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SPECIAL FEATURE: REVIEW ARTICLE

Utility of contrast-enhanced ultrasonography for the pancreaticobiliary region

Usefulness of contrast-enhanced ultrasonography for biliary tract disease

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Abstract
Conventional ultrasonography (US) for biliary tract disease shows high time and spatial resolution. In addition, it is simple and minimally invasive, and is selected as a first-choice examination procedure for biliary tract disease. Currently, contrast-enhanced US (CEUS), which facilitates the more accurate assessment of lesion blood flow in comparison with color and power Doppler US, is performed using a second-generation ultrasonic contrast agent. Such agents are stable and provide a timeline for CEUS diagnosis. Gallbladder lesions are classified into three types: gallbladder biliary lesion (GBL), gallbladder polypoid lesion (GPL), and gallbladder wall thickening (GWT). Bile duct lesions can also be classified into three types: bile duct biliary lesion (BBL), bile duct polypoid lesion (BDPL), and bile duct wall thickening (BDWT). CEUS facilitates the differentiation of GBL/BBL from tumorous lesions based on the presence or absence of blood vessels. In the case of GPL, it is important to identify a vascular stalk attached to the lesion. In the case of GWT, the presence or absence of a non-contrast-enhanced area, the Rokitansky–Aschoff sinus, and continuity of a contrast-enhanced gallbladder wall layer are important for differentiation from gallbladder cancer. In the case of BDWT, it is useful to evaluate the contour of the contrast-enhanced medial layer of the bile duct wall for differentiating IgG4-related sclerosing cholangitis from primary sclerosing cholangitis. CEUS for ampullary carcinoma accurately reflects histopathological findings of the lesion. Evaluating blood flow in the lesion, continuity of the gallbladder wall, and contour of the bile duct wall via CEUS provides useful information for the diagnosis of biliary tract disease.

Keywords US · CEUS · Biliary tract disease · Gallbladder · Bile duct

Introduction

Abdominal ultrasonography (US) is a first-choice imaging procedure for biliary tract disease. With adequate use, it is recognized as a noninvasive examination method. Continuous advances in fundamental imaging, and new techniques such as color/power Doppler or harmonic imaging methods and endoscopic ultrasonography (EUS), have improved its diagnostic utility for biliary tract disease[1, 2]. On the other hand, contrast-enhanced diagnostic imaging involving blood flow assessment is essential for the qualitative diagnosis of abdominal diseases. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) facilitate the assessment of lesion blood flow characteristics, improving the diagnostic utility. Their reproducibility and objectivity are favorable, facilitating the diagnosis of malignant disease progression or visualization of distant metastasis; these procedures are primarily selected to evaluate the stage. However, contrast-enhanced CT and MRI are contraindicated in patients with iodine contrast agent allergy, renal hypofunction, or wearing a cardiac pacemaker. US exhibits its favorable time and spatial resolution, being the most appropriate for examining lesions. For ultrasonic diagnosis, contrast-enhanced ultrasonography (CEUS) with a contrast agent is also performed. It is available for patients with iodine contrast agent allergy, renal hypofunction, or those wearing a cardiac pacemaker [3]. However, in the abdominal

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area, most sessions of CEUS are performed for liver disease examination. To date, many studies have demonstrated the usefulness of this procedure in patients with biliary system disease [4]. US is minimally invasive and is performed for screening. However, use of an ultrasonic contrast agent may make US the ultimate detailed examination. In this article, we reviewed the usefulness of CEUS for biliary tract disease.

Ultrasonography

US of the gallbladder is routinely performed in the supine position. Usually, a convex probe is used at 3 to 4 MHz. The gallbladder is readily influenced by artifacts, such as multiple reflections and side lobes, and the use of a linear probe set at a higher frequency and performing the examination at the examinee's left-side position are useful. A postural change facilitates a definitive diagnosis when the lesion is a gallbladder stone or biliary sludge [5].

Ultrasonic contrast agents

Second-generation ultrasound contrast agents contain microscopic bubbles of gas in an encapsulating shell that are highly reflective compared to background tissue. They are characterized by interacting with intravascular imaging, oscillating in response to low-intensity ultrasound fields, and being destroyed in response to high-intensity ultrasound fields. The movement causes a strong nonlinear phenomenon in the reflected wave, generating harmonics. By suppressing the reflected fundamental wave and extracting only the harmonics on the screen, the signal from the background tissue, which is weakly nonlinear and contains few harmonics, is suppressed, and the backscattered signal mainly from the microbubbles is constructed. These techniques show pure vascularity with excellent spatial resolution. Furthermore, CEUS examinations of longer duration are facilitated by contrast agents with a stable shell. The microbubble diameter is small enough to pass through the pulmonary circulation and reach various organs. Microbubbles are excreted in expired air, and microbubble contrast agents are also applicable for examinees with liver or kidney hypofunction. Even at a small volume, these contrast agents exhibit sufficient effects, and low-dose usage is recommended to prevent artifacts related to an excessive volume and facilitate detailed observation. The recommended dose of Sonazoid®, which is used in Japan, is 0.015 mL/kg [6, 7].

