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Review

The role of endoscopy and endoscopic ultrasonography in the diagnosis of gastrointestinal neuroendocrine tumors

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SUMMARY

Gastrointestinal neuroendocrine tumors are rare malignancies that have been classified by the peptides they secrete and the resulting clinical symptoms. They constitute less than 2% of all gastrointestinal cancers. Fifty percent of neuroendocrine tumors in clinical practice are the so-called carcinoid variety and are found incidentally at operation, after metastasis has occurred in the small intestine. Approximately 60% of pancreatic gastrinomas are concentrated in an area sub-tented by the head of the pancreas, gastric antrum, and first portion of the duodenum. The role of endoscopic techniques (upper GI endoscopy, push enteroscopy, and colonoscopy) in the diagnosis of endocrine gastrointestinal tumors seems to be quite important. Although there are no specific endoscopic features allowing the accurate and safe endoscopic diagnosis of an endocrine tumor, endoscopy could aid in the final diagnosis reached by identifying and removing the lesion or taking biopsies and sending them for histology. On the other hand, endoscopic ultrasonography, in experienced hands, not only visualizes the tumor itself but offers the ability to obtain smears for cytologic examination via fine needle aspiration. The invention of the wireless capsule which transfers high quality endoscopic pictures of the whole small bowel, will probably replace the classical small bowel barium follow-through in patients with suspected small bowel endocrine tumor.

Key words: Neuroendocrine tumors, Endoscopy, Gastrointestinal hormones

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1. INTRODUCTION

Gastrointestinal neuroendocrine tumors are rare malignancies that have been classified by the peptides they secrete and the resulting clinical symptoms[1]. They constitute less than 2% of all gastrointestinal cancers[2]. The gastrointestinal endocrine cells are characterized by similar cytochemical and ultrastructural characteristics[3]. More than 30 gut hormone genes and other bioactive peptides have been identified, which makes the gut truly the largest endocrine organ in the body[4].

Fifty percent of neuroendocrine tumors in clinical practice are the so-called carcinoid variety and are found incidentally at operation. The remaining fraction comprises approximately 50% gastrinomas, 30% insulinomas, 13% VIPomas, 5%-10% glucagonomas and less than 5% neurotensinomas, somatistatinomas and ectopic hormone-secreting tumors.

Nonsecretory tumors were thought to make up the bulk of pancreatic tumors, but with better immunohistological staining for endocrine cells, there is increasing recognition that tumors masquerading as carcinomas of the liver, small cell carcinoma of the lung and the like are, in fact, endocrine tumors[5]. Most of these nonsecretory tumors actually store and secrete pancreatic polypeptide.

Approximately 60% of pancreatic gastrinomas are concentrated in an area subtented by the head of the pancreas, gastric antrum, and first portion of the duodenum. Other neuroendocrine tumors may be distributed more evenly across the pancreas or in ectopic sites such as adrenal medulla, whereas carcinoid tumors most frequently occur in the appendix and small intestine.

In this review we attempt to clarify the role of endoscopy in facilitating the diagnosis of these tumours, which, although quite significant from the clinical point of view,

are relatively rare.

2. THE ROLE OF ENDOSCOPY IN THE DIAGNOSIS OF GASTROINTESTINAL NEUROENDOCRINE TUMORS

The role of endoscopic techniques (upper GI endoscopy, push enteroscopy, and colonoscopy) in the diagnosis of endocrine gastrointestinal tumors could be considered as quite important. Although there are no specific endoscopic features allowing the accurate and safe endoscopic diagnosis of an endocrine tumor, endoscopy can aid in the final diagnosis reached by removing the lesion and/or taking biopsies for histology. Endoscopic ultrasonography, a sophisticated endoscopic technique requiring special training and talent of the endoscopist, not only visualizes the tumor itself, but offers the ability to obtain smears for cytologic examination via fine needle aspiration. The invention of the wireless capsule, which transfers high quality endoscopic pictures of the whole small bowel, will probably replace the classical small bowel barium follow-through in patients with suspected small bowel endocrine tumor.

