Adenocarcinoma of the Gallbladder (Classical Gallbladder Cancer) 147

ICD-O code 8140/3 (intestinal type; 8144/3)

Contents

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Abstract

Ordinary gallbladder carcinoma (adenocarcinoma) develops in a gallbladder that has undergone secondary changes, often due to long-standing cholelithiasis and associated alterations. Gallbladder carcinoma is detected in about 2–3 % of all cholecystectomy samples and accounts to approximately 60 % of all cancers of the extrahepatic biliary system. The neoplasm can be associated with epithelial precursor lesions and presents with various macroscopic growth patterns. Part of the tumors show, similar to cholangiocarcinomas, a marked desmoplastic stromal reaction and cause a circumscribed or diffuse thickening of the gallbladder wall. Other tumors grow a nodular lesion, sometimes large and obstructing the gallbladder lumen, or present in the form of polyps that grow into the lumen. Histologically, most of the neoplasms are glandular adenocarcinomas with various levels of cellular differentiation. The tumors can grow through the gallbladder wall, show perineural invasion, extend into the gallbladder bed, and invade, depending on stage, into the liver and adjacent organs.

Introduction

In the WHO classification of tumors, carcinoma of the gallbladder (CG) is defined as a malignant neoplasm, usually with biliary, intestinal, foveolar, or squamous differentiation, arising in the gallbladder (Alobores-Saavedra et al. 2010). In most cases, CG develops in an orthotopic gallbladder that may have undergone secondary changes, often due to long-standing cholelithiasis and associated alterations. Rarely, CG develops in gallbladder remnants after incomplete gallbladder resection (Cowley and Wood 1964; Tanga et al. 1973). In the present chapter, emphasis is placed in adenocarcinomas of the gallbladder, special types such as mucinous and squamous cell carcinomas being treated in another chapter. Carcinoma of the gallbladder and its relationship with gallstone disease and chronic cholecystitis have been studied since long.

Selected References: Beadles (1897), Musser (1889), Thomas and Nocia (1896), Warthin (1900), Treutlein (1901), Friedheim (1904), Proescher (1907), Riedel (1911), Smithies (1919), Magoun and Renshaw (1921), Deaver (1924), Lentze (1926), Luelsdorf (1927), Judd and Baumgartner (1929), Rolleston and McNee (1929), Finsterer (1932), Judd and Gray (1932), Seide and Geller (1933), Aiga (1935), Erdmann (1935), Boyce and McFetridge (1936), Cooper (1937), Jankelson (1937), Hochberg and Kogut (1939), Liebowitz (1939–1940), Mohardt (1939), Lam (1940), Lichtenstein and Tannenbaum (1940), Campbell (1941), Kirshbaum and Kozoll (1941), Greenlee et al. (1941), Warren and Balch (1940), Mattson (1942), Vadheim et al. (1944), Benjamin (1948), Burdette (1957), Koga et al. (1985), Levin (1999), Goldin and Roa (2009).

Epidemiology

CG is an important cancer of the gastrointestinal tract, with an estimated 6,000 new cases per year in the USA. In old autopsy series from a time period with a low rate of gallbladder surgery, the prevalence of CG in necropsies ranged from 5 % to 6 % (Kaumann 1909). In a more recent large autopsy series from Japan, CG was found in 2.1 % (Kimura et al. 1989). In a series of 540 consecutive cholecystectomies from Japan, CG was detected in 2.2 % (Terada 2013). Around 60 % of all cancers of the extrahepatic biliary system arise in the gallbladder (Narula 1971). There are marked differences in incidence from one region of the world to the other. Based on cancer registry data, it was found that the highest CG incidence rates worldwide were reported for women in Delhi, India (21.5/100,000); South Karachi, Pakistan (13.8/100,000); and Quito, Ecuador (12.9/100,000), and high incidences were found in Korea, Japan, and some Central and Eastern European countries (review: Randi et al. 2006). There are also differences in prevalence within

one the same country, due to ethnic variables. In North America, CG is more frequent in American Indians and Hispanic Americans than in whites or African Americans. In an autopsy series of 287 patients with CG, the ratio of men to women was 1:2.64–1:3.7 (Gupta et al. 1980; Sons et al. 1985), but in older series an even higher female preponderance was found (Kaufmann 1909). The average age of women at the time point of diagnosis was 70 years, and that of man, 69.5 years (Sons et al. 1985). The disease occurs on the average at a younger age in females than in males (Gupta et al. 1980). In part of patients, CG is diagnosed as an unsuspected lesion in cholecystectomy specimens (incidental CG; Varshney et al. 2002; Mazer et al. 2012). In a Korean study of 527 patients with gallbladder resection for benign biliary disease, unsuspected CG was found in 1.89 %, 50 % of these patients showing early CG with invasion confined to the mucosa (stage T1) (Kwon and Chang 1997). In a French registry of 218 cases of incidental CG, 67 patients were male and 151 female, with a median age at presentation of 64 years (Fuks et al. 2011). In a systematic review of 30 publications, 276 CGs were detected in Western studies reporting a total of 61,542 cholecystectomy specimens (prevalence of 0.4 %), and of these, 65 % were expected pre- or intraoperatively, while 344 cases of CG were found in 37,365 specimens from Asian studies (prevalence of 1.2 %), with 45 cases being expected pre- or intraoperatively (Swank et al. 2013). In one study analyzing cases of laparoscopic cholecystectomy, the ratio between incidental and non-incidental was 9 out of 19 (Cavallaro et al. 2012).

