15.9.2 Carcinoid syndrome 2870

15.9.2 Carcinoid syndrome 2870

SECTION 15 Gastroenterological disorders 2870 Ramos-Álvarez I, et al. (2015). Insights into bombesin receptors and ligands: highlighting recent advances. Peptides, 72, 128–44. Sandoval D, D'Alessio D (2015). Physiology of proglucagon pep- tides: role of glucagon and GLP-1 in health and disease. Physiol Rev, 95, 513–48. Sanger G, Furness J (2015). Ghreline and motilin receptors as drug targets for gastrointestinal disorders. Nat Rev Gastroenterol Hepatol, 13, 38–48. Seino Y, Fukushima M, Yabe D (2010). GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Investig, 1, 8–23. Steinhoff M, et al. (2014). Tachykinins and their receptors: contribu- tions to physiological control and the mechanisms of disease. Physiol Rev, 94, 265–301. Troke R, Tan T, Bloom S (2014). The future of gut hormones in the treatment of obesity. Ther Adv Chronic Dis, 5, 4–14. Vaudry D, et al. (2009). Pituitary adenylate cyclase-activating polypep- tide and its receptors: 20 years after the discovery. Pharmacol Rev, 61, 283–357. Zhang H, et al. (2008). Correlation of gut hormones with irritable bowel syndrome. Digestion, 78, 72–6. 15.9.2 Carcinoid syndrome B. Khoo, T.M. Tan, and S.R. Bloom ESSENTIALS Carcinoid syndrome is a paraneoplastic syndrome caused by the re- lease of 5-hydroxytryptamine (5-HT or serotonin) and other vasoactive substances from neuroendocrine tumours (NETs), typically those arising from the duodenum, jejunum, ileum, and also from bronchial NETs. Characteristic clinical features, which typically arise when tumours have metastasized to the liver, are flushing and secretory diarrhoea, and occasionally wheezing. Carcinoid crisis is an acute and life-threatening manifestation with sustained flushing, hyperdynamic shock, and acute kidney injury. Carcinoid heart disease typically manifests in the right side of the heart with valvular insufficiency and heart failure. Diagnosis is made by a combination of the characteristic clinical syndrome, biochemical markers such as 5-hydroxyindoleacetic acid (a metabolite of 5-HT), histopathological examination of tissue from tumour deposits, and imaging with conventional cross-sectional modalities as well as somatostatin receptor scintigraphy. Treatment is most often directed at control of symptoms, with the standard of care for control of the carcinoid syndrome being a somatostatin analogue. Symptomatic therapies are used to palliate diarrhoea. Niacin supplements should be given to forestall the de- velopment of pellagra. Multiple modalities for treatment of NETs exist, which should be dir- ected by a multidisciplinary team. Their general prognosis is good with median overall survival of

9.3 years, but the presence of carcinoid syn- drome reduces this to 5.0 years, and is reduced even more in the pres- ence of heart disease. Early identification and management of carcinoid syndrome and heart disease is key to improving survival and quality of life. Introduction and terminology The term Karzinoide was originally used by Obendorfer in 1907 to describe tumours of the gastrointestinal tract with the histopatho- logical features of carcinoma but with a radically different behaviour with slow growth and a reduced tendency to metastasize. The term ‘carcinoid’ has now been superseded by ‘neuroendocrine tumour’ (NET) or ‘neuroendocrine neoplasm’ (NEN), which are defined as epithelial cell tumours arising from cells with predominant neuro- endocrine differentiation. The term ‘neuroendocrine carcinoma’ (NEC) is applied to those NETs which are relatively undifferentiated and demonstrate a high proliferation rate and/or aggressive behav- iour. Nevertheless, the name lives on in the ‘carcinoid syndrome’, first described by Ransom in 1912, and in the term ‘carcinoid heart disease’. This chapter focuses primarily on those NETs associated with these two presentations. Other NETs are sometimes associated with specific functional syndromes due to the hypersecretion of other hormones such as, for example, gastrin, insulin, glucagon, somatostatin, pancreatic poly- peptide, glucagon-like peptide-1 (GLP-1), ACTH, and parathyroid hormone-related peptide. Most patients (81%) presenting with NETs do not have the car- cinoid syndrome. In the 19% who do have carcinoid syndrome, the most common type of NET are gastroenteropancreatic (GEP)-NETs originating from the duodenum, jejunum, and ileum in 40%, fol- lowed by lung/bronchial NETs in 13%, colon/rectum GEP-NETs in 10%, caecal GEP-NETs in 5%, and appendix GEP-NETs in 2%. Other subtypes of NET account for 30%. Rarely, pancreatic NETs can cause the carcinoid syndrome. The carcinoid syndrome does not develop when the tumour drains through a normal liver due to first-pass metabolism of the tumour metabolites, and so GEP-NETs associated with carcinoid syndrome have almost always metastasized, usually to the liver, be- fore symptoms develop. By contrast, tumours that drain directly into the systemic circulation such as bronchial NETs may cause the syn- drome without liver metastasis. The carcinoid syndrome, where present, has a clear impact on pa- tient quality of life, with increased fatigue, poorer general health, poorer physical function compared to NET patients who do not have the syndrome. In addition, there is a palpable cognitive impairment associated with the syndrome, linked to niacin deficiency. Carcinoid syndrome is associated with a higher mortality, hence identification and treatment of the syndrome is of clinical importance. Clinical manifestations Flushing The classical feature of the carcinoid syndrome is the flush, which occurs in 60 to 85% of patients with the syndrome. It predominantly involves the head and upper thorax, and is usually associated with tachycardia, hypotension, and increased skin temperature. Rarely, flushing extends to the trunk and limbs. Attacks are paroxysmal and usually unprovoked, although precipitating factors include al- cohol or food ingestion, stress, emotion, or exertion. Flushing ini- tially lasts for only a few minutes, but as the disease progresses, it may become almost continuous, and such patients often develop a

