Oncocytic Biliary Cystadenocarcinoma

A Case Report and Review of the Literature

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• We report an unusual case of biliary cystadenocarcinoma with oncocytic differentiation. The patient was a 43-year-old woman who presented with right upper quadrant pain. Imaging revealed a 16 × 10 × 10-cm, heterogenous, right hepatic mass with extension into the right atrium. Surgical resection revealed a papillary neoplasm of malignant cells with atypical hyperchromatic nuclei and prominent nucleoli lining fibrovascular cores. Mesenchymal stroma was not present. The majority of the epithelial cells had abundant eosinophilic granular cytoplasm, consistent with oncocytic differentiation. There was extensive stromal and hepatic parenchymal invasion. Immunohistochemical staining revealed a "biliary pattern" of cytokeratin subset immunoreactivity, with positivity for cytokeratin 7 and an absence of staining with cytokeratin 20. The tumor was negative for mucin, carcinoembryonic antigen, α-fetoprotein, calretinin, CD31, and chromogranin. There was granular cytoplasmic staining with phosphotungstic acid hematoxylin, consistent with the presence of abundant mitochondria. Electron microscopy revealed abundant mitochondria within the neoplastic cells. This case is quite unusual because female patients only rarely lack the characteristic ovarian-like mesenchymal stroma of biliary cystadenomas/cystadenocarcinomas. Furthermore, to our knowledge, oncocytic differentiation in this neoplasm has been reported previously on only 2 occasions. The biologic behavior and prognostic significance, if any, of the lack of mesenchymal stroma in female patients or the presence of oncocytic differentiation remains to be further elucidated as more of these cases are described.

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Biliary cystadenomas and cystadenocarcinomas are rare tumors that comprise less than 5% of all intrahepatic cystic neoplasms of biliary origin.[1] Cystadenomas occur almost exclusively in middle-aged women and are usually accompanied by a densely cellular, ovarian-like stroma. These benign tumors are generally slow growing and may be quite large, with a mean size of 15.0 cm. Most patients do quite well with complete surgical excision. The malignant counterpart, biliary cystadenocarcinoma, affects men and women with essentially equal frequency and generally presents 1 to 2 decades later than cystadenomas. Biliary cystadenocarcinoma is a rare neoplasm; fewer than 100 cases have been reported in the literature to date.[1–6] These lesions are predominantly papillary and may arise in association with areas of benign cystadenoma. In women, a characteristic ovarian-like mesenchymal stroma is usually present, underlying the epithelial cells. In men, this stroma is typically lacking. To our knowledge, oncocytic differentiation in biliary cystadenocarcinomas has been reported previously in only 2 patients.[3,6] Both cases involved men, displayed papillary architecture, and lacked cellular mesenchymal stroma. We describe a papillary biliary cystadenocarcinoma arising in a 43-year-old woman; the mass in this case lacked mesenchymal stroma and demonstrated prominent oncocytic differentiation.

REPORT OF A CASE

The patient was a 43-year-old woman with no significant past medical history. She presented with rather abrupt onset of right upper quadrant pain. She had no history of cholelithiasis, previous hepatitis, or other hepatobiliary signs or symptoms. Physical examination revealed a large abdominal mass in the right upper quadrant. Laboratory evaluation revealed a mild microcytic anemia, mild elevations of serum alkaline phosphatase and aspartate aminotransferase levels, but normal serum bilirubin level, alanine aminotransferase level, prothrombin time, and activated partial thromboplastin time. A computed tomographic scan of the chest, abdomen, and pelvis identified a large hypervascular hepatic mass in the right lobe with tumor thrombus extending from the hepatic vein into the inferior vena cava and right atrium (Figure 1). The mass was heterogenous in appearance. Metastatic disease was considered and the patient was evaluated appropriately. Gynecologic examination, including Papanicolaou testing and endometrial biopsy, was negative for neoplasm. Results of esophagogastroduodenoscopy and colonoscopy were normal. A diagnostic laparoscopy with laparoscopic liver biopsy was performed. During image-guided biopsy of the hepatic mass, it was noted that the neoplasm "deflated somewhat" as the biopsy was obtained.

Pathologic examination revealed a low-grade papillary neoplasm. No evidence of mucin formation or stromal or parenchymal invasion was present. The working diagnosis was that of a low-grade papillary neoplasm. The patient underwent en bloc surgical resection via a right hepatic trisegmentectomy and atriotomy on cardiopulmonary bypass with extraction of inferior vena caval and atrial tumor and patch repair of the vena cava. After an initial stay in the intensive care unit, the patient's condition stabilized, and she was discharged after a hospital stay of 21 days. She went home alert and oriented, ambulatory, and tolerating food orally.

