An Atypical Presentation of Hepatocellular Carcinoma with Multisite Metastasis following a Curative Liver Transplant

Patrick Gidley[1]   Anand Patel[2]   Guliz A. Barkan[3]   Anugayathri Jawahar[4]

[1] Department of Radiology, Loyola University Medical Center, Maywood, Illinois, United States

[2] Loyola University Chicago- Stritch School of Medicine, Maywood, Illinois, United States

[3] Department of Pathology, Loyola University Medical Center, Maywood, Illinois, United States

[4] Department of Radiology, Northwestern University- Feinberg School of Medicine, Chicago, Illinois, United States

Address for correspondence Anugayathri Jawahar, MD, Department of Radiology, Northwestern University- Feinberg School of Medicine, 676, N St. Clair Street, Chicago, IL 60611, United States (e-mail: anugayathri.jawahar@nm.org).

Abstract

Keywords
► hepatocellular carcinoma
► HCC metastases
► pancreatic metastases
► gastric metastases
► post-liver transplant metastases

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, and liver transplantation is usually curative. HCC recurrences are rare after curative treatment options, although they are prevalent depending on various risk factors. We present a 71-year-old female patient with an unusual pattern of disease progression following a curative liver transplant with a metastatic presentation in the absence of alpha-fetoprotein elevation after 3 years of disease-free clinical presentation. We present this case to emphasize the importance of intermittent cross-sectional imaging in addition to ultrasound screening in HCC surveillance.

Introduction

A 71-year-old female patient with a history of chronic hepatitis C, cirrhosis, and portal hypertension had a 3.2 cm arterial enhancing lesion with washout in hepatic segment II consistent with hepatocellular carcinoma (HCC). Since the patient was already listed for a liver transplant, it was decided on consensus at the multidisciplinary team discussion to be treated with yttrium-90 radioembolization. The patient had a favorable treatment response without extrahepatic disease. (►Fig. 1A–E) The native liver hepatectomy specimen showed an intact nodular surface with multiple nodules, the largest nodule measuring 1.8 cm, which was reported to be moderately differentiated HCC with negative margins.

Transplant liver ultrasound surveillance was negative for recurrence, and serum alpha-fetoprotein (AFP) levels were normal until 3 years later when she presented to the emergency department with hematemesis causing hemodynamic instability. She underwent esophagogastroduodenoscopy, which revealed a nonbleeding gastric ulcer with an adherent clot and gastric antral severe erythema (►Fig. 2A, B). Both lesion biopsies with hematoxylin and eosin (►Fig. 3A) and immunohistochemical staining showed strong, homogenous positivity for glutamine synthetase (►Fig. 3B) and CK8/18 (►Fig. 3C), similar immunostaining as the HCC of native liver.

