Ahead of print

Med Ultrason 2024:0, 1-8 Online first
DOI: 10.11152/mu-4382

How CEUS improves gallbladder pathology evaluation. A comprehensive pictorial and review of the literature

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Abstract

Gallbaldder disorders represent a prevalent pathology encounterd in daily practice, both in emergency and ambulatory settings. Transabdominal ultrasound has a high accuracy for the diagnosis of gallstones and acute cholecystitis. Contrast enhanced ultrasound (CEUS) can depict and characterized the vascular pattern in cases of inflammatory or malignant processes. In an emergency situation such as acute cholecystitis in patients with comorbidities, CEUS can acurate identify a gangrenous cholecystitis; subsequently the medical management can rely on this technique. The differential diagnosis of benign vs malignant pathology, in cases of segmental or diffuse wall thickening, can also benefit from CEUS. In this paper we aimed to discuss and to illustrate the role of CEUS in gallbladder pathology.

Keywords: gallbladder; contrast-enhanced ultrasound; acute cholecystitis; polyps; gallblader carcinoma

Introduction

Gallbladder (GB) pathology is very common, gall stones affecting around 10-15% of Western population, and the accuracy of ultrasound is highly recognized for its diagnosis [1]. If stones are easily depicted and characterized by transabdominal ultrasound in grey scale, several differential diagnoses can be challenging, such as the type of gallbladder polyps (pseudo-polyps, inflammatory, adenomyiomatosis, adenomas and malignant polyps), or a segmental or a diffuse enhanced gallbladder wall thickening in different clinical scenarios, especially in aging patients with comorbidities. Contrast-enhanced ultrasonography (CEUS) enables the detection of a very slow blood flow in vessels measuring as little as 40 microns, being valuable in the characterization of a circulatory bed and in the differentiating inflammatory from malignant circulatory pattern [2]. The main indications of CEUS in gallbladder pathology are to differentiate benign from malignant processes if transabdominal ultrasound depicts sludge, segmental or diffuse wall thickening, or polyps. Other indications might also benefit from CEUS in an emergency such ase wall rupture and haemobilia or if a mass is depicted at the surgical site after a cholecystectomy [3].

The aim of this review is to review the main applications of CEUS in cholecyst pathology and to illustrate these situations with examples from our database.

Ultrasound technique

The ultrasound (US) examination of the gallbladder starts with grey scale, using the convex transducer (frequency 2.25–3.5 MHz for adults, 5 MHz for children). First, an optimal examination window is selected, the whole GB being visualized. The "real-time" examination is multidirectional and assesses the aspect and size of the GB, wall thickness, content, pain at transducer palpation (US Murphy's sign) [4]. Secondly, the selection of the region of interest (ROI) is performed. Thirdly, for CEUS some specific adjustments of the equipment for the "contrast" feature are selected. The image is divided into two fields, focus is placed on the ROI, the mechanical index (MI) is lowered (acoustic power) to an average of 0.10. The examination is continuous and starts when the con-

Received 10.02.2024 Accepted 12.04.2024
Med Ultrason
2024:0 Online first, 1-8
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trast agent (CA) is injected, marked as "0" second on the screen clock. The examination has two phases: an arterial phase (up to 20-30 seconds after CA injection), and the venous one (evidenced after up to 2-3 minutes). In the arterial phase the echogenicity of the GB wall increases. In the venous phase the wall seems to "melt" into the echogenic mass of the liver parenchyma [5]. Subsequently, an extensive examination of the liver is recommended, based on the patient's complaints and the clinical features [4]. A recording in "wmw" format is obtained. The result will be formulated for each time separately (arterial, venous, late for liver parenchyma). Time-intensity curves (TIC) allows a qualitative and quantitative image analysis. Parametric processing of the image is useful for fast blood flow in some diseases.

Normal gallbladder

After CA administration the gallbladder wall enhances uniformly without discontinuity or wall irregularities. The same homogeneous upload of contrast should be seen in adjacent liver parenchyma. The gallbladder lumen may be completely anechoic or may contain low level echoes, but there should not be any enhancement.

Pathology

Acute cholecystitis

Acute cholecystitis is a potentially life-threatening condition; to reduce the rate of complications prompt diagnosis and treatment are essential. Grey scale US is the most widely used method to diagnosis acute cholecystitis. The presence of cholelithiasis combined with a positive US Murphy sign (maximal tenderness with transducer pressure over the gallbladder) is the most specific sonographic findings of AC [6]. Other US signs are distention to hydrops of gallbladder lumen, fluid around gall bladder, gall bladder wall thickening more than 3 mm [7]. Beside diagnosis, the assessment of severity might help the clinical management. Is it gangrenous cholecystitis? Are micro-abscesses or liver abscesses associated? Is gallbladder wall perforation present? All these aspects are relevant for medical and surgical treatment. Ischemia and necrosis of the gallbladder wall due to increased intraluminal pressure characterized the gangrenous cholecystitis. It is depicted in grey scale US by sloughed mucosal membranes, focal wall bulge, ulceration, and disruption. It is associated with increased risk of gallbladder perforation [7]. The presence of air inside the gallbladder in the absence of a previous endoscopic maneuver on bile ducts is a sign of severity.