2.1 Upper GI endoscopy

Gastric carcinoids

There represent the most frequent GI endocrine tumors. The incidence of this tumor is estimated to be 15 cases per 1 million people. They account for 13% to 34% of all tumors of the small bowel and 17% to 46% of all malignant tumors of the small bowel[6]. The incidence of gastric carcinoids has increased considerably during the last few decades[7]. The recognized propensity of powerful antisecretory drugs (such as proton pump inhibitors) to increase plasma gastrin levels has been proposed as a possible etiologic factor for the increasing incidence of these tumors. However, increased endoscopic surveillance and proper pathological evaluation have both undoubtedly been responsible for the increased incidence of these tumors observed recently world-wide. Generally, carcinoids are found in the gut wall, although they can occur in the pancreas, rectum, and other organs as well. The appendix is the most common location for carcinoid tumors within the gastrointestinal tract. Duodenal carcinoid tumors are uncommon. Biliary carcinoids are also quite rare, with fewer than 30 cases reported in the literature[8]. Cecal carcinoid represents only 2%-3% of all gastrointestinal carcinoid. It is not known whether the latter behave more like carcinoid tumors in the appendix (indolent course) or those in the ileum (often virulent)[9]. A carcinoid tumor located in the ampulla of Vater is an extremely rare entity[10].

Carcinoids usually grow slowly and are often clinically silent for many years before becoming manifest after metastases have occurred, related mainly to tumor size. The incidence of metastases is less than 15% with a carcinoid tumor smaller than one cm, but rises to 95% with tumors larger than 2 cm. Tumors may be symptomatic only episodically, and their existence may go unrecognized for many years. The average time from onset of symptoms attributable to the tumor and diagnosis is 9 years. Diagnosis is often made only after symptoms of carcinoid syndrome occur. It must be stressed however, that carcinoid syndrome occurs in less than 10% of all patients with carcinoid tumors[11]. Their peak incidence occurs in the sixth and seventh decade of life although they can occur at any age.

It is well established that carcinoid tumors are associated with pernicious anemia, severe atrophic gastritis, and chronic thyreoiditis[12]. Body-predominant atrophic gastritis is considered as a risk factor for carcinoid and gastric cancer. Gastric carcinoid and gastric adenocarcinoma can occur concurrently in patients with atrophic gastritis, reinforcing the concept that the epithelial and neuroendocrine cells of the gastrointestinal tract both result from multidirectional differentiation of a primitive cell[13].

Gastric carcinoids are uncommon, accounting for less than 5% of all gastric polyps and less than 10% of all submucosal polyps. Gastric carcinoids are typically located on either end of the stomach, with the cardiofundic and prepyloric area being the major sites of origin. A smooth submucosal lesion would be a typical appearance. Other less common appearances include multiple tiny polyps or focal ulcerated areas resembling the type IIa appearance of early gastric cancer.

In cases where a carcinoid tumor has been endoscopically removed, close endoscopic follow-up at regular intervals (every 1 to 2 years), plus multiple biopsies is indicated in order to look for the appearance of other lesions. Timing of follow-up of patients with atrophic gastritis (a well-known premalignant upper GI condition predisposing to the development of carcinoid tumors) is largely unknown. However, recent reports have claimed that performing the first follow-up every 4 years is probably satisfactory for detection of potential neoplastic lesions[14].

The correct diagnosis of liver metastases of gastric carcinoid is usually made with the help of liver biopsy and then only if the bioptic material is stained for

chromogranin, synaptophysin or NSE. Otherwise, tumors are erroneously considered to be adenocarcinoma, with obvious consequences for the patient.

