

Squamous Cell Cancer of the Liver Arising from a Solitary Benign Nonparasitic Hepatic Cyst

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A case of squamous cell carcinoma arising from a solitary benign nonparasitic hepatic cyst (SBNHC) causing bile duct obstruction is presented. A review of the literature regarding SBNHC suggests that, although these lesions may appear benign, they may also undergo metaplastic and subsequent malignant transformation. This appears to be particularly true when the SBNHC is lined with squamous epithelium. Once squamous cell carcinoma arises from one of these lesions, the prognosis is extremely grave, despite all forms of surgical and medical management.

INTRODUCTION

Benign nonparasitic cysts of the liver are rare lesions. Fewer than 300 solitary benign nonparasitic hepatic cysts (SBNHC) have been noted in the literature (1). The exact incidence and behavior of these lesions is not known. In 1944, Eliason and Smith (2) reviewed 20,000 consecutive autopsies and found only 28 SBNHC, all of which were believed to be incidental findings. However, it is likely that the frequency of diagnosis of these cysts will increase with the current availability of computerized axial tomography (CAT) and ultrasonography. Hopefully, this will result in a better description and understanding of these cysts as a clinical entity and further define their true malignant potential.

SBNHC are thought by some investigators to arise from Meyenburg complexes, that is, congenital rests of biliary epithelium (3, 4). It is hypothesized that the squamous epithelial lining of these cysts arises from chronic inflammation and metaplasia. However, these cysts can have varied epithelial linings. Henson *et al.* (5) reported cuboidal, columnar, squamous, and even ciliated epithelium lining solitary benign hepatic cysts.

Squamous cell carcinoma and tumors containing major squamous components are rare primary hepatic neoplasms (6). Furthermore, although squamous cell carcinoma arising in a SBNHC has been described, it is exceedingly rare. It is thought that squamous cell

carcinoma of the liver arises from metaplastic and subsequent neoplastic transformation of biliary epithelium in congenital or developmental cysts (7).

A review of the literature reveals four previously reported cases of squamous cell carcinoma arising from a SBNHC (1, 3, 7, 8) (see Table 1). Five other cases of either primary squamous cell carcinoma of the liver or tumor of the liver with major malignant squamous elements, but not arising specifically from a SBNHC, have also been previously described (6, 9-12) (see Table 2.). Therefore, the patient reported here represents only the fifth case of squamous cell carcinoma of the liver arising in a SBNHC reported in the literature. The origin or source of a presumed sixth case of squamous cell carcinoma of the liver reported by Geddes *et al.* was not mentioned and was associated with an elevated alpha-fetoprotein (13). This suggests that this lesion may have actually represented a case of primary hepatocellular carcinoma (12).

Because these lesions are so rare, the pathology of SBNHC must be reviewed critically and with a high degree of suspicion. This patient was diagnosed as having a complex SBNHC involving major bile duct and vascular structures. Removal of this lesion would have required a major extirpative and reconstructive effort to maintain the patient's hepatobiliary anatomy. Such an extensive procedure was felt not to be justified in view of the original benign diagnosis. However, in 3 months, this lesion demonstrated itself to be highly invasive and unequivocally malignant. Whether this final diagnosis would have justified a more aggressive initial surgical approach remains unclear.

CASE REPORT

A 63-yr-old, chronic schizophrenic male originally presented with a 1- to 2-month history of acholic stools and dark urine. His local physician noted that he was jaundiced. His total bilirubin was then 11.4 mg/dl. The patient was referred to the Ann Arbor Veterans Administration Medical Center (AAVAMC). Available past medical history was sketchy. Previous operations in-

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TABLE 1
Literature Review of All Known Cases of Primary Squamous Cell Carcinoma of the Liver Arising from a SBNHC*

