Noninflammatory Gallbladder Diseases: An Approach based on Ultrasonographic Findings

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Learning objectives

The purpose of this exhibit is to:

- Review the imaging appearance of noninflammatory gallbladder diseases.

- Describe the imaging features that are associated with a higher malignancy risk.

- Discuss the appropriated management of these lesions.
Background

A broad spectrum of noninflammatory diseases can affect the gallbladder wall including systemic diseases, benign entities, malignant tumors and metastasis. These pathologies can appear on radiologic exams as subtle abnormalities or as polypoid mass, focal or diffuse gallbladder wall thickening. Ultrasonography is nowadays the first image modality to evaluate gallbladder diseases. CT and MRI are image methods used to complement the ultrasound evaluation.
Findings and procedure details

The gallbladder is a hollow pear-shaped organ with thin and regular walls, located in the right upper quadrant, on the surface of the liver between segments IV and V, and is connected to the hepatic duct through the cystic duct. The gallbladder is divided into the fundus, which usually projects beyond the inferior border of the liver, the body, and the neck. It is usually 7-10 cm long and 2.5 cm wide, and the wall measures less than 3 mm in thickness (Fig 1). The gallbladder serves as the repository for bile produced in the liver, with an average volume of 30-50 ml. The gallbladder wall is composed of four layers: a mucosa; a second layer comprising an irregular smooth muscular tissue; a third layer constituted by loose connective tissue; and a last layer formed by the serosa. (3,10,13).

In cases of suspected gallbladder disease, sonography is often the first imaging technique because of its relatively low cost, widespread availability and a high sensitivity in the detection of gallbladder wall thickening. Gallbladder US is routinely performed with a convex transducer. In order to acquire appropriate images, a systematic scanning should be carried out with longitudinal and cross sectional views of the organ, evaluating its shape, dimensions, wall thickness, regularity and texture pattern of its walls and contents, besides locoregional and Doppler velocimetric alterations (3).

By means of US it is possible to identify three layers: the innermost, corresponding to the mucosa, that is linear, echogenic and presents a regular surface; the second one, corresponding to the muscular layer, is thin and slightly hypoechoic; and outermost layer corresponding to the organ's serosa, that is linear, echogenic and regular (3,10).

According to several authors, the upper limit for normality of the gallbladder wall thickness is 3 mm. However, in patients under inappropriate fasting, the parietal thickness may exceed such a limit because of the organ's smooth muscle contraction. So, at least 6-8 hour fasting before the examination is recommended (2,11,13).

Gallbladder wall thickening is a common yet nonspecific finding that can occur in a wide range of gallbladder diseases and extracholecystic conditions (Table 1).

Distinguishing among the wide variety of conditions associated with gallbladder wall thickening is important for diagnosis and appropriate management. An initial important observation is whether the pattern of thickening is focal or diffuse (Fig.2).
Although ultrasound is usually the initial imaging modality for the evaluation of suspected acute gallbladder disorders, contrast enhanced CT also can be useful to evaluate gallbladder pathology, particularly when the ultrasound findings are equivocal. Nuclear medicine studies and MRI may be used to further characterize difficult diagnostic dilemmas. Contrast-enhanced ultrasound using microbubbles is less well established than routine sonography in the evaluation of gallbladder and biliary disease but has the potential advantage of use in patients with renal impairment. (12).

1. Diffuse Pattern

Besides inflammatory conditions, systemic diseases may cause diffuse wall thickening including heart and renal failure, liver dysfunction and portal venous hypertension. Other causes of diffuse wall thickening include infiltrative processes, such as gallbladder carcinoma, and hyperplastic changes, as seen in adenomyomatosis, although these may also appear as a focal thickening (12).

1.1 Pseudothickening

The thickness of the gallbladder wall depends on the degree of gallbladder distention, and pseudothickening can occur in the postprandial state. It is important not to mistake this normal physiologic phenomenon for pathologic thickening of the gallbladder wall (2,12).

1.2 Systemic diseases

Systemic diseases, such as heart or renal failure, may cause gallbladder wall thickening in the absence of gallbladder inflammation, possibly related to elevated portal venous pressure, low intravascular osmotic pressure, or a combination of these factors (Fig.3). Hypoalbuminemia is another cause of gallbladder wall thickening (2,12).

1.3 Adenomyomatosis

Adenomyomatosis is a benign acquired hyperplastic process of the gallbladder. It is a relatively common condition, identified in at least 5% of cholecystectomy specimens. It is frequently an incidental finding, has no intrinsic malignant potential, and usually requires no specific treatment (8).

The wall thickening of adenomyomatosis involves hyperplasia of both mucosa and muscularis propria. Adenomyomatosis is characterized by excessive proliferation of surface epithelium with abnormally deepened and branching invaginations (Rokitansky-
Aschoff sinuses) that extend deep into the muscular layer of the gallbladder wall. Cholesterol accumulation in adenomyomatosis is intraluminal, as cholesterol crystals precipitate in the bile trapped in Rokitansky-Aschoff sinuses, intramural diverticula lined by mucosal epithelium. (2, 8, 12)

Gallbladder involvement by adenomyomatosis is variable in extent and location, with different imaging appearances corresponding to diffuse, segmental, and focal diseases. Diffuse or generalized adenomyomatosis consists of widespread gallbladder involvement.

