Early Gallbladder Carcinoma
A Clinicopathologic Study of 13 Cases of Intramucosal Carcinoma

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Abstract
We report the clinicopathologic features of 13 cases of intramucosal carcinoma (IMC) of the gallbladder. All IMCs were incidental findings in cholecystectomy specimens for cholelithiasis. However, one of the patients had a carcinoma of the pancreas, and the gallbladder incidentally removed during the Whipple procedure showed an IMC. Another patient had a small cell carcinoma of the gallbladder, and one of the sections showed an IMC. Of the IMCs, 10 were well-differentiated adenocarcinomas, 1 was a moderately differentiated adenocarcinoma, 1 was an undifferentiated carcinoma, and 1 was a squamous cell carcinoma. Of the patients, 8 were disease-free from 3 to 11 years, and 2 patients died, one as a result of the pancreatic ductal carcinoma and the other with disseminated metastases of the small cell carcinoma. The follow-up of another patient was too short to be significant. Two patients were lost to follow-up. Our findings suggest that a simple cholecystectomy is a curative procedure for IMCs of the gallbladder.

The prognosis of carcinoma of the gallbladder continues to depend primarily on the extent of the tumor and histologic type.1-3 Depth of tumor invasion and the presence of regional or distant metastasis are the most significant prognostic factors.1-3 Invasive papillary carcinomas are characterized by a less aggressive clinical course than conventional adenocarcinomas and mucinous and adenosquamous carcinomas.1-3 The 5- and 10-year relative survival rates of small cell carcinoma of the gallbladder are 8% and 0%, respectively.4,5 Because early gallbladder carcinomas are usually asymptomatic, they are most commonly detected incidentally in gallbladders removed for cholelithiasis, a procedure now generally performed laparoscopically. When incidental carcinomas are detected in laparoscopic cholecystectomy specimens, reoperation with resection of the gallbladder bed, cystic duct remnant, and portal lymph nodes provides improved survival for patients with carcinomas invading into the muscularis or through the wall into adjacent soft tissues.5

In 1986, we described and illustrated the first example of intramucosal carcinoma (IMC) of the gallbladder, which was an incidental finding in a cholecystectomy specimen for cholelithiasis.7 At that time, the clinical course of this early stage of gallbladder carcinoma, defined as invasive carcinoma confined to the lamina propria (pT1a), was unknown. To our knowledge, there have been no studies of IMC of the gallbladder to determine the clinical behavior of these tumors and the best form of surgical management. Because of the higher rates of laparoscopic cholecystectomies in the treatment of gallstone disease, more cases of early gallbladder carcinoma are now being detected, and, consequently, we are beginning to better understand the patient outcomes after cholecystectomy alone.
The purposes of this study were to describe the clinicopathologic features of 13 cases of IMC of the gallbladder, define morphologic criteria for diagnosis, determine the survival rate of the patients, and make therapeutic recommendations.

Materials and Methods

From the personal consultation files of 2 of us (J.A.-S., 12 cases and D.S.K., 1 case), 13 cases of IMCs were retrieved and evaluated. H&E-stained sections were available for review in all 13 gallbladders, which were submitted in total. An average of 11 sections per case was examined. The histologic grading and subtyping of the carcinomas were defined according to previously described criteria. In addition, immunostains for cytokeratin (CK) 7 and CK20 were examined in 7 cases. In 4 of these 7 cases, immunostains for MUC1, MUC2, and CDX2 were also reviewed, as were the corresponding control samples. Follow-up was obtained through the referring physicians or the clinical charts.

Results

All IMCs were not recognized grossly and were incidental microscopic findings in cholecystectomy specimens for cholelithiasis; they were pT1a, as defined by the American Joint Committee on Cancer. The age of patients at diagnosis ranged from 42 to 79 years (mean age, 63 years) with a female predominance (9 women and 4 men). A diagnosis of carcinoma of the gallbladder was not suspected preoperatively in any of the patients. However, one of the patients had a clinically diagnosed carcinoma of the head of the pancreas that proved to be a well-differentiated ductal carcinoma, intestinal type. During the Whipple procedure, the gallbladder was removed because of cholelithiasis and contained an undifferentiated IMC. Another patient had a small cell carcinoma of the gallbladder that was extensively sampled. One of the sections showed an incidental IMC in proximity to but separated from the small cell carcinoma.