| Case No. | Author, Yr | Age/Sex | Presenting Signs and Symptoms | Operation/Clinical Course | Gross Morphology | Histology | Survival |
|----------|------------------------------------|---------|--|--|---|---|----------|
| 1 | Edmondson, 1958 (8) | 56/M | Unknown | Death; otherwise unknown | Left lobe liver SBNHC | Squamous cell carcinoma arising from cyst | Unknown |
| 2 | Greenwood <i>et al.</i> , 1972 (1) | 37/M | Dyspepsia, wt loss, jaundice, RUQ mass | Celiotomy, death | SBNHC right lobe liver extending into left hepatic lobe | Squamous cell carcinoma arising from cyst | 2 mo |
| 3 | Bloustein <i>et al.</i> , 1976 (3) | 30/M | RUQ abdominal pain, hepatomegaly | Celiotomy with drainage, repeat celiotomy with Roux-En-Y drainage of cyst, celiotomy with right hepatic lobectomy, death | Large SBNHC right lobe of liver | Benign cyst, squamous cell carcinoma arising from cyst (poorly differentiated) | 6 mo |
| 4 | Gresham <i>et al.</i> , 1985 (7) | 78/M | Epigastric pain, anorexia, jaundice, ascites, hepatomegaly | Death | SBNHC-large central hepatic mass | Squamous cell carcinoma | 2 mo |
| 5 | Present case | 63/M | Jaundice, RUQ, fullness, and pain | Celiotomy with unroofing of cyst and drainage; repeat celiotomy with subtotal hepatic cystectomy | Large SBNHC | Benign cyst; lined with mature squamous epithelium, squamous cell carcinoma arising from cyst | 6 mo |

* SBNHC, solitary benign nonparasitic hepatic cyst.

TABLE 2
Literature Review of All Known Cases of Primary Squamous Cell Carcinoma of the Liver Not Arising from a SBNHC*

| Case No. | Author, Yr | Age/Sex | Presenting Signs and Symptoms | Operation/Clinical Course | Gross Morphology | Histology | Survival |
|----------|------------------------------------|---------|--|---|--|---|----------|
| 1 | Imai, 1934 (9) | 32/M | Epigastric mass? | Death | Hepatic mass, teratoma | Squamous cell carcinoma arising from a hepatic teratoma | |
| 2 | Irwin <i>et al.</i> , 1944 (10) | 30/M | Abdominal pain | Exploration for appendicitis; celiotomy death | Large solitary nonparasitic cyst-common bile duct | Squamous cell carcinoma | 3 mo |
| 3 | Pianzola <i>et al.</i> , 1971 (11) | 44/M | Fever, vomiting, wt loss, RUQ abdominal pain | Celiotomy, death | Large hepatic mass centrally located | Mucoepidermoid carcinoma of the liver | 1-2 mo |
| 4 | Barr <i>et al.</i> , 1975 (6) | 85/M | Hepatomegaly, wt loss | Death | Large multicystic hepatic mass | Adenosquamous carcinoma | |
| 5 | Song <i>et al.</i> , 1984 (12) | 43/M | RUQ abdominal pain, acholic stools, dark urine | Celiotomy with left subtotal hepatic lobectomy and cholecystectomy; death | Left hepatic mass, intrahepatic cholesterol stones | Squamous cell carcinoma | 6 mo |

* SBNHC, solitary benign nonparasitic hepatic cyst.

cluded an appendectomy and an undocumented esophageal procedure. He was a heavy cigarette smoker. There was no history of alcohol abuse. No known allergies were identified. His oral medications consisted of Thorazine 200 mg qd, Tranxene 3.7 mg bid, and Dilantin 100 mg bid.

Physical examination revealed a cachectic, jaundiced white male in no acute distress. There was fullness in the right upper quadrant (RUQ) associated with moderate pain to deep palpation, but no evidence of either organomegaly, abnormal masses, or ascites.

Ultrasound showed an 8-cm homogeneous mass in the porta hepatis with dilation of the intrahepatic and proximal extrahepatic bile ducts. Diagnostic aspiration cytology yielded hepatic cells and mature, benign appearing, keratinized, squamous cells. Abdominal computerized axial tomography (CAT) demonstrated a large mass adjacent to the plane of the anatomic divi-

sion of the right and left lobes of the liver that extended deep into the porta hepatis and was distinct and separate from the gallbladder (Fig. 1). There was no evidence of hepatic metastases. A percutaneous transhepatic cholangiogram (PTC) showed smooth tapering of the common hepatic duct and dilation of the intrahepatic and proximal extrahepatic biliary tree. There was no flow of contrast into the duodenum. Chest x-ray, colonoscopy, and esophagogastroduodenoscopy were normal. Visceral angiography identified a large hypovascular to avascular mass in the region of the porta hepatis that extended into the medial segment of the left lobe of the liver. There was no evidence of tumor vascularity or vascular encasement.

