Review Article

Algorithmic approaches to the diagnosis of gallbladder intraluminal lesions on ultrasonography

Chia-Hung Wu a,b, Yukun Luo c, Xiang Fei c, Yi-Hong Chou a,b,d,* Hong-Jen Chiou a,b, Hsin-Kai Wang a,b, Yi-Chen Lai a,b, Yung-Hui Lin a,b, Chui-Mei Tiu a,b,c,†, Jane Wang a,b

a Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
b National Yang-Ming University, School of Medicine, Taipei, Taiwan, ROC
c Ultrasound Department, The General Hospital of People’s Liberation Army, Beijing, China
d Yuanpei University of Medical Technology, Hsinchu, Taiwan, ROC
† Yee Zen Hospital, Taoyuan, Taiwan, ROC
† Lo-Hsu Medical Foundation Lotung Poh-Ai Hospital, Yilan, Taiwan, ROC

Received January 10, 2017; accepted June 4, 2017

Abstract

Ultrasound is a frequently used diagnostic tool for gallbladder diseases. Polypoid lesions are commonly depicted at routine abdominal ultrasonography (US). The characteristics of these lesions vary. Since most early malignant tumors in the gallbladder are asymptomatic, differentiation between malignancy and benignity is crucial. Knowledge of gallbladder polypoid lesions is important so that they can be appropriately included in the differential diagnosis in patients presenting with intra-gallbladder nodules on US. This article summarizes the algorithmic approach to the diagnosis of these lesions and our recent experience with contrast-enhanced US. The clinical and imaging features of gallbladder polypoid lesions are reviewed. Copyright © 2018, the Chinese Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Adenocarcinoma; Gallbladder; Polypoid lesions; Pseudotumors; Ultrasound

1. Introduction

Polypoid lesions of the gallbladder are common findings at abdominal ultrasonography (US). The term “polypoid” is defined as a focal elevation or a protrusion into the gallbladder lumen from the wall.1,2 However, not all polypoid lesions are malignant. In fact, most incidentally found polypoid lesions in the gallbladder are benign.3 Since most malignant tumors in the gallbladder are asymptomatic and usually diagnosed when advanced, differentiation between malignancy and benignity is crucial.4,5 Mellnick and colleagues classified different types of gallbladder lesions into pseudotumors, benign tumors and malignant tumors.1 To evaluate a gallbladder polypoid lesion on US, we suggest confirming a “true” polypoid lesion first. After a “true” polypoid lesion is established, the next step is to distinguish pseudotumors from true tumor lesions. Finally, the differential diagnoses should be grouped into benign and malignant tumors separately. Several clinical factors have also been described to aid the differential diagnosis, including age, comorbidities and presence of clinical symptoms.

The study was performed following the ethical principles. Approval was waived for our study because the results for publication only involved unidentified imaging.

2. Intraluminal polypoid mimickers

The first step of evaluation of a gallbladder polypoid structure is to rule out the pseudo-mucosal lesions. A
Gallbladder polypoid lesion is defined as a mucosal lesion elevating or protruding into the gallbladder lumen. Since a polypoid structure is derived from the gallbladder mucosa, it should be connected to the gallbladder wall. However, some intraluminal lesions contacting the mucosa can mimic the mucosal connection, and may thus be misdiagnosed.

Gallbladder sludge is a mixture of precipitates of cholesterol crystals, calcium bilirubinate pigments and other calcium salts. It is mostly seen in fasting patients, especially those who are on parenteral nutrition. Typically, it is a mobile intraluminal lesion and without connection to the gallbladder wall. However, some sludges may not show significant mobility due their relatively sticky or stiffened nature.

Among these pseudo-mucosal lesions, gallbladder sludge is the most common, especially tumefactive sludge (Fig. 1). Gallbladder sludge, including tumefactive sludge, presents no real blood flow signal on color Doppler US. Occasionally, pseudo-flows or twinkle artifacts are present because of the engulfed larger crystals or small stones (Fig. 2). Posterior acoustic shadowing may be observed due to occasional contents of calcium or engulfment of a gallstone. It may be difficult to differentiate a gallbladder sludge from a true polypoid lesion when atypical, and follow-up study is needed in case of malignancy.

The formation of a tumefactive sludge is a process of coacervation and thixotropy. According to Ando and associates, tumefactive sludge is a precipitate of inspissated bile, multiple calculi, pigmented granules, cholesterol crystals, hemobilia and, possible, purulent bile or pus. These particles tend to separate in the bile due to coacervation and precipitate to the dependent portion of the gallbladder due to thixotropy. Because of the relatively weak forces between particles and unstable folding, tumefactive masses may turn into numerous small particles when external strong tapping force is applied. The tapping maneuver may aid in the differential diagnosis when changes of the position have failed to demonstrate the mobile nature of the tumefactive masses.

Gallstones may mimic polypoid lesions on US. Posterior acoustic shadowing is often present and may be obscured by the superimposed bowel gas or prominent fatty tissue. Although gallstones are often noted in patients with acute or chronic cholecystitis, the presence of gallstones does not rule out the possibility of malignancy.