Imaging methods

The tissue harmonic imaging method is primarily adopted [1, 8, 9]. The most popular technique is low mechanical index contrast imaging. The level of the low mechanical index in this technique usually ranges from 0.2 to 0.3. A dual-screen monitor is used. On the tissue harmonic imaging-mode screen, the mechanical index is low; therefore, tissue signals are reduced, and a target lesion may be missed. Therefore, an echo probe is accurately matched to a target lesion on another monitor screen (Figs. 1, 3). Due to differences in blood supply components, two phases (arterial and venous phases) are defined in the liver, which is supplied with blood from the hepatic artery and portal vein. If the arterial phase is accelerated, it may start 10 to 20 s after infusion of the contrast agent, and continue for 30 to 50 s (total: 1 min) [10–16]. Subsequently, the portal phase may start 30 to 50 s after infusion of the contrast agent, and continue for 80–90 s (total: 2 min) [17–22]. Only arteries are responsible for blood supply to the biliary tract, and it is not

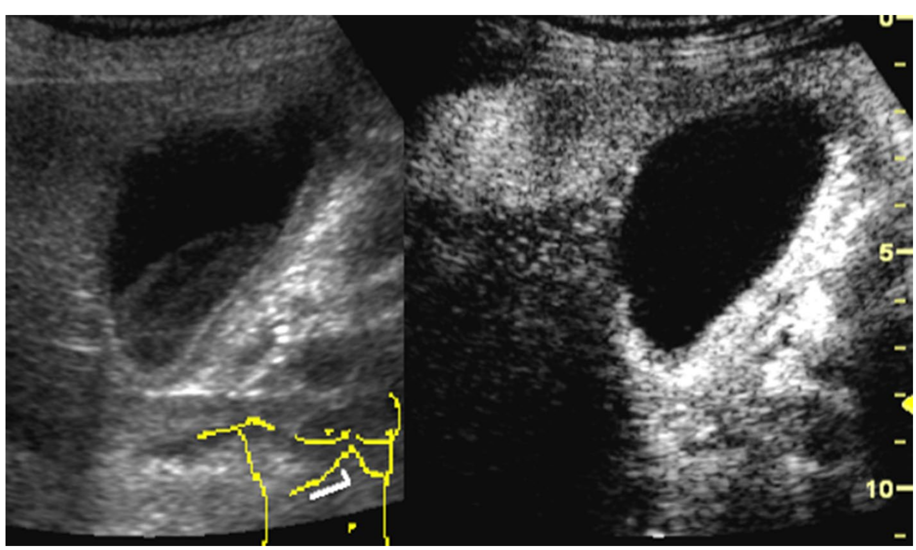

Fig. 1 A sludge ball. The monitor screen (**a**). CEUS showed an avascular gallbladder lesion. There was no abnormality in the gallbladder wall to which the sludge ball had adhered (**b**)

meaningful to distinguish phases based on different blood supply routes. However, previous studies distinguished two phases, i.e., a phase with a contrast-enhancement-related increase in the echo level and a phase with a decrease, with the same timing as for the liver [23–25]. Briefly, the interval until 30 s after infusion of the contrast agent is regarded as the early arterial phase, and that until 30–180 s, as described for the portal phase of the liver, as the late arterial phase. However, this definition may confuse the CEUS diagnosis of gallbladder lesions. The late vascular phase in the liver follows the late arterial phase, and is defined as an interval until vascular microbubble disappearance [14, 15, 20, 26, 27]. Only arteries are responsible for blood supply to the biliary tract, and the duration of contrast effects is short, differing from the liver parenchyma supplied from the portal vein in addition to arteries; therefore, they may be misunderstood as washout, and it is necessary to avoid diagnosing malignant tumors incorrectly. In the liver, phagocytosis of microbubbles by Kupffer cells, which exist in the liver, contributes to the diagnosis of a liver mass, but there is no advantage to examining the biliary tract where Kupffer cells are absent. Only in the case of malignant biliary tract lesions can liver infiltration and metastatic liver tumors be evaluated in the late vascular phase.

Biliary tract disease

Biliary tract lesions are classified into gallbladder biliary lesion (GBL), gallbladder polypoid lesion (GPL), and gallbladder wall thickening (GWT) [28]. GBLs include biliary sludge, gallbladder stone, and parasitosis. GPLs include gallbladder polyps represented by benign cholesterol polyps, gallbladder adenoma, and gallbladder cancer. GWT is represented by adenomyomatosis, acute cholecystitis, chronic cholecystitis, and gallbladder cancer. GWT includes conditions related to systemic diseases, such as IgG4-related disease, and reactive thickening in response to inflammation of adjacent organs, such as acute hepatitis, liver cirrhosis, portal hypertension, and ascites [29]. Bile duct lesions can also be classified similarly. Bile duct biliary lesions (BBLs) include debris of the bile duct, bile duct stone, and parasitosis of the bile duct, as described for gallbladder lesions. Most bile duct polypoid lesions (BDPLs) are evaluated as cholangiocarcinoma. Bile duct wall thickening (BDWT) is associated with cholangiocarcinoma, IgG4-related sclerosing cholangitis (IgG4-SC), and primary sclerosing cholangitis (PSC).

Biliary sludge, gallbladder stone

Saturation and precipitation of biliary lipid, calcium components, and bilirubin in the biliary tract lead to biliary sludge. Its solid crystals are termed biliary tract stone. These calculi show acoustic shadows on standard ultrasonography, and can be readily diagnosed. However, biliary sludge does not show any acoustic shadow, and sometimes comprises a large structure, suggesting a mass. Large biliary sludge is called a "sludge ball". A sludge ball also does not show any acoustic shadow, and it becomes immobile when adhering to the gallbladder wall [30]. Even when there is a postural change, a sludge ball is immobile, making differentiation from biliary tract cancer difficult. For the diagnosis of biliary sludge, it is important to evaluate the presence or absence of blood flow at the lesion site (Fig. 1). In the case of a sludge ball, internal artifacts sometimes make differentiation from blood flow difficult on Doppler US imaging. CEUS is an effective method to evaluate the presence or absence of pure blood flow. Miwa et al. [31] recommended that a high-MI contrast mode should be adopted to eliminate background fundamental imaging for the diagnosis of a sludge ball. Carla et al. [32] reported that evaluation using CEUS was impossible in four patients who had gallbladder stones in the presence of acoustic shadows among 43 patients with gallbladder lesions in whom CEUS was performed before cholecystectomy. In the other 39 patients, it was possible to evaluate the presence or absence of sludge using CEUS. Sixteen patients were regarded as having sludge, and 23 as having no sludge. Both the sensitivity and specificity were 100%. Furthermore, Hui-Ping et al. [33] indicated that the ability to diagnose sludge in 11 of 105 patients with gallbladder lesions in whom CEUS was performed before cholecystectomy was 100% [33]. Sludge diagnosis based on the presence or absence of blood flow is straightforward, but a tumorous lesion may be latent in the sludge-adhered gallbladder wall. In other words, sludge may have adhered due to the non-smooth gallbladder lumen. Even when evaluating blood flow as absent in the prominent part of a lesion on CEUS, it is important to closely examine the lesion-adhered gallbladder wall.

