Carcinogenesis of malignant lesions of the gall bladder
The impact of chronic inflammation and gallstones

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 cholecystectomy 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.
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 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