 chronically reddened and cyanotic facial hue, with widespread tel- angiectasia, the ‘leonine facies’. This fixed flush is more commonly seen with bronchial NETs. When bronchial NETs trigger flushing, this can cause severe attacks lasting for hours or days, occasionally with profound hypotension and even anuria. Other symptoms such as tremor, periorbital oedema, tearing from the eye, salivation, and peripheral oedema may occur with bronchial NETs. Diarrhoea and gastrointestinal symptoms The other characteristic feature of the syndrome is secretory diar- rhoea, which occurs in 60 to 80%. This may be profuse and accom- panied by electrolyte disturbance, cramping abdominal pain, nausea, and vomiting. Hepatic

metastases may cause right hypochondrial pain, particularly if the liver capsule is involved or stretched, and acute exacerbations may occur if metastases become ischaemic and undergo autonecrosis. Weight loss and, in the later stages, cachexia are common because of anorexia, malabsorption, and increased catabolism. Pellagra Pellagra with dermatitis of sun-exposed areas may occur, due to the increased consumption of tryptophan by the tumour, limiting the availability of this amino acid for niacin synthesis, and causing deficiency (see Chapter 11.2). Heart disease Carcinoid heart disease affects about 20% of patients with the car- cinoid syndrome; historically this prevalence was as high as 50%, but the picture appears to have been modified by the widespread use of somatostatin analogues. The heart disease is due to the deposition of plaques of myofibroblasts and smooth muscle cells in a collagenous stroma on the endocardial surface of valvular cusps and leaflets, cardiac chambers, and occasionally the intimal surface of the pul- monary artery or aorta. The pathogenesis is thought to be activation of 5-hydroxytryptamine (HT)2b receptors on valvular interstitial cells, leading to secretion of extracellular matrix and the develop- ment of fibrosis. The valves and other endocardial surfaces on the right side of the heart are most often involved, for example, in the form of tricuspid regurgitation and pulmonary stenosis, leading to right ventricular failure, manifesting as peripheral oedema, ascites, and dyspnoea. This tropism occurs as the causative mediators flow directly from metastases in the liver to the right side of the heart; the left side is protected by inactivation of the mediators in the lung capillary beds. Left-sided cardiac damage occurs in 10% of cases, in association with bronchial NETs, which drain into the left atrium, or atrioseptal defects with right-to-left shunting. Uncommonly, in 4% of patients, a NET metastasis in the heart is the cause of the carcinoid heart disease. Other features The other causes of breathlessness in association with the carcinoid syndrome are bronchospasm, which affects a small number of pa- tients, often occurring with flushing attacks, and metastatic involve- ment of the lung and pleura. An atypical carcinoid syndrome is sometimes seen with type III gastric NETs, where the flushing is associated with raised, local- ized, wheal-like rashes, which are usually pruritic and which may migrate. The ‘carcinoid crisis’ is an acute, life-threatening manifestation of the carcinoid syndrome, manifesting as flushing, hyperdynamic shock, and acute kidney injury. It can be provoked during tumour biopsy, tumour surgery, or even anaesthesia for unrelated surgical procedures. It is also reported after embolization procedures, radio- nuclide therapy, or chemotherapy. Biochemistry The biologically active metabolite characteristically produced by those NETs associated with the carcinoid syndrome is 5-HT (sero- tonin), synthesized from the amino acid tryptophan (Fig. 15.9.2.1). 5-HT probably plays a part in the pathogenesis of some of the symp- toms of the carcinoid syndrome, particularly the diarrhoea and bronchoconstriction. It is metabolized to 5-hydroxyindoleacetic acid (5-HIAA), which accounts for 95% of the urinary excretion of 5-HT. A variety of other vasoactive substances are implicated in the pathogenesis of the flush. Flushing can be provoked by intravenous noradrenaline, which has been shown to activate kallikrein in the tumour, leading to synthesis and release of bradykinin. Other possible mediators of the flush include histamine, the tachykinins substance P, neurokinin A and neuropeptide K, and prostaglandins E and F, although the flush is rarely affected by inhibitors of prosta- glandin synthesis, such as indomethacin. Gastric NETs are derived from histamine-producing enterochromaffin-like cells and hista- mine is likely the cause of the characteristic wheal-like flush seen with these tumours. Fig. 15.9.2.1 Biochemical pathway for the synthesis and degradation of 5-hydroxytryptamine.

