Noninflammatory Tumor-Like Changes of the Gallbladder

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Abstract

The gallbladder can be subject to an entire spectrum of noninflammatory tumor-like changes. A typical example is cholesterolosis of the gallbladder, defined by a mucosal lesion characterized by accumulation of cholesteryl esters and triglycerides in foamy macrophages. Multiple mucosal yellowish to white lesions produce a macroscopically striking lesion termed strawberry gallbladder. Large accumulations of foamy cells give rise to cholesterol polyps that may protrude into the gallbladder lumen and mimic a neoplastic polyp. These polyps may undergo ulceration followed by secondary inflammatory changes. The adipose tissue situated around the gallbladder can undergo steatonecrosis followed by formation of numerous lipogranulomas. The gallbladder is rarely involved with malakoplakia, a reactive lesion more commonly occurring in the urogenital tract. Gallbladder malakoplakia presents in the form of yellowish plaques or nodules and histologically consists of large macrophages with distinct calcifications, the Michaelis-Gutmann bodies. The gallbladder is the site of endometriosis, endometrioma, several types of metaplasia, and tissue ectopias, whereby misplaced pancreatic tissue is the most common variant.

Cholesterolosis of the Gallbladder

Introduction

Cholesterolosis (synonyms: cholesterosis, cholesterinosis) is defined by a mucosal lesion of the gallbladder characterized by accumulation of cholesteryl esters and triglycerides in macrophages, which show the morphology of foam cells. Cholesterolosis was first described by Rudolf Virchow in 1857 (Virchow 1857). Typically, cholesterolosis displays a multifocal mucosal distribution, with multiple yellowish and sharply delineated foci distributed on the dark red-green background of the mucosa, a phenotype which somewhat resembles the morphology of the skin of a strawberry ("strawberry gallbladder"). Cholesterolosis can, however, produce endophytic lesions manifest as polyps, lesions that may radiologically mimic true gallbladder tumors.

Selected References: MacCarty 1919; Judd and Mentzer 1927a; Mackay 1937; Arnell 1941; Lewis and Peterson 1943; Womack and Haffner 1944; Mitty and Rousselot 1957; Reid 1962; Salmenkivi 1964; Heino and Ritama 1965; Andersson and Bergdahl 1971; Jacyna and Bouchier 1987; Csendes et al. 1998; Izzo et al. 2001; Owen and Bilhartz 2003.

Epidemiology

Cholesterolosis of the gallbladder is a common lesion. In a study of 633 consecutive necropsies, 134 strawberry gallbladders (diffuse cholesterolosis), 61 polypous forms, and 29 combined forms were found. None of the persons was under 15 years, and only three were under 20 years of age (Mentzer 1925). In a study of 1,000 surgical cases of cholesterolosis of the gallbladder, 26 % of the stone-free and 82 % of the gallstone cases occurred in females. The age incidence in the two groups was essentially alike, the greatest number of cases in each group occurring between the ages of 35 and 40 years (Judd and Mentzer 1927a). In 1,323 cholecystectomy preparations, cholesterolosis was detected in 15.6 % of cases (Celoria et al. 1994). In a more recent hospital-based retrospective study, 549 patients underwent cholecystectomy and hepatic resection for hepatocellular carcinoma, the prevalence of cholesterolosis of the gallbladder was 6.6 %, and the prevalence of cholesterol polyp of the gallbladder was 0.9 % (Lai 2011).

Among 549 consecutive patients who had cholecystectomies for various gallbladder disorders, 13.4 % had cholesterolosis. Cholesterolosis with coexistent gallstones was documented in 63.3 %, and 85.1 % of the cases were reported to have abnormally high fasting serum cholesterol levels (Khairy et al. 2004). The prevalence of cholesterolosis is higher in obese patients, being 38 % in obese vs. 6 % in nonobese patients in one study (Dittrick et al. 2005) and 37 % in another

(Csendes et al. 2003). In a study of 1,000 cases of gallbladder cholesterolosis, stones were present in half of the specimens, and multiple stones were found in 69 %, 99 % of the stones being cholesterol stones. Cholesterolosis alone, as the typical strawberry gallbladder, was the diagnosis in 53 % of the stone-free group and in 82 % of the stone group, and polypous cholesterolosis was detected in 47 % and 18 %, respectively. Diffuse and local/polypous forms were combined in 34 % of the stone-free and in 10 % of the stone-containing specimens (Judd and Mentzer 1927b).

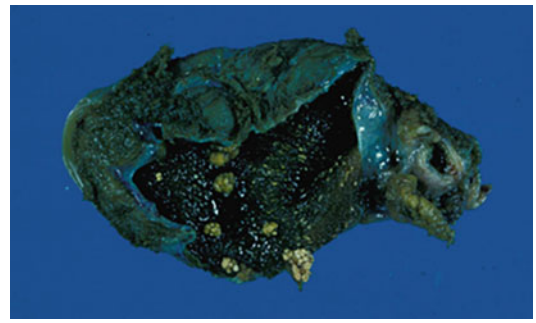

Fig. 1 Cholesterolosis of the gallbladder with cholesterol polyps

Clinical and Imaging Features

Isolated cholesterolosis is clinically silent in most cases. In the era preceding CT and MRI studies, imaging for cholesterolosis using X-ray was associated with a high percentage of errors (Judd and Mentzer 1927b; Damore et al. 2001), although other authors consider ultrasonography as an efficient tool (Price et al. 1982; Sandri et al. 2003). In an ultrasonography study of 853 patients who underwent laparoscopic cholecystectomy, 56 had gallbladder polyps, including cholesterolosis polyps, 75 % of them being smaller than 10 mm. Overall US-based diagnosis of gallbladder polyp was inaccurate in 82 % (Akyürek et al. 2005).

