Review article

Gastrointestinal Neuroendocrine Tumors

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SUMMARY

Neuroendocrine tumors of the gastrointestinal tract are relatively rare neoplasms derived from the diffuse endocrine system (DES), and classified as APUDomas. These neoplasms include mainly pancreatic endocrine tumors (islet cells) and carcinoids. Although malignant, these tumors are often slow-growing. Frequently, these neoplasms secrete hormonal peptides and vasoactive amines that can produce specific endocrine syndromes (islet cell syndromes and carcinoid syndrome). One of the most common symptoms accompanying these syndromes is chronic diarrhea, which can be refractory to standard therapies. Recent advances in understanding the pathophysiology of these tumors have led to better medical therapies for controlling symptoms, diarrhea, and tumor growth. Surgery, chemotherapy, somatostatin analogues, and biologic therapies can all contribute to treatment. This review will cover recent advances in diagnosing and treating these neoplasms and the symptoms they produce.

Key words: Gastrointestinal, Neuroendocrine, Tumor, chronic diarrhea.

INTRODUCTION

Gastrointestinal neuroendocrine tumors are rare malignancies that constitute less than 2% of all gastrointestinal cancers[1]. However, they attract special attention since they can generate unusual paraneoplastic syndromes through the overproduction of endocrine products. Often the symptoms they generate are extreme-

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ly specific depending on the secreted hormones. However, not infrequently they produce nonspecific symptoms resembling any number of other more common diseases. One of the most common symptoms associated with these tumors is diarrhea[2]. Rarely, chronic diarrhea may be the first and primary symptom of a tumor such as a VIPoma. More often the chronic diarrhea may simply be one of many symptoms forming a constellation of problems, as with carcinoid syndrome. This review will focus on diarrhea associated with gastrointestinal neuroendocrine tumors, their incidence, pathophysiology and treatment. One needs to remember that although these diseases are listed in the differential diagnosis for patients presenting with chronic diarrhea, they obviously account for only a fraction of a percent of patients who present with this complaint.

CLASSIFICATION AND HISTOLOGY

The gastrointestinal mucosa and pancreas contain over 15 different cell types that produce hormonal peptides and biogenic amines involved in gastrointestinal motility, digestion and metabolism. These cells belong to a family of endocrine tissues found throughout the body, called the diffuse endocrine system (DES)[4]. Similar tissues can be found scattered in such organs as the thyroid, lung, genitourinary (GU) tract and neuronal tissues[1]. These cells share certain metabolic enzymes, such as neuron-specific enolase, and the ability to package amines and peptide hormones in secretory vesicles. Most cells express granule-associated glycoproteins, such as the chromogranins or synaptophysin, and a high level of surface somatostatin receptors. When tumors arise from these tissues, they almost invariably retain the ability to express these products.Gastrointestinal neuroendocrine tumors can be divided into submucosal carcinoid tumors and islet cell tumors of the pancreas. These tumors are indistinguishable from one another by light microscopy, and are defined by their location of origin and by their

production of secretory products[2-5]. Most tumors synthesize multiple peptides and hormones; however, the clinical syndromes they produce are defined by elevated levels of specific hormones associated with resulting clinical symptoms.

Pancreatic Endocrine Tumors (PETs)

PETs are rare with an incidence of 0.4/100,000 population, and are diagnosed in approximately 1% of patients presenting with pancreatic masses[4]. PETs are defined as functional when they secrete hormones that generate a clinical syndrome. Insulinoma, gastrinoma, glucagonoma, somatostatinoma, vipoma, and GRFoma are examples of functional PETS. Approximately one third of patients will have tumors not associated with endocrine symptoms, and these are defined as nonfunctional tumors[15]. Tumors in this category include those producing neurotensin and pancreatic peptide (PPoma). Except for insulinomas, which are almost always benign, the remaining PETs behave similarly and will metastasize to either lymph nodes or liver as often as 50% to 90% of the time[20]. All PETs can be part of the Multiple Endocrine Neoplasia-syndrome- Type I- (MEN-I). Gastrinomas and insulinomas are the most common[6-7].

