PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

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TOPIC HIGHLIGHT

John Geibel, MD, Dsc and Walter Longo, MD, *Series Editors*

Gastrointestinal manifestations of endocrine disease

Christina Maser, Arnbjorn Toset, Sanziana Roman

Christina Maser, Arnbjorn Toset, Sanziana Roman, Department of Surgery, Yale University School of Medicine, 333 Cedar Street, New Haven CT 06520, United States
Correspondence to: Sanziana Roman, MD, Department of Surgery, Yale University School of Medicine, 333 Cedar Street, New Haven CT 06520, United States. sanziana.roman@yale.edu
Telephone: +1-203-7852563 Fax: +1-203-7374067
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Abstract

The hormonal interactions among the systems throughout the body are not fully understood; many vague clinical symptoms may in fact be manifestations of underlying endocrine diseases. The aim of the following review is to discuss gastrointestinal manifestations of surgically correctable endocrine diseases, focusing on abnormalities of thyroid function, cancer and finally autoimmune diseases. We also review manifestations of pancreatic endocrine tumors, and multiple endocrine neoplasia.

Key words: Functional thyroid disease; Autoimmune thyroid disease; Thyroid malignancy; Islet cell tumors

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INTRODUCTION

Endocrine disorders are common, and the effects of endocrine disorders present with a wide range of clinical manifestations. This review encompasses the gastrointestinal manifestations of common endocrine diseases and the diagnostic and surgical interventions which may aid in the treatment of neuroendocrine abnormalities.

THYROID DISEASES

Functional thyroid disease

The true incidence of gastrointestinal manifestations of patients with functional abnormalities of the thyroid is not well documented. Gastrointestinal motor dysfunction, manifested by altered intestinal motility and transit time, has widely been accepted as the leading cause of gastrointestinal symptoms of thyroid disease[1]. The reported frequencies of gastrointestinal symptoms in hyperthyroid patients vary between 30% and 50%[2,3]. Patients with hyperthyroidism can experience frequent bowel movements, diarrhea, even malabsorption with steatorrhea[1,3]. Chronic dyspeptic symptoms such as epigastric pain and fullness, as well as eructation, nausea and vomiting are also frequently seen in these patients. Less commonly, hyperthyroidism has been reported to cause persistent and intractable vomiting[4]. The mechanism behind this is not clear; however, direct hormonal effects or stimulatory actions in the central nervous system have been suggested. Treatment of the thyrotoxicosis with beta-blocking agents and anti-thyroid drugs greatly improves these symptoms[4].

Dysphagia is a rare finding in thyrotoxicosis. The dysphagia can have either an acute or insidious onset, and may result from direct mechanical compression from a goiter, or altered neurohumoral regulation[5,6]. Clinically apparent symptoms vary with involvement of either the oropharyngeal or the esophageal phase of swallowing. There tends to be a higher incidence of oropharyngeal dysphagia than esophageal dysmotility. Clinically, these patients demonstrate easy drooling, nasal regurgitation, and weak phonation. They may have a higher incidence of aspiration pneumonia than do those patients with esophageal dysmotility. Dysphagia of thyrotoxicosis usually resolves shortly after resolution of the hyperthyroidism[5,6].

The overall decreased metabolic function seen in patients with hypothyroidism manifests in the GI tract with sluggish intestinal motility, ranging from mild constipation to paralytic ileus and colonic pseudo-obstruction[7]. Insidious symptoms of vague abdominal pain and distension may be present, and can be misdiagnosed as functional bowel disease. The exact biochemical mechanism by which thyroid disorders affect the gastrointestinal system are not fully understood. Changes may be seen on a molecular level with alteration of hormone receptors, dysfunction of the autonomic nervous system and myoelectrical enteric activity, as well as changes on a tissue level in the form of myopathy[3].

Altered gastroenteric myoelectrical activity has been documented by electrogastrography (EGG)[8]. Most studies in the literature detect a lack of correlation between the EGG and gastric emptying in non-euthyroid patients,

with manifestations of smooth muscle dysfunction, dissociation between the electrical signal and muscle response, pylorospasm, and lack of coordination between the antrum and the duodenum[9]. Hormonal effects on the GI tract may be a direct result of thyroid hormone, or as a result of synergistic effects of catecholamines. Tenore et al. investigated the effect of thyroxin (T4) on the intestinal chloride/bicarbonate exchange in hypo- and hyperthyroid rats. They found that alterations in intestinal ion exchange, mainly the flux of chloride, led to mucosal effects and resultant diarrhea. These findings were not seen when T4 was added ex vivo to rat ileum, suggesting that the effect on electrolyte transport likely requires systemic factors[10]. Furthermore, the beta-adrenergic antagonist propranolol inhibits intestinal transit in hyperthyroidism, thereby indicating that some of the dysmotility may be mediated through the adrenergic/catecholamine system[11]. Dysfunction of the autonomic nervous system (ANS) may modify the neuro-hormonal milieu, and result in alterations of myoelectric activity. However, there are no clear data regarding the exact mechanisms involved.