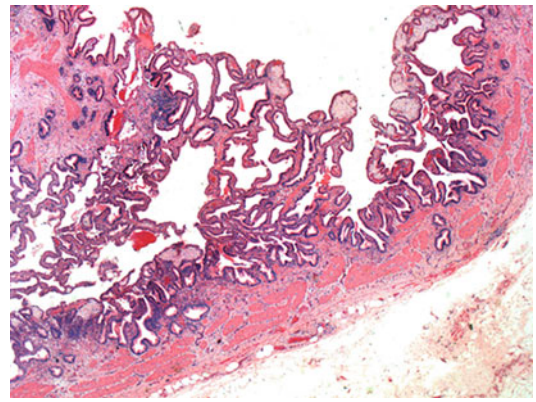

Fig. 2 Cholesterolosis of the gallbladder. Foamy, lipid-rich macrophages have accumulated in the tips of mucosal folds (hematoxylin and eosin stain)

Pathology

Macroscopy

Macroscopically, cholesterolosis of the gallbladder shows small yellowish elevations when the mucosa is inspected in the fresh specimen (Fig. 1). These elevations form circumscribed lesions or coalesce to form short bar-like or hook-like structures or an incomplete network reflecting the fine mucosal fold pattern of the gallbladder (Cooke 1931; Lewis and Peterson 1943; Feldman and Feldman 1954). The lesions, which occupy the tips of mucosal ridges, are 1 mm in diameter or less. Seventy-eight percent of cases showed grossly visible fatty changes (cholecystosteatosis) in the wall of the gallbladder (Judd and Mentzer 1927a).

Histopathology

The histology of gallbladder cholesterolosis has been studied in detail (Guerra et al. 1963). The lamina propria of the mucosa and in particular the tips of the delicate mucosal folds are densely infiltrated by large and clear, markedly vacuolated macrophages (foamy cells, Figs. 2 and 3). Cholesterolosis is often associated with papillary epithelial hyperplasia of the gallbladder (Elfving et al. 1968; Celoria et al. 1994) and sometimes with adenomyosis (Helpap and Huegel 1988). The foamy macrophage accumulations can develop regressive changes, associated with release of cholesteryl esters into the extracellular

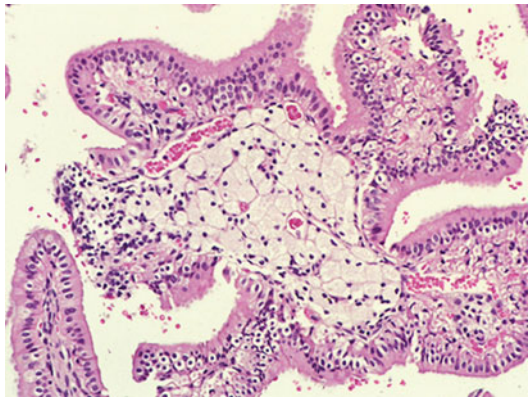

Fig. 3 Cholesterolosis of the gallbladder at higher magnification (hematoxylin and eosin stain)

space, an inflammatory response of the foreign-body type, and formation of cholesterol crystals and cholesterol granulomas, with foreign-body giant cells apposed to crystals (Womack and Haffner 1944). In old lesions, collections of cholesterol granulomas, sometimes in band-like formations, may be noted in deep layers of the gallbladder, in part of the cases associated with formation of lymph follicles and germinal centers. This process can induce mucosal ulceration, granulation tissue, and scarring, sometimes followed by inspissated bile depositions and dystrophic calcifications of the gallbladder wall (Womack and Haffner 1944). Exceptionally, osseous metaplasia can develop in such lesions (Ortiz-Hildalgo and Baquera-Heredia 2000). Released cholesterol and its esters may be transported to locoregional lymph nodes, where they can form "metastatic" cholesterol granulomas in the subcapsular sinus (Womack and Haffner 1944). Rarely, cholesterolosis has been found in association with carcinoma in situ (Akiyama et al. 1996).

Electron Microscopic Findings

Cholesteryl ester-laden macrophages in cholesterolosis show numerous protruded processes, which also contain organelles, lipid droplets, and abundant lysosomes. In foam cells, the cytoplasm is filled with large lipid droplets containing cholesteryl esters. Adjacent epithelial cells also show ultrastructural signs of high cholesterol content, with small lipid droplets and a well-developed agranular endoplasmic reticulum (Nevalainen and Laitio 1972; Koga 1985; Satoh and Koga 1997). Epithelial cells of the cystic duct in cholesterolosis of the gallbladder showed mucous secretory granules that appear dilated, and peculiar intracellular cholesterol deposits are detectable in the apical and subapical region of cells and around condensed mitochondria (Gilloteaux et al. 1997), suggesting that the cystic duct mucosa may participate in cholesterolosis of precursor lesions of this condition.

Tumor-Like Cholesterol Polyps of the Gallbladder

In clinico-radiologic work-ups, tumorous lesions of the gallbladder larger than 10 mm have a high incidence of malignancy. In rare instances, cholesterol polyps of the gallbladder can grow to sizes exceeding 1 cm, forming large papillary masses with a diameter of up to 3 cm and thus mimicking gallbladder cancer (Kaido et al. 2004).

Pathogenesis

Cholesterolosis of the gallbladder is considered to be multifactorial, and first ideas about pathogenic pathways date back to more than 50 years (Graham and Elman 1932). As part of investigations documented a correlation between high serum cholesterol levels and the prevalence of cholesterolosis of the gallbladder (Khairy et al. 2004), excess of cholesterol production was regarded as a pathogenic factor. However, in a study on 446 patients with cholesterolosis associated with gallstones and 190 patients without stones, cholesterolosis was not associated with high plasma cholesterol levels (Méndez-Sanchez et al. 1997). In patients with cholesterolosis, a positive correlation was obtained between the cholesterol saturation of bile and the content of

esterified cholesterol in the gallbladder mucosa (Sahlin et al. 1995). Free sterols can be transferred from bile to the gallbladder mucosa (Tilvis et al. 1982), where free cholesterol is esterified within cells, mainly mucosal macrophages. Cholesteryl ester accumulation is not caused by reduced efflux of cholesterol due to a defective sterol 27-hyroxylase mechanism (Strömsten et al. 2004). There is evidence that cholesteryl ester synthesis of gallbladder mucosa might play a role in the pathogenesis of cholesterolosis, as the activity of acylCoA-cholesterol ester acyltransferase is increased (Watanabe et al. 1998).