CEUS consolidates the diagnosis of gallbladder wall inflammation and its severity. The ischemia is depicted as the lack of CA load in the arterial phase at the level of gall balder wall (fig 1). In case of gangrenous cholecystitis, CEUS depicts discontinuous or irregular gallbladder wall enhancement of the CA (fig 2). In grey scale intramural abcesses are hypoechoic or transonic focal images inside an enlarged gallbladder wall; CEUS confirms the the lack of vessels corresponding to the necrosis process, surrounded by an important load of the contrast agent at the level of inflammated wall (fig 3). In some cases of acute severe cholecystitis false images of tumor might be detected; based on pattern of vesels distribution an acurate differential diagnosis might be achieved by CEUS, confirming the inflammatory nature of "pseudotumor" by the lack of vessels (fig 4). Xanthogranulomatous cholecystitis, a rare inflammatory disease of the gallbladder might also be detected as a false tumor mass. The abnormal thickening of the wall and severe proliferative fibrosis with the formation of multiple intramural nodules might be translated into a pseudotumor in imaging studies. CEUS might accurate deliniate the inflammatory bounderies and exclude the malignancy (fig 5).

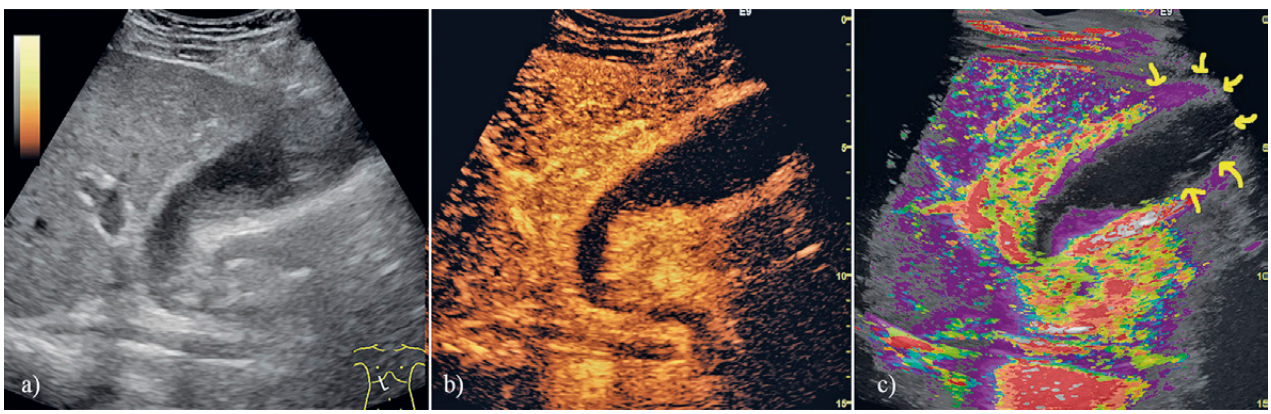

Fig 1. Ischaemic acute cholecystitis. Ultrasonographic exploration in grayscale (a), arterial CEUS (b), and parametric analysis of CEUS exploration (c). Lack of signal in the fundic region (arrows).