Biliary sludge may induce occlusion of the biliary tract, causing acute cholangitis. On the other hand, malignant disease-related occlusion of the biliary tract may induce biliary sludge. When biliary sludge is present, it is clinically important to search for malignant tumor-related occlusion of the biliary tract.

Adenomyomatosis

Hyperplasia of the Rokitansky–Aschoff sinus (RAS), thickening of the fibromuscular tissue, and mucosal epithelial hyperplasia are involved in the pathogenesis of adenomyomatosis. It is classified into three types based on lesion localization: localized, segmental, and diffuse types. Localized or segmental adenomyomatosis is characterized by localized thickening of the gallbladder wall, and diffuse adenomyomatosis by circumferential thickening. On US, an anechoic area suggestive of hyperplasia of the bile-filled RAS can be recognized in the inner area of the thick gallbladder wall. In the RAS, comet-tail, V-shaped, ring-down, or twinkling artifacts are sometimes produced, which is termed multiple reflection, associated with repeated ultrasonic pulse reflections in the RAS (34). Recognition of these artifacts leads to a definitive diagnosis of adenomyomatosis, and is useful for ruling out gallbladder cancer [35, 36]. On CEUS, the RAS is avascular, and the anechoic area of the RAS is clearly visualized with a contrast-enhancement-related increase in the echo brightness of the gallbladder wall around the RAS [33, 37] (Fig. 2). Matteo et al. [38] reported that the RAS could be recognized in all phases from the start of contrast enhancement by adding contrast agent to US, and that it could be the most accurately evaluated 70–100 s after infusion of the contrast agent. They indicated the usefulness of RAS identification for ruling out gallbladder cancer. However, Yuan et al. [39] investigated 41 patients with histopathological evidence-based adenomyomatosis, and reported that a non-contrast area representing the RAS could be identified using CEUS in only 23 patients (56.1%). On the other hand, Ijin et al. [40] found that a smooth high-echo layer maintained in the gallbladder wall on US was useful for ruling out gallbladder cancer and making a diagnosis of adenomyomatosis even when the RAS was not visualized. Tang et al. [41] retrospectively evaluated 21 patients with localized wall thickening at the fundus of the gallbladder in whom cholecystectomy led to a diagnosis of adenomyomatosis. As a result, an intramural anechoic area corresponding to the RAS could be identified using US in 14 patients (66.7%). A non-contrast area corresponding to the RAS could be identified using CEUS in all 21 patients (100%), suggesting the usefulness of CEUS. In addition, when examining the high-echo layer of the gallbladder wall, the wall was unclear on US in 17 of the 21 patients, but CEUS confirmed a clear high-echo layer in the arterial phase in three patients. The study concluded that CEUS was more useful than US for the following reasons: this procedure improves the degree of RAS visualization, and the absence of abnormalities in the gallbladder wall can be confirmed.

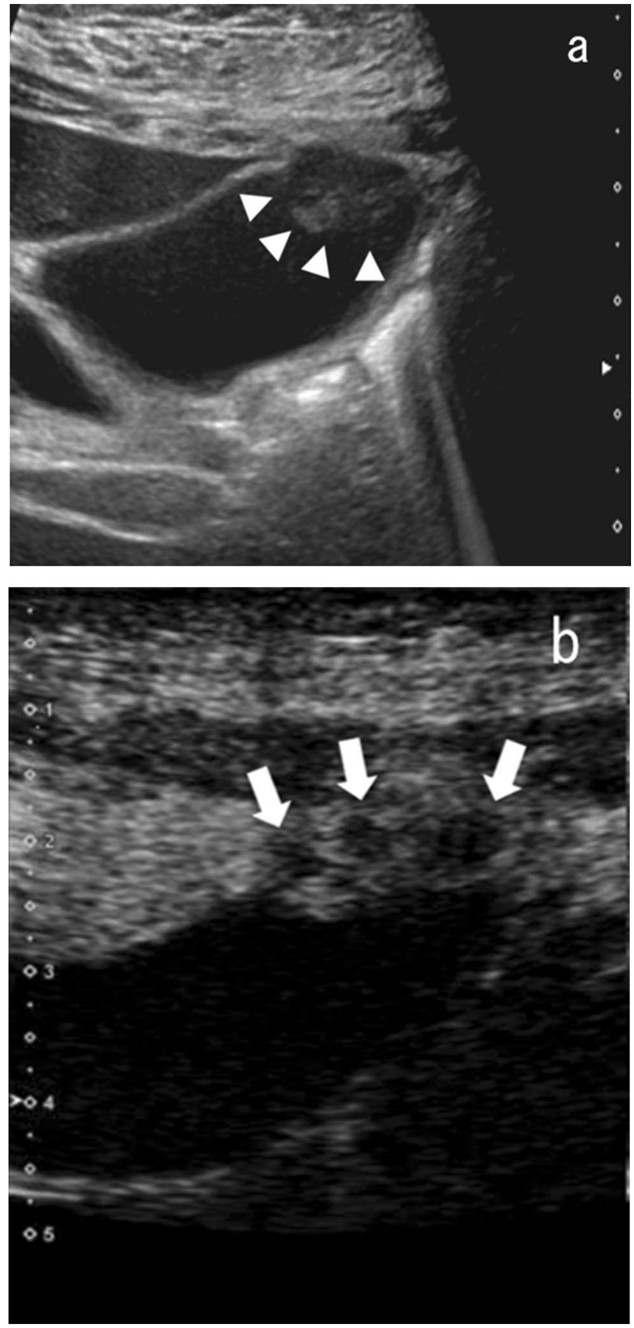

Fig. 2 Adenomyomatosis. Fundamental imaging showed thickening of the gallbladder wall, of which the inner area was heterogeneous, at the fundus of the gallbladder (arrowhead) (**a**). CEUS revealed an avascular lesion suggestive of the presence of RAS in the thickened gallbladder wall (arrow) (**b**)

