Overview of Diseases of the Gallbladder

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Introduction

The gallbladder (GB) is a small size, pear-shape, simple structure organ which temporarily stores bile. The GB lies on the inferior surface of the right lobe of the liver and has distinct anatomic zones (fundus, body/infundibulum, neck, and cystic duct). Histologically, the GB has four layers: mucosa, consisting of columnar epithelium and lamina propria; a thin layer of smooth muscle; a perimuscular layer of connective tissue; and a serosal layer [1]. The gallbladder, despite its simple structure and function, is a complex organ [2].

Diseases of the GB are relatively common, with the most common pathology, cholelithiasis, affecting 10–15% of the adult population, while the worldwide occurrence of gallbladder cancer is less than 2/100,000 individuals with a great geographic variation [3].

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Currently, imaging studies such as ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS) can detect lesions in the lumen and the wall of GB. The contractile function of GB can be measured by cholecystokinin-cholescintigraphy (CCK-CS).

Almost all the patients come to the hospital with the symptoms (acute RUQ pain or recurrent RUQ vague discomfort to pain) or for evaluation of abnormal image findings (gallstone, polyp, wall thickening, and tumor) of the gallbladder.

RUQ Pain Suggesting Acute Cholecystitis

Differential Diagnosis

The differential diagnosis for RUQ pain suggesting acute cholecystitis should include diseases which simulate cholecystitis: gastrointestinal tract (perforated or penetrating ulcer and acute appendicitis), pancreas (acute pancreatitis and pseudocyst), kidney (acute pyelonephritis and renal colic), lung (pleurisy, right basilar pneumonia, empyema, and pleurodynia), heart (myocardial infarction and pericarditis), and pre-eruptive herpes zoster [4].

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Patients with acute cholecystitis may have a history of biliary colic attacks or remains asymptomatic until the presenting episode [5].

Plain abdominal radiographs can reveal radiopaque gallstones in about 10% of cases of acute cholecystitis and gas within the gallbladder wall in emphysematous cholecystitis [5] Initial imaging modality considered for acute cholecystitis is ultrasonography. CT or MR imaging may be required for evaluating complications of acute cholecystitis and to exclude other pathologies that can present with right upper quadrant pain [6] (see chapter 'Imaging Diagnosis of Diseases of the Gallbladder: US, CT and MRI'). Biliary scintigraphy (hepato-iminodiacetic acid [HIDA] scan) is the gold standard when the diagnosis remains uncertain after ultrasonography [5].

Laboratory examinations of acute cholecystitis are CBC, liver function tests, amylase, and CRP (see chapter 'Laboratory Examinations of Diseases of the Gallbladder'). TG18/TG13 severity grading for acute cholecystitis is a useful indicator from the prognostic perspective [7].

Acute Calculous Cholecystitis

Acute cholecystitis is most often caused by gallstones. Gallstones are present in about 10–15% of adults, and more than 80% of them are asymptomatic. Acute cholecystitis develops in 1–3% of patients with symptomatic gallstones [3, 5, 8, 9].

As an initial examination, transabdominal ultrasonography can detect gallstones with distended GB, edematous GB wall, and pericholecystic fluid, and Murphy's sign can be elicited during the examination [5]. In addition, abnormal findings of the bile duct (dilatation and stone) and the pancreas (enlargement, peripancreatic fluid collection, and intrapancreatic parenchymal necrosis) can be detected.

If a stone in the common bile duct is highly suspected by liver function tests, MRCP may be helpful. When a CBD stone is found, preoperative ERCP with EST or intraoperative bile duct exploration can remove the stone.

About 20% of patients with acute cholecystitis need emergency surgery. Patients with acute cholecystitis who undergo early laparoscopic cholecystectomy (before symptoms have lasted for 72–96 hours) have lower complication rates, lower conversion rates, and shorter hospital stays than those undergoing interval surgery, which is performed 6–12 weeks after the acute episode to allow the inflammatory process to resolve [5].

Percutaneous cholecystostomy is a minimally invasive procedure that can benefit patients with high risk from surgery (see chapter 'Percutaneous Transhepatic Gallbladder Drainage (PTGBD)'). Endoscopic transpapillary and transmural gallbladder drainage are helpful in patients who are not good candidates for percutaneous therapy or surgery [5, 10] (see chapter 'Endoscopic Drainage of the Gallbladder').

Acute Acalculous Cholecystitis

Acute acalculous cholecystitis accounts for 5–14% of cholecystitis. Acalculous cholecystitis tends to occur in critically ill patients and results may be life-threatening. Risk factors include severe trauma or burns, major surgery (such as cardiopulmonary bypass), long term fasting, total parental nutrition, sepsis, diabetes mellitus, atherosclerotic disease, systemic vasculitis, acute renal failure, and AIDS [5, 11, 12].

