Polypoid Lesions of the Gallbladder: Disease Spectrum with Pathologic Correlation

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Abbreviations: FDG = fluorine-18 fluorodeoxyglucose, H-E = hematoxylin-eosin, PSC = primary sclerosing cholangitis

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Galbladder polyps are seen on as many as 7% of gallbladder ultrasonographic images. The differential diagnosis for a polypoid gallbladder mass is wide and includes pseudotumors, as well as benign and malignant tumors. Tumefactive sludge may be mistaken for a gallbladder polyp. Pseudotumors include cholesterol polyps, adenomyomatosis, and inflammatory polyps, and they occur in that order of frequency. The most common benign and malignant tumors are adenomas and primary adenocarcinoma, respectively. Polyp size, shape, and other ancillary imaging findings, such as a wide base, wall thickening, and coexistent gallstones, are pertinent items to report when gallbladder polyps are discovered. These findings, as well as patient age and risk factors for gallbladder cancer, guide clinical decision making. Symptomatic polyps without other cause for symptoms, an age over 50 years, and the presence of gallstones are generally considered indications for cholecystectomy. Incidentally noted pedunculated polyps smaller than 5 mm generally do not require follow-up. Polyps that are 6–10 mm require follow-up, although neither the frequency nor the length of follow-up has been established. Polyps that are larger than 10 mm are typically excised, although lower size thresholds for cholecystectomy may be considered for patients with increased risk for gallbladder carcinoma, such as patients with primary sclerosing cholangitis.

Introducion

Gallbladder polyps are defined as sessile projections of the gallbladder wall into the lumen. They are typically incidentally found at ultrasonography (US). Unlike gallstones, gallbladder polyps are not significantly associated with female sex, obesity, or multiparity (1). Management of gallbladder polyps relies on imaging findings and various clinical factors. Potential courses of action range from no further action to open cholecystectomy and lymph node sampling. There is some overlap in the appearance of benign and malignant gallbladder polyps. In this article, we describe common and uncommon types of gallbladder polyps with pathologic and radiologic examples and discuss appropriate management of these lesions.

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the spectrum of polypoid lesions of the gallbladder.
- List the salient features that may help guide differential diagnosis of these lesions.
- Discuss the management of polypoid lesions of the gallbladder.

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TEACHING POINTS

- At US, cholesterol polyps appear as small, round, smoothly contoured, intraluminal lesions that are attached to the wall. The stalk is rarely seen, an appearance that gives rise to the “ball on the wall” sign.
- At MR imaging, the Rokitansky-Aschoff sinuses cause a “pearl necklace” sign of multiple round spaces that are hyperintense on T2-weighted images, a finding that has been reported to have 92% specificity for adenomyomatosis.
- At US, inflammatory gallbladder polyps have a nonspecific appearance. A diagnosis of inflammatory polyps may not be made with certainty at imaging.
- In patients with PSC, a substantial number (60%) of gallbladder polyps are malignant.
- US clues to a polypoid gallbladder carcinoma include a solitary polyp larger than 10 mm, a wide polyp base, focal wall thickening of more than 3 mm, and coexisting gallstones.

Clinical Considerations

Gallbladder polyps are relatively common, with a reported prevalence of 3%–7% at abdominal US and 2%–12% in cholecystectomy specimens (1–5). A wide array of pseudotumors, as well as benign and malignant tumors, may manifest as gallbladder polyps. By far, most gallbladder polyps are benign. Nevertheless, it is important to recognize gallbladder cancer at an early stage, when it may be resectable for cure. Radiologic findings can be used to stratify gallbladder polyps into three groups: those that need no further follow-up, those that require follow-up, and those that should be excised (ie, cholecystectomy). In addition to the likelihood of malignancy on the basis of imaging findings, a surgeon’s judgment on whether to perform cholecystectomy relies on clinical factors, such as patient age, medical comorbidities, and the presence of symptoms that are attributable to gallbladder disease.