At US echogenic intramural foci from which emanate V-shaped comet tail reverberation artifacts are highly specific for adenomyomatosis, representing the unique acoustic signature of cholesterol crystals within the lumina of Rokitansky-Aschoff sinuses (8) (Fig. 4 and 5).

CT is less specific in the detection of adenomyomatosis, and may show cystic-appearing thickening of the gallbladder wall or enhancing epithelium within intramural diverticula surrounded by relatively unenhanced hypertrophied gallbladder muscularis (12). MR imaging demonstrates the mural thickening and multiple intramural cystic spaces that are hyperintense on T2-weighted images (bile filled Rokitansky-Aschoff sinuses) (13).

The radiologic differential diagnosis may include other benign gallbladder conditions, such as polyposis and adenoma, and as well as malignancies such as gallbladder adenocarcinoma, cholangiocarcinoma, hepatocellular carcinoma, and metastatic cancer.

1.4 Malignancy

Gallbladder carcinoma is the fifth most common gastrointestinal malignancy. Clinical presentation of the disease is often vague, there are no specific signs and symptoms, and the majority of patients with gallbladder carcinoma present with advanced disease. It is more commonly seen in women and in the elderly and has a strong association with gallstones (present in about 80% of cases) (2, 12, 13).

Primary gallbladder carcinoma has various imaging appearances and most often manifests as a diffusely infiltrating lesion that replaces the gallbladder and extends into the liver. Less frequently, it appears as asymmetric mural thickening or an intraluminal polypoid mass. The ultrasound visualization of pronounced wall thickening (>10 mm) associated with irregularity or asymmetry is suspicious for malignancy. In cases of diffusely infiltrating lesions, ultrasound findings suggestive of malignancy include irregular wall thickening and an extraluminal mass extending into the liver (1, 12).

2. Focal Pattern
Noninflammatory focal gallbladder wall diseases can be divided into polypoid alterations and focal wall thickening.

Gallbladder polyps can have neoplastic and nonneoplastic causes. Focal wall thickening can be due to focal adenomyomatosis and carcinomas.

Gallbladder polyps are a relatively common finding in abdominal US exams (reported prevalence of 3%-7). A wide range of benign and malignant tumors as well as pseudotumors may manifest as gallbladder polyps. Although most gallbladder polyps are benign, it is important to diagnose gallbladder cancer at an early stage, when it may be resectable (9, 18).

The most important radiologic findings to be observed in a gallbladder polyp are:

- the size and shape (e.g., pedunculated or sessile),
- presence of gallstones (which increase the likelihood that the polyp is a neoplastic lesion),
- gallbladder wall thickening adjacent to the polypoid lesion,
- number of polyps,
- biliary strictures,
- hepatic masses and
- presence of vascularization (Doppler).

The most common benign causes of noninflammatory gallbladder polyps are cholesterol polyps, adenomyomatosis and tumefactive sludge mimicking a polypoid lesion.

2.1 Cholesterol polyps

Cholesterol polyps are the most common polypoid lesions found in the gallbladder, accounting for approximately 60%-70% of gallbladder polyps. These lesions occur predominantly in middle-aged women, are typically multiple and have no malignant potential. They are formed due to deposition of triglycerides and cholesterol esters within macrophages in the lamina propria, so this polyp is covered by normal epithelium. At US, cholesterol polyps are small round, smoothly contoured, echogenic intraluminal lesions attached to the wall and with no acoustic shadowing (Fig 6 and 7). The stalk is rarely seen (“ball on the wall” sign). When multiple cholesterol polyps may be confluent and/or larger than 1 cm, and in this situation they cannot be definitively differentiated from other benign or malignant lesions at imaging (9).

2.2 Focal adenomyomatosis
The focal form of adenomyomatosis frequently involves the gallbladder fundus and imaging features at US include echogenic intramural foci that emanate comet-tail reverberation artifacts (Fig 8). The segmental form most often affects the body of the gallbladder appearing as a concentric circumferential wall thickening that may give rise to an hourglass configuration of the gallbladder. Exclusion of malignancy may be difficult in cases of segmental and focal adenomyomatosis and additional imaging exams as CT and MR may be necessary (9, 12).

2.3 Adenomas

Gallbladder adenomas are rare and typically incidentally found. They are most frequently found in patients with primary sclerosing cholangitis (PSC) and gastrointestinal polyposis syndromes and the role of gallbladder adenomas in the pathogenesis of gallbladder carcinoma is controversial (9).

At US, gallbladder adenomas are usually solitary with sessile or pedunculated appearance. They may vary in size (up to 20 mm) and demonstrate internal vascularity at color Doppler (Fig 9 and 10). At CT and MR imaging, gallbladder adenomas typically have enhancement pattern similar to that of adenocarcinoma. At imaging, adenomas cannot be reliably differentiated from polypoid gallbladder adenocarcinoma (9).

2.4 Gallbladder Carcinoma

Primary adenocarcinoma is the most common malignant gallbladder polyp. It carries a very poor prognosis because it is often detected at an advanced stage.

