“A Tale of 2 Demons”—Concomitant Presence of Hepatocellular Carcinoma and Primary Neuroendocrine Tumor of Liver: A Case Report and Review of Literatures

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Abstract
Neuroendocrine tumors usually originate from the neuroendocrine cells of gastrointestinal tract and their presence in the liver is mostly in the form of metastases. A primary neuroendocrine tumor in the liver concomitantly with hepatocellular carcinoma is an infrequent phenomenon. We present a 66-year-old woman with a remote history of breast cancer coming with postprandial fullness, later found to have multiple liver masses. After a thorough investigation, she was found to have a combined type of hepatocellular and primary neuroendocrine tumor of liver with pulmonary metastases. She was not a surgical candidate due to distant metastases. She was treated with chemotherapy, immunotherapy, and targeted therapies but continued to deteriorate clinically, and finally succumbed to her illness. The presence of this combined type of tumor in our patient is unique in many different ways: It is extremely rare, she did not have any risk factors for liver cancer, no genetic mutation till date could tie all these cancers (breast cancer, neuroendocrine tumor, and hepatocellular carcinoma) together, and not a lot of literatures/studies performed on this illness.

Keywords
hepatocellular carcinoma, primary neuroendocrine tumor of liver, breast cancer

Case Report

Presentation
A 66-year-old woman presented to her oncologist for postprandial fullness and pain in right upper abdomen for several months. She had a history of invasive ductal carcinoma of left breast 23 years ago and invasive lobular carcinoma of

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right breast 15 years ago. She previously underwent lumpectomy for both the breast masses, followed by 5-flourouracil and methotrexate as adjuvant chemotherapy. Pathological testing showed estrogen receptor expression and genetic testing was negative for BRCA1/BRCA2 mutation. She underwent regular oncologic follow-up, including annual mammography, age-appropriate colonoscopy, and dual-energy x-ray absorptiometry scan following the completion of chemotherapy.

During her recent visit for postprandial fullness, she was found to have hepatomegaly on physical examination. There was no lymphadenopathy, breast mass, or skin lesion detected. Ultrasonography of abdomen showed multiple heterogeneous masses in the liver, the largest one was 12.7 × 7.7 × 9.2 cm.

Her labwork showed mildly elevated liver function tests with total bilirubin 1.29 mg/dL, aspartate aminotransferase 95 U/L, alanine aminotransferase 158 U/L, and alkaline phosphatase 349 U/L. Hepatitis viral panel was negative. She had elevated alpha-fetoprotein (AFP) at 19872 ng/mL (normal < 6.1), chromogranin A at 58 ng/mL (normal < 15), and cancer antigen (CA) 125 of 98 U/mL (normal < 35). CA 19-9, CA 27-29, and carcinoembryonic antigen were normal.

Computed tomography (CT) chest showed at least 30 nodules scattered throughout all lobes of the lungs, the largest one being 2.3 × 2.0 cm in size. CT abdomen and pelvis revealed multiple bilobar large malignant appearing lesions, the largest one occupying most of the inferior right lobe extending in an exophytic fashion inferior to the liver, 13.7 × 9.7 cm in transverse diameter and up to 14.4 cm in cranio-caudal extent. At least 30 additional scattered liver metastases were present. Multiple hepatic metastases demonstrated rims of peripheral hypervascularity. However, CT head showed no metastases (Figures 1 & 2).

**Biopsy**

Three core biopsies were obtained from the liver. The neoplastic cells contained round to slightly irregular nuclei, were uniform in appearance, and contained moderate amount of cytoplasm. The cells were arranged in irregular interdigitating islands, also in small nests and cords. Significant necrosis was not seen. The fibrous stroma contained scattered thin-walled mildly ectatic vessels and comprised of well-developed collagen containing fibroblast nuclei. The mononuclear cells were dispersed throughout, but in scant amount. The carcinoma had a histological appearance suggestive of a neuroendocrine tumor. The neuroendocrine marker synaptophysin was positive in a patchy fashion.

In addition to the neuroendocrine features, AFP, indicative of a hepatocellular/hepatoid component, was also moderate to strongly positive in a patchy fashion. Smaller number of cells also stained with the hepatocyte markers HepPar 1 and arginase 1. Cytokeratin (CK) 7 and 19, commonly seen with cholangiocarcinoma and some cases of HCC, were also positive. There was no evidence of gland or duct formation, making cholangiocarcinoma a less likely possibility in this patient. Taken together, the histological and immunocytochemical features appeared most consistent with a primary hepatocellular neoplasm, along with a strong neuroendocrine co-expression (Figures 3–8).

Immunohistochemistry (IHC) was negative for CK20, CDX2, TTF-1, PAX-8, ER, GCDFP-15, WT-1, P40, and GATA-3. Mucicarmine, PAS (Periodic Acid-Schiff), and PAS-D (Periodic Acid-Schiff with diastase) special stains for mucin were negative.
The tumor was microsatellite stable and did not express PDL-1.

