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Low-Grade Dysplastic Intracholecystic Papillary Neoplasia: A Case Report

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 71-year-old
Final Diagnosis: Hepatic epithelioid angiomyolipoma
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: —
Specialty: Pathology • Surgery

Objective: Rare disease

Background: The World Health Organization classification of premalignant gallbladder lesions includes adenomas, intraductal papillary neoplasms, biliary intraepithelial neoplasia, and intracystic papillary neoplasms. Noninvasive neoplastic lesions >1 cm that originate from the pancreatobiliary system are defined as intraductal papillary neoplasia when they occur in the biliary ducts. The clinical and pathological features of preinvasive lesions arising in the gallbladder are not yet well defined. However, the most widely accepted classification is that of intracholecystic papillary neoplasm (ICPN).

Case Report: We present the case of a 71-year-old woman referred to a General Surgery outpatient clinic for suspicious findings on imaging of the gallbladder, namely irregular infundibular parietal thickening. The patient underwent a laparoscopic cholecystectomy and histological examination revealed a thickened gallbladder with mucosa partially surrounded by ICPN with an intestinal pattern and some foci of low-grade dysplasia but no foci of high-grade dysplasia or invasive neoplasia. At follow-up at 30 months, the patient remains clinically well, with no changes visible on computed tomography scan.

Conclusions: ICPN of the gallbladder appears to be part of a spectrum of alterations encompassing bile duct or pancreatic lesions. Although it is uncommon, more than half of the lesions are known to have foci of invasive neoplasia at the time of diagnosis. Despite that, the prognosis for these neoplasms is more favorable than for gallbladder neoplasia that originates from another type of lesion. Pathological study of ICPN is essential to define the main characteristics that impact prognosis and survival in these patients.

Keywords: Biliary Tract Neoplasms • Cholecystectomy • Gallbladder Neoplasms • Pathological Conditions, Anatomical

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Background

The pathological features of gallbladder intraepithelial neoplasia are not well understood. In 2018, the World Health Organization published a classification of premalignant gallbladder lesions that included adenomas, intraductal papillary neoplasms, biliary intraepithelial neoplasia, and intracystic papillary neoplasms [1]. Although various terminologies have been proposed for these lesions and attempts made to classify them, specific criteria for discriminating among them have still not been defined There is growing evidence that some types of gallbladder lesions have significant variability in cell lines, differing grades of dysplasia, and distinct patterns of papillary or tubular growth [2]. Noninvasive neoplastic lesions that measure >1 cm and originate in the pancreaticobiliary system are defined as intraductal papillary neoplasia (IPN) when they occur in the biliary ducts. Lesions that come from the pancreas are classified as intraductal papillary mucinous neoplasia (IPMN) and intraductal tubulopapillary neoplasia, in accordance with production of mucin [3]. Although the clinical and pathological characteristics of noninvasive lesions of the biliopancreatic system are relatively well defined, the same is not true for similar lesions originating in the gallbladder. The most widely accepted definition is that for intracholecystic papillary neoplasm (ICPN) [4]. This recent classification may facilitate individualized study of these lesions and help to distinguishing them from lesions in the biliopancreatic system.

Case Report

We present the case of a 71-year-old woman who was referred to the General Surgery outpatient clinic because of suspicious findings on imaging of the gallbladder, namely irregular infundibular parietal thickening on outpatient ultrasound. The patient presented with frequent upper-right abdominal pain and nausea after meals, with no history of weight loss or anorexia. Laboratory testing, thoracoabdominal-pelvic computed tomography (TAP-CT), and abdominal magnetic resonance imaging (MRI) were performed. The laboratory results revealed no significant changes, with normal values for tumor markers. The TAP-CT scan confirmed the presence of a distended gallbladder, with slightly irregular parietal thickening mainly involving the vesicular fundus, no endoluminal images, and no changes in the liver (**Figure 1**). The MRI corroborated the findings from the other tests: a gallbladder with diffuse parietal thickening, mainly in the infundibular region, and a pleated appearance (**Figure 2**).