3. Polypoid lesions

After a “true” polypoid lesion is established, the next step is the differentiation of pseudotumors and true tumor lesions. Although there is an existence of mucosal connection to the polypoid lesion, it may not be clearly depicted on US, especially when they are small in size. Polypoid lesions can be observed as sessile, with stalk, or infiltrative (Fig. 3). Most lesions with stalk are relatively benign as compared with sessile lesions. Infiltrative lesions are mostly malignant.

4. Pseudotumors

Some of the polypoid lesions of the gallbladder are non-tumorous lesions. These pseudotumors comprise mostly cholesterol polyps, adenomyomatosis and inflammatory polyps.

Cholesterol polyps are derived from engulfment of triglyceride by phagocytes. Typical cholesterol polyps accumulate on the gallbladder wall, presenting a “balls on the wall sign” (Fig. 4). Less commonly, cholesterol polyp may present as a solitary polypoid lesion with subtle vascularity (Fig. 5). Heterogeneous enhancement of the lesion is also noted on contrast-enhanced US (CEUS) (Fig. 6). To further differentiate these atypical cholesterol polyps from other polypoid malignancies, endoscopic ultrasonography (EUS) is recommended. On EUS, cholesterol polyp tends to have a thin visible stalk and display homogeneous echogenicity, while gallbladder adenocarcinoma presents with a thick stalk and heterogeneous echogenicity. Other imaging characteristics, including incomplete gallbladder wall and invasion of the adjacent liver parenchyma, often indicate malignant nature. It is also generally believed cholesterol polyps have barely any risk of malignant changes.

Adenomyomatosis are bile acid crystal precipitates in the intramural diverticula (also known as Rokitansky-Aschoffsinuses) of the gallbladder. Multiple interfaces are formed due to crystals, and therefore produce the typical comet-tail artifacts (Fig. 7). On color Doppler US, the crystals in the intramural diverticula may present with tinkle artifacts (Fig. 8). Adenomyomatosis often coincides with thickening of the gallbladder wall.

Different morphological changes may present with three types of adenomyomatosis, namely diffuse, segmental and focal types. Ootani and colleagues proposed that segmental adenomyomatosis had strong relation with gallbladder cancer after reviewing over 3000 gallbladder specimens (Fig. 9).

The formation of inflammatory polyps is due to chronic cholesterol precipitates and chronic inflammation, which stimulate the mucosal wall and further form granulation and fibrosis. Inflammatory polyps may proceed to mucosal dysplasia.
The ultrasonographic features of inflammatory polyps are nonspecific and often related to chronic inflammation. It is sometimes difficult to differentiate these lesions from malignancy due to the presence of blood flow on color Doppler US.

5. Benign polypoid tumors

Adenomas are mostly seen in patients with primary sclerosing cholangitis and intestinal polyposis syndrome. It is almost not possible to differentiate adenoma from adenocarcinoma on US since both are associated with internal vascularity (Fig. 10). The use of 10-mm diameter as an indicator of higher risk of malignancy had been widely accepted in clinical practice. Although malignant transformation of a smaller gallbladder polypoid lesion exists, the managements of lesions of diameter less than 10 mm without other risk factors for malignancy depend on clinical conditions.

The differences between adenoma and adenocarcinoma are usually subtle on ultrasonography. Adenomas may present with sizes larger than 10 mm, and usually possess internal vascularity. The general consensus of 10-mm diameter as a cutoff level between benign
Fig. 5. **Cholesterol polyp.** (A) Cholesterol polyp can sometimes present as a solitary polypoid lesion, and it is a challenging differential diagnosis with other polypoid lesions. (B) Color Doppler shows subtle vascularity.

Fig. 6. **Cholesterol polyp.** (A) Contrast-enhanced ultrasonography (CEUS) depicts the enhancement at 15 s after injection. (B) Pre-contrast image is shown in gray scale.

Fig. 7. **Adenomyomatosis.** (A) The crystals in the Rokitansky-Aschoff sinuses form multiple layered interfaces, and therefore create this diagnostic comet-tail artifact. (B) Twinkle artifacts indicate the presence of crystals inside the Rokitansky-Aschoff sinuses in the gallbladder wall.
and malignant tumors is applicable at screening ultrasonography. When symptoms exist, further evaluation is usually needed. Dynamic studies, including computed tomography (CT), magnetic resonance imaging (MRI) and CEUS should be arranged to further differentiate adenoma from other malignancies. On CEUS, adenoma shows eccentric enhancement and intact gallbladder wall underneath the lesion. The reported specificity of using these two imaging features to distinguish adenoma from adenocarcinoma is 93.3%. Papillomas are relatively rare. These lesions are relatively commonly seen in elderly males. Papillomas have malignant potential to form papillocarcinomas.

