Review paper

Clinical features of gastroenteropancreatic tumours

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Abstract

Gastroenteropancreatic (GEP) endocrine tumours (carcinoids and pancreatic islet cell tumours) are composed of multipotent neuroendocrine cells that exhibit a unique ability to produce, store, and secrete biologically active substances and cause distinct clinical syndromes. The classification of GEP tumours as functioning or non-functioning is based on the presence of symptoms that accompany these syndromes secondary to the secretion of hormones, neuropeptides and/or neurotransmitters (functioning tumours). Non-functioning tumours are considered to be neoplasms of neuroendocrine differentiation that are not associated with obvious symptoms attributed to the hypersecretion of metabolically active substances. However, a number of these tumours are either capable of producing low levels of such substances, which can be detected by immunohistochemistry but are insufficient to cause symptoms related to a clinical syndrome, or alternatively, they may secrete substances that are either metabolically inactive or inappropriately processed. In some cases, GEP tumours are not associated with the production of any hormone or neurotransmitter. Both functioning and non-functioning tumours can also produce symptoms due to mass effects compressing vital surrounding structures. Gastroenteropancreatic tumours are usually classified further according to the anatomic site of origin: foregut (including respiratory tract, thymus, stomach, duodenum, and pancreas), midgut (including small intestine, appendix, and right colon), and hindgut (including transverse colon, sigmoid, and rectum). Within these subgroups the biological and clinical characteristics of the tumours vary considerably, but this classification is still in use because a significant number of previous studies, mainly observational, have used it extensively.

Introduction

Gastroenteropancreatic (GEP) endocrine tumours (carcinoids and pancreatic islet cell tumours) are composed of multipotent neuroendocrine cells that exhibit a unique ability to produce, store, and secrete biologically active substances and cause distinct clinical syndromes. The classification of GEP tumours as functioning or non-functioning is based on the presence of symptoms that accompany these syndromes secondary to the secretion of hormones, neuropeptides, and/or neurotransmitters (functioning tumours). Non-functioning tumours are considered to be neoplasms of neuroendocrine differentiation that are not associated with obvious symptoms attributed to the hypersecretion of metabolically active substances [1]. However, a number of these tumours are either capable of producing low levels of such substances, which can be detected by immunohistochemistry but are insufficient to cause symptoms related to a clinical syndrome, or alternatively, they may secrete substances that are metabolically inactive or inappropriately processed. In some cases, GEP tumours are not associated with the production of any hormone or neurotransmitter. Both functioning and non-functioning tumours can also produce symptoms due to mass effects compressing vital surrounding structures. Gastroenteropancreatic tumours are usually classified further according to the anatomic site of origin: foregut (including respiratory tract, thymus, stomach, duodenum, and pancreas), midgut (including small intestine, appendix, and right colon), and hindgut (including transverse colon, sigmoid, and rectum) [2]. Within these subgroups the biological and clinical characteristics of the tumours vary considerably, but this classification is still in use because a significant number of previous studies, mainly observational, have used it extensively [3].

Gastroenteropancreatic tumour behaviour is somewhat heterogeneous, with the majority of them exhibiting long periods of relatively small growth, spontaneous standstill, or even tumour regression, although a subset can show explosive growth and behave in a highly malignant manner [4]. In order to overcome these inherent limitations the WHO, and more recently the European Neuroendocrine Tumour Society (ENETS), have adopted a classification system based on morphological, immunohistochemical, and functional characteristics, specifically based on tumour biology using estimation of the Ki-67 labelling index and tumour extent using the TNM classification [5].

