World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i26.3375

World J Gastroenterol 2012 July 14; 18(26): 3375-3378
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

GUIDELINES FOR CLINICAL PRACTICE

How can portal vein cavernous transformation cause chronic incomplete biliary obstruction?

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Received: November 02, 2011 Revised: February 27, 2012
Accepted: March 19, 2012
Published online: July 14, 2012

Abstract

Biliary disease in the setting of non-cirrhotic portal vein thrombosis (and similarly in portal vein cavernous transformation) can become a serious problem during the evolution of disease. This is mostly due to portal biliary ductopathy. There are several mechanisms that play a role in the development of portal biliary ductopathy, such as induction of fibrosis in the biliary tract (due to direct action of dilated peribiliary collaterals and/or recurrent cholangitis), loss of biliary motility, chronic cholestasis (due to fibrosis or choledocholithiasis) and increased formation of cholelithiasis (due to various factors). The management of cholelithiasis in cases with portal vein cavernous transformation merits special attention. Because of a heterogeneous clinical presentation and concomitant pathophysiological changes that take place in biliary anatomy, diagnosis and therapy can become very complicated. Due to increased incidence and complications of cholelithiasis, standard treatment modalities like sphincterotomy or balloon sweeping of bile ducts can cause serious problems. Cholangitis, biliary strictures and hemobilia are the most common complications that occur during management of these patients. In this review, we specifically discuss important issues about bile stones related to bile duct obstruction in non-cirrhotic portal vein thrombosis and present evidence in the current literature.

Key words: Portal vein cavernous transformation; Cholelithiasis; Hemobilia; Portal ductopathy; Portal biliopathy

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Harmanci O, Bayraktar Y. How can portal vein cavernous transformation cause chronic incomplete biliary obstruction? *World J Gastroenterol* 2012; 18(26): 3375-3378 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i26/3375.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i26.3375

INTRODUCTION

The thrombosis occurring secondary to various causes results in acute and generally asymptomatic thrombosis in an extra-hepatic portion of portal vein transformation (PVT). Eventually, portal vein cavernomatous transformation (PVCT) forms as a compensatory reaction 3 wk to 3 mo after the initial event at the hilum of the liver. However, this salvage also results in inevitable anatomical or functional changes at surrounding structures including the biliary tree, gallbladder and pancreas[1-4]. These changes are secondary to perfusion changes, neovascularization, fibrosis reaction or compression of ducts by newly formed but highly perfused vessels.

Recent terminology uses the term "portal biliopathy" to denote overall anatomical, morphological and functional changes in the biliary tree[5]. The manufactured term "biliopathy" originates from a combination of the Latin word "bilis" (meaning bile) and the Greek word "pathos" (meaning disease) suggesting a disease of liq-

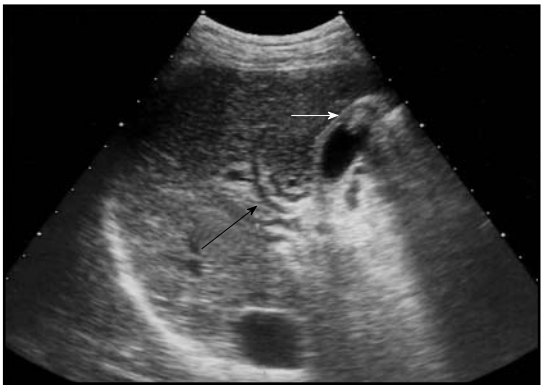

Figure 1 Liver ultrasound image showing stone (white arrow) and portal vein cavernomatous transformation (black arrow) in gallbladder.

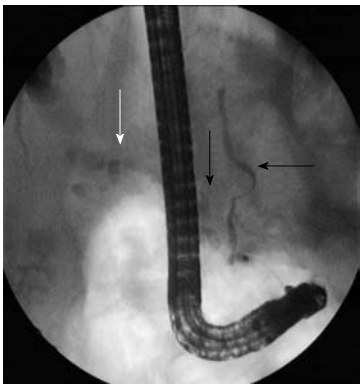

Figure 2 "Portal double ductopathy" sign with stones. Endoscopic retrograde cholangiopancreatography image of a patient with chronic portal vein cavernomatous transformation showing irregular pancreatic duct and biliary ducts (black arrows). Main bile duct shows local stricture and dilations with cholelithiasis (white arrow).

uid bile or its constituents. However, current knowledge lacks compelling evidence of formation of diseased bile in patients with PVCT. Therefore in this review, the term "portal ductopathy" (PD) will be used instead of portal biliopathy as suggested by our group previously[6].