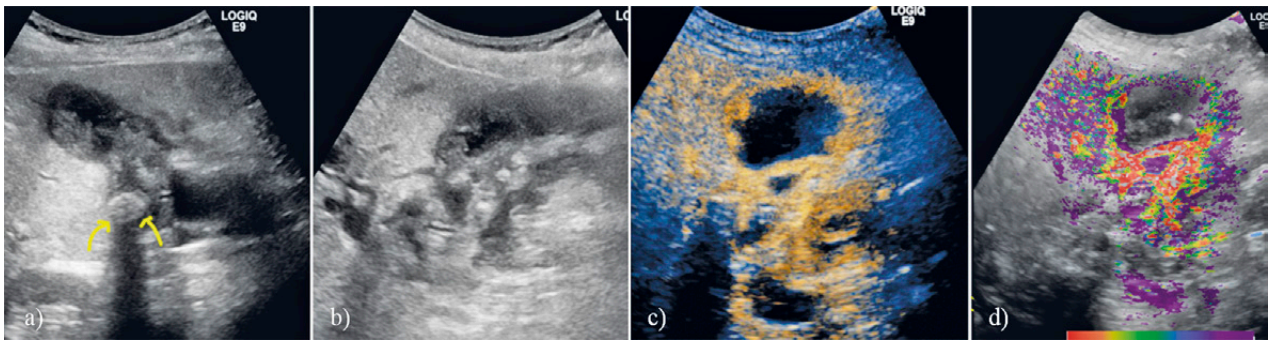

Fig 2. Severe acute cholecystitis (gangrenous cholecystitis). Ultrasonographic exploration in grayscale (a,b) (perpendicular sections; gallbladder lumen filled with cellular debris; in the fundic region – arrow – presence of a stone image); CEUS exploration in arterial phase (c) (uneven and irregular loading of the walls observed). Parametric analysis of angioperfusional behavior in arterial phase (d).

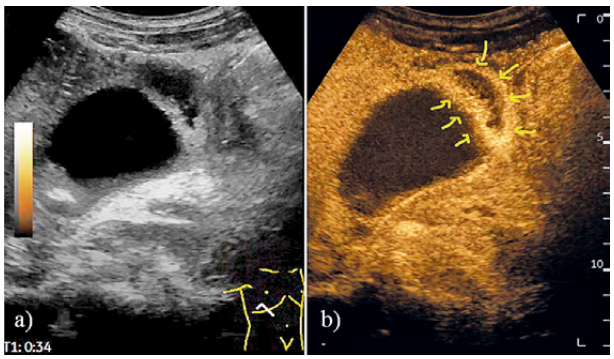

Fig 3. Acute cholecystitis: a) grayscale; b) CEUS exploration in arterial phase (arrows). Fundic intramural abscess.

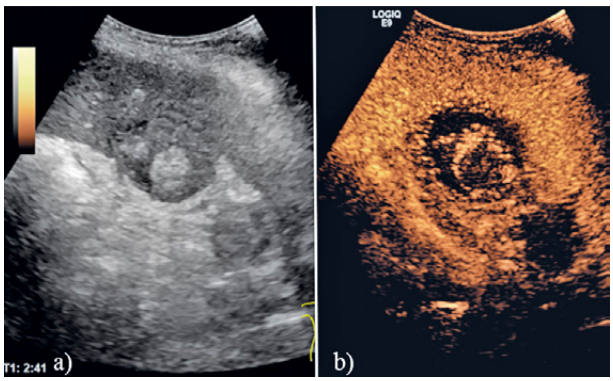

Fig 4. Acute cholecystitis. False tumor. Ultrasonographic exploration in grayscale (a) (mass inside the gallbladder observed around a central stone). CEUS exploration (the mass inside the gallbladder does not capture contrast agent; neoplasia is excluded) (b).

The CEUS liver assessment might reveal associated parenchymal abscesses (fig 6) and signs of severe cholangitis. The portal vein blood flow should also be investigated, as portal vein thrombosis might be associated.

The first study regarding the usefulness of CEUS in acute cholecystitis was published on 2001, by a Japanese team, using Sonazoid [8]. They investigated 27 patients with acute cholecystitis and reported that perfusion defects had a positive predictive value of 100 %, and negative predictive value of 70.6 % in detecting gangrenous cholecystitis.

Ravel et al [9] in a prospective study on 56 patients with acute cholecystitis evaluated the diagnosis accuracy of preoperative CEUS, using SonoVue and corelated its vascular pattern with the histological appearance. Discontinuous or irregular gallbladder wall enhancement

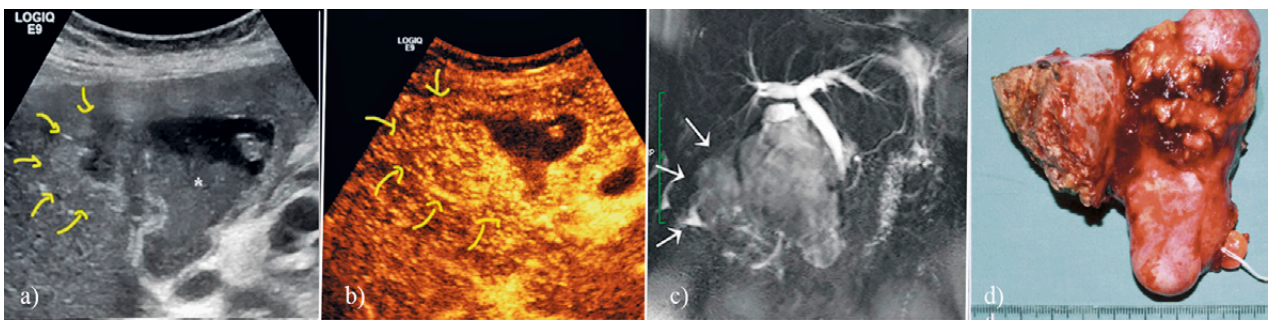

Fig 5. Xanthogranulomatous acute cholecystitis: a) grayscale (gallbladder lumen marked with an asterisk; arrows indicate inflammation demarcation) b). CEUS exploration (arrows show the inflammation boundary); c) MRI exploration (falsely appearing as neoplasia); d) Surgical specimen.

