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Specific and non-specific biomarkers in neuroendocrine gastroenteropancreatic tumors

Neuroendocrine tumors (NETs) are a heterogeneous group of rare malignancies that can arise in almost all organs, although gastroenteropancreatic site (GEP) is the most common.

Symptoms are rarely specific, and clinical manifestations may be evident only in the case of metastatic disease.

NETs are usually classified, based on the patterns of secreted peptides and amines, as non-functional or functional (associated with the related clinical syndrome). Functioning GEP NETs may produce many biologically active substances, released into the blood, capable of causing specific clinical manifestations and used as biochemical markers for NETs.

Among the circulating specific markers of NETs, serotonin (5-hydroxytryptamine, 5-HT), a biogenic peptide, is secreted mainly by the enterochromaffin cells of the small intestine, as well as by the serotoninergic neurons of the central nervous system. The biological functions of the 5-HT include vasocostriction, sleep regulation, mood, appetite, and gastrointestinal motility. The clinical features of carcinoid syndrome, resulting from an excessive production of 5-HT, may vary based on concomitant secretion of other biologically active amines, such as tachykinins, prostaglandins and kallikrein, while in atypical carcinoid syndrome, symptoms are often related to histamine secretion. The measurement of circulating 5-HT is generally useless, due to fluctuations in secretion and interindividual variations, while it is recommended to assess its urinary metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in 24-hour urine.

Gastrin is a peptide hormone that promotes the release of gastric acid and stimulated gastrointestinal tract motility. Measurement of fasting serum gastrin (FSG) is recommended in case of suspected gastrinoma associated to Zollinger–Ellison syndrome (ZES). Provocative tests, using stimulus with secretin, calcium gluconate or glucagon, can be used to obtain more reliable results, especially when FSG is only slightly increased, or in patients taking proton pump inhibitors (PPIs).

Insulin-producing tumors, insulinomas, are almost exclusive to the pancreas and are the most common functioning pancreas NETs. Insulinomas show elevated serum insulin levels and patients classically present with symptomatic Whipple's triad.

Glucagon, somatostatin, vasoactive intestinal peptide (VIP) are specific markers for the other functioning NETs, respectively glucagonomas, somatostatinomas, VIPomas.

Among the non-specific neuroendocrine markers, chromogranin A (CgA) is a glycoprotein secreted by neurons and neuroendocrine cells and belongs to the granin family.

Syndrome	Symptoms	Biomarker
Carcinoid syndrome	Flushing Diarrhea Wheezing Dyspnea	Urinary 5-HIAA Serum 5-HIAA (less reliable)
Zollinger–Ellison syndrome	Recurrent peptic ulcer Gastro-esophageal reflux	Fasting serum gastrin Secretin stimulation test Calcium stimulation test Glucagon stimulation test
Insulinoma	Hypoglycemia	Insulin (72 h fasting) C-peptide Proinsulin Glucagon stimulation test
Glucagonoma	Necrolytic migratory erythema Diabetes mellitus or impaired glucose tolerance Muscle wasting Weight loss	Fasting serum glucagon
Somatostatinoma	Diabetes mellitus Diarrhea Cholelithiasis Weight loss Hypochlorhydria	Fasting serum somatostatin
VIPoma	Watery diarrhea Hypokalemia Achlorhydria	Serum VIP

Fig. 1. xpression of different markers according to clinical manifestations. Features of tumors gastroenteropancreatic-neuroendocrine (GEP-NET)-associated clinical syndromes. 5-HIAA: 5-hydroxy-indolacetic acid; VIP: vasoactive intestinal peptide

Serum CgA is not always reliable in clinical practice because several factors could increase the risk of false positives. Several drugs, such as PPIs and steroids, as well as several oncological (i.e. prostate cancer) and non-oncological (i.e. kidney failure) conditions or endocrine diseases (i.e. hyperthyroidism) increase serum CgA levels. The specificity of the CgA assay decreases up to 50% in populations with concomitant conditions so CgA should not be used as a first-line diagnostic test. CgA is currently the most used biomarker in follow up of NETs as its concentration well correlates with disease progression, prognosis and response to treatment.

Neuron-Specific Enolase (NSE) is a isomer of the enolase enzyme found in neurons and neuroendocrine cells. Serum NSE has low specificity and sensibility to differentiate NETs from non-endocrine tumors. Overexpression of serum NSE is usually indicative of poorly differentiated neoplasm.

In conclusion, when a NET is suspected, the presence of signs and symptoms should guide the choice of specific markers to allow a correct diagnosis. Furthermore, during therapy, the change in the production and release of these biomarkers could provide additional information on prognosis and response to treatment.

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