The changes that take place in the biliary ducts during the course of PVCT can be summarized as strictures, dilatations and varicose veins located at the ductular walls and gallbladder. In the long term, these changes result in biliary stasis, jaundice, cholangitis and cholelithiasis adding more to morbidity and even resulting in mortality (Figures 1 and 2). The superimposition of cholelithiasis observed in the setting of PD is very important since these patients are prone to secondary biliary cirrhosis, a complication observed in 4% of patients[7]. The clinical problem of cholelithiasis observed in chronic, non-cirrhotic PVCT patients is an under-mentioned topic and forms the basis of this compact review. Other clinical problems such as cirrhotic patients, biliary strictures or surgical management related to PD are beyond the scope of this paper.

PATHOGENESIS OF CHOLELITHIASIS IN PORTAL VEIN CAVERNOMATOUS TRANSFORMATION

Theoretically, cholelithiasis in the setting of PD and PVCT may be secondary to chronic cholestasis, changes in the constituents of bile or other factors such as reduced portal flow and associated liver atrophy.

Cholestasis and gallbladder functions

Cholestasis and related clinical findings such as jaundice, pruritus and cholangitis are the most common presenting symptoms in the setting of symptomatic PD and occurs in 5%-30% of all patients[8,9]. Chronic biliary stasis (due to compression in the biliary outflow and loss of bile duct contractility due to either fibrosis or ischemia[8]) may eventually result in stones formed *de novo* located in biliary ducts and/or gallbladder. The evidence for the proof of this hypothesis is obtained from clinical studies which generally observed pigment stones, located just proximal to the site of ductular stenosis without associated stones in the gallbladder[10,11]. The reduced contractile function of the gallbladder may also contribute to development of stones due to the presence of varicose veins in the gallbladder wall, but in one study the contractile function of gallbladder has been found to be unchanged[12]. Thus, cholestasis is believed to develop at later stages of PD secondary to fibrosis and compression of newly formed vessels, which are a major factors for development of stones. Once formed, stones further contribute to cholestasis and stricture formation by initiating recurrent cholangitis attacks.

Change in the constituents of bile

There is a small amount of evidence in the literature to indicate a change in the composition of bile resulting in a tendency for development of cholelithiasis. Previous studies investigating the contribution of reduced portal flow for development of cholelithiasis found that there is an increased tendency towards formation of stones after selective portal vein ligation in dogs[13]. Also, temporary interruption of portal flow leads to decreased bile acid synthesis and biliary flow[14]. There is no human study in the literature to indicate definitive changes in biliary composition take place during PVCT. Hypothetically speaking, presence of abnormal portal inflow might contribute to formation of lithogenic bile either by causing hypersplenism and increased pigment load in bile or abnormal enterohepatic circulation of bile acids due to portal hypertension.

FREQUENCY AND CLINICAL FINDINGS OF CHOLELITHIASIS IN PORTAL VEIN CAVERNOMATOUS TRANSFORMATION

The findings obtained from key studies concerning cholelithiasis observed in PVT-PVCT (in adult and pediatric populations) are summarized in Table 1. The frequency of cholelithiasis is highly variable (0%-84%). Probably, this variability is secondary to the problem of potential

Table 1 Cholelithiasis and important findings from selected studies

Author	Patient population	Frequency and location of cholelithiasis (%)	Notes
Bayraktar *et al*[1]	47 PVT patients evaluated by ERCP	8 (19) located in CBD	Unselected PVCT patients irrespective of symptoms, had a control group of 22 patients with other causes of portal hypertension
Condat *et al*[11]	25 consecutive patients in 2 yr evaluated by MRCP	4 (16)	Cholelithiasis associated with abrupt elevation of transaminase level, obstructive jaundice and cholangitis (2 patients)
Khare *et al*[27]	13 patients with obstructive jaundice evaluated by ultrasound	4 (31) located in GB, 4 (31) located in CBD	Retrospective selection of patients with obstructive jaundice
Sezgin *et al*[19]	10 consecutive patients in 6 yr presenting with jaundice and/or cholangitis evaluated by ERCP	0	Only patients with biliary symptoms are evaluated; Total number of patients or prevalence of cholelithiasis is not mentioned
Oo *et al*[16]	13 patients with symptoms related to PD in 13 yr	11 (84) located in GB, 9 (69) located both in GB and CBD	Symptomatic patients selected
Dumortier *et al*[28]	6 consecutive patients presented as case series	4 (66) located in GB, 2 also had stones in CBD	Upon follow up 3 patients suffered from cholecystitis and cholangitis requiring cholecystectomy
Chaudhary *et al*[20]	9 symptomatic PD patients managed surgically	2 (22) located in CBD	Selected patients with indications for surgery; Bile aspirates during surgery revealed *Escherichia coli* in patients with stones
Agarwal *et al*[29]	39 symptomatic PD patients managed surgically	12 (30) located in GB, 7 (18) located in CBD	Selected patients with indications for surgery
Dhiman *et al*[17]	53 symptomatic and asymptomatic patients	11 (20) (7 located in GB while 4 in CBD)	Stones were found more frequently in patients with symptoms than asymptomatic patients
Ozkavukcu *et al*[30]	16 patients diagnosed with PVT evaluated by MRCP	0 (there are 3 patients with history of cholecystectomy but the reasons are not given)	Patients with history of, chronic liver diseases, liver abcess and hydatid cyst were not eliminated with potential interference with findings of biliary system
Chiu *et al*[31]	29 children with PVT diagnosis evaluated for Rex shunt	5 (17) located in GB, 4 (14) had biliary sludge	Only children evaluated for possible surgery included
Yamada *et al*[32]	21 children with PVT	3 (14) located in GB	21 patients selected out of 35, selection criteria not mentioned