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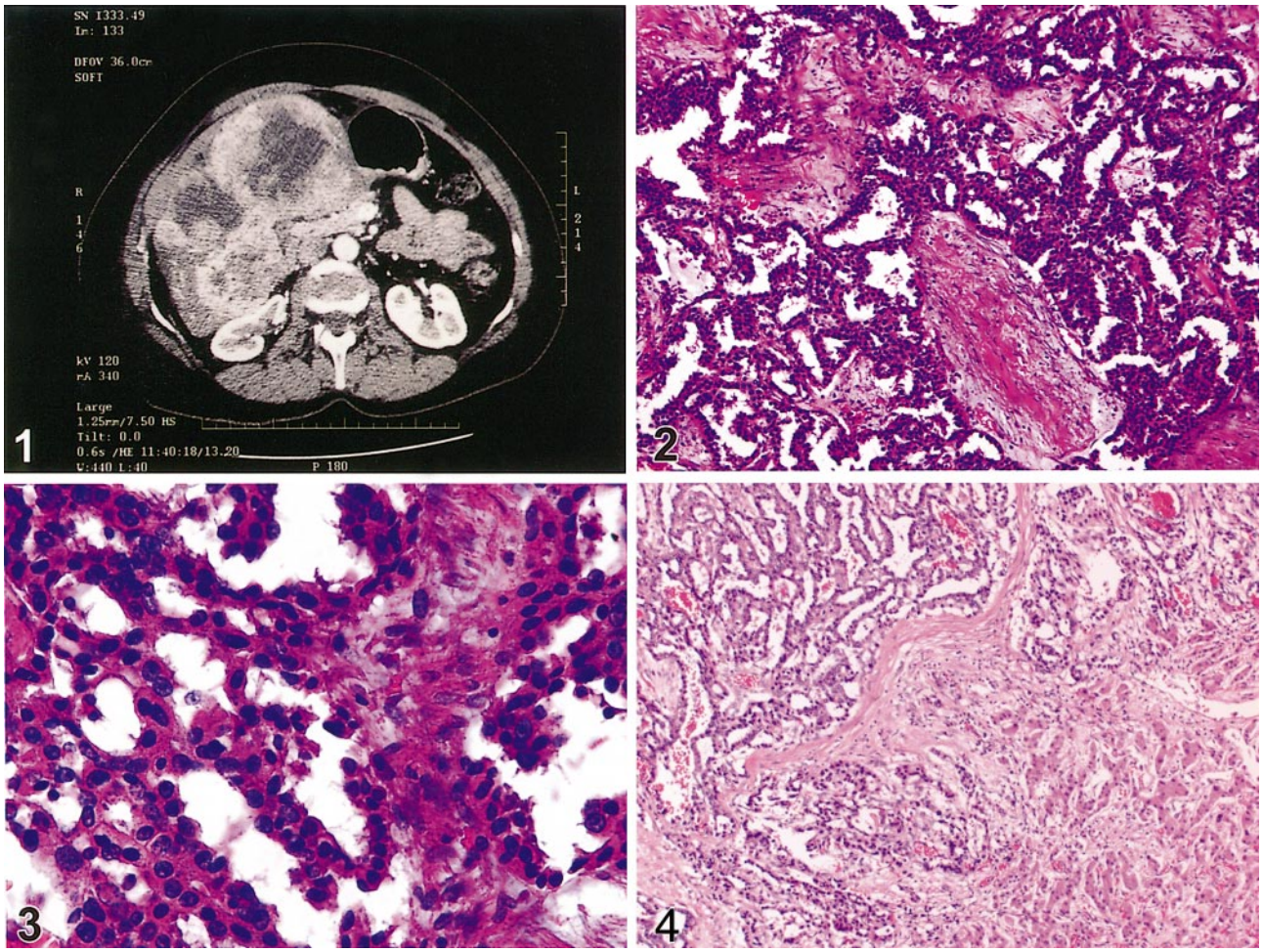

Figure 1. *Computed tomographic image of the heterogenous, poorly circumscribed, right hepatic lobe mass demonstrating widespread replacement of hepatic parenchyma and large radiolucent zones of necrosis.*

Figure 2. *Low-power view demonstrating a papillary architecture with fibrovascular stalks lined by atypical epithelial cells projecting into cystic spaces (hematoxylin-eosin, original magnification ×200).*

Figure 3. *Higher-magnification view showing moderate cytologic atypia, pleomorphism, and prominent nucleoli. The oncocytic nature of the cytoplasm is evident by deep eosinophilic staining (hematoxylin-eosin, original magnification ×400).*

Figure 4. *Biliary cystadenocarcinoma with invasion into surrounding hepatic parenchyma (hematoxylin-eosin, original magnification ×200).*