The diagnosis of acute acalculous cholecystitis may be ambiguous in critically ill patients as Murphy's sign is difficult to elicit and many imaging findings are either insensitive or nonspecific [12].

Management involves percutaneous cholecystostomy, surgical cholecystectomy, or endoscopically placed metal stent through the gastrointestinal tract into the gallbladder [10, 12] (see chapter 'Acalculous Cholecystitis: Diagnosis and Treatment').

Unexplanied Recurrent RUQ Vague Discomfort or/and Pain

Differential Diagnosis

Diagnostic tests for differential diagnosis of a patient with recurrent unexplained RUQ vague discomfort or/and pain should focus on excluding more common diseases including malignancy, GB microlithiasis or sludge, GERD, peptic ulcer disease, functional dyspepsia, chronic pancreatitis, and musculoskeletal syndrome [13, 14].

Although initial ultrasound examination may show no abnormal findings, repeat examination may be of use for the evaluation of biliary colic. In a patient with suspected microlithiasis, EUS may be more valuable than ultrasonography (see chapter 'EUS of Diseases of the Gallbladder'). EGD is also essential to exclude common causes within GI tracts. Abdominal CT and MRI should be reserved for patients with persistent symptoms.

Gallbladder Dyskinesia

Gallbladder dyskinesia is a motility disorder characterized by biliary pain without structural and mechanical cause for the pain. Recently, diagnostic criteria for gallbladder dyskinesia was defined in Rome IV criteria [13, 14].

Although the etiology of GB dyskinesia is not known, there are several hypotheses. GB dyskinesia is a diagnosis of exclusion in patients with typical biliary pain. To exclude structural abnormality and malignancy of the biliary duct and pancreas, various laboratory tests including bile examination and imaging studies with EUS can be done. Cholecystokinin-cholescintigraphy (CCK-CS) is an important diagnostic tool for gallbladder ejection fraction (GBEF). A decreased GBEF (<40) is considered an objective measure of gallbladder disorder [13] (see chapter 'Dyskinesia of the Gallbladder').

Gallstone

Differential Diagnosis

Ultrasonography can detect almost all gallstones accurately except for microlithiasis. The lesions for differential diagnosis of gallstone include cholesterol polyp and small sludge ball. These lesions can be differentiated with EUS or other imaging studies such as CT or MRI.

Management

Gallstones are classified into cholesterol stones and pigment stones based on composition. Black pigment stones can be caused by chronic hemolysis; brown pigment stones typically develop in obstructed and infected bile ducts [15].

Risk factors for gallstones include female sex, age, pregnancy, physical inactivity, obesity, and overnutrition. Metabolic syndrome increases the risk of developing gallstones and forms the basis for primary prevention with lifestyle modifications [15]. There are studies about genetic background as a risk factor of gallstone (see chapter 'Pathogenesis and Treatment of Gallbladder Stones').

The therapeutic option for gallstone disease is based on a few crucial steps, i.e., presence/absence of typical symptoms such as colicky pain, presence of complications, and gallbladder function, as well as composition and size of gallstones [16].

Common bile duct (CBD) stones are found in 5–10% of patients undergoing cholecystectomy for symptomatic cholelithiasis [17–19]. Currently, cholecystectomy after removal of stone in the CBD with EST is the usual method for patients with stones in both GB and CBD. However, prophylactic cholecystectomy in patients with GB stones after CBD stones removal by EST remains controversial (see chapter 'Prophylactic Cholecystectomy in Patients with Concomitant Gallstones After Removal of CBD Stones by ERCP').

Gallbladder Polyp

Differential Diagnosis

The prevalence of gallbladder polyps varies from 0.3 to 12% in healthy adults who undergo abdominal ultrasonography. GB polyps are classified into two groups: neoplastic (adenoma and adenocarcinoma) and nonneoplastic (cholesterol polyps, inflammatory polyps, and adenomyomatosis). However, only 5% of polyps are considered to be true gallbladder polyps, meaning that they are malignant or have malignant potential [20, 21].

Adenomas have malignant potential, and there are reports suggesting adenoma–carcinoma sequence in the GB [21–23].

Transabdominal ultrasonography is the current mainstay for the radiological investigation of gallbladder polyps. In case of uncertainty, additional imaging modalities and EUS may be used for therapeutic decision (see chapters 'Differential Diagnosis by Imaging Between Benign and Malignant Lesion with Imaging' and 'Role of EUS').