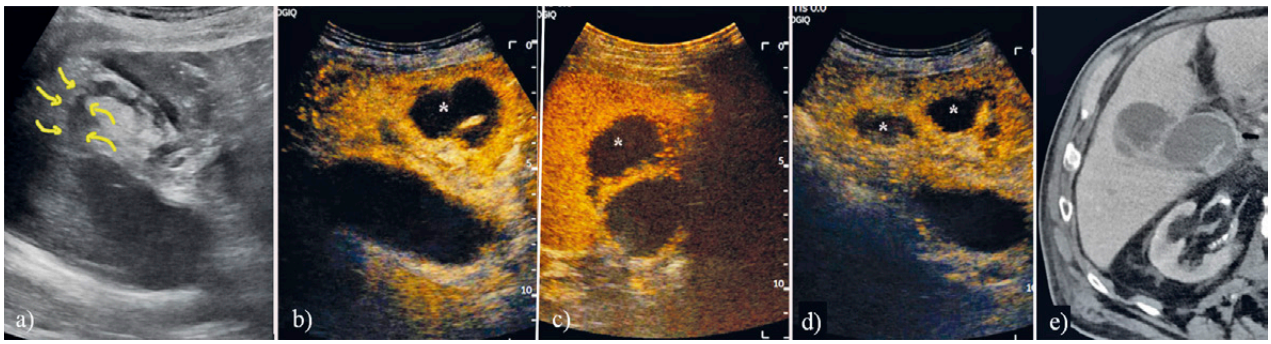

Fig 6. Acute cholecystitis, gallbladder perforation: a) grayscale (arrows indicate perforation); b), c) and d) CEUS exploration (asterisk indicates liver abcesses); e) CT exploration (transversal).

was reported in 83% patients with gangrenous acute cholecystitis and showed an association with the presence of gangrene at pathology (p=0.001). In this study the interobserver agreement for the presence of discontinuous or irregular gallbladder wall enhancement on CEUS images was good. In 2016, similar findings were reported by Ripolles et al [10] on a larger prospective cohort of 150 patients.

In retrospective studies on a small size cohort of patients with complicated acute cholecystitis (gallbladder perforation and/or pericholecystic hepatic abscess) who underwent conventional US and CEUS, the high potential of CEUS to detect perforation and pericholecystic abscesses was highlighted [11,12]. CEUS revealed hyperenhancement of the gallbladder wall during the early arterial phase, and a defect was seen in every patient. The pericholecystic masses showed heterogeneous enhancement with a honeycomb-like appearance during the arterial phase-interpreted abscesses. Young et al [13] reported a case in which the oral administration of CA permitted the detection of a cholecystoduodenal fistula.

Chronic cholecystitis

Irreversible inflammation of the gall bladder wall, often associated with biliary lithiasis might lead to two entities: the porcelain gallbladder (diffuse or localized calcification of the wall) and xantogranulomatous cholecystitis [4]. CEUS will evidence hyper loading at the wall level in the arterial phase, without significant clearance of the CA in the late phase [4,5].

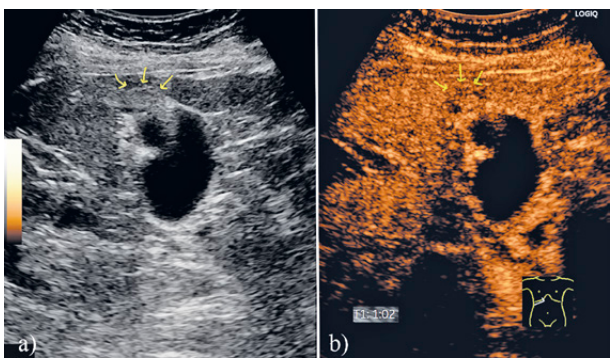

Fig 7. Fundic adenomyomatosis (arrows): a) grayscale; b) CEUS, venous phase. Arrows indicate the region of interest.

Gallbladder cholesterolosis

In gallbladder cholesterolosis there is an infiltration of the lamina propria of gallbladder wall with lipid-loaded macrophages. Two macroscopic forms are known: polypoid and diffuse. Frequently cholesterolosis is associated with gallstones [4]. On CEUS, cholesterolotic polyps are hyper-capturing in the arterial phase in most of the cases, and become hypo- or iso- capturing in the late phase [14,15].

