Adenocarcinoma of the Gallbladder: Risk Factors and Pathogenic Pathways

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Abstract

For ordinary adenocarcinoma of the gallbladder, several risk factors have been identified. The most important risk factors are cholelithiasis, female gender, advancing age, and an elevated maximum body mass index. Gallstones and associated inflammatory gallbladder disease are the most common risk factors for gallbladder cancer. At least three quarters of patients with gallbladder carcinoma have gallstones at the time point of diagnosis, but cholelithiasis seems to be a cofactor for carcinogenesis. There is a relationship between gallbladder carcinoma and chronic inflammatory disease of the gallbladder, including xanthogranulomatous cholecystitis. Also chronic sclerosing and hyalinizing cholecystitis with or without calcification is associated with gallbladder carcinoma. Other carcinogenic associations include anomalous pancreaticobiliary junction and an increasing number of genetic, epigenetic, and molecular alterations.

Cholelithiasis

The most important risk factors for carcinoma of the gallbladder (CG) are cholelithiasis, female gender, advancing age, and elevated maximum body mass index (Strom et al. 1995; Sheth et al. 2000; Pandey 2003; Miller and Jarnagin 2008; Rustagi and Dasanu 2012). Gallstones and

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associated inflammatory gallbladder changes are the most common risk factors for CG (Slade 1905; Fawcett and Rippmann 1913; Luelsdorf 1926–1927; Goldschmidt 1963; Wenckert and Robinson 1966; Hardy and Volk 1970; Hart et al. 1971; Balaroutsos et al. 1974; Beltz and Condon 1974; Arnaud et al. 1979; Hamrick et al. 1982; Vitetta et al. 2000; Tazuma and Kajiyama 2001; Chen et al. 2014; Cariati et al. 2014). It is estimated that three quarters of patients with CG have gallstones at the time point of diagnosis (Balaroutsos et al. 1974). Piehler and Crichlow (1978), in a review of the literature, found a 73.9 % incidence in 2,000 cases. Overall, the risk of CG is approximately four to five times higher in patients with gallstones than in patients without gallstones (reviews: Lowenfels et al. 1985; Lowenfels et al. 1999). Currently, it is considered that gallstones as such are a cofactor for carcinogenesis, but formal proof that they directly cause CG is lacking (review: Shrikhande et al. 2010).

Chronic Inflammatory Gallbladder Disease

There is a relationship between CG and chronic inflammatory disease of the gallbladder, including xanthogranulomatous cholecystitis (Zhuang et al. 2013). Chronic sclerosing and hyalinizing cholecystitis with or without wall calcification (porcelain gallbladder) is associated with CG (Polk 1966; Berk et al. 1973; Stephen and Berger 2001; Khan et al. 2011; Patel et al. 2011; Gupta and Jauhari 2012; Wong and Weissglas 2013). Porcelain gallbladder is a rare condition which was found in only 0.06–0.80 % of cholecystectomy specimens. It is more common in female patients. A recent investigation demonstrated that the risk of harboring CG in patients with porcelain gallbladder is lower than recently anticipated (Schnelldorfer 2013), and in one study, no association between porcelain gallbladder and CG was identified (Towfigh et al. 2001). The significance of gallbladder polyps in predisposing to CG is probably overstated (Pilgrim et al. 2013). Environmental agents, such as heavy metals, have been proposed to be related to gallbladder carcinogenesis (Pandey 2006). In earlier times, thorotrastosis was a well-recognized cause of CG (Hashizume et al. 1980), but most patients who had been investigated by the use of Thorotrast are now no longer alive. Rarely, CG has been found in the setting of primary sclerosing cholangitis (Lewis et al. 2007). There is an association of higher CG risk and chronic salmonellosis (Welton et al. 1979; Caygill et al. 1995; Kumar et al. 2006; Andia et al. 2008; Tewari et al. 2010; Walawalkar et al. 2013). Chronic *Salmonella* carriage is a well-known feature in this infection, and *Salmonella* can form robust biofilms on gallbladder epithelium, the bacterium being able to adhere to and invade polarized gallbladder epithelial cells apically (Gonzalez-Escobedo and Gunn 2013; Gunn et al. 2014). *Salmonella* carriage can induce a smoldering inflammation promoting carcinogenesis and *Salmonella* secretes a genotoxic toxin (Nath et al. 2010). A case-control study in the USA showed that chronic typhoid carriers died of hepatobiliary cancer six times more often than matched controls (Welton et al. 1979). Also in Northern India, a potential association between chronic typhoid fever carriage (*Salmonella typhi* and *Salmonella paratyphi* A) and CG was observed (Nath et al. 1997, 2008).