Imaging Protocols

Gallbladder polyps are mostly identified at US but are increasingly seen at computed tomography (CT), magnetic resonance (MR) imaging, and positron emission tomography (PET). Patients should fast for several hours before undergoing US to allow distention of the gallbladder. Typically, a phased-array sector or curvilinear-array probe with a relatively low frequency (2–5 MHz) is used. US protocols should include multiplanar gray-scale images, as well as color and spectral Doppler images of detected lesions (6). Lesions should be imaged in more than one position (eg, supine and left decubitus) to avoid mistaking mobile sludge balls for polypoid lesions (Fig 1). It is important to note the size and shape (eg, pedunculated or sessile) of a polypoid lesion and the presence of gallstones, which increase the likelihood that the polyp is a neoplastic lesion (7,8). Other findings to note include gallbladder wall thickening adjacent to the polypoid lesion, multiple polyps, biliary strictures, and hepatic masses. The presence of twinkling artifact may help diagnose adenomyomatosis (9). Size comparison with prior imaging studies, including CT and MR imaging, is helpful. When contrast material–enhanced US is available, lesion enhancement may be a useful discriminator between benign and malignant polyps (10).

CT, PET/CT and MR imaging may also depict larger polypoid lesions within the gallbladder (11,12). These modalities are usually used for staging of known or suspected gallbladder cancer (13). MR imaging has good sensitivity for depiction of vascular and bile duct invasion, and the protocol should include thin- and thick-section MR cholangiopancreatography, as well as diffusion-weighted and multiphase contrast-enhanced imaging (14).

Mimics of Gallbladder Polyps

Adherent gallstones and gallbladder sludge may be immobile and mimic true gallbladder polyps. The characteristic acoustic shadowing of gallstones may be difficult to visualize in obese patients or when calculi are deep in the gallbladder neck. Gallbladder sludge is usually easy to diagnose and is seen as mobile small intraluminal, hyperechoic, nonshadowing, nonvascular balls. However, adherent, tumefactive sludge may appear as a mass lesion (Fig 2). In cases in which tumefactive sludge is suspected but cannot be confirmed, a short-term follow-up examination may be of use, particularly if the original study was performed after a prolonged period of fasting (15).

Classification of Gallbladder Polyps

Gallbladder polyps may be classified as pseudotumors, benign tumors, or malignant tumors. The imaging and clinical aspects of each of these groups are discussed herein.

Pseudotumors

Cholesterol polyps, adenomyomatosis, and inflammatory polyps, in that order of frequency, constitute the major polypoid pseudotumors. Cholesterol polyps and adenomyomatosis are hyperplastic noninflammatory conditions with different histologic features. The gallbladder wall is composed of four layers: mucosa, lamina propria, muscularis propria, and serosa. It does not have a muscularis mucosae or a submucosa layer. The wall thickening that occurs in adenomyomatosis involves hyperplasia of both the mucosa and muscularis.
Cholesterol Polyps. — The cholesterol polyp is by far the most common polypoid lesion found in the gallbladder, accounting for 60%–70% of lesions in some studies (2,17). It predominantly occurs in middle-aged women. Cholesterol polyps are typically multiple and need not be associated with gallstones (18). At gross examination, the diffuse form of cholesterolosis manifests as a bright red mucosa with interposed areas of yellow lipid, an appearance referred to as a “strawberry gallbladder” (19). Cholesterol polyps have no malignant potential (12).

At US, cholesterol polyps appear as small, round, smoothly contoured, intraluminal lesions that are attached to the wall. The stalk is rarely seen, an appearance that gives rise to the “ball on the wall” sign (Fig 3) (20). Cholesterol polyps are usually echogenic with no acoustic shadowing; however, particularly when multiple cholesterol polyps are confluent and/or larger than 1 cm, they cannot be definitively differentiated from other benign or malignant lesions at imaging.

propria. In adenomyomatosis, cholesterol accumulation is intraluminal, and crystals precipitate in bile trapped in intramural diverticula (Rokitansky-Aschoff sinuses) lined by the epithelial layer of the mucosa. Gallbladder wall thickening and intramural diverticula containing cholesterol crystals, or calculi, are pathognomonic of adenomyomatosis (16). In contrast, in cholesterol polyps, there is deposition of triglycerides and cholesterol esters within macrophages in the lamina propria, and the polyp is covered by normal epithelium.

Figure 1. Mobile sludge ball in a 37-year-old woman with abdominal pain. US images obtained with the patient lying down (a) and standing (b) show a polypoid intraluminal gallbladder mass (arrowhead) that moves to a different location in the gallbladder when the patient stands, a classic feature of a sludge ball. The presence of acoustic shadowing (arrow in a) indicates that small stones are likely present within the sludge ball.

