Carcinosarcoma of the liver, defined by Ishak et al as hepatocellular carcinoma (HCC) "combined with differentiated sarcomatous elements," is a rare entity with a poor prognosis. Little is known about the risk factors, epidemiology, and pathogenesis of this entity. No more than 11 cases are found within the English literature in the past 40 years.2±12 The other 8 cases are differing views on the pathogenesis of this tumor. Findings in this case support the view that metaplasia of carcinomatous cells gives rise to the sarcomatous elements.

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Carcinosarcoma of the liver, defined by Ishak et al as hepatocellular carcinoma (HCC) "combined with differentiated sarcomatous elements," is a rare entity with a poor prognosis. Little is known about the risk factors, epidemiology, and pathogenesis of this entity. No more than 11 cases are found within the English literature in the past 40 years.2±12 The risk factors may be similar to those of HCC. Nine of the past 11 cases of liver carcinosarcoma have been reported in men. Five of the 11 cases report finding cirrhosis, 1 reports precirrhotic fibrosis, and 1 does not specify if cirrhosis was present. Two cases report patients with positive hepatitis B surface antibody and negative hepatitis B surface antigen with no apparent history of vaccination.5,10 Both cases were associated with cirrhosis. Alcoholic cirrhosis was reported in 1 case.12 The other 8 cases reported no history of toxic or viral exposure. Liver carcinosarcoma appears to be a disease of older adults, with an age range of 46 to 84 years.

All cases reviewed report a fatal outcome shortly after initial presentation or diagnosis, the longest survival being 9 months after diagnosis.10 Interestingly, 6 of the 11 cases reported are from Japan. This may result from a higher report rate, a higher rate of diagnosis, or a truly higher prevalence of this tumor in Japan compared with other countries. Most patients present in the same way as patients with other liver tumors: abdominal pain or distension, anorexia, and weight loss. Because this entity is rare, carcinosarcoma of the liver has in all of the cases been clinically mistaken for more common liver tumors, such as HCC, prior to resection or autopsy. Presented here is an autopsy case of carcinosarcoma of the liver and a review of the literature, pathogenesis, and classification of mixed tumors of the liver.

REPORT OF A CASE

A 51-year-old white woman with hypertension and insulin resistance presented with 2 months of right-sided abdominal pain. There was no history of alcohol or illicit drug use. Computed axial tomography scan revealed an 8.0-cm right liver mass and 1.0-cm abdominal lymph nodes. Chest radiograph and colonoscopy yielded negative results. Positron emission tomography scan demonstrated increased metabolism within the liver mass and paracaval lymph nodes. Percutaneous needle biopsies of the liver mass were interpreted as a spindle cell neoplasm and sent to 2 separate consultants. One believed the tumor to be a spindle cell sarcoma. The other interpreted the tumor to be a sarcoma, HCC, or cholangiocarcinoma. The patient was treated with imatinib. She reported a 20-pound weight loss in the month prior to admission for exploratory laparotomy. Laboratory findings included: serum carcinoembryonic antigen (CEA), 73.8 ng/mL (73.8 μg/L); α-fetoprotein, 66.7 ng/mL (66.7 μg/L); CA 19-9, 391 U/mL (391 kU/L); alanine aminotransferase, 34 U/L; aspartate aminotransferase, 143 U/L; alkaline phosphatase, 224 U/L; and γ-glutamyltranspeptidase, 143 U/L; and alanine phosphatase, 224 U/L. Hepatitis serologies were not drawn. On exploratory laparotomy, portal vein thrombosis, extensive tumor within the liver, and enlarged splenic lymph nodes were found. The gallbladder was removed and showed few serosal tumor implants and a normal cystic duct. Seventy-six sections of tumor were studied. They were interpreted as metastatic small cell carcinoma to the liver, gallbladder, and splenic lymph nodes; liver adenocarcinoma with metastases to the gallbladder; and primary HCC. Splenic lymph node sent for flow cytometry showed no lymphoproliferative disorder but a large population of CD56-positive, CD45-negative cells. The patient developed hepatoportal syndrome and died on postoperative day 12. An autopsy was performed.

