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Dysplasia in Gallbladder: What Should We Do?

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Abstract

Introduction On occasional cholecystectomies, pathologists encounter incidental dysplasia in the gallbladder mucosa in the sections submitted per protocol for histologic examination. If dysplasia is identified, additional sections are taken and/or the gallbladder is entirely submitted to rule out underlying adenocarcinoma. The aim of our study was to assess the incidence of subsequent identification of invasive adenocarcinoma on additional sections, after an incidentally detected dysplasia was noted on a routine cholecystectomy section. We also aimed to study the significance of the incidental detection of dysplasia and adenocarcinoma, as well as showing the association of gallbladder dysplasia to synchronous or metachronous dysplasia/neoplasia in the biliary tract.

Material and Methods Our study was approved by the Institutional Review Board. We retrospectively identified 41 consecutive cases of routine cholecystectomies from 1991 to 2017, which had no clinical suspicion of neoplasia, and did not have any identifiable mass lesion, but on histopathologic analysis, had neoplasia (adenocarcinoma in 4 cases, and dysplasia in 37 cases). The pathologies of all cases were reviewed, and the diagnosis and grade of dysplasia were confirmed. The clinical information was obtained from the electronic medical records.

Results Of the 37 cases with dysplasia, 10 (27%) had high-grade dysplasia (HGD) and the remaining showed low-grade dysplasia (LGD). All 4 cases of adenocarcinoma had some gross abnormalities (such as porcelain gallbladder, or ruptured, thickened, and roughened walls, or a granular mucosa). In contrast, none of the 37 cases with dysplasia had any gross abnormality. In 24 (of 37) cases of dysplasia, additional sections were submitted (median 8; ranging from 2 to 29), and in 11 cases, the gallbladder was entirely submitted. None of these cases showed any additional pathologic finding on the extra sections. Interestingly, 7 cases with dysplasia (18.9%; 6 LGD and 1 HGD) were associated with a concomitant pancreatobiliary malignancy. For the remaining 30 cases, follow-up information was available in 16 cases (53.3%) with a mean follow-up of 76.5 months (ranging from 12 to 204 months). None of these showed any subsequent development of pancreatobiliary neoplasms.

Conclusion Incidentally detected gallbladder dysplasia in a cholecystectomy specimen, without any gross abnormality, has almost no risk of a hidden invasive carcinoma. Although cholecystectomy is sufficient treatment for gallbladder dysplasia, in our study cohort, 18.9% of cases with incidental dysplasia in gallbladder had an associated pancreatobiliary carcinoma, which supports the hypothesis of multifocal neoplastic potential in the pancreatobiliary tree (also known as field effect). Although follow-up on 16 cases shows no subsequent development of any other pancreatobiliary neoplasm, this number is probably not enough to rule out a serial imaging follow-up of patients who have reported dysplasia in their gallbladder, to assess for subsequent development of neoplasia elsewhere in the pancreaticobiliary tree.

Keywords Gallbladder · Incidental dysplasia · Hepatobiliary malignancies · Follow-up

Introduction

Cholecystectomy is one of the most common surgical procedures performed in the USA. Gallbladders are removed either as a part of a complex resection (such as liver transplants and pancreatoduodenectomies for pancreatic head, ampullary, or duodenal lesions) or exclusively for symptomatic gallbladder disease, mostly inflammatory in nature. Rarely, a gallbladder mass may be detected preoperatively, and after appropriate staging, a definitive resection is undertaken, often locoregionally extensive,

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such as combined with hepatic resection, lymphadenectomy, and with or without bile duct excision. At our institution, all cholecystectomy specimens are routinely sent for histopathological evaluation. An overwhelmingly majority of the cases show chronic and sometimes acute inflammation, with or without cholelithiasis and/or cholesterolosis. Infrequently, there can be a focal lesion, spanning a spectrum of benign to malignant neoplastic processes.

Rarely, routine histopathologic examination reveals incidental low- or high-grade dysplasia without any clinical, radiographic, or gross abnormality. This raises concern for an unapparent invasive adenocarcinoma in the gallbladder, resulting in additional tissue being submitted for evaluation. The incidence of gallbladder dysplasia is variably reported to range from 3.3%[1] to as low as 0.25%.[2] This incidence is highly dependent on sampling and the clinical judgment when grossing these specimens. Sasatomi et al. have recommended submitting up to 3 sections for adequate sampling.[3] However, when incidental dysplasia is identified, the common practice is to submit additional sections and sometimes even submitting the entire gallbladder for histologic evaluation. The aim of our study is to evaluate the incidence and significance of adenocarcinoma associated with incidentally detected dysplasia in gallbladder. We also aim to show the association of gallbladder dysplasia to synchronous or metachronous dysplasia/neoplasia elsewhere in the biliary tract.