Computed tomographic (CT) chest, abdomen, and pelvis revealed multiple metastases, including a 10 cm left lower
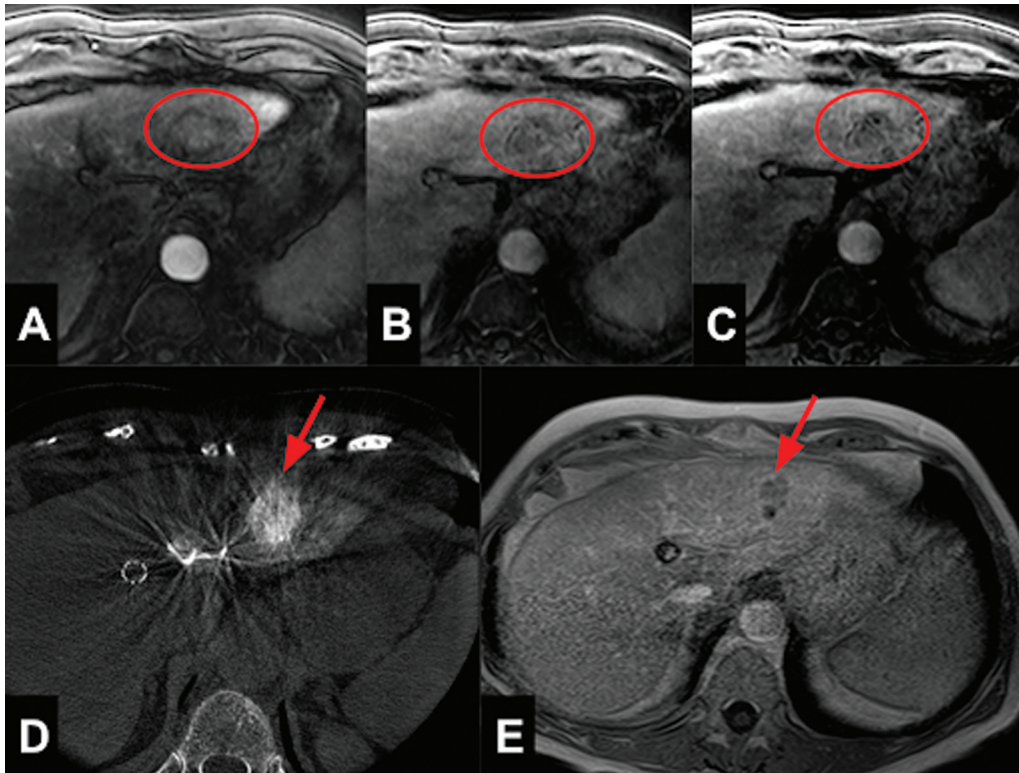
Fig. 1 (A) Pretreatment magnetic resonance imaging (MRI): Axial T1 post-contrast sequence in early arterial phase demonstrating 2.9 cm arterial enhancing lesion in segment 2 of the liver (circle), categorized as LI-RADS 4 lesion. Post-contrast T1-weighted images in the portal venous phase (B) and delayed phase (C) demonstrating contrast washout in the lesion (circle). (D) Pre-yttrium 90 planning computed tomography image demonstrating arterial enhancing lesion in segment 2 (arrow). (E) 3-month post-treatment MRI, post-contrast axial T1 weighted sequence with fat suppression showing the decreased size and absent enhancement in the treated lesion (arrow). LI-RADS, liver imaging reporting and data system.
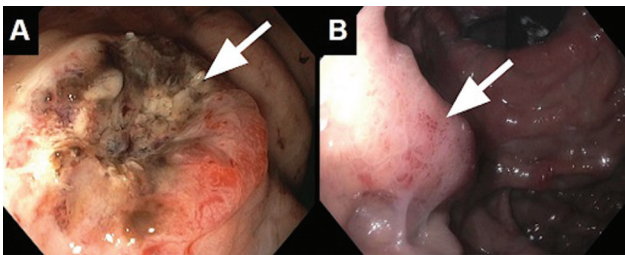

Fig. 2 (A) Endoscopic images of the gastric fundus demonstrating an ulcerated mass (arrow) and (B) a second inflamed and erythematous region with contact bleeding (arrow).

lobe solid pulmonary mass with central necrosis invading the left inferior pulmonary vein (►Fig. 4A, B) and bilateral small pleural effusions; new pathologic compression deformities at L1 and L3 vertebral bodies (►Fig. 4E); an infiltrative, 10 cm hypoenhancing solid mass with areas of necrosis in the pancreatic body and tail (►Fig. 4C), with tumor thrombus in the splenic and main portal veins (►Fig. 4D). Fine-needle aspiration of the pancreas with Papanicolaou stain (►Fig. 5A), Diff-Quik stain (►Fig. 5B), and immunohistochemical staining showed positivity for glutamine synthetase (►Fig. 5C) and CK8/18 (►Fig. 5D), similar to the primary HCC in the native liver and gastric biopsy results. Findings were incidental without clinical symptoms related to the organ of origin. The follow-up CT 4 weeks later revealed multiple new arterially-enhancing hepatic lesions with early

venous washout, consistent with recurrent multifocal HCC in the transplanted liver (►Fig. 6A, B) Patient's AFP levels were normal: pre-transplant 3.1 ng/mL, post-transplant 1.8 ng/mL, and upon detection of metastatic disease 3.7 ng/mL. CA 19-9 was normal, measured at 8 U/mL.

She had poor tolerance to two infusions of oxaliplatin and hence discontinued. The patient opted for comfort care measures. She expired at home 4 months later.