Steatonecrosis, Panniculitis, and Lipogranulomas of the Gallbladder

Severe transmural and specifically fistulating and perforating cholecystitis can induce necrosis and inflammation in the pericholecystic adipose tissue (panniculitis). This process can lead to numerous and in part cystic lipogranulomas, eventually producing a mass effect. Fat necrosis (steatonecrosis, adiponecrosis) of the gallbladder is uncommonly found in patients with acute pancreatitis (Chitkara 1995). It presents as whitish flecks or patches in the subadventitional adipose tissue, identical to the lesions found in peripancreatic adipose tissue. Steatonecrosis of the gallbladder may be marked and associated with direct extension from fat necrosis of the hepatoduodenal ligament, causing an ill-defined mass (Schein et al. 1993). A rare instance of membranous fat necrosis of the gallbladder has been reported (Ohtsuki et al. 2012). Membranous fat necrosis (synonyms: membranocystic change, lipomembranous panniculitis) is usually observed in skin-related diseases but may become a systemic alteration. The tissue contains wavy sudanophilic fluffy membranes that can elicit vigorous foreign-body reactions with giant cells. Gallbladder panniculitis can rarely be a manifestation of the panniculitis disorder, Weber-Christian disease (Ishida et al. 1993).

Cholecystosteatosis (Nonalcoholic Fatty Gallbladder Disease)

Obesity may cause fatty infiltration of multiple internal organs, including liver, heart, kidney, and pancreas, associated with organ and tissue dysfunction. Adipose tissue and tissues having fat overload form a dynamic endocrine organ regulating energy expenditure and adipokine turnover. Obesity is also associated with cholecystosteatosis. Cholecystosteatosis (synonym: nonalcoholic fatty gallbladder disease, NAFGBD) denotes increased fat deposition in the gallbladder wall (review, Pitt 2007). Increased gallbladder tissue lipids comprise free fatty acids, phospholipids, and triglycerides (Goldblatt et al. 2006; Mathur et al. 2008). It has been found that there is a relation between the type of cholecystitis and total gallbladder wall fat. Patients with acalculous and calculous cholecystitis have increased gallbladder fat compared to nondiseased controls, and this increased fat may lead to poor gallbladder emptying and biliary symptoms and signs (Al-Azzawi et al. 2007). Increased lipids enhance inflammatory reactions of the gallbladder (steatocholecystitis) resulting in an abnormal wall structure and decreased contractility (review: Tsai 2009).

Malakoplakia of the Gallbladder

Malakoplakia is a rare and unusual inflammatory process first described in the early 1900s (see the chapter on malakoplakia of the liver). Very few cases of gallbladder malakoplakia have been reported (Hanada et al. 1981; Charpentier et al. 1983; Hide et al. 2001; Agnarsdottir et al. 2004; Di Tommaso et al. 2005; Vaiphei et al. 2012). Gallbladder malakoplakia has been found in association with diabetes mellitus type 2 (Vaiphei et al. 2012). Macroscopically, yellowish plaques or nodules were noted. Histopathologically, accumulation of large macrophages with von Kossa-positive Michaelis-Gutmann bodies, associated with lymphocytic infiltration, is the hallmark. In

hematoxylin and eosin-stained sections, Michaelis-Gutmann bodies appear as targetoid cytoplasmic inclusions, and these bodies are PAS positive with and without diastase treatment and are also positive for the colloidal iron stain.

In the presence of typical targetoid, von Kossa-positive Michaelis-Gutmann bodies, the macrophage-rich lesions can hardly be confounded with other granulomatous inflammatory lesions.

Endometriosis and Endometrioma of the Gallbladder

Introduction

Endometriosis is defined as the presence of functioning endometrial tissue outside the uterine cavity. The prevalence of endometriosis has been estimated to be between 8 % and 18 % in young women. Endometriosis outside the pelvic cavity and ovaries mainly involves the abdominal wall, the gastrointestinal tract, and the urinary tract. Rare locations include muscle tissue, inguinal canal, umbilicus, mediastinum, bronchi, pleura, and even nasal region (nasolacrimal endometriosis). Endometriosis, which is well documented for the liver (see the respective paragraph), very rarely occurs in the gallbladder (Saadat-Gilani et al. 2007; Saldaña et al. 2010; Iafrate et al. 2013). Clinically, gallbladder endometriosis was manifest as chronic and vague or colicky abdominal pain, most severe in the right hypochondrium and accentuated during menstruation, and eventually an upper abdominal mass (Iafrate et al. 2013). The cyclic pain is thought to be caused by intrafocal bleeding during menstruation. Gallbladder endometriosis may be an isolated manifestation of this disorder or may be accompanied by endometriotic nodules situated elsewhere, e.g., the abdominal wall (Iafrate et al. 2013).

Pathology

Macroscopically, endometriotic foci may be situated in any part of the gallbladder but predominate in the fundus. The foci may adhere to the gallbladder surface or form internal nodules. The lesions may grow to macroscopic size and mimic cancer (gallbladder endometrioma; Saldaña et al. 2010). Histopathologically, endometriotic foci show preserved or markedly altered endometrial tissue consisting of endometrial glands in various phases of proliferation or secretion and the typical cellular stroma. Secondary changes mainly comprise fresh and old hemorrhage, with accumulation of hemosiderin-containing macrophages and free hemosiderin granules, necrosis, and fibrosis.