Carcinoid Tumors

Gastrointestinal carcinoid tumors share many histologic, ultrastructural and biochemical features with PETs including neurosecretory granules and their associated proteins, hormonal peptides and biogenic amines[8]. In some carcinoid tumors, high levels of the enzyme dopa decarboxylase combined with the production of hydroxytryptophan leads to the synthesis of high levels of 5-hydroxytryptamine (serotonin).

Serotonin exerts a large number of effects responsible for carcinoid syndrome, but is normally inactivated rapidly into 5-hydroxyindoleacetic acid (5-HIAA) within the liver. Carcinoid syndrome usually occurs only if serotonin is released directly into the systemic venous blood, thus avoiding rapid hepatic inactivation. Although serotonin cannot be reproducibly quantitated in the blood due to its short half-life and fluctuating levels, its metabolite 5-HIAA can be measured within the urine and acts as a reliable assay for measuring serotonin production. A major difference between PETs and carcinoid tumors is that carcinoids are found throughout the gastrointestinal tract. Their behavior is related to their site of origin[9].

Foregut carcinoids occur in the thymus, lung, stomach and duodenum, and are least commonly associated with carcinoid syndrome due to low levels of the enzyme dopa decarboxylase and serotonin[10]. Midgut carcinoids occur less commonly than bronchial carcinoids, but are responsible for the majority of cases of carcinoid syndrome (75% to 87%)[26]. These tumors are most often located in the small bowel and especially the terminal ileum. Although these tumors initially produce high levels of serotonin, carcinoid syndrome will not be apparent due to rapid hepatic metabolism of the serotonin. Presenting symptoms are frequently related to anatomic small bowel obstruction secondary to fibrosis.

Carcinoid syndrome does not occur until significant liver metastases produce serotonin and release it directly into the systemic venous circulation. Finally, hindgut carcinoids are the least common and occur in the distal colon and rectum. Carcinoid syndrome is rare and patients more often present with symptoms of bowel irritation and bleeding from bulky tumors. The appendix is the most common site for carcinoids with an incidence of nearly one per 200 appendectomies and a similar rate in autopsy series. Most tumors less than 1 cm remain clinically silent and only lesions greater than 2 cm have an appreciable rate for metastasizing[10].

Neuroendocrine Tumor Syndromes

Although gastrointestinal neuroendocrine tumors share many features, the clinical syndromes they produce are quite specific and dependent on their hormone production. These are listed in Table 1[4].

Zollinger-Ellison syndrome results when gastrinomas cause oversecretion of stomach acid through ectopic gastrin production. Classically, patients present with refractory gastric ulceration, but the syndrome can present with diarrhea or as part of the MEN-I syndrome. Previously, the pancreas was felt to be the most frequent site of gastrinomas, but more recent localization techniques, such as endoscopic ultrasound, have demonstrated that gastrinomas occur in the duodenum three times more fre-

Table 1. Gastrointestinal Neuroendocrine Tumors Producing Diarrhea[4]

	Incident cases per million/yr.	Frequency of Diarrhea (%)
Gastrinoma	1.0	30-75
VIPoma	0.1	98-100
Glucagonoma	0.01-0.1	14-25
Somatostatinoma	<0.01	30-97
Carcinoid Tumor	10-50	30-80

quently than in the pancreas[11].

One of the most dramatic neuroendocrine syndromes results from ectopic production of vasoactive intestinal peptide (VIPoma). Profuse watery diarrhea can lead to hypokalemia and dehydration with stool volumes of greater than 3 liters per day [12]. These tumors are almost always metastatic at presentation arising from a pancreatic primary site[20]. VIPomas are quite rare, occurring 20 times less frequently than gastrinomas[6].