Hypothyroidism characteristically results in accumulation of glycosaminoglycans, mostly hyaluronic acid, in interstitial tissues throughout the body. This leads to interstitial edema that is particularly evident in the skin, heart muscle, and skeletal muscle, but also in the gastric smooth muscle. Edema in the gastric muscle may predispose to abnormalities of gastric myoelectric activity and thus the dysmotility seen in hypothyroid patients[12].

Thyroid malignancy

Patients with familial adenomatous polyposis (FAP), while known to be at high risk for colorectal cancer, also have an increased risk of thyroid malignancy. Papillary thyroid cancer (PTC) was first documented in a patient with FAP in 1949, and in 1968 a relation between FAP and PTC was suggested by Camiel *et al*[13,14]. The relative risk for PTC in FAP patients under 35 years of age has been found to be 160 times that of the general population. Thyroid cancer may be the first finding in patients with FAP, and 30% of thyroid carcinomas are diagnosed 4 to 12 years before the diagnosis of polyposis[15].

It has been suggested that FAP-associated thyroid tumors share unusual histological findings, such as the cribriform morular-variant of PTC (CMPTC)[16-20]. While the overall incidence of CMPTC in FAP patients has yet to be determined, analysis of large FAP registries suggests that it affects about 1%-2% of patients[20,21]. Similar to sporadic PTC, this disease demonstrates female predominance, and multifocality[22-26]. A recent series of seven such patients published by Tomoda et al demonstrated that all patients were female, with a mean age at presentation of 25 years[27]. Despite seemingly aggressive pathology, patients with CMPTC follow a highly favorable long-term course, with 5- and 20-year survivals of FAP-associated CMPTC reported to be 90% and 77%[16]. Patients diagnosed with CMPTC should be screened for FAP[27].

Autoimmune thyroid disease (AITD)

AITD, such as chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) and Graves' disease, has been linked to autoimmune disorders of the gastrointestinal tract, namely celiac disease and atrophic gastritis. This association is not surprising considering that these disease entities share a common haplotype, HLA DR3-DQ2, which is common to many autoimmune diseases[28,29].

Celiac disease, a gluten-induced small bowel mucosal inflammation, demonstrating crypt hyperplasia and villous atrophy, is associated with an increased frequency of AITD. Patients with AITD are affected by celiac disease 5-10 times more than the general population. Also, 4%-10% of patients with celiac disease will also manifest AITD. Positive anti-thyroid antibodies can be seen in 10%-15% of patients with celiac disease. The significance of this discovery of subclinical thyroiditis is uncertain. Patients with AITD who remain hypothyroid despite adequate thyroid hormone supplementation, should undergo screening for celiac disease, as mucosal abnormalities may preclude full absorption of levothyroxine[30].

Atrophic gastritis is a chronic disease characterized by disappearance of oxyntic glands, loss of production of hydrochloric acid and intrinsic factor, as well as demonstration of parietal cell autoantibodies (PCA)[31,32]. Autoimmune gastritis is an early event in juvenile patients with AITD and detectable PCA. The lack of gastric symptoms in this young population often leads to a delay in diagnosis, thus screening for PCA with biochemical markers of gastric damage, such as gastrin levels, is warranted. Abnormal levels help to select patients who may benefit from further investigation with gastroscopy. Segni et al, determined that 30% of juvenile patients with AITD had positive PCA, and demonstrated that 45% of these patients had mild to severe hypergastrinemia[33]. Screening of juvenile patients with AITD is warranted, as atrophic gastritis is associated with a higher risk of gastric cancer and carcinoid tumors[34,35]. Premalignant gastric lesions can be found in up to 26% of these relatively young patients with detectable PCA[36].