As endometriosis is an estrogen-dependent disease, endometriotic foci express estrogen receptors, a phenomenon which may help in the correct classification of stromal foci in the hepatobiliary tract (review: Burns and Korach 2012). Biologically, active estrogens are available to endometriotic tissue via several mechanisms, specifically aromatase activity. The rapid estrogen effects on endometriotic tissue are mediated by both membrane-associated estrogen receptors alpha and G protein-coupled receptor 30/GPER (Plante et al. 2012; Samartzis et al. 2012). Estrogen receptor-beta levels are more than 100 times higher in endometriosis than in normal endometrial tissue (Bulun et al. 2012). Also the estrogen-regulated genes, GREB1, c-MYC, and cyclin D1, are overexpressed in endometriotic foci (Pellegrini et al. 2012).

Differential Diagnosis

Endometriosis occurs in the liver and can be situated close to the gallbladder. Endometriosis sometimes develops on the undersurface of the diaphragm (Triponez et al. 2010).

Osseous Metaplasia of the Gallbladder

Introduction

Osseous metaplasia (heterotopic bone) denotes a tissue alteration characterized by the development of immature and/or mature bone within

connective tissue of various organs. Osseous metaplasia of the gallbladder wall is an uncommon finding and has mainly been observed in the setting of chronic fibrosing cholecystitis (Indyk and Shipton 1957; Duchini 1967; Yosepovich et al. 2002; Nelson and Kahn 2009; Rege and Vargas 2011).

Pathology

Histologically, one most often notes a delicate network of osteoid trabecules lined by osteoblasts, embedded in a collagenous matrix with or without associated lymphocytic infiltration ("cholecystitis ossificans"). Mature mineralized bone may also develop in part of the cases. Osseous metaplasia sometimes exclusively involves the gallbladder mucosa (Nelson and Kahn 2009). In one patient with cholecystitis and cholelithiais, osseous metaplasia of the gallbladder wall was associated with a fasciitis-like fibroblastoid proliferation containing osteoclast-like giant cells (Rege and Vargas 2011).

Differential Diagnosis

Ossifications occur in part of gallbladder carcinosarcomas (Nakagawa et al. 1996). Impacted calcified gallstones may mimic circumscribed osseous metaplasia.

Pancreatic Ectopia of the Gallbladder

Introduction

Misplaced pancreatic tissue (ectopic pancreas, heterotopic pancreas) can occur in the wall of the gallbladder. This alteration was first described by Poppi in 1916. Since then, numerous descriptions of this clinicopathologic entity have appeared in the literature.

Selected References: Mutschmann 1946; Elfving 1959; Monfreda et al. 1967; Dolan et al. 1974; Qizilbash 1976; Ben-Baruch et al. 1986; Lai and Tompkins 1986; Collard et al. 1989; Jarde et al. 1989; Murakami and Tsutsumi 1989; Jeng et al. 1991; Hadzi-Nikolov et al. 1997; Kondi-Paphiti et al. 1997; Bhana and Chetti 1999; Mboti et al. 2003; Meshikhes et al. 2003; Pilloni et al. 2006; Beltran et al. 2007; Elpek et al. 2007; Neupert et al. 2007; Shiwani and Gosling 2008; Bromberg et al. 2009; Al-Shraim et al. 2010; Cerullo et al. 2011; Gucer et al. 2011; Klimis et al. 2011; Sroczynski et al. 2013.

Instead of pancreatic heterotopia or ectopia, the term pancreatic choristoma of the gallbladder is employed to denote this lesion (Beltran et al. 2007). At least half of the cases are located to the gallbladder neck, which embryologically is more close to the pancreas anlage.

Clinical Features

In the majority of cases, heterotopic pancreatic tissue in the gallbladder is an asymptomatic, incidentally found alteration. In part of patients, the lesion can induce, or be associated with, acute or chronic cholecystitis in part of patients (Bhana and Chetty 1999; Mboti et al. 2003; Elpek et al. 2007; Shiwani and Gosling 2008; Bromberg et al. 2009; Al-Shraim et al. 2010; Klimis et al. 2011; Elhence et al. 2012; Sroczynski et al. 2013). Cholecystitis may be related to obstruction, as it was found in pancreatic heterotopia located to the gallbladder neck (Weppner et al. 2009; Limaiem et al. 2012). The lesion rarely presents with symptoms and signs of pancreatitis, as the ectopic pancreatic tissue can undergo acute inflammation, similar to the orthotopic organ (Qizilbash 1976; Pilloni et al. 2006). Sometimes, pancreatic heterotopia gives rise to a suspicious tumefaction (Collard et al. 1989; Foucault et al. 2012), and in one patient, the heterotopia was associated with hypertrophic ectopic pancreatic ducts mimicking an adenomyoma (Pilloni et al. 2006). One case with malignant change of pancreatic heterotopia of the gallbladder was reported (Jeng et al. 1991). The lesion may be associated with high levels of

amylasuria (Klimis et al. 2011) or may cause an elevation of pancreatic enzymes in gallbladder bile (Sato et al. 2012).

Pathology

Macroscopically, pancreatic heterotopia is usually manifest as a mere thickening of the gallbladder wall, with circumscribed nodules of pancreatic tissue embedded in fibrous stroma. The heterotopia can, however, also present as gross, tumor-like nodules of 1 cm diameter or even more (Mboti et al. 2003). Histologically, all cellular systems of the normal pancreas can be present, including acinar cells, duct cells, and endocrine islet-type cells or fully developed islets of Langerhans with expression of insulin and somatostatin (Pilloni et al. 2006; Beltram et al. 2007). In some cases, large parts of the gallbladder wall are involved by pancreatic exocrine tissue, the pancreatic ductules and ducts resembling Rokitansky-Aschoff sinuses (Pilloni et al. 2006). Pancreatic heterotopia can be associated with synchronous heterotopic gastric mucosa of the gallbladder (Jaerve and Meurman 1964).

