

A Rare Nonhepatocytic Primary Liver Neoplasm with an Unusual Presentation: Ossifying Malignant Mixed Epithelial and Stromal Tumor

Abstract

We present a case of a rare liver neoplasm – Ossifying malignant mixed epithelial and stromal tumor. This entity has well-delineated morphological and immunohistochemical features, and so can be easily diagnosed, even with core biopsy tissue. Our patient was a middle-aged male, which is unheard of in the literature of this disease. He had a bad recurrence of the disease after surgical removal of the tumor, unlike the previously reported cases with the same diagnosis, where the patients lived for almost a decade after surgery without recurrence. This neoplastic disease can thus take a destructive course, and a change in treatment methods such as neoadjuvant or adjuvant chemotherapy should be thought of, to make it more beneficial and effective.

Keywords: Adenocarcinomatous, mixed, nonhepatocytic, ossifying, primary, sarcomatous

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Introduction

Ossifying malignant mixed epithelial and stromal tumor of liver is a rare nonhepatocytic primary liver neoplasm.^[1] Our case is peculiar because of the age and sex of the patient, the course of the disease, and the site of its recurrence. This provokes thought as to whether other modalities of treatment such as neoadjuvant or adjuvant chemotherapy or radiation should be administered in similar cases.

Case Report

A 52-year-old male patient presented to a gastrointestinal surgeon with complaints of vague abdominal pain of 2 months' duration. He was a smoker for 30 years and consumed alcohol two to three times a week for 30 years.

A physical examination revealed enlarged liver with tenderness in the right hypochondrium and epigastric region.

A computed tomography (CT) scan of the abdomen was done, with oral and intravenous bolus contrast. A large mass, occupying segments 1, 5, 6, and 4 of the liver, was detected [Figure 1]. The tumor measured 14 cm × 10 cm. Magnetic resonance imaging (MRI) done showed a large, moderately defined, lobulated, heterogeneously T2 hyperintense/T1

hypointense mass lesion [Figure 2]. The lesion had peripheral irregular soft-tissue component showing diffusion restriction. There was a peripheral irregular rim of heterogeneous enhancement in arterial phase with varying levels of washout in portal and delayed phases, with central nonenhancing areas denoting necrosis and cystic changes in CT and MRI. Hepatocellular carcinoma with calcification was suspected. No other lesion was detected in the abdomen.

Before surgery, viral markers were negative. Alpha fetoprotein (AFP) was 1.65 ng/ml; carcino-embryonic antigen was 1.2 ng/ml and CA19-9 was 31 U/ml.

A diagnostic biopsy was done which showed extensive areas of calcification with intervening areas of spindle and multinucleate giant cells, with mitoses around 3/10 high-power fields (HPFs).

A whole body positron emission tomography-CT scan with fludeoxyglucose showed a hypermetabolic lesion in the liver, with no suggestion of metastasis anywhere else.

Peroperatively, through a Mercedes-Benz incision, a large tumor, occupying segments 4, 5, 6, and 1 of liver and abutting transverse mesocolon were found, invading the common bile duct and the right branch of portal vein. Inferior vena cava was free of tumor invasion. There was no metastatic

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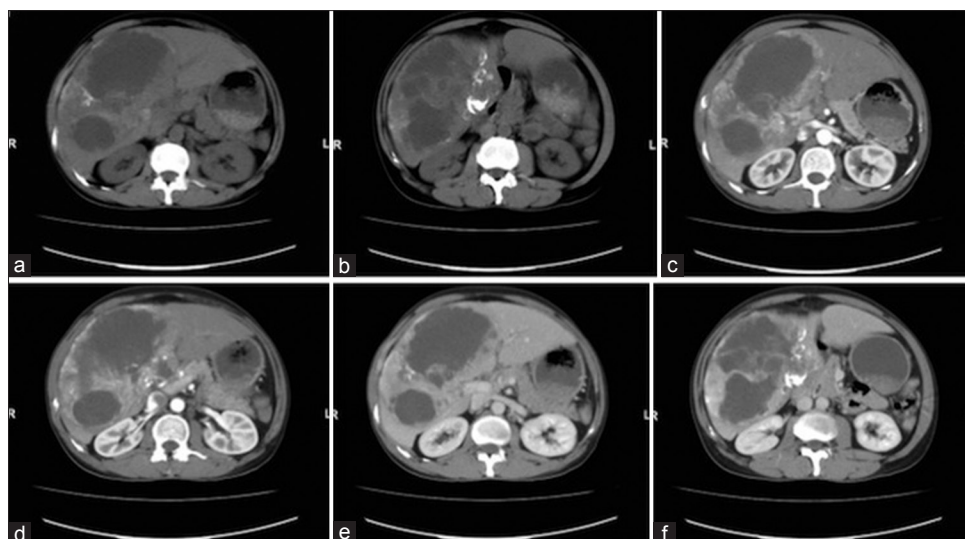