Materials and Methods

This was an IRB-approved study conducted at Washington University School of Medicine and Barnes-Jewish Hospital. We performed a retrospective search in our database to identify all cases of dysplasia and incidentally detected adenocarcinoma in routine cholecystectomies, from Juanuary 1991 to August 2017. Certain key words were used in our search, including "gallbladder," "cholecystectomy," "dysplasia," and "carcinoma." Final selection of cases was based on the review of clinical history and availability of archival slides for histologic review. All clinical and follow-up information were retrieved from the electronic medical records. All archival H&E slides were reviewed by two pathologists (RR, DC) to confirm the diagnosis and classify the grade of dysplasia into low and high grades. No special stains or immunohistochemical stains were used. Epithelia showing nuclear enlargement, hyperchromasia, pseudostratification, and increased mitoses, but without conspicuous nucleoli and loss of polarity, were classified as low-grade dysplasia (LGD). Epithelia showing nuclear atypia with pleomorphism, rounding, prominent nucleoli, and loss of polarity were classified as high-grade dysplasia (HGD). All cases were routinely submitted for histology to include the cystic duct margin (inked) and a representative section of the gallbladder wall from the neck, body, and fundus. If dysplasia was identified, the standard practice in our department during this time was the submission of additional sections for further evaluation and in some cases the entire gallbladder.

Results

After reviewing the pathology report and the archival slides among routine cholecystectomy cases, 37 cases with dysplasia were identified (24 females and 13 males), along with 4 cases of incidentally detected adenocarcinoma (3 females and 1 male), yielding a total of 41 cases ($n = 41$). During the same time period (January 1991 to August 2017), a total of 19,262 cholecystectomies were performed at our institution, giving an incidence rate for incidental gallbladder dysplasia at 0.19%, and the incidence of incidental carcinoma at 0.02%. The median age of patients with dysplasia was 67.5 (33–91 years) and incidental carcinoma was 70 (57–85 years). Of the 37 cases of dysplasia, 10 cases (27%) showed the presence of HGD (Fig. 1a) and the remaining showed LGD (Fig. 1b). None of these cases had any gross abnormality, such as intramural mass/focal thickening identified. In contrast, all 4 cases with a diagnosis of incidental adenocarcinoma had some gross abnormality. The gross lesions included 1 case with porcelain gallbladder (Fig. 1c), 2 cases with focally thickened and roughened wall with extensive adhesions leading to piecemeal surgery or rupture during surgical maneuver, and 1 case with an abnormal area of granular mucosa, distinct from the background mucosa (Fig. 1d). In 24 cases of dysplasia (64.9%), additional sections were submitted (median 8; ranging from 2 to 29), and in 11 cases (29.7%), the gallbladder was entirely submitted. None of these cases showed any additional pathologic findings. Interestingly, 7 cases with dysplasia (6 LGD and 1 HGD) were associated with concomitant pancreatobiliary malignancies (3 cases of pancreatic adenocarcinoma and 2 cases each of hepatocellular carcinoma and extrahepatic cholangiocarcinoma). The concomitant pancreaticobiliary malignancies were the primary reason for the surgery in all of these cases. Gallbladder was part of the routine specimen in the complex resection, and dysplasia was identified incidentally in the gallbladder. For the remaining 30 cases, follow-up information was available in 16 cases (53.3%) with a mean follow-up period of 76.5 months (ranging from 12 to 204 months). None of these patients showed any subsequent development of pancreatobiliary neoplasms.

Discussion

Epithelial dysplasia is a recognized premalignant condition that predisposes to gallbladder carcinoma.[3] Flat epithelial dysplasia has no abnormalities on gross examination in contrast to other premalignant conditions such as adenomas or anomalous

