Pathogenesis of Portal Cavernoma Cholangiopathy: Is it Compression by Collaterals or Ischemic Injury to Bile Ducts During Portal Vein Thrombosis?

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The pathogenesis of portal cavernoma cholangiopathy (PCC) is important as it can impact the choice of treatment modalities. PCC consists of a reversible component, which resolves by decompression of collaterals as well as a fixed component, which persists despite the decompression of collaterals. The reversible component is due to compression by large collaterals located adjacent to the bile duct as well as possibly intracholedochal varices. The fixed component is likely to be due to ischemia at the time of portal vein thrombosis, local ischemia by compression as well as encasement by a solid tumor-like cavernoma comprising of fibrous hilar mass containing multiple tiny collateral veins rather than markedly enlarged portal collaterals. Although cholangiographic abnormalities in portal hypertension are common, the prevalence of symptomatic PCC is low. This is likely to be related to the cause of portal hypertension, the duration of portal hypertension and possibly the pattern of occlusion of the splenoportal axis. There may possibly be higher prevalence of symptomatic PCC in extension of the thrombosis to the splenomesenteric veins. (J CLIN EXP HEPATOL 2014;4:S27–S33)

The biliary changes seen in extrahepatic portal vein occlusion (EHPVO) are referred to as portal cavernoma cholangiopathy (PCC). While these biliary changes are seen on imaging in the majority of patients with EHPVO, they can become symptomatic in some of these patients. The pathogenesis of PCC has been a subject of debate. The pathogenesis is important as it can impact choice of treatment modalities. While external pressure by portal cavernoma and collaterals appear to be an obvious possible cause, the lack of reversal by decompression of the collaterals has led to the consideration that ischemia may play a role. Any theories regarding the pathogenesis of PCC must take into account both the reversible component after decompression of collaterals as well as the fixed cholangiographic abnormalities, which persist despite decompression. The bile duct and the liver have a unique dual blood supply and the development of portal venous thrombosis results in changes in their blood supply

and the development of collaterals, which have implications in the development of PCC.

THE NORMAL BLOOD SUPPLY TO THE LIVER AND THE BILE DUCT

The liver has a peculiar dual afferent blood supply with 75% of the blood being supplied by the deoxygenated blood from the portal vein and the remaining 25% being supplied by the well-oxygenated blood from the hepatic artery. Unlike the portal vein, which exclusively supplies the sinusoids, the hepatic artery does not directly supply blood to the sinusoids, but rather supplies the liver parenchyma through arteriportal communications at different anatomic locations before its blood reaches the sinusoids. The artery supplies three compartments within the portal tract: the peribiliary vascular plexus, the portal tract interstitium and the portal vein vasa vasorum. These drain into the hepatic artery-derived portal system, which joins the regular portal system or inlet venule or perfuse the lobule. The artery outside the portal tract, the isolated artery, supplies 2 compartments: the Glisson's capsule and the vasa vasorum of the hepatic veins.^{1,2}

The hepatic arterial buffer response (HABR) is a unique mechanism by which the hepatic artery can produce compensatory increase in arterial flow in response to a decrease in portal venous flow. The HABR can be explained by the adenosine hypothesis. Adenosine is released at a constant rate in the space of Mall (the thin fluid space surrounding the portal triad). Adenosine is regulated by washout by the portal vein and the hepatic artery. If the

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Abbreviations: PVT: portal vein thrombosis; PCC: portal cavernoma cholangiopathy; EHPVO: extrahepatic portal vein occlusion; HABR: hepatic arterial buffer response; MR: magnetic resonance; ERC: endoscopic retrograde cholangiography; ITBL: ischemic-type biliary lesions

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portal vein blood flow is reduced, less adenosine is washed away from the space of Mall and the elevated adenosine level leads to hepatic artery dilatation and increased hepatic arterial flow. Because the portal vein cannot control its blood flow, there is no reciprocal HABR seen in cases of hepatic arterial thrombosis.³ This may explain why acute portal vein thrombosis is well tolerated while acute arterial thrombosis causes significant liver dysfunction.