Secretory products

Carcinoid tumours are attributed to neoplastic proliferation of enterochromaffin (EC) or Kulschitsky cells; these cells are ubiquitous but predominate in the gastrointestinal (GI) and urogenital tracts, and bronchial epithelium [6]. The most prominent secretory products of carcinoid tumours are amines, kallikrein, and prostaglandins; one of their main characteristics is the synthesis, storage, and secretion of serotonin (5-HT). Serotonin is synthesised from tryptophan through its precursor, 5-hydroxytryptophan (5-HTP), and by the enzyme aromatic acid decarboxylase, and is subsequently metabolised by monoamine oxidase to 5-hydroxyin-doleacetic acid (5-HIAA), which is excreted in the urine. In normal subjects, approximately 99% of tryptophan is used for the synthesis of nicotinic acid, and 1% or less is used to synthesise 5-hydroxytryptamine (5-HT). In patients with carcinoid tumours there is a shift towards the production of 5-HT and eventually 5-HIAA. When 5-HT and other products are secreted into the portal circulation they are efficiently metabolised by the liver and do not usually cause any systemic signs or symptoms. However, when liver metastases are present or when the primary lesions are found in the bronchus and/or ovaries, the systemic features of carcinoid syndrome (CS) become evident. Foregut carcinoids (gastric and bronchial) lack the enzyme aromatic amino decarboxylase that converts 5-HTP to serotonin; such tumours produce 5-HTP and histamine instead of serotonin. Hindgut carcinoids (transverse, descending colon and rectum) cannot convert tryptophan to serotonin and other metabolites and therefore rarely cause carcinoid syndrome even if they metastasise to the liver. Alterations in tryptophan metabolism may account for many symptoms that accompany carcinoid syndrome. Serotonin in particular is the most likely cause of many features of carcinoid syndrome as it stimulates intestinal motility and secretion and inhibits intestinal absorption. Serotonin may also stimulate fibroblast growth and fibrogenesis via the 5-HT2B receptor and may thus account for peritoneal and valvular fibrosis encountered in such tumours; serotonin, however, is not associated with flushing. The diversion of tryptophan to serotonin may lead to tryptophan deficiency as it becomes unavailable for nicotinic acid synthesis, and is associated with reduced protein synthesis and hypoalbuminaemia; this may lead to the development of pellagra (skin rash, glossitis, stomatitis, confusion/dementia). Histamine, another amine produced by carcinoid tumours (particularly foregut), may be associated with an atypical flushing and pruritus; increased histamine production may account for the increased frequency of duodenal ulcers observed in these tumours. In addition to serotonin, carcinoid tumours may secrete a number of other substances: peptide hormones such as corticotrophin (ACTH), substance P, neurotensin, prostaglandins, kallikrein, and tachykinins [7]. Kallikrein, a protein that cleaves kinin from plasma kininogen, is a potent vasodilator and may account for the flushing and increased intestinal mobility. Although prostaglandins E and F are overproduced in carcinoid tumours, their role in the development of symptoms of carcinoid syndrome is not well established (Table I).

Clinical presentation

Foregut carcinoids have a low content of serotonin (5-HT), and often secrete the serotonin precursor 5-HTP, histamine, and a multitude of polypeptide hormones. Foregut carcinoids are associated with an atypical CS and have the particular potential to metastasise to the bone [4, 6]. Midgut carcinoids have a high 5-HT content and can also release several other vasoactive compounds such as kinins, prostaglandins, and substance P; these tumours are more likely to cause classic CS with the development of hepatic metastases, and rarely metastasise to the bone. Hindgut carcinoid tumours rarely contain 5-HT or 5-HTP or cause CS; however, they can contain numerous gastrointestinal hormones and very infrequently metastasise to the bone. Taking into consideration the prominent clinical manifestation of carcinoid tumours, CS has a prevalence of approximately 10%; most midgut, as well as hindgut carcinoid tumours, are regarded as non-functioning [8]. The majority of carcinoid tumours are sporadic but can also occur in the context of familial syndromes; approximately 10% of carcinoid tumours are associated with multiple endocrine neoplasia (MEN)-1 syndrome but can also occur in MEN-2, neurofibromatosis type 1 (NF1) and occasionally in familial polyposis coli.