Management and Follow-up

Retrospective studies have found the risk of malignancy for polyps rises sharply from 10 mm and upwards, and the general consensus is that patients with polyps of 10 mm or greater should be treated with cholecystectomy [24–26]. Polyps under 10 mm should undergo surveillance unless significant risk factors are present in which cholecystectomy should be offered [24].

A case report showed a malignant transformation of a 5 mm polyp into a 20 mm carcinoma over a period of two years [27]. Babu et al. [25] reviewed 10 studies which looked at the follow-up of gallbladder polyps between six months and seven years, and found that 7.6% of polyps increased in size during the follow-up.

The recommended follow-up for patients with gallbladder polyps depends on the size of the polyps and the presence of risk factors for malignancy (see chapter 'Diagnostic and Therapeutic Algorithm: Polypoid Lesions of the Gallbladder').

GB Wall Thickening

Differential Diagnosis

Diffuse GB wall thickening (>3 mm) can result from a broad spectrum of pathologic conditions, including surgical and nonsurgical diseases: cholecystitis (acute calculous and acalculous, and chronic), liver diseases (hepatitis, cirrhosis, and portal hypertension), extracholecystic inflammation (pancreatitis, colitis, peritonitis, and pyelonephritis), systemic diseases (congestive heart failure, renal failure, sepsis, and hypoalbuminemia), malignancy (primary GB carcinoma and lymphoma), adenomyomatosis, pseudothickening (contracted state), and atypical infection (tuberculosis and Dengue hemorrhagic fever) [28, 29].

Focal wall thickening of the GB can be seen in polyps (adenomas and cholesterol polyp), malignancy (primary GB carcinoma and metastases), focal adenomyomatosis, and focal xanthogranulomatous cholecystitis [28, 30].

Distinguishing early-stage cancer from benign wall thickening of GB is important. The contour of lesion, patterns of wall thickness, intramural cystic space, and patterns of GB wall enhancement are used as differential points [31, 32] (see chapter 'Diagnostic Strategies for Early Diagnosis').

Ultrasonography may be the initial imaging modality for GB wall thickening, but further evaluation with contrast-enhanced CT and/or MRI may be needed when the findings are equivocal. EUS can better define the characteristics of GB wall thickening. There are many reports on differentiating benign and malignant wall thickening using MRI (conventional and/or diffusion-weighted imaging), contrast-enhanced US, real-time GB elastography, multi-detector CT (MDCT), nuclear medicine and contrast-enhanced harmonic EUS (CEUS) [28,

33, 34] (see chapters 'Differential Diagnosis by Imaging Between Benign and Malignant Lesion with Imaging' and 'Role of EUS').

Management

Diffuse GB wall thickening can result from a broad spectrum of systemic pathological condition, and sometimes a short-term follow-up examination with ultrasonography, and inquiring the list of broad etiologies for difficult cases may prove to be helpful.

Corwin et al. [30] analyzed retrospectively 116 patients with incidental focal fundal GB wall thickening on contrast-enhanced CT, and found four cases (3.4%; 95% CI, 0.9–8.6%) of malignancy which showed characteristic findings of GB wall (hyperenhancing/heterogeneous enhancement in three cases and full thickness homogeneous enhancement in one case). The mean thickness of the malignant lesion was significantly greater than the benign lesion (15.8 ± 8.1 mm vs. 9.0 ± 3.1 mm, $p < 0.0001$, respectively).

For early detection of carcinoma of the gallbladder, it seemed essential to pay careful attention to mild mucosal changes, as more than 50% of early cancer did not show apparently protruding lesions [35].

The diagnostic and therapeutic algorithm of wall thickening of GB is discussed in chapter 'Imaging Features of Gallbladder Lesions Manifesting Wall Thickening'.

GB Tumor

Differential Diagnosis

GB tumors are rare compared to gallstone disease, and its prevalence varies from 3 to 7% in the general population [36, 37].

GB tumors are classified as malignant and benign tumors. Malignant tumors include epithelial tumors (adenocarcinoma, undifferentiated carcinoma, adenosquamous carcinoma, squamous carcinoma, and neuroendocrine tumor), non-epithelial tumors (lymphomas and sarcomas), and metastatic tumors (melanoma, kidney, and breast). Benign tumors include epithelial tumors (adenoma, adenomyomatosis, papillomatosis, and heterotopic tissue), non-epithelial tumors (leiomyoma, lipoma, and neural tumors), and pseudotumors (cholecystitis, cholesterolosis, and inflammatory polyp) [36] (see chapter 'Pathology: Non-neoplastic and Neoplastic Diseases of the Gallbladder').

The most frequent benign tumors and pseudotumors of the gallbladder are cholestesterol polyp, adenoma, adenomyomatosis, and cholesterolosis [36–38].

