Case 4

Primary hepatic neuroendocrine tumors

Introduction

Primary hepatic neuroendocrine tumor (PHNT) is an extremely rare condition. More commonly, neuroendocrine tumors of the liver result from metastases from other sites. Literature review of primary hepatic neuroendocrine tumors yielded 150 case reports globally thus far.In a review by Benjamin Quartey, the average age of diagnosis for primary hepatic neuroendocrine tumors is 51.9 +/- 16.5 with similar incidence in men and women, 50.8% and 49.2% respectively. Symptomatic presentation can be found in 73.3% of cases, most commonly abdominal pain (65%), jaundice (45%), and abdominal mass (12.5%) with only 6.8% of patients with classical symptoms of carcinoid syndrome.

The pathogenesis of primary hepatic neuroendocrine tumor is unclear, but several theories have been posited including 1) possible transformation of liver malignant stem cells, 2) differentiation of ectopic pancreatic or adrenal tissue located in the liver, and 3) transformation of neuroendocrine cells in the epithelium of the intrahepatic biliary duct.(4)

Diagnosis of primary hepatic neuroendocrine tumor depends on exclusion of the more commonly found extrahepatic neuroendocrine tumor with liver metastasis and immunohistochemistry staining of liver tissue that is consistent with neuroendocrine tumor. 24-hour urine 5-HIAA which has a 73% sensitivity and 90% specificity for diagnosing neuroendocrine tumors with carcinoid syndrome.

According to the 2019 WHO classification and grading criteria for

Table 2. Classification and grading criteria for neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm^2)	Ki-67 index*
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2–20	3–20%
NET, G3		High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High†	>20	>20%
NEC, large-cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated‡	Variable‡	Variable‡	Variable‡

LCNEC, Large-cell neuroendocrine carcinoma; MiNEN, Mixed neuroendocrine–non-neuroendocrine neoplasm; NEC, Neuroendocrine carcinoma; NET, Neuroendocrine tumour; SCNEC, Small-cell neuroendocrine carcinoma.
*Mitotic rates are to be expressed as the number of mitoses/2 mm^2 as determined by counting in 50 fields of 0.2 mm^2 (i.e. in a total area of 10 mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher-grade category.
†Poorly differentiated NECs are not formally graded, but are considered high-grade by definition.
‡In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indices in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.

neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs as shown in Table 1.

Radiologic findings of primary hepatic neuroendocrine tumors

Anatomic imaging e.g., abdominal ultrasound, CT scan, and magnetic resonance imaging (MRI) have low specificity for differentiating primary hepatic neuroendocrine tumor from other hepatic tumors. Neuroendocrine tumors may appear as single lesions or multiple lesions on plain CT scans and will be hypodense in non-contrast imaging and hyperdense in arterial phase, portal phase, and delayed phase of contrast enhanced CT, MRI will reveal hypointensity signal on T1W and hyperintensity signal on T2W with marked enhancement in post contrast MRI. Currently, anatomical imaging methods are unable to differentiate primary hepatic neuroendocrine tumors from other hepatic tumors; therefore, functional imaging such as octreotide scan which has a 90% sensitivity and 83% specificity for diagnosing

neuroendocrine tumors has been introduced.(10) Additionally, the 68Ga-DOTATATE PET/CT is another modality with a higher sensitivity and specificity than the octreotide scan.

Management of primary hepatic neuroendocrine tumor

Surgery remains the first line treatment for primary hepatic neuroendocrine tumors as with neuroendocrine tumors of other origins. Patients who undergo complete surgical resection have a 6-year survival rate of up to 74-78% varying among case series.

Medical therapy: The main objective of systemic therapy is to reduce symptoms and delay tumor growth. Somatostatin analogues (SSA) are the initial mainstay treatment in functioning NETs with SSTR positive on imaging and may improve up to 70-80% of symptoms of carcinoid syndrome e.g., flushing and diarrhea. IFN-alpha have been used to treat midgut NETs with SSTR negative status on imaging. Systemic chemotherapy is indicated in non-resectable liver metastasis or distant metastasis.

MTOR inhibitors e.g.everolimus from the RADIANT-4 study was done on nonfunctioning NETs of the lung or GI tract founded that median PFS was 11 months in patients who received everolimus compared to 3.9 months in patients who received placebo (HR 0.48).

PRRT: radionuclide therapy:^{177} Lutetium (^{177}Lu) labeled SSAs is a new option in treatment of progressive SSTR positive NET tumors. Presently, ^{177} Lutetium (^{177}Lu) is more commonly used than ^{90}Yttrium (^{90}Y) due to lower kidney toxicity. In the NETTER-1 study, overall

biochemical response was merely 17% but clinical response was favorable with improvement of diarrhea in 74% and improvement of flushing in 64%.

Long-term postresection prognosis of primary neuroendocrine tumors of the liver

Despite complete surgical resection of primary hepatic neuroendocrine tumor, there is a high recurrence rate of 19-20%

Reference

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