Ectopic Liver of the Gallbladder

Introduction

Ectopic liver tissue (liver choristoma, accessory liver, hepar succenturiatum) is a rare condition that most often involves the pancreas, stomach, gastrohepatic ligament, umbilical ligament, gallbladder, omentum, adrenal glands, esophagus, and thoracic cavity, including mediastinum, lung, and heart. Ectopic liver of the gallbladder is a rare clinical entity that is usually asymptomatic and observed incidentally in the setting of laparoscopy, cholecystectomy for other reasons, or autopsy. Ectopia of liver tissue in the gallbladder wall was first described in 1922 under the term supernumerary liver lobe implanted on the inferior surface of the gallbladder (Corsy 1922).

Epidemiology

Overall, the incidence of ectopic liver in the abdominal and thoracic cavities has been estimated from 0.24 % to 0.47 %. The incidence of ectopic liver of the gallbladder is probably low but seems to be the most common intra-abdominal site of liver ectopia (Griniatsos et al. 2002; Algin et al. 2008; Triantafyllidis et al. 2009). In a study of 5,500 autopsies, only three cases were detected (0.05 %; Eiserth 1940). In a more recent investigation on 1,060 laparoscopies, three cases were identified (0.28 %; Watanabe et al. 1989).

Clinical Features

Most cases of ectopic liver of the gallbladder are incidental findings without symptoms and signs. However, ectopic liver can produce a mass lesion that may be confounded with a gallbladder tumor (Hamdani and Baron 1994). In unusual situations, ectopic liver can undergo secondary changes that are symptomatic, including torsion of pedunculated lesions, acute hemorrhage, compression, obstruction of the gallbladder, or malignant transformation.

Selected References: Eiserth 1940; Klein 1955; Bassis and Izenstark 1956; Horanyi and Fuesy 1963; Ashby 1969; Costero et al. 1975; Collan et al. 1978; Torchio and Maconi 1978; Natori et al. 1986; Fellbaum et al. 1987; Tejada and Danielson 1989; Watanabe et al. 1989; Castro Viera et al. 1990; Iacconi and Masoni 1990; Svane and Knudtzon 1991; Hamdani and Baron 1994; Kodama and Yokoyama 1996; Sato et al. 1998; Djuricic et al. 1999; Acar et al. 2002; Griniatsos et al. 2002; Sakarya et al. 2002; Lundy et al. 2005; Wang and Liu 2006; Koh and Hunt 2007; Triantafyllidis et al. 2009; Catani et al. 2011; Dettmer et al. 2011; Nagar et al. 2011; Martinez et al. 2013.

Pathology

Macroscopy

Most cases of liver ectopia of the gallbladder showed liver tissue attached to the outer surface of the organ. The lesion may be pedunculated and forming a polypoid structure, with a thick or thin stalk of variable length connecting it with the gallbladder and containing blood vessels (Lundy et al. 2005; Triantafyllidis et al. 2009). Very few reports documented the presence of ectopic liver tissue in inner parts or the gallbladder wall (intramural ectopia) or even the mucosa (Torchio and Maconi 1978; Natori et al. 1986). Ectopic liver tissue of the gallbladder usually manifests as small brownish nodules measuring from a few mm to 1 or 2 cm (Natori et al. 1986), but lesions measuring several cm in diameter have also been observed (Lundy et al. 2005). Due to circulation failure, ectopic liver tissue can undergo necrosis associated with acute hemorrhage, the lesion presenting as a dark red nodule on the gallbladder surface (Nagar et al. 2011).

Histopathology

Histologically, the ectopic liver tissue usually shows a normal architecture, although the lobules may be deformed and/or undersized (Griniatsos et al. 2002). In at least part of the cases, ectopic liver contained portal tracts with small bile ducts, arteries, and venous branches. The ectopic liver tissue is sometimes cholestatic, with accumulation of bile in canaliculi (Svane and Knudtzon 1991). Interestingly, these livers or liverlets do however not always show cholestasis, although a connection to the gallbladder lumen or the cystic duct cannot, or not easily, be identified. Hepatocytes located in ectopic liver may undergo changes similar to that of orthotopic hepatocytes, apart from cholestasis, such as fatty change (Eiserth 1940), hemosiderosis (Tejada and Danielson 1989), and cirrhosis (Watanabe et al. 1989). In one case of ectopic liver localized to the gallbladder fundus, retention of alpha-1-antitrypsin was detected in the ectopic hepatocytes (Dettmer et al. 2011).

Ectopic Liver and Malignancy

Ectopic liver tissue has a propensity to develop hepatocellular carcinoma/HCC, especially in oriental patients (see the respective chapter; Arakawa et al. 1999; Caygill and Gatenby 2004; Leone et al. 2004). In the study of Arakawa and coworkers (1999), which focused at ectopias other than those of the gallbladder, 22 out of 48 cases developed HCC. HCC can also develop in ectopic liver of the gallbladder (Tamura et al. 1985; Arakawa et al. 1999). Interestingly, the incidence of HCC is much lower in ectopic liver tissue of the gallbladder: only one of 33 cases developed cancer (Arakawa et al. 1999). The reason for this striking difference is unknown. Ectopic liver of the gallbladder may have less time to undergo carcinogenesis, because the involved gallbladders may be removed early. It has also been suggested that the difference might be related to the finding that ectopic liver attached to the gallbladder is an anomaly occurring later in ontogenesis and is thus well differentiated and composed of more stable tissue (Griniatsos et al. 2002).

Pathogenic Pathways

It is assumed that ectopic liver of the gallbladder arises from residual liver primordial cells located in the caudal part of the liver primordium.

