History of Neuroendocrine Neoplasia

1

Emilio Bajetta, Domenico De Toma, Adelmo Antonucci, Roberto Bajetta, and Monica Valente

1.1 Introduction

Neuroendocrine tumors are a group of malignant neoplasms that originate in neuroendocrine cells and can affect any part of the body. They are rare (≤5/100.000) and have been extremely difficult to discover and investigate; however, their incidence has risen in the last 20 years [1]. These tumors are nicknamed "zebras" due to their rarity, but despite their sporadic occurrence, physicians have been fascinated by their complexity and distinct clinical presentation. Carcinoid tumors are the most common endocrine tumors occurring in the gut. They may, however, develop in the bronchus, rectum, ovary, lung, and elsewhere. They grow slowly and are often clinically silent for many years before being recognized and metastasizing. The discovery of neuroendocrine tumors has been a challenge, first of all, for the pathologists with regard to diagnosis, as we can see following the different classifications that we have had over the past few years, and for the clinicians with regard to medical treatments.

1.2 Early History

The first pathological conditions defined as neuroendocrine were described in the Old Testament and in an Egyptian medical papyrus dating back to 1552 BC, known as the "Ebers Papyrus," in which cases of patients with disease conditions similar to acromegaly, gigantism, diabetes mellitus and neurofibromatosis type 1 were reported for the first time [2]. The Ebers papyrus is a handbook of Ancient Egyptian medicine and contains 879 individual texts in 110 columns, which cover nine medical topics. It is named after its discoverer, the Leipzig Egyptologist and novelist George Ebers, who purchased it from a Coptic antiquarian in Upper Egypt and transferred it to the University Library in 1873. The papyrus is currently kept at the Library of the University of Leipzig, in Germany. This is the first evidence of the existence of these diseases and several years were to elapse before neuroendocrine tumors began to be investigated and studied in a more

E. Bajetta (✉)
Fondazione Policlinico di Monza, Monza, Italy
e-mail: emilio.bajetta@policlinicodimonza.it

D. De Toma
Medical Oncology, Policlinico di Monza, Monza, Italy

A. Antonucci
Oncology Surgery, Policlinico di Monza, Monza, Italy

R. Bajetta
ATS Lodi, Lodi, Italy

M. Valente
Center for Immuno-Oncology, Medical Oncology and Immunotherapy Division, University Hospital of Siena, Siena, Italy

G. Beretta et al. (eds.), *Neuroendocrine Neoplasia Management*,
https://doi.org/10.1007/978-3-030-72830-4_1

systematic way. The first pathological description of these types of tumors was given by the German pathologist Theodor Langhans in 1867, when he described a carcinoid-like tumor at autopsy in a 50-year-old woman with tuberculosis [3]. He described a submucosal tumor that projected into the lumen of the small intestine, and he commented upon the very sharp borders without any evidence of peri-tumoral invasion. His report was principally a histological description of the tumor without discussion of growth and clinical behavior of this undocumented neoplasm. In 1888, the German pathologist Otto Lubarsch described two cases of ileal tumors during an autopsy examination [4]. In one case, the ileum contained numerous tubercular ulcers and nodules; in the second case, he described multiple small carcinomatous growths in the ileum, although he was initially reluctant to identify these lesions as carcinomas. Diarrhea was the main symptom in the latter patient, a possible manifestation of carcinoid syndrome, but he was unaware of a similar correlation with these types of tumors. After some scientific research, he was able to identify the records of 35 cases of intestinal carcinomas near the ileocecal valve and opined that in his estimation, several of these were not "true" carcinomas. In 1890, the British physician William Ransom was the third person to describe a case of a patient with a lesion similar to a carcinoid tumor with liver metastases. The patient, a 50-year-old woman, presented a pathological condition characterized by diarrhea, which had been persistent for more than 2 years, and wheezing upon eating. The autopsy revealed several small nodules in the ileum and in the liver (metastases) [5]. Despite these initial observations, a distinct pathological entity that united these pathological conditions had not yet been recognized. In 1895, a German pathologist, A. Notthafft, described three tumors of the upper ileum during an autopsy in a patient who had died of pneumonia [6]. These tumors had been uncharacteristically identified in the submucosa and histologically were not true carcinomas; he referred to them as "beginning carcinomas."

The existence of a group of gastrointestinal cells, different from the others due to their "yellow" chromate staining properties, was recognized for the first time in 1870 by the German physiologist Rudolf P. H. Heidenhain [7] and again, after a few years, followed by the Russian anatomist and histologist Nikolai K. Kultschitzky in 1897 [8]. In his paper "Zur Frage über den Ban des Darmkanals," he pointed out the differences between these cells and those that were "classical" mucus-secreting and absorbing mucosa cells. After this first description, these cells were variously called enterochromaffin cells, argentaffin cells, clear cells, enteroendocrine cells, and Kultschitzky cells [9]. The French surgeon Antonin Gosset and the French-Canadian pathologist Pierre Masson demonstrated the argentaffin-staining proprieties of carcinoid tumors, using silver impregnation techniques. They showed a silver-colored pattern and speculated on the etiology of a specific type of tumor from the enterochromaffin cells, Kultschitzky's cells, and of the intestinal mucosa [10, 11].