Clinical and Imaging Features

Dominating symptoms and signs in patients with CG are upper abdominal discomfort or pain, weight loss, jaundice, fatigue, and a palpable mass (Illingworth 1935; Cooper 1937; Kelly and Speed 1946; Danzis 1948; Sainburg and Garlock 1948; Arminski 1949; Cooke et al. 1953; Fortner and Pack 1958; Gerst 1961; Bossart et al. 1962; Chandler and Fletcher 1963; Polk 1966; Robertson and Carlisle 1967; Hardy and Volk 1970; Tanga and Ewing 1970; Solan and Jackson 1971; Krain 1972; Adson 1973; Ohlsson and Aronsen 1974; Donaldson and Busuttil 1975; Melson et al. 1976; Richard and Cantin 1976; Piehler and Crichlow 1977; Arnaud et al. 1979; Jönsson and Pettersson 1982; Pandey et al. 2001; Xu and Zou 2007; Giang et al. 2012). Jaundice was detected in CG patients in up to 58 % (Arnaud et al. 1995), suggesting that invasion and obstruction of extrahepatic bile ducts is a common feature of CG. Part of the increased gallbladder mass may be due to hydrops or hemocholecyst. CG can cause rupture of the gallbladder, eventually followed by biliary peritonitis (Bakaleinik 1976). Very rarely, mucus secreted by CG can accumulate in bile duct lumens and cause obstruction of the common bile duct (Hughes et al. 1997). CG can synchronously occur in conjunction with other neoplasms of the biliary tract, such as carcinoma of the common bile duct (Fujii et al. 2004).

CG can readily be identified by various ultrasonography and other imaging techniques (Pettersson 1974; Olken et al. 1978; Yeh 1979; Fultz et al. 1988; Franquet et al. 1991; Kumar and Aggarwal 1994; Rooholamini et al. 1994; Ohtani et al. 1996; Pandey et al. 2000; Levy et al. 2001; Schwartz et al. 2002; Oikarinen 2006; Lee et al. 2009). Invasive CG presents as wall thickening or polypoid growths in conventional and CT images (Melson et al. 1976; Levy et al. 2001; Levy et al. 2002) and ultrasonography images (Olken et al. 1978; Allibone et al. 1981). In contrast to advanced invasive CD, early CG may be difficult to identify by ultrasonography/US (Nilsson et al. 1989). In one study of 15 patients with pT1 and pT2 disease, US allowed diagnosis in only 5 patients (Kapoor et al. 1996). At US, CG may present as lumen-filling tumors, polypoid masses, or infiltrating masses (Kumar et al. 1990). On both US and CT images, distinguishing the protruding type of CG from polypoid adenomas may be difficult, but benign neoplasms have a more homogeneous texture, spaces between the lesion and the gallbladder wall, and a relatively normal configuration of the gallbladder wall (Jin et al. 2013). The depth of

invasion can be assessed by the use of endoscopic ultrasound/EUS. EUS examination of CG resulted in four distinct phenotypes of cancer growth, i.e., Type A (a pedunculated mass with a fine-nodular surface in an intact wall), Type B (a broad-based mass with an irregular surface and intact outer hyperechoic layer of adjacent wall), Type C (irregular outer hyperechoic layer due to mass echo), and Type D (outer hyperechoic layer disrupted by a mass echo). Each of these types correlated well with the histologically determined depth in cancer invasion (Fujita et al. 1999). CT images in CG show various patterns, including lesions classified as "massive," "thickened wall," or "intraluminal" (Itai et al. 1980).

Fig. 1 Gallbladder carcinoma. There is stone disease with a *large black* concrement in the gallbladder (to the *right*) and a smaller stone in the large bile duct. The liver shows several cancer metastases (necropsy specimen)

Pathology

Macroscopy

In their macroscopic presentation, CGs markedly differ between early and advanced cancers. The examination and documentation of macroscopic and other findings in cases of CG have been standardized (Henson et al. 2000).

Early carcinomas, which now comprise tumors of stages T1a and T1b (Cangemi et al. 2006), are usually manifest in the form of circumscribed thickenings of the mucosa or, less commonly, as small polypoid lesions having an adenoma-like morphology. The main gross presentations of early CG comprise flat, superficial-raised, sessile, or pedunculated lesions (Figs. 1, 2, 3, and 4; Tsuchiya 1991). Another classification divided early carcinomas into protruding or superficial lesions, whereby protruding tumors were further subdivided into pedunculated or sessile neoplasms, whereas superficial tumors were subdivided into elevated, flat, or depressed lesions. Among protruding tumors, the majority are sessile, and 88 % of these sessile tumors were accompanied by superficial elevated and/or flat tumors. Overall, 86 % of these early CGs were T1a and 14 % T1b (Wakai et al. 2012). Japanese investigators described that early carcinomas display granular, flat, or gastric area-like mucosal

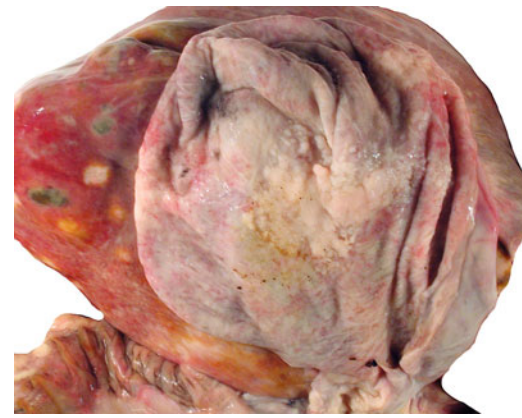

Fig. 2 Same specimen as in Fig. 1, after removal of stones. The gallbladder wall shows carcinoma in the form of a nodular plaque (*center*). Several liver metastases are seen (necropsy specimen)

patterns, which are however not specific for CG, as they may also occur in non-tumorous conditions of the gallbladder. Stereomicroscopic analyses of gallbladders with early CG of the flat type revealed three distinct patterns, i.e., grooved, pitted, or papillary, each of which further subdivided into regular or irregular. The frequency of the grooved (52.2 %) and papillary (52.2 %) patterns was significantly higher in CG than in nonneoplastic lesions, mostly with an irregular subtype, while there was no significant