MATERIALS AND METHODS

Tissue for light microscopy was fixed in 10% neutral buffered formalin, processed for routine paraffin embedding, and stained with hematoxylin-eosin. Immunohistochemistry was performed with the labeled streptavidin-biotin system by means of an automated immunostainer (Ventana NexES; Ventana Medical Systems, Tucson, Ariz). The following monoclonal antibodies were applied: AE1/AE3 (1:200; Dako Corporation, Carpinteria, Calif), cytokeratin 20 (1:2000; Dako), cytokeratin 7 (1:10; Dako), epithelial membrane antigen (1:200; Dako), α-fetoprotein (1:400; Dako), CD31 (1:20; Dako), chromogranin (1:100; Dako), factor VIII (1:800; Dako), carcinoembryonic antigen (1:25; Biomeda, Foster City, Calif), and calretinin (prediluted; Ventana). Negative controls consisted of antibody diluent (catalog No. 251-018, Ventana). Positive controls reacted accordingly. Mucicarmine stain was performed on an automated stainer (Ventana NexES; Ventana) using a mucicarmine staining kit (catalog No. 860-011, Ventana) with normal small intestine control. Mallory phosphotungstic acid hematoxylin stain was performed manually[7] using a normal skeletal muscle control. Electron microscopy was performed on tissue obtained from a block after paraffin embedding.

RESULTS

Gross Pathologic Findings and Light Microscopy

The hepatic resection specimen was involved by an 18.0 × 13.5 × 8.0-cm, poorly circumscribed, heterogenous, tan mass, which encompassed approximately 50% of the specimen. The mass was predominantly solid and had multiple cystlike areas of necrosis. The mass extended into the hepatic vein and inferior vena cava, and focally invaded the outer muscular layer of the gallbladder wall. Histologic examination demonstrated distinct papillary architecture with fibrovascular cores lined by neoplastic epithelium projecting into cystic spaces (Figure 2). The tumor cells exhibited irregular hyperchromatic nuclei with prominent nucleoli, moderate pleomorphism, and frequent mitotic figures. The abundant cytoplasm was eosinophilic and prominently granular, resulting in distinctly oncocytoid differentiation (Figure 3). Mesenchymal stroma was not present. Although the tumor had a thick fibrous capsule focally, most of the mass was unencapsulated and

invasive into the surrounding hepatic parenchyma (Figure 4).

Review of the patient's original biopsy material revealed a papillary neoplasm with epithelial cells lining fibrovascular cores. Less pleomorphism and atypia were identified, compared to the surgical resection specimen. We found no evidence of invasion into the surrounding hepatic parenchyma or stroma. This mass was interpreted as a papillary neoplasm of uncertain malignant potential. A definitive diagnosis of malignancy could not be made.

Immunohistochemistry and Special Stains

The majority of tumor cells from the resection specimen stained positively for cytokeratin AE1/AE3. Cytokeratin subset analysis revealed a biliary pattern of reactivity, with intense, patchy positivity for cytokeratin 7 and no reactivity for cytokeratin 20. Epithelial membrane antigen was focally positive. Mucicarmine, carcinoembryonic antigen, α-fetoprotein, calretinin, CD31, factor VIII–related antigen, and chromogranin stains were negative. The phosphotungstic acid hematoxylin stain displayed abundant to patchy, granular cytoplasmic staining.

Electron Microscopy

Electron microscopy revealed abundant intracytoplasmic mitochondria within the neoplastic cells.

COMMENT

Biliary cystadenocarcinomas are rare neoplasms, comprising approximately 1% of all primary hepatic carcinomas.[8] Some studies have suggested a female predominance, yet most agree that males and females are affected nearly equally.[2,4] The histogenesis of these lesions continues to be an area of great debate. It has been postulated that cystadenocarcinomas with mesenchymal or ovarian-like stroma arise from ectopic ovarian tissue incorporated into liver or intrahepatic peribiliary gland tissue.[9] The former seems unlikely, as heterotopic ovarian tissue does occur, but it is generally restricted to the pelvis and lower peritoneal cavity.[10] Another proposed theory is development from ectopic remnants of primitive foregut sequestered within the liver.[11] Many researchers believe that at least some cystadenocarcinomas arise from cystadenomas. Support of this concept comes from the observation that cystadenocarcinomas often contain areas of cystadenoma in the same sample.[4,5] Devaney et al[2] found areas of benign cystadenoma in 6 of 18 cystadenocarcinomas they examined. Wheeler and Edmondson[4] found areas of malignant change in 4 of 17 cystadenomas. Others contend that cystadenocarcinomas do not arise from preexisting cystadenomas but from dysplasia of normal bile ducts. This point of view is supported by the finding that cystadenocarcinomas without mesenchymal stroma have been induced experimentally in animal models treated with aflatoxin.[12]

Clinical presentation is usually mild and vague. Many patients are asymptomatic, but may eventually note increased abdominal girth or may palpate an abdominal mass. When symptomatic, most patients complain of epigastric or right upper quadrant pain, nausea, jaundice, or fatigue. Ascites, jaundice, and bone pain may occur in patients with disseminated metastatic disease.