The hepatic artery has historically been considered to be the main provider of blood and oxygenation of the biliary ducts.^{4,5} However, the portal venous blood flow may have a significant contribution through hepatic artery-portal venous anastomoses. Animal studies have shown the presence of arteriportal communications in the peribiliary plexus.^{6,7} The bile ducts are supplied blood by a peribiliary vascular plexus, which is fed by the hepatic artery, the portal vein and the branches of the gastroduodenal artery. Slieker et al⁸ analyzed the microvascular blood flow in the common bile duct in 15 patients who underwent pancreaticoduodenectomy with a combination of laser Doppler flowmetry and reflectance spectrometry. Compared to baseline measurements, the microvascular flow through the common bile duct was decreased to 62% after clamping the portal vein, 51% after clamping the hepatic artery and 31% after clamping both. This study emphasized the contribution of portal venous blood flow to the common bile duct. It must however be mentioned that the conditions of this study were far from physiological. The measurements reflected an acute

change in microvascular blood flow through the CBD and it is possible that, in time, redistribution may occur within the microcirculation. Besides, in these patients who underwent pancreaticoduodenectomy, neovascularization or alterations in the region due to cancer of pancreatic head that affect microvascular blood flow in the hepatoduodenal ligament could have influenced results.

The venous drainage of the bile duct and gallbladder consists of two venous plexuses, namely, epicholedochal venous plexus of Saint⁹ and paracholedochal veins of Petren.¹⁰ The epicholedochal venous plexus of Saint forms a fine reticular network on the outer surface of the common bile duct and hepatic ducts. In contrast, the paracholedochal venous plexus of Petren runs parallel to the bile duct. The right sided paracholedochal plexus can communicate with the gastroduodenal trunk and pancreaticoduodenal vein and drain into the cystic duct or directly into the liver while the left-sided plexus can communicate with the first jejunal trunk, left and right gastric veins and the left portal vein.^{11,12} The venous drainage of the bile duct is depicted in Figure 1.

PATHOPHYSIOLOGICAL CHANGES ON THE DEVELOPMENT OF PORTAL VEIN THROMBOSIS

The patient usually has a silent presentation at the time of portal thrombosis despite the loss of portal venous blood flow, which accounts for 50% of the oxygen requirement

Figure 1 Venous drainage of the bile duct: The venous drainage of the bile duct is by two plexuses: the epicholedochal venous plexus of Saint which forms a fine reticular meshwork on the surface of the bile duct and the paracholedochal plexus of Petren. The right paracholedochal plexus communicates with the gastroduodenal trunk, pancreaticoduodenal veins and the cystic duct. The left-sided paracholedochal plexus communicates with the first jejunal vein, left and right gastric veins and the left portal vein. The anterosuperior pancreaticoduodenal vein drains into the gastroduodenal trunk, which communicates across the pancreatic head to the posterosuperior pancreaticoduodenal vein, which joins the portal vein near the hepatic hilum. The inferior pancreatic veins drain into the first jejunal vein or less commonly directly into the superior mesenteric vein.

of the liver. This silent presentation is likely to be due to two factors. The loss of portal blood flow after portal vein occlusion is compensated initially by the dilatation of the hepatic arterial system in response to the decrease in portal venous blood flow by the HABR. Subsequently there is a rapid development of venous collaterals with formation of cavernoma as well as varices. An immediate increase in arterial blood flow has been seen after portal vein embolization.¹³ In animal studies, portal branch ligation was produced an initial microcirculatory failure with liver atrophy followed by a hepatic arterial buffer response, microvascular remodeling, normoxygenation and hepatocellular proliferation.¹⁴

There is scarce data on the effects of decreased portal blood flow on the biliary system. An experimental study of portal branch ligation in rabbits showed only slight dilatation of the bile ducts in the affected lobes after 6–12 months.¹⁵ However PCC has been shown to occur early after acute portal vein thrombosis in humans. In a study that included 22 patients with acute portal vein thrombosis, 30% developed significant changes of PCC within 1 year.¹⁶ The dilated biliary system may act as a risk factor for development of biliary stones, which may contribute to symptoms in PCC.