Fig. 3 Carcinoma of the gallbladder with a component growing into the lumen. The large tumor has massively invaded the liver substance

Fig. 4 Carcinoma of the gallbladder. Transmural cancer growth, marked extension of the carcinoma into the liver, and intrahepatic metastatic disease are seen

difference for the pitted pattern (Ryozawa et al. 1997). In contrast to invasive CG, its precursor lesions, including high-grade dysplasia, are not detectable macroscopically (Renshaw and Gould 2012), and also early CG is detectable pre- and/or intraoperatively in 24 % of cases only (Wakai et al. 2012).

The main growth patterns found in advanced CG are a circumscribed form and a diffuse form of cancer. The circumscribed form presents in four patterns, i.e., a platelike pattern characterized by a firm, more or less delineated plaque causing wall thickening; a nodular pattern with soft or firm tumor nodules effacing the wall and eventually bulging into the lumen; a polypoid pattern with exophytic tumor masses growing into the lumen, forming cauliflower-like masses; and so-called scar cancer, where a grossly ill-defined cancer is situated in scar tissue found in a shrunken gallbladder containing impacted stones. Circumscribed tumor masses within the lumen are usually ulcerated at their surface. Large tumors with necrosis can cause gallbladder perforation. In the diffuse growth pattern of CG, the entire gallbladder wall is firm and sometimes thickened, due to diffuse cancer cell infiltration, without a visible tumor mass. Whereas circumscribed tumors can cause significant enlargement of the gallbladder, diffuse CG is often associated with gallbladder shrinkage. Infiltrative CG can invade the infundibulum and the cystic duct, causing effacement and destruction of the cystic duct, which may no longer be found at gross examination. In case the cystic duct is still open, the gallbladder contains bile and mucus, while complete cystic duct obstruction can result in gallbladder hydrops, but only in non-shrunken gallbladders. Among 287 autopsy cases, most tumors (67.7 %) showed a diffuse infiltrative growth and 32.3 % a polypoid-exophytic growth (Sons et al. 1985). Polypoid tumors were, however, not always found at a high frequency; in one report of 173 cases of CG, only 10 % showed a polypoid pattern (Tragermann 1953).

As CG often develops in gallbladders with long-standing inflammatory change, the organ can show pericholecystic scarring or is sometimes embedded in scar tissue filling the gallbladder fossa. The fibrous adhesions may contain accumulations of pus or even true abscesses, the latter most often in case of perforation, while gallbladder empyema is rather an uncommon CG (Zenker 1889; Haribhakti et al. 1997). CG presents a characteristic local invasion and metastatic pattern. Large cancers often show invasion of the liver substance, and infiltration of neighboring organs can be observed, most often transverse colon and duodenum, and less frequently stomach and pancreas. Rarely, the tumor protrudes through the gallbladder neck and cystic duct into the extrahepatic bile duct system, where it can produce a

tumor thrombus in the common bile duct (Xin-Wei et al. 2013). CG can invade the anterior abdominal wall. In very advanced CG, the tumor can form a large conglomerate inseparably situated between the liver, abdominal wall, stomach, pancreas, and colon, encroaching upon and stenosing large bile ducts and blood vessels, including the portal vein. Owing to its invasive features, CG can produce fistulations between the gallbladder and invaded neighboring organs, most often vesicocolonic fistula, and much rarer vesicoduodenal or vesicogastric fistulas.

Locoregional lymph node metastases may cause impressive lymphadenomegaly. CG commonly produces hepatic metastases, which are manifest as macroscopic metastases of micrometastases. Micrometastases are defined as discrete nodular hepatic lesions, having a diameter of less than 5 mm, or as metastatic deposits located within venous vessels of the liver. Micrometastases are more frequent within 1 cm of the gallbladder bed than 1–2 cm from it, suggesting cancer spread through the vascular network of the gallbladder fossa. Micrometastases showed a strong correlation with the extent of blood vessel invasion around the primary tumor and were often detected in patients with a primary tumor localized on the hepatic side and with more than 3 cm of subserosal invasion (Endo et al. 2004). Although CG invades the entire gallbladder wall and reaches the subserosal space, peritoneal spread (peritoneal carcinomatosis) is not a common feature and is preferentially seen in the diffuse (scirrhous) growth pattern of CG.

Histopathology

Gallbladder carcinoma presents with a wide spectrum of histologies, whereby tubular and solid adenocarcinoma (the "classical" types of CG) predominates (Figs. 5, 6, and 7; Albores-Saavedra et al. 2010; Table 1). The current WHO classification is based on previous classifications published by the WHO and by the Armed Forces Institute of Pathology/AFIP in 2000.

In fact, adenocarcinoma with various proportions of tubular, solid, and/or diffusely growing components is found in most cases (84.6 % in a large autopsy series; Sons et al. 1985). Adenocarcinoma usually grows in the form of nodular or polypoid masses, but diffuse mucosal carcinoma has also been described (Haratake et al. 2002).