The usual radiographic appearance on computed tomographic imaging is that of a low-density cystic mass with papillary infoldings, solid nodular areas, and internal septae. Areas of necrosis or calcification may also be noted. These tumors may be quite large, with both benign and malignant lesions having a mean diameter of approximately 15 cm.

Most cystadenocarcinomas are papillary or tubulopapillary neoplasms with epithelium-lined fibrovascular stalks that project into cystic cavities. The epithelium is usually columnar to cuboidal and demonstrates stratification, loss of polarity, pleomorphism, atypia, and mitotic figures. Cystadenocarcinomas typically have features characteristic of cystadenoma, yet also demonstrate cytologic atypia and pleomorphism. Malignant epithelial cells often invade into the stroma, through the capsule, and into the adjacent hepatic parenchyma or other organs. The differential diagnosis varies with the degree of cyst formation and includes other cystic lesions, such as congenital hepatic cyst, hydatid cyst, hepatic abscess, cystic hamartoma, Caroli disease, posttraumatic cyst, and polycystic disease.[1,2] Cholangiocarcinoma, hepatocellular carcinoma, primary carcinoid tumors, metastatic papillary carcinoma, and metastatic cystadenocarcinoma must also be distinguished.

The stroma of biliary cystadenomas and cystadenocarcinomas is varied. In most cystadenomas, the stroma adjacent to the epithelium consists of closely packed spindled cells with an appearance reminiscent of ovarian stroma or the primitive mesenchymal elements associated with the developing biliary system in the fetus. By both light and electron microscopy, this stroma is shown to be variably composed of fibroblasts, smooth muscle, adipose tissue, capillaries, and undifferentiated cells. Gourley et al[5] found these mesenchymal stromal cells to have the immunohistochemical characteristics of myofibroblasts. They postulated that these are reactive contractile cells that may proliferate in response to the expanding lesion and female hormones, and that they differ immunohistochemically from ovarian stromal cells. Devaney et al[2] found 85% of 52 examined cystadenomas to contain such stroma. All of these patients were women. Of the 5 patients lacking the ovarian-like stroma, 3 were women and 2 were men. Of 18 cystadenocarcinomas examined by this group, all 6 tumors with ovarian-like stroma occurred in women. In 12 cases, involving 8 men and 4 women, this stroma was lacking. Our review of the literature produced 28 reported cases of biliary cystadenocarcinoma lacking ovarian-like stroma.[2–4,6] Nineteen of these neoplasms occurred in men and 9 in women. It is argued that 2 distinct types of biliary cystadenocarcinomas exist. The first develops exclusively in women and is accompanied by ovarian-like mesenchymal stroma. These lesions generally follow a more indolent course.[2,4] The other type lacks ovarian-like stroma, occurs predominantly in men, and follows a more aggressive course. The course of cystadenocarcinomas lacking ovarian-like stroma, yet occurring in women, remains unclear. It is uncertain whether these tumors behave in an aggressive fashion, as they do in men, or whether they carry a more favorable prognosis, as lesions with stroma do.

Various epithelial cell types have been described in biliary cystadenomas/cystadenocarcinomas, illustrating the range of differentiation that can be found in hepatic biliary cystic neoplasms. Areas of mucinous differentiation, intestinal metaplasia with goblet cells, Paneth cells, endocrine cells containing peptide hormones, spindle cell metaplasia (pseudosarcomatous), squamous cells, and oncocytic cells have been described previously.[1–3,5,6] To our knowledge,

oncocytic differentiation, as seen in this case, has been reported previously in only 2 other patients. Oncocytic change in hepatocytes has been described in a number of conditions, including liver cell adenoma and the fibrolamellar variant of hepatocellular carcinoma.[3] In contrast, oncocytic differentiation in biliary epithelium is exceptional, and only rare cases have been reported in primary biliary cirrhosis.[3] The present case was characterized by pronounced oncocytic differentiation. Oncocytic change has been well described in malignancies of other organs, including the pancreas, salivary glands, ovary, and breast.[3] In contrast, ''true oncocytomas,'' tumors that are composed entirely of oncocytes, are usually benign.[13] The significance, if any, of oncocytic differentiation in biliary cystadenocarcinomas is unclear, as we know of only 2 other previously reported cases. The first case involved a 71-year-old man who presented with peritoneal dissemination at the time of diagnosis.[6] The second case involved a 56-year-old man who died 25 months after initial presentation of disseminated disease.[3] Both of these previously reported tumors lacked mesenchymal stroma. Too few cases have been reported to draw any prognostic conclusions regarding oncocytic differentiation in these neoplasms.

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