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Carcinogenesis of malignant lesions of the gall bladder

The impact of chronic inflammation and gallstones

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Abstract Gallbladder carcinoma is an uncommon but highly malignant tumor with a poor 5-year survival rate. The presence of gallstones is a well-established risk factor for gallbladder carcinoma, and the risk seems to correlate with stone size. Metaplastic changes of the gallbladder epithelium present in chronic cholecystitis may be a premalignant lesion. Solitary polyps with a size of greater than 1 cm are recognized as a predisposing factor for gallbladder carcinoma when their characteristics are echopenic, sessile, and high cell density. Endoscopic ultrasound is the most useful technique to detect the early changes of malignancy in polyps. Anomalous junction of pancreaticobiliary ducts (AJPBD) without a choledochal cyst and porcelain gallbladder is an additional risk factor for gallbladder malignancy. At the molecular level, it has been proposed that chronic inflammation of the gallbladder may lead to the loss of p53 gene heterozygosity and excessive expression of p53 protein. Furthermore, a proposed mechanism underlying the high risk of gallbladder carcinoma in patients with AJPBD is that chronic reflux of pancreatic juice causes intestinal metaplasia, hyperplasia, and dysplasia with the mutation of p53 and K-ras. In contrast, the causal relationship between porcelain gallbladder and malignancy is yet to be established. In this article, recognition of risk factors for gallbladder carcinoma was summarized with special attention to gallstones and chronic inflammation.

Keywords Cholecystitis · Anomalous junction of the pancreaticobiliary duct · Porcelain gallbladder · Adenomyomatosis · Metaplasia

Introduction

Gallbladder carcinoma is fifth in incidence of gastrointestinal carcinoma [1], and the well-known risk factors are gallstones, anomalous junction of pancreaticobiliary ducts (AJPBD), and porcelain gallbladder [2]. Female gender is also associated with gallbladder carcinoma, and this may be, in part, due to the increased incidence of gallstones in women when compared with men. Despite drastic improvement in diagnostic techniques, it is not yet easy to detect gallbladder carcinoma at an early stage, and, thus, most cases are diagnosed at an advanced stage. Accordingly, less than 10% of patients have resectable tumors at the time of diagnosis, and the median survival is less than 6 months; the overall 5-year survival rate is less than 5% [3].

Furthermore, the therapeutic strategy for metastatic gallbladder carcinoma is unfortunately restricted and, therefore, prevention or detection at an early stage is required for improving the survival rate. In this regard, the evaluation of risk factors for gallbladder carcinoma should be clarified, and prophylactic cholescystectomy must somehow be beneficial to manage this fatal tumor.

In this article, predisposing factors for gallbladder carcinoma and circumstances associated with such malignant lesions are summarized with attention concentrated on the presence of gallstones, chronic inflammation associated with gallstones, and underlying mechanism(s) in such a process.

Table 1 Types of gallstones

Cholesterol stones: >cholesterol, commonly present in the gallbladder	
Pure radiate cholesterol stones	>90% Cholesterol
Mixed stones	Cholesterol and calcium bilirubinate
Combination stones	Radiate cholesterol stones as a center with an outer-layer shell, structurally similar to mixed stones
Pigment stones: >50% calcium bilirubinate, present in gallbladder and bile duct	
Black stones	Insoluble bilirubin polymer; in gallbladder
Brown stones	Calcium bilirubinate; in gallbladder and bile duct
Other types	

Gallstone disease

Gallstone disease is common with incidence ranging from 10% to 20% of the world population; this incidence increases with age and is higher among women of any age than men [4, 5]. Gallstones are associated with various pathological circumstances: hemolytic anemia, liver cirrhosis, postoperative state after gastrectomy or cardiac valvular replacement, diabetes mellitus, biliary inflammation, and intake of hypolipidemic agents or contraceptives. Gallstones are classified according to components and locations (Table 1) and the pathogenic mechanisms vary.

Cholesterol gallstone pathogenesis

It is proposed by Small [6] to subdivide cholesterol gallstone disease into five stages: (1) genetic–metabolic, (2) chemical, (3) physical, (4) growth, and (5) clinical. Bile cholesterol saturation is caused by two metabolic defects in biliary lipid secretion, cholesterol hypersecretion and bile acid hyposecretion [7]. Excessive cholesterol secretion is related to increased cholesterol synthesis in the liver, and this is associated with obesity, aging, pregnancy, hyperlipidemia, oral contraceptive use, and hypolipidemic agents. In contrast, bile acid hyposecretion is related to impaired bile acid synthesis and/or abnormal intestinal bile acid loss. In combination, these defects result in bile cholesterol supersaturation.