Adenocarcinoma, Biliary Type

This is the most common adenocarcinoma of the gallbladder, and these neoplasms are usually well- to moderately differentiated lesions. Biliary-type adenocarcinoma consists of tubular gland-like structures of variable length, lined by columnar cells of varying height and cuboidal cells. The

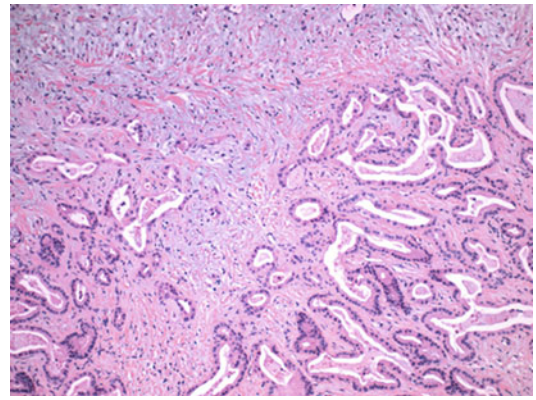

Fig. 5 Well-differentiated adenocarcinoma of the gallbladder (hematoxylin and eosin stain)

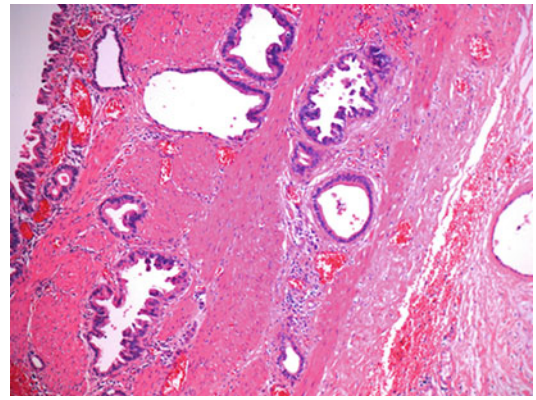

Fig. 6 Adenocarcinoma of the gallbladder with micropapillary components. The tumor has invaded the muscular layer and is clearly distinguishable from a dilated mucosal pocket (hematoxylin and eosin stain)

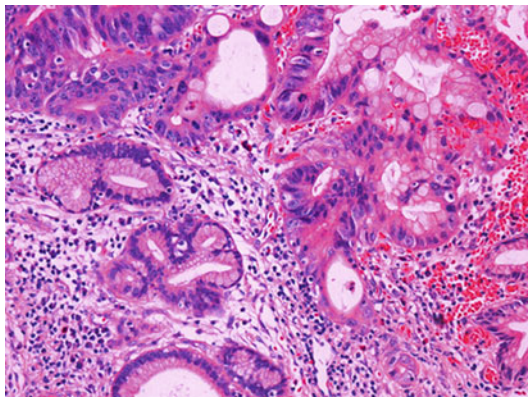

Fig. 7 Moderately differentiation adenocarcinoma of the gallbladder (to the *top* and *right*). Note the clear difference between cancerous tissue and the normal gallbladder glands seen to the *left* and *bottom* (hematoxylin and eosin stain)

Table 1 Histologic types of gallbladder carcinoma

Classical types of gallbladder carcinoma
Adenocarcinoma, biliary type
Adenocarcinoma, intestinal type
Adenocarcinoma, gastric foveolar type
Papillary carcinoma
Carcinoma in situ
Rare carcinoma variants
Signet ring cell carcinoma
Mucinous (colloid) carcinoma
Clear cell carcinoma
Cribriform carcinoma
Micropapillary carcinoma
Squamous cell carcinoma
Adenosquamous carcinoma
Carcinoma with lymphoid stroma
Giant cell carcinoma
Hepatoid carcinoma
Carcinoma with morule-like features
Adenocarcinoma with choriocarcinoma-like features
Small cell carcinoma
Undifferentiated carcinoma
Pleomorphic carcinoma
Carcinomas with sarcomatoid features

cells resemble the cells lining bile ducts and can reliably be identified in fine needle aspiration material (Yadav et al. 2013). Part of the neoplastic cells contain mucin that is sometimes secreted into the tubules, but not forming "mucin lakes" that characterize colloid carcinomas. Approximately a third of well-differentiated biliary-type CG shows focal intestinal differentiation, sometimes with formation of goblet cells. Part of gallbladder adenocarcinomas may contain cell types other than columnar cells, such as Paneth cells, and/or neuroendocrine cells (Koga et al. 1991). Some tumor contains numerous neuroendocrine cells that are reactive for peptide hormones and/or serotonin. Argentaffin cells as a component of CG are a rather uncommon finding, and only a few cells have been detected in one study (Azadeh and Parai 1980). A variant of well-differentiated adenocarcinoma of the gallbladder can mimic minimal deviation adenocarcinoma of the cervix (Tashiro et al. 2000). The nuclei of invasive CG are generally larger than those of in situ lesions, a phenomenon that has been objectively proven by the use of stereologic estimation of mean nuclear volume (Elpek et al. 1999). Classical adenocarcinoma of the gallbladder exhibits variable degrees of desmoplasia (stromal reaction), however, usually without the massive sclerosing stromal reaction characterizing Klatskin tumors. Similar to desmoplastic areas in cholangiocarcinomas, the stroma of CG can undergo secondary changes, including advanced fibrosis/sclerosis, hyalinization, and rarely osseous metaplasia (Cavazza et al. 1999), the latter discussed in more detail in a separate paragraph. In comparison with biliary-type carcinomas of the extrahepatic bile duct, desmoplasia of CG is usually less pronounced. CG may undergo necrosis, hemorrhage, and calcification (Parker and Joffe 1972; Rogers et al. 1973; Hori et al. 2008). Calcification of CG (see below) seems to be an inherent, albeit not yet clarified, feature of some forms of CG, as calcification can also occur in lymph node metastases of these carcinomas (Yun et al. 2011).