Gallbladder adenocarcinoma most commonly manifests as a mass in the gallbladder fossa but in 20-30% of cases it manifests as a focal irregular wall thickening or, less often, as an intraluminal polyp. US features that are more associated with polypoid adenocarcinoma include a solitary polyp larger than 10 mm, a wide polyp base, focal wall thickening of more than 3 mm, and coexisting gallstones (1,9,15) (Fig 11, 12 and 13). At color and spectral Doppler US, linear color signal at the polyp base and an increased resistive index may indicate a cancerous polyp (16). In the cases of suspected malignancy CT and MR imaging can provide additional information.

2.5 Metastases

Metastatic disease involving the gallbladder is a rare entity and although it can occur with any primary malignancy typically in the setting of widespread metastatic disease it is most commonly associated with melanoma. Imaging features include focal irregular wall thickening and enhancing polypoid masses (9, 12).
3. Management of gallbladder wall thickening

The imaging features of noninflammatory gallbladder wall thickening may, at times, indicate a specific diagnosis, but there is an overlap in the appearances of benign and potentially malignant gallbladder lesions.

Considering the diffuse wall thickening pattern the features that are associated with a higher malignancy risk are asymmetric or heterogeneous irregular wall thickening and the presence of an intraluminal mass extending into the liver parenchyma.

The management of asymptomatic polypoid lesions of the gallbladder includes the evaluation of many factors and according to the available literature one of the most important factor is the size of the polyp. Many studies series agree that polyps larger than 10 mm have an increased potential of malignancy and a cholecystectomy should be performed (6,9,15,17).

The management of polyps measuring between 6-10 mm is controversial. In general, asymptomatic polyps of this size should be followed with serial imaging. The frequency and duration of follow up examinations is not well established but recent studies support a screening interval of every 6 to 12 months. An increase in size to more than 10 mm or the onset of biliary symptoms may indicate a need for cholecystectomy (6,9,17,18).

Management of polyps that measures 5 mm or less is also controversial. Some studies report that among this group some polyps were not seen at follow up US and no focal lesion was seen in the majority of cholecystectomy specimens (9). Probably a substantial number of polypoid lesions of this size are adherent stones or sludge. In the literature some authors recommend follow up those small polyps (18,19) and others assume that no follow up is required (5,9).

It is important to notice that the size of a gallbladder polyp is not the only feature to be taken into consideration. Other factors, such as the presence of gallstones, a patient age over 50 years, a wide polyp base, and focal gallbladder wall thickening of more than 3 mm, should favor surgical management (9).
Images for this section:

**Fig. 1:** US image of normal gallbladder

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| Congestive heart failure | Cholesterol          |
| Renal failure           | Adenomatous          |
| Hypoalbuminemia         |                      |
|                        |                      |

| Liver diseases          | Malignancy           |
|                        | Primary gallbladder carcinoma |
|                        | Metastasis            |
| Cirrhosis               |                      |
| Portal hypertension     |                      |
|                         |                      |

| Adenomyomatosis         |                      |
| Malignancy              |                      |
| Primary gallbladder carcinoma |          |
| Lymphoma                |                      |
Fig. 2: Types of gallbladder wall thickening

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**Fig. 3:** Congestive heart failure. US image shows diffusely thickened gallbladder wall.

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**Fig. 4:** Diffuse adenomyomatosis. Longitudinal US image of the gallbladder shows diffuse wall thickening with multiple reverberation artifacts.

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**Fig. 5:** Diffuse adenomyomatosis. Transversal US image of the gallbladder shows diffuse wall thickening with multiple reverberation artifacts.

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**Fig. 6:** Cholesterol polyp. US image of the gallbladder shows a hyperechoic polyp attached to the wall and with no acoustic shadowing.

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**Fig. 7:** Cholesterol polyp. Longitudinal US image shows a hyperechoic polyp in the gallbladder.

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**Fig. 8:** Focal adenomyomatosis. Longitudinal US image of the gallbladder shows focal wall thickening of the gallbladder fundus. There are multiple reverberation artifacts emanating from the thickened gallbladder.

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Fig. 9: Gallbladder adenoma. US image shows a nodular lesion in the gallbladder fundus.

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**Fig. 10:** Gallblader adenoma. US image shows a nodular lesion in the gallbladder fundus with vascularization.

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**Fig. 11:** Gallbladder carcinoma. Longitudinal US image of the gallbladder shows a focal wall thickening (arrow).

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Fig. 12: Gallbladder carcinoma. US image. Focal wall thickening with retraction of the gallbladder walls.

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**Fig. 13:** Gallbladder carcinoma. US image. Focal irregular wall thickening. Associated gallbladder stones.

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Conclusion

Ultrasound remains the first line modality for imaging the gallbladder. It is the greatest importance in guiding clinicians during the investigation of noninflammatory gallbladder conditions. Although there is an overlap in the appearances of benign and potentially malignant gallbladder lesions, it is important that radiologists identify the features that require follow up or immediate surgery in order to avoid delayed diagnoses that may compromise the treatment and the patient prognosis.
References