Bile cholesterol is carried in both bile acid micelle and lecithin-cholesterol vesicles. The excessive cholesterol is carried predominantly by lecithin-cholesterol vesicles; such cholesterol-rich vesicles tend to aggregate and fuse to each other, eventually forming cholesterol monohydrate crystals as an initial and essential step in the cholesterol gallstone formation process (Fig. 1). In this regard, rapid nucleation is enhanced in bile containing unsaturated fatty acid-rich lecithins [8]. In addition to directly affecting the physical chemical stability of vesicles, unsaturated fatty acids are released from lecithins by phospholipase A2, and free fatty acids are absorbed by the gallbladder. Arachidonate, especially, is utilized for prostanoid synthesis, which is associated with stimulation of mucin production. The secretion of mucin produced within the gallbladder wall is indirectly stimulated by free fatty acids and lysolecithins. The excessive mucin form a gel

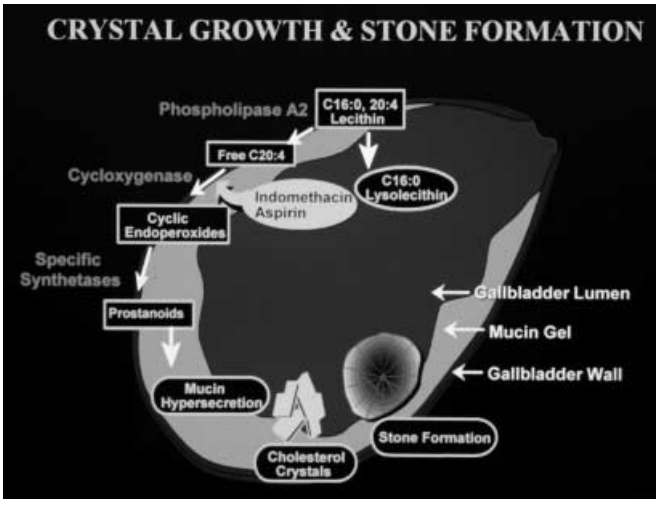

Fig. 1 Cholesterol crystal nucleation process. Bile cholesterol is carried by bile acid micelles and lecithin–cholesterol vesicles. The excessive cholesterol is carried predominantly by lecithin–cholesterol vesicles, and such cholesterol-rich vesicles tend to aggregate and fuse to each other, eventually forming cholesterol monohydrate crystals as an initial and essential step in the cholesterol gallstone formation process. Another transitional form to carry such an excessive cholesterol is phospholipid lamella (discoidal particles), which also plays a role in cholesterol crystal nucleation

bed on the surface of the gallbladder epithelium, providing a preferential circumstance for cholesterol crystal growth to a macroscopic stone (Fig. 2).

Cholesterol crystal nucleation is regulated by the balance between promoting and inhibitory factors present in bile – promoting factors, mucin and glycoproteins; inhibitory factors, apolipoproteins. The gallbladder itself plays a crucial role in the process of cholesterol crystal growth to form a macroscopic stone. Thus, impaired gallbladder emptying leads to bile stasis in the gallbladder, promoting cholesterol precipitation and, further, providing the time needed for crystal growth. This is enhanced by long-term hyperalimentation, pregnancy, and the use of contraceptives.

Pigment gallstone pathogenesis

Black stones are formed in the gallbladder, consisting dominantly of insoluble unconjugated bilirubin polymers and mucin glycoproteins. Pathogenic factors are: (1) excessive