Acute cholecystitis

This disorder can be diagnosed relatively easily based on US findings and clinical symptoms. US findings, such as gallbladder swelling and thickening of the gallbladder wall, in addition to right hypochondriac pain or fever, lead to a definitive diagnosis. Furthermore, it is diagnostically helpful to confirm pressure pain while recognizing the gallbladder during US. As a merit of CEUS, it may reinforce the diagnosis of complications, such as perforation of the gallbladder. The disappearance of strongly contrast-enhanced gallbladder wall continuity corresponds to the site of perforation [42].

Chronic cholecystitis

Most patients with chronic cholecystitis have gallbladder stones or biliary sludge. Pathologically, this disorder refers to mild chronic gallbladder inflammation with fiber components, subserous inflammatory cell infiltration, and thickening of the proper muscular layer. US findings include uniform thickening of the gallbladder wall, with its structure being maintained. Adamietz et al. [43] performed CEUS in eight patients with chronic cholecystitis and 20 with acute cholecystitis, and reported that the gallbladder wall showed non-contrast, iso-contrast, and strong contrast areas in two, six, and none of the patients with chronic cholecystitis and in none, four, and 16 of the patients with acute cholecystitis, respectively. They concluded that CEUS facilitated differentiation between acute and chronic cholecystitis, although both types of cholecystitis were characterized by thickening of the gallbladder wall on US (Fig. 3).

Porcelain gallbladder

This refers to chronic cholecystitis with calcification of the gallbladder wall. As an extensive, strong acoustic shadow occurs, it is difficult to evaluate the lumen of the gallbladder. Ultrasound does not reach the lesion site, and visualization via US is impossible.

Xanthogranulomatous cholecystitis (XGC)

This is a subtype of chronic cholecystitis characterized by granulomatous wall thickening consisting of form cells, which are pathologically histiocytes. On imaging, marked thickening of the gallbladder wall and marked peripheral inflammation are observed; therefore, it is difficult to differentiate XGC from gallbladder cancer with liver infiltration. Yuan et al. [44] performed CEUS in 43 patients with XGC in whom surgical treatment led to a definitive diagnosis and 17 patients with gallbladder cancer, and compared the results. The hypoenhancement time (washout time of contrast agent) of XGC was 78.9 s, and that of gallbladder cancer was 56.0 s ($p=0.002$). Diffuse thickening was noted in 70.6% of the patients with XGC and in 23.3% of those with gallbladder cancer ($p=0.001$). A continuous inner wall was observed in 70.6% and 9.3%, respectively ($p=0.000$). Hypoechoic nodules were present in 58.8% and 25.6%, respectively ($p=0.015$). Based on these findings, they concluded that CEUS findings of XGC to rule out gallbladder cancer included delayed washout, diffuse thickening, a sustained inner wall, and the presence of a hypoechoic nodule. XGC induces marked inflammation outside the gallbladder wall, making differentiation from peripheral infiltration of gallbladder cancer difficult. In this case, there is a contrast to the liver parenchyma where contrast effects are enhanced in the late vascular phase; therefore, the contour of inflammation becomes clear, and this disorder can be differentiated from infiltration of gallbladder cancer (Fig. 4).

Gallbladder polyp

GBLs include gallbladder polyps, gallbladder adenoma, and gallbladder cancer. Most benign gallbladder polyps are cholesterol polyps, and it is always necessary to differentiate benign from malignant lesions. Many researchers have reported the size, number, growth rate, shape, surface contour, internal echotexture, and internal structure of gallbladder polyps on fundamental imaging [45]. Although there are exceptions, respectively, a consensus on the characteristics of benign polyps has been reached: size, ≤ 10 mm; number of lesions, several; no increase in the size; pedunculated polyp; granule component with relatively deep notches on

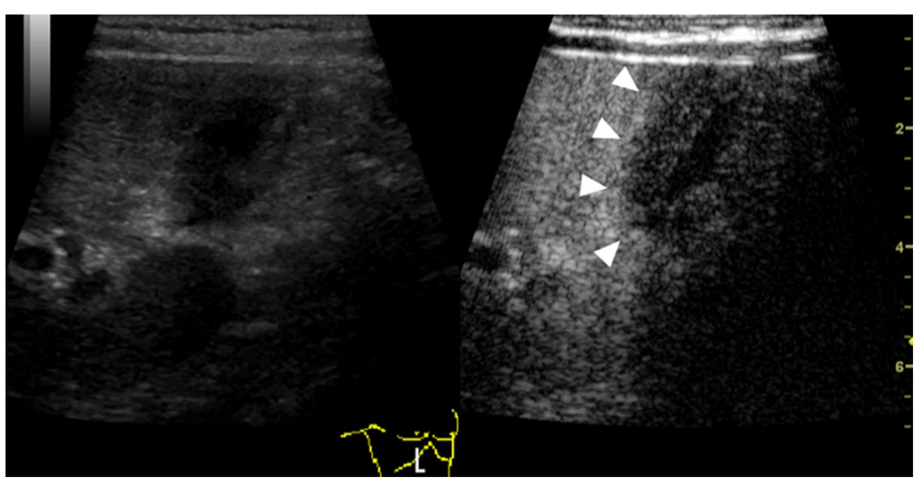

Fig. 3 Chronic cholecystitis. The monitor screen (**a**). On CEUS, the distribution of the thickened gallbladder wall contrasts was uniform, and the contrast effect was weak (arrowhead) (**b**)