The patient underwent exploratory celiotomy. At operation a large, white, smooth, encapsulated mass was found arising primarily from the medial segment of the left lobe of the liver extending into the right lobe

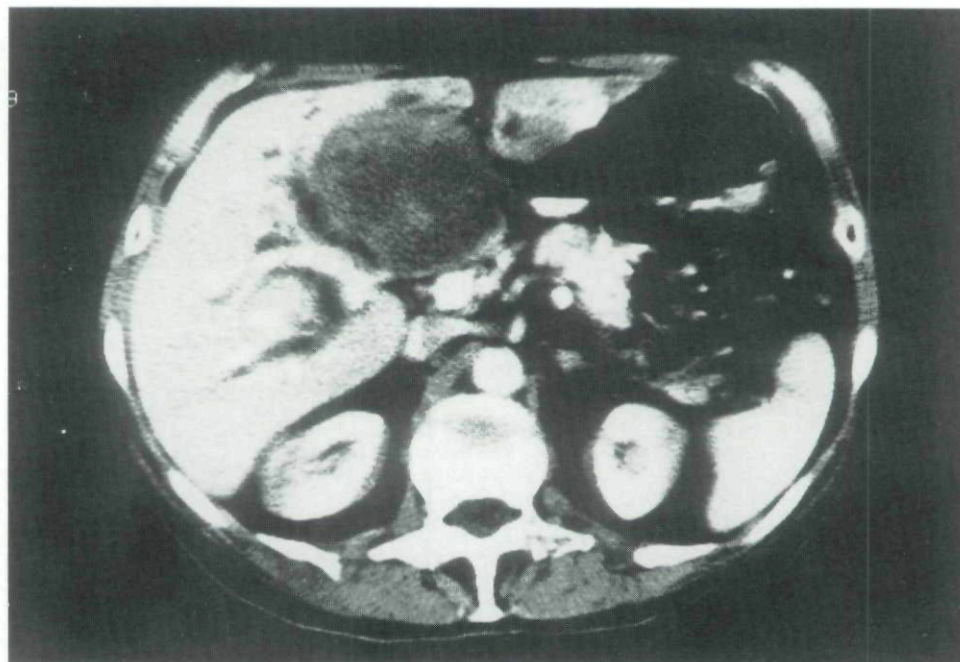


FIG. 1. Abdominal computerized axial tomography with 1-cm contiguous slices, and utilizing both oral and intravenous contrast, demonstrating a large mass in the region of the porta hepatis with secondary biliary obstruction.

of the liver and posteriorly onto the right, left hepatic, common hepatic, and bile ducts. The mass was densely adherent to these structures. The right hepatic artery was also firmly adherent to the posterior surface of the mass. The gallbladder and duodenum were adherent, but could be separated. A cholecystectomy was performed. The mass was entered during the course of obtaining multiple incisional biopsies. It was cystic and filled with an amorphous, cheesy material resembling sebaceous cyst contents. The base of the cyst contained crystals and flecks of bile pigment. The cyst cavity communicated directly with the right and left hepatic ducts (HD). The mass further extended toward the inferior vena cava (IVC) posterior-inferiorly, toward the hepatic veins anterior-superiorly, and was contiguous with the lateral aspect of the portal vein. There was no plane between the cyst wall and liver parenchyma. Multiple biopsies of the cyst wall on frozen section showed a benign, squamous cell-lined hepatic cyst. No other mass lesions were appreciated in either the remaining liver, abdominal cavity, or peritoneal surfaces. In view of the anatomic location and the presumed benign diagnosis, the cyst was unroofed and evacuated. The right HD was intubated with the distal limb of a T-tube extending into the common bile duct (CBD). The residual cyst cavity and subhepatic space were drained.

Postoperatively, the patient's jaundice resolved promptly. The final pathology report described amorphous intracystic, keratinous material and several pieces of tissue consisting of benign squamous cell

epithelium with underlying connective tissue (Fig. 2). Electron microscopy demonstrated mature squamous cells arising from the intrahepatic mass. Liver function studies were normal except for an elevated alkaline phosphatase of 254 U/L, at the time of discharge. A biliary fistula was managed uneventfully on an outpatient basis. A subsequent T-tube cholangiogram demonstrated rapid emptying onto the duodenum without obstruction, and the T-tube was removed. The patient did well for 3 months until he presented complaining of RUQ pain, increasing somnolence, anorexia, and dark urine.