Symptoms in PCC are seen to occur in 5–38% of cases of EHPVO. Unlike variceal bleed, which usually occurs in the first two decades of life in EHPVO, the patients with PCC develop symptoms at a higher age and longer duration of disease. The symptoms in EHPVO may occur either due to chronic cholestasis from biliary strictures/compression or due to biliary stones which can cause biliary colic or cholangitis. Patients with prolonged duration of PCC can develop clinical and biochemical evidence of hepatic dysfunction.¹⁷

REVERSIBLE COMPONENT OF PORTAL CAVERNOMA CHOLANGIOPATHY

Collaterals form following portal vein thrombosis, which have been implicated in the reversible component of PCC

that may resolve after decompression of these collaterals. In PCC, the dilated venous collaterals cause external pressure and protrusion over the common bile duct and the hepatic ducts, which are thin and pliable.^{18–21} In PCC, the dilatation of the plexus of Saint causes fine irregularities in the biliary tract while the dilatation of the plexus of Petren causes extrinsic compression over bile duct.¹⁸ The left hepatic duct is more commonly involved in PCC, which could be related to the formation of prominent collateral veins where the umbilical vein joins the left branch of the portal vein.²²

In addition to extrinsic collaterals causing compression, *intra bile duct collaterals* have also been shown which may contribute to the biliary abnormalities. On EUS paracholodochal varices have been shown to perforate the wall of the bile duct and lie in the subepithelial layer of the bile duct.^{23,24} There are rare case reports of portal biliopathy characterized localization of the portal cavernoma in the wall of the bile duct causing thickening of the walls of the bile duct along with dilatation of the intrahepatic biliary ducts with no evidence of extrinsic compression by collaterals on magnetic resonance (MR) imaging.²⁵

The evidence in favor of compression by dilated venous collaterals comes in the form of:

- Imaging evidence of collaterals impinging on bile duct lumen.

Collaterals impinging on bile duct lumen can cause cholangiographic changes. MR cholangiographic studies coupled with MR portography studies have demonstrated that the cholangiographic abnormalities resulted from impingement on the bile duct lumen by the dilated veins of the portal cavernoma.²⁰

- Resolution of cholangiographic abnormalities by decompression of the collaterals.

Partial or complete resolution of these changes of PCC on endoscopic retrograde cholangiography (ERC) has been shown after shunt surgery^{18,26–30} and after transjugular intrahepatic portosystemic shunt.^{31,32} The evidence of

Table 1 Studies Showing Reversibility of Portal Biliopathy After Decompression of Collaterals.

Author	Number of patients	Modality of decompression	Resolution of biliary strictures
Dhiman et al ¹⁸	5	Shunt surgery	Partial reversal – 3 Complete reversal – 1 No reversal – 1
Chaudhary et al ²⁷	7	Shunt surgery	5
Khare et al ²⁶	4	Shunt surgery	3
Agarwal et al ²⁸	37	Shunt surgery	23
Vibert et al ²⁹	10	Shunt surgery	7
Chattopadhyay et al ³⁰	43	Portosystemic shunting or splenectomy-devascularization	38

resolution of PCC by decompression of the collaterals is summarized in Table 1.

The persistence of changes of PCC after shunt surgery has led to the conclusion that ischemia may play a significant role in the pathogenesis of PCC. However, it is well known that occasionally, the portosystemic collaterals may persist despite effective portal decompression in patients with intra- or extrahepatic portal hypertension.^{33,34} Thus, despite shunt surgery for portal hypertension, it would be no surprise that the shunt surgery may not result in complete disappearance of the collaterals and thus the cholangiographic changes may persist.