Adenocarcinoma, Intestinal Type

Intestinal-type CG is less common than CG and presents under two phenotypes. The more frequent one is characterized by tubular gland-like structures closely resembling those found in

colorectal carcinomas, composed of tall columnar cells with pseudostratified elongated or ovoid nuclei, with mitotic figures having left the basal position and found higher up in the cancer epithelium. Nuclear debris or apoptotic bodies may be found in the epithelial lining. The second, less common variant contains numerous goblet cells, intermingled with Paneth cells and neuroendocrine cells. Immunohistochemically, both variants are typically reactive for MUC2, CEA, and the transcription factor CDX2 (review: Albores-Saavedra et al. 2010).

Adenocarcinoma, Gastric Foveolar Type

This is a rare variant of well-differentiated adenocarcinoma that consists of tall columnar cells with abundant cytoplasm containing mucin and basally placed nuclei. The tumor cells are usually reactive for MUC5A. This carcinoma either occurs as a pure form or exists in combination with other adenocarcinoma variants.

Papillary Carcinoma of the Gallbladder

Papillary adenocarcinoma of the gallbladder is a distinct variety of CG characterized by a papillary growth pattern, a tendency for exophytic growth, and a more favorable biology of disease (Egeberg et al. 1949; Frank and Spjut 1967; Hart et al. 1972; Gunn and Dyte 1985; Akiyama et al. 1995; Onuma et al. 2013). Papillary carcinoma is rare and has been observed in only 4.2 % of all CG (Nuzzo et al. 2005). It has also been found in the setting of anomalous pancreaticobiliary junction (Nuzzo et al. 2005). The intraluminally growing component of papillary carcinomas is well-differentiated and consists of slender papillae covered by columnar cells. Less or even poorly differentiated cell populations have been noted at the base of the papillary structures by some authors (Glenn and Hays 1954; Lund 1960). Large papillary carcinomas may suffer from poor vascularization and undergo marked necrosis (Onuma et al. 2013). Previously, noninvasive and invasive forms of papillary carcinoma were lumped together. In a comparative analysis, it surfaced that noninvasive papillary carcinoma is a distinctive variant occurring more often in females, predominantly showing a biliary phenotype and rarely an intestinal phenotype, associated with cholelithiasis in the majority of cases, and revealing no metastasis and an excellent prognosis. In contrast and similar to ordinary CG, invasive papillary CG can produce lymph node metastasis and is associated with poor prognosis (Albores-Saavedra et al. 2005). A more favorable outcome thus depended on lymph node dissection (Wolma and Lynch 1961).

Intestinal-Type Carcinoma of the Gallbladder

Intestinal-type CG is a variant of well-differentiated adenocarcinoma of the gallbladder characterized by the presence of intestinal features (Albores-Saavedra et al. 1986). Part of these neoplasms resemble colorectal carcinoma, whereas others exhibit a composition characterized by absorptive columnar cells, numerous goblet cells, Paneth cells, and some neuroendocrine cells. The latter may be reactive for serotonin, somatostatin, cholecystokinin, and/or pancreatic polypeptide. The carcinomas are sometimes associated with intestinal metaplasia of the uninvolved mucosa (Albores-Saavedra et al. 1986).

Adenocarcinoma of the Gallbladder with Marked Desmoplasia

In contrast to Klatskin tumors, desmoplasia in CG is usually of moderate degree. There exists, however, a subset of gallbladder adenocarcinomas having marked stromal fibrosis (Wang et al. 2006). In these neoplasms, ultrasound shows that the gallbladder wall is irregularly thickened or exhibits nodosity, but the growth pattern is usually diffuse. A second form of CG associated with copious connective tissue formation is carcinoma

associated with porcelain gallbladder or hyalinizing cholecystitis. Carcinomas developing in this form of cholecystitis did not form distinct tumor masses or a significant wall thickening, but showed widely scattered and bland-appearing glands embedded in the thin band of hyaline stroma, often with microcalcifications and granular intraluminal debris (Patel et al. 2011).

Carcinoma In Situ

Carcinoma in situ (CIS) occurs in the gallbladder either as an isolated lesion or as a lesion associated with invasive carcinoma (Kott and Urca 1974; Albores-Saavedra et al. 1980). Similar to other organs, CIS of the gallbladder is considered to be a malignant neoplasm in its preinvasive phase of evolution. However, in a given case, it cannot be reliably judged whether CIS would have switched to an invasive phenotype in the future or rather persisted as a stable lesion. Among 200 consecutive cholecystectomy specimens removed for cholelithiasis or cholecystitis, CIS was identified in 3.5 %. CIS was also found in the mucosa adjacent to invasive CG in 79 % of surgical cases and in 52.9 % of autopsy cases (Albores-Saavedra et al. 1980). In an analysis of 18 cases of CIS of the gallbladder, all patients were females with an age range of 29–83 years at diagnosis (mean, 55 years). Macroscopically, the CIS lesions could not be distinguished from chronic cholecystitis, with one exception. Histologically, CIS presents as either a papillary lesion or a more common non-papillary lesion. CIS of the gallbladder may extend from the surface epithelium to invaginations and then to antral-type glands, the latter being associated with CIS in more than half of the cases (Albores-Saavedra et al. 1984).

Rare Variants of Gallbladder Carcinoma

A small fraction of CG is characterized by a histology different from adenocarcinoma. These rare carcinoma variants mostly share features with similar neoplasms occurring in other organs (Albores-Saavedra et al. 1981, 1996). The diverse forms of tumors are treated in separate chapters.

Mixed Carcinomas

A minority of CG shows more than one histologic component. Mucinous CG with a separate nodule of anaplastic carcinoma was observed (Mizuno et al. 1999), and there is a very rare reported case of gallbladder adenocarcinoma associated with a choriocarcinoma, sometimes with immunoreactivity for beta-HCG (Albores-Saavedra et al. 1981; Abu-Farsakh and Fraire 1991).