Carcinoid syndrome

The principal features of carcinoid syndrome (CS) are diarrhoea and flushing. Carcinoid syndrome is the

Table I. Gastroenteropancreatic tumours: anatomical, clinical, and biochemical features

Site	Peptide/Amines	Clinical features	Metastases	MEN 1 [%]
Foregut, bronchi, thymus, stomach, duodenum, pancreas	5-HTP, histamine, ACTH, CRH, GH, gastrin	Pulmonary obstruction, atypical flush and hormone syndromes	Liver, LMN, bone	10
Midgut, duodenum, jejunum, ileum, right colon	5-HT, tachykinins, prostaglandins, bradykinins and others	Bowel obstructions, typical pink/red flush, wheeze/diarrhoea (carcinoid syndrome)	Liver (60–80%) LMN metastases	–
Hindgut, transverse colon to rectum	Local production SS, peptide Y, glicentin, neurotensin, 5-HTP	Incidental finding, local symptoms	Bone metastases (5–40%)	–
Insulinomas	Insulin, proinsulin	Neuroglycopaenia, Whipples triad	Liver (10%)	5–10
Glucagonoma	Gastrin	ZES (peptic ulcer, diarrhoea, epigastric pain)	Liver (60–90%)	25
VIPoma	VIP	Watery diarrhoea, hypokalaemia, achlorhydria	Liver (80%)	10
Glucagonoma	Glucagon	Necrotic migratory erythema, diabetes mellitus, cachexia	Liver (80–90%)	5–17
Somatostatinoma	SS	Gallstones, diabetes mellitus, steatorrhoea, achlorhydria	Liver (60–79%)	5–10
Non-functioning tumours	PP	Symptoms related to mass effect	Liver (60%)	20–30
GRFoma	GRF	Acromegaly	–	20

5-HT – 5-hydroxytryptamine, 5-HTP – 5 hydroxytryptophan, VIP – vasoactive intestinal peptide, SS – somatostatin, GRF – growth hormone releasing factor, LMN – lymph node, ZES – Zollinger-Ellison syndrome.

result of the synergistic interaction of tumour factors (5-HT, kinins, kallikrein, prostaglandins) entering systemic circulation and thus by-passing the metabolism in the portal or pulmonary arterial circulation. Patients with the more common (95%) classic (typical) CS present with flushing (90%), diarrhoea (70%), abdominal pain (40%), valvular heart disease (40–45%), telangiectasia (25%), wheezing (15%), and pellagra (5%). The typical flush found in patients with the classic CS (midgut carcinoids) is of sudden-onset, usually of a pink to red colour involving the face and upper trunk, and lasting for only a few minutes. It can appear many times per day and may be triggered by alcohol or tyramine-containing foods, chocolate, walnuts, and/or bananas. As opposed to menopausal flushing, it tends to be 'dry' and not associated with sweating. This typical flush does not seem to be related directly to serotonin but most probably to tachykinins, neuropeptide K, and substance P. In contrast, the atypical syndrome (5%) consists of a purplish colour flush that may last for hours, leaving telangiectasia and hypertrophy of the skin of the face and upper neck; in addition, it can also involve the limbs, which may become acrocyanotic. Occasionally, headache, lacrimation, hypotension, cutaneous oedema, and bronchoconstriction may also develop. These are usually found in patients with foregut carcinoid tumours and are thought to be mediated by 5-HTP, histamine, and other biogenic amines. Rarely, another histamine-induced flush, a bright red patchy flush, is occasionally seen in patients with chronic atrophic gastritis and enterochromaffin-like (ECL)-hyperplasia. The diarrhoea of the CS follows no specific pattern and initially may be intermittent owing to secretory and gastrointestinal dysmotility factors, but later may be continuous owing to gut lymphangiectasia and bacterial overgrowth factors, including serotonin, tachykinins, histamine, kallikrein, and prostaglandins, which stimulate peristalsis and intestinal secretion or small bowel ischaemia secondary to fibrosis [9]. Although a true asthma attack is not often evident in patients with CS, bronchial constriction occurs, probably mediated via tachykinins and bradykinins, which constrict the bronchial smooth muscle.

