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The neuroendocrine tumors of the ileum

Review Article

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Abstract: Neuroendocrine tumors arise from the diffuse neuroendocrine system and secrete several peptides and bioactive amines (serotonin, histamine, dopamine, norepinephrine, corticotropin, calcitonin, bradykinin, kalikrein, gastrin, cholecystokinin, prostaglandins). The most common occurrence site of neuroendocrine tumors is the ileum. The symptoms of small bowel carcinoids are represented by intermittent intestinal obstruction and carcinoid syndrome. Presence of the carcinoid syndrome usually indicates hepatic or retroperitoneal metastases. The typical carcinoid syndrome is characterized by flushing, diarrhea, nonspecific abdominal pain and bronchospasm. The diagnosis of small bowel tumors is often difficult due to their rarity and the nonspecific and variable nature of the presenting signs and symptoms. The most useful initial diagnostic test for the carcinoid syndrome is to measure 24-hour urinary excretion of 5-hydroxyindolacetic acid (5 HIAA), which is the end product of serotonin metabolism. Capsule endoscopy is a more recent diagnostic tool. Surgery is the radical form of curative therapy for carcinoid tumors. Numerous therapies are available for palliation including surgery, pharmacologic therapy, interventional radiologic therapy, embolization and chemoembolization of hepatic metastases, immunotherapy (Interferon alfa) and chemotherapy. We carefully reviewed the available literature on this topic before beginning our study.

Keywords: *Neuroendocrine tumors • Carcinoid syndrome • Liver metastases*

1. Introduction

Neuroendocrine tumors arise from cells of the diffuse neuroendocrine system. They have neurosecretory properties, producing the secretion of different peptides and bioactive amines (serotonin, histamine, dopamine, norepinephrine, corticotropin, calcitonin, bradykinin, kalikrein, gastrin, cholecystokinin, prostaglandins) responsible for the clinical presentation. The diffuse neuroendocrine cell gives rise to a heterogeneous population of tumours which differ in their morphological and functional features. The term 'carcinoid', although well established in medical terminology, is therefore no longer adequate to cover the entire spectrum of neuroendocrine neoplasms. Here we use the term "neuroendocrine tumours" which was suggested in the WHO classification of 2000. We review the most important neuroendocrine tumor entities that are currently recognised in the gastrointestinal tract, highlighting their distinguishing features.

2. Epidemiology

The overall incidence of neuroendocrine tumours is difficult to determine because many are asymptomatic [1].

In a series of 13,715 neuroendocrine tumors reported to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the age-adjusted incidence rates for Caucasian men and women over the last decade were 2.47 and 2.58 per 100,000, while they were somewhat higher for black men and women (4.48 and 3.98 per 100,000 population per year) [2].

An extensive analysis of the anatomic location of neuroendocrine tumors using data from the SEER [3,4] showed that these tumors occur most frequently in the gastrointestinal tract (74%). Less frequently they can occur in the bronchopulmonary system (25%). The remaining 1% occur in a variety of locations, including the ovary [5], gallbladder [6], extrahepatic bile ducts [7], thymus [8], testis [9], liver, cervix, spleen, breast, and

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Figure 1. Microscopic aspect of a neuroendocrine tumor.

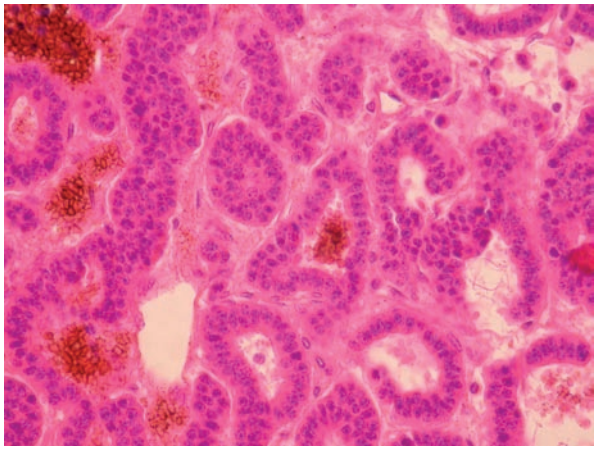
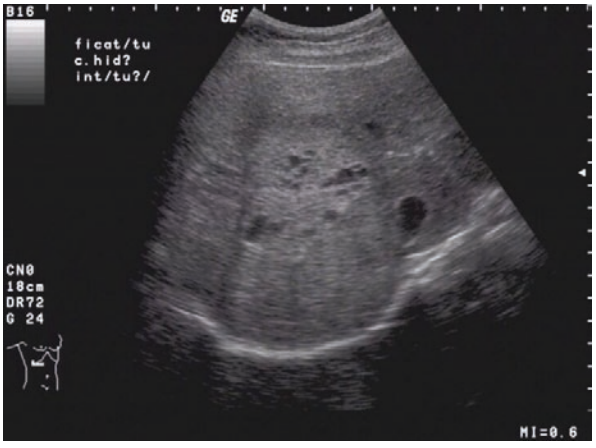


Figure 2. Liver metastasis of ileal neuroendocrine tumor.



larynx. Within the gastrointestinal tract, most carcinoids arise in the small intestine (most commonly in the ileum), followed by the appendix, rectum, colon and stomach [10].