Given the patient's symptoms and the results of testing, surgery was proposed. A laparoscopic cholecystectomy was performed, which was uneventful. There were no complications during the postoperative period and the patient was discharged on the third day. Histological examination revealed a 93 cm gallbladder with thickening mainly in the body and fundus, mucosa partially surrounded by ICPN lesions over an area measuring approximately 1.5×2 cm, with an intestinal pattern and some foci of low-grade dysplasia but no foci of high-grade dysplasia or invasive neoplasia (**Figure 3**). Immunohistochemical testing for cytokeratin (CK) 20, CK7, and CDX2 revealed diffuse positivity for CK7 in the papillary proliferation as well as in the intrinsic biliary epithelium. CK20 and CDX2 positivity were seen in the papillary proliferation but not in the biliary epithelium. This immunohistochemical profile revealed an intestinal pattern of intracholecystic papillary proliferation. No invasive components were identified. At follow-up at 30 months, the patient

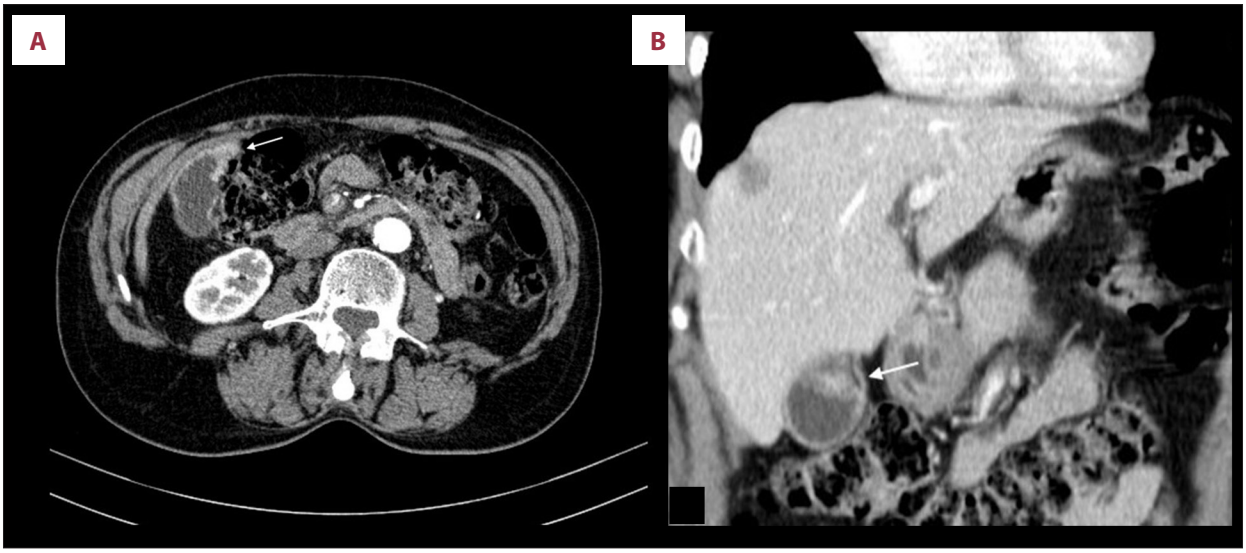

Figure 1. Computed tomography scan. (**A**) Sagittal image. (**B**) Coronal image The gallbladder is distended, with slightly irregular parietal thickening (white arrow), mainly involving the vesicular fundus. There are no changes in the liver, except some biliary cysts.

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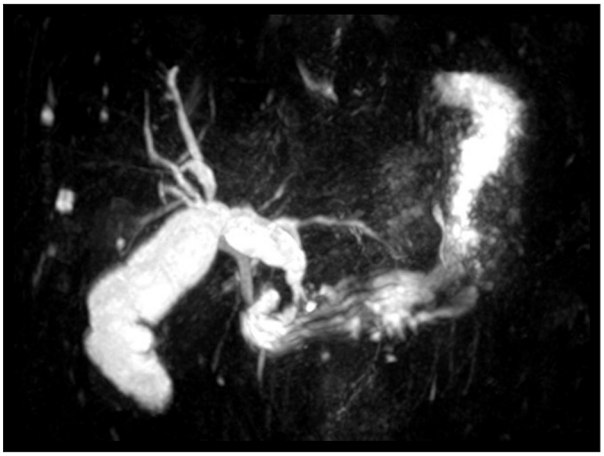

Figure 2. Magnetic resonance cholangiopancreatography. The gallbladder has diffuse parietal thickening, which is mainly in the infundibular region and looks pleated.

was clinically well and her pain and dyspepsia had subsided. On CT scan, no changes were seen.