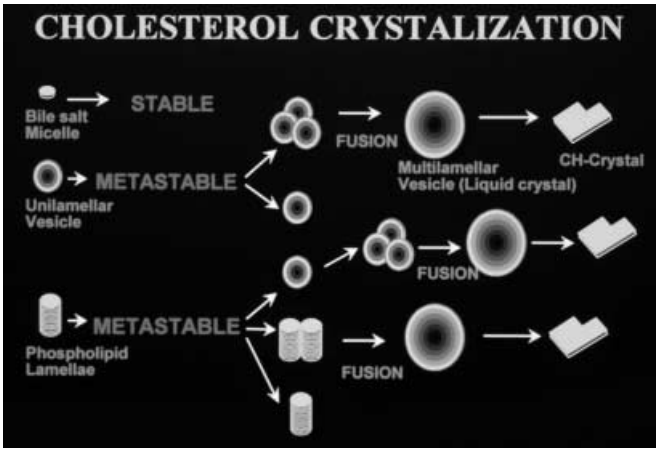

Fig. 2 Role of gallbladder in gallstone formation process. In addition to the direct effect on the physical chemical stability of vesicles, unsaturated fatty acids are released from lecithins by phospholipase A2, and free fatty acids are absorbed by the gallbladder. Arachidonate is especially utilized for prostanoid synthesis; this is in association with stimulation of mucin production. Mucin secretion from the gallbladder is stimulated by free fatty acids and lysolecithins. The excessive mucin forms a gel bed on the surface of the gallbladder epithelium, which provides a preferential circumstance for cholesterol crystal growth into a macroscopic stone

bilirubin secretion into bile based upon the increased production of bilirubin, i.e., hemolytic anemia, liver cirrhosis, and pathogenic circumstances after cardiac valvular operation or artificial organs and (2) decrease of bile acid secretion into bile resulting in decreased bilirubin solubility and increased ionized calcium in bile. On this basis, nonbacterial hydrolysis of conjugated bilirubin is enhanced to produce the excess of free bilirubin, and, thus, bilirubin polymers are formed to precipitate with free ionized calcium [9].

In contrast, brown stone formation is pathogenically associated with biliary stasis and bacterial infection. Bacteria and injured biliary epithelium release beta-glucuronidase and phospholipase into bile. These enzymes hydrolyze conjugated bilirubin and lecithin to produce unconjugated bilirubin, free fatty acids, and lysolecithin. On one hand, these products precipitate as calcium bilirubinate crystals to eventually form brown stones. On the other hand, polyunsaturated free fatty acids are absorbed by the gallbladder wall and utilized in the prostanoid pathway, stimulating mucin glycoprotein synthesis. Lysolecithin and polyunsaturated fatty acids are also stimulators for mucin secretion from the gallbladder wall, and the mucin gel in the gallbladder provides a preferential circumstance under which precipitated calcium bilirubinates grow up to a macroscopic brown stone [10].

Gallstone and cholecystitis

Biliary colic pain is the principle symptom in gallstone patients. This visceral pain is the result of transient obstruction of the cystic duct by a stone, and it becomes serious when accompanied by acute inflammation or acute cholecystitis. In pathology, chronic cholecystitis is frequently diagnosed in gallstone patients; thus, gallstone formation is followed by chronic inflammation, to some extent, regardless of the severity and frequency of symptoms.

Cholecystitis and malignant lesions

It is well established that gallstones are associated with gallbladder carcinoma. In a previous report, 1% of patients undergoing operation of symptomatic cholelithiasis are incidentally diagnosed with gallbladder carcinoma [11]. The pathogenic mechanism whereby gallstones are related to gallbladder carcinoma is yet to be established. Stone size and duration of gallstone disease seem to play a role, as proposed by an epidemiological study [12], suggesting that gallstones directly initiate neoplastic transformation such as carcinoma in situ in the gallbladder epithelium through forming dysplastic lesions. In the previous study, relatively large stones with a diameter of greater than 3 cm were detected more frequently in gallbladder carcinoma patients than in those without malignancy, suggesting that the physical property of such large stones play a pathogenic role in oncogenesis and initiating transformation of the gallbladder mucosa.

Metaplasic changes of the gallbladder epithelium, considered to be a premalignant lesion, are observed in chronic inflammation which is frequently associated with the presence of gallstones. In this regard, symptomatic gallstones in association with chronic cholecystitis are very likely related to a high incidence of gallbladder carcinoma. Symptomatic gallstones are predominantly cholesterol stones. Furthermore, epidemiological investigations in the North American population revealed that they predominantly carry lithogenic genes and, also, that they have the high prevalence of gallbladder carcinoma [13, 14, 15, 16], indicating a causal relationship between cholesterol gallstones and gallbladder carcinoma. At the molecular level, chronic inflammation of the gallbladder has been shown to lead to an allele-specific mutation – loss of heterozygosity of the p53 gene and overexpression of p53 encoding protein. This mutation is considered to result in malignant transformation of the gallbladder mucosa [17, 18].

