Neuroendocrine tumor: How to diagnose?

by

Dr. Hung Van Tran

School of Medicine, Tan Tao University

Neurendocrine tumors (NETs) is a rare tumor with incidence about 2 cases per 100,000 persons but they represent a clinical challenge because of their varied presentations and initial studying images to locate the tumors may be inconclusive. Based on the characteristic of peptide and amine producing of those tumor cells, the intracellular markers of endocrine tissue, such as chromogranin A, synaptophysin, and neuron-specific enolase can be used in the diagnosis. NETs can be classified as carcinoid tumors or functional and non-functional NETs. While functional NETs and carcinoid tumors can be revealed by their dramatic clinical symptoms due to it over production of endogenous hormones or vasoactive substances, nonfunctional NETs are silent and therefore may be metastasized at the time of detection. This review will summarize the heritable tumor syndromes that related to NETs, the main clinical symptoms as well as the methods to diagnose NETs.

Heritable tumor syndromes with increased risk of NETs

The majority of NETs are carcinoid tumors that arise from enterochromaffin cells. Those cells are mainly found throughout the GI tract and release serotonin. In contrast, functional and non-functional tumors account for 0.4% of NETs and derived throughout the body from the lung, pancreas, thymus, adrenal glands and thyroid gland. Multiple endocrine neoplasia type 1 and 2 (MEN1; MEN2), neurofibromatosis type 1 (NF1), von Hippel-Lindau (VHL) disease and tuberous sclerosis (TSC) are heritable tumor syndromes with significant increase risk for NETs development. The altered gene productions and associated NET types have been listed on table 1[1]. Patients with tumor syndromes should be screened for NETs, such as screening for hyperthyroidism in MEN1.

Table 1

Heritable Tumor Snydrome associated with neuroendocrine tumors

Syndrome	Gene product	Associated NET type
MEN type 1	Menin	Gastrinoma > nonfunctional NET> Insulinoma> Other NET
MEN type 2	RET receptor tyrosine kinase	Medullary thyroid cancer, pheochromocytoma
Neurofibromatosis type 1	Harmatin	Somatostatinoma
VHL disease	pVHL tumor suppressor protein	Nonfunctional NET
Tuberous sclerosis	Tuberin	Rarely develp nonfunctional NET, Insulinoma, and gastrinoma

Diagnosis

Clinical symptoms

The widely varied presentations of NETs make those tumors difficult in diagnosis. However, functional NETs may be clinically recognized due to the overproduction of certain hormones or physiologically active tumor products. The syndromes and related hormones secretion as well as clinical features are performed on Table 2.

Table 2

Clinical features related to hormone secretion

Hormone	Associated syndrome	Clinical features
Serotonin	Carcinoid	Flushing, diarrhea, asthma, carcinoid heart disease
Insulin	Insulinoma	Hypoglycemia
Gastrin	Zollinger-Ellison	Abdominal pain, diarrhea, gastroesophageal reflux, peptic ulcers
Vasoactive intestinal peptide	Verner-Morrison	Watery diarrhea, hypokalemia, achlorhydria, dehydration
Glucagon	Glucagonoma	Deratitis
Somatostatin	Somatostatinoma	Diabets
Pancreatic polypeptide	Nonfunctional NRT	None

Anatomic imaging

Conventional imagings, including computed tomography (CT), magnetic resonance imaging (MRI), transabdominal ultrasonography, GI endoscopy and endoscopic ultrasonography EUS have important roles in evaluation patients with suspected NETs. Among all, CT and MRI are frequently used thanks to their high sensitivity [2, 3]. Nevertheless, those anatomic imaging studies do not delineate the biologic activities of these tumors.

Functional imaging

Those studies are used to target receptors, uptake pathways or metabolism unique to NETs. Somatostatin receptor scintigraphy (SRS) is a nuclear medicine based on the fact that over 80% of NETs express somatostatin receptors. However, the sensitivity of SRS varies according to tumor type. The combination with single photon emission computed tomography (SPECT) or nuclear medicine imaging with meta-iodobenzylguanidine (123I-MIBG) can be used to enhance the sensitivity of SRS [4,5]. In addition, endoscopic techniques can be used to evaluate and obtain tissue from gastroduodenal and pancreatic lesions. When combined with fine needle aspiration (FNA), the sensitivity and specificity can reach to 98% and 100% respectively [6] .

Serologic studies

As mentioned above, neuron-specific enolase and chromogranin A can be used as an indicator of tumor and response to therapy. Chromogranin A has been more successful than neuron-specific enolase although either cannot be used as the sole marker for tumor development or remission

In functional NETs, specific markers should be used to evaluate the tumor. For example, in Zollinger- Ellison syndrome, fasting gastrin has a sensitivity of 64% to 80% for detecting gastrinoma [7] . Insulin and proinsulin increase in 90% of insulinomas [8] . However, functional NETs may change their primary secretory hormone over the course of the disease and therefore, different syndromes can be manifested over the time.

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