Invasion Patterns

Perineural invasion is a typical feature of CG, and this neoplasm shares this important prognostic alteration with carcinomas of the extrahepatic bile ducts. Cancer cell spread along perineural spaces follows the distinct anatomy of gallbladder nerves. These nerves form a mucosal plexus resembling the intestinal Meissner's plexus, transmural branches, and a nervous plexus on the exterior surface of the gallbladder, the latter plexus also containing ganglion cell clusters (Hermann 1952). Perineural invasion may be mimicked by florid pyloric gland metaplasia of the gallbladder, where the perineural space and the intraneural compartment may be infiltrated by cytologically bland cuboidal or columnar mucin-containing cells (Albores-Saavedra and Henson 1999). Invasive CG has a strong tendency to extend from the mucosa of the gallbladder, where the neoplasm takes its origin in most instances, into the muscle layer and from there into the subserosal space. In part of patients, invasive CG and also CIS were found to extend into Rokitansky-Aschoff sinuses (Albores-Saavedra et al. 2004). Similar to cholangiocarcinomas of the extrahepatic ducts, perineural invasion is a characteristic feature of CG. This type of invasion was identified in 10 of 14 CG (Nagakawa et al. 1993), and perineural

invasion extended to the extramural biliary or pancreatic nerve plexuses in part of cases.

Lymph Node Metastases

Lymph node metastases in CG are either of the macrometastatic or micrometastatic variant and are frequent events of spread. They prevail in the nodular infiltrative form of CG with a histology of moderately differentiated adenocarcinoma, but are less common in papillary adenocarcinoma (Sumiyoshi et al. 1991). In a study of 135 patients with CG undergoing radical resection, lymph node metastasis was found histologically in 44 % (Shirai et al. 2012). In case of micrometastases, the identification of small clusters of carcinoma cells spread to lymph nodes may be difficult by conventional histologic examinations. The detection rate depends in the size and geometry of micrometastases. Tiny aggregates of cancer cells can be detected by means of cytokeratin immunohistochemistry in histologically negative lymph nodes (Yokoyama et al. 1999; Natarajan et al. 2005; Sasaki et al. 2006). In one study, 7 out of 255 HE-negative lymph nodes (2.7 %) were found to be positive for micrometastases by the use of cytokeratin immunostaining (Tajima et al. 1999).

Lesions Associated with Gallbladder Carcinoma

In part of CG with transmural invasion, associated inflammatory infiltrates or populations of immunological effector cells may spill over into the liver substance of the gallbladder bed. Similar to other cancers, CG contains tumor-infiltrating lymphocytes (TILs). High levels of CD4(+) and CD8(+) cells were detected in 51–1 % and 37.8 % of CG cases, respectively, and also infiltrates of natural killer cells were observed (Nakakubo et al. 2003). Part of TILs are FoxP3+ and IL-17-producing T cells that affect tumor progression and prognosis in CG after surgery (Goeppert et al. 2013; Zhang et al. 2013). CG also contains tumor-associated macrophages (TAMs), but these cells are less frequent than TILs. The hepatic bed remaining after cholecystectomy can show various alterations, including granulation tissue, remnants of adherent adipose tissue with lipogranulomas, and sometimes foreign body-type granulomas. Rarely, eosinophil-containing necrotizing granulomas have been observed in the hepatic bed following tumor cholecystectomy, associated with peripheral eosinophilia (Ohtsuki et al. 2012).

Ultrastructural Findings

SEM pictures of well-differentiated CG revealed that CG cells are irregularly shaped columnar cells with less developed and pleomorphic microvilli, whereas transmission EM demonstrated well-developed cytoplasmic organelles, variably differentiated mucus granules, abundant lysosomes, and chromatin changes shared with other malignancies (Koga et al. 1991). In classical CG, mucin-producing secretory columnar cells predominate, intermingled with narrow and dark-staining pencil-like cells (Larraza-Hernandez et al. 1984).

Immunohistochemistry

CG, including its lymph node metastases, is consistently positive for cytokeratins 8 and 18 (Yokoyama et al. 1999). Part of CG are immunoreactive for CK7 and, less often, CK20 (Kalekou and Miliaras 2011). An entire panel of immunohistochemical stains, including cytokeratins, vimentin, epithelial membrane antigen, and carcinoembryonic antigen, is required to reliably diagnose poorly differentiated and undifferentiated forms of gallbladder carcinomas (Diebold-Berger et al. 1995). A significant fraction of CG expresses the mucins, MUC1 and MUC4. High MUC1 expression was correlated with more differentiated neoplasms, whereas a high MUC4 expression was correlated with a negative nodal status (Kim et al. 2012). However, a relationship between MUC1 expression and differentiation was not detected in another

investigation (Ghosh et al. 2005). MUC4 is preferentially expressed in the apex of cancer cells (Miyahara et al. 2008). Expression of CA 242 seems to be a promising marker in CG diagnosis (Rana et al. 2012). Intestinal-type CGs express an intestinal goblet cell marker (Hughes and Bhatal 2013), and CGs with features of pyloric gland metaplasia are reactive for class II mucins (Tatematsu et al. 1988). The majority of CGs express p53 protein in the nuclei (The et al. 1994; Doval et al. 2014). CGs express EGFR, Cox-2, and cyclin D1 (Doval et al. 2014). Part of CG expressed estrogen and progesterone receptors (Gupta et al. 2012). Other immunoreactivities in CG that may be useful in diagnosis of CG include CD151 (a member of the tetraspanin family; Matsumoto et al. 2014), CD117/c-Kit (Langner et al. 2004), EphB1 and Ephrin-B (Yuan et al. 2014), the von Hippel-Lindau gene product, maspin, IMP3, and S100P (Shi et al. 2013). Aberrant maspin expression was noted in focal and patchy areas of gallbladder epithelium and intestinal metaplasia of the gallbladder in patients with cholelithiasis (Maesawa et al. 2006); its expression seems to be involved in early carcinogenesis of CG (Kim et al. 2010). Maspin (mammary serine protease inhibitor) is a member of the serine protease inhibitor/non-inhibitor superfamily and plays a role in the biology of several cancers, where it is downregulated or overexpressed, suggesting differential roles in various cell types. Selectively increased cell adhesion by the expression of maspin is thought to contribute to the inhibition of metastatic spread (review: Berardi et al. 2013). CG shows variably elevated proliferation indices when examined by the use of PCNA or Ki-67 immunohistochemistry (Roa et al. 1993).