Glucagonomas also originate in the pancreas and are characterized by the constellation of diabetes and diarrhea accompanied by a distinctive dermatitis, necrolytic migratory erythema (NME)[13]. NME usually starts as a benign-appearing erythema in intertriginous areas and progresses to a more diffuse, raised dermatitis with eventual central bullae. The rash may precede other symptoms by years. However, at time of diagnosis, 80% of patients will have metastatic disease[13].

Finally, somatostatinomas are PETs that cause a distinct syndrome including diabetes, diarrhea, weight loss and cholelithiasis[14]. There is an association between von Recklinghausen's disease and duodenal somatostatinomas, but these patients rarely develop the characteristic syndrome[14]. Patients with syndrome almost invariably have pancreatic primaries with 70% having metastases at diagnosis[14]. All of these syndromes produce diarrhea in a majority of patients except for glucagonomas (15% to 25% association)[16].

However, it must be remembered that the last 3 tumors occur with an incidence of one per 10,000,000 and thus are a curiosity rather than a consideration when evaluating a patient with diarrhea.

Carcinoid syndrome almost always occurs in patients with bulky tumor metastatic to the liver. The release of large quantities of serotonin as well as tachykinins induces characteristic episodes of vascular hypersensitivity with flushing, palpitations and diarrhea. Bronchospasm is relatively uncommon and carcinoid heart disease requires years of exposure to serotonin in order to develop into chronic valvular heart disease.

The carcinoid flush is probably the most distinctive component of the carcinoid syndrome. It can occur spontaneously or be provoked by any number of stimuli that changes vascular tone, including exertion, emotional stress, and various foods. With chronic flushing, telangiectasia can develop with a permanent plethora. Diarrhea is the most common symptom, occurring in 75% of patients with carcinoid syndrome at the time of diagno-

sis[15]. It is generally mild with a volume of less than 1 litre per day. The etiology is complex but appears related to increased GI motility rather than secretory mechanisms. Since many patients have had previous intestinal surgery, short bowel syndrome and mesenteric fibrosis may contribute.

Diarrhea

Diarrhea induced by neuroendocrine tumors has variable characteristics depending on the syndrome it is associated with. As mentioned above, VIPomas induce profuse diarrhea, with up to 70% of patients having volumes greater than 3 liters per day. This is directly attributable to the effects of vasoactive intestinal polypeptide (VIP), which induces a secretory state in the jejunum. None of the other syndromes are associated with such large volumes. Even in carcinoid syndrome less than one-third of patients have stool volumes greater than 1 litre per day. Steatorrhea is quite variable but is often present with diarrhea induced by gastrinomas, pancreatic somatostatinomas and carcinoid syndrome. As many as 70% of patients may have mild to moderate fat malabsorption with these syndromes. This can be induced directly by inhibition of pancreatic enzyme secretion (somatostatinomas) or indirectly by inactivation of pancreatic enzymes by excess acid (gastrinomas)[16].

DIAGNOSIS

Although gastrointestinal neuroendocrine tumors remain on the list of differential diagnoses for many common intestinal complaints, it is not sound medical practice to seriously entertain such rare disorders in the initial evaluation of the average patient. For example, in a study of 193 patients with chronic diarrhea, a panel of eight hormone peptides was used to screen for neuroendocrine syndromes. Although 45% of patients had an abnormal test, none of the patients proved to have a neuroendocrine syndrome or tumor[17]. The authors felt that these expensive tests should be used only selectively. A rational approach to these tumors is to consider them when the clinical situation warrants it. For instance, a patient with profuse secretory diarrhea of greater than 3 liters per day could be presenting with a VIPoma.

