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Endoscopic diagnosis and treatment of neuroendocrine tumors of the digestive system

DOI 10.1515/med-2016-0067
received August 10, 2016; accepted September 6, 2016

Abstract: The authors evaluated the role of endoscopic techniques in the diagnosis and in the potential treatment of neuroendocrine tumors (NET) localized in the gastro-entero-pancreatic system, on the basis of their experience and of the international literature. NET are rare tumors that arise from neuroendocrine cells of the gastrointestinal tract and pancreas. It is a possibility that both the digestive endoscopy and EUS play an important role in the diagnosis, staging and surveillance of this disease. In some cases, especially in the early stages, surgical endoscopy allows the treatment of such tumors.

Keywords: Neuroendocrine tumors; Digestive endoscopy; Endoscopic ultrasonography

1 Introduction

Neuroendocrine tumors (NET) of the gastro-entero-pancreatic system, although rare, tumors account for 20% of all gastrointestinal tumors, and altogether are 70% of all neuroendocrine tumors [1, 2]. They occur generally small in size and are located mainly in the deeper part of the mucosa or in the submucosa of the intestinal wall,; in some cases they have multiple locations. This can lead to difficulties in diagnosis and in the choice of treatment.

Current endoscopic equipment allows exploration of various procedures, including the entire digestive tract. With this equipment the Digestive tract can be evaluated, surgeons can simultaneously perform biopsies of lesions highlighted, we can diagnose and, in selected cases, treat endoscopically, neuroendocrine tumors.

According to our experience and to the literature, the presence of a NET, is detected during an endoscopic investigations performed for non-specific symptoms, such as dyspepsia, and abdominal pain. In other can occur a sub-occlusive crisis, or an enterorrhagia, determined by the presence of a tumor mass. In some patients can be observed a classic carcinoid syndrome, with cutaneous flushing and diarrhea, due, in approximately 10%, to the production of active substances [3].

Not infrequently, during endoscopic surveillance, of patients with autoimmune chronic gastritis, or particular syndromes such as Zollinger-Ellison syndrome, MEN-1, are found small gastric polyps, that result in a carcinoid on the histological examination of the resected specimen.

2 Digestive endoscopy

Neuroendocrine tumors of the digestive tract may appear endoscopically as polypoid formations, nodules, masses, ulcers or stenosis, with sizes ranging from a few millimeters, to several centimeters, they can be single or multiple. Depending on their location along the gastrointestinal tract NETs may have specific characteristics. These tumors are extremely rare in esophagus, (about 50 cases reported), occur mainly at the lower third as large sessile polypoid formations and have invasion of the wall and lymph node metastasis in more than 50% of cases at the time of the diagnosis [3]. Stomach is one of the most frequent locations of NET. They are classified into three

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types: type I, the most frequent, is associated with autoimmune atrophic gastritis, at endoscopic examination it looks like a small polypoid formation, single or multiple, of the gastric body- fundus (Figure 1); type II, is associated with Zollinger-Ellison syndrome and the MEN-1 syndrome, and appears as a single or multiple polypoid nodule of the gastric fundus and antrum; in the case of Zollinger-Ellison syndrome the endoscopic appearance is completed by the presence of multiple peptic ulcers due to the acid hypersecretion produced by the increased production of gastrina; type III, sporadic, not associated with other pathological conditions. In these cases the remaining gastric mucosa shows no significant histological alterations and the NET endoscopically appears as a single mass with variable location in any part of the stomach, showing aggressive behavior with early local invasiveness and remote metastases [4].

Duodenal NETs include gastrinoma, somatostatinoma, and gangliocytic paraganglioma. Non-functioning tumors and poorly differentiated tumors may be sporadic or associated with other diseases (MEN-1, Zollinger-Ellison syndrome, von Recklinghausen).

They are localized predominantly in the I and II duodenal portion preferring the peripapillary region and appear under endoscopic vision as a single lesion, small in size (often <1 cm). They can also be multiple or associated with neuroendocrine tumors of other organs.

The NET jejuno-ileal have the greatest diagnostic difficulties, and are at times detectable only in the course of study with videocapsule.