Figure 1: Computed tomography abdomen scan showing liver mass with necrosis and peripheral calcification. Computed tomography plain (a and b). In arterial phase (c and d). In venous phase (e and f)

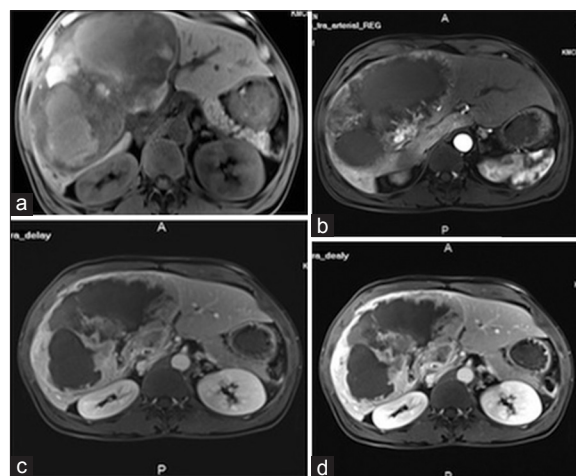


Figure 2: Magnetic resonance imaging scan of abdomen. Plain (a). In arterial phase (b). In portal venous phase (c). In venous phase (d)

lesion or gross lymph node invasion or ascites. An extended right hepatectomy was done using a cavitron ultrasonic surgical aspirator and harmonic scalpel diathermy. Bile duct was resected up to the left lateral segment duct. A Roux-en-Y hepaticojejunostomy to segment III bile duct was done. A portion of gastric pylorus found attached to the tumor was also resected.

Gross findings

The right hepatectomy specimen of liver measured 22 cm × 21.5 cm × 11.5 cm. Cut section showed a solid and cystic lesion measuring 19 cm × 15 cm × 13 cm, with a few bony areas. The liver capsule was completely intact.

Microscopic description

The tumor consisted of extensive sheets of pleomorphic spindle cells with mitotic figures up to 5/10 HPFs. Many scattered osteoclastic giant cells, new bone spicules,

and osteoid were frequently seen [Figure 3a-c]. The small portion of pylorus showed focal pools of mucin with tiny clumps and glands of mildly pleomorphic cells [Figure 3d and e], along with bone, osteoid, sarcomatous spindle cells, and osteoclastic giant cells. The tumor areas were surrounded by a fibrous wall and muscle layer of pylorus focally, the resection margin thus free of tumor involvement.

A histologic diagnosis of ossifying malignant mixed epithelial and stromal tumors of the liver was made.

Immunohistochemistry was done. Vimentin was strongly positive in plump stromal cells [Figure 4a]. Smooth muscle actin (SMA) was focally positive in stromal cells [Figure 4b]. Pan-cytokeratin, CK19 [Figure 4c], and CK7 were positive in epithelial cells. CK20, Hep-par1 [Figure 4d], AFP, desmin, and S-100 were negative.

The patient was followed up on similar lines as the previous cases with this diagnosis.^[1] After 2 months, the patient appeared cachectic with a poor performance status and had a subcutaneous nodule in the epigastrium, above the previous surgical site, with histological features same as the primary [Figure 3f]. A surgical removal was done. Radiation to the site was suggested, which the patient declined. The patient is on follow-up for the past couple of months.