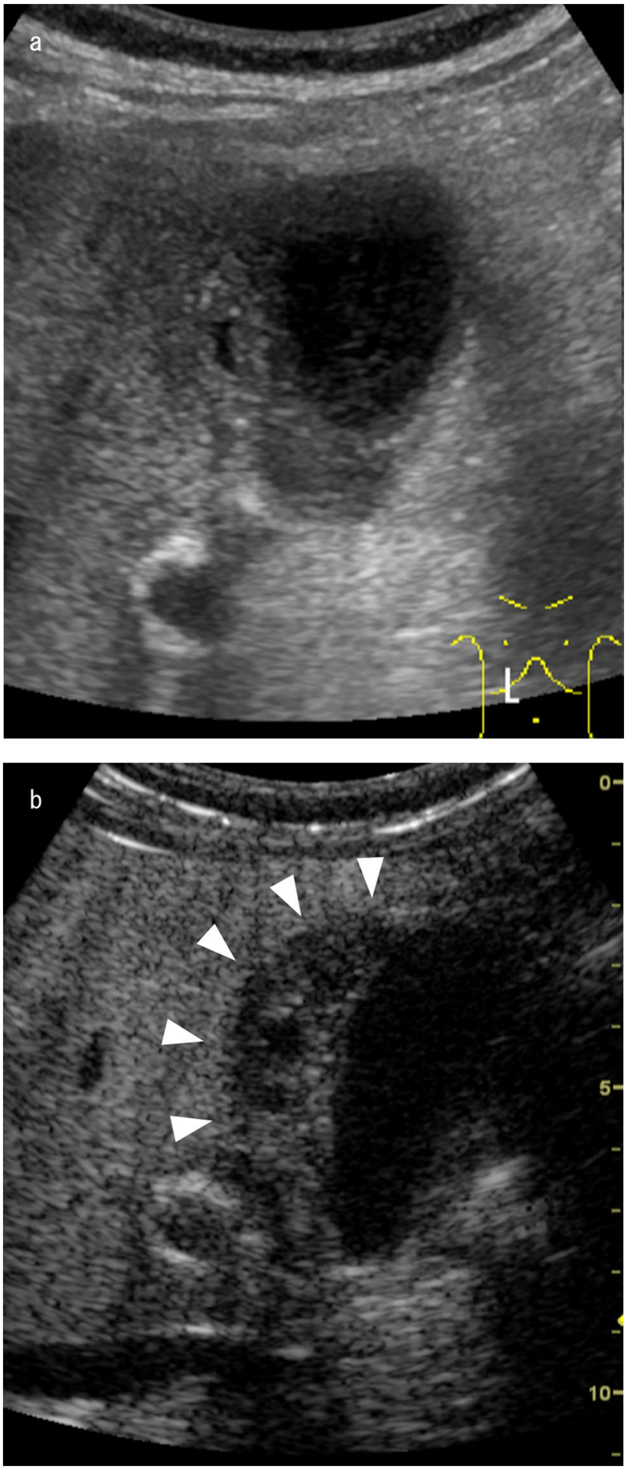

Fig. 4 Xanthogranulomatous cholecystitis (XGC). Fundamental imaging showed a hypoechoic lesion, with an unclear contour, involving the gallbladder wall to liver (**a**). On CEUS, the contour of the gallbladder wall adjacent to the liver was clear. The contour was regular, and the possibility of a malignant lesion was ruled out (**b**)

the polyp surface; relatively hyperechoic texture; and the presence of a high-echo inner spot. Concerning CEUS, the most important finding of benign polyps, which can be readily evaluated, is proof of presence of a stalk. On fundamental or Doppler imaging, visualization is impossible when the stalk is thin, with blood flow below Doppler sensitivity. In particular, when a large pedunculated polyp lies on the mucosal surface of the gallbladder, it sometimes resembles a sessile shape. A pedunculated polyp can be demonstrated by presenting a vascular stalk using CEUS (Fig. 5). Gallbladder polyp blood vessels have been expressed as dotted, linear, irregular, branching, and tortuous [23, 46–48], and investigators have attempted to differentiate benign polyps from gallbladder cancer. However, when adopting former-generation ultrasonic contrast agents in which microbubbles are destroyed by sound pressure for imaging, the imaging time is short; findings in the early phase of contrast enhancement have been discussed. Second-generation ultrasonic contrast agents, which are currently used, provide a longer time for imaging, and reports on late arterial and late vascular phases have been increasingly published. The number of studies on the pattern classification of vascular shapes in the early arterial phase has decreased because of difficulties in shape definition and observers' subjectivity. Inoue et al. [49] performed CEUS with a former-generation ultrasonic contrast agent in 90 patients, and evaluated intra-lesion blood vessels. Gallbladder cancer was detected in 14 patients, with a size of ≥ 15 mm. Of 25 patients with gallbladder polyps, the polyp size was ≤ 10 mm in 21 and ≥ 15 mm in four. In 12 patients with gallbladder cancer, a type 1 or 2 contrast pattern was observed: type 1, branch-like blood flow; type 2, heterogeneous staining. In 23 patients with gallbladder polyps, the type 3 contrast pattern was noted: homogenously spotted blood flow. Based on these results, they suggested that these contrast patterns characterize gallbladder cancer/polyps as CEUS findings. However, gallbladder cancer measuring 15 mm was classified as type 3, and gallbladder polyps measuring 15 and 20 mm, respectively, as type 1; therefore, they reported that vascular assessment in their study markedly depended on the lesion size. Miwa et al. [7] proposed that the vascular shape of gallbladder polyps should be evaluated using two parameters: thickness (dilated or thin) and shape (regular or irregular) [7].