- c) There are no cases reported of bile duct stenosis developing before the development of a cavernoma.²⁰

FIXED COMPONENT OF PORTAL CAVERNOMA CHOLANGIOPATHY

The resolution of abnormalities cholangiographic abnormalities is not universal and is often partial which suggests that mere compression by collaterals or portal cavernoma is a simplistic view of the etiology. Smooth strictures open after shunt surgery and proximal dilatation disappear in most patients. The indentations and caliber irregularities disappear after shunt surgery, whereas angulations and ectasias of biliary ducts persist.¹⁸

Rigidity of strictures, which has been observed, also supports the ischemic etiology.^{17, 35} While some authors have shown imaging evidence of collaterals causing biliary compression, this is not seen in all the patients. Dhiman et al²¹ evaluated the relationship of biliary changes with portal cavernoma using MR cholangiography coupled with MR portography in 18 patients with EHPVO and found that in nine patients with dominant stricture of the bile duct, only five (55%) of them were caused by compression from adjacent collaterals and no such relationship was seen in the remaining four (44%); and hence, presumed an ischemic etiology.

The various causes of the persistent component of PCC are – (i) ischemia at the time of portal vein thrombosis, (ii) local ischemia due to prolonged local wall compression by collaterals, and (iii) encasement by a fibrous “solid tumor-like cavernoma” which encases the bile duct.

Extension of the thrombotic process to small venules of the bile ducts has been proposed to cause ischemia of the bile ducts.³⁶ Historically, the hepatic artery has been considered mainly responsible for biliary blood flow. However, the contribution of the portal vein to the microvascular blood flow through the bile duct is being recognized. Sliker et al⁸ have shown that clamping the portal vein decreased the microvascular flow through the common bile duct by 62%. The reciprocal hepatic arterial response, which causes a dilatation of the hepatic arterial system in response to a decrease in the portal venous

flow, is an adaptive protective phenomenon that results in a diversion of blood flow toward the sinusoids. It is possible that this may result in reduced supply toward the bile ducts. The importance of portal venous blood flow in ischemic-type biliary lesions (ITBL) after liver transplantation is also being recognized. Following segmental portal vein thrombosis, patients with liver transplant have been seen to develop ITBL in the affected segments in the presence of normal arterial blood flow.³⁷

There may be formation of new vessels and connective tissue resulting in solid tumor-like cavernoma comprising of fibrous hilar mass containing multiple tiny collateral veins. Laparoscopy may reveal compression by a fibrous hilar mass containing multiple tiny collateral veins rather than markedly enlarged portal collaterals.^{20, 27, 37, 38} MR has shown this “solid tumor-like cavernoma” to be characterized by a uniform mass-like structure with a solid appearance mimicking a tumor in which the venous collaterals could not be individualized clearly.²⁰ Histology and morphological studies have shown that the cavernous transformation is not only a dilatation of periportal collaterals but also involves neogenesis and formation of connective tissue with increasing duration of thrombosis.³⁹ In such cases having a frozen portal hilum, decompression of portal collaterals may not relieve biliary obstruction.

PATHOGENESIS OF GALLSTONES IN PORTAL CAVERNOMA CHOLANGIOPATHY

Cholelithiasis in the setting of PCC may be due to chronic cholestasis, changes in the lithogenicity of bile or other factors such as reduced portal flow and associated liver atrophy.⁴⁰ Reduced contractile function of the gallbladder has also been proposed to contribute to development of gallstones due to the presence of gallbladder wall collaterals. Patients with asymptomatic PCC may not have a critical level of extrahepatic biliary obstruction resulting in abnormal emptying of gallbladder and bile lithogenicity.⁴¹ Animal studies have shown decreased bile acid synthesis and bile flow following interruption of portal flow with an increased tendency toward formation of stones.^{42,43} Pigment stones have been seen to develop in patients with ductal stenosis without stones in the gallbladder.^{20,44}

HOW DO WE EXPLAIN THAT SYMPTOMATIC PCC IS SEEN IN ONLY A FEW CASES OF PORTAL HYPERTENSION?

Although biliary abnormalities in portal hypertension are extremely common, symptomatic PCC is seen only in a small fraction. The low prevalence of symptomatic PCC is likely to be related to the cause of portal hypertension,

the duration of portal hypertension and the pattern of occlusion of the splenoportal axis.