Carcinoid heart disease

Carcinoid heart disease occurs in 60–80% of patients with CS, although it is clinically significant in a much smaller percentage. Carcinoid heart lesions are characterised by plaque-like, fibrous endocardial thickening, mostly in the right side, but in approximately 10% of patients, also in the left side of the heart [10]. The most common lesions are tricuspid regurgitation followed by tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis. Patients with CS and carci-

noid heart disease have significantly higher 5-HIAA levels and other vasoactive substances, suggesting that higher serotonin levels may be responsible. Right-sided heart disease is associated with substantial morbidity and mortality in such patients; following the introduction of successful treatment of the tumour and its secretory products approximately 25% of the patients who die of CS succumb to heart failure. In a recent detailed study involving 252 patients with CS, 52 patients were found to have evidence of carcinoid heart disease, with the tricuspid and pulmonary valve being involved in 90% and 69%, respectively [11–13]. Interestingly, 87% of the 15 patients who were found to have left sided lesions had a patent foramen ovale. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is an excellent biomarker of carcinoid heart disease and it exerts a high negative predictive value [14–16].

Pulmonary and thymic carcinoids

Pulmonary carcinoids are classified as part of a spectrum of pulmonary neuroendocrine tumours (NETs) with different biological characteristics, such as typical carcinoid tumours (TC), atypical carcinoid tumours (AC), large-cell neuroendocrine carcinomas (LCNEC), and small-cell lung carcinoma (SCLC) [17, 18]. Typical bronchial carcinoids are generally more benign than AC, but both types can metastasise to regional lymph nodes or to the liver, bones, and brain. Patients with TC (well-differentiated NETs) usually present in the 5th decade of life, while the vast majority are located centrally, close to the hilum, and are associated with symptoms suggestive of a mass effect. Central bronchial obstruction with obstructive pneumonia or atelectasis is one of the most common symptoms [19]. Other common symptoms include cough, wheezing, and haemoptysis; wheezing is more commonly due to central airway obstruction rather than the secretion of biogenic amines. In addition, up to 25–30% of patients are asymptomatic and the diagnosis is made incidentally or even postmortem [20, 21]. These tumours may also be associated with clinical syndromes, secondary to secretion of other hormones, such as Cushing's syndrome from ectopic secretion of ACTH, acromegaly owing to ectopic secretion of growth hormone releasing hormone (GHRH), or syndrome of inappropriate antidiuretic hormone (SIADH) due to ectopic ADH secretion. Some tumours produce histamine, and these patients may experience atypical CS. Typical carcinoids are usually indolent, commonly identified as early-stage localised disease (80–90%). Metastases develop in less than 15% of cases, with 5-year and 10-year survival rates of around 90%. Atypical carcinoids occur in older patients, most commonly in the 6th decade of life, are larger than well-differentiated TC tumours, and occur more commonly in the peripheral lung fields. Atypical carcinoids have a more aggressive clinical course, metastasise to lymph nodes in 30–50% of cases, and have a 10-year survival rate of 35–49%. Large-cell neuroendocrine carcinomas are closely related to smoking behaviour and, although less aggressive, have a similar clinical course and prognosis to SCLC. Thymic carcinoids are rare, primarily affecting white males, and are related to MEN-1 in approximately 25% of cases; rarely, such tumours maybe encountered in MEN-2A [22, 23]. Thymic carcinoids develop metastases frequently and have a poor outcome.

Gastric carcinoids

Gastric carcinoids (GC) are divided into three distinct groups: GC associated with chronic atrophic gastritis type A (CAG), GC associated with Zollinger-Ellison syndrome (ZES), and sporadic GC. GC type A carcinoids occur in the 6th or 7th decade of life, and patients have hypochlorhydria and hypergastrinaemia, which results in enterochromaffin-like (ECL) cell hyperplasia; the majority of these patients also have pernicious anaemia [24]. Tumours are less than 1 cm in diameter, usually multifocal, and are found in the body or fundus of the stomach or in the transitional zone to the antrum. CAG type A-associated carcinoids are usually indolent, metastasising in 8–23%, with distant metastases in 5%, and associated with CS in 4% of cases. Following the widespread use of endoscopy, many of these lesions are identified at an earlier stage. Between 5% and 10% of gastric carcinoids are associated with ZES and occur almost exclusively in the context of MEN-1 syndrome. These tumours are thought to arise from hyperplastic ECL-cells, are not associated with the CS, and their prognosis is similar to CAG type A-associated carcinoid tumours. Sporadic gastric carcinoid tumours account for 15–25% of gastric carcinoid tumours; they are usually greater than 1 cm in diameter, arise from mucosa that appears normal, and can develop atypical CS via histamine release. They often contain a variety of endocrine cells and produce 5- HTP in contrast to type 1 and 2 gastric carcinoids, which produce 5-HT.

