.

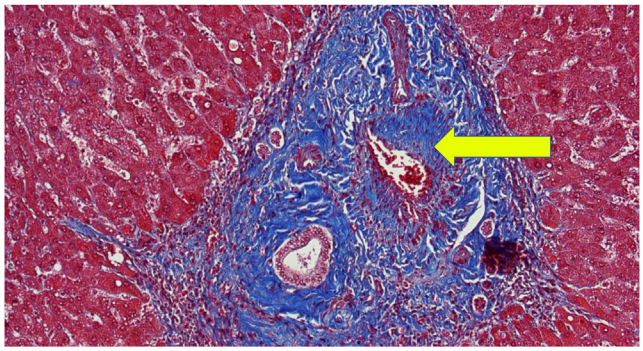

Figure. Portal tract with a portal vein (yellow arrow) that is sclerosed (trichrome stain 100X).

Discussion

PSVD is the latest term used to encompass various histologic changes in the liver in the presence of PHT, including HPS.[1] In this report, we sought to describe a cohort of patients with HPS who were clearly defined by the histologic finding of sclerotic PV tributaries with associated PHT. The lesion may be identified with hematoxylin and eosin stain, but trichrome and elastin stains may also be helpful in defining the portal structures. Sclerosed PV can be seen in other conditions including cirrhotic livers.[5] The determination of PHT without cirrhosis and other conditions should trigger a pathologic assessment for HPS, nodular regenerative hyperplasia (NRH), and sinusoidal obstructive syndrome (SOS).[6] These lesions may be overlooked if the clinical presentation is not considered.

HPS has been associated with multiple diseases, as in our series, a significant number being autoimmune conditions and prior exposure to chemotherapy.[7,8] Drug toxicity from cancer chemotherapy or from immunosuppressive agents to hepatic endothelial cells are likely mechanisms for these injuries. Several of our patients also had congenital vascular anomalies causing hemodynamic mechanical injury. We believe HPS may develop by multiple mechanisms of endothelial injury leads to occlusive thrombosis, or fibrointimal proliferation resulting in PHT. The latter mechanism seems more likely as we found no histologic evidence of organizing thrombosis in any of our cases.

Other conditions that result in PSVD have reported associations with autoimmune disorders and malignancies.[9,10] Most notably, NRH and SOS may present with complications of non-cirrhotic portal hypertension, like HPS. SOS occurs after drug or toxin exposure, classically in blood and marrow transplant recipients.[10] While NRH does not have a specific described histologic vascular abnormality, as is seen in HPS and SOS, it has been reported with HPS and SOS.[5,9] Most experts agree that NRH is likely due to ischemic or other hemodynamic changes.[5] SOS is defined by sinusoidal endothelial injury with subsequent obstruction of the terminal sinusoids at or near the central veins. Given the similarities between HPS, SOS, and NRH, it may be that they are different manifestations of the same endothelial and/or vascular injury, or an injury that is occurring in different location(s) within the hepatic circulation.[11] In these 3 conditions, the clinical approach is similar—treating any underlying cause and managing the complications of PHT.[3,11] In patients with complications of PHT refractory to medical therapy, TIPS or even LT can be considered in appropriately selected patients.

Conclusion

In our series, as is typical for HPS, very few patients were recognized based solely on their clinical presentation or imaging findings. Only 1 of our patients had classic radiographic features of attenuation and delayed filling of the PV branches.[12] Interestingly, 9 patients were radiographically determined to have advanced fibrosis which was not confirmed by histology.

HPS is in the spectrum of PSVD. The diagnosis requires recognizing characteristic histologic findings in patients who have PHT in the absence of cirrhosis. Most of our study cohort had a condition that could have contributed to the development of HPS and required treatment to manage the complications of PHT. A significant proportion required LT because of complications refractory to medical therapy, including HE and hepatopulmonary syndrome. Outcomes after LT were acceptable.

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Correspondence:
Address correspondence to: Raouf E. Nakhleh, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32224. e-mail: Nakhleh.raouf@mayo.edu.

Authors' Contributions:
Nazia Khatoon; Andrew P. Keaveny; Gian P. Carames; Raouf E. Nakhleh: Data collection. Nazia Khatoon; Andrew P. Keaveny; Gian P. Carames; Murli Krishna; Jason Lewis; Raouf E. Nakhleh: Data analysis. Nazia Khatoon; Andrew P. Keaveny; Murli Krishna; Jason Lewis; Raouf E. Nakhleh: Manuscript preparation and editing.

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