1.2.1 Carcinoid: The Origin of the Term

The word "carcinoid," from the German "karzinoid," was introduced by the German pathologist Siegfried Oberndorfer in 1907, to identify some gastrointestinal tumors that presented a prognosis and a more favorable clinical history than adenocarcinomatous lesions. He presented his discovery in his seminal paper "Karzinoide Tumoren des Dünndarms" in which he used the term "Karzinoide Tumoren" for these different types of benign gastrointestinal neoplasms [12].

All tumors described were located in the submucosa of the ileum, and the peculiarity was the discovery of multiple primary malignant tumors in the same organ. As a result of his observations, Oberndorfer identified five distinct characteristics of these tumors: (a) they were mostly small, patients commonly demonstrated multiple tumors; (b) the tumor cells were usually

surrounded by undifferentiated tissues, possibly demonstrating gland formation; (c) the tumors had not previously been described, and they had the potential to become invasive; (d) they did not metastasize; and (e) they apparently grew extremely slowly, achieving no substantial size and therefore appeared to have a harmless nature. The merit of Oberndorfer was to identify these tumors as actually true cancers, but without the tendency to grow rapidly and to metastasize, as in the case of carcinomas. For these reasons, he used the term "karzinoide" ("carcinoma-like") to describe these types of lesions more accurately. After some years, Oberdnorfer revised his initial observations about the benign behavior of these tumors in a manuscript, in which he described 36 carcinoid tumors of the appendix and small intestine, and he emphasized the possibility that they might exhibit malignant features and metastasize [13].

1.2.2 Carcinoid Classifications

In 1914, the surgeon Andre Gosset and the pathologist Pierre Masson hypothesized the origin of carcinoid tumors from the enterochromaffin cells of the gastrointestinal district, using silver impregnation techniques, and then, they demonstrated the argentaffin-staining properties of carcinoid tumors. Furthermore, the Austrian pathologist Friedrich Feyrter explained how the enterochromaffin cells were present not only in the digestive tract but also in many other anatomic districts, practically in all mucosal-lined organs of the body. Feyrter introduced the concept of the "diffuse" endocrine system on solid glands [14] and, subsequently, the concept of the "widespread neuroendocrine system" was developed. After that, another significant discovery was to distinguish between two different categories in this system: endocrine cells that discharged their hormonal content into the blood ("true" endocrine cells) and those that limited their action to a restricted anatomic field delimited by the dendrite-like prolongations present in those cells ("paracrine" cells) [9]. In 1952, the Italian pharmacologists Vittorio Erspamer and Biagio Asero identified serotonin (5-HT) as the main hormone produced by the enterochromaffin cells of the gastroenteropancreatic tract [15], and subsequently, its metabolite, urinary hydroxyindoleacetic acid (5-HIAA), was identified as another marker in cancer carcinoid patients. Only after some years, in the 1960s, was there the need to classify the tumors that develop from enterochromaffin cells in subtypes on the basis of their histological appearance and type of secretory product. In 1962, the British pathologist Elizabeth Williams classified the carcinoid tumors based on their origin from different embryonic segments of the gut, foregut, midgut, and hindgut [16]. This approach was a result of the work of the British pathologist Anthony Pearse, who developed the hypothesis of the "diffuse endocrine system," with cells located in different anatomical districts and different organs, but with a common embryological origin from the neural crest, a transient neural structure unique to vertebrates located on both sides of the embryonic neural plate, at the junction with the normal ectoderm.

The neural crest is composed of a pluripotent cell population, which migrates throughout the body during the normal embryonic development, and gives rise to different cell types, such as neurons, melanocytes, chromaffin cells of the adrenal medulla and extra-adrenal paraganglioma, and thyroid C cells. Pearse, then, established the APUD (Amine Precursor Uptake and Decarboxylation) concept [17]. Later, this gives rise to the terms "diffuse neuroendocrine system" (DNES) and "confined neuroendocrine system" (CNES) to identify those groups of cells capable of producing and releasing hormones, whether they are present in a widespread way in the body or confined to organs. DNES includes nerve and endocrine cells found in organs and tissues, CNES includes glandular tissue recognized by the traditional endocrinology [18, 19]. Almost half of these cells are in the gastroenteropancreatic (GEP) system where most neuroendocrine tumors occur (Table 1.1).