A patient, with a family history of endocrine disorders and personal history of elevated calcium with reflux and diarrhea, could be presenting with MEN-I and gastrinoma. The patient with flushing and diarrhea may have carcinoid syndrome, but should have obvious liver metastases evident on simple imaging studies. Without strong clues such as these, it is far more likely that a

patient suffering with a common symptom such as diarrhea has an uncommon presentation of a common disorder such as diabetes, malabsorption, hyperthyroidism or even HIV infection. Although the average time from first symptom to diagnosis is up to six years for many of the GI neuroendocrine tumors, early screening or workup for these disorders is not cost-effective and difficult to justify.

Treatment

The initial approach to the treatment of GI neuroendocrine tumors is to attempt curative resection. In the past two decades, new medical treatments such as omeprazole and octreotide, have allowed for better control of endocrine syndromes for patients undergoing elective surgery[18]. However, at the time of diagnosis, the majority of symptomatic carcinoid tumors and more than 60% of non-insulinoma PETs will have metastases and will not be curable[19-20]. Since these tumors usually grow in an indolent fashion, re-operation to debulk symptomatic metastatic disease is often justified. However, salvage surgery is almost never curative and, therefore, medical palliation is often necessary. When pain or hormonal syndromes such as diarrhea are not too severe, standard supportive therapies can be used to manage symptoms. Mild diarrhea can often be controlled with loperamide or diphenoxylate. However, as tumor bulk and symptoms increase, more specific and aggressive therapies become necessary to target the tumor or its hormonal products.

SURGERY AND REGIONAL THERAPY

For the patient with isolated hepatic metastases, resection is still the most definitive debulking therapy. In a series from the Mayo Clinic, 70 patients with neuroendocrine tumors (50 with carcinoid tumor) who underwent hepatic resection had a four-year survival of 73% and a symptom-free survival of 30% at four years[21]. Operative morbidity was minimal in this highly selected group who benefited from intervention. Whether surgical intervention prolongs survival is difficult to establish without a randomized prospective study. A retrospective review using matched control patients from Johns Hopkins[22] demonstrated a significant difference in 5-year survival for patients undergoing hepatic resection (73% vs. 29%). Although the study was flawed due to selection bias, it underscores the relationship between the burden of disease and a patient's prognosis. Certainly, control of endocrine symptoms justified such aggressive resections as long as resections could be performed with tolerable morbidity.

Newer techniques such as radiofrequency ablation are especially suited for cytoreduction, especially when they can be performed laparoscopically with minimal morbidity[23].When hepatic metastases become too extensive for local surgical approaches, embolization has proved useful. Relying on the dual blood supply of the liver, and the vascular nature of neuroendocrine tumors, embolization with occlusive agents with or without intra-arterial chemotherapy can generate radiographic and biochemical responses in 50% of patients. This is especially useful in patients with surgically and medically refractory disease in need of palliation[24-25].

Hormonal Therapy

Since the late 1970's, somatostatin analogues have revolutionized the treatment of neuroendocrine tumors. Native somatostatin binds to cell surface membrane receptors, which are present on an extensive number of endocrine and gastrointestinal tissues, and their malignant counterparts. Receptor activation dramatically inhibits the release of neuroendocrine vesicles and in general decreases secretory rates in the stomach, pancreas and intestines. However, the half-life of somatostatin is one minute, making it an ineffective drug for clinical use. Long-acting synthetic octapeptides (octreotide and lanreotide) have made this treatment clinically practical. Multiple clinical trials have demonstrated the dramatic benefits of these analogues in treating PETs and carcinoid syndromes[26-27]. Most studies on carcinoid syndrome have reported a reduction of 70% in flushing episodes and 50% in diarrhea with either analogue. Biochemical responses, as measured by the urinary 5-HIAA or serum Chromogranin A level, occur in the order of 40% to 70%. Although rare, anecdotal tumor regressions have been reported with the administration of somatostatin analogues[30].