Discussion

HCC is the most common primary liver cancer and the second most common cause of death from all malignancies.[1–3] Treatments for HCC vary based on initial staging, but transplants tend to be curative when the disease is confined to the liver. Selection for liver transplantation has traditionally been based on tumor size and number according to the Milan criteria. HCC recurrence is reported in 15 to 20% of patients despite treatment.[4,5] The risk for recurrence depends on various factors, including nonresponse to treatment before transplant, waiting time to transplant, time to recur after treatment, viral etiology, elevated AFP levels, increased metabolic activity on positron emission tomography-computed tomography (PET-CT), tumor staging, and microvascular invasion on histology.[6,7] Literature reports recurrence within the first year of liver transplantation with single-site disease, and AFP levels less than 100 ng/mL are associated with better survival.[6,8] However, detecting recurrence can be
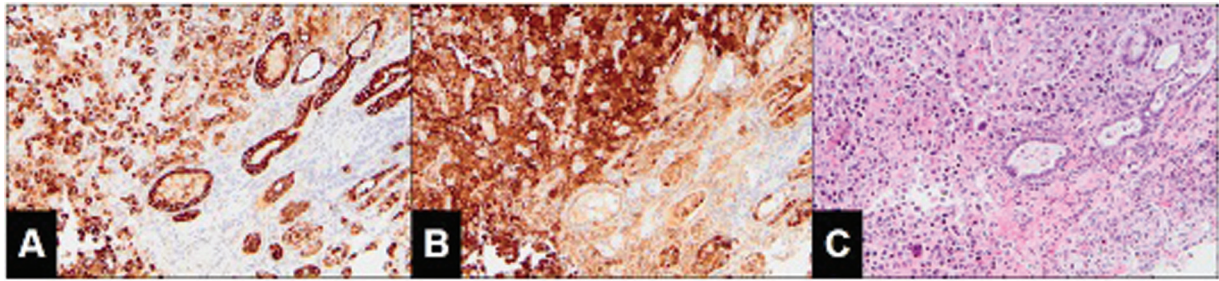
Fig. 3 Gastric biopsy: (A) Hematoxylin and eosin staining: Sections show a poorly differentiated carcinoma with focal signet ring cell features between the benign gastric glands. The tumor cells are pleomorphic, hyperchromatic, and are focally associated with necrosis. Immunohistochemical staining, high power: Tumor cells show diffuse, strong, and homogenous positivity for glutamine synthetase (**B**) and CK8/18 (**C**), in keeping with the hepatic origin of the tumor.
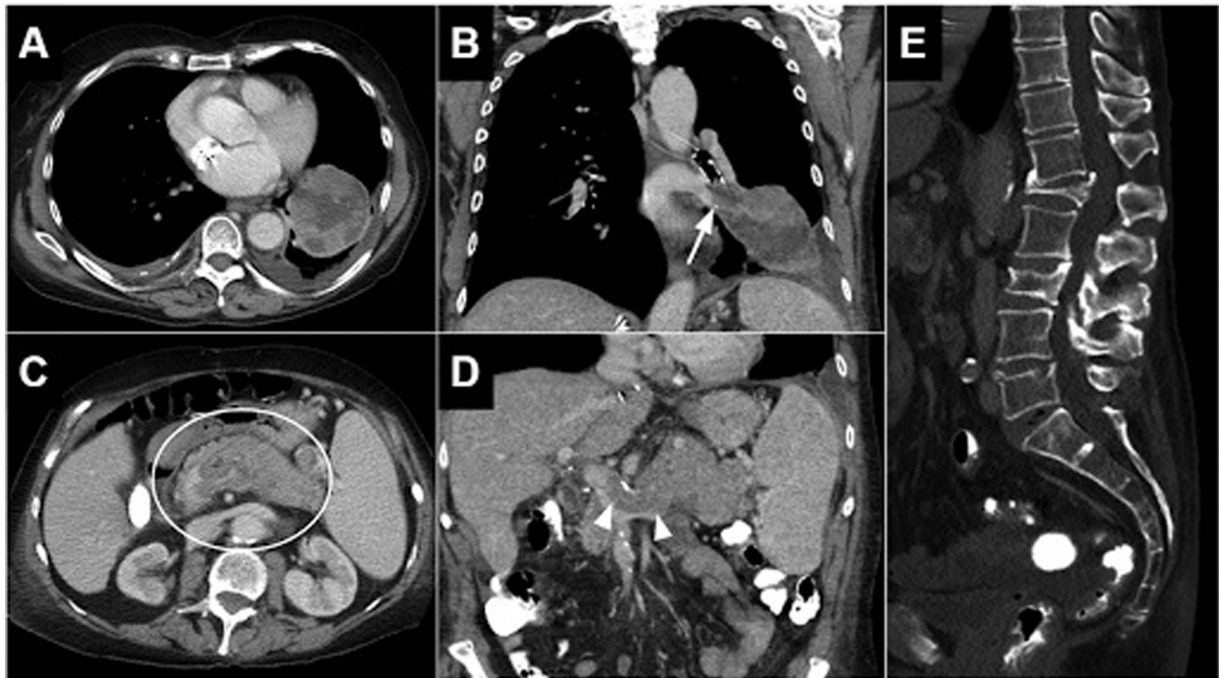