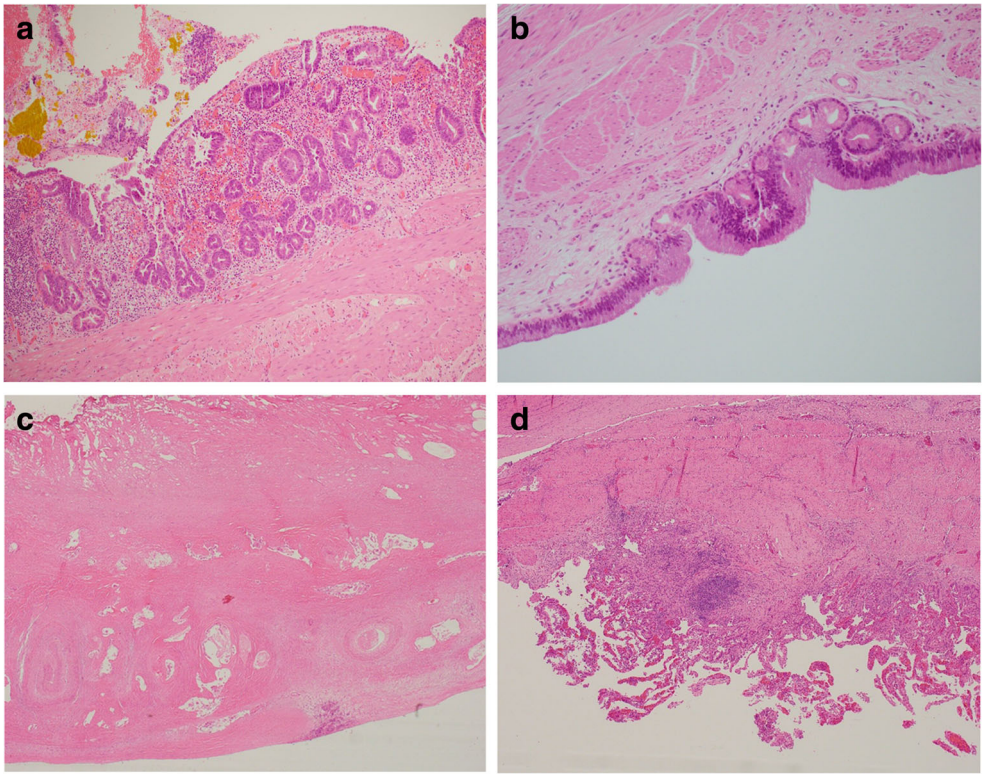

Fig. 1 **a** Epithelium showing nuclear atypia with pleomorphism, rounding, prominent nucleoli, and loss of polarity, classified as high-grade dysplasia. **b** Epithelium showing nuclear enlargement, hyperchromasia, pseudostratification, and increased mitoses, but without conspicuous nucleoli and loss of polarity, classified as low-grade dysplasia. **c** Inflammatory scarring of the gallbladder wall "porcelain gallbladder" can be a gross finding associated with underlying adenocarcinoma. **d** Granular mucosa of the gallbladder wall can also be a gross finding associated with underlying adenocarcinoma

pancreaticobiliary junction. Long-standing chronic inflammation with gallstones (over 10–15 years) has also been identified as a potential risk factor for developing atypia, dysplasia, and carcinoma, particularly if there is development of porcelain gallbladder.[4]

While it is important to be aware of the pathologic conditions that predispose to gallbladder cancer, the incidence of cancer in routine cholecystectomy specimens is extremely low, with a reported incidence of 0.25%.[2] Even in association with grossly identifiable precancerous lesions such as intracholecystic papillary-tubular neoplasms, the incidence of invasive carcinoma is reportedly 56%, and mainly occur in a background of extensive high-grade dysplasia.[5] In the Chilean population where the incidence of gallbladder carcinoma is one of the highest, the incidence of invasive carcinoma is not commonly associated with incidental dysplasia of the gallbladder mucosa.[6] Another study by Dowling et al. reported only 1 case of dysplasia in 277 cholecystectomy specimens.[7]

While it may seem logical to assume that submitting more sections should help identify microinvasions,[8] our results show this practice to be fruitless. In our study, all four incidentally detected gallbladder adenocarcinomas were associated with a gross abnormality. In contrast, all the cases with dysplasia had no gross lesion. In addition, the question arises as to what is the significance of dysplasia even if microinvasion is present.[9] Per NCCN guidelines (version 2.2018) and supported by several studies, a simple or laparoscopic cholecystectomy is sufficient treatment for gallbladder adenocarcinoma presenting at stage T1a.[10] In those cases if a clean resection margin is obtained, the 5-year overall survival is 100%.[11–13]

Among other studies in literature, related to submission of additional sections for detection of gallbladder carcinoma when incidental dysplasia is noted, one of the biggest is by Renshaw et al., who reviewed 16,611 gallbladder resections. They found 90 cases (0.05%) with dysplasia, of which 9 were high-grade dysplasia and 81 low-grade dysplasia; however, all of the cases were identified on the initial section submitted.[9] They then subsequently submitted a median of 37 extra sections without yielding any additional information, and concluded that a maximum of 4 sections should suffice for complete examination.