Thyroid Ectopia of the Gallbladder

In the course of thyroid anlage descent, groups or clusters of thyrocyte precursors can lodge at various non-eutopic sites and thus give rise to ectopic tissue. The most common sites of ectopic thyroid tissue are lingual, sublingual, thyroglossal, laryngotracheal, and lateral cervical sites. Thyroid ectopia in the gallbladder wall has been reported few times (Harach 1998; Ihtiyar et al. 2003; Venditti

et al. 2007; Cassol et al. 2010; Liang et al. 2010; review, Klubo-Gwiezdzinska et al. 2011).

Macroscopically, thyroid ectopia can produce a gallbladder mass (Liang et al. 2010), but this is a highly unusual event as ectopic thyroid tissue is usually detected histologically as an incidental finding. Histology is characterized by normal-looking thyroid tissue, with or without a lobular texture, follicles sometimes being embedded in a collagenous matrix. A potential differential diagnosis of thyroid ectopia is gallbladder metastasis of well-differentiated follicular thyroid carcinoma.

Pathogenic Pathways

Similar to thyroid ectopia in the liver (see the respective paragraph), ectopic thyroid tissue in the gallbladder wall is thought to arise via aberrant migration of thyroidocyte progenitors in the course of the thyroid anlage descent from the foramen cecum to the mediastinum. The descending thyroid anlage is, in a certain phase of embryogenesis, in close contact with the mesenchyme of the future septum transversum, and cell exchange may occur during this developmental phase.

Adrenocortical Ectopia

Very rarely, ectopic adrenal cortex was found in the form of small nodular structures in the subserosal space of the gallbladder (Busuttil 1974).

Gastric Mucosal Heterotopia in the Gallbladder

Introduction

Gastric mucosal heterotopia (GMH) of the gallbladder is a congenital abnormality characterized by the presence of usually circumscribed areas of gastric mucosa replacing the original gallbladder mucosa. Gallbladder GMH was first described in 1934, based on a polypoid lesion (Egyedi 1934), and relatively few observations have been documented since.

Selected References: Williams and Humm 1953; Curtis and Sheahan 1969; Summers et al. 1970; Bentivegna and Hirschl 1972; Keramidas et al. 1977; Mooney et al. 1979; Adam et al. 1989; Pradines et al. 1989; Boyle et al. 1992; Vallera et al. 1992; Schimpl et al. 1994; Uchiyama et al. 1995; Hamazaki and Fujiwara 2000; Inoue et al. 2000; Xeropotamos et al. 2001; Isik et al. 2002; Lombay et al. 2003; Madrid et al. 2003; Sciumè et al. 2005; Cöl et al. 2007; Triki et al. 2008; Hayama et al. 2010; Bulus et al. 2012; Liang et al. 2013.

GMH of the gallbladder is an uncommon condition, while pseudopyloric or pyloric gland metaplastic epithelium in the gallbladder is a common finding, detectable in 66–84 % of cholecystectomy specimens, whereas intestinal metaplasia is present in 12–52 % of gallbladders and is often associated with pyloric metaplasia (review, Xeropotamos et al. 2001). Gallbladder GMH is almost equally distributed among sexes, with an age range at diagnosis of 6–77 years, a considerable proportion of cases being reported for the pediatric age group. In almost a third of cases, gallstones were present. GMH can lead to mucosal defects, including peptic ulcerations (Kehrer and De Minjer 1951; Larsen et al. 1985), sometimes causing massive hemobilia (Adam et al. 1989; Yoon et al. 2005), and hematemesis and melena (Larsen et al. 1985). GMH may occur in gallbladders with preexisting anatomical abnormalities, including duplicate gallbladder (Bailie et al. 2003), or anomalous union of the pancreatobiliary duct (Wakiyama et al. 1998). Apart from the gallbladder, GMH can develop in the cystic duct (Orizio et al. 2011). GMH and intestinal metaplasia of the gallbladder are considered to be precancerous (Yamagiwa and Tomiyama 1986). Etiology and pathogenesis of gastric mucosal heterotopias are not known.

Pathology

Macroscopy

Macroscopically, gallbladder GMH can present as a flat or plaque-like lesion, but GMH growing

as pedunculated or sessile polypous masses is also well known (Yamamoto et al. 1988, 1989; Schimpl et al. 1994; Uchiyama et al. 1995; Leyman et al. 1996; Sciumè et al. 2005; Hayama et al. 2010). In case of polypoid lesions, gallbladder carcinoma may suspected based on imaging results (Hayama et al. 2010), also because polypous GMH may grow to a size exceeding 2 cm. Gallbladder GMH can also present as a firm nodular mass or as a multiloculated lesion (Xeropotamos et al. 2001). Large GMH masses can cause symptom-producing tumors (Bentivegna and Hirschl 1972). On CT images, GMH appears as a slightly high density area which is intermediately enhanced early after bolus injection of contrast medium (Inoue et al. 2000). The lesions are often located in the gallbladder fundus, but GMH also occurs in the gallbladder neck (Sciumè et al. 2005).

Histopathology

Histologically, GMH reveals a gastric-type superficial epithelium and associated gastric glands, including pyloric glands, corpus glands, and fundic glands, chief cells and parietal/oxyntic cells being present (Runge et al. 1978). The epithelium overlying the glandular structures may show hyperplastic changes. Neuroendocrine/APUD cells have been found in part of the cases (Vallera et al. 1992). GMH can be associated with extensive adjacent pyloric and/or pseudopyloric metaplasia, staining red with the Alcian blue-PAS stain (Xeropotamos et al. 2001), or intestinal gallbladder metaplasia (Tavli et al. 2005). It can undergo secondary changes, such as cystic change (Popkharitov et al. 2008) or squamous metaplasia (Daud et al. 2007). Gallbladder GMH can be associated with other types of heterotopia/ectopia, such as pancreas and thyroid tissue (Murakami and Tsutsumi 1999), or with adenoma of the gallbladder (Summers et al. 1970). On gastric-type epithelium of the gallbladder, no *Helicobacter pylori* was detected (Arnaout et al. 1990).