Adenomyomatosis

Adenomyomatosis is characterized by the presence of intramural diverticuli, associated or not with wall thickening. There is also intraluminal accumulation of cholesterol, with possible cholesterol crystals precipitated from the bile trapped inside the intraparietal diverticuli. Even if it is not associated with adenomatous development, it might represent a premalignant condition [4]. Grey scale US may detect echoic foci due to cholesterol deposits, with comet-tail artefacts – a highly specific sign [4]. The gallbladder wall thickening may be diffuse or localized. The administration of a CA leads to an uneven, focal load of the gallbladder wall, without washout in the venous phase [4] (fig 7).

Gallbladder polyps

Lesions that project from the gallbladder wall into the gallbladder interior are called gallbladder polyps. Most of the patients with gallbladder polyps are diagnosed as an incidental finding of a routine abdominal US. Most of the gallbladder polyps are benign. The clinicians should make an etiological differential diagnosis based on ultrasound features. Benign polyps are represented by pseudotumors (cholesterol polyps, inflammatory polyps; cholesterolosis and hyperplasia), epithelial tumors (adenomas) and mesenchymatous tumors (fibroma, lipoma, and hemangioma). Malignant polyps are gallbladder car-

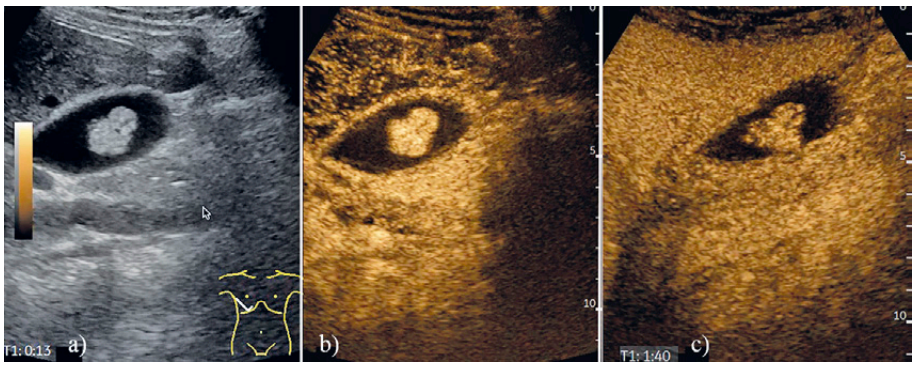

Fig 8. Adenomatous polyp a) grayscale;b) and c) CEUS (lack of contrast discharge indicates the non-neoplastic nature).

cinomas. As gallbladder carcinoma has a poor prognosis it is important to differentiate between benign polyps and malignant or premalignant polyps [14,15]. On ultrasound the polyps are visualized as fixed, hyperechoic lesion protruding into the lumen of the gallbladder, with or without an acoustic shadow.

Benign polyps

The most common feature of benign polyps on CEUS are homogeneous hyperenhancement during arterial phase relative to normal liver parenchyma and isoechoic appearance during portal venous phase (fig 8). The gallbladder wall is intact and adjacent organs are normal. Typical enhancement features of an adenoma are homogeneous enhancement including the adjacent normal gallbladder wall without evidence of invasion of nearby organs. Pulsatile arterial blood flow and linear blood vessels have been described in adenomas [16,17]. CEUS may provide information to distinguish adenoma from a cholesterol polyp. The enhancement intensity, stalk of lesion, and vascularity were described as independent predictors for adenoma in the study of Fei et al [18]. In the study of Yuan et al based on 37 cases of adenoma gall bladder lesions, grey scale features were isoechogenicity and an eccentric enhancement pattern; "fast-in and synchronous-out" contrast enhancement pattern and homogeneous at peak-time enhancement in CEUS [19].

Malignant polyps

As CEUS has high accuracy in depicting small vessel flow and to characterize the vascular pattern it might reveal the neoangiogenic processes [2]. In the study of Miwa et al [19] beside the sessile shape of the polyp, the depiction of dilated vessels or irregular vessels and a heterogeneous enhancement on CEUS were significantly correlated with malignant gallbladder lesions). On CEUS, the diagnostic criterion for malignant polyps was defined as having one or more of the above four features because of the highest accuracy [20]. In the study of Zhuang et al [21], based on a cohort of 88 patients with focal gallbladder lesions confined to the gallbladder wall, the features suggestive for malignancy were an irregular shape, branched intralesional vessels and hypo-enhancement in the late phase. Bae et al [22] investigated the quantitative parameters of CEUS derived from the time intensity curve as potential feature to discriminate of benign versus malignant polypoid lesions. They reported that the rise time, mean transit time, time to peak, and fall time of non-neoplastic GB polyps were significantly shorter than those of neoplastic polyps

