EDITORIAL

Polypoid Lesions of the Gallbladder: Diagnostic and Management Challenges

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Since the use of ultrasonography (US) imaging technique became widespread and popular, detection of polypoid lesions of the gallbladder (PLG) has increased significantly [1-4]. Initial studies estimated that PLGs are found in 2.6% to 12.1% of cholecystectomy specimens [4]. In a large study of 3,608 Danish subjects, the prevalence of PLG was found to be 4.6% for men and 4.3% for women, and, similar to other studies, these lesions had a higher prevalence in the third and fifth decades of life. Currently, most agree that the average prevalence of PLG in cholecystectomy specimens is about 3% to 12%.

Early studies using autopsy material and cholecystectomy specimens found that the majority of gallbladder polypoid lesions are benign, most commonly of the cholesterol polyp type [5]. Subsequent studies have been carried out preoperatively using ultrasonography, other radiological techniques, and, lately, newer imaging modalities.

In general, the sensitivity of US in detecting PLG ranges from 36% to 90%, and may reach 99% if no gallstones are present, because gallstones may obscure polypoid lesions [3]. A thick gallbladder wall may also mask small polyps. The prevalence of PLG found by US studies is 3% to 6% in healthy populations. In a review of 100 cases of PLGs, Terzi and coworkers showed that of 34 patients without gallstones, PLGs were diagnosed by US in 25 patients (74%). In contrast, of 66 patients who had both PLGs and gallstones, US diagnosed the PLGs in only 11 patients (17%) indicating that coexistence of gallstones and PLGs decreases the sensitivity of preoperative detection of PLGs [4]. Other imaging studies, including oral cholecystography, computed tomography and endoscopic cholangiopancreatography (ERCP) appear less sensitive than US in diagnosing PLG.

More recently, several studies have evaluated the utility of endoscopic ultrasonography (EUS) and positron emission tomography (PET) scan for diagnosing PLG. In one study, 89 patients were evaluated preoperatively by US and EUS, and the latter was found to be more accurate in detecting PLG; 86.5% of these polyps were accurately diagnosed by EUS, while only 51.7% were diagnosed by US [6]. In another study, 65 PLGs evaluated preoperatively by both US and EUS and compared with subsequent histologic diagnosis on resected specimens, showed that EUS differentiated PLG more precisely than US (97% vs. 71%). The authors recommended the routine use of EUS for the differential diagnosis of PLG when US does not show features of cholesterol polyp or adenomyomatosis [7].

Histologic classification and identification of the nature of PLG remains a dilemma. It is well established that this is an uncommon group of heterogeneous neoplastic and non-neoplastic lesions [8-12]. In fact, the classification of PLG was very confusing until the introduction of an acceptable, meaningful and simplified classification of benign tumors and pseudotumors by Christensen and Ishak in 1970, based on a large study of 180 such lesions [5]. A recent comprehensive review in 2002 of benign tumors and tumorlike lesions of the gallbladder and extrahepatic bile ducts conducted by the Armed Forces Institute of Pathology (AFIP) provided in-depth classification and detailed description of the radiologic and clinicopathologic features of each of these individual lesions [11]. This by far is the most detailed study on the subject in the English literature with thorough descriptions of each specific entity.

Most PLGs are benign non-neoplastic lesions that only rarely cause symptoms. The most common type of PLG, as reported in several large studies, is the cholesterol polyp (up to 70%). Polypoid pseudotumors include adenomatous and adenomyomatous hyperplasias, heterotopias, and inflammatory polyps. Benign tumors include adenomas, hemangiomas, lipomas, leimyomas and granular cell tumors. Adenomas or adenomyomatous polyps are very rare, and, in one large study, were discovered in only 9 of 2145 (0.4%) patients who underwent cholecystectomy for gallbladder disease [10].

We read with great interest the recent case report of a gallbladder pyloric-type adenoma by Constanza et al.
in the March issue of the *Journal of Gastrointestinal and Liver Diseases* [13]. These authors describe an unusual case of gallbladder adenoma in a 77-year-old woman who had imaging studies suspicious for gallbladder tumor. The cholecystectomy revealed a 15x15x10 mm tubular adenoma with pyloric-type glands and inflammatory infiltrate. As noted earlier, gallbladder adenomas are rare but well documented benign epithelial tumors. They are usually found incidentally in cholecystectomy specimens or during preoperative imaging studies, especially US, for abdominal pain [11,12]. Although they are usually asymptomatic, they may present as a result of associated symptomatic gallstones, or from cystic duct obstruction due to large adenoma. Adenomas may be sessile, pedunculated or just polypoid projections, and most are accompanied by gallstones. Histologically, they can be tubular, papillary or tubulopapillary. The tubular type is most prevalent and is composed of pyloric or intestinal type glands. These adenomas often coexist with hyperplastic and metaplastic lesions, may contain heterogeneous cell populations, and may show a wide range of morphologic patterns that further complicate the histologic interpretation. Only a small proportion of gallbladder adenomas appear to progress to carcinoma [11, 12]. Kijima et al studied 51 early gallbladder carcinomas and found evidence of tubular adenomas in 7 (13.7%) [12].