Figure 2. Tumefactive sludge in a 62-year-old man with right upper quadrant abdominal discomfort. US images show a nonmobile polypoid mass (arrowhead) in the gallbladder that does not move when the patient changes position. Results of pathologic analysis confirmed the presence of sludge and underlying chronic cholecystitis.
Adenomyomatosis.—Adenomyomatosis may be seen in as many as 9% of cholecystectomy specimens and accounts for about 25% of all polypoid lesions in the gallbladder (17,21). The focal form of adenomyomatosis may be seen as a fundal polypoid lesion at imaging. The segmental form typically affects the body, demonstrates concentric circumferential wall thickening, and may give rise to an hourglass configuration of the gallbladder. Although some studies have reported an association between segmental adenomyomatosis and gallbladder cancer, others have not (21–24). Current thinking is that adenomyomatosis is not premalignant but may be seen in chronically inflamed gallbladders, which have a higher risk for developing cancer.

Imaging findings of adenomyomatosis parallel its histologic features: intramural diverticula that may be filled with inspissated bile and appear as multiple small cystic spaces that are anechoic at US. When the intramural diverticula contain sludge, stones, or papillary projections, they appear echogenic with multiple acoustic interfaces at US, creating twinkling or comet-tail artifacts (25). The cystic spaces may be visible at CT, which can help differentiate between fundal adenomyomatosis and gallbladder carcinoma (26). At MR imaging, the Rokitansky-Aschoff sinuses cause a “pearl necklace” sign of multiple round spaces that are hyperintense on T2-weighted images, a finding that has been reported to have 92% specificity for adenomyomatosis (Fig 4) (27). There have been reports of increased uptake of fluorine-18 fluorodeoxyglucose (FDG) within areas of adenomyomatosis at PET, a potential source of false-positive results when characterizing gallbladder lesions (28).

Inflammatory Polyps.—Inflammatory polyps represent 10% of all gallbladder polyps in surg-
cal series and are usually multiple and small, measuring less than 10 mm in diameter (17). They typically occur secondary to gallstones and chronic inflammation. It is thought that they develop from chronic deposition of cholesterol in the gallbladder wall and subsequent mucosal irritation, which leads to formation of granulation and fibrous tissue. As is the case with chronic cholecystitis, inflammatory polyps may lead to mucosal epithelial dysplasia (29). However, there is no definitive evidence that inflammatory gallbladder polyps have an increased risk for adenocarcinoma.

Tumorous Polyps

The most important considerations are epithelial lesions, adenoma, and adenocarcinoma. Benign mesenchymal tumors, such as leiomyomas, lipomas, neurofibromas, and neuroendocrine tumors, account for 1% of gallbladder polyps (17). Rarely, metastases and lymphoma may manifest as polypoid gallbladder lesions.

Adenomas.—Gallbladder adenomas are rare, occurring in 0.15% of all cholecystectomy specimens and accounting for 4%–7% of all gallbladder polyps (17,33). In contrast to colonic polyps, for which an adenoma-to-carcinoma sequence is well established, the role of gallbladder adenomas in the pathogenesis of gallbladder carcinoma is controversial (34). Studies, including genetic analyses, have shown that a dysplasia-to-carcinoma sequence is more likely to occur than malignant transformation of adenomas (35,36).

Adenomas may cause symptoms but are typically incidentally found. They are most frequently...
seen in patients with primary sclerosing cholangitis (PSC) and gastrointestinal polyposis syndromes, such as Peutz-Jegher and Gardner syndromes. Cytologically, gallbladder adenomas may be classified as having a pyloric (most common), intestinal, foveolar, or biliary subtype (34).

At US, gallbladder adenomas may vary in size (up to 20 mm), have a sessile or pedunculated appearance, demonstrate internal vascularity at color Doppler interrogation, and are typically solitary. At CT and MR imaging, gallbladder adenomas typically demonstrate enhancement similar to that of adenocarcinoma (Fig 6). Adenomas cannot be reliably differentiated from polypoid gallbladder adenocarcinoma at imaging.