Neuroendocrine tumors of the small intestine are the most clinically important tumors because of their frequency of presentation, their more advanced stage at diagnosis, and their association with the carcinoid syndrome. Approximately 40% of the tumors occurred within 2 feet of the ileocecal valve, with very few in the proximal small intestine. Thirty-five percent of patients had more than one lesion, and most primary tumors were 2.0 to 4.0 cm in diameter [1].

3. Pathology

Neuroendocrine tumors were so named because they seemed morphologically different and clinically less aggressive than the more common intestinal adenocarcinoma. They arise from enterochromaffin cells of the gastrointestinal tract. The term enterochromaffin refers to the ability to stain with potassium chromate (chromaffin), a feature of cells that contain serotonin. Grossly carcinoid tumors appear as solid yellow-tan lesions. Those in the stomach and ileum, which may be multicentric, are usually solitary. In the gastrointestinal tract they are often submucosal but may cause ulceration. A striking feature of carcinoids is the intense desmoplasia within and surrounding the tumor. This may in some cases lead to gastrointestinal obstruction or vascular occlusion secondary to anatomic distortion caused by the surrounding tissue reaction [11].
Figure 1 shows the microscopic aspect of a neuroendocrine tumor.

4. Classification

Carcinoid tumors have traditionally been classified according to their embryologic region of origin. The classification includes tumors of the foregut (including the lungs, bronchi and stomach), the midgut (including the small intestine, appendix, and proximal colon), and the hindgut (including the distal colon, rectum, and genitourinary tract). The different types of tumors correlate with their morphologic pattern, silver affinity, and clinical behavior. Foregut and hindgut carcinoids are typically argyrophil**,** and midgut carcinoids are argentaffin. Immunohistochemical stains of neuroendocrine tumors usually yield positive results for markers of neuroendocrine differentiation.

One-third of midgut carcinoids are symptomatic. One-tenth are associated with carcinoid syndrome. In comparasion, hindgut carcinoids are usually asymptomatic and rarely cause carcinoid syndrome, even when metastatic [12].

5. Clinical characteristics of small bowel neuroendocrine tumors

Neuroendocrine tumors originating in the small intestine are the most common cause of the carcinoid syndrome. These tumors typically progress slowly and have an extended disease course, and although they often present with metastases at diagnosis. In comparasion, hindgut tumors are usually asymptomatic and rarely cause carcinoid syndrome, even when metastatic.

The majority of patients with neuroendocrine tumors are asymptomatic, and the tumor is diagnosed incidentally at endoscopy, surgery, or autopsy.

The symptoms of small bowel neuroendocrine tumors

are represented by intermittent intestinal obstruction and carcinoid syndrome.

Bowel obstruction and abdominal pain may be due to the mechanical effect of the tumor, or mesenteric ischemia due to local fibrosis or angiopathy (mesenteric artery occlusion).

The carcinoid syndrome is present in approximately 5 to 7% of these patients. Presence of the carcinoid syndrome usually indicates hepatic or retroperitoneal metastases and is an ominous indicator of an unfavorable outcome [1]

Figure 2 shows the ultrasonographic aspect of a neuroendocrine ileal tumor. Approximately one third of patients exhibit regional nodal metastases only, and another third show distant metastases [11]. The prevalence of distant metastases increases with size of the primary tumor. The rate of metastases from tumors smaller than 1 cm was 2%; from tumors 1 to 2 cm, 50%; and from tumors larger than 2 cm, 80% [13].

The symptoms of the carcinoid syndrome vary in frequency.

Flushing is the most frequent, followed by diarrhea, nonspecific abdominal pain, bronchospasm, pellagra-like skin reactions, and progressive right-sided congestive heart failure. In most cases, carcinoid syndrome is related to the presence of hepatic metastases from a midgut primary tumor [1].