Management and Clinical Course

The patient was started on sorafenib (400 mg twice a day) and octreotide (30 mg IM [intramuscular] every 4 weeks) to treat hepatocellular and neuroendocrine component of the tumor, respectively. The patient continued to lose appetite and eventually lost 45 lbs. AFP went up to 57,908 ng/mL, although chromogranin decreased to less than 5 ng/mL. She was started on anti-hypertensives secondary to sorafenib-induced hypertension. She also developed nausea refractory to ondansetron. Repeat CT imaging showed interval progression of hepatic and lung metastatic nodules and mild new hydronephrosis. As a result, decision was made to stop sorafenib. She was started on nivolumab, folfox, bevacizumab along with continued octreotide. Her liver function continued to worsen. AFP peaked at 78,639 ng/mL and chromogranin at 30 ng/mL. After the fourth cycle of nivolumab-folfox-bevacizumab-octreotide therapy, the patient succumbed to her disease.

Discussion

Histologically, mixed primary tumor of the liver can exist either in a combined or a collision form. A combined form is the one in which 2 subtypes of the cancer intermingle in a way that they cannot be distinguished from each other, whereas, in collision type, the 2 histological subtypes will have a distinct territory often separated by a fibrous band.7-9

Figure 3. Neoplastic cells containing round to slightly irregular nuclei with moderate amount of cytoplasm. Cells are existing in irregular interdigitating islands. There is no evidence of significant necrosis.

Figure 4. Neoplastic cells with irregular nuclei and moderate amount of cytoplasm. The fibrous stroma containing scattered thin-walled ectatic vessels and well-developed collagen with fibroblast nuclei.

Figure 5. Staining positive for synaptophysin.

Figure 6. Staining positive for HepPar 1.
The incidence of combined tumor in the liver is 2% to 3.6%, whereas collision tumor is 0.1% to 1%. These mixed tumors can have a rare combination of hepatic, neuroendocrine, and/or biliary components. A pooled analysis conducted by Mao et al reported only 28 cases of mixed hepatic (HCC) and primary neuroendocrine tumor (PHNET) of liver over a period of 29 years. About 93% of these patients were men with a median age of 68 years. Most of these patients had risk factors for HCC. Hepatitis B or C infection was seen in 78% (n = 22) of the cases along with liver cirrhosis found in 35% (n = 10) patients. About 82% of patients underwent surgical resection, with or without combination of chemotherapy and radiofrequency ablation. Three patients underwent transcatheter arterial chemoembolization (TACE), as hypervascularity to the tumor is a common CT finding (seen in our patient as well). The cancer is associated with poor outcomes with a median survival of only 17.8 months. Hepatitis viral infection (univariate analysis) and tumor recurrence time (both univariate and multivariate analyses) are 2 statistically significant factors contributing to survival.

Our patient is only the third female case of this rare mixed cancer mentioned in literature. She did not have any risk factors for cirrhosis or hepatocellular cancer such as hepatitis B/C infection, excessive alcohol/tobacco consumption, or fatty liver disease. The absence of any masses in gastrointestinal tract as per radiological findings, mixed components on histopathology examination, and IHC confirmed that the liver was the primary site of malignancy. Due to widespread disease, surgical resection was not possible. She was started on treatment to tackle both the hepatocellular and neuroendocrine components; however, her condition continued to worsen. She succumbed to her disease within 5 months of diagnosis.

There are 4 hypotheses speculated behind the development of PHNET in liver: (1) derivation from hepatic progenitor cells, (2) from pluripotent stem cells, (3) chronic inflammation causing intestinal metaplasia, and (4) ectopic pancreas or adrenal gland in the liver. The origin from hepatic progenitor cells is supported by development of neuroendocrine tumor in a morphologically normal liver, and/or presence of CK7 and CK19 markers in the tumor which are strongly expressed in bile duct epithelium, whereas the origin from pluripotent stem cells is supported by the simultaneous presence of hepatic, biliary, and neuroendocrine components in a single tumor. Interestingly, the tumor in our patient stained positive for the CK7/CK19, as well as simultaneous expression of hepatocellular and neuroendocrine components supported the first 2 hypotheses. She did not have any inflammatory disorders, or her imaging and tissue sampling did not show any evidence of ectopic pancreas or adrenal gland in the liver, contradicting the latter 2 hypotheses.

Studies have shown that the prognosis of such tumor is determined by the neuroendocrine component, given its aggressive nature, tendency to metastasize, and shortened survival time. Patients with sarcomatous change in the liver and no history of hepatitis viral infection carry even a worse prognosis. Given the rarity of the disease and few published cases, treatment strategies are not very clear. Surgery is the most recommended modality, provided patient has a single mass and no metastases. However, chemotherapy (platinum based, fluorouracil, octreotide), radiation, and TACE can also be other modalities used in patients with or without surgery depending on staging and comorbidities. Liver transplantation could be the last resort for some patients.

Conclusion

The co-existence of hepatocellular and neuroendocrine component in the liver is rare; as a result, our knowledge about the origin of the disease, its clinical course, and treatment modalities is currently limited.
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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

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