Gallbladder cancer

Many image comparison studies of gallbladder lesions have been conducted to differentiate each lesion from gallbladder cancer. On fundamental imaging, the morphology of early gallbladder cancer is contrary to that of benign gallbladder polyps, being characterized by a solitary lesion, sessile shape, hypoechoic area, uneven internal echo, and

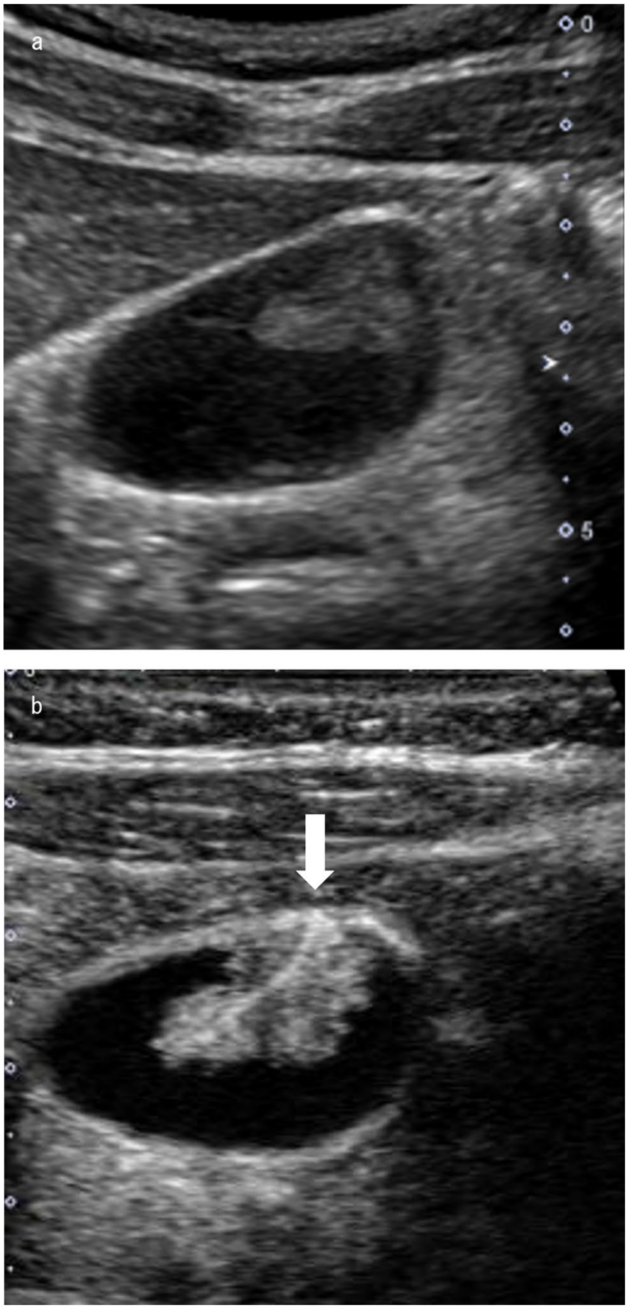

Fig. 5 A cholesterol gallbladder polyp. Fundamental imaging showed a protruding gallbladder lesion (**a**). CEUS revealed a feeding blood vessel from the gallbladder wall, suggesting a pedunculated lesion. The feeding blood vessel was linear and regular, and there was no dilation of the vessel. However, the vascular shape was subjectively evaluated (**b**)

gallbladder wall thickening with an irregular contour. A diagnosis is made at various stages: lesions with slight gallbladder wall thickening alone on fundamental imaging to those occupying the lumen of the gallbladder and infiltrating the liver, with liver metastasis or peritoneal dissemination. Carla et al. [32] performed CEUS using a second-generation ultrasonic contrast agent in nine patients with gallbladder cancer and 14 with benign gallbladder lesions. As a result, washout of the contrast agent was noted after 60 s in all nine patients with gallbladder cancer (9/9) and in only two of the 14 patients with benign gallbladder lesions (2/14). The sensitivity and specificity of differential diagnosis between benign and malignant lesions based on washout of contrast agent after 60 s were 100 and 85%, respectively. Kumar et al. [50] also attempted to differentiate benign from malignant gallbladder lesions based on washout of contrast agent. In their study, the washout time was defined as the time of transition of a gallbladder lesion from isoechoic to hypoechoic compared with the adjacent normal liver parenchyma. As a result, the washout time for benign lesions was 78.4 ± 30.9 s, and that for gallbladder cancer was 46.58 ± 8.4 s. Based on this, they reported that the washout time of contrast agent showed the highest area under the curve, with a cutoff value of 53 s, showing high sensitivity and specificity for the diagnosis of cancer. In addition, many investigators reported that the characteristics of gallbladder cancer included a short contrast agent washout time [24, 51–54]. On the other hand, anatomically, the gallbladder does not have any muscularis mucosae; therefore, tumor cells readily infiltrate adjacent organs. On CEUS, the medial and lateral layers of the gallbladder wall become clearer than on fundamental imaging, and it is important to evaluate a lack of continuity of the two layers [53] (Fig. 6).

According to basic research using the pinning method in a resected gallbladder, the inner hypoechoic layer includes the mucosa, muscularis propria, and subserosal fibrous layer, while the outer hyperechoic layer includes the fat layer and serosa [55]. This fact complicates the evaluation of the T factor in gallbladder cancer. There are no useful reports on CEUS in the literature to resolve this discussion, making this an issue for future study.