In a chemical aspect, certain constituents in bile could be stimulator substances for gallbladder epithelium inflammation. Endogenous substances physiologically present in bile are lipids, i.e., cholesterol, bile acids and lecithins, and organic anions such as bilirubin. Those biliary constituents and their metabolites play a pathogenic role in gallbladder inflammation either directly or indirectly, or both. Biliary cholesterol hypersecretion is associated with an increase in bile of hydrophobic bile acids, i.e., chenodeoxychoic and deoxycholic acids. Bile cholesterol supersaturation caused by the excess cholesterol relative to the theoretical solubility is prerequisite for

cholesterol gallstone formation, and this is associated with a relatively high proportion of unsaturated fatty acids of lecithin in bile from the cholesterol gallstone patient [19]. These changes provide the following pathogenic circumstances: (1) increased mucin production in and secretion from the gallbladder through the arachidonate–prostanoid pathway; and thereby, (2) accelerated growth of crystals and stones; and (3) bile stasis because of enhanced viscosity. The mucin production and secretion are stimulated by hydrophobic bile acids, lysolecithin, and free fatty acids, but not lecithin, in bile. Accordingly, the step of enzymatic digestion of lecithin by phospholipase A2 is crucial for a series of events. The presence of gallstones induces bile stasis in the biliary tree, gallbladder and bile ducts, and provides a pathogenic circumstance for pancreatic enzyme refluxing and bacterial infection, consequently inducing the production of free unsaturated fatty acids and lysolecithins. In this regard, AJPBD possibly has, somehow, a causal relationship since a pancreatic juice containing phospholipase A2 is frequently refluxed into bile ducts.

Arachidonate metabolites play a significant role in gallbladder pathophysiology. The prostanoids, cyclooxygenase (COX) metabolites, are involved in gallbladder muscle contraction and mucosal water transport [20, 21], and mediate gallbladder inflammatory responses, which are inhibited by nonsteroidal antiinflammatory drugs (NSAIDs) [22, 23]. Thus, biliary pain associated with gallstone disease is mediated by prostanoids, and is treated with NSAIDs [24, 25]. The synthesis of prostanoids is mediated by COX-1 and COX-2, and the latter enzyme frequently is induced in response to inflammatory stimulators, lysolecithin, and cytokines in order to produce prostanoids [26, 27, 28]. Prostanoids and COX enzymes have also been shown to associate with carcinogenesis in various tumors, including gallbladder carcinoma [29, 30, 31, 32, 33, 34]. Gallbladder carcinoma and colon carcinoma have several analogous characteristics: (1) important association with inflammatory diseases, cholecystitis, and inflammatory bowel diseases; (2) a high incidence of polypoid lesion; and (3) increased COX enzymes in lesion and a therapeutic action of NSAIDs. In fact, the selective COX-2 inhibitor has recently been reported to inhibit replication of the gallbladder cancer cells, and then to induce their apoptosis [34]. This suggests that COX enzymes and prostanoids play a role in the development of gallbladder carcinoma and that COX-2 inhibitors may have a therapeutic role in the prevention of gallbladder carcinoma.

Polyps and premalignant lesions

Gallbladder polyps are recognized as a predisposing factor of gallbladder carcinoma. The prevalence of gallbladder polyps is 3–6%; differentiating malignant from benign polypoid lesions is sensitively performed by CT and endoscopic ultrasound. Endoscopic ultrasound is also sensitive to staging the extent of tissue invasion in malignancy of the gallbladder. The size, number, shape, and echogenecity of polypoid lesion are important factors used to distinguish malignancy. The prevalence of carcinoma increases correspondingly with polyp size: less than 10 mm, 0–5%; 10–15 mm, 11–13%; greater than 15 mm, 46–70%. The majority of malignant lesions are solitary (80–100%), and a third of sessile polyps harbor carcinoma. Echogenecity of malignant polyps is frequently isoechoic with the liver parenchyma or echopenic. Furthermore, the age of patients (>50 years old) and associated gallstones are other important risk factors.

Anomalous junction of the pancreaticobiliary duct

AJPBD is a congenital defect in the union of pancreatic and biliary ducts. AJPBD is principally diagnosed by endoscopic retrograde cholangiopancreatography (ERCP) and is found in 1–2% of patients undergoing ERCP for any indication. Endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) are also sensitive in the diagnosis of AJPBD. Gallbladder carcinoma is associated with AJPBD in approximately 10% of patients. In this regard, several investigations revealed that among AJPBD patients without a dilatation of common bile duct, the incidence of gallbladder carcinoma is higher than in those with choledochal cyst, a cystic dilatation of common bile duct [35, 36, 37].