Differences of CG frequencies in various populations suggest effects of genetic factors. Also familial CG supports a role of genetic mechanisms. In addition, there is evidence that genetic factors are involved in the pathogenesis of gallstone disease, therefore indirectly affecting gallbladder carcinogenesis.

Anomalous Pancreaticobiliary Junction

In Eastern countries, specifically in Japan, anomalous pancreaticobiliary junction is considered to be an important risk factor for CG (Kimura et al. 1985; Lin et al. 1988; Ozmen et al. 1991; Chijiiwa et al. 1993; Tseng et al. 1993; Hanada et al. 1996; Uetsuji et al. 1996; Yang et al. 1997; Egami et al. 1998; Chao et al. 1999; Yoshida et al. 1999; Ng 2000; Elnemr et al. 2001; Nakayama et al. 2001; Sakurai et al. 2001; Yano et al. 2001; Takayashiki et al. 2002; Hu et al. 2003; Kang et al. 2007; Noda et al. 2007; Hori et al. 2008; review: Tsuchida et al. 2003). In an investigation of the Japanese Study Group of Pancreaticobiliary Maljunction (PBM), PBM was found in 52 (3 %) of 1,722 patients investigated with ERCP, and of these, 14 patients had developed CG (Egami et al. 1998). This association was identified in Western patients at a much lower frequency (Tuech et al. 2000). Detailed histologic studies have demonstrated that CG carcinogenesis in the presence of maljunction proceeds along a complex pathway, starting with hyperplastic mucosal changes in the gallbladder associated with upregulated cell kinetics, followed by various grades of metaplasia, dysplasia, and transition to carcinoma (Yamamoto et al. 1991; Sai et al. 2005; review: Hanada et al. 1999a). Epithelial cell proliferation of the gallbladder is increased in patients with maljunction (Hanada et al. 1996; Yang et al. 1997). Maljunction-induced increased gallbladder cell proliferation may be an event initiated early in life, as increased proliferative activity of mucosal epithelia was detected in children with maljunction (Tanno et al. 1999; Tokiwa et al. 1999). The mechanisms involved in the induction of this sequence of events are only partially known, but it is suggested that pancreatic juice reflux into the biliary tract followed by inflammation, epithelial cell loss, and consecutive hyperregeneration play a significant role (review: Chao et al. 1999). In fact, CG has been found in association with pancreaticobiliary reflux in the absence of maljunction (Sai et al. 2006). This pathway was found to be accompanied by p53 gene mutations and mutations in codon 12 of the K-RAS gene (Iwase et al. 1997; Chao et al. 1999; Hanada et al. 1999a, b; Masuhara et al. 2000). Point mutations of the K-RAS gene in CG have also been found in tumors that had developed in patients with congenital biliary dilatation (Tomono et al. 1996).

Genetic and Molecular Alterations

In CG, an array of genetic abnormalities has been identified, often involving chromosomes 3p, 8p, 9q, and 22q (Wistuba et al. 2002a; Malik 2004; Srivastava et al. 2011; Andrén-Sandberg 2012; Boutros et al. 2012; Maurya et al. 2012). Also aberrations of other chromosomal sites, including chromosomes 1p, 3p,4, 5p, 8p21, 9p, 9q, 13q, 16q, 17p, and 18q21, are considered to play pathogenic roles (Wistuba and Albores-Saavedra 1999; Kuroki et al. 2005; Dixit et al. 2012). Microsatellite instability was detectable in 17 % of CG patients (Yoshida et al. 2000). LOH at a locus on chromosome 3p is associated with abnormalities of the fragile histidine triad gene in CG (Wistuba et al. 2002a,b; Riquelme et al. 2007). Microsatellite instability (MSI) was detected in 17 % of CG, and there was an inverse correlation between MSI and the presence of LOH in CG (Yoshida et al. 2000).