IgG4-SC and PSC

IgG4-SC is recognized as a bile duct symptom of IgG4-related disease. It is characterized by an increase in the serum IgG4 level, marked fibrosis related to the bile duct infiltration of IgG4-positive plasma cells/lymphocytes, and thickening of the bile duct wall. The extrahepatic bile duct is targeted in many cases. This disorder is complicated by autoimmune pancreatitis in most cases [56]. On the other hand, PSC is characterized by fibrous stenosis of the intrahepatic and extrahepatic bile duct, and the prognosis of PSC patients is poor with the progression of biliary cirrhosis to liver failure or cholangiocarcinoma. PSC is complicated by ulcerative colitis in many cases [57]. US is not regarded as a tool essential for the diagnosis of either disease. A consensus on the following findings has been reached, reflecting that the

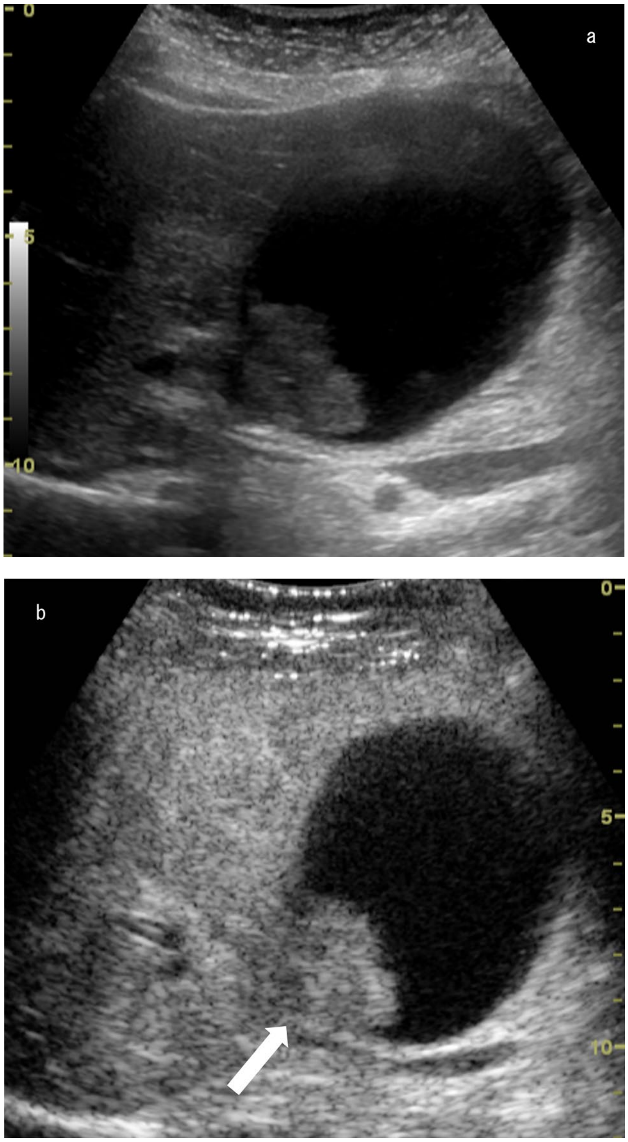

Fig. 6 Gallbladder cancer. Fundamental imaging showed a protruding gallbladder lesion (**a**). CEUS revealed a sessile lesion in the gallbladder. Washout of contrast agent in the gallbladder lesion was observed in the late vascular phase, and the area was hypoechoic in comparison with the liver parenchyma (**b**). At the lesion center, the gallbladder wall was non-continuous, suggesting a malignant lesion with liver infiltration (arrow)

locus of an IgG4-SC lesion is present in the bile duct wall: EUS showed wall thickening, with a smooth intimal surface, involving an extensive area: the lower bile duct to hilar bile duct [56]; and intraductal US revealed circumferential symmetric thickening of the bile duct wall, with smooth medial and lateral layers of the bile duct, and the internal echo of the bile duct was uniform and hypoechoic in many cases [58]. Few studies have shown typical US findings of PSC due to the variety of bile duct findings. However, direct cholangiography findings include band-like stricture, beaded appearance, pruned tree appearance, and diverticulum-like outpouching [56]. To detect these findings, it is necessary to evaluate the contour of the bile duct wall. CEUS, in which the bile duct wall may be clearly recognized by improving the contrast resolution, may be useful (Fig. 7).

Cholangiocarcinoma

CEUS is routinely performed to detect intrahepatic cholangiocarcinoma, which is characterized by intrahepatic mass formation, and perihilar cholangiocarcinoma as liver tumors. However, few researchers have reported CEUS for perihilar cholangiocarcinoma without liver mass formation or distal cholangiocarcinoma. According to Fontán et al. [59], CEUS findings of perihilar cholangiocarcinoma included an infiltrating, enhancing lesion at the biliary confluence with a hypoechoic mass washed out in the late phase of contrast enhancement, whereas those of distal cholangiocarcinoma included hyperenhancement and posterior washout. In their study, CEUS was performed for 59 patients in whom US revealed idiopathic obstructive jaundice, including 22 with cholangiocarcinoma, and 36 of 42 patients with malignant lesions and 15 of 17 patients with benign lesions were correctly identified (sensitivity: 85.7%, specificity: 88.2%). The positive predictive value of CEUS for malignant lesions was 94.7%, and its negative predictive value was 71.4%. They concluded that CEUS for bile duct lesions contributed to differentiation between tumorous lesions and non-contrast-enhanced inert materials (Table 1).

Ampullary neoplasm

Ampullary neoplasms are minute and surrounded by gas. It is difficult to identify them using US unless they are large lesions. Several articles suggested the usefulness of EUS, the spatial resolution of which is more favorable than that of US, facilitating digestive tract gas removal. However, there have been few reports on US. Kiura et al. [60] performed CEUS with a former-generation ultrasonic contrast agent in 12 patients with ampullary carcinoma, and indicated that neither tumors containing a large amount of connective tissue in the inner area nor periductal invasive tumors were contrast enhanced, that the intraluminal papillary-type enhancement shape was round and irregular, and that the presence of a continuous unenhanced area between the tumor and pancreatic parenchyma reflected the absence of tumor infiltration in the pancreas. They reported that CEUS findings of ampullary carcinoma were correlated with histopathological findings.