Gallbladder carcinoma

Even rare, gallbladder carcinoma has a poor prognosis with a 5-year survival rate of <5%. Gallbladder cancer confined to the mucosa is potentially curable. Gallbladder carcinoma might have variable appearances. As most of the cases are diagnosed in late phases, the most common appearance is that of a mass infiltrating the gallbladder wall and adjacent structures. In early phases, the appearance is that of an intraluminal polypoid or sessile lesion. While destruction of the gallbladder wall has been described as the most reliable differentiator between a carcinoma and a benign tumor, other features including hyperenhancement and rapid washout of CA within 35 seconds has been reported as highly suspicious of malignancy [16] (fig 9). Tortuous tumor vascularity has also been reported as an indicator of carcinoma [23]. In a large cohort study, Zhang et al reported the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CEUS were 94.1%, 95.5%, 80.0%, 98.8% and 95.2%, respectively [24]. CEUS performed with high frequency transducers is helpful to achieve better visualization of gallbladder fundus and make differential diagnosis of gallbladder lesions, as revealed by the study of Dong et al. [25].

Neuroendocrine tumors

Neuroendocrine tumors are rare tumors of the gallbladder. Frequently, there are large tumors that invades the surroundings at diagnosis. Grey scale US depicts the tumor and the invasion in the liver parenchyma [26].

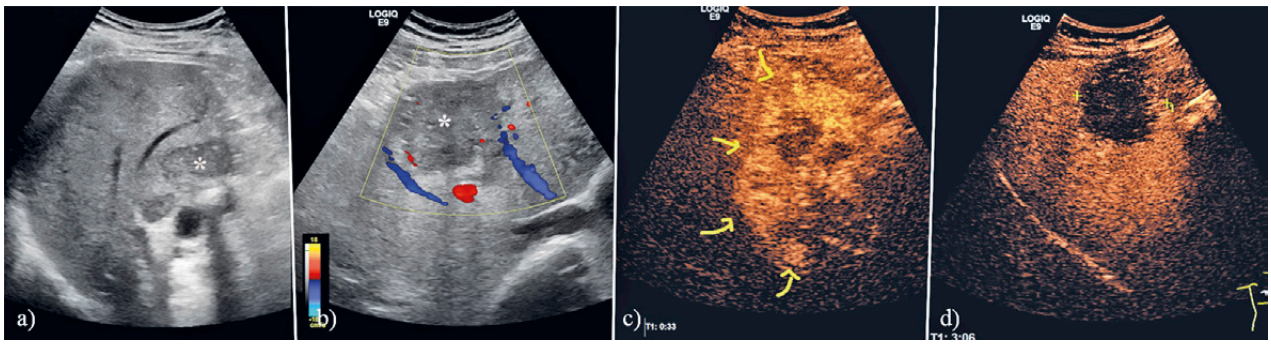

Fig 9. Gallbladder carcinoma: a) grayscale (asterisk); b) colour Doppler (asterisk); c) CEUS, arterial phase (arrows); d) CEUS, venous phase.

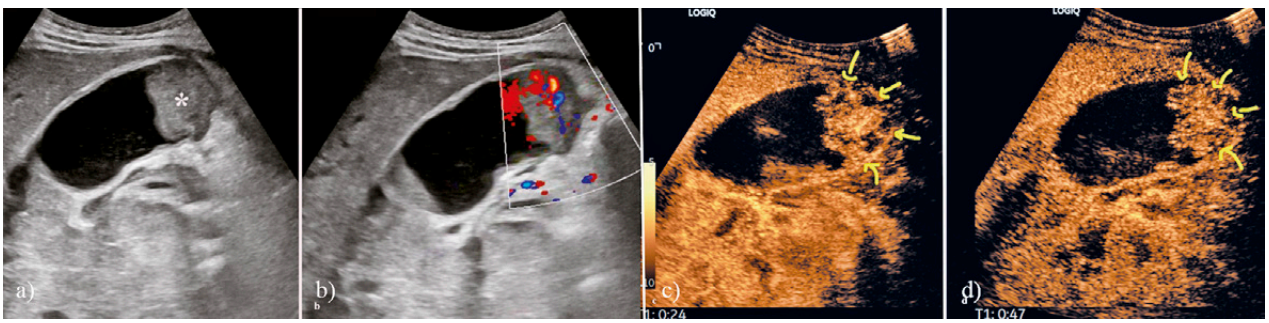

Fig 10. Neuroendocrine gallbladder carcinoma: a) grayscale (asterisk); b) colour Doppler (colour signal observed at the tumor periphery); c) and d) CEUS exploration (arrows).