A proposed mechanism underlying the high risk of gallbladder carcinoma in AJPBD patients is metaplasic changes of the gallbladder epithelium caused by chronic reflux of pancreatic juice into the gallbladder. Premalignant transformation of the gallbladder epithelium such as intestinal metaplasia, hyperplasia, or dysplasia, is associated with the mutation of p53 and K-ras [38, 39, 40]. Because the hydrostatic pressure within the pancreatic duct is higher than that in the bile duct, pancreatic juice flows easily into the bile duct of patients with AJPBD. This provides a possibility that bile constituents such as lecithin are enzymatically broken down into lysolecithin and free fatty acids by activated phospholipase A2 in pancreatic juice. In fact, increased lysolecithin and pancreatic enzymes are evident in AJPBD [41], and such a cytotoxic metabolite presumably stimulates the gallbladder transformation continuously. Although the high concentration of phospholipase A2 in bile is also thought to provide lithogenic circumstance, the frequency of gallstones in patients with AJPBD and gallbladder carcinoma is low. In contrast, incidence of adenomyomatosis, a fundic type, is considerably high in AJPBD patients without a cystic dilatation of common bile duct; adenomyomatosis is also proposed to be another premalignant lesion, although no direct information mechanistically supporting this has been established [42, 43].

Other risk factors for gallbladder carcinoma

Porcelain gallbladder

Calcification of the gallbladder wall, "porcelain gallbladder", is a well-defined premalignant condition. It is estimated that approximately 20% of porcelain gallbladders harbor gallbladder carcinoma, and patients with incomplete calcification of the gallbladder wall carry a greater risk than those with complete calcification. This is explained by the complete loss of gallbladder mucosal epithelium, which means no space to harbor malignancy remains. However, the pathogenic relationship of calcification of the gallbladder to malignancy has yet to be established.

Adenomyomatosis

When the gallbladder mucosa forms the cyst-like structure Rokitansky-Ashoff sinus (RAS) in the muscular layer, it is considered to be adenomyomatosis. Adenomyomatosis is often free from symptoms, but is frequently associated with small stones, which may cause colic pain. Thus, adenomyomatosis is one of the risk factors for gallbladder carcinoma, especially when chronic inflammation is associated with complicated gallstones. However, thickening of the gallbladder wall itself is one characteristic of adenomyomatosis and, therefore, differentiating the malignant lesion from focal thickening of gallbladder wall is not easy by use of visual images. In general, adenomyomas located in the fundus having a diameter of 10–20 mm or those with a small ulceration on the surface seem to harbor gallbladder carcinoma.

Bacterial infections

Bile from symptomatic gallstone patients frequently contains bacteria, predominantly *Escherichia coli*; this is more incidental in gallbladder carcinoma associated with gallstones, suggesting that bacteria play a role in the gallbladder carcinoma pathogenesis such as producing carcinogen [44]. Such an action is presumably enhanced by the presence of gallstones. Furthermore, bile-resistant *Helicobacter* species, *Salmonella typhi* or *paratyphi*, are found in bile from patients with chronic cholecystitis, and their presence is considered to be a risk factor for malignancy. However, the pathogenic relationship between bacteria and gallbladder carcinoma remains unclear.

Table 2 Proposed indications for prophylactic cholecystectomy

Definite indications
1 Anomalous junction of the pancreaticobiliary duct without choledochal cyst
2 Porcelain gallbladder
Possible indications
1 Polyps: >1 cm, solitary, sessile
2 Symptomatic gallstones with chronic cholecystitis: nonsurgical therapy is not promising

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a progressive liver disease with intrahepatic cholestasis [45]. This is frequently associated with inflammatory bowel diseases such as ulcerative colitis. In addition, the high incidence of associated biliary stones suggests that PSC may be associated with gallbladder carcinoma. Proposed causes of PSC are as follows: (1) chronic portal bacteremia; (2) absorption of colon toxins or toxic bile acids; (3) chronic infection; (4) ischemic injury; (5) genetic predisposition; or (6) immunological abnormalities. Thus, the etiology of PSC itself is unknown, and further studies are needed to clarify the relationship between PSC and gallbladder carcinoma.

Summary and conclusions

Gallbladder carcinoma is highly malignant, and its 5-year survival rate is less than 5%. In this article, predisposing factors for gallbladder carcinoma and circumstances associated with such malignant lesions are summarized, especially focusing on gallstones and inflammation. Though it is certainly essential to accurately identify patients with risk factors for gallbladder carcinoma, it is also true that prophylactic cholecystectomy is beneficial for patients carrying such risks. Proposed indications for such a prophylactic cholecystectomy are shown in Table 2.

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