3 Gastro-entero-pancreatic Neuroendocrine Tumors

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3.1 Syllabus-Classification-Epidemiology

The understanding of the structure and functioning of the neuroendocrine system has engendered impressive developments since the late nineteenth century, along with corresponding changes in its nomenclature [1, 2]. Assumptions about a distinct role began to be expressed, initially by the German physiologist Heidenhain [3–5] (Fig. 3.1) and subsequently by the Russian physician Kulchitsky [3, 6] (Fig. 3.2), after the localisation in the intestine of individual cells or populations of cells having secretory vesicles with chromophilic properties ['chromaffin', potassium dichromate (K2Cr2O7)] staining.

Although these cells were already called Kulchitsky (in honour of the man who discovered them), a few years later, MC Ciaccio (1877–1956) characterised them as entero-chromaffin [8, 9]. Their role remained unclear for a long time, until silverchrom staining ('argentachromaffin') [10] and silver staining ('argentaffin') [11] characteristics were observed and the concept of endocrine function was added. Similar cells were also found in the lungs, thymus and thyroid gland. F Feyrter (1895–1973) was the first to formulate the concept of a *diffuse endocrine system* ('Diffuse Endokrine Epitheliale Organe') that included 'helle Zellen' with local 'paracrine' activity due to the secretion of biologically active peptides [12].

APUD Neoplasms (Apudomas): A few decades later (1966), Antony Pearse observed that some of these cells possess the ability to pick up and decarboxylate precursor amines as well as produce and store peptides in their secretory vesicles. He introduced the term APUD (**A**mine **P**recursor **U**ptake and **D**ecarboxylation cells), which is considered to be the first attempt to determine the neuroendocrine system [13–15]. Moreover, he thought that these were complementary to the autonomic nervous system with regard to the control of organ function and that they had a common embryologic origin from the neural crest as 'misplaced' neuronal cells. Although the use of the term has fallen out of favour,[1] the acronym APUD has demonstrated the connection between neuronal and endocrine

[1]This is because there are endocrine cells (parathyroid gland cells) that do not express APUD behaviour and exocrine cells (Lieberkühn's Paneth cells) that surprisingly express APUD behaviour; additionally, it is well known that the neuroendocrine cells of the gastrointestinal tract have an endodermal, rather than exodermal, embryologic origin [20].

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Fig. 3.1 Rudolf P.H. Heidenhain (1834–1897) [3, 5]

Fig. 3.2 Nikolai K. Kulchitsky (1856–1925) [6, 7]

cells, leading to the more relevant determination of these cells as *neuroendocrine* [16–18]. The latter constitutes a population of cells with marked *neuroendocrine* differentiation (Table 3.1), including cells potentially displaying a *neuroendocrine phenotype* after the activation of specific genetic switches [19].

The neuroendocrine system has elements of the central and peripheral nervous system (neuroblasts and paranaglial cells, neurons of the submucosa and myenteric intestinal neural plexus) and endocrine organs (pituitary gland, adrenal medulla, endocrine pancreas, thyroid C cells and parathyroid chief cells) as well as clusters of transiently distributed neuroendocrine cells predominantly localised in the gastrointestinal tract (δ-cells of the mucosa), lungs, skin (Merkel cells) and, less frequently, in the thymus, breasts, larynx, bladder and genital organs [18–21]. In particular, the gastrointestinal δ-cells constitute a broad set of at least 16 different endocrine cells, which produce over 50 different regulatory peptides [22]. They are perhaps the single most important and most complex organ of the endocrine system.

Table 3.1 The phenotype of a neuroendocrine cell

- The presence of secretory vesicles in the cytoplasm in which they are stored and from which neurotransmitters or neuroregulatory peptides with endocrine, paracrine or autocrine activity are released by exocytosis (after external stimulation). Two types of secretory vesicles have been described so far: (a) dense core secretory vesicles, which consist of the characteristic secretory structures of the endocrine cells and (b) synaptic-like microvesicles, which resemble the synaptic vesicles of nerve endings.
- The expression of a wide range of neuroendocrine immunohistochemical markers: (a) General markers, i.e. chromogranin-A, synaptophysin, enolase, protein gene product 9.5 and (b) Specific markers, i.e. neuroendocrine secretion protein-55, ghrelin.
- The absence of neuro-axial projections or neuronal synapses.