 Investigations Biochemical tests The diagnosis of carcinoid syndrome is made based on the char- acteristic syndrome in association with elevated

concentrations of 5-HIAA in an acidified 24-h urine collection. Urinary 5-HIAA acts as a marker of disease progression. Plasma 5-HIAA measurement is currently being evaluated for its diagnostic performance. Various foods, including avocados, bananas, aubergines, pineapples, plums, walnuts, and pecans should be avoided while collecting specimens to prevent false-positive results. Several drugs and other substances can interfere with the assay: paracetamol, ephedrine, phenobarbital, diazepam, nicotine, and caffeine can give false-positive results, and aspirin, phenothiazines, methyldopa, monoamine oxidase inhibi- tors, and tricyclic antidepressants false negatives. Chromogranin A, an acidic glycoprotein, is present in the secretory granules of enterochromaffin cells and NETs, and which is secreted into circula- tion, is often raised in NETs. Histopathology The gold standard for diagnosis is histopathological examination of the primary tumour or metastatic deposits. Typically, the NETs as- sociated with carcinoid syndrome are well-differentiated tumours with relatively uniform cells containing abundant neuroendocrine granules, and which are arranged in trabecular, gyriform, or nested patterns. The classic histochemical argentaffin stain of Masson and Gosset is based on the capacity of 5-HT to reduce silver salts. However, immunostaining for neuroendocrine markers such as the chromogranins A, B, and C, synaptophysin, and neuron-specific enolase are used more routinely to classify these tumours as NETs. Assessment of proliferation indices (e.g. Ki-67 immunopositivity, mitotic index) is essential for the grading of NETs according to the World Health Organization (2010) criteria. Structural imaging The initial imaging modality of choice is a triple-phase CT scan, with images obtained precontrast, during the arterial phase (20 s after intravenous contrast medium is injected) and during the portal venous phase (70 s after injection; Fig. 15.9.2.2). Typically, with mid-gut NETs, a mesenteric metastatic mass is frequently observed with a characteristic desmoplasia around the mass (Fig 15.9.2.3). CT scanning is 82% sensitive and 86% specific. Enhancement of otherwise isodense liver metastases can be ob-served during the arterial phase with a drop in enhancement during the portal venous phase: the sensitivity of CT for this pur- pose is 84% with a specificity of 92%. NET metastases are quite often detected as metastatic masses on ultrasound scanning of the liver, which is useful for guiding biopsy. Where expert interpretation is available, MRI is an alternative modality that enables serial imaging for restaging of NETs without incurring ionizing radiation exposure. Radionuclide imaging Somatostatin receptor scintigraphy with tracers such as 111-In octreotide, 68-Ga DOTATATE, 68-Ga DOTANOC, and 68-Ga DOTATOC exploits the fact that most differentiated NETs express receptors for somatostatin (particularly subtype 2a), enabling tracer uptake into tumours and metastases (Fig 15.9.2.2). Positron emission tomography (PET) scanning with the aforementioned 68-Ga labelled tracers, where available, increases the sensitivity to greater than 90% due to the higher spatial resolution of the technique versus single-positron emission computed tomography (SPECT; Fig 15.9.2.2). Other tracers have higher affinity for other somatostatin receptor subtypes such as 5 for DOTATOC, and 3 and 5 for DOTANOC. Positive somatostatin receptor scintigraphy imaging also opens the possibility of peptide receptor radionuclide therapy. 18-F fluorodeoxyglucose (FDG) PET scanning is occasionally useful, especially in the case of NECs. Fig. 15.9.2.2 Comparison of imaging modalities (A, arterial phase CT; PV, portal venous phase CT; SPECT, 111-In octreotide SPECT/CT; PET, 68-Ga DOTATATE PET/CT) for NET metastases to liver in the same patient. Thick, red arrows indicate two major liver metastases which are appreciated on arterial phase CT (anterior metastasis has some enhancement, posterior metastasis remains isodense) and portal venous CT (anterior metastasis becomes isodense, posterior metastasis becomes hypodense). 111-In octreotide SPECT/CT scan shows uptake of tracer in anterior metastasis with poorer uptake in posterior metastasis. Metastases are better appreciated in 68-Ga DOTATATE PET/CT scanning. Fig. 15.9.2.3 CT scan from patient with an ileal NET, demonstrating mesenteric mass (thick arrow),