ISLET CELL TUMORS OF THE PANCREAS

Islet cell tumors of the pancreas are rare entities which can range in presentation with respect to functionality, malignancy, and pattern of inheritance. The first descriptions of endocrine tissue in the gut came during the late 1800's with the recognition of 'islands' of cells in the pancreas by Langerhans, followed later by the discovery of chromaffin cells in the stomach by Rudolf Heidenhain, and then in the intestinal mucosal crypts of Lieberkuhn by Nikolai Kulchitsky. The recognition and intermittent reporting of islet cell adenomas began in 1902. However it was not until 1921 that the first reported clinical implication of these adenomas became known. Over the next 50 years several different peptides secreted by these tumors were identified, and eventually they were recognized as amine precursor uptake and decarboxylation (APUD) cell lesions, and coined apudomas. Based on functionality, these lesions were classified into clinical syndromes[37].

The clinical presentation of patients with pancreatic endocrine tumors varies from vague complaints of

abdominal pain and nausea to debilitating diarrhea. Due to the variability in clinical symptoms, a biochemical diagnosis is necessary. Once a definitive diagnosis is made based on serum markers, localization often necessitates multiple imaging modalities. Ultrasound is often the first test utilized, but has a low sensitivity, up to 31%[38-40]. Computed tomography (CT) and magnetic resonance imaging (MRI) technologies have improved sensitivity for small lesions, up to 40%-70%[38-41]. In cases where conventional imaging fails to adequately localize the lesion, invasive testing, such as intra-arterial stimulation and venous sampling, provides additional data. While these procedures can be invasive and technically challenging, the results are reliable and specific[42,43].

Labeled octreotide scanning is useful, as many islet cell tumors demonstrate type 2 somatostatin receptors[40]. Positron emission tomography utilizing a serotonin precursor 5-hydroxy-tryptophan has shown excellent results in a preliminary study from Eriksson and colleagues[44]. Endoscopic ultrasound has rapidly come to the forefront in localization studies. While operator dependent, it is highly sensitive in detecting even small tumors. Limitations include tumors in the distal pancreas and those that are pedunculated. In addition, fine needle aspiration can be preformed at the same time for both diagnosis and tattooing of the lesion to allow easy identification at the time of resection[40].

The operative approach varies on the type and extent of tumor. Enucleation is the procedure of choice for benign tumors, while malignant lesions require en bloc resection due to local invasion or presence of metastases. Laparoscopy is appropriate in some cases where enucleation or distal pancreatectomy is required[45].

Insulinoma

Insulinoma is the most common islet cell tumor. It was first described by Wilder and W. J. Mayo in 1927[37]. This tumor is typically solitary, small, and benign. It may be sporadic or associated with MEN I[40]. Hyper-secretion of insulin is often associated with the clinical findings of the "Whipple's triad", which consists of symptoms and signs of hypoglycemia during times of fasting or exertion, a serum glucose level less than 2.5 mmol/L during these symptoms, and resolution of the symptoms with administration of glucose[40,46]. Documenting elevated insulin levels during hypoglycemic periods, levels of endogenous insulin secretion with a C-peptide measurement and calculating the insulin:glucose ratio confirm the diagnosis. Adenomas, islet cell hyperplasia or nesidioblastosis can be the cause of hyperinsulinemia. The adenomatous lesions tend to be small and may be difficult to localize pre-operatively. Localization should be performed with conventional imaging including endoscopic US (EUS), CT, MRI, octreoscan, as well as calcium stimulated arterial-venous sampling (Doppman-Imamura test) for regionalization, if needed. Intraoperative ultrasound is extremely sensitive in localizing small lesions with a sensitivity of 91% in one series[47].

Enucleation is the preferred surgical treatment. In patients with diffuse disease, or tumors too small to localize, a regional resection is warranted after the general location of the tumor is identified by pre-operative arterial stimulation and venous localization[38,43]. Blind resection is not recommended.

Gastrinoma

Zollinger and Ellison described the gastrinoma syndrome (ZES) in 1955[37]. ZES includes a tumor associated with hypergastrinemia, peptic and distal duodenal ulcers. This is the most common islet cell tumor in MEN I, seen in up to 40% of patients. Although considered an islet cell tumor, this lesion is more frequently located in the duodenum, and can arise anywhere within the gastrinoma triangle, which is bounded by the confluence of the cystic and hepatic bile ducts, the junction of the 2nd and 3rd portions of the duodenum, and the neck of the pancreas. The rate of malignancy was noted to be 52% in one of the largest published series by Norton *et al*[48]. Clinically, patients present with recurrent ulcer disease, abdominal pain, diarrhea, and melena; they all demonstrate hypergastrinemia. Symptoms can be controlled with proton pump inhibitors to provide and opportunity to localize the lesion. Imaging with CT and MRI can be diagnostic; EUS has also proven useful as the majority of these tumors are located in the wall of the duodenum. Difficult localization or regionalization can be obtained by visceral arterial stimulatory testing using either secretin or calcium as a secretogogue, with hepatic venous sampling[38,39,42,48,49].