Neuroendocrine Neoplasms (NENs): Neuroendocrine neoplasms (NENs) are neuroendocrine cell tumors. They are a heterogeneous set with different clinical behaviours depending on the organ involved, the size and degree of volume differentiation and whether they are functioning. The identification of these neoplasms as 'neuroendocrine' is controversial. While it does not suggest a common embryological origin [20], it continues to be used mainly because of the common biochemical markers of neuroendocrine cells with nerve cells (chromogranin A, B, C, synaptophysin, neuron-specific enolase). Although there are few who favour this definition of 'endocrine', both names for these tumors are considered equivalent. There is also a

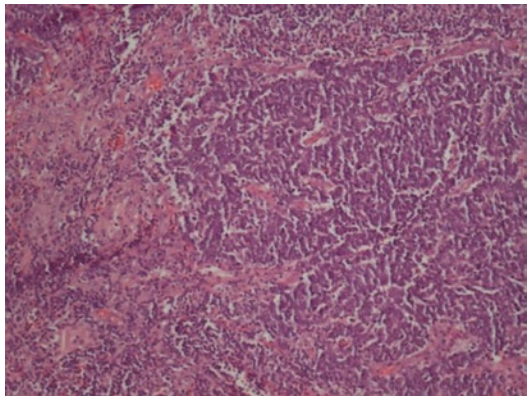

Fig. 3.3 Histological section of a Merkel cell carcinoma of the skin metastatic to lymph node (Haematoxylin-Eosin ×10)

controversy about whether 'tumor' or 'neoplasia' should be used. The latter is more accurate since NENs are potentially malignant; however, the term 'neuroendocrine tumors' dominates internationally, reflecting only the concept of a mass lesion [23, 24].

Gastro-entero-pancreatic Neuroendocrine Tumors (GEP-NETs): Gastro-entero-pancreatic neuroendocrine tumors such as carcinoid tumors and pancreatic tumors (insulinoma, glucagonoma, somatostatinoma, gastrinoma, VIPoma, PPOMa), catecholamine seizures (pheochromocytoma, paraganglioma, neuroblastoma), myeloid carcinoma of the thyroid, adenomas and carcinomas of the pituitary and parathyroid glands, small-cell lung carcinoma and Merkel cell carcinoma (derived from the homonymous cells, (Fig. 3.3)), pheochromocytoma of the adrenals, pituitary adenomas and neoplasms derived from the diffuse neuroendocrine system (DNS)—such as neuroendocrine tumors of the lungs, the gastrointestinal tract and pancreas—are categorised as NENs. GEP-NETs comprise the majority of NENs (about 75%) [25]. Although they account for only 2% of gastric intestinal system tumors [26], given their clinically silent nature, they are the most common neoplasms, after colon cancer, of the digestive system [27]. Reports of unusual invasive processes in the small intestine, probably GEP-NETs, have existed since the nineteenth century [28–30].

GEP-NETs constitute neoplasms with significant differences in the clinical, laboratory and histological profile as well as in their ability to metastasise. This, coupled with the continuous development of the neuroendocrine system concept and the discovery of neoplasms in the NEN spectrum, has made it extremely difficult to classify them. The first attempt at classification by Williams et al. [31] was based on their embryological segmental origin, morphological idiotype and silverchrom staining ('argenta-chromaffin') and concerned three categories: '*foregut*' for tumors originating from the stomach, duodenum, proximal jejunum, pancreas, lungs and thymus gland, 'midgut' for tumors originating from the distal jejunum, ileum, appendix, cecum, and ascending and proximal half of the transverse colon and 'hindgut' for the tumors of the remaining parts of the colon and rectum. This classification failed to gain widespread acceptance but is still used in everyday clinical practice.

From an *epidemiological* point of view, GEP-NETs are much rarer than adenocarcinomas. Their incidence in the general population is about 2.5–5 cases per 100,000 people, while carcinoid tumors (bronchial-pulmonary and gastrointestinal) generally account for 0.46% of all malignant neoplasms [25]. It is clear however that both the incidence and prevalence of carcinoids have increased significantly in recent decades. The clinical behaviour of GEP-NETs is strikingly diverse in relation to both the manifestation of symptoms and the outcome of the disease. For instance, the 5-year survival rate for all carcinoids is 67.2%, whereas the corresponding survival rate for neuroendocrine pancreatic tumors ranges from 97% (mild insulinoma) to about 30% (on non-functioning, clinically silent endocrine tumors of the pancreas). These data support the need to revise the view of GEP-NETs as relatively benign lesions with slow growth.