Table 1 Types of gallbladder ectopia

Retroposition of the gallbladder
Intrahepatic gallbladder
Left-sided gallbladder (transposition)
Gallbladder interposition
Extraabdominal gallbladder

Ectopic Gallbladder

Ectopic gallbladder, albeit a rare condition, has clinical significance because it can lead to misdiagnosis and misinterpretation as a tumorous lesion. Several types of gallbladder ectopia are known (Table 1).

A retroposed gallbladder (retrohepatic gallbladder) may suggest the presence of a cystic tumor on the underside of the liver (Feldman and Venta 1988; Chowbey et al. 2004). A retrohepatic gallbladder can be contained in the coronary ligament (Principe et al. 1979). Ectopic gallbladder may be situated within the liver substance, with or without stones (Glasionov 1961; Schulz et al. 1975; Velchik and Noel 1987; Lobo et al. 2007), and can mimic an intrahepatic cystic tumor (Schneider et al. 1979). If it is situated away from the peritoneum, signs of acute cholecystitis may be absent. In some cases, ectopic gallbladder has an own mesenterium (mesovesicula) containing feeding vessels (Popli et al. 2010), the ectopic gallbladder then being a hanging lesion that can undergo torsion and gangrenous infarction (the "floating gallbladder"; Havrilla et al. 1978). A floating gallbladder on a long "mesovesicula" can also herniate through the foramen of Winslow into the lesser sac, with signs of strangulation (Blanton et al. 1974). In rare instances, the gallbladder is situated in a suprahepatic position (Faintuch et al. 1979; Youngwirth et al. 1983; Sheu et al. 1995), sometimes associated with malformations of the right liver (Hsu et al. 1994) or inverted liver (Hibbs and Ahmad 2010). It can also occur intrathoracically (Labitzke 1991), and in few instances, the gallbladder was transposed to the left underside of the liver (gallbladder transposition; Duimstra and Greenfield 1977; Keller et al. 1982; Wong et al. 2001; Dhulkotia et al. 2002) or was malpositioned in the

region of extrahepatic bile ducts (gallbladder interposition; Walia et al. 1986). The gallbladder can be situated on the left side of the common bile duct and the cystic duct, arising from the right hepatic duct (Chung et al. 1997).

Reactive Vascular Mass Lesions of the Gallbladder

Introduction

Similar to extrahepatic and intrahepatic bile ducts, the gallbladder can be involved in a variety of reactive vascular alterations that may produce mass effects or pseudotumors mimicking neoplastic disease. The most important changes include gallbladder varices and pseudoaneurysms of the cystic artery.

Gallbladder Varices

In part of patients with portal hypertension, ectopic varices (varicose veins) as dilated venous collaterals can develop in the wall of the gallbladder.

Selected References: Malusev 1951; Salam et al. 1979; Lebrec and Benhamou 1985; West et al. 1991; Chawla et al. 1994, 1995; Safadi et al. 1996; Gabata et al. 1997; Palazzo et al. 2000; Chu et al. 2002; Radhi 2003; Ito et al. 2009; de Alcantara et al. 2013.

It is estimated that the incidence of gallbladder varices in cirrhotic and non-cirrhotic portal hypertension amounts to up to 30 % (West et al. 1991; Chawla et al. 1994; Helbich et al. 1994; Rathi et al. 1996). Gallbladder varices have also been described in the pediatric age group (Helbich et al. 1994; Rathi et al. 1996). The varices may or may not be associated with extrahepatic portal vein occlusion (West et al. 1991) but are sometimes associated with portal vein cavernoma (Lebrec and Benhamou 1985). Varices cause fixed filling defects (Rosen and Wilson 1980) and thickening of the gallbladder wall suspicious of malignancy (Saigh et al. 1985). Rupture of varices leads to variceal bleeding, sometimes followed by life-threatening or fatal abdominal hemorrhage (Holmlund and Lundström 1977; Chu et al. 2002; Kevans et al. 2009; Vilallonga et al. 2012). The dilated gallbladder veins can be visualized by means of color Doppler sonography (Kainberger et al. 1990; Helbich et al. 1994; Safadi et al. 1996; Mishin 2005). A direct communication of the varices to intrahepatic portal vein branches can be demonstrated by Doppler sonography and CT (Gabata et al. 1997).

Aneurysmatic Changes and Related Vascular Disorders

The most common alteration in this group is cystic artery pseudoaneurysm (CAP). Pseudoaneurysms (synonyms: false aneurysm, aneurysma spurium, aneurysma falsum) are characterized by a periarterial hematoma following a tear in the arterial wall involving intima and media but leaving the adventitia intact in classical cases. However, in some of these aneurysms, the hematoma will break through the adventitia with time. CAP is most often observed in the setting of acute cholecystitis (Machida et al. 2008; Hague et al. 2010; Dewachter et al. 2012; Fung et al. 2013) and can develop as a complication of xanthogranulomatous cholecystitis (Ahmed et al. 2010). CAP can protrude into the gallbladder lumen, producing masses of up to 2 cm in diameter (Ahmed et al. 2010). This vascular lesion can cause acute internal hemorrhage (Fung et al. 2013) and hemoperitoneum (Ghoz et al. 2007), sometimes with fatal outcome (Olbrycht 1965). Pseudoaneurysms can also develop in the right hepatic artery and rupture into the gallbladder (Schubert et al. 1980; Lin et al. 2010). Percutaneous liver biopsy can be complicated by arterial-portal fistula causing a gallbladder polyp as a manifestation of hemorrhage (Lin et al. 2005).

Arteriovenous and Other Vascular Malformations of the Gallbladder

Arteriovenous malformations of the gallbladder are very unusual alterations characterized with the presence of serpentine around and within the gallbladder wall. Angiographically, dilated and tortuous cystic artery branches, a racemose vascular network, and early filling branches of the cystic vein have been noted (Tajima et al. 1997; Osada et al. 2007). The gallbladder is rarely involved in the setting of Osler-Weber-Rendu disease, with multiple telangiectasias in the gallbladder wall (Baba et al. 1995).