Of the patients, 11 underwent laparoscopic cholecystectomies, 1 patient was treated with a Whipple procedure and a cholecystectomy, and 1 patient underwent an open cholecystectomy. No patient was subjected to surgical reexploration or hepatic resection, and none of the patients with only IMC of the gallbladder received chemotherapy or radiotherapy. Of the 13 patients, 8 were disease-free from 3 to 11 years (mean, 4.8 years) after cholecystectomy; 2 died, one as a result of ductal carcinoma of the pancreas and the other with disseminated metastases of small cell carcinoma of the gallbladder, tumors coincident but unrelated histologically to the IMC of the gallbladder. The follow-up of 1 patient was too short to be significant, and 2 patients were lost to follow-up.

Microscopic Pathology

Of the 13 IMCs, 2 were polypoid and 1 arose in a tubular adenoma pyloric type. Classification of the IMCs resulted in 10 classified as well-differentiated adenocarcinomas, 1 as a moderately differentiated adenocarcinoma, 1 as an undifferentiated carcinoma, and 1 as a squamous cell carcinoma. Of the carcinomas, 7 had an intestinal phenotype (CK20+, MUC2+,
and CDX2+), 5 a biliary phenotype (CK7+ and MUC1+), and 1 a squamous phenotype. A dense inflammatory infiltrate was seen in 2 IMCs (Image 3). The undifferentiated carcinoma arose in a background of cholesterolosis (Image 4). The IMC that arose in a tubular adenoma pyloric type had an intestinal phenotype (Image 5A). All tumors expanded the lamina propria, but the muscle layer was not involved.

The mucosa adjacent to 11 IMCs showed high-grade dysplasia/carcinoma in situ. A desmoplastic stroma was present in only 1 IMC, and there was no lymphovascular invasion in any of the tumors. The cystic lymph node was examined in 7 cases and was free of tumor. The autopsy of the patient with small cell carcinoma did not reveal adenocarcinoma in any of the metastases. A biopsy of a metastatic deposit from the patient with carcinoma of the pancreas revealed a well-differentiated ductal carcinoma intestinal type similar to the primary pancreatic tumor and unlike the undifferentiated IMC of the gallbladder.

**Image 2**  
**A**, Low-power view of an intramucosal adenocarcinoma that coexisted with but was separated from a small cell carcinoma (arrow) (H&E, ×10).  
**B**, Higher magnification of the neoplastic glands lined by columnar cells with an intestinal phenotype. An abnormal mitotic figure is seen (H&E, ×250).

**Image 3**  
**A**, Well-differentiated intestinal-type adenocarcinoma containing few goblet cells. Small clusters of neoplastic cells including signet ring cells infiltrate the lamina propria between neoplastic glands (arrow and inset) (H&E, ×25).  
**B**, Moderately differentiated intramucosal carcinoma containing a dense lymphocytic infiltrate (H&E, ×30).
IMCs have been described and characterized in the esophagus, stomach, and colon. They have been the source of controversy regarding clinical course and surgical management. Depending on the origin of the carcinoma, some authorities have advocated conservative endoscopic treatment, whereas others have recommended a more aggressive surgical approach because a small proportion of IMCs may recur or metastasize. IMCs of the gallbladder are practically unknown, and, therefore, little is known about their demographics, histologic features, and biologic behavior. Similar to invasive gallbladder carcinomas that extend beyond the lamina propria, IMCs are more common in females. However, the mean age of patients is 8 years younger than patients with invasive carcinomas that extend beyond the lamina propria.

As IMCs of the esophagus, stomach, and colon, those arising in the gallbladder were confined to the expanded lamina propria. In contrast with colonic and similar to esophageal and gastric IMCs, the vast majority of IMCs of the gallbladder developed through the high-grade dysplasia carcinoma.
sequence. Of the 13 IMCs, 11 were associated with high-grade dysplasia/carcinoma in situ in the gallbladder mucosa adjacent to the tumors. Only 1 of the 13 gallbladder tumors reported herein arose in a tubular adenoma pyloric type, again emphasizing that most gallbladder IMCs arise from flat dysplastic precursors rather than polyoid adenomas. All 13 IMCs expanded the lamina propria, but only 1 showed a desmoplastic stromal response, a finding also typical of IMCs of the tubular gastrointestinal tract. There was no vascular invasion in any of the tumors. Most gallbladder IMCs (11/13) were well- or moderately differentiated adenocarcinomas, one was classified as undifferentiated carcinoma, and another was classified as squamous cell carcinoma. There were no cases of signet ring cell carcinomas, as have been described in the stomach and the colon. However, we have described 2 cases of signet ring cell carcinoma in situ of the gallbladder similar to those reported in the stomach and colon.5