Fig. 4 (A, B) Axial and coronal computed tomography (CT) of the chest with IV contrast demonstrating large 10 × 7 cm solid left lower lobe pulmonary mass with central necrosis, infiltrating the left inferior pulmonary vein (arrow). Bilateral small pleural effusions were present. (C, D) Axial and coronal CT of the abdomen with IV contrast demonstrating an infiltrative, 10 cm hypoenhancing mass in the body and tail of the pancreas (circle). A tumor thrombus infiltrates the splenic and main portal vein (arrowheads). (E) Pathologic compression deformities at the L1 and L3 vertebra.

difficult because patients may remain asymptomatic or present with nonspecific symptoms.

The most common sites for extrahepatic metastases are lungs, abdominal lymph nodes, bone, and adrenal glands.[1,2,8–11] Gastric and pancreatic metastases are particularly rare, especially after curative liver transplantation. Gastric metastasis from HCC was first reported in 1985 with 0.08% reported incidence.[2,12,13] These are usually incidental or present with hematemesis/unexplained anemia and have a poor prognosis.[2,9] They more commonly directly spread from the left lobe HCC or rarely hematogenous spread of tumor thrombi from hepatofugal flow in patients with HCC and portal hypertension.[9,13–15]

Similarly, the incidence of pancreatic metastasis from HCC is reported as 2.7 to 5.6%, either synchronous metastases at the time of primary tumor diagnosis or detected as an incidental finding on autopsy.[1,11,16] It is difficult to differentiate primary from metastatic pancreatic malignancy as they have similar clinical and imaging presentations, although the treatment and prognosis differ.[1] Pathological diagnosis with immunohistochemical staining remains the mainstay of differentiating these.[1]

While there is no standard protocol to monitor HCC recurrence in transplant patients, often a combination of serum AFP levels and ultrasound or magnetic resonance imaging is used for surveillance due to poor sensitivity and specificity of AFP levels alone.[2,17] The pitfall with normal AFP levels in HCC patients can be due to small size or well-differentiated primary tumor.[1] Similarly, CA 19-9 is nonspecific since increased levels can be seen in biliary tract infections and other gastrointestinal malignancies.[1] PET-CT is reserved for staging workup to evaluate disease extent
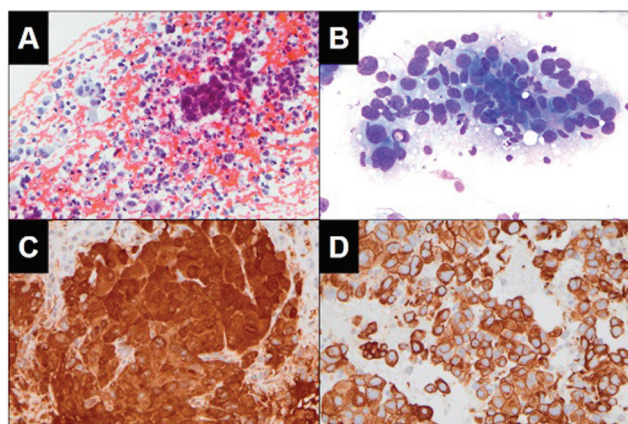
Fig. 5 Pancreas fine-needle aspiration: (A) The Papanicolaou stained smear shows scattered single cells and occasional three-dimensional clusters formed by pleomorphic cells with high nuclear-cytoplasmic ratio, scant granular cytoplasm, centrally located nuclei with occasional bi- or multinucleation, and prominent nucleoli. (B) The Diff-Quik stained smears show a poorly differentiated carcinoma with hints of glandular formation and occasional cells with binucleation. Immunohistochemical stains, high power: The tumor cells show a diffuse, strong, and homogeneous positivity for glutamine synthetase (**C**) and CK8/18 (**D**) similar to the gastric biopsy.

with a sensitivity of 77% and specificity of 98%.[2] The sensitivity decreases further when metastases are small or well-differentiated.[2,17]

The management of metastatic pancreatic cancer depends on the multiplicity of lesions and resectability. Resection is for solitary lesions amenable to resection, especially when it presents as a synchronous metastatic tumor with primary HCC.[1] In other patients, chemotherapy with gemcitabine or Folfirinox is given for metastatic pancreatic and/or gastric cancers.[1]

Liver transplants remain curative for localized, well-differentiated HCC. However, recurrences do occur in these patients without atypical symptoms. Hence, vigilant surveillance with cross-sectional imaging and ultrasound surveillance, and serum AFP is vital, particularly for diagnosing recurrence and metastatic disease, given the poor sensitivity and specificity of serological markers.