Physical examination at that time demonstrated a temperature of 39°C, jaundice, and fullness in the RUQ. An abdominal CAT scan demonstrated a recurrent 6- to 7-cm hepatic cyst in the porta hepatis, a low attenuation mass in the anterior lateral aspect of the medial segment of the left lobe of the liver, and a large ill-defined mass contiguous with the cyst extending to the head of the pancreas. Percutaneous drainage with a 8.3 Fr pigtail catheter was performed to manage what was believed to be an infected biloma.

The patient was reexplored. A diffuse, infiltrative process with an aggressive desmoplastic reaction involving the residual cyst wall and adjacent liver and recurrent accumulation of the sebaceous-like material was noted. The hepatic artery and CBD could not be identified. The cyst wall infiltrated both the right and left HD and the portal vein. This precluded total removal of the cyst in this chronically ill patient. The cyst was debulked by excising a 1-cm rim of liver parenchyma



FIG. 2. Low power view of the fibrotic cyst wall lined by a thin layer of benign squamous epithelium. $\times 80$.

circumferentially with the cyst wall, leaving only the posterior cyst wall immediately involving the HD and portal vessels. Metastatic disease was identified in the left lobe of the liver.

Pathologic examination of the resected specimen showed a well-differentiated squamous cell carcinoma with desmoplastic reaction. The overall configuration was that of a benign cyst lined by mature squamous epithelium. The histologic appearance of the carcinoma was consistent with origin from this epithelium, in that, it was well differentiated with gradual change from benign to clearly malignant and invasive elements (Figs. 3 and 4, respectively). The carcinoma infiltrated adjacent liver parenchyma which also contained prominent chronic inflammation and neocholangiolar proliferation. Our pathologists concluded that this was a squamous cell carcinoma arising in a hepatic cyst. No specific adjuvant treatment was recommended by the oncology service. The patient was subsequently discharged, but died of complications of his disease 6 months after his initial presentation. No autopsy was obtained.

DISCUSSION

This is the first report of a SBNHC causing extrahepatic bile duct obstruction. In addition, the well-documented change from a benign simple cyst to a widely infiltrating, invasive carcinoma over 3–4 months suggests rapid spread from an occult focus of squamous metaplasia with malignant transformation (squamous neoplasm). It cannot be determined with any degree of

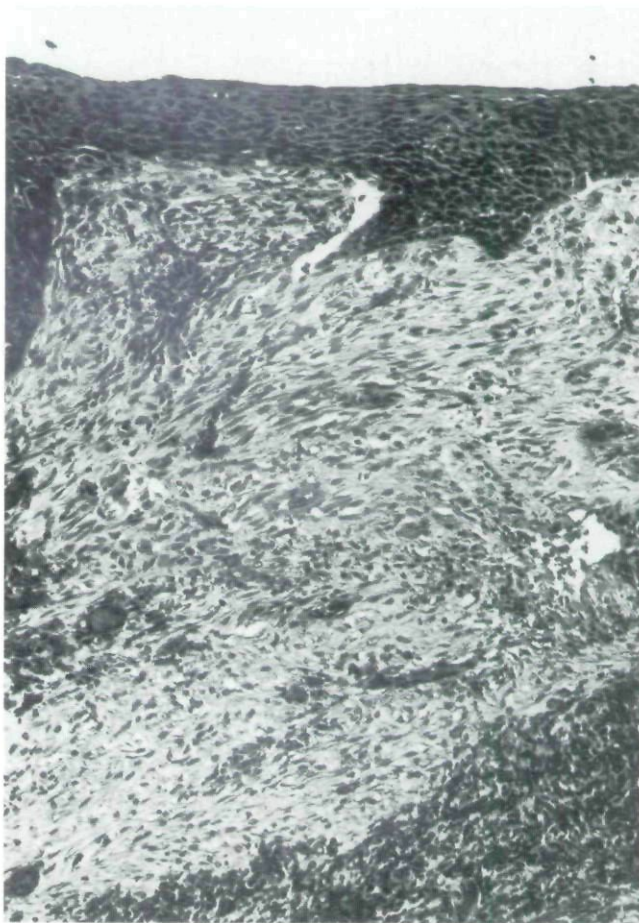


FIG. 3. Medium power view of tissue from the last operative procedure. The epithelial lining of the cyst in this area is thicker but still that of benign squamous type. $\times 190$.