Secondary Changes of Gallbladder Carcinoma

CG can undergo marked necrosis, preferentially the exophytically growing forms (Sakurai et al. 2001; Hori et al. 2008). Due to necrosis/infarction, polypoid lesions may detach from the stalk and freely float in the lumen. Necrosis and/or accumulation of mucin, or exudate, can lead to the formation of cystic structures with carcinoma, eventually mimicking adenomyosis/adenomyomatosis at imaging (Tian et al. 2003; Yoshimitsu et al. 2005). Intratumoral cystic components were found in 3 of 35 proven CG by MR examination. All these tumors were well-differentiated adenocarcinomas and cystic changes were caused by abundant mucin production, mucin being accumulated in dilated Rokitansky-Aschoff sinuses (Yoshimitsu et al. 2005). In case of vesicointestinal, and particularly vesicocolonic fistulation, entry of intestinal bacteria into tumor can lead to puriform liquefaction or gangrene of cancer and, rarely, gas gangrene.

As already noted above, gallbladder carcinoma can undergo extensive calcification (Parker and Joffe 1972; Rogers et al. 1973): two main patterns of calcification occur. Calcified carcinomas may have calcium salt deposits mainly in the stroma, numerous mineralization grains being placed between stromal cells and/or along connective tissues fibers. The incidence of this change is not known, but may be more frequent in case one would test for microcalcifications by the use of the von Kossa stain. The second pattern is characterized by sometimes marked calcification in CG with high mucin content (Parker and Joffe 1972; Tian et al. 2003). In rare cases, calcification present in the primary tumor is also found in lymph node metastases (calcified nodal metastasis; Parker and Joffe 1972; Yun et al. 2011) or in liver metastases (Nakadaira et al. 2008). Calcifications and/or osseous metaplasia occurs on malignant gallbladder neoplasms other than CG, e.g., carcinosarcoma with calcified or bony components (Grote and Kaemmerer 1986; Ishida et al. 2012). Calcifications can also develop in mucinous cholangiocarcinoma (Nagakura et al. 1999).

A very rare secondary change in CG is osseous metaplasia (heterotopic ossification), which develops within tumor stroma and is characterized by the formation of immature bony tissue or osteoid within the spindle cell background (Cavazza et al. 1999). Heterotopic ossification in tumors may be induced by production of bone morphogenetic proteins (Imai et al. 2001; Komai et al. 2006). Carcinosarcomas of the gallbladder

can contain foci of osseous metaplasia (Nakagawa et al. 1996).

Precursor Lesions

Several investigations indicate that CGs derive from a foregut cell lineage and that at least a large part of CGs develop in the setting of a hyperplasia/metaplasia-dysplasia-carcinoma in situ-invasive carcinoma sequence, or a cascade leading from gallbladder adenoma with or without significant atypia to carcinoma (Sawyer 1970; Albores-Saavedra et al. 1980; Kozuka et al. 1982; Laitio 1983; Yamagiwa 1987; Yamamoto et al. 1989a, b; Aldridge and Bismuth 1990; Kim et al. 2001; Adsay 2007; Stancu et al. 2007; Trivedi et al. 2008; Feng et al. 2011; Hughes and Bhathal 2013; Segovia Lohse and Cuenca Torres 2013; Kijima et al. 2014).

The overall prevalence of metaplastic changes developing in chronic inflammatory gallbladder disease varies considerably among different studies and was higher than 25 % in some analyses. Metaplastic changes appear to be more frequent in cases with microlithiasis and are associated with chronic gallbladder wall thickening (Seretis et al. 2014). Intestinal metaplasia, in part with goblet cells, was found at rates of 4.0 % and 30.6 % in cases without and with cholelithiasis, respectively. Metaplasia was detected at rates of 69.8 % and 61.1 % in cases with dysplasia and carcinoma, respectively, suggesting that intestinal metaplasia of the gallbladder may precede dysplastic changes (Yamagiwa and Tomiyama 1986). The prevalence of dysplasia varies as a function of genetic background of patients, presence or absence of risk factors such as stone disease and chronic cholecystitis, and definitions/criteria employed to identify dysplasia. Overall, incidental gallbladder dysplasia (IGBD) seems to be a fairly common incidental histologic finding after cholecystectomy for gallstone disease (Solaini et al. 2014). In a Japanese study of 200 gallbladders removed for presumed benign disease, dysplasia was present in 14.5 % (12 % mild dysplasia, 2.5 % moderate to severe dysplasia), while epithelial hyperplasia was diagnosed in 27 % of cases (Mukada et al. 1985). In one analysis, over 80 % of invasive CG presented areas adjacent to flat dysplasia and carcinoma in situ (Rao et al. 2006). There is evidence that K-RAS mutations play a role in the development of premalignant gallbladder lesions and early carcinogenesis (Kim et al. 2000). In contrast to flat dysplasia, an adenoma-carcinoma sequence does not seem to be a pathway for gallbladder carcinogenesis as common as that of dysplasia, as adenomas are uncommon (less than 1 % of cholecystectomies), and adenomatous remnants in the neighboring mucosa to early CG were detected less than 3 % of cases (Roa et al. 2006). However, adenomatous residues were found in up to 19 % of invasive CG (Kozuka et al. 1982). In part of cases of CG, the invasive neoplasm is spatially associated with carcinoma in situ/CIS. CIS disclosed a superficial extension into Rokitansky-Aschoff sinuses and mucous glands (Yamaguchi et al. 1992). CG is known to occur in the setting of gallbladder papillomatosis (Kunisch et al. 1997). What is the time period required for the transformation of dysplasia to frank carcinoma? There is still scarce information regarding the timely evolution of gallbladder precursor lesions, owing to the fact that dysplastic lesions are silent, and early CGs are usually asymptomatic. In an investigation on resected gallbladders, the mean age of patients showing gallbladder dysplasia was 46.3 years, that of early CG 57.5 years, that of advanced CG 59 years, and that of CG with metastases 61.1 years (Roa et al. 1996), suggesting that the carcinogenic progression from dysplasia may require at least 15 years. In addition to precursor lesions, the role of cancer stem cells in the carcinogenesis of CG has been discussed. CG can contain CD133-positive cells classified as self-renewing potential carcinoma stem cells (Shi et al. 2011).