Gallbladder Hemorrhage and Hematoma

Introduction

Gallbladder hematomas can occur under various conditions, including trauma, inflammation, coagulation disorders, vascular accidents, and malignant neoplasms. More commonly, blood accumulates within the gallbladder lumen and produces a hemocholecyst, but various conditions also cause intramural gallbladder bleeding which results in wall thickening, mass effect, and sometimes extensive wall dissection. Gallbladder hemorrhages and hematomas can be divided into several anatomical categories (Table 2).

Hemorrhagic Cholecystitis

Gallbladder hemorrhage is a relatively rare complication of hemorrhagic cholecystitis (Parekh and Corvera 2010) and is sometimes associated with pathological coagulopathy or the administration of anticoagulative therapies (Morris et al. 2008; Chen et al. 2010), uremia (Lai and Tarng 2009), or cytostatic therapy. Hemorrhagic cholecystitis can result in hemobilia (Bazzoni et al. 1993) or in gallbladder rupture with massive intraperitoneal bleeding (Tavernaraki et al. 2011). Hemorrhagic cholecystitis, with its alteration in wall structure and contractility, may simulate gallbladder carcinoma (Gremmels et al. 2004).

Table 2 Categories of gallbladder hemorrhage and hematoma

Hemorrhagic cholecystitis
Intraluminal hematoma (hemocholecyst, hematocele)
Intramural gallbladder hematoma
Hemorrhagic tumors

Intraluminal Hematoma (Hemocholecyst)

Acute or continuous bleeding into the gallbladder lumen causes the formation of a blood clot that may completely fill the lumen (hemocholecyst, gallbladder hematocele, Scharling and Geisinger 1993) and which reveals characteristic sonographic and CT features (Grant and Smirniotopoulos 1983; Kauzlaric and Barmeir 1985). Intraluminal blood masses may be mixed with bile, gallstones, mucus, exudate, and tissue debris. Intraluminal blood escapes through the cystic duct and hence causes hemobilia in more distal parts of the biliary tract. In severe and rapidly progressing hemorrhage, gallbladder rupture may result. Important causes of hemocholecyst mainly comprise blunt trauma with gallbladder contusion (Sandblom 1948; Saad et al. 1979; Fröschle et al. 1990; McNabney et al. 1990; Erb et al. 1994), gallbladder malignancy (Faure et al. 1969; Uchiyama et al. 1998; John et al. 1999; Heise et al. 2000; Kubota et al. 2000), coagulation disorders (e.g., hemophilia; Shimura et al. 2000), complications of anticoagulant therapy (Brawner et al. 1966; Mikou et al. 2004; Zangrandi et al. 2009), chemotherapy, radiofrequency ablation therapy of malignant liver tumors (Yamamoto et al. 2003; Shin et al. 2011), benign tumors and polyps (Cappell et al. 1993), hemorrhagic cholecystitis (Ku et al. 2004), ruptured artery and venous aneurysms and pseudoaneurysms (Barzilai and

Kleckner 1956; Hakami et al. 1976; Miura et al. 1998), and venous hemorrhage in portal hypertension (Krustev et al. 2002). In the setting of portal hypertension, gallbladder varices may develop, followed by variceal hemorrhage (Chu et al. 2002; Kevans et al. 2009). Intraluminal gallbladder hematoma was also induced by percutaneous liver biopsy (Kwon et al. 2002). Hemocholecyst can present as a tumorous mass and may mimic a gallbladder neoplasm (Jung et al. 2011).

Intramural Hematoma

Intramural hematoma of the gallbladder is less common than hemocholecyst (Tesler and Cantor 1957; Pilling 1979). Hematoma confined to the wall results in a mass that exerts pressure. The hematoma may remain confined to the wall or may rupture into the gallbladder lumen or through the serosal covering into the peritoneal cavity. Hematoma of the gallbladder wall may be associated with infiltrating hematoma of the hepatic pedicle (Dao et al. 1989). Intramural hematoma as a "pushing" or infiltrating mass can mimic a gallbladder neoplasm on sonographic, CT, or MR images (Tan et al. 2005; Jung et al. 2011).

Hemorrhagic Tumors

Malignancies of the gallbladder can give rise to hemorrhage, both hemocholecyst and mural hematomas at the site of the tumor, whereby the tumors themselves may be hemorrhagic (Petrin 1966; Faure et al. 1969; Piotrowski et al. 1975; Calmat et al. 1979; Fourdan et al. 1994; Osawa et al. 1996; Jones et al. 1997). Metastases to the gallbladder also cause hemorrhage and hemobilia, e.g., metastases of renal cell carcinoma (Fullarton and Burgoyne 1991) or of hepatocellular carcinoma (Chang et al. 1998). In addition to malignant tumors, also benign gallbladder neoplasms can give rise to tumor hemorrhage (Cho et al. 2001).

Pathology

Macroscopy

In acute hemorrhagic cholecystitis, the gallbladder wall is thickened, with edema and bleeding in the extramuscular tissue. The mucosa has lost its fine texture and appears as a dark red to blackish surface with overlying blood coagula and exudate on ulcerated parts. On cut sections, the wall has lost its layers and is visualized as a dark red and often friable tissue. Hemocholecyst is macroscopically characterized by liquid or coagulated blood filling the gallbladder lumen. In recently developing cases, the blood is easily removable from the mucosa, while with time the coagulated blood may adhere to the mucosal surface. In formalin-fixed specimen, the blood forms a dark and hard mass that usually falls off when cutting through the organ. Intramural hematomas, which are either an isolated phenomenon or are combined with hemocholecyst, appear as blood masses of variable size that dissect the gallbladder wall and may bulge into the lumen, mimicking a hemorrhagic tumor.

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