Rare mass forming lesions mimicking neoplasm of GB include hematoma and tumefactive sludge [39, 40]. Mass forming lesion of GB can also be seen in patients with malakoplakia and IgG4-related sclerosing cholecystitis [41, 42] (see chapter 'IgG4 Related Cholecystitis').

The cross-sectional imaging patterns of gallbladder carcinoma have been described as a mass replacing the gallbladder in 40–65% of cases, focal or diffuse gallbladder wall thickening in 20–30%, and an intraluminal polypoid mass in 15–25% [43–47].

Ultrasonography, contrast-enhanced CT, and EUS may be valuable in the differential diagnosis of GB tumor. Tumor markers such as CA 19-9 and CEA should be checked. Serum IgG4 is helpful for the diagnosis of mass forming IgG4-related sclerosing cholecystitis. Equivocal mass lesions of the gallbladder can be diagnosed histologically by EUS-FNA or percutaneous needle biopsy (see chapters 'Tissue Acquisition of Diseases of the Gallbladder: Percutaneous Ultrasound-Guided Biopsy' and 'Tissue Acquisition for Diagnosis of the Gallbladder Disease: EUS-Guided Biopsy').

Gallbladder Cancer (GBC)

The worldwide occurrence of gallbladder cancer is less than 2/100,000 individuals, but this has been recorded with extensive variance in

geography, ethnicity, and cultural differences [3, 48, 49] (see chapter 'Epidemiology').

The development of GBC has been linked to various genetic and environmental factors. Many studies concerning the genetic predisposition of GBC have been conducted (see chapter 'Gene Mutations and its Clinical Significance'). Well known GBC risk factors include advanced age, female sex, polyps greater than 1 cm, porcelain GB, anomalous pancreaticobiliary ductal union (APBDU), and gallstone [48–50]. Chronic infection of GB or/and environmental exposure to specific chemicals, heavy metals, and even many dietary factors have also been found to be associated with GBC formation [51, 52] (see chapters 'Gallbladder Lesions in Patients with Pancreaticobiliary Maljunction' and 'Risk Factors').

Preoperative imaging should include CT with MRI. PET may be of use in selected cases of suspected metastatic disease (see chapters 'Staging by Radiological Imaging' and 'Roles of PET/CT in Evaluating Gallbladder and Hepatobiliary Tumors'). Laboratory testing, including CBC, comprehensive metabolic panel including liver function tests, and coagulation factors, are appropriate [53]. Tumor markers currently used are CA 19-9 and CEA. Endoscopic ultrasonography can be useful for assessing depth of invasion and for fine-needle aspiration of the lesion in question [54, 55].

GB cancers identified incidentally on cholecystectomy account for less than 1% of cholecystectomy specimens. Incidentally discovered GB cancers after cholecystectomy have improved survival, because they are often diagnosed at an earlier stage. For incidental GBC after laparoscopic cholecystectomy, observation is recommended for pT1a and for pT1b or greater, more extensive resection is necessary [53, 56–58] (see chapter 'Incidental Gallbladder Carcinoma').

Patients with T2 or greater disease seem to benefit most from adjuvant therapy following definite resection [53, 59–61] (see chapter 'Recent Advances of Surgical Treatment for Gallbladder Carcinoma').

In order to improve survival in patients with locally advanced T3/T4 tumors and lymph node involvement, adjuvant chemotherapy and chemoradiotherapy following surgical resection are recommended [62, 63]. While neoadjuvant chemotherapy may increase resectability and survival, there are concerns regarding a delay in the surgical resection and disease progression. The results of neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACRT) in patients with GBC were reviewed recently [64] (see chapters 'Neoadjuvant and Adjuvant Chemotherapy' and 'Role of Radiation Therapy').

If jaundice is present, gallbladder drainage can be done via endoscopic (transpapillary or transmural), or percutaneous routes. Chemotherapy, radiation, or both may improve survival and palliation of symptoms. Patients who recur early should be managed similar to those with initial metastatic disease [53, 59, 65–67] (see chapter 'Patterns of Recurrence and its Effective Treatment').

Conclusion

Currently, we can diagnose most of the patients with diseases of the gallbladder using various imaging modalities (abdominal ultrasonography, CT, and MRI) and endoscopic ultrasonography. Patients are treated by laparoscopic cholecystectomy, percutaneous cholecystostomy or endoscopic drainage of gallbladder depending on the physical status without difficulties. However, the prognosis of gallbladder cancer is dismal due to delayed diagnosis and absence of adequate personalized target therapy. In the chapters of this book, up-to-date information on all aspects of diseases of the gallbladder will be described.

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