Episodic flushing is the clinical hallmark of the carcinoid syndrome, and occurs in 30 to 85% of patients. As the disease progresses, the episodes may last longer and the flushing may be more diffuse and cyanotic. Most flushing episodes occur spontaneously, but they can be provoked by emotional or physical stress, medication (calcium, pentagastrin), alcohol ingestion, large meals, or intake of certain foods (e.g., cheese, chocolate), defecation, palpation of the liver, and anesthesia [14]. Episodes induced by anesthesia may last hours and be accompanied by severe hypotension ("carcinoid crisis"). Venous telangiectasia similar to those seen in *acne rosacea*, appear late in the course of the carcinoid syndrome.

The diarrhea of carcinoid syndrome does not necessarily correlate with flushing. Diarrhea appears to be related to increased gut motility and serotonin is directly responsible for this symptom [15]. Serotonin antagonists (methysergide maleate, cyproheptadine, ondansetron hydrochloride, ketanserin) are frequently helpful in alleviating diarrhea, suggesting a prominent role of serotonin in the pathogenesis of this portion of the carcinoid syndrome [16].

Other symptoms experienced by carcinoid syndrome patients include nonspecific abdominal pain (15% to 72%), cardiac symptoms caused by endomyocardial fibrosis typically involving the right side of the heart (45% to 77%), bronchospasm (2% to 19%), and pellagra-like skin reactions associated with niacin deficiency (2% to 5%) [17,18]. Rare manifestations of carcinoid syndrome include Cushing's syndrome caused by corticotropin secretion, depression, anorexia, arthritis, ophthalmologic changes, ureteral obstruction secondary to retroperitoneal fibrosis, and Peyronie's disease [17]. The cardiac disease associated with the carcinoid syndrome is an endomyocardial fibrosis typically involving the right side of the heart, although left-sided lesions have been described. Fibrotic deformation of the tricuspid and pulmonary valves usually leads to pulmonary stenosis and tricuspid insufficiency.

Carcinoid crisis, or the acute exacerbation of carcinoid syndrome, may occur in a number of situations but most commonly in association with surgical or anesthetic stresses. Hyperglycemia, flushing, hyper- or hypotension, tachyarrhythmia, and refractory bronchospasm, possibly resulting in patient death, may characterize these episodes. All patients with known carcinoid disease should receive somatostatine analogs before surgery (preoperative preparation with 150 to 500 μg of somatostatine analogs) [19].

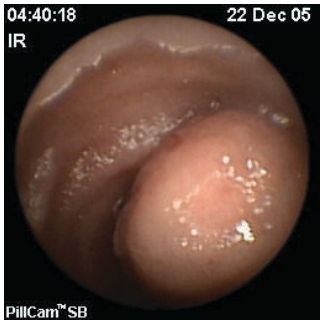
6. Diagnosis

The diagnosis of small bowel tumors is often difficult due to their rarity and the nonspecific and variable nature of the presenting signs and symptoms. Thus, delay in diagnosis is common, which may result in the discovery of disease at a late stage and a poor treatment outcome.

Biochemical testing for the carcinoid syndrome: the most useful initial diagnostic test for the carcinoid syndrome is to measure 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), which is the end product of serotonin metabolism. This test has a sensitivity of 75% and specificity of up to 100% [20], but is fraught with errors that may be induced by the ingestion of certain foods (e.g.: bananas, walnuts, and pecans) and medications (e.g., acetaminophen, salicylate, isoniazid). In most laboratories, the upper limit of normal for 24-hour urinary 5-HIAA excretion is 6 to 10 mg. Determination of the whole blood serotonin concentration is often helpful when urinary 5-HIAA testing yields equivocal results.

Provocation of flushing using epinephrine or pentagastrin is useful in evaluating patients who describe flushing, but have normal or only marginally elevated biochemical markers.

Figure 3. Ileal neuroendocrine tumor: viewed by videopill.



Octreotide scan, a radionuclide imaging using octreotide is a useful technique for localization of carcinoids because tumor cells almost always contain somatostatin receptors. Octreotide imaging has a greater than 90% sensitivity for identifying carcinoid tumors in patients with carcinoid syndrome, and is superior to metaiodobenzylguanidine (MIBG) scintigraphy [21].

Magnetic resonance imaging (MRI) and computed tomograpy (CT) with intravenous and oral contrast are occasionally useful in identifying large primary tumors and regionally involved lymph nodes; they are primarily used to identify metastatic disease.

Wireless video endoscopy or video capsule endoscopy is a novel noninvasive technology designed primarily to provide diagnostic imaging of the small intestine, an anatomic site that has proved peculiarly difficult to visualize [22].

Figure 3 shows an ileal neuroendocrine tumour detected by video-pill.

Enteroclysis is useful for identification of intraluminal disease.