Carcinoids located in the appendix comprise no more than 10% of the total number of 11,842 cases coming from 64 different countries[15] Carcinoids located in the ileocecal valve give the appearance of hyperemia on the colic side of the ileocecal valve. The ileocecal valve usually appears to be substenotic. Biopsy usually reveals micronodules formed by chromogranin-A-positive neuroendocrine cells[16]. Staining with Chromogranin-A can aid the correct diagnosis in combination with other recently described neuropeptides, such as Catestatin[17]. Staining for six specific regions of the Chromogranin-A molecule can be used as a diagnostic tool for the characterization of neuroendocrine tumors[18].

Duodenal carcinoids

Duodenal carcinoid tumors can be successfully diagnosed by upper GI endoscopy. Because the duodenum is the least common site for carcinoid tumors in the small intestine, the likelihood of an asymptomatic submucosal polyp being a carcinoid is low, even for polyps greater than one centimeter in maximum dimension. A duodenal carcinoid can present endoscopically as a smooth sessile lesion with or without mucosal ulceration, or as a submucosa mass. Endoscopic biopsy provides the accurate diagnosis in the majority of cases (78%). Upper GI endoscopy also has the ability to act therapeutically as endoscopic excision of the tumor located in the duodenum can be achieved in most cases. It must be stressed, however, that in these cases endoscopic follow-up is indicated[19].

Jejunal carcinoids

The greatest problems encountered are in localizing small bowel carcinoids, which may be quite small. In such cases push enteroscopy can be of value as it can demonstrate a mass with mucosal ulceration located in the jejunum. Push enteroscopy can also offer the ability to obtain biopsies from the lesion to confirm the diagnosis[20].

Imaging capsule

The development of wireless capsule endoscopy offers the possibility of examining the whole gastrointestinal tract, having the advantage being completely painless. Although, so far, there are no data referring exclusively to endocrine gastrointestinal tumors, it seems that this method could be of significant value in detecting endocrine tumors located in the duodenum, jejunum and ileum[21].

2.2 Lower GI endoscopy

Large bowel carcinoids

Carcinoids of the cecum, right colon and hindgut carcinoids are usually diagnosed by colonoscopy. Apart from the rectum, the colon is a rare site for carcinoid tumors. Carcinoids appear at colonoscopy as smooth, glistering, sessile lesions, without ulcerations, ranging in size between 1 and 2 cm with a pale yellow cast to the mucosa. Carcinoids of the colon can be removed endoscopically quite safely. A carcinoid in the rectum has the appearance of a small submucosa tumor without specific diagnostic characteristics. Recent publications also describe rectal carcinoids as pedunculated polyp that can manifest by rectal bleeding[22]. Colonoscopy may not only be used to diagnose a large bowel carcinoid tumor but to totally resect the tumor mass successfully[23].

Gastrinoma syndrome

The gastrinoma syndrome is characterized by severe ulcer diathesis and persistent basal gastric acid hypersecretion because of hypergastrinemia. This syndrome exists in multiple forms: benign sporadic, malignant metastatic, and as part of the MEN-1 syndrome. It needs to be distinguished from the G-cell hyperplasia syndrome and from those rare cases in which acid hypersecretion cannot be ascribed to gastrin. 66% of gastrinomas are sporadic. Most tumors in the pancreas are solitary and have malignant potential in 60%-85% of cases. Sporadic tumors generally occur in the pancreas, although primary tumors also may occur in the body of the stomach, duodenum, and jejunum, accounting for up to 23% of tumors found at operation. Less than 40% of these are malignant. Ectopic tumors have been identified in peripancreatic lymph nodes, spleen, root of mesentery, omentum, liver, gallbladder, and the ovary. Solitary tumors in these sites are less likely to be malignant. In several studies, gastrinomas were located in extrapancreatic sites, including the duodenal wall in 43%-77% of patients[24].

3. ENDOSCOPIC ULTRASONOGRAPHY

Endoscopic ultrasonography is generally accepted as a fairly sensitive method for the detection of small pancreatic tumors[25]. It allows the detection of both pancreatic endocrine tumors and tumors of the papilla of Vater as well. The sensitivity of the method in various studies fluctuates between 87% to 96%) (Table 1). It allows the correct determination of the tumor size and tumor spread into the peripancreatic structures, especially the large vessels[26]. However, endoscopic ultrasonography fails to detect extrapancreatic gastrinomas in almost 50% of cases[27].