surrounded by desmoplasia (thin arrows).

15.9.2 Carcinoid syndrome 2873 In those cases where the syndrome occurs in the absence of liver metastases, a careful search using a combination of CT scanning and somatostatin receptor scintigraphy (especially 68-Ga based PET) is invaluable in locating the primary, which may be amenable to curative resection. Screening for cardiac disease Patients with markedly elevated 5-HIAA excretion (>300 µmol/24 h) and/or frequent flushing with three or more episodes per day are particularly at risk of carcinoid heart disease and should be screened. N-terminal pro-B-type natriuretic peptide (NT pro-BNP) levels are a useful and simple biomarker for screening during the follow-up of patients with NETs. Where NT pro-BNP levels are elevated, such pa- tients should have a transthoracic echocardiogram by a practitioner experienced in the evaluation of carcinoid heart disease. Cardiac CT and MRI, where available, are valuable adjunctive investigations for the estimation of valvular heart disease burden, ventricular func- tion, and for the detection of cardiac metastases. Management Patients with NETs should be treated by multidisciplinary teams that include surgeons (upper gastrointestinal, hepatopancreaticobiliary, colorectal, thoracic), gastroenterologists, endocrinologists, onco- logists, palliative medicine specialists, interventional radiologists, nuclear medicine physicians, and specialist nurses. In those uncommon cases where the carcinoid syndrome is pre- sent with no metastases, for example, in the case of an isolated bronchial NET, a curative resection may eliminate the syndrome entirely. However, most cases present with numerous, unresectable liver metastases and hence the realistic aim of therapy is control of symptoms and reduction of complications. Control of symptoms Somatostatin analogues The standard treatment is a somatostatin analogue (SSTA), such as octreotide or lanreotide. These are effective at alleviating symp- toms in more than 90% of patients. They are commonly adminis- tered as monthly slow-release injections, for example, octreotide LAR (given as a deep intramuscular injection) or lanreotide Autogel (given as a deep subcutaneous injection). Octreotide can additionally be administered as short-acting subcutaneous injec- tions, every 8 h, if the long-acting injections fail to give adequate symptom control. SSTAs act by binding to somatostatin receptor subtypes 2 and 5, inhibiting secretion from the tumours, and leading to a reduction in 5-HIAA excretion. An added benefit of these analogues is that they slow the growth of NETs and extend progression-free survival, as demonstrated by the PROMID Phase III and CLARINET trials. SSTAs are remarkably well tolerated. Common side effects include steatorrhoea due to iatrogenic pan- creatic exocrine deficiency, solved by enzyme supplements, and the development of gallstones, which rarely causes significant issues. Interferon-α Interferon-α is occasionally used for the treatment of GEP-NETs, with an overall response rate of 20% and a biochemical response rate of 63%. However, its adverse effects—flu-like symptoms, myelotoxicity, weight loss and fatigue, depression, and on occasion, suicidal ideation—limit the dose and duration of treatment. Reduction of tumour mass Cytoreductive surgery is advocated by some authorities, but re- mains controversial. Hepatic transarterial embolization with bland microspheres (TAE), with microspheres and chemotherapy (TACE), or even with 90-Y labelled microspheres (selective in- ternal radioembolization therapy [SIRT]), can reduce tumour and symptom burden in selected patients, but requires suitable radio- logical expertise. Patients undergoing such embolization should be pretreated with high-dose octreotide to reduce the risk of car- cinoid crisis. Peptide receptor radionuclide therapy Peptide receptor radionuclide therapy with 177-Lu DOTATATE has recently been shown in a phase III trial (the NETTER-1 study) to ex- tend progression-free survival and to be associated with an objective tumour size response in 18% versus 3% for high-dose octreotide LAR. Where available, this treatment should be considered for pa- tients who demonstrate radiological