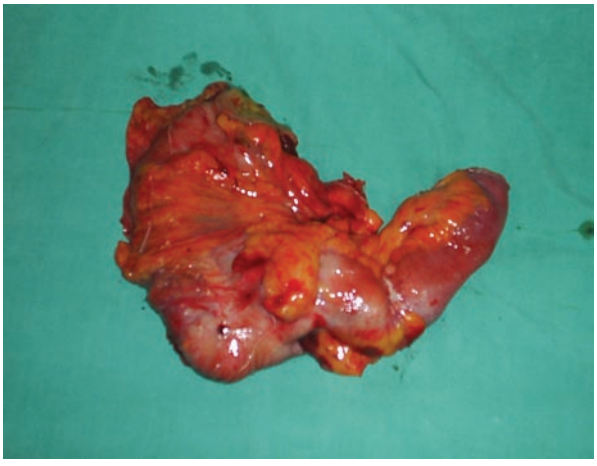
Enteroclysis involves the instillation of contrast material – barium (usually administered through a nasoenteric tube) into the small bowel using a pump (making it considerably less comfortable than a standard small bowel follow-through). It provides more detailed visualization of the small bowel compared with a standard upper gastrointestinal series. Suggestive findings include submucosal thickening, single or multiple stenoses, adhesions, and fistula formation [23].

7. Therapy

Surgery is the only form of curative therapy for carcinoid syndrome. A removed intestinal neuroendocrine tumor is showed in Figure 4.

However, most patients are not candidates for curative treatment. For these individuals the focus of therapy is palliation of symptoms. Numerous therapies are available for this purpose, including surgery, pharmacologic therapy, interventional radiologic therapy, embolization and chemoembolization of hepatic metastases, immunotherapy (Interferon alfa) and chemotherapy [24,25].

Figure 4. Ileal neuroendocrine tumor: viewed by videopill.



The metastasis should be removed by segmental resection and mesenteric lymph node excision. Surgical treatment of liver metastases may relieve endocrine symptoms and result in an overall five year survival rate of 47% [26].

Other approaches to the treatment of hepatic metastases include the use of radiofrequency ablation and cryoablation, either alone or in conjunction with surgical debulking.

For patients with carcinoid syndrome, surgery is combined with continuous biotherapy with long acting somatostatine analogues, which may alleviate symptoms and stabilize disease or slow progression.

Chemotherapy is carried out with fluorouracil, dacarbazine, streptozocin, (and/or?) cyclophosphamide. Most reports suggest response rates of less than 25%, with a short duration of response. Chemotherapy should be reserved for symptomatic patients for whom more effective forms of palliative therapy are unsuccessful [20].

Pharmacologic therapy: Many of the agents used in the control of carcinoid syndrome are directed at serotonin. Inhibitors of serotonin synthesis include methyldopa and parachlorophenylalanine. Methysergide maleate (5-HT_1), cyproheptadine hydrochloride (5-HT_{1+2}), ketanserin ($5HT_2$), and ondansetron hydrochloride ($5HT_3$) have all been utilized with some success. These agents are generally more successful in controlling gastrointestinal symptoms than flushing. Somatostatine and its analogs are thought to affect carcinoid tumors by partially inhibiting synthesis and release of tumor-produced amines and peptides and by blocking their effect on target tissues [20]. Somatostatine analog therapy

is the most effective palliative therapy for carcinoid syndrome patients. Octreotide is very effective in the control of flushing and diarrhea: it is effective in 50% to 87% of carcinoid syndrome patients who display these symptoms. A biochemical response occurred with an octreotide dose range between 300 and 375 μg/day [27].

8. Prognosis

Neuroendocrine tumors are characterized by slow growth. Even when metastases are present, survival is measured in terms of years rather than months. The prognosis of the neuroendocrine tumors is largely based upon the size, invasiveness, and histology of the primary tumor; those that are judged to have a typical (versus atypical) histology have a better prognosis [27].

Favorable survival and appreciable quality of life can be expected from combined treatment (surgery and somatostatin analogues), even for patients with advanced midgut tumors [28].

Data derived from the United States National Carcinoid Register revealed a median five-year survival for all patients of 82%. Five-year survival varied with the extent of disease; median survival was less than two years. Subjects with smaller tumor than 2.5 cm and less invasive tumors had an excellent prognosis [28].

The presence of the carcinoid syndrome confers a poorer median survival, ranging from less than one year to 38 months. These data were collected in studies performed before the availability of newer treatments. Thus, the current prognosis might be somewhat better [29].

9. Conclusions

The neuroendocrine tumours represent a rare but important pathological condition of the gut. Sometimes the diagnosis is difficult, mainly in early cases. The endoscopic pill is usefull in detecting the tumor.

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