6. Malignant polypoid tumors

Most early malignant tumors in the gallbladder are without specific clinical symptoms and display advanced or with extracholecystic invasion when diagnosed. Some imaging features of malignancy have been described, including size over 10 mm, focal thickening of the gallbladder wall (>3 mm) and incomplete gallbladder wall beneath the lesion. Adenocarcinomas are the most common malignant tumors in the gallbladder. Risk factors of adenocarcinomas include older age, gallstones, chronic cholecystitis, porcelain gallbladder, choledochal cysts and primary sclerosing cholangitis. Unifocal polyloid lesions are more likely to be malignant. The imaging characteristics of typical adenocarcinomas include relatively larger size, wider base, incomplete gallbladder wall (Fig. 11) and coexistence of chronic cholecystitis. Presence of vascularity is not specific, for blood flow can be observed in both adenomas (Fig. 10) and adenocarcinomas. As a result, sonomorphological changes and sizes of the lesions may be more important than the presence of color Doppler signal. The extracholecystic routes of spreading of adenocarcinomas include direct invasion, lymphangitic and hematogenous spreading. The most common route is direct invasion, and the liver is the most common organ involved. The invaded liver parenchyma is typically hypoechogenic and associated with ill-defined border with the gallbladder. According to WHO classification, the preneoplastic lesions of the gallbladder include dysplasia and mass-forming lesions. The metaplasia-dysplasia-carcinoma model has been well-established. Mukhopadhyay and associates reviewed four hundred cholecystectomy specimens and described the progression from metaplasia to dysplasia.

Fig. 8. Adenomyomatosis with twinkle artifacts. (A) Adenomyomatosis in the gallbladder. Mild wall thickening of the gallbladder is noted. (B) Twinkle artifact is observed (arrow), indicating the presence of crystals in the intramural diverticulum.

Fig. 9. Segmental-type adenomyomatosis. (A) Annular and segmental mural thickening with tiny cystic structures representing adenomyomatosis (arrows), separating the gallbladder into two compartments. (B) Close-up image shows similar findings with segmental narrowing of the gallbladder.
has been proposed.\textsuperscript{34,35} Metaplasia may be a reaction to mucosal injury caused by chronic inflammation, and further increase the susceptibility to carcinoma.

Metastatic tumors are rare in the gallbladder. Stomach is the most common origin in Asian patients. Metastatic melanoma, renal cancer and lung cancer have also been reported. Direct invasion of cholangiocarcinomas and hepatocellular carcinomas are not rare, and may mimic the imaging findings of direct invasion of liver parenchyma by gallbladder cancer.\textsuperscript{36}

Primary gallbladder lymphomas are less frequently found than secondary ones. Secondary lymphomas with adjacent lymphadenopathy are more common. Due to lack of lymphatic tissues in the gallbladder, primary lymphomas may derive from chronic cholecystitis. Ultrasonographic findings are not specific, and lymphadenopathy in the abdomen may be observed.\textsuperscript{37}

7. Endoscopic ultrasonography (EUS)

The sonographic images in this article are based on transabdominal ultrasonography. Endoscopic ultrasonography (EUS) is another diagnostic tool for gallbladder polypoid lesions. EUS is superior to transabdominal US in demonstrating the layering pattern of the gallbladder wall.\textsuperscript{33,34} Loss of the multiple layering pattern of the thickened gallbladder wall has been described as one of the important signs of malignancies.\textsuperscript{35} Some authors have even suggested routine use of EUS before cholecystectomy.\textsuperscript{14} Whether EUS is superior to transabdominal US or not is beyond the scale of this article. It is obvious that EUS has
poorer availability and may carry discomfort due to its relatively invasive endoscopic approach. Considering the above clinical settings, high-resolution US (HRUS) is still the imaging of choice in the evaluation of the gallbladder pathology, for it provides a similar or even higher sensitivity in differentiating gallbladder polypoid lesions than EUS. The diagnostic accuracy of differentiation between benign and malignant polypoid lesions of the gallbladder is similar for HRUS and EUS. Some reports showed higher diagnostic accuracy and sensitivity of HRUS in comparison with EUS. HRUS also provides accurate T categorization of gallbladder carcinoma in TNM staging. Thus, EUS may be used as an ancillary tool.

In conclusion, US is the first-line diagnostic tool for gallbladder polypoid lesions. It is important for radiologists to understand the imaging characteristics of these lesions (Fig. 12). The first step of evaluation is to rule out pseudopolypoid lesions. After establishing “true” polypoid lesions, pseudotumors should be separated from tumor lesions. Finally, tumors can be grouped into benign and malignant ones based on several imaging factors.

Acknowledgments

This study is partially supported by the Wong Vung-Hau Radiology Foundation, Taipei, Taiwan, ROC. The authors would like to thank Ms. Chih-Ping Chiu and Ms. Pei-Hsuan Chiu for their assistance in preparation of the article.

References


Fig. 12. Algorithmic approaches to the diagnosis of gallbladder intraluminal lesions on ultrasonography.