PVT: Portal vein transformation; ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancreatography; PD: Portal ductopathy; CBD: Common bile duct; GB: Gallbladder; PVCT: Portal vein cavernomatous transformation.

bias in patient selection criteria. Most of the studies only included patients with symptoms in a retrospective design or included patients with chronic liver disease-cirrhosis or with mass-occupying lesions. In most of these studies, investigation methods [endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography or ultrasound] were not uniform so it was not possible to make a definitive conclusion about incidence and prevalence of stones. The choice of investigation method has been found to have a clear impact on the results of anatomical location of cholelithiasis found in the biliary system. Therefore, current literature lacks prospective and well-designed studies to reveal the exact prevalence and incidence of cholelithiasis in a group of well selected PVCT patients irrespective of presence of symptoms.

The clinical findings related to cholelithiasis in PVCT patients are not different from patients who do not have PVCT, but it is evident that it results in a high frequency of PD symptoms. Cholelithiasis is found more commonly in patients with biliary findings such as jaundice, biliary colic, cholangitis and elevated liver enzymes compared with asymptomatic patients[7,15].

TREATMENT

The management of stones in patients with PVCT merits its special attention since concomitant changes in the biliary system may jeopardize standard therapeutic procedures. The collaterals of Petren and Saint around major bile ducts enlarge in response to PVCT and they form the basis of collateral vessel compression to major bile ducts in PD[6,7]. Also, secondary to ischemic injury and development of fibrous tissue in the major biliary ducts, biliary interventions should be performed with caution. Since these varicose collaterals and fibrous strictures may result in detrimental complications like hemobilia or recurrent cholangitis, clinicians should follow special management strategies being aware of these potential risks. Otherwise, therapeutic strategies for cholelithiasis in PD are not different from other patient groups.

In previous studies focusing on treatment of PD, the major concern and attention was given to the problem of biliary strictures. The treatment of strictures and associated cholestasis is important since resolving these factors also reduces the risk of formation or recurrence of cholelithiasis. Biliary stricture and associated jaundice can be managed by medical treatment with ursodeoxycholic acid[11,16] or by interventions like biliary stenting[16-18], balloon dilatation[19] or portosystemic shunting[20]. If present, cholelithiasis should first be managed by evaluation of varicose veins around the common bile duct, either by magnetic resonance angiography or endoscopic ultrasonography[17]. After elimination of varicose veins, standard sphincterotomy and balloon trawl for extraction of common bile duct stones and/or sludge should be employed[10]. The presence of any collateral varicose vein is very important since inadvertent interventions

like basket removal of stones or biliary stenting might result in bothersome hemobilia[21-25] requiring massive transfusions, injection sclerotherapy[26], terlipressin[25] or urgent portosystemic shunting[21] . In our personal experience, we propose that papillotomy should be performed at earlier stages of disease as a prophylactic measure to make future ERCP procedures safer and easier. If not performed earlier, varices and fibrosis in the distal main bile duct can preclude or complicate safe papillotomy.

In conclusion, cholelithiasis and choledocholithiasis in the setting of PVCT and PD is a specific problem that needs special attention. Stones can become very problematic and interventions may result in severe hemobilia. Stone extraction by balloon or basket trawl can be gruelling due to strictures and fibrosis in biliary system. If present, biliary strictures and severe vascular compression should be treated by medical or interventional treatments in order to facilitate stone extraction and reduce recurrence. Further well designed prospective studies are required to clearly understand the exact natural history of cholelithiasis in PVCT patients.

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S- Editor Gou SX **L- Editor** O'Neill M **E- Editor** Li JY