3.2 Therapeutic Approaches Towards Neuroendocrine Tumors

In patients, neuroendocrine tumors may appear as a single lesion, with or without regional or distal metastases. The usual location of these metastases is the liver. These tumors, if non-functioning, may remain clinically silent until there is a significant burden to the liver due to the tumor-volume pressure on the hepatic parenchyma. Therapeutic options include surgery, administration of somatostatin analogues (SSA), therapeutic schemes with interferon, chemotherapy, targeting the molecules, loco-regional therapies and peptide receptor radionuclide therapy (PRRNT). Supportive palliative care and pain control play an important role in the management of these patients. These options are not exclusive and are, as a rule, interchangeable in their application. Care options, including PRRNT, should be applied in a correct line strategy by an experienced multidisciplinary team. This approach should provide the maximum benefit, minimising risks and side effects and ensuring the best possible quality of life achievable for the patient.

3.2.1 Interventional Approach

A surgical approach with therapeutic intent should be the method used whenever possible. In selected cases and through a multidisciplinary process, radiopeptide therapy (PRRNT) may be beneficial as an adjuvant treatment to make a patient more accessible to the impending surgery. For functionally active tumors, cytoreductive strategies—such as trans-arterial chemoembolisation (TACE), trans-arterial embolisation (TAE), radiofrequency ablation (RFA)—and other techniques, such as selective internal radiation therapy (SIRT), should be applied with the intention of improving clinical symptoms.

The optimal management of neuroendocrine tumors requires early surgical removal prior to the development of metastases. Unfortunately, there are many patients with metastatic disease whose tumors cannot be completely eradicated. Removing the primaries is indicated to prevent complications, such as bleeding or small bowel obstruction. Even with the presence of liver metastases, the removal of the primary lesion has many advantages and a positive prognostic effect on the survival of these patients [32–35]. Mono- or well-delineated hepatic metastases can be surgically removed, while diffuse hepatic infiltration is best dealt with by applying a loco-regional approach.

Loco-regional approaches or loco-suppressive therapies are mainly applied to hepatic metastases; they aim at controlling the tumor and facilitating the recession of the accompanying functional syndromes. Different techniques are applied according to the associated findings (such as the size and distribution of the number of hepatic lesions), morphology (focal or diffuse), vascularisation, their functioning or non-functioning tumor activity and the therapist's knowledge. In cases of oligo-focal liver localisations with a primary already excised, it is preferable to surgically exclude these few hepatic sites by treating them by RFA application or laser-diathermy suppression. In cases of multiple hepatic localisations or diffuse liver disease of high tumor burden, the application of TACE or TAE would be the best option [36, 37]. Embolisation techniques are particularly useful for treating patients with functionally active liver metastases. After chemoembolisation, a successful response of the symptoms has been reported at a rate up to 60–95%, a biochemical response up to 50–90% and a radiological response up to 33–80% [38–40]. Response time without recurrent symptoms ranged from 18–24 months. Similar responses have been achieved by implementing only TAE [18]. Generally, the procedure requires more than one session to ensure the efficacy and stability of the outcome and to minimise the potential risk of complications. The newly introduced SIRT technique demonstrates varying success rates [41]. Unfortunately, prospective studies on this are missing. In a single prospective study of 34 patients, the objective response was 50% [40]. Given the lack of other comparative studies with other different loco-suppressive applications,