Development of PCC is related to the duration of portal hypertension. PCC is a rare cause of childhood cholangiopathy.⁴⁵ It usually takes two or three decades to develop PCC usually in adulthood.⁴⁶ On long term follow up of 82 children with extrahepatic portal vein obstruction, three patients (3.6%) developed symptomatic intrahepatic and extrahepatic biliary dilatation or stenosis (2 at 12 years of age and other at 14 years).⁴⁷ Similar results have been shown by Zargar et al⁴⁸ who followed up 69 children with EHPVO for an average of 15 years, three (4%) of whom developed biliary obstruction secondary to PCC. It is likely that this time lag between development of portal hypertension and development of symptomatic PCC is related to progression in size of collaterals around the bile duct, development of fibrosis in the cavernoma, development of local ischemic necrosis of the bile duct due to prolonged pressure by the enlarged collaterals or development of biliary stones in the dilated biliary tract.

Llop et al¹⁶ have shown that the appearance of PCC is an early event in the natural history of portal vein thrombosis (PVT) and once PCC appears, the biliary tree abnormalities remain stable. They followed up 67 consecutive patients of PVT, which included 22 patients with acute PVT, for progression of cholangiographic abnormalities development of symptomatic PCC. They graded the cholangiographic changes of PCC as grade I (minimal irregularities), grade II (stenosis without dilatation) and grade III (stenosis with dilatations). They found that symptomatic PCC occurred only in patients with grade III PCC. They found that PCC developed early after acute PVT in 30% and the capacity of biliary abnormalities to progress after 1 year was extremely low. They also found that despite early development of significant PCC, the prevalence of symptomatic PCC increases only with longer period of time and development of biliary stones was a trigger of symptoms in 50% of their cases.

That significant/symptomatic PCC may never develop in many patients with PVT may be explainable by the pattern of development of collaterals. Walser et al⁴⁹ compared the anatomy and clinical features of 19 patients of PVT with PCC to 41 patients of PVT without PCC. They found that patients without PCC were more likely to have cirrhosis. On the other hand, patients with PCC were more likely to have extension of the thrombus into the spleno-mesenteric venous thrombosis (95% vs. 2%), lower gastroesophageal varices (16% vs. 49%), smaller coronary vein diameter and acute angulation of the common bile duct at the superior border of the pancreatic head (associated with compression by pancreaticoduodenal veins). They also found that PCC patients had higher incidence of hypercoagulable states. They hypothesized that in patients without PCC, there was a gradual decrease in hepatopedal flow, which causes the coronary vein to dilate. Therefore,

when the portal vein finally thromboses, this results in portal decompression into gastroesophageal varices rather than into peripancreatic venous structures. In contrast, when patients with a hypercoagulable state and a normal liver develop an acute thrombosis of the portal and mesenteric veins, there are no portosystemic shunts from chronic portal hypertension and the first large collateral may be the gastroduodenal trunk off the superior mesenteric vein. The blocked superior mesenteric vein may result in retrograde flow via gastroduodenal trunk into the pancreaticoduodenal veins. The posterior pancreaticoduodenal vein joins the portal vein near the hepatic hilum. This is more likely to cause a different collateral pathway in the setting of PCC where the portomesenteric occlusion results in preferential peribiliary collateral flow (retrograde gastroduodenal trunk to pancreaticoduodenal venous flow) rather than the commoner gastroesophageal variceal. It is possible that this peribiliary venous pathway may be responsible for bile duct compression.⁴⁹

CONCLUSION

PCC consists of both a reversible component, which resolves by decompression of collaterals as well as a fixed component, which persists despite the decompression of collaterals. The reversible component is due to compression by large collaterals located strategically close to the bile duct as well as possibly intracholedochal varices. The fixed component is likely to be due to ischemia at the time of portal vein thrombosis, local ischemia by compression as well as encasement by a solid tumor-like cavernoma comprising of fibrous hilar mass containing multiple tiny collateral veins rather than markedly enlarged portal collaterals.

Despite cholangiographic abnormalities in portal hypertension being common, the low prevalence of symptomatic PCC is likely to be related to the cause of portal hypertension, the duration of portal hypertension and the pattern of occlusion of the splenoportal axis. There may possibly be higher prevalence of symptomatic PCC in occlusion of the spleno-mesenteric veins.

CONFLICTS OF INTEREST

The author has none to declare.

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