PATHOLOGIC FINDINGS

At autopsy, there was more than 5000 mL of serous ascites. The cirrhotic liver weighed 2200 g. An estimated...
40% of the liver parenchyma was replaced by multiple, diffuse tumor nodules. The right liver contained the largest mass (14.0 × 15.0 × 9.0 cm). Large soft tan masses contained firmer gray-tan nodules, areas of necrosis, and calcified areas. A large tumor embolus occupied the hepatic veins, extending into the inferior vena cava. Portal vein thrombosis was due to compression by tumor. The para-aortic, juxtaesophageal, celiac, and splenic lymph nodes measured up to 6.0 cm, and some were completely calcified. The body and tail of the pancreas contained a 6.0 × 4.0 × 2.5-cm hemorrhagic, multinodular lesion. Forty-two sections of tumor were studied. No lesions of the bile ducts, endometrium, mesentery, kidneys, lungs, or gastrointestinal tract suggested malignancy.

**Histology**

The carcinomatous component consisted of HCC, fibrolamellar type; neuroendocrine carcinoma; and adenocarcinoma. The HCC consisted of cords of polygonal hepatocytes with pleomorphic nuclei and periodic acid-Schiff-negative cytoplasmic clear inclusions, separated by lamellated fibrous bands (Figure 1). The cells stained positive for hepatocyte-specific antigen (HSA). Clear cell HCC found within portal veins stained positive for HSA. On sections taken during exploratory laparotomy, the HCC cells were focally positive for cytokeratin (CK) 7 and negative for CK20, CEA, and α-fetoprotein. The nonneoplastic hepatic parenchyma consisted of regenerating nodules separated by bands of bridging fibrosis. Right liver sections showed sheets of small round blue cells (Figure 2). They stained positive for neuron-specific enolase and synaptophysin and negative for CD45, chromogranin, leukocyte common antigen, and CEA. Metastases to vertebral bone marrow, the tail and body of the pancreas, left ovary, and right lung were found. The aforementioned flow cytometry results supported the diagnosis of neuroendocrine carcinoma. Adjacent to this cell population in the liver were atypical cells forming glandular structures (Figure 3) positive for CEA, CK7, and CK20 and negative for α-fetoprotein and HSA. Few signet ring cells were admixed with hepatocytes.

The sarcomatous component included undifferentiated spindle cell sarcoma, rhabdomyosarcoma, leiomyosarcoma, and osteosarcoma. In the liver were areas of spindle cell stroma with abundant mitoses. These were vimentin positive and focally positive for muscle-specific actin. Spindle cell neoplasm was found within the hepatic vein and inferior vena cava. Within a para-aortic lymph node, this cell population stained focally positive for smooth muscle actin (Figure 4). Bone formation with bizarre atypical osteocytes, representing osteosarcoma, was identified in the spindle cell stroma of the liver and nodes (Figure 5). The nodes also contained an additional population of poorly differentiated cells with highly pleomorphic nuclei and bizarre mitotic figures. These cells stained positive for CK7 and CK20 and focally positive for HSA. Scattered cells within this poorly differentiated cell population were plump with eosinophilic cytoplasm and eccentric nuclei, resembling rhabdomyoblasts. Rare “strap” cells were identified (Figure 6). The eosinophilic cells and strap cells stained positive for desmin. All carcinomatous and sarcomatous tumor components stained negative for CD117 (c-Kit).

The HSA and chromogranin stains were purchased from Novocastra Laboratories, Newcastle upon Tyne, UK. The CEA stain was purchased from Boehringer Mannheim, Mannheim, Germany. All other stains were from DakoCytomation, Carpinteria, Calif.

**COMMENT**

Few cases of carcinosarcoma have been described in the literature. According to Ishak et al,1 the term **carcinosarcoma of the liver** should be reserved for hepatic tumors with both HCC and a non–spindle cell sarcoma such as osteosarcoma, chondrosarcoma, or rhabdomyosarcoma. By this definition, the case described here meets the criteria for carcinosarcoma of the liver. Ishak et al1 report finding 1 case in the literature in addition to 3 cases known to the Armed Forces Institute of Pathology.3,5 One of these 3 cases was HCC with leiomyosarcoma, and 2 were HCC with osteosarcoma. In an attempt to update the literature, an exhaustive search of the English literature was performed, revealing 11 additional cases6-12 in the past 40 years that fulfill the definition of carcinosarcoma of the liver according to Ishak et al.1 In contrast, Nomura et al,13 in a case reported in this journal in 2000, used the definition of carcinosarcoma according to the World Health Organization, in which the carcinomatous component may be either cholangiocellular or hepatocellular. They classified their case of cholangiocarcinoma with chondrosarcoma as liver carcinosarcoma.