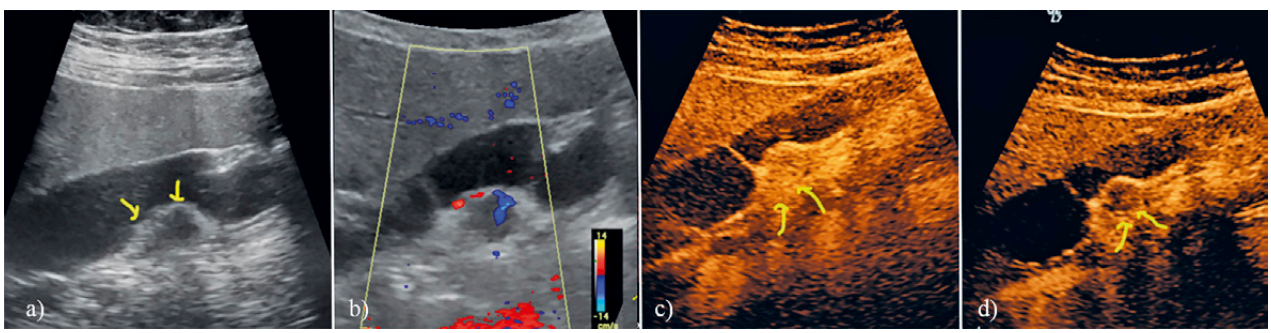

Fig 11. Cholecystic metastasis (ovarian carcinoma): a) grayscale (arrows); b) color Doppler ; c) and d) CEUS exploration, arterial and venous phase (arrows) – highlighting loading and unloading with tumoral significance.

CEUS evidences a quick loading of the CA by the tumor [4,26] ; the grade of differentiation of the neuroendocrine tumor is translated into imaging studins in the rate of CA wash-out in the venous phase. In the well differentiated neuroendocrine tumor the architecture of the neoangiogenic vessels is "preserved" and the wash-out might be delayed (fig 10). In the neuroendocrine carcinoma, the neoangiogenesys is chaotic, with large arterio-venous malformations and the CA wash-out is very quick.

Intracholecystic metastases

The gallbladder metastases (5% of gallbladder malignancies) may have as its origin, the stomach, colon, rectum, liver, uterus, skin (melanoma), ovaries, or appendix [27]. Greyscale US evidences wall thickening and calcifications, parenchymatous masses adhering to the wall and protruding into the lumen and/or infiltrating the liver [4]. CEUS depicts the metastases in the form of gaps situated in the gallbladder lumen or wall, with marked load in the arterial phase and washout in the venous phase [4] (fig 11).

Gallbladder sludge

Sludge regarded as microscopic precipitants from bile has a wide range of appearance on ultrasound from echogenic matter to tumor like appearance. No enhancement is observed at any time during CEUS, as microbubble CA remain entirely intravascular. CEUS provides an advantage over greyscale US by utilizing the presence or absence of vascularity [17] (fig 12, fig 13).

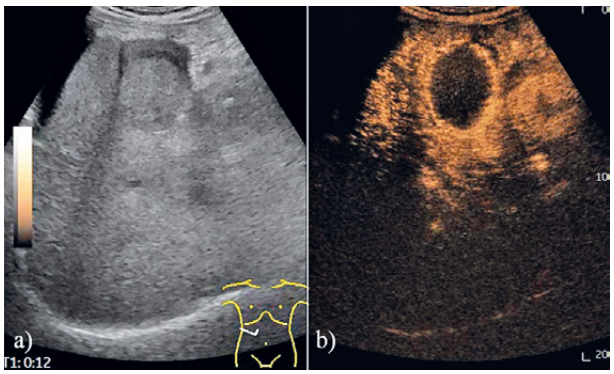

Fig 12. Gallbladder sediment (hepatization): a) grayscale; b) CEUS exploration.

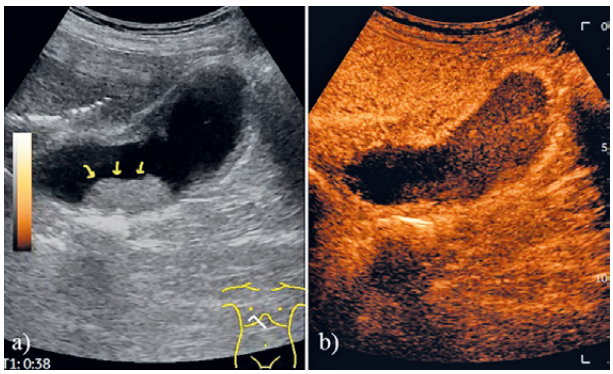

Fig 13. Pseudotumoral sediment: a) grayscale; b). CEUS exploration (lack of loading indicates the non-neoplastic nature of the grayscale image).