In those lesions that are difficult to localize pre-operatively, a thorough search must be undertaken in the gastrinoma triangle intra-operatively. Intraoperative endoscopy for identification of small intramural duodenal adenomas can be helpful. A duodenotomy is performed to allow clear evaluation of the wall of the duodenum and resection of lesions. If no obvious abnormality can be found, then a pancreaticoduodenectomy may be performed[40]. The role of resection of liver metastases for gastrinoma is not well defined at the present time. Debulking of > 90% of tumor burden may help in overall palliation of symptoms, and may be accomplished surgically or in combination with radiofrequency ablation and/or cryotherapy ablation[40].

VIPoma

These rare tumors, described by Verner and Morrison in 1958, are defined by the oversecretion of vasoactive intestinal peptide (VIP)[37]. The clinical syndrome is one of voluminous secretory watery diarrhea, with hypokalemia and hypochlorhydria. The profound diarrhea leads to significant losses of chloride and potassium, producing symptoms of incapacitating muscle weakness[46,51]. Other symptoms include flushing, due to vasodilatory effects of VIP, hyperglycemia due to glycogenoloytic activities of VIP, and hypercalcemia. The triad of severe secretory diarrhea, elevated fasting levels of VIP, and identification of an islet cell tumor is diagnostic. In a study performed by Koch *et al*[52] the determination of VIP levels can differentiate between patients with chronic diarrhea of other sources, patients with a non-functional islet cell tumor and those due to a functional tumor. VIP levels in patients with a functional tumor were 160-5975 ng/L compared to 80-120 ng/L in those with a non-functional

tumor. Most patients produce diarrhea in excess of 5 L/d, but no less than 0.7 L/d. Localization can be accomplished with conventional imaging, as both CT scan and MRI are sensitive tests for pancreatic and liver lesions. Octreoscan is useful in individuals with equivocal imaging. The most common location for this tumor is the tail of the pancreas, and a majority of these patients will have liver metastases at diagnosis[51].

Octreotide reduces circulating levels of VIP and allows for improvement of the diarrhea. After preoperative optimization, surgical exploration for resection is the most effective treatment. As a significant portion of these patients will have malignant disease at the time of exploration, careful examination of the liver and lymph nodes is necessary. Debulking may have a benefit in improving the symptoms by lowering VIP levels[40,46]. In cases of unresectable disease, adjuvant therapy with octreotide, streptozotocin, 5-fluorouracil and doxorubicin can palliate the symptoms[40]. However, a portion of patients may not respond to octreotide, or may become refractory to the drug due to down-regulation of receptors. Mean survival is 3.6 years, with a possible long-term survival of up to 15 years[51].

Glucagonoma

Glucagonoma was identified by McGarvran *et al*[37] in 1966. While rare, this islet cell tumor may have the most distinctive clinical syndrome. It arises from cells resembling alpha islet cells, is the third most common functioning endocrine tumor, and may be both sporadic or associated with MEN I[40]. Symptoms of excessive glucagon secretion are manifested by a migrating skin rash, diabetes, malnutrition, weight loss, anemia, thrombophlebitis, and glossitis. The necrolytic migratory erythema that is pathognomonic for this condition is felt to be secondary to hypoaminoacidemia associated with elevated levels of glucagons. Restoration of serum amino acids may alleviate this condition. However the data are contradictory. Malignancy is common with these tumors, and the prognosis is worse than with other types of islet cell tumors. The most common age at diagnosis is between 50-60 years. Patients often present with the characteristic pruritic skin rash located on the lower extremities and groins, glucose intolerance or frank diabetes mellitus. Thromboembolic disease is common, and can be the cause of death in some patients[46].

Biochemical diagnosis is based on elevated levels of plasma glucagon. Localization can be accomplished with CT scanning, as these tumors are typically large and located in the distal pancreas. Hepatic metastasis at the time of diagnosis is common[40]. Preoperative preparation involves control of hyperglycemia, treatment of thrombosis, and optimization of nutritional status with total parenteral nutrition. Octreotide has occasionally been used to aide in reduction of plasma glucagons levels, allowing improvement of nutritional status, and alleviation of the rash[46].

An aggressive operative approach is the mainstay of treatment. En bloc resection is required due to the high risk of malignancy, and liver metastases should be resected at the same setting if possible. Hepatic artery embolization, chemotherapy with 5-fluorouracil and streptozotocin, as well as long-term octreotide may be adjunctive. Liver and pancreatic transplantation have been performed in rare instances. The metastatic disease can be indolent, leading to survival for many years[46].