Adenocarcinoma.—The most common malignant gallbladder polyp is primary adenocarcinoma of the gallbladder. It is the fifth most common gastrointestinal malignancy worldwide, with higher incidences in Chile and Japan (37). It is more commonly seen in women and the elderly.

Gallbladder carcinoma carries a very poor prognosis because it is often detected at an advanced stage. It has a strong association with gallstones; in one large autopsy series, over 95% of cases of gallbladder cancer had concomitant cholelithiasis (7). Chronic gallbladder inflammation may also lead to wall calcification—the so-called porcelain gallbladder—which is associated with gallbladder cancer. Other risk factors for gallbladder cancer include PSC, anomalous pancreaticobiliary ductal union, and most types of choledochal cysts (5,38–40). In patients with PSC, a substantial number (60%) of gallbladder polyps are malignant (Fig 7) (41).

Gallbladder adenocarcinoma is divided into multiple subtypes, the most common of which is the papillary form, although signet ring and mucinous adenocarcinomas, among others, also occur. Pathologically, papillary adenocarcinomas appear as densely cellular papillary fronds protruding into the gallbladder lumen, with dysplasia and increased mitoses (19). Although adenocarcinoma represents the overwhelming majority of primary gallbladder tumors, adenosquamous
Carcinoma, small cell carcinoma, and sarcomas have also been described; however, it is uncommon for these rare tumors to manifest as a polyp. Even less common are primary neuroendocrine carcinoma and melanoma of the gallbladder.

Gallbladder adenocarcinoma most commonly manifests as a mass in the gallbladder fossa, with engulfed gallstones or irregular eccentric gallbladder wall thickening at imaging. In 15%-25% of cases, it may manifest as an intraluminal polyp (13,42,43). US clues to a polypoid gallbladder carcinoma include a solitary polyp larger than 10 mm, a wide polyp base, focal wall thickening of more than 3 mm, and coexisting gallstones (Fig 8) (44). At color and spectral Doppler US, linear color signal at the polyp base and an increased resistive index...
Figure 7. Gallbladder adenocarcinoma in a 34-year-old man with long-standing PSC. Endoscopic retrograde cholangiopancreatogram shows classic irregular biliary duct strictures (arrowheads) and polypoid filling defects (arrows) along the gallbladder wall. Endoscopic US-guided biopsy demonstrated adenocarcinoma arising from PSC.

Figure 8. Synchronous gallbladder cancer in a 74-year-old man with esophageal cancer. (a) US image shows a 3-cm wide-based mass (arrowhead) with adjacent focal wall thickening (arrows). (b) Axial contrast-enhanced MR image shows the frondlike mass (arrowhead), which demonstrates enhancement. (c) Axial PET/CT image obtained to stage esophageal carcinoma shows the mass (arrowhead), which demonstrates marked FDG uptake. (d) Photomicrograph (original magnification, ×20; H-E stain) of a surgical specimen shows the dense cellularity and atypical architecture (arrowhead) of the fronds, an indicator of cancer. The cellular characteristics of malignancy were seen at higher-power evaluation.

may indicate a cancerous polyp (6). Diffuse or branched enhancement and an abruptly rising, persistent time-intensity enhancement curve at contrast-enhanced US have been associated with malignant gallbladder lesions (45).

Endoscopic US has been suggested as a superior modality to transabdominal US for imaging gallbladder lesions because of its use of high-frequency probes, which provide better resolution of small lesions (46). Endoscopic US may be useful for identifying benign features of a polyp—such as cystic spaces or comet-tail artifact, which is associated with adenomyomatosis—that may not be visible with a transabdominal approach (46). An endoscopic US scoring system to predict malignancy in a gallbladder polyp on the basis of its size, its internal echo pattern, and the presence of hyperechoic spotting has been suggested, with sensitivity and specificity of 78% and 83%, respectively (47).

FDG PET has also been shown to be useful in the setting of gallbladder cancer. Although it is chiefly used for staging in the setting of a known carcinoma, FDG uptake within a gallbladder polyp greater than that in the background liver is an indication of malignancy (Fig 8) (48). Delayed FDG uptake and retention of
radiotracer within a gallbladder lesion is a useful characteristic for diagnosing gallbladder malignancy (49). However, false-positive results may occur in the presence of acute cholecystitis, a limitation of FDG PET.

