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Letter to the Editor

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All Neuroendocrine Tumors Seem to Look Alike but Some Look Alike More Than Others

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Keywords
Neuroendocrine tumors · Functioning neuroendocrine tumors · Hereditary neuroendocrine tumors · Multiple endocrine neoplasia

Todos os tumores neuroendócrinos parecem iguais, mas uns são mais iguais que outros

Palavras Chave
Tumores neuroendócrinos · TNE · TNE funcionante · TNE hereditário · Síndrome de neoplasia endócrina múltipla (MEN)

Digestive neuroendocrine tumors (DNETs) are still considered rare tumors, although their incidence has been rising since the 1970s [1, 2]. In the past 2 decades, important advances in diagnosis and treatment have been made, so since the 2010s, survival has increased as well [1, 2]. As a consequence, DNETs turned to be one of the most prevalent neoplasia (170,000 cases in the USA until 2020) [3]. Due to DNET heterogenicity and rarity, these tumors should be managed at reference centers by multidisciplinary teams including gastroenterology, endocrinology, pathology, surgery, medical oncology, interventional radiology, and nuclear medicine specialists, among others. According to recent guidance papers, small pancreatic neuroendocrine tumors (<2 cm) can be followed by "watch-wait" surveillance [4]. Nevertheless, some groups as the Portuguese Pancreatic Club, question this recommendation, arguing that beside the size, other preoperative factors may help stratify the risk of malignant behavior [5]. The question of functionality and hereditary should also be considered, as for instance, a small sporadic gastrinoma should be operated because of its metastatic potential [6]. Besides, although frequently benign, a small insulinoma <2 cm should also be treated because of life-threatening symptoms [6].

Unlike other cancers, DNET diagnostic and treatment goals are focused not only on tumor burden, but also on hormone secretion by the primary tumor and its metastasis. In contrast to the global rise in incidence, the proportion of functioning tumors has been decreasing, from 40 to 50% in older studies [7, 8], to the 15–30% actually described [9]. In recent studies, non-functioning pancreatic endocrine tumors were twice as frequent as functioning PETs [8]. Whenever this incidence proportion reduction is real or due to underdiagnosis of hypersecretion syndromes, or both is unknown, but the fact

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that these tumors are managed by several specialities and often not referred to experienced centers favours the consideration of the last hypothesis.

Duodenal and pancreatic gastrinomas can be easily missed since the spread use of proton pump inhibitors (PPIs) can mask traditional symptoms of peptic ulcer disease due to hypergastrinemia. Gastrinoma should be suspected in the presence of recurrent peptic ulcer disease, in the absence of *Helicobacter pylori*, in chronic diarrhea that responds to PPI, as well as in patients who do not tolerate PPI withdrawal due to severe dyspeptic symptoms [6, 10, 11]. According to 2023 ENETS recommendations, gastrinemia measurement is mandatory in all DP-NETs, when Zollinger-Ellison syndrome is suspected [6]. Hypoglycemia caused by insulinoma can present with neuroglycopenic symptoms such as confusion, blurred vision, and incoherent speech, besides the autonomic nervous system symptoms such as tremor, sweating, hunger, and tachycardia characteristic of hypoglycemia [6, 10, 11]. Additionally, during the course of the disease, progression and dedifferentiation of non-functioning metastatic tumors can be associated with de novo hypersecretion, sometimes with synchronous or metachronous secretion of multiple peptides and hormones [6, 10, 11]. Even metastatic midgut tumors associated with carcinoid syndrome only manifest the typical symptoms of flushing and diarrhea in advanced stages of the disease [11]. Symptoms mimicking irritable bowel syndrome are frequently found in early stages of the disease, when intermittent abdominal pain, nausea, vomiting, and acute changes of intestinal habits are often responsible for sporadic health care visits and are usually misdiagnosed as acute gastroenteritis or attributed to alimentary excesses [10, 11].

On the other side, hereditary syndromes should be suspected, particularly in patients diagnosed under 40 years old with DP-NETs, with two or more endocrine tumors or with a family history of endocrine tumors. Type 1 multiple endocrine neoplasia (MEN1), caused by inactivating mutations of menin gene is the most frequent hereditary syndrome associated with DP-NETs; however, other syndromes have recently been identified, as MEN4 caused by germline mutations of CDKN1B, encoding p27 protein. Von Hippel-Lindau disease; type 1 neurofibromatosis; and tuberous sclerosis complex should also be considered [6, 12].

In conclusion, although nonfunctioning DNETs are more frequent than functioning tumors, the possibility of hypersecretion must be kept in mind. Carcinoid syndrome must be excluded in all metastatic midgut NETs. DP-NETS should be carefully evaluated in order to avoid misdiagnosis of gastrinoma, insulinoma, and other rare functioning syndromes, as well as hereditary disease.

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