The ileum is a frequent localization site [5], the detection of these tumors occurs in the course of an intervention for intestinal obstruction. The endoscopic framework is typically characterized by a single nodular or ulcerated lesion which can determine stenosis or bleeding; in some cases multiple lesions can be found. The clinical symptoms are often insidious and the biological behavior is frequently aggressive, therefore in most cases the disease is already in an advanced stage at the time of diagnosis with metastatic ability and can be associated with other cancers too. In about 20% of cases there is a typical carcinoid syndrome. Even in the colon develop good part of the gastrointestinal NET, with a preference for the cecum. The endoscopy identifies them generally as bulky lesions, often> 2 cm., sometimes bloody, they can also be associated with other malignancies and have the worst prognosis than the other NET of the digestive tract. In the rectum often it is possible to find small, less than one centimeter polypoid lesions, with favorable prognosis;, more voluminous lesions > 2 cm., have a greater metastatic capacity [6]. (Figure 2)

After the endoscopic diagnosis, in many cases, EUS can provide detailed information about the location of the lesion and the possible infiltration of the wall layers and highlight the presence of regional lymph node site.

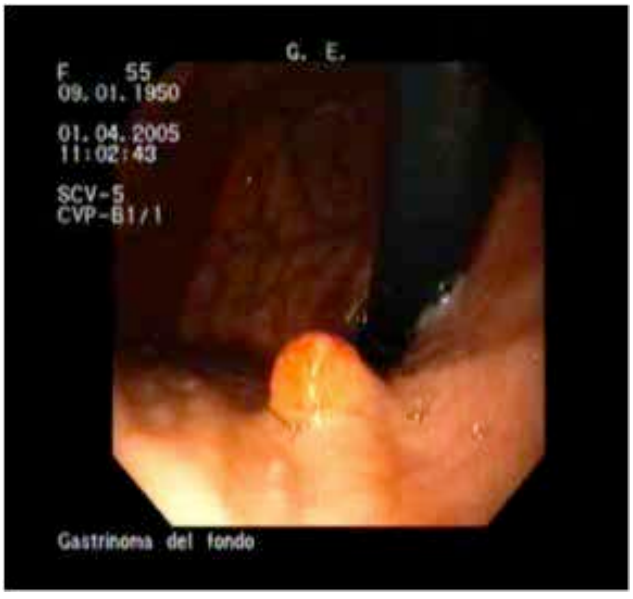

Figure 1: Fundic Gastrinoma

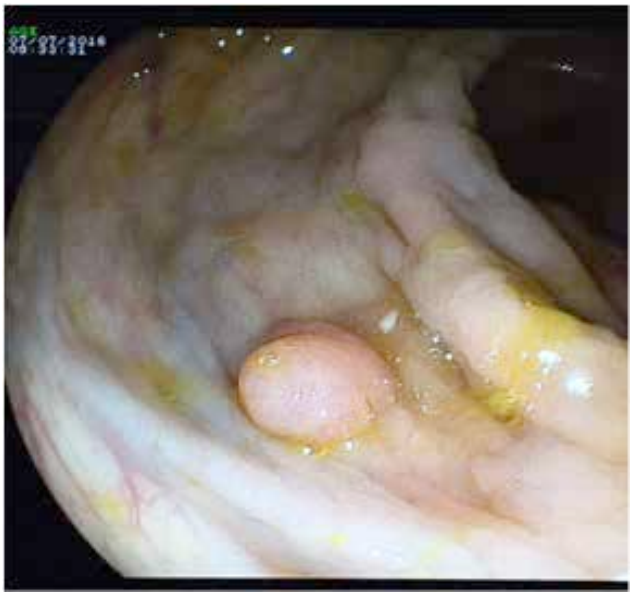

Figure 2: Rectal NET

3 EUS (endoscopic ultrasonography)

Pancreatic neuroendocrine tumors (pNETs) account for about 20-50% of digestive NET, and include: insulinoma, gastrinoma, vipoma, glucagonoma, somatostatinoma and non-functional tumors [7]. In case of non-functional tumors, which are the most frequent pNETs currently diagnosed, the detection of the lesions is often incidental during imaging examinations performed for other diseases or non-specific symptoms. However, in the presence of a specific clinical syndrome, the diagnosis is based on the symptoms and the laboratory tests tumor localization, the EUS examination, along with multislices spiral CT, MRI and all'Octreoscan are the main diagnostic methods employed to localize the tumor.