progression in their NET des- pite maximal SSTA therapy. Peptide receptor radionuclide therapy is generally well tolerated but is associated with fatigue, abdom- inal pain, diarrhoea, neutropenia, and thrombocytopenia, which is generally temporary. The number of doses that can be given in the long term is limited by bone marrow suppression (and possible myelodysplasia) as well as renal toxicity. Other types of radionuclide therapy such as 90-Y octreotate peptide receptor radionuclide therapy and 131-I MIBG therapy have been used in the past but have been largely superseded by 177-Lu-based agents. Chemotherapy Chemotherapy with conventional cytotoxic agents is not commonly used as response rates are poor, but may be considered where other treatments have failed to halt progression, or in the case of NECs with high proliferation indices. Symptomatic treatments Symptomatic treatments such as codeine phosphate and loperamide may help to control diarrhoea. Peripheral 5-HT antagonists such as cyproheptadine, a 5-HT2 receptor blocker, and the 5-HT3 receptor antagonist ondansetron can alleviate diarrhoea and nausea. In the case of gastric NET-associated atypical carcinoid syndrome, H1- and H2-receptor blockade may be useful. Telotristat etiprate is a selective inhibitor of peripheral tryptophan hydroxylase and therefore the synthesis of 5-HT, and has been shown to be effective at reducing the frequency of diarrhoea. It is currently licensed in the United States of America for the relief of carcinoid syndrome diarrhoea. Carcinoid crisis In cases where patients present with carcinoid crisis, they should be admitted immediately to high dependency or intensive care units for appropriate monitoring and treatment of fluid and electrolyte status. High-dose octreotide infusions are given to suppress tumour secretion, and glucocorticoids may be given to improve haemo- dynamics. Although theoretically catecholamines may increase the

SECTION 15 Gastroenterological disorders 2874 output of vasoactive factors, in practice, inotropes may be given with monitoring. Avoidance and treatment of complications Vitamin supplements Vitamin supplements containing niacin are necessary when pa- tients have pellagra, and these can be given prophylactically. Supplementation with the fat-soluble vitamins A, D, E, and K should be considered in patients who are being given SSTAs. Heart disease The medical treatment of carcinoid heart disease is the same as for right-sided cardiac failure of other causes, for example, diuretics and mineralocorticoid antagonists. Although renin–angiotensin– aldosterone axis blockade, digoxin, and vasodilators can be con- sidered, they have no clear effect on mortality in this population. Valve replacement is currently the most effective treatment option for advanced carcinoid heart disease. It is presently unclear whether telotristat might be useful in delaying carcinoid heart disease progression. Bony metastases Patients with bony metastases may benefit from palliative radio- therapy if the metastases are painful, and should be given antiresorptive agents such as zoledronic acid and denosumab, as for other patients who have solid tumour metastases in bone. Prognosis Most NETs follow an indolent course, and the median overall survival of all patients with NETs is 9.3 years (including those with localized disease). However, the presence of carcinoid syndrome does shorten median overall survival to 5.0 years. Active treatment of the carcinoid syndrome is very worthwhile in these patients, in terms of improving quality of life, and delaying or preventing the development of carcinoid heart disease. The prognosis is especially poor in those patients with untreated carcinoid heart disease, with a 3-year survival of 31% compared to 68% without heart disease. Proactive screening and management (e.g. with valve replacement) is key to improving the prognosis of patients with heart disease. FURTHER READING Dasari A, et al. (2017). Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol, 3, 1355–42. de Herder WW, et al. (2016). A short history of neuroendocrine tu- mours and their peptide hormones. Best Pract Res Clin Endocrinol Metab, 30, 3–17. Halperin DM, et al. (2017). Frequency of carcinoid

syndrome at neuro- endocrine tumour diagnosis: a population-based study. Lancet Oncol, 18, 525–34. Hicks RJ, et al. (2017). ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. Neuroendocrinology, 105, 295–309. Pavel M, et al. (2017). ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: systemic therapy— biotherapy and novel targeted agents. Neuroendocrinology, 105, 266–80. Sundin A, et al. (2017). ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological, nuclear medicine and hybrid imaging. Neuroendocrinology, 105, 212–44.

Revision #1
Created 2026-01-22 16:39:03 UTC by Omar Ayman
Updated 2026-01-22 16:39:03 UTC by Omar Ayman