Hemobilia

Hemobilia is rarely described in the literature (secondary to lithiasic cholecystitis, trauma, tumors, vascular abnormalities, coagulation disturbances). In clinical practice it is found after interventional procedures such as trans jugular portosystemic shunt or endoscopic retrograde cholangiopancreatography. It is difficult to be clinically assessed but sometimes is confirmed by endoscopy [4]. Gallstones and tumors might be missed in these circumstances. CEUS shows non-capturing hematoma or clots. In cases of active hemorrhage (arterial or venous) the CA extravasation from the vascular bed may be seen [4] (fig 14).

Arterial malformation

Arterial malformation of the gallbladder is very rarely described in literature. A pseudotumoral aspect might be encountered; a correct depiction of vessel flow might differentiate between pathological processes or anatomical arterial malformation in this context (fig 15).

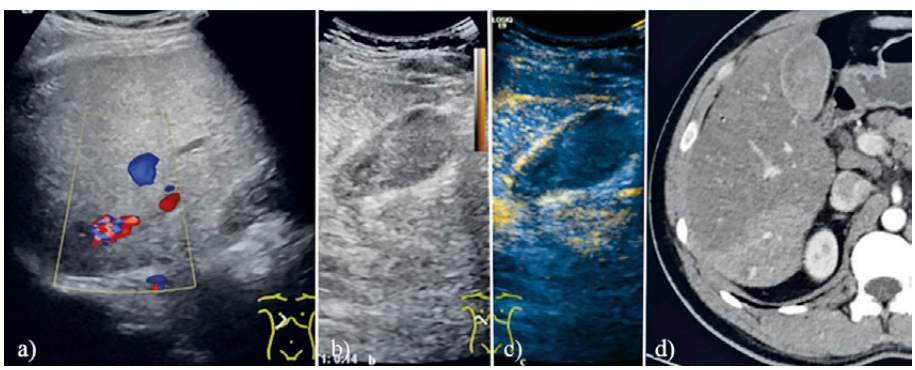

Fig 14. Hemobilia. Exploration performed in relation to an interventional procedure (transjugular biopsy) resulting in intrahepatic arteriovenous fistula communicating with the biliary ducts and hemobilia: a) color Doppler; b) grayscale; c) CEUS (excludes active bleeding); d) CT exploration (arterial, transversal).

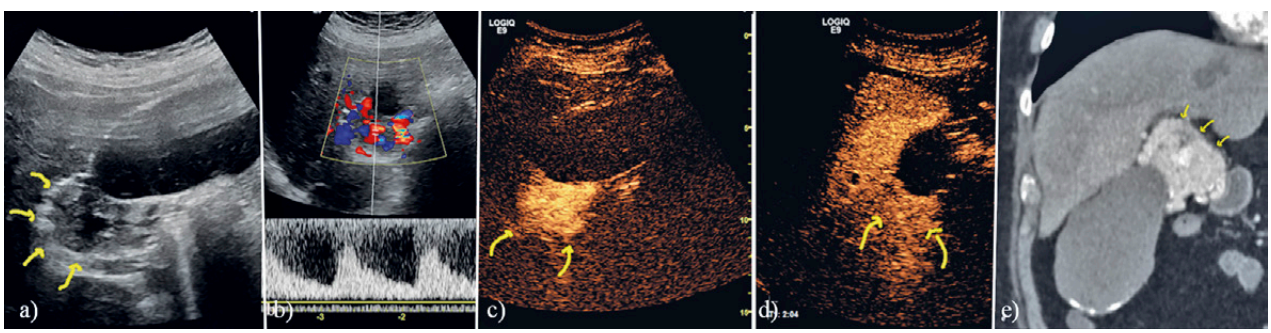

Fig 15. Cholecystic artery malformation (arrows). Ultrasonographic exploration in grayscale (a), Color and spectral Doppler (b), CEUS in arterial (c) and venous (d) phases. CT appearance (arterial phase) (e).

Conclusions

CEUS increases the confidence of ultrasound diagnosis of gallbladder pathology. In acute circumstances, CEUS had a higher accuracy than conventional ultrasound in the diagnosis of gangrenous cholecystitis. Based on its ability to depict the vascular pattern of neoangiogenic processes it helps in the differential diagnosis of gallbladder polyps. This technique should be more widely used as it might offer clues in difficult differential diagnosis, especially in polyps larger than 10 mm. In monitoring patients after surgery, interventional endoscopy or interventional radiology CEUS might acurate detect bleeding or abcesses, being non-invasive, non-iradiating and easy to perform. Rare pathologies, such as malformations or xantogranulamtous cholecystitis also might benefit from CEUS.

Conflict of interest: none

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