Duodenal and pancreatic carcinoids

Duodenal carcinoids are relatively uncommon small tumours that appear to have a good prognosis. They exhibit significantly lower serotoninergic hormone levels, but up to 20% stain for somatostatin and rarely for calcitonin and pancreatic polypeptide. Because over 90% are not associated with a clinical syndrome, the diagnosis is made either by symptoms due to the tumour itself or by changes seen during upper GI en-

doscopy (33%). When these tumours are of larger size (> 2 cm) or located around the ampulla they can cause pain (37%), obstructive jaundice (18%), pancreatitis or bleeding (21%), and may develop metastases to regional lymph nodes or the liver in 45% of patients [6]. Rarely, they can produce symptoms due to ZES, CS, or Cushing's syndrome [25].

Small intestine carcinoids

The small intestine is the most common site for GI carcinoid tumours, which are thought to arise from serotonin-producing intraepithelial endocrine cells. These tumours are mostly located in the distal ileum and can be multicentric. The majority of patients present in the 6th or 7th decade of life, with abdominal pain (which may be present for years, mimicking irritable bowel disease), small bowel obstruction, and with metastases to the lymph nodes and the liver; 7–28.6% of patients may present with the CS. Asymptomatic tumours are discovered while searching for a primary in patients with newly diagnosed liver metastases or during routine endoscopy. In this group of patients, tumour size is an unreliable predictor of metastatic disease, although tumours larger than 2 cm are more likely to metastasise. However, metastases have been reported even from tumours measuring less than 0.5 cm in diameter; approximately 65% of small gut carcinoids (< 1 cm) show microscopic spread to lymph nodes, and almost half have liver metastases. Small bowel carcinoids are frequently associated with an extensive mesenteric reaction-fibrosis, leading to 'bulking' of the intestine, partial or complete small bowel obstruction even though the primary tumour is not large enough to obstruct the intestinal lumen, and mesenteric ischaemia [26].

Appendiceal carcinoids

Carcinoid tumours are the most common tumours of the appendix, and they are thought to arise from subepithelial endocrine cells of the lamina propria and submucosa of the appendix wall. They are most often diagnosed in the 4th or 5th decade of life, and they appear to be more common in women than in men; most patients are asymptomatic; and occasionally patients may present with pain in the right lower abdomen or right testis [27]. The majority are located in the distal third of the appendix and are unlikely to cause obstruction. Besides their location, mesoappendiceal invasion (> 3 mm), histological atypia, and the size of the tumour (> 2 cm) are the best predictors of prognosis, particularly because more than 95% of appendiceal carcinoids are less than 2 cm in diameter; subserosal invasion is not regarded as an adverse prognostic sign. Association with CS is extremely rare and is estimated to occur in < 1% of cases. Patients with such small tumours only rarely metastasise, in contrast to approximately 30% of patients with larger tumours, who may have either nodal or distant metastases. The 5-year survival rate is 94% for patients with local disease and 85% for patients with regional metastases. In the presence of hepatic metastases, which can be associated with CS, the 5-year survival rate is 34%. Goblet cell carcinoids of the appendix possess morphological features suggestive of both carcinoid and glandular differentiation. Concomitant distant metastases are found in 11% of patients, mostly in the ovaries, abdominal cavity, and extra-abdominal sites.

Carcinoids of the colon

Carcinoid tumours of the colon are thought to arise from serotonin-producing epithelial endocrine cells; however, only 60–70% of these tumours show positive serotonin immunohistochemistry. They are mainly located in the caecum followed by the ileocecal region and show predominance in a white ethnic background [28]. Owing to the high capacitance of the right colon the majority of the tumours do not become symptomatic until they reach a large size. The majority of patients present in the 7th decade of life, with symptoms of pain, anorexia, blood loss, and weight loss, and have clinically palpable tumours; while less than 5%, mainly with tumours of the proximal colon, present with CS. In more than 90% of patients the tumour size is greater than 2 cm, and over two-thirds of patients have either nodal or distant metastases at presentation; only 16% of caecal tumours are localised at diagnosis. The 5-year survival rates are 70% for patients with local disease, 44% for patients with regional metastases, and 20% for those with distant metastases [29, 30].