Discussion

Less than thirty cases of malignant mixed hepatic tumors of the liver have been reported so far in adults.^[1] Many of these were later found to be mixed hepatoblastoma, primary hepatocellular carcinoma with sarcomatous metaplasia, and epithelioid hemangioendothelioma.^[1] Most of the mixed tumors of liver described earlier were in children and adolescents.^[2] In adults, the mixed hepatic tumors are different from hepatoblastomas histologically and are frequently associated with calcification.^[3]

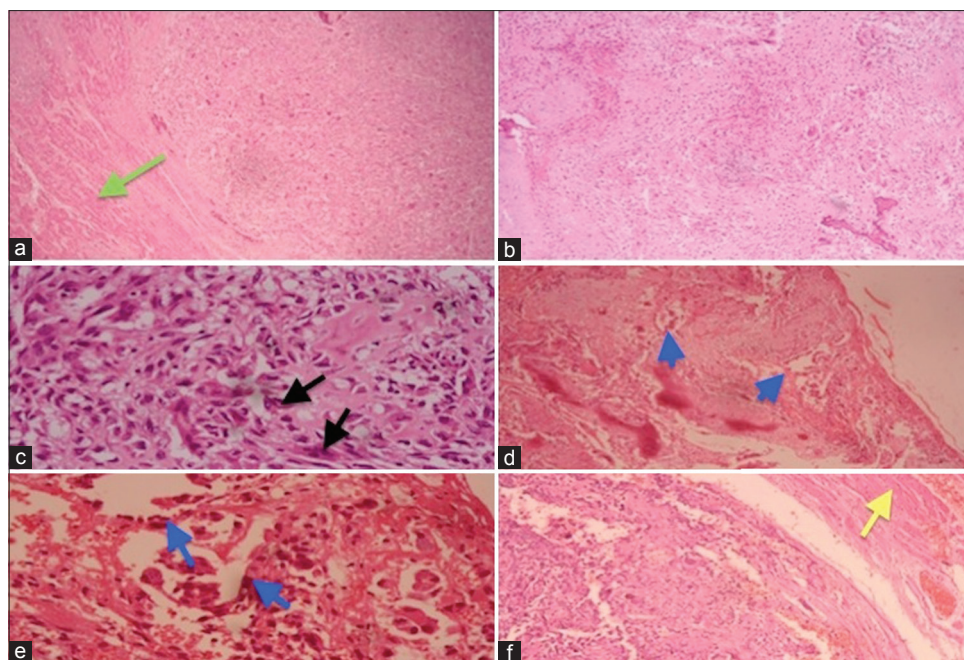


Figure 3: Microscopic picture: Sarcomatous areas with osteoid, separated from normal liver parenchyma (green arrow) (H and E, $\times 100$) (a). Tumor with spindle cells, multinucleated giant cells, and ossification (H and E, $\times 100$) (b). Ossification and multinucleated giant cells (black arrow) (H and E, $\times 400$) (c). Glandular areas (blue arrow) (H and E, $\times 100$) (d). Glandular areas (blue arrow) (H and E, $\times 400$) (e). Tumor metastasis in the subcutaneous region, rimmed by skeletal muscle (yellow arrow) (H and E, $\times 100$) (f)

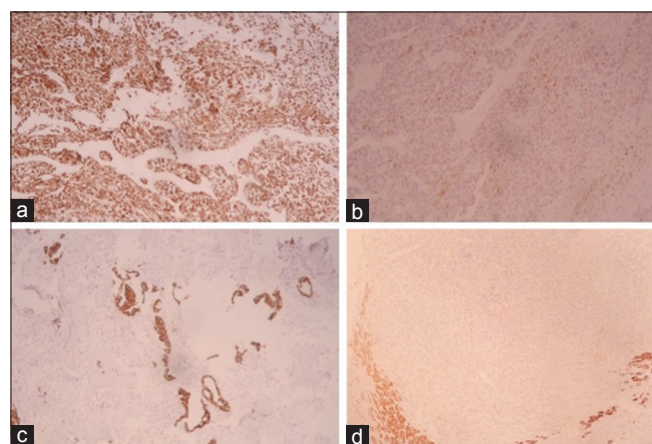


Figure 4: Immunohistochemistry: Vimentin is positive in the stromal cells ($\times 100$) (a). Smooth muscle actin is faintly positive in the stromal cells ($\times 100$) (b). CK19 is positive in the epithelial cells ($\times 100$) (c). Hep-par 1 is negative in the tumor ($\times 100$) (d)