In our study, additional sampling led to no additional or beneficial information for our clinicians. Despite reporting dysplasia, our clinical team feels there is no additional therapeutically helpful or beneficial options that may be presented to the patients. Of the 37 cases of dysplasia that we studied retrospectively, not all cases had the correct grade of dysplasia classified in the original report; however, our clinical team indicated that it did not affect any of their further management. They did not require an addend report to that effect. This is quite a contrast to the stress it poses to a pathologist when confronting a case of dysplasia in the gallbladder. Submitting the gallbladder entirely or submitting multiple additional sections significantly increases the laboratory costs on the other hand. The cost to process each additional block has been estimated to be 20

dollars in our laboratory, which is a busy academic center. We assume, the costs could be even more in a smaller setup. The reimbursement based on standard billing codes for the lab on the other hand, is per specimen, not per block. Apart from direct costs involved in processing of the specimens, it consumes more professional time involved in the additional grossing, microscopic evaluation, and peer review. It also delays reporting of the case. More importantly, it causes unnecessary panic in rendering such a diagnosis. Therefore, after reviewing other studies, analyzing our own data, and speaking to our clinical team, we feel strongly that the practice of submitting extra sections when there is no focal abnormality on careful gross examination is unnecessary. In our cohort, 6 cases with LGD and 1 case with HGD had a concurrent pancreatobiliary malignancy, including pancreatic adenocarcinoma and hepatocellular carcinoma. Current literature suggests that patients with dysplastic gallbladders develop future biliary tract malignancies[9] but the management and prophylactic treatment as this point are unclear. In 16 cases with dysplasia, follow-up information was available, with a mean follow-up of 76.5 months. There was no subsequent hepatic or pancreatobiliary tree neoplasm identified. Additional studies are needed to establish the relationship of gallbladder dysplasia to other pancreatobiliary neoplasms.

Conclusion

Not only clinically suspicious, but even incidentally detected gallbladder adenocarcinomas present with abnormal gross findings. On the other hand, dysplasia in gallbladder has no grossly identifiable abnormality. In the absence of gross findings, submission of additional sections in cholecystectomies to search for a hidden gallbladder carcinoma is a futile exercise. The significance of detection of incidental dysplasia in gallbladder however may lie in the association with other pancreatobiliary neoplasms, which need further studies for validation. This may therefore affect the follow-up of patients who have an incidental detection of gallbladder dysplasia on routine cholecystectomy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Albores-Saavedra J, Henson DE, Klimstra DS. In: Rosai J, ed. Tumors of the Gallbladder, Extrahepatic Bile Ducts and Ampulla of Vater. 3rd ed. Washington, DC: Armed Forces Institute of Pathology; 2000.
2. Wrenn SM, Callas PW, Abu-Jaish W. Histopathological examination of specimen following cholecystectomy: Are we accepting resect and discard?. Surg Endosc. 2017;31(2):586–593.
3. Sasatomi E, Tokunaga O, Miyazaki K. Precancerous conditions of gallbladder carcinoma: overview of histopathologic characteristics and molecular genetic findings. J Hepatobiliary Pancreat Surg. 2000;7:556–567.
4. Fairweather M, Balachandran VP, D'Angelica MI. Surgical management of biliary tract cancers. Chin Clin Oncol. 2016;5(5):63.
5. Argon A, Barbet FY, Nart D. The Relationship Between Intracholecystic Papillary-Tubular Neoplasms and Invasive Carcinoma of the Gallbladder. Int J Surg Pathol. 2016;24(6):504–11.
6. Duarte I, Llanos O, Domke H, Harz C, Valdivieso V. Metaplasia and precursor lesions of gallbladder carcinoma. Frequency, distribution, and probability of detection in routine histologic samples. Cancer. 1993;72(6):1878–84
7. Dowling GP, Kelly JK. The histogenesis of adenocarcinoma of the gallbladder. Cancer 1986; 58:1702–8.
8. Bivins BA, Meeker WR Jr, Weiss DL. Carcinoma in situ of the gallbladder: a dilemma. South Med J. 1975;68:297–300.
9. Hartman Renshaw AA, Gould EW. Submitting the entire gallbladder in cases of dysplasia is not justified. Am J Clin Pathol. 2012;138(3):374–6.
10. Lee SE, Jang JY, Lim CS, Kang MJ, Kim SW. Systematic review on the surgical treatment for T1 gallbladder cancer. World J Gastroenterol. 2011;17(2):174–80.
11. Benoist S, Panis Y, Fagniez PL. Long-term results after curative resection for carcinoma of the gallbladder. French University Association for Surgical Research. Am J Surg 1998; 175: 118–122
12. You DD, Lee HG, Paik KY, Heo JS, Choi SH, Choi DW. What is an adequate extent of resection for T1 gallbladder cancers?. Ann Surg 2008; 247: 835–838
13. Ogura Y, Mizumoto R, Isaji S, Kusuda T, Matsuda S, Tabata M. Radical operations for carcinoma of the gallbladder: present status in Japan. World J Surg 1991; 15: 337–343