Whole-exome and targeted gene sequencing of CG identified recurrent mutation in the ErbB pathway. Mutated ErbB signaling pathways were found in 36.8 % of CG samples (Li et al. 2014). Several investigations indicate that abnormalities in the TP53 (chromosome 17p13) and p16(Ink4)/CDKN2 (chromosome 9p21–22) gene loci are early and frequent events in the carcinogenesis of CG. The role of p53 gene alterations in CG is still not clarified (Ajiki et al. 1996b; Jonas et al. 1997; Kim et al. 2001a,b; Quan et al. 2001; Koda et al. 2003; Wang et al. 2006; Ghosh et al. 2013, review: Rai et al. 2011). Overall, p53 is expressed in CG with a high frequency (Fujii et al. 1996; da Rocha et al. 2004; Kalekou and Miliaras 2004; Wang et al. 2006). There is evidence that p53 expression is more prevalent in the gallbladder with gallstones in patients with CG (Misra et al. 2000). One subset of CG seems to develop de novo in the setting of predominant p53 gene mutations, with low rate of K-RAS mutations (Itoi et al. 1996). The expression rate of p53 seems to reflect the dysplasia-carcinoma sequence (Agrawal et al. 2010). p53 expression was found in 32.4 % of dysplastic lesions, 44.7 % of CIS, and 65.4 % of invasive carcinomas (Wistuba et al. 1996). Mutations of the TP53 locus seem to be associated with the growth pattern of CG, as the incidence of p53 immunoreactivity was greater in flat CG than in polypoid CG (Hanada et al. 1997). In contrast to CG, p53 expression was not detectable in gallbladder adenoma but in carcinoma arising in adenoma (Takei et al. 1996). Mutations in the K-RAS gene have been identified in patients with CG, however, at a low frequency, in contrast to adenomas (Saetta et al. 1996; Saetta 2006; Pai et al. 2011; Javle et al. 2014). There is evidence that such mutations may occur either early or later in the carcinogenic pathway. In contrast to other studies, no mutations in K-RAS were found in adenoma or gallbladder dysplasia in one study, but in 20 % of established CG (Kim et al. 2001a). Conversely, an earlier investigation reported K-RAS gene mutation even in gallbladder dysplasia at an incidence similar to that in CG (Ajiki et al. 1996a). There is evidence that alterations in DNA repair genes may be involved in CG carcinogenesis (Srivastava et al. 2010). Altered gene expression patterns involved in CG carcinogenesis are also promoted by aberrant promoter hypermethylation as epigenetic mechanism (House et al. 2003; Takahashi et al. 2004; Garcia et al. 2009). The acquisition of epigenetic alterations of several gene promoter sites of tumor suppressors may contribute to carcinogenic pathways in chronic cholecystitis and dysplastic changes (House et al. 2003). A gene that frequently undergoes epigenetic inactivation in CG is 3p, which is therefore considered a site of candidate tumor suppressor genes (Riquelme et al. 2007).

Apart from the nuclear genome, CG also showed alterations in the mitochondrial genome. Mutation analysis of this genome, in particular the D-loop, showed a wide range of point mutations and polymorphisms in the mitochondrial genome of CG (Maurya et al. 2013).

Factors Involved in Growth and Cell Cycle Regulation

Proliferative activity of CG cells is correlated with overexpression of several factors regulating the cell division cycle, including cyclin E (Eguchi et al. 1999; Mishra et al. 2011). Nuclear expression of the p16(INK4a) gene product was expressed in 39.1 % of CG and 31.6 % of high-grade dysplastic gallbladder epithelia, but not in normal epithelium (Lynch et al. 2008). Inactivation of p16 in CG occurs through two pathways, i.e., via LOH at 9p21–22 and through homozygous gene deletion, the latter being a combination of LOH and promoter hypermethylation (Tadokoro et al. 2007). Cell proliferation in CG is also regulated by a novel member of the Krüppel C2H2-type zinc finger protein family, zinc finger X-chromosomal protein, which promotes growth, but also migration, of CG cells (Tan et al. 2013). Cell proliferation of CG cells is induced by the morphogen, hepatocyte growth factor/HGF (Li et al. 1998; Yang et al. 2012), whereby the cancer cells express the HGF receptor, c-Met (Sasaki et al. 2012). In CG, c-Met is immunohistochemically localized in the cell membrane (Sanada et al. 2010). CG also showed an aberrant activation of the Sonic hedgehog signaling pathway (Xie et al. 2014). ErbB2 signaling in CG is linked to MUC4 expression, as ErbB2 interacts with MUC4 at the carcinoma cell apex, associated with hyperphosphorylation of erbB2, MAPK, and Akt, and with the overexpression of cyclooxygenase-2. Experimentally, MUC4 amplifies cell proliferation in the presence of heregulin through potentiating the phosphorylation of ErbB2 and its signaling pathways (Miyahara et al. 2008).