As indicated, 2 patients in our series died with second-primary synchronous carcinomas. These 2 cases serve to emphasize the propensity for multicentric neoplasia within the pancreaticobiliary tree, as previously reported.15-17 Furthermore, these examples have led to the concept that a field of carcinogenesis exists in the gallbladder, extrahepatic bile ducts, ampulla, and pancreas.18 Carcinomas have co-occurred in the gallbladder, extrahepatic bile ducts, ampulla, and in the pancreas, all foregut derivatives that have a common embryologic origin.15-17,19,20 Metachronous multiple biliary cancers have been reported in only 12 cases.21,22 In 1 case, metachronous bile duct carcinoma developed 9 years after resection of a primary gallbladder cancer.23 Double primary cancers of the gallbladder and extrahepatic biliary ducts not associated with an anomalous junction of the pancreatico-biliary duct system have also been reported.23,24 In addition, these double primary tumors have often had different genetic and immunohistochemical profiles.21

The fact that none of the 10 patients with IMCs of the gallbladder with adequate follow-up died as a result of the gallbladder neoplasm suggests that a simple cholecystectomy is a curative surgical procedure. However, the question whether these patients should be subjected to a reexplanation remains open. First, the number of patients included in this study is small, and only 1 case of undifferentiated carcinoma (a highly aggressive neoplasm) was included. It is therefore clear that more information is needed based on larger series and, ideally, long-term follow-up. On the other hand, a reexplanation with liver resection (segmentectomy) and dissection of the porta hepatis lymph nodes is a radical procedure associated with a risk of morbidity and mortality that has proven to be beneficial only in T2 and T3 gallbladder carcinomas.25 For patients with T1 disease only, the benefits for additional surgery are less clear.26 Since the general T1 category includes muscle-invasive carcinomas (pT1b) and IMC (pT1a), the need for reexplanation following laparoscopic cholecystectomy for IMC will likely be difficult to demonstrate.

Because of the increasing number of laparoscopic cholecystectomies for the treatment of gallstone disease, we believe the detection of IMC of the gallbladder will increase (11 of 13 cases in the current series were diagnosed after 1995).27,28 To exclude invasion into the muscularis propria and learn more about the biologic behavior of IMC of the gallbladder, it is prudent to make the following recommendations for surgical pathologists: The entire gallbladder should be submitted for microscopic examination, and at least 3 levels should be obtained from each paraffin block demonstrating carcinoma. For diagnosis, the tumor should be confined to the lamina propria, and the muscle layer (muscularis propria) should not be involved. It is important to remember that the gallbladder lacks a muscularis mucosa and a submucosa. If present, the cystic lymph node should be examined microscopically. A detailed search for lymphovascular invasion should be made. The histologic type of carcinoma should be recorded. By following these recommendations, pathologists can provide useful information to stage the tumor and help to determine the best form of therapy.

We reported 13 cases of IMC of the gallbladder, 11 of which were diagnosed after 1995. Two patients had symptomatic synchronous second-primary malignant neoplasms, one a ductal carcinoma of the pancreas and the other a small cell carcinoma of the gallbladder, that were responsible for the death of the patients. Eight patients remained asymptomatic from 3 to 11 years (mean, 4.8 years). The follow-up of another patient was too short to be significant. Two patients were lost to follow-up. Most of the neoplasms were well-differentiated adenocarcinomas with an intestinal or a biliary phenotype. Only 1 undifferentiated carcinoma and 1 squamous cell carcinoma were included in the series. In contrast with colonic IMCs, only 1 IMC in the current series arose in a tubular adenoma pyloric type. Our results suggest that a simple cholecystectomy is a curative procedure for IMCs of the gallbladder. Because of the small number of cases, however, we believe that larger series with long-term follow-up are needed to confirm our findings.

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References