The mixed tumors of liver with three distinctive features such as nests of malignant spindle cells, adenocarcinomatous areas, and occasional-to-extensive ossification were descriptively named “ossifying malignant mixed epithelial and stromal tumors of liver.”^[1] Other names such as “nested stromal epithelial tumor (NSET) of the liver, ossifying stromal epithelial tumor, and desmoplastic nested spindle cell tumor” were also given to similar tumors.^[4] These tumors morphologically lacked bile, cells resembling hepatocytes, and also bile canaliculi.^[1] They could be classified as nonhepatocytic liver tumors.^[1,5] In our case, a differential diagnosis of hepatoblastoma, which rarely

occurs in adults,^[6] was ruled out because of the absence of blastemal elements and unelevated AFP. The possibility of the other mixed liver tumor in adults, carcinosarcoma, was also eliminated since the epithelial component in our case was not resembling that of hepatocellular carcinoma,^[7,8] and it was negative for Hep-par 1. The stromal component did not show poorly differentiated spindle cells, rhabdomyosarcoma, leiomyosarcoma,^[7] fibrosarcoma, or pleomorphic sarcoma.^[8]

The previously affected adults with ossifying malignant mixed epithelial and stromal tumors of liver were mostly women^[9,10] and aged <33 years.^[4]

A male patient of the same age as our case has not been reported so far. Some of the cases described earlier presented with Cushing syndrome due to excessive adrenocorticotrophic hormone (ACTH) secretion.^[4,11] Our patient, however, did not present with such features. CT scan done with contrast showed calcification in the enhancing tumor, which should arouse the suspicion of a calcifying mixed tumor.^[12] MRI being more efficient in cases of liver imaging was done following CT scan.^[13]

Immunohistochemically, the epithelial tumor cells in this neoplasm stain positive for cytokeratin AE1/3, focally for CK19, while the nested spindle cells and stroma stain positively with vimentin^[1,4] and SMA. ACTH, CD117, CD56, and CD99 might also be positive in the epithelioid cells^[11,14] (Atlas of Genetics and Cytogenetics in Oncology and Haematology. www.AtlasGeneticsOncology.org, www.e-immunohistochemistry.info).

Partial hepatectomy has been the choice of treatment in ossifying malignant mixed epithelial stromal tumors^[1,4,5] and so was it in our case. Chemotherapy has been tried earlier in pediatric unresectable NSETs of liver, but this being a rare neoplasm, the advantage has not been clear.^[11] While hepatoblastomas have been found to be chemosensitive,^[6] and in adult hepatoblastomas, chemotherapy using doxorubicin, cisplatin, vincristine, 5-fluorouracil, and cyclophosphamide has been considered, especially in large tumors, to shrink the lesion and enable complete resection,^[6,15,16] surgical resection has been the treatment of choice in carcinosarcomas and ossifying mixed epithelial and stromal tumors.^[7,8]

Prognosis has been variable in ossifying epithelial stromal tumors,^[1,4,17,18] though most patients have survived for almost a decade after the surgical removal of the tumor by partial hepatectomy. This has been considered a low-grade malignancy.^[4,17] However, our case is an exception since it recurred and behaved aggressively.

Conclusion

Thus, the impression that this category of liver tumors is usually of low-malignant potential is re-thinkable. A change in treatment modality for this tumor, such as adjuvant or neoadjuvant chemotherapy, might also be warranted. Diagnosis of this entity on radiology, along with tru-cut biopsies, is possible and should be considered if morphological features are consistent with, that can help in planning the correct modality and intensity of treatment. Accounts of this neoplasm, such as this one, may help to further our knowledge about the biology of the disease, and thus the management of the same.

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Conflicts of interest

There are no conflicts of interest.

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