Wnt/Beta-Catenin Signaling Pathway

In contrast to gallbladder adenomas, altered expression of beta-catenin, such as nuclear or cytoplasmic expression and loss of cell membrane expression, is not a common feature in gallbladder dysplasia and CG, but cytoplasmic and nuclear expression of beta-catenin in CG was correlated with a less aggressive behavior of the neoplasms (Chang et al. 2002).

Apoptosis

Apoptosis is a common phenomenon in CG and is regulated by diverse pro- and antiapoptotic factors. The frequency of apoptosis may increase with CG progression (Sasatomi et al. 1996). One protein regulating apoptosis is p53. p53 gene mutations are a rather common event in CG and were observed in up to 35.7 % of cases (Kim et al. 2001b). There seems to be a positive correlation between expressions of p53 and Bcl-2 (Sasatomi et al. 1996). 65.4 % of CG revealed a decreased expression of Bax-interacting dactor-1/Bif-1, suggesting that loss of Bif-1 might play a role in gallbladder tumorigenesis (Kim et al. 2008). TSG101, a protein involved in resistance against apoptosis, is overexpressed in CG (Liu et al. 2011).

Invasion and Spread

As already specified above (paragraph on prognosticators), several types of matrix metalloproteinases (MMPs) are expressed in CG and are involved in the initiation and progression of the invasion cascade. Genetic variants of MMP-2, MMP-7, and MMP-9 are associated with higher susceptibility of gallbladder cancer (Sharma et al. 2012). Heparanase is a further enzyme playing a role in invasion and metastasis (Dutta and Poomachandra 2008; Wu et al. 2008). Heparanase is an endo-beta-glucuronidase which splits heparan sulfate and is frequently expressed in CG. Trophinin, an adhesion molecule that was first identified in human trophoblast cells and involved in embryo implantation, promotes cancer cell invasion in CG cells (Chang et al. 2009). Trophinin interacts with tastin and bystin, cytoplasmic proteins required for trophinin's activity as an adhesion molecule (Fukuda and Sugihara 2012). Invasive features of CG cells are also promoted hepatocyte growth factor/HGF interacting with the membranous c-Met receptor (Li et al. 1998). Part of CG exhibit overexpression of c-Met in cells of the invasive component, in association with expression of beta-catenin and cyclooxygenase-2 (Moon et al. 2005). However, other subsets of CG that have been analyzed revealed lack of c-Met expression in the invasive part of the tumor (Sanada et al. 2010).

Angiogenesis

As in other carcinomas and non-epithelial malignancies, tumor-induced angiogenesis is a critical mechanism in the setting of tumor growth and progression. A major driving force that induced angiogenic pathways is tumor hypoxia. Hypoxia-inducible factors 1alpha and 2alpha are upregulated in many CG, and this upregulation is strongly associated with increased expression of vascular endothelial growth factor/VEGF and augmented angiogenesis (Giatromanolaki et al. 2006). However, lower expression of hypoxia-inducible factor-1alpha and elevated expression of the von Hippel-Lindau (VHL) gene in CG are important markers for tumor progression, in that highly invasive tumors show decreased HIF-1alpha expression (Yang et al. 2011). VEGF-C, which has a central role in neoplastic lymphangiogenesis and angiogenesis through VEGF receptor 3 and VEGF receptor 2, respectively, expressed in endothelial cells, promotes progressive growth and invasion of CG (Chen et al. 2010). A further factor involved in tumor angiogenesis in CG is cyclooxygenase-2. Overexpression of this enzyme in CG cells is associated with increased angiogenesis, which in turn affects tumor progression and patient survival (Legan et al. 2009). Basigin (EMMPRIN/CD147), a multifunctional membrane glycoprotein involved in invasion and angiogenesis of diverse malignancies, is overexpressed in CG, expression pattern being correlated with stage and survival rate (Xiao and Tang 2009).

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