In the case of larger gallbladder polyps, CT and MR imaging can provide some of the same diagnostic information as US, namely, the shape, size, number, and location of lesions. At CT, lesions that are larger than 10 mm and visible on unenhanced images may be more likely to be malignant (50). Enhancement characteristics of gallbladder polyps at MR imaging, such as early prolonged enhancement without washout, which is more common in malignant lesions than in benign lesions, may be useful (51). Several studies have indicated that, at diffusion-weighted imaging (DWI), malignant gallbladder lesions tend to have a lower apparent diffusion coefficient (ADC) than do benign lesions (Fig 9) (52–54). It is best to incorporate DWI with the protocol for assessing hepatobiliary disease; the presence of hyperintensity on high-\(b\) value diffusion-weighted images may raise concern for malignancy in lesions that are indeterminate on MR images obtained with conventional sequences (55,56).

**Metastatic Disease and Lymphoma.**—Metastases to the gallbladder can occur with any primary malignancy and typically do so in the setting of widespread metastatic disease. In the western medical literature, the most common primary tumor to metastasize to the gallbladder is melanoma, which represents 60% of all gallbladder metastases (Fig 10) (57). In the Asian medical literature, the most common source of gallbladder metastases is gastric cancer (58). Cancers of the kidney and lung may hematogenously spread to the gallbladder, whereas hepatocellular carcinoma and cholangiocarcinoma...
may directly invade the gallbladder (Fig 11). Patients with gallbladder metastases are usually asymptomatic, but they may develop acute cholecystitis if the cystic duct becomes obstructed.

Lymphoma of the gallbladder is rare and occurs either as a primary tumor or, more commonly, as a result of secondary involvement of the gallbladder by adjacent lymphadenopathy. Because lymphoid tissue is not normally found in the gallbladder wall, it has been suggested that primary gallbladder lymphoma arises in the setting of chronic inflammation (59). The most common subtypes of lymphoma involving the gallbladder are diffuse large B-cell and mucosa-associated lymphoid tissue (MALT) lymphoma. As at other sites, lymphoma of the gallbladder may have varied appearances (59).

Management Algorithm

Although imaging features of gallbladder polyps may, at times, indicate a specific diagnosis, there is a large degree of overlap in the appearances of benign and potentially malignant gallbladder lesions. According to the management algorithm, which was determined by a review of the literature, management of gallbladder polyps primarily relies on the size of the lesion (Fig 12) (1,3,17,44,60,62–71). Two large series confirmed that a size larger than 10 mm is the best indicator of malignancy and warrants cholecystectomy (60,61).

There is controversy regarding the risk for malignancy in polyps that measure 6–10 mm. Some studies have reported that this risk is close to zero at long-term follow-up US (62–65). In a study of cholecystectomy specimens that were 6–10 mm at preoperative US, 7% were malignant (61). In general, incidental polyps of this size may be followed with serial imaging rather than being surgically removed. The frequency and duration of follow-up examinations has not been established. It is our practice to image polyps of this size after 6 and 12 months and, if they are stable,
to perform annual follow-up US. An increase in size to more than 10 mm or the onset of biliary symptoms may indicate a need for surgery. Management of polyps that measure 5 mm or less is also not clearly established. A study found that, among patients with sub–5-mm polyps at preoperative US, no focal lesion was seen in cholecystectomy specimens from more than 80% of patients (66). Another study reported that 24% of sub–5-mm polyps were not seen at follow-up US (63). It is probable that a substantial number of polypoid lesions of this size are adherent stones or sludge. A recent large study suggested that polyps of this size have no malignant potential and may be ignored (67). In our practice, we do not follow up patients with pedunculated polyps smaller than 5 mm. It is important to note that the size of a gallbladder polyp should not be viewed in a vacuum. 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. In addition, patients with PSC should be considered for cholecystectomy if a gallbladder polyp of any size is identified (5). The role of contrast-enhanced and endoscopic US in determining management of smaller polyps requires further research.

Conclusions
Imaging plays a pivotal role in evaluation of gallbladder polyps, not only in determining lesion size but also in depicting other important findings. The radiologist must integrate imaging findings with clinical features to determine the risk for gallbladder malignancy and recommend management.

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