We also had similar observations of PLGs at our institution. In our experience, cholesterol polyps are the most commonly encountered. We have seen fair number of non-neoplastic inflammatory lesions, adenomas, adenomyomas, and adenocarcinomas. The vast majority of the adenocarcinomas were *de novo* cancers without preexisting adenomas.

Investigations indicate that the most accepted incidence rate of malignancy in PLG is 3% to 8% [3]. In a study by Yeh et al of 123 PLGs found in cholecystectomy specimens, 116 (94.3%) were benign and 7 (5.7%) were malignant [7]. This study revealed that 4% of all laparoscopic cholecystectomies contained polypoid lesions. There are rare reports of unusual gallbladder polypoid lesions such as adenocarcinoma arising from polyps in patients with primary sclerosing cholangitis. As a result of increased risk of biliary and colon cancers in such patients, it is recommended to perform cholecystectomy in these patients for PLG, even when it is less than 1.0 cm in size [13]. An unusual polypoid leiomyosarcoma associated with adenomyomatous hyperplasia and gallbladder stones has also been reported [14].

Although most PLGs are benign, whether neoplastic or non-neoplastic, preoperative diagnosis and differentiation from gallbladder cancer is critical and remains difficult. In the study by Terzi et al of 100 cases of PLGs confirmed in cholecystectomies (36 were diagnosed by preoperative US evaluation), 74 were benign and 26 were malignant (4). Also, in the same study, 66 patients had associated gallstones; 44/74 (59%) were in patients with benign PLGs, and 22/26 (85%) were in patients with malignant PLGs, clearly indicating higher incidence of malignant PLGs in patients with gallstones. Several other studies attempted to assess the preoperative features that distinguish benign from malignant PLG. In one study that correlated clinical and US findings with postoperative histologic examination, risk factors for malignancy were patient age over 60 year, coexistence of gallstones, and PLG size over 1.0 cm. The authors recommended that these patients should undergo cholecystectomy, while asymptomatic patients under 60 years old with PLG smaller than 1.0 cm and not associated with gallstones should be evaluated with regular US examinations [4]. Several studies were conducted to identify the indications for cholecystectomy in patients with PLG [4, 15-17]. Yeh and coworkers, using multivariate analysis, showed that the age (more than 50 years) and size of lesion (more than 1.5 cm) are significantly correlated with neoplastic lesions [15]. However, size of the lesion (more than 1.5 cm) was the only independent factor predicting malignancy in PLG. Other investigators concluded that operative indications for PLG include: maximum diameter of 1.0 cm or more, patient over 50 years old with a single wide base lesion, coexistent gallstones, and PLG with an irregular thickened gallbladder wall [2]. Chijiwa and Tanaka also found that 44 of 716 consecutive cholecystectomies had preoperatively diagnosed PLG (32 benign and 12 malignant). They noted that lesion size (> 10 mm), number of polyoid lesions (single) and patient age (> 60 year-old) were significant indicators of malignancy [18].

The introduction of EUS during the last several years has added more promise in our ability to discriminate benign from malignant PGLs in the preoperative setting [6, 7]. Preoperative determination of a benign lesion of the gallbladder may have significant implications on the treatment and management, and therefore early detection of a malignant PLG can result in satisfactory outcome after surgery.

Most authors now believe that the majority of gallbladder adenocarcinomas arise from flat dysplasia, and only few arise from preexisting adenomas [19-23]. Many authors consider the metaplasia, dysplasia, adenocarcinoma in-situ sequence to be the usual pathway for the development of gallbladder cancer. Some studies have investigated tumor markers and molecular abnormalities by immunohistochemical staining and reported involvement of certain oncogenes, such as p16, p53 and p21, in the carcinogenesis process. More recently, microsatellite instability (MSI) was investigated in 59 surgical specimens of gallbladder adenocarcinoma [24] by Polymerase Chain Reaction (PCR) method. It was found that premalignant lesions adjacent to the cancers MSI were detected in dysplasias (83%) and metaplasias (33%) indicating that inactivation of mismatch repair genes occurs early in gallbladder carcinogenesis.

In conclusion, we believe that PLGs are interesting not uncommon lesions and that it is difficult to predict their significance. Ultrasonography remains the most sensitive and practical method for their preoperative detection and diagnosis. The majority of them are benign neoplastic or non-neoplastic in nature, although they can rarely be malignant. Using generally agreeable criteria of size (>1.0 cm), patient’s
age (>50 year) and presence of gallstones can usually predict malignant PLGs. Symptomatic and solitary PLGs are also in favor of malignant lesions. Benign PLGs can usually be managed conservatively by regular follow-up US studies every 3-6 months initially and then annually. Suspected malignant PLGs require surgical intervention and removal by open exploration, while laparoscopic cholecystectomy is sufficient for suspected benign lesions.

References