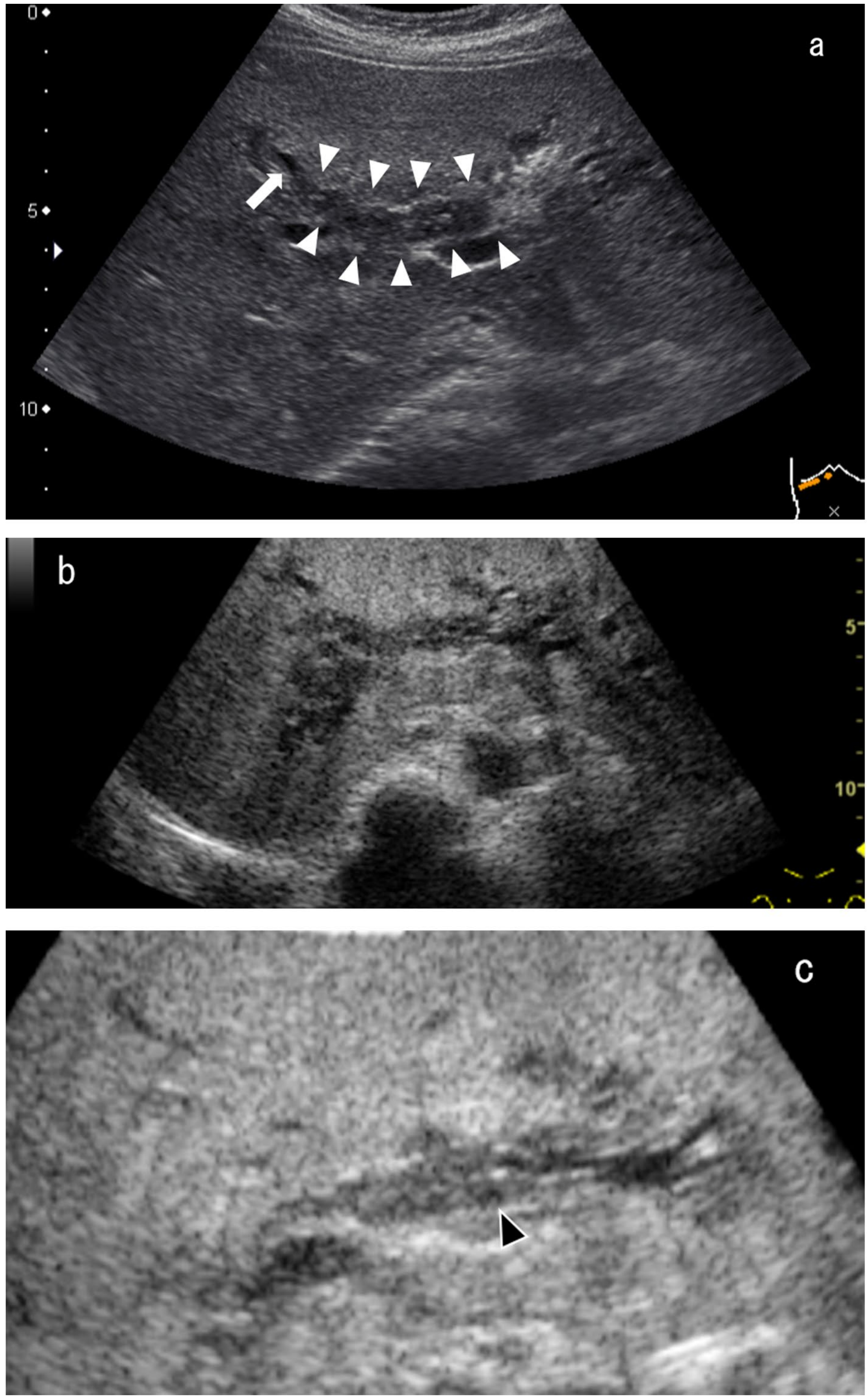

Fig. 7 PSC. Fundamental imaging (**a**) showed diffuse wall thickening of the intrahepatic bile duct (arrowhead). The upstream bile duct was slightly dilated (arrow). On CEUS, hypoechoic wall thickening of the intrahepatic bile duct was clear. The most medial layer of the bile duct wall was hyperechoic, facilitating contour assessment. This layer was non-continuous and punctate, suggesting marked inflammation of the bile duct epithelium, as suggested by direct cholangiography (**b**). Diverticulum-like outpouching could be regarded as a non-vascular area of the bile duct wall (arrow) (**c**)

Table 1 Contrast-enhanced ultrasonography in the diagnosis of biliary tract disease

Classification	Diseases	Benefits of using contrast agent
GBL, BBL	Sludge (debris), stone, and parasitosis	No blood flow
GPL	Cholesterol polyp	Presence of stalk with blood flow
GWT	Adenomyomatosis	Avascular lesion suggestive of the presence of RAS in the thickened gallbladder wall
GWT	Acute cholecystitis	Disappearance of contrast-enhanced gallbladder wall continuity corresponds to the site of perforation Strong enhancement of thickened gallbladder wall
GWT	Chronic cholecystitis	Weak enhancement of thickened gallbladder wall Continuity of the contrasted gallbladder wall is preserved and contours are regular Slow washout of contrast from the gallbladder wall (> 60 s)
BPL, GWT	Gallbladder cancer	Rapid washout of contrast from the gallbladder wall (< 60 s) Disappearance of gallbladder wall continuity and contours are irregular
BDWT	IgG4-related sclerosing cholangitis	Facilitates assessment of the inner layer of the bile duct Reveals the smooth inner surface of the bile duct
BDWT	Primary sclerosing cholangitis	Facilitates assessment of the inner layer of the bile duct Reveals the irregular inner surface of the bile duct
BDPL, BDWT	Cholangiocarcinoma	Hyperenhancement with posterior washout

GBL gallbladder biliary lesion, *BBL* bile duct biliary lesion, *GPL* gallbladder polypoid lesion, *GWT* gallbladder wall thickening, *BDPL* bile duct polypoid lesion, *BDWT* bile duct wall thickening

Conclusion

CEUS is useful for biliary tract lesions. It should be further applied in the future.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

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