CG was identified in close spatial relationship with adenomyomatosis (Paraf and Potet 1988), but a causal relationship between adenomyomatosis and carcinogenesis remains uncertain. A recent investigation showed that the status of adenomyomatosis in gallbladders with CG was significantly associated with T stage, nodal metastasis, distant metastasis, and shorter survival, and

that adenomyomatosis-positive CG is more often diagnosed clinically in the advanced stages (Kai et al. 2011). CG can also arise in Rokitansky-Aschoff sinuses (Terada 2008), but such relationships are difficult to assess, as invasive CG and CIS can secondarily involve these sinuses (Albores-Saavedra et al. 2004).

Differential Diagnosis

CG may histologically be confounded with an entire spectrum of nonneoplastic lesions, including diverse forms of metaplasia, adenomyomatosis foci with atypia, regenerative changes in previously damaged Rokitansky-Aschoff sinuses, and hyperplastic Luschka ducts (Singhi et al. 2011; Giang et al. 2012). Mass-forming adenomyomatosis of the gallbladder may be masquerade as CG (Shimoji et al. 2001; Ray et al. 2012). Mucin-containing Rokitansky-Aschoff sinuses with extracellular mucin deposits may mimic mucinous adenocarcinoma of the gallbladder (Albores-Saavedra et al. 2009). Pseudotumorous lesions, e.g., intramural gallbladder hematomas (Tan et al. 2005) and gallstone granulomas (Tham and Ng 2001; Jung et al. 2011), may also mimic CG. Rare mass-producing specific inflammations of the gallbladder can produce presentations similar to that of cancer, including gallbladder tuberculosis (Hegler 1925; Ramia et al. 2006; Soufi et al. 2011; Verma et al. 2012), brucellosis (Ögredicie et al. 2010), and actinomycosis (Hefny et al. 2005; Lee et al. 2007).

Paraneoplastic Organ Changes in Gallbladder Carcinoma

A small subset of CG is associated with paraneoplastic features/syndromes (Table 2). The disorders comprise acanthosis nigricans (Lam 1940; Lichtenstein and Tannenbaum 1940; Campbell 1941; Werko 1945; Jacobs and Rigel 1981), bullous pemphigoid (Post et al. 1973), exfoliative dermatitis/erythrodermia (Kameyama et al. 2005), polymyositis (Adli et al. 2013), dermatomyositis (Yiannopoulos et al. 2002; Ni et al. 2013), neuropathy (Mitobe et al. 1970), paraneoplastic opsoclonus (Corcia et al. 1997), Guillain-Barré syndrome (Phan et al. 1999), erythrocytosis (Manigand et al. 1971), thrombocytosis (Wakabayashi et al. 1978), leukemoid reactions (Pozza et al. 1966), hemolytic anemia (Barletta et al. 1989; de la Sierra et al. 1989), Sweet's syndrome (Jindal et al. 2012), production of granulocyte colony-stimulating factor (Takahashi et al. 1985; Takeda et al. 1990; Furihata et al. 1999; Suzumura et al. 2014), hypercalcemia (Vilabona et al. 1986; Watanabe et al. 1989;), Cushing's syndrome (Brickner et al. 1961), synthesis and secretion of chorionic gonadotropin/beta-HCG (Fukuda and Ohnishi 1990; Sato et al. 2010), and AFP-producing CG (Sugaya et al. 1989) which is discussed in a separate paragraph. Paraneoplastic disorders of the CNS in CG should

Table 2 Paraneoplastic syndromes/disorders in gallbladder carcinoma

Cutaneous alterations
Acanthosis nigricans
Bullous pemphigoid
Erythrodermia
Soft tissue alterations
Dermatomyositis
Polymyositis
Hematological alterations
Erythrocytosis
Thrombocytosis
Leukemoid reactions
Production of granulocyte colony-stimulating factor
Autoimmune hemolytic anemia
Hemolytic microangiopathic anemia
Sweet's syndrome
Paraneoplastic thrombosis
Neuromuscular alterations
Neuropathy (sensory, mixed)
Opsoclonus
Guillain-Barré syndrome
Metabolic alterations
Paraneoplastic hypercalcemia
Cushing's syndrome
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Paraneoplastic hyponatremia
AFP production

not be confounded with effects of metastases, e.g., myelopathy due to spinal metastases (Newman et al. 1977).

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