Discussion

Intrahepatic and extrahepatic cholangiocarcinoma develops according to an adenoma-dysplasia-carcinoma sequence. To date, 2 main precursor lesions have been identified: biliary intraepithelial neoplasia and IPN of the bile duct [5]. The former consists of flat or micropapillary microscopic dysplastic lesions of the epithelium. The latter consists of at least 1 macroscopic lesion spreading through the biliary tract and is characterized by intraluminal growth, prominent papillary proliferation of the dysplastic epithelium with frequent intestinal metaplasia, and mucin hypersecretion [6]. IPN of the bile duct is analogous to IPMN of the pancreas and they share the same histological subtypes. Similar lesions can appear in the gallbladder as ICPN. In this scenario, ICPN constitutes dysplastic, intramucosal lesions with exophytic growth that project into the lumen of the gallbladder and are compact but measure >1 cm [3]. Like dysplastic lesions originating in the bile duct and pancreas, ICPN can have various cell lineages (biliary, gastric, intestinal, and oncocytic) [7]. Although lesions measuring <1 cm have a very low potential for neoplastic transformation, the same thing cannot be assumed about larger lesions, which are prone to neoplastic transformation through the adenoma-dysplasia-carcinoma sequence [8].

ICPN is uncommon, with incidence in women twice as high as in men [1]; several studies have reported an overall incidence <0.5% [2,3]. Although these lesions have potential for neoplastic transformation, the vast majority of invasive gallbladder and bile duct carcinomas originate from flat intraepithelial