However, in a prospective series of 103 patients from the German Sandostatin Multicentre Study Group, there were no reports of objective partial responses in neurendocrine tumors[28]. Interestingly, up to one third of patients experienced disease stabilization for at least three months with 10% having stabilization of disease for as long as three years. A second study involving 34 patients from Memorial Sloan Kettering also demonstrated stabilization in up to 50% of patients when treated with octreotide[29]. Although the somatostatin analogues have proved extremely useful in treating the symptoms of neuroendocrine tumors, these agents are cumbersome to administer as they require subcutaneous injection up to three times a day. An important innovation with somatostatin analogues has been the development of depot

forms of drug.

Ruszniewski et al, reported on the use of lanreotide LAR (Long-Acting Release) in 39 patients with carcinoid syndrome[30]. Biochemical and symptomatic responses were comparable to results from trials using daily subcutaneous injection schedules. The drug was administered as a 30 mg intramuscular (IM) injection every 2 weeks and generated only transient injection site discomfort.

A large randomized trial of Octreotide LAR (Long-Acting Formulation) injected monthly in patients with carcinoid syndrome demonstrated a success rate of 60–70% in improving diarrhea and flushing. Optimal dose was determined as 20 mg per month with all doses being effective in controlling diarrhea. Higher doses were more effective at controlling flushing[31]. Clinical limitations of somatostatin analogues include tachyphylaxis and inconsistent tumor responsiveness. Many investigators have tried to find predictors of tumor responsiveness using positive octreotide scintigraphy with mixed results. Nonetheless, despite any shortcomings, long acting formulations have had a dramatic impact on the treatment and palliation of patients with gastrointestinal neuroendocrine tumors.

Radiopharmaceuticals

Highly specific receptors on tumor cell surfaces and unique biochemical processes have allowed for novel strategies in targeting cytotoxic therapy at these tumors. One of the more extensive experiences involves the use of 131I-Metaiodobenzylguanidine (131I-MIBG). Structurally similar to norepinephrine, MIBG is taken up by cells of neural crest origin, including pheochromocytomas, neuroblastomas, medullary thyroid carcinomas and carcinoids. Radioactively labelled MIBG was first used in the early 1980's to image these tumors. Over the past decade, large doses of high specific activity 131I-MIBG have been used to treat patients with carcinoid syndrome[32-33]. Recently Taal et al, from the Netherlands reported on the use of 131I-MIBG in 30 patients with carcinoid tumors. Fourteen of 20 patients with carcinoid syndrome had improvement in symptoms. Unfortunately, there were no objective radiographic responses and only 2 from 14 biochemical responses[34]. Other efforts have used radioactively labelled somatostatin analogues, such as octreotide, to direct the cytotoxic therapy directly to the cell surface. Both yttrium and indium labelled analogues are being tested in preliminary phase I trials with reports of early success[35,36]. The technology of radioactive peptide labelling is complex and can be toxic. The ideal radioactive agent and analogues have yet to be identified.

Chemotherapy

The use of chemotherapy in treating neuroendocrine tumors and their syndromes has met with mixed success. Streptozocin is a unique agent in its seeming specificity for neuroendocrine pancreatic islet cells. It has been combined with other agents with modest activity such as doxorubicin, fluorouracil, dacarbazine, and epirubicin[37–39]. In combination, these drugs can produce tumor regression in more than 60% of patients with PETs, but the response rate in carcinoid tumors is less, and the toxicity is significant enough to preclude their use as palliative agents. The rarity of these tumors makes randomized trials impractical. It is unclear whether any combination of chemotherapy agents offers survival benefit for treated patients.

CONCLUSION

In summary, GI neuroendocrine tumors remain a complex family of tumors. Most are malignant and all are rare. Each tumor has unique features, but they all share commonalities, including indolent growth patterns, the tumor marker chromogranin A and the association of diarrhea. Hormonal therapies, including somatostatin analogues, have positively impacted our management of these diseases and the syndromes they generate.Long-acting analogues allow patients relief from syndromes, which can be fatal. Unfortunately, cytotoxic therapy and surgery rarely cure these diseases. The challenge is to find new effective therapies providing anti-tumor effect.

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