Table 1. Sensitivity of endoscopic ultrasonography in the detection of endocrine tumors of the pancreas.

	Pancreatic tumors		Extrapancreatic tumors	
Author	**No of patients**	**Sensitivity**	**No of patients**	**Sensitivity**
Zimmer 1994	18	94%	8	6
De Angelis 1999	23	87%	8	3 (37.5%)
Zimmer 2000	40	96%	50%	
Nesje 2002	9	72%	-	-
Gouya 2003	32	94%		

In experienced hands, endoscopic ultrasonography increases the ability to detect pancreatic gastrinomas, and localization rates of 80-100% have been described. However the ability of this technique to detect tumors less than 5mm in size or occult duodenal lesions is less certain[28]. Endoscopic ultrasonography is the most accurate method for detecting insulinomas of the pancreas. The sensitivity can reach the level of 94%[29]. We can certainly support the assumption that after endoscopic ultrasonography, (irrespectively of the result of the procedure) further diagnostic procedures are unnecessary in most cases. Some descriptions have claimed that endoscopic ultrasonography is more accurate in diagnosing gastrinomas than insulinomas of the pancreas[30].

Endoscopic ultrasonography has successfully been used to establish the diagnosis of duodenal somatostatinoma and gastrinoma of the prepyloric area by means of fine needle aspiration[31,32].

Pancreatic endocrine tumors can be detected at an early stage on asymptomatic patients with multiple endocrine neoplasia type 1, by using endoscopic ultrasonography, and thus improving prognosis and facilitating prompt surgical intervention[33].

Insulinomas

Approximately 30% of insulinomas are less than 1 cm in diameter, 10% are multiple, 10-15% are malignant, and 10% will have either islet cell hyperplasia or nesidioblastosis and no tumor at all. A firmly established diagnosis of an insulin-secreting lesion of the pancreas is essential to successful management. Endoscopic ultrasonography can detect the tumor, allowing the correct diagnosis to be made through a biopsy specimen obtained by fine needle aspiration.

Vasoactive Intestinal Peptide Tumor (Vipoma)

The acronym WDHHA for watery diarrhea, hypokalemia, hypochlorydria and acidosis because of bicarbonate wasting, must be the most accurate term for this disorder. The absence of gastric hypersecretion and even achlorydria were documented in this kind of tumor. Again this tumor might be detected endoscopically and confirmed histologically.

Somatostatinoma

Somatostatinomas involving the gastrointestinal tract are extremely rare neoplasms that typically present with indolent, non-specific symptoms. Of the reported primary tumors, 60% were found in the pancreas and 40% in the duodenum or jejunum. Regarding extrapancreatic locations, approximately 50% originate in the duodenum, approximately 50% in the ampulla and rarely in the jejunum. Somatostatinomas are often associated with multiple endocrine neoplasia-1 Syndrome and von Recklinghausen's disease. Somatostatinoma has been described on a patient with celiac sprue[34]. 80% of patients with pancreatic somatostatinomas are metastatic at diagnosis, while the corresponding feature in intestinal tumors is nearly 50%. Thus, in 70% of cases, metastatic disease is present at diagnosis[35]. Diagnosis could be facilitated by endoscopy, although there are no data in the literature.

Pancreatic Polypeptide Ppoma

In mammals, 93% of cells producing Pancreatic Polypeptide are located in the pancreas. Circulating PP is regulated by meal ingestion, cerebral stimulation and hormone administration[36]. Endoscopic ultrasonography can detect the tumor mass in certain.

Neurotensinomas

Neurotensin, a 13 amino acid polypeptide isolated from the human GI tract, has important pharmacologic effects, including hypotention, tachycardia, cyanosis and stimulation of secretion from small intestine. The majority of tumors are located in the pancreas. Endoscopic ultrasonography can be of value in the diagnosis of this rare endocrine tumor.

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