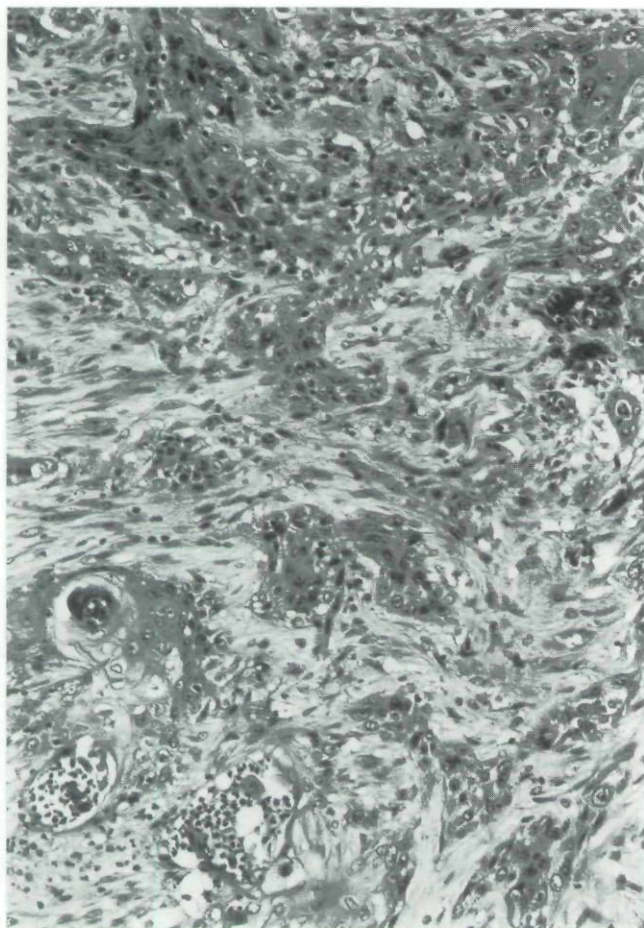


FIG. 4. This higher power section show invasive squamous cell carcinoma within the liver. Portions are very well differentiated but clearly invasive. $\times 480$.

certainly, at this time, whether or not this invasive carcinoma ultimately was derived from biliary ductal epithelium. However, since SBNHC are thought by some to arise from Meyenburg complexes (congenital rests of biliary epithelium) (3, 4), this distinction may be moot. Furthermore, there has been no documented case of survival beyond 6 months for any patient with squamous cell carcinoma of the liver, regardless of its origin (see Tables 1 and 2).

The prognosis of squamous cell carcinoma of the liver is grave despite extensive procedures to achieve total or near total removal of the lesion (3, 12). Neither chemotherapy nor radiation therapy have been shown to be beneficial in the management of this lesion (3). Survival from the time of diagnosis has not exceeded 1 yr, regardless of the form of treatment utilized (1, 3, 6-12).

The surgical management of solitary nonparasitic cysts of the liver has not been rigidly defined (14). Hepatic anatomic and local resections, drainage, marsupialization, and aspiration all have been described to give satisfactory results (14-17). Furthermore, the in-

cidence of malignancy in solitary nonparasitic hepatic cysts is exceedingly low. Therefore, major hepatic resections are not believed to be warranted when simple removal is precluded by the attachment of the hepatic cyst to vital structures or when there is extensive multilobular involvement. However, it is possible that, as additional reports of malignancy arising in such cysts are accumulated, these recommendations may be revised. It is also conceivable that certain histomorphological criteria may be defined that permit identification of those cysts from which carcinoma is likely to arise. Furthermore, it is possible that cell surface markers of malignancy or malignant potential will become available that will permit the identification of a case such as this one to be either malignant or significantly at risk for malignant transformation. It should be noted that adenocarcinomas arising from unilocular and multilobular cysts have also been reported and are similarly rare occurrences (4, 18, 19).

Only one out of 12 cases of unilocular hepatic cysts reported by Henson *et al.* (5) were lined with squamous epithelium. Furthermore, during a period of 36 yr and from 20,000 autopsies, only one case of squamous cell carcinoma arising from a hepatic cyst was observed (7).

The benign appearance of the epithelium lining the cyst wall in the present case (Fig. 3) emphasizes the fact that this carcinoma presumably arose from an occult focus of squamous neoplasia in the cyst wall. This underscores the point that, despite their benign appearance, these cysts may be potentially malignant.

We are reporting the fifth case of a squamous cell carcinoma arising from a solitary benign nonparasitic cyst. Data from such cases suggest that squamous epithelium in this setting may be susceptible to metaplasia and subsequent malignant transformation. Firm recommendations regarding the diagnosis and management of carcinoma arising in a SBNHC must await further experience and study.

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