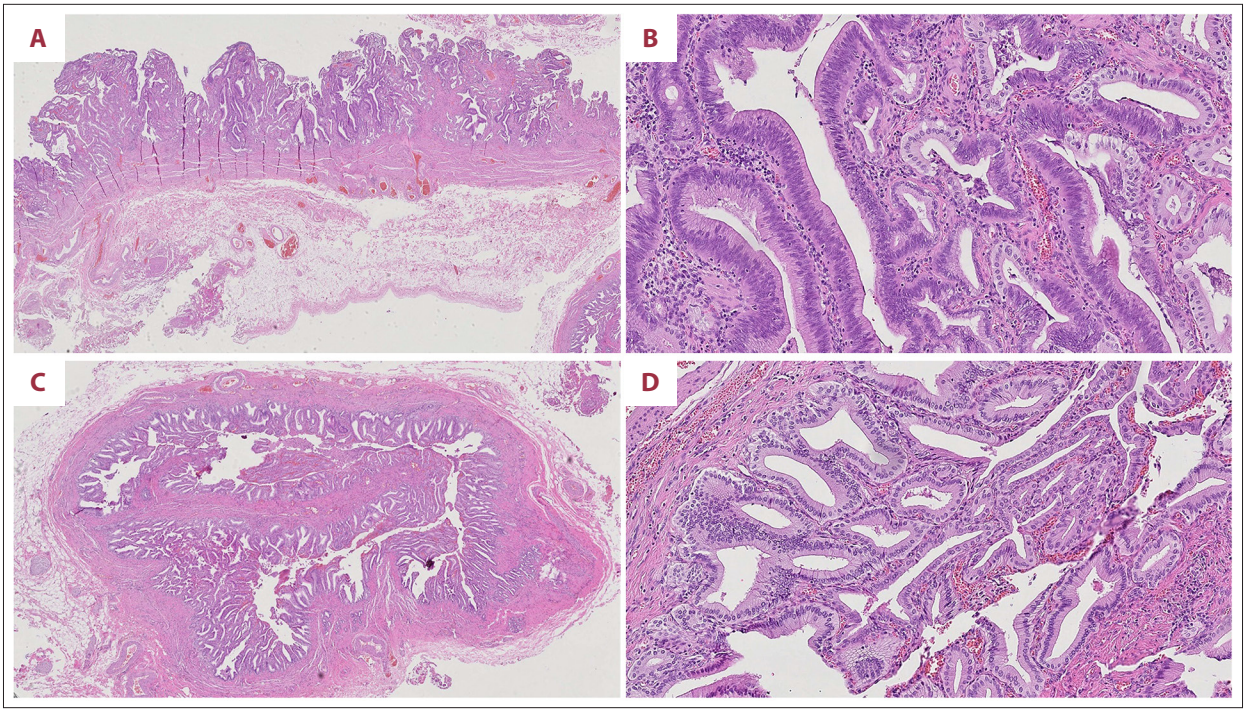

Figure 3. Hematoxylin & eosin-stained histological sections. (**A**) Magnification ×40. (**B**) Magnification ×200. (**C**) Magnification ×40. (**D**) Magnification ×200. The intestinal phenotype is intracholecystic papillary neoplasm (ICPN). Morphologically, the ICPN has complex tubulo-papillary epithelial growth with pseudostratified nuclei and basophilic cytoplasm. Mitotic activity is scarce and essentially on the basal side of the epithelium.

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lesions. Thus, several studies have shown that ICPN is responsible for only 20% of invasive gallbladder neoplasms [9] and only 6% of gallbladder carcinomas [1]. However, more than half the lesions found to be ICPN have foci of invasive carcinoma at diagnosis [3]. The main factors related to the likelihood of developing foci of invasive carcinoma are the presence of a papillary pattern, high-grade dysplasia, and the predominance of a non-gastric cell line. Regarding symptoms, they may be similar to cholelithiasis or gallbladder and biliary tract neoplasia. Patients with ICPN can present with abdominal pain or dyspepsia, symptoms of obstructive jaundice, and findings on imaging [6]. In some of these cases, dyspepsia and abdominal discomfort are associated with gallstones, which have been reported in approximately 22% of cases [2].

ICPN can be diagnosed only after analysis of a cholecystectomy specimen. Surgery often is recommended, as in our case, because of the presence of biliary colic and/or endoluminal masses or nonspecific gallbladder thickening on imaging. Pathologic analysis is essential to establish the diagnosis and determine the prognosis for these lesions. Identification of ICPN should be followed by an exhaustive search for invasion, and high- or low-grade dysplasia, as well as characterization of cell lines and papillary/tubular histological patterns. More than 75% of cases of ICPN are exclusively papillary, which is the histological pattern most often associated with the development of invasive carcinoma [10]. In some cases, tubulopapillary growth can be seen.

Immunohistochemical markers are a well-established tool for daily diagnostic practice and can help define tumor lineage when antibodies for specific tumor antigens are used. In particular, the differential expression profile of various CK types by cells can be essential in determining the original line. CK20 is normally expressed in the gastrointestinal epithelium, whereas CK7 can be detected in normal tissue and biliary tumors. *CDX2* is a gene encoding a nuclear transcription factor involved in proliferation and differentiation of intestinal epithelial cells. Thus, the identified pattern is compatible with an intestinal lineage.

The prognosis for ICPN is much better than that for invasive gallbladder carcinomas; 3-year survival averages 90% for lesions with no foci of invasion versus 60% for those with foci of invasion [3]. It is important to point out that even ICPN that progresses to invasive carcinoma has a better prognosis than gallbladder carcinoma that originates in another type of lesion [11]. This prognostic advantage is independent of lesion size [3]. In the present case, pathological examination revealed the presence of ICPN with foci of low-grade dysplasia but with no evidence of invasive foci; therefore, no further intervention or additional testing was required.

Conclusions

IPCN originates in the gallbladder and, although little studied, appears to be part of a spectrum of alterations that include bile duct or pancreatic lesions. All of these entities appear to share clinical and pathological features and it is possible to determine which are most likely to experience neoplastic transformation. Although more than half the cases of ICPN are known to have foci of invasive neoplasia at diagnosis, the prognosis for these neoplasms is more favorable than for gallbladder neoplasia that originates from another type of lesion. Pathological study of this type of lesion is essential to identify the main characteristics that influence patient prognosis and survival.

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