Pancreatic islet cell tumours

Pancreatic neuroendocrine tumours can be divided on a clinical and pathologic basis into several classes: insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas, ACTHomas, GHRHomas, or non-functioning.

Functioning tumours

Insulinoma

Insulinomas account for 60% of islet cell tumours and are typically hypervascular, solitary small tumours, with 90% measuring less than 2 cm and 30% measuring less than 1 cm in diameter [31]. Insulinomas can occur at any age, but mainly in middle age, and show a female prevalence. Approximately 10% are multiple, 10% are malignant, and 7% are associated with MEN-1; when

associated with MEN-1, insulinomas are usually multiple and can be malignant in up to 25% of cases [32]. Almost all insulinomas are located within the pancreas, even though aberrant cases have been described in the duodenum, ileum, lung, and cervix [1]. Insulinomas are characterised by hypersecretion of insulin and the subsequent development of symptoms of neuroglycopaenia (headache, lethargy, dizziness, diplopia, blurred vision, amnesia, and more rarely, seizures, coma, or permanent neurological deficits), and symptoms resulting from the catecholaminergic response (tremor, anxiety, palpitations, nausea, hunger, and sweating). Hypoglycaemic episodes typically occur early in the morning and may be triggered by exercise; weight gain (secondary to the anabolic effect of insulin) is observed in many patients harbouring an insulinoma; however, recently postprandial symptoms are increasingly being recognised [33, 34].

Gastrinomas

Gastrinomas are gastrin-secreting tumours that are derived from either the duodenum or the pancreas, causing ZES by hypersecreting gastrin, which results in hypochlorhydria and gastric mucosal thickening shown as hypertrophy on endoscopy and imaging [35]. The majority of gastrinomas arise in the gastrinoma triangle (an area defined by the duodenum, pancreatic head, and hepatoduodenal ligament) and occur in either the sporadic form (mean age of 50 years with a male prevalence) or in association with MEN-1 in up to 25%; MEN-1 related gastrinomas are usually small, located in the duodenum, and frequently multifocal [36]. The majority of gastrinomas are truly malignant; lymph node and liver metastasis is present in 70–80% at diagnosis and bone metastases in 12%. The diagnosis of gastrinoma is considered in patients with unusual and/or complicated peptic ulcer disease that is refractory to conventional treatment, including *Helicobacter pylori* eradication. Ulcers are typically less than 1 cm in diameter and recur much more often than in patients with sporadic ulcer disease; in contrast to older series, the majority of patients present with single rather than multiple ulcers. Other commonly encountered symptoms are abdominal pain (75–98%), bleeding (44–75%), nausea and vomiting (12–30%), and weight loss (7–53%). Diarrhoea results from the large volume of gastric acid produced that cannot be reabsorbed by the small intestine and colon: the extremely low pH that enters the intestinal lumen exceeds the neutralising capacity of pancreatic bicarbonate secretion and inactivates pancreatic enzymes, thus affecting the emulsification of fat by bile acids; in addition, intestinal epithelial cells and villi are also damaged leading to malabsorption in addition to maldigestion. Duodenal gastrinomas are frequently small (< 1 cm), located in the first and second portion of the duodenum, and metastasise to regional lymph nodes in 30–70% of patients. Approximately 40% of gastrinomas are located within the duodenal submucosa; this prevalence may reach 90% in MEN-1 patients with ZES. MEN-1 occurs in patients at an earlier age, and although the gastrinoma can be the presenting lesion, most patients have hyperparathyroidism or pituitary disease at the time of presentation of the ZES. In these patients the trophic effects of prolonged hypergastrinaemia on ECL cells lead to the formation of gastric carcinoids, mainly involving the body and fundus of the stomach; patients with MEN-1 have a 20–30 fold higher chance of developing an ECLoma than patients with the sporadic form [36].