EUS is still the best method available for imaging of the pancreas and it is able to produce high-resolution images of both the parenchyma and pancreatic ductal system. Reliability of EUS imaging is not only much higher than conventional ultrasound, but also than new radiological imaging methods, highlighting structures and lesions of 2-3 mm in size. A further advantage of endoscopic ultrasound is the ability to supplement the information obtained from the imaging assessment with a EUS-guided FNA. The proximity of the instrument and the ultrasonographic probe with the target lesion is a factor in favor of EUS for the possibility to make the procedure even on very small lesions and for the significant reduction of the risk of dissemination of neoplastic cells along the needle path compared to echo or TC guided FNA.

At EUS evaluation pancreatic insulinoma, which represent the most frequent functioning lesion, appear, in most cases (over 80%), as a solid lesions with regular margins and hypoechoic echotexture compared to the surrounding pancreatic parenchyma (8). The use of Doppler often highlights a rib of hypervascularization in the peripheral zone. It is well known that pNETs are often hypervascularized and this peculiarity allows the differential diagnosis with adenocarcinomas, which are generally hypovascularized. The employment of contrast enhanced ultrasound, now available also with EUS, makes this feature much more evident because a few seconds after contrast agent injection, the lesions become markedly hyperenhanced.

Also with regard gastrinoma EUS is considered the most accurate method of identifying or exclusion lesions in pancreatic seat, while the accuracy falls below 50% for the diagnosis of extrapancreatic lesions.

EUS can also be highly useful for the diagnostic confirmation by means of a FNA, especially in non-functioning lesions. Considering, indeed, that the outcome of the patients with localized non functioning p-NETs, after surgical resection is very favourable and even in case of metastatic pNETs an adequate medical treatment can reduce significantly the progression of the disease, it is essential to achieve a definite diagnosis as soon as possible.

A further application of EUS, particularly for the small gastro enteric NETs concerns the staging, in order to select those lesions which could be treated by an endoscopic resection. For this purpose can be very useful the high frequency ultrasound with miniprobes. These instruments are very thin and can be pushed through the operative channel of a standard endoscope so that the miniaturized ultrasonic probe can be placed very close to the lesion which have to be evaluated, under endoscopic view.

4 Endoscopic treatment

The endoscopic operating techniques allow the removal of small neoplastic lesions in the early stage of mucosal or submucosal invasion of the intestinal wall. The endoscopic approach may be indicated in selected cases only after a careful staging of the lesion to rule out a possible lymph-node involvement.

The endoscopic removal using a polypectomy or mucosectomy is indicated: in case of gastric type I and II carcinoids with diameter <1 cm if the lesions are no more than 5, for rectal lesions <1 cm or between 1 and 2 cm, in the absence of lymph node involvement, and for duodenal lesions <1 cm, only after excluding any lymph node metastases [9]. In a few cases the endoscopic removal can

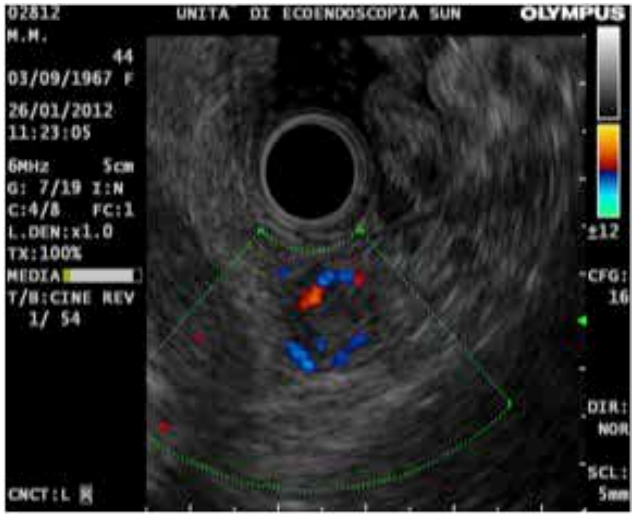

Figure 3: Insulinoma corpo pancreas

be technically difficult, in particular for lesions located in the perivaterian area.

In any case it is essential to make sure that the removal was complete and submit the patient to close endoscopic and histological surveillance [10-15].

Sources of funding: All authors have no source of funding.

Conflict of interest: The authors declare that they have no conflict of interest or financial support.

Author contribution

Luigi Sivero: Partecipated substantially in conception, design,and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Donato Alessandro Telesca: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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Maurizio Amato: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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Cesare Formisano: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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Manuela Avellino: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Vincenzo Napolitano: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

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