There remains controversy regarding the pathogenesis of liver carcinosarcoma. Several authors argue that the tumor arises from a multipotent hepatic blastema, which may differentiate into both carcinomatous and sarcomatous neoplasms.3,4,12 Other authors favor the stance that there is transformation of HCC into mesenchymal elements.2,3 The presence of transitional or transformational zones between carcinoma and sarcoma in their cases supports this view. Keratin-positive sarcoma cells in the context of carcinosarcoma suggest that there is an epithelial origin of the sarcomatous component.9 Others believe that there is transformation of HCC into multipotent immature cells, which in turn redifferentiate into sarcomatous components such as rhabdomyoblastic cells.8 In 2 reported cases of liver carcinosarcoma, immunohistochemical stains showed that a subset of sarcomatous cells stained positive for S100.10,11 In 1 case, this occurred in cells appearing to be chondroid,10 whereas in the second case, these cells were believed to have a schwannomatous differentiation.11 Clonality studies of relatively more common carcinosarcomas, such as those arising in the uterus, lungs, breast, and gastrointestinal tract, suggest a monoclonal origin.14 With the variability seen in this case, an aberrant multipotent stem cell origin was considered. However, CD117 staining was negative for all components of the tumor.

It appears clear from previous reports and the current report that the vast majority of liver carcinosarcomas are combination tumors rather than collision tumors. In the case presented, there were sarcomatous elements found within the lymph node metastases that were not found within the primary liver tumor. The use of HSA immunohistochemical stain has not been reported in the previous cases of liver carcinosarcoma. Cells within the poorly differentiated regions stained positive for HSA, and thus it is possible that this indicates an area of transformation or dedifferentiation of hepatoma cells. These results, however, should be interpreted with caution. The sensitivity and specificity of HSA staining of carcinosarcomas are unknown, although such staining appears to be a helpful...
Figure 1. A, Hepatocellular carcinoma, fibrolamellar type, showing clear cytoplasmic inclusions and lamellar fibrosis (hematoxylin-eosin, original magnification ×100). Inset (B) shows pale bodies (hematoxylin-eosin, original magnification ×200).

Figure 2. Neuroendocrine carcinoma within the liver consisting of small round blue cells (hematoxylin-eosin, original magnification ×100).

Figure 3. Adenocarcinomatous element within the liver consisting of malignant mucus-producing glands (hematoxylin-eosin, original magnification ×200).

Figure 4. Spindle cell sarcoma stains focally positive for smooth muscle actin within a lymph node (original magnification ×200).

Figure 5. Focus of osteosarcoma within a lymph node displaying osteoid formation amid malignant sarcomatous cells (hematoxylin-eosin, original magnification ×200).

Figure 6. Rhabdomyoblasts found within an area of poorly differentiated sarcoma in a lymph node (hematoxylin-eosin, original magnification ×400).
marker for HCC and hepatoblastoma. Of note, Ojima et al report a case of liver carcinosarcoma in which HCC was not identified in the liver, despite thorough sampling, but was found within the metastases to lymph nodes, thyroid, pericardium, and intravascular spaces. These observations support the view that there is an extreme form of metaplasia of carcinoma into sarcoma underlying this unusual neoplasm.

Several cases that authors have classified as mixed malignant tumor of the liver, hepatoblastoma, and other terms, by the aforementioned Armed Forces Institute of Pathology definition, carcinosarcomas. Tumors in which HCC is associated with a spindle cell component without further differentiation are classified as spindle cell or sarcomatoid HCC. In addition, mixed tumors of the liver may occur with well-differentiated sarcomatous elements and carcinomatous elements in the absence of HCC. These tumors are designated as nonhepatocytic malignant mixed tumors.1

In this case, the bulk of the tumor resided in the liver and contained a component of HCC of the fibrolamellar type adjacent to regions of osteosarcoma, spindle cell sarcoma, adenocarcinoma, and small cell carcinoma. Several lymph nodes contained all components of the tumor, and separate nodules within the liver contained various mixtures of carcinoma and sarcoma. The possibility of the neuroendocrine carcinoma arising in the pancreas rather than the liver cannot be ruled out. Thorough sampling of the pancreas showed no other tumor components. No neuroectodermal tumor was identified, thus separating this tumor from a teratoma. The underlying hepatic tissue in this case revealed cirrhosis, which is a well-known risk factor for HCC. The cause of cirrhosis in this patient is not known. To our knowledge, this is the first case of liver carcinosarcoma with this many differentiated heterologous sarcomatous features arising in the fibrolamellar variant of HCC.

References