Somatostatinoma

Identification of somatostatinoma was made by Larssen *et al* and Ganda *et al* in 1977[37]. These rare tumors are frequently located in both the duodenum and pancreas, and secrete excess somatostatin. Overproduction of this inhibitory peptide leads to vague symptoms, marked by a decrease in gastrointestinal function. Clinically, it may present with cholelithiasis (70%), mild diabetes (60%), steatorrhea (30%-68%), hypochlorhydria (33%-53%) and weight loss[46]. Many of these tumors are identified incidentally on imaging studies for vague abdominal complaints, or at the time of cholecystectomy. The biochemical diagnosis is made by increased serum levels of somatostatin. Most of these tumors are located in the head of the pancreas or duodenum, and are usually solitary. Pancreaticoduodenectomy is often necessary due to the high risk of malignancy[40].

OTHER FUNCTIONAL AND NON-FUNCTIONAL NEUROENDOCRINE TUMORS

Islet cell tumors of the pancreas can secrete a variety of other hormones, including pancreatic polypeptide, grhelin, corticotropin, neurotensin, and calcitonin[46,51]. The majority of these tumors produce vague symptoms of abdominal discomfort and diarrhea. They can be difficult to diagnose, and should be approached in a similar manner to other functional islet cell tumors[40,46].

Tumors that produce peptides not associated with a clinical syndrome are considered to be non-functional. These lesions often produce symptoms associated with mass effect, such as abdominal discomfort or pain, nausea, emesis, obstruction, cachexia, bleeding, and obstructive jaundice[54]. Due to the lack of functional symptoms, these tumors are typically large when diagnosed, and have been noted to average 10 cm in two published series[54,55]. Conventional imaging with CT will identify these tumors, but they are difficult to distinguish from pancreatic adenocarcinoma. Operative approach to these lesions should be with intent of curative resection by pancreaticoduodenectomy, or distal pancreatectomy. If the lesion cannot be safely resected, an open biopsy should be obtained prior to palliation with gastrointestinal bypass. In a large series published by Liang *et al*, adjuvant chemotherapy and radiation therapy provided a disease-free survival of up to 45 mo, with an overall 5 and 10 year survival of 58% and 29%[54].

Multiple endocrine neoplasia syndromes (MEN)

MEN 1 is characterized by pituitary lesions, islet cell tumors of the pancreas, and hyperparathyroidism. The MEN 1 pancreas can manifest any of the previously mentioned tumors, the most common being gastrinoma. The pancreatic pathology can be in the form of a macroadenoma, microadenoma, islet cell hypertrophy,

hyperplasia, dysplasia, and carcinoma; approximately 50% of MEN 1 patients have tumors which are duodenal in origin. It has been shown that early detection can improve long-term survival, therefore early screening with pancreatic polypeptide and gastrin is advocated for family members of MEN 1 patients[46]. In addition, measurement of insulin, proinsulin, glucagon, and chromogranin A can be utilized. If two of these markers increase over the course of 6 mo, further investigation should be undertaken, and those patients should be referred for surgical exploration[56]. Cure for gastrinoma is difficult due to the size and multiplicity of lesions. The largest series of surgical resection and cure comes from the University of Michigan in which and an 80% pancreatectomy, thorough exploration of the duodenum, and enucleation of smaller pancreatic lesions has been performed[46]. Total pancreatectomy, pancreaticoduodenectomy and pancreas-preserving total duodenectomy have also been reported[46,57].

MEN 2 is subdivided into MEN 2A, characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid hyperplasia; and MEN 2B which includes MTC, tumors of the adrenal medulla (pheochromocytoma, and/or ganglioneuroma), intestinal and mucosal neuromas, and marfanoid habitus. These syndromes can manifest a host of GI symptoms, including diarrhea associated with hypercalcitonemia of MTC, constipation associated with hypercalcemia, and most notably, Hirschsprung's disease associated with MEN 2B[46]. Ganglioneuromas of the intestinal mucosa can lead to manifestations of Hirschsprung's disease with significant symptoms of constipation, pain, distension, and difficulty swallowing. The majority of these patients require surgical intervention for their colonic disease[58].

In summary, endocrine disorders of the thyroid and pancreas often have significant gastrointestinal symptoms. Given the often vague and general quality of these symptoms, diagnosing their endocrine etiology requires a high index of suspicion. Treatment can be achieved both medically, and surgically, if indicated or feasable.

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