the choice of the technique followed depends largely on the physician's experience and skills as well as related criteria such as the number, size, vasculature and distribution of the lesions. In the available medical treatments, octreotide and lanreotide are the two most commonly used somatostatin receptor agonists. They play a key role in controlling both symptomatic and asymptomatic neuroendocrine tumors and should therefore be considered to be first-line therapeutic peptides. Cold somatostatin is to be used in conjunction with the aforementioned therapeutic techniques. Because the majority (87–92%) of neuroendocrine tumors overexpress subtype 2 (sst2) receptors, somatostatin therapy should be offered in parallel with other treatment options to enhance the therapeutic effect. Long-acting somatostatin (SSA-LAR) is characterised by an inhibitory secretory activity and has been shown to reduce the symptoms of carcinoid syndrome, such as flashing, diarrhoea and bronchospasm, and prevent seizures in 40–90% of the patients [42, 43]. Nonetheless, patients may be resistant to the control of the syndrome and require a gradual increase in SSA dosing. Most patients with progressive tumor behaviour resort to PRRNT. A recent PROMID study in Germany demonstrated the efficacy of long-acting SSA as an inhibitory agent in the progression of midgut neuroendocrine tumors [44, 45].

3.2.2 Interferon Alfa (IFN-α)

This has been used to treat patients with neuroendocrine tumors, especially those with carcinoid syndrome, for more than 25 years. It is considered to be the main antisecretory, active drug used for the treatment of functioning tumors [46]. IFN-α effectively reduces hypersecretion in patients with carcinoid syndrome, similar to cold somatostatin analogues (SSAs). A partial response (PR) to tumor growth was also observed in 10–15% of patients with malignant carcinoids and in 39% of patients with disease stabilisation (SD). IFN-α has also been proven effective in treating pancreatic endocrine tumors [47]. Its most common side effect, i.e. 'flu-like' symptoms, limits both the use of higher doses and the duration of treatment as this intolerance causes it to be discontinued.

3.2.3 Systemic Chemotherapy

Systemic chemotherapy is effective in some patients, especially those with low-differentiated NETs (grade 3, WHO, 2010) or progressive NETs of the pancreas. However, in well-differentiated midgut neuroendocrine tumors (NET 1 to 2 WHO, 2010), the response rate to chemotherapy is low (7–20%), without a survival advantage [48–52]. Classical treatment for neuroendocrine tumors (grade 3) is cisplatin in combination with etoposide. The response rate to this combination is 42–67%, and its duration is often short, ranging from 8–9 months [34]. The combination of irinotecan and cisplatin [50] or FOLFOX [Folinic acid + Fluorouracil (5-FU) + Oxaliplatin (Eloxatin)] chemotherapy can be an alternative therapeutic scheme [51]. Streptozotocin-based systemic chemotherapy (Zanosar, STZ) is considered to be the (classical) established therapy for worsening (progressive) neuroendocrine pancreatic tumors, with low or moderate proliferative capacity. A combination of STZ and 5-fluorouracil and/or doxorubicin has been shown to result in a partial response (PR) of the disease at 35–40% [52–54]. Recent Phase II chemotherapy studies have shown efficacy based on temozolomide in combination with antiangiogenic drugs or capecitabine [55, 56]. The standards for patient care in the use of chemotherapy have been extensively defined by the European Society of Neuroendocrine Tumors (ENETS) [57].

In recent years, the efficacy of radio-molecular targeting therapies for treating NETs has been evaluated by clinical trials. These targeting therapies include angiogenesis inhibitors, mono- or poly-inhibitors of tyrosine kinase and the new somatostatin analogue, pasireotide, for which clinical trials are currently in progress. As of now, other drugs with the highest mark of efficacy are sunitinib and everolimus. Both lead to the prolongation of 'progression free survival' (PFS) in patients with advanced pancreatic

NET. Furthermore, there is evidence that everolimus, an mTOR inhibitor, controls NETs, predominantly of pancreatic origin, locally advanced or with metastases accompanied by carcinoid syndrome (most commonly reported with adverse events as stomatitis, anaemia and hyperglycaemia) [58–61]**.** The most developed antiangiogenic drugs are sunitinib and bevacizumab, the anti-VEGF antibody [58, 59]. The former is used in cases of advanced, progressive, well-differentiated pancreatic NET. Globally, the supportive approach towards PRRNT patients is a key component of care, focusing on diet and pain control. Analgesic therapy in patients with NET follows the general principles performed in adult or minor oncological patients [62]. Effective treatment of neuroendocrine tumors, with PRRNT for instance, can relieve pain, including bone pain. Treatment of depressive bone metastases is also required via the administration of bisphosphonates as supportive therapy.

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