Note
Support was provided in the form of imaging equipment. The patient described in the manuscript was from the Department of Radiology, Loyola University Medical Center, Maywood, Illinois, United States. The pathology examination was from the Department of Pathology, Loyola University Medical Center, Maywood, Illinois, United States.

Author Contributions
The manuscript has been read and approved by all the authors, and the requirements for authorship, as stated above, have been met by all the authors. This manuscript represents honest work by all the authors.

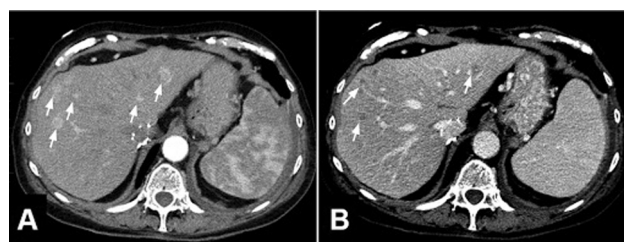### Conflict of Interest
None declared.

Fig. 6 (**A, B**) Axial computed tomography of the abdomen with IV contrast 4 weeks after the metastasis detection demonstrates multiple arterially-enhancing lesions in both lobes of the liver with early venous washout, consistent with recurrent multifocal hepatocellular carcinoma (arrows).

References

1 Zhang Y, Han T, Wang D, et al. Hepatocellular carcinoma with pancreatic mass as the first symptom: a case report and literature review. Ann Palliat Med 2019;8(05):740–745

2 Abouzied MM, Fathala A, AlMuhaideb A, et al. Gastric wall metastases from hepatocellular carcinoma: case report and review of the literature. Radiol Case Rep 2020;16(03):550–554

3 McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology 2021;73(Suppl 1):4–13

4 Santopaolo F, Lenci I, Milana M, Manzia TM, Baiocchi L. Liver transplantation for hepatocellular carcinoma: where do we stand? World J Gastroenterol 2019;25(21):2591–2602

5 Hammami A, Elleuch N, Jaziri H, et al. Synchronous hepatocellular carcinoma in a patient with primary gastric cancer: an exceptional association. Case Rep Gastroenterol 2020;14(02):299–305

6 Filgueira NA. Hepatocellular carcinoma recurrence after liver transplantation: risk factors, screening and clinical presentation. World J Hepatol 2019;11(03):261–272

7 Viveiros A, Zoller H, Finkenstedt A. Hepatocellular carcinoma: when is liver transplantation oncologically futile? Transl Gastroenterol Hepatol 2017;2:63

8 Woo SM, Park JW, Han SS, et al. Isolated pancreatic metastasis of hepatocellular carcinoma after curative resection. World J Gastrointest Oncol 2010;2(04):209–212

9 Yildiran GS, Dizdar O, Oguz A, et al. An unusual case: gastric metastasis of hepatocellular carcinoma. Intern Med 2014;4:170

10 Katyal S, Oliver JH III, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. Radiology 2000;216(03):698–703

11 Lowe CJ Jr, Riepe SP, Wood WC. Hepatocellular carcinoma presenting as a pancreatic head mass: report of an unusual case. Am J Clin Oncol 1997;20(05):509–510

12 Ishikura H, Fukasawa Y, Ogasawara K, Natori T, Tsukada Y, Aizawa M. An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. Cancer 1985;56(04):840–848

13 Hu ML, Tai WC, Chuah SK, et al. Gastric metastasis of hepatocellular carcinoma via a possible existing retrograde hematogenous pathway. J Gastroenterol Hepatol 2010;25(02):408–412

14 Sakumura M, Tajiri K, Sugiyama T. Gastric metastasis of hepatocellular carcinoma mimicking early gastric cancer. Clin Gastroenterol Hepatol 2018;16(10):e99–e100

15 Wang MH, Wu MS, Wang HP, Change YL, Lin JT. Endoscopic manifestations of metastatic hepatocellular carcinoma to the stomach: report of two cases. Gastrointest Endosc 2000;52(02):273–275

16 Sugai Y, Watanabe Y, Hasoya T, Yamaguchi K. Pancreatic metastasis from hepatocellular carcinoma. Am J Roentgenol 1999;172(03):839–840

17 Hennedige T, Venkatesh SK. Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring. Cancer Imaging 2013;12(03):530–547