Glucagonoma

Glucagonomas are rare, slow-growing tumours arising from the pancreatic α-cells, commonly associated with a characteristic syndrome as a result of excessive secretion of glucagon and other peptides [37]. The majority are sporadic, but between 5% and 17% are associated with MEN-1 or, rarely, familial adenomatous polyposis. Glucagonomas can be as large as 6 cm and are highly malignant, with over 80% of the sporadic tumours having documented mainly hepatic metastases at diagnosis. The most common symptoms are weight loss (70–80%), rash (65–80%), diabetes mellitus (75%), cheilosis or stomatitis (30–40%), and diarrhoea (15–30%); the most characteristic of these symptoms is the rash, necrolytic migratory erythema (NME) [38]. This dermatitis-like lesion typically evolves over 7–14 days, beginning as small erythematous lesions in the groin and extending to the perineum, lower extremities, and perioral regions. Histologically, superficial necrolysis with separation of the outer layers of the epidermis and perivascular infiltration with lymphocytes and histiocytes is observed, but the changes are not specific. There are only a few sporadic reports of patients with glucagonomas who have not developed NME. Dermatological manifestation of glucagonomas comprise dystrophic nails, angular cheilitis, atrophic glossitis, and buccal mucosal inflammation.

Patients without established metastases have a good outcome following surgery alone, with a survival rate of over 85% at a mean follow-up of 4.7 years, whereas this figure falls to 60% in patients with malignant disease.

VIPoma

Most VIPomas are sporadic islet-cell tumours presenting in the 4th to 5th decade of life and approximately 70–80% originate from the pancreas, mostly from the pancreatic tail. Primary tumours are usually large, greater than 2 cm, and 50–60% of pancreatic VIPomas have

already developed metastases at the time of diagnosis. VIPomas can also be (10–12%) of neural origin, mostly in children, as ganglioneuromas, ganglioblastomas, or neuroblastomas. In contrast to pancreatic VIPomas, in neurogenic VIPomas the presence of metastases is much less common (29%) and mainly involves the lymph nodes. VIPomas are multifocal in 4% of cases, and in 8.7% there is an association with MEN-1.

The great majority of clinical manifestations of VIP-secreting tumours are the result of excessive VIP production, which binds to epithelial intestinal cells leading to activation of cellular adenylate cyclase, which results in net fluid and electrolyte secretion into the lumen; prostaglandin E2 may occasionally also be secreted by the tumour. Severe, watery diarrhoea, secretory in nature, is a universal symptom typically unremitting with fasting, intermittent in 53%, and continuous in 47% of cases. Patients typically produce more than 3 l of watery stool per day with a range up to 30 l/day, leading to severe fluid and electrolyte (mainly potassium and bicarbonate) loss with subsequent marked asthaenia, cramps leading to tetany, cardiac alterations, and even sudden death. Hypocalaemia is often severe (K^+ < 2.5 mmol/l, losses > 400 mmol/day) associated with severe hyperchloraemic acidosis. The stools are tea-coloured, odourless, with features of secretory diarrhoea, such as persistence with fasting, high sodium concentration, and low stool osmolar gap. Achlorhydria or hypochlorhydria is present in over two-thirds of patients [39, 40].

Non-functioning pancreatic endocrine tumours

These tumours account for about 40–50% of all endocrine pancreatic tumours and are not associated with clinical syndromes caused by hormonal hypersecretion. Their clinical silence may be related to either inactive hormonal production, co-secretion of peptide inhibitors, or downregulation of peripheral receptors. They are most often diagnosed in the 5th to 6th decade of life and are mainly situated in the pancreas. These tumours are usually large and are diagnosed either as incidental findings or by symptoms caused by an expanding mass (obstructive jaundice, abdominal pain, palpable mass) or metastases (weight loss, haemorrhage, enlargement of the liver) because approximately two-thirds are truly malignant. The majority of non-functioning pancreatic tumours are unifocal except when associated with MEN-1 in approximately 20–30%, where multiple tumours are generally found throughout the pancreas [41].

Conflict of interest

The authors declare no conflict of interest.

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