Regarding the hypersecretion of hormonal substances, some neuroendocrine tumors are biologically active called "biologically active neuroendocrine tumors" (BANTs) and others are biologically inactive called "biologically inactive neuroendocrine tumors" (BINTs). The BANTs, independently of the levels of hormonal substances present in the blood or of the immunopositivity identified in the tissue, present some symptoms and signs correlated to the effects of one of the hypersecreted hormones from which the syndrome takes its name. Otherwise, BINTs are not capable of secreting hormonal substances and they have no correlated syndromes so, since then, these tumors have been diagnosed via immunohistochemical investigation [19].

Over the years, there have been several classifications for neuroendocrine tumors. Since 1995, the Italian pathologist Carlo Capella suggested the term "neuroendocrine tumors" for all tumors relating to the digestive system instead of the term "carcinoid tumors" [20]. This classification was updated by another Italian pathologist Enrico Solcia and other expert pathologists in the first World Health Organization (WHO) classification in 2000 [21], in which the tumors were classified into: (a) well-differentiated endocrine tumors or a more aggressive grade with metastases, well-differentiated endocrine carcinomas; (b) poorly differentiated endocrine carcinomas; and (c) mixed exocrine-endocrine tumors.

In 2010, the WHO classification was updated [22] in the following categories, depending on mitotic counts and the Ki-67 labeling index:

a. well-differentiated neuroendocrine tumors G1;
b. well-differentiated neuroendocrine tumors G2;
c. neuroendocrine carcinomas; and.
d. mixed adeno-neuroendocrine carcinomas.

The WHO grading system was revised in 2017 [23], and in 2019 [24], a new subset of well-differentiated neuroendocrine neoplasms (NENs) has been recognized (Table 1.2).

Table 1.1 Neuroendocrine system (modified from Percopo V. Neuroendocrine tumors general aspects. In: GEP and multiple neuroendocrine tumors. Piccin 1996)

Diffuse neuroendocrine system (DNES)	Confined neuroendocrine system (CNES)
Gastroenteropancreatic apparatus	Pituitary
Respiratory apparatus	Thyroid and parathyroid
Urogenital apparatus	Hypothalamus
Kidney	Adrenals
Skin	Ganglia and paraganglia
Myocardium	Carotid body
Thymus	Pineal gland
Spleen	Placenta

1.2.3 Clinic History of Carcinoids

There were several symptoms and signs that were found in carcinoid diagnoses, such as flushing, diarrhea, edema, wheezing, now commonly referred to as the "carcinoid syndrome." The German pathologist, A. Schotle, was the first who described this condition in 1931, in a

Table 1.2 WHO 2019 Classification for neuroendocrine neoplasms of the gastrointestinal tract (modified from Nagtegaal ID et al. Histopathology 2020)

Terminology	Differentiation	Grade	Mitotic rate	Ki-67 index
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2–20	3–20%
NET, G3		High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High	>20	>20%
NEC, large-cell type (LCNEC)			>20	>20%
MiNEN	Well/poorly differentiated	Variable	Variable	Variable

47-year-old male with an ileal carcinoid tumor, who complained of diarrhea, cough, lower extremity edema, and cardiac failure. Indeed, at autopsy, a hard thickening of the tricuspid valves and irregular endocardial thickening of the right atrium were evident, likely representing the first documentation of carcinoid heart disease [25]. In 1954, the Swede A. Thorson published the first series of patients presenting with pulmonary stenosis, tricuspid insufficiency, peripheral vasomotor symptoms, bronchoconstriction, and cyanosis in malignant carcinoid tumors of the small intestine with liver metastases and their symptomatology related to hypersecretion of 5-HT into the system circulation [26]. In the same year, B. Pernow and J. Waldenström described flushing, another sign of carcinoid syndrome [27], and in 1964, J. Oates demonstrated that some carcinoid tumors release kallikrein, which activates bradykinin, a potent vasodilator, and suggested that it might play a role in the flushing episodes so characteristic of the disease [28]. The role of 5-HT, as a plasma marker in carcinoid syndrome, and of 5-HIAA, the main 5-HT urine metabolite, was demonstrated by I. Page in 1954. Another sign we frequently observe in carcinoid tumors is fibrosis. In 1961, the American researcher, C. Moertel, first described the relationship between fibrosis and carcinoids, because these tumors stimulate fibroblastic reactions in the peritoneum, mesentery, and retroperitoneum, as well as in the lungs and cardiac valves [29]. In 1968, two physicians, Ladislav Krulich and Samuel McCann discovered an inhibitor of the growth hormone (GH) released from the pituitary gland [30], which attracted much attention because of its functional inhibitory role in the regulation of a wide variety of physiological functions such as the inhibition of both endocrine and exocrine secretion, cell proliferation, and survival. The dual actions of these products (inhibition of hormone release and cell growth) have made them ideal candidates for the treatment of neuroendocrine disorders. In 1973, a growth hormone inhibitor was isolated named somatostatin [31], and for this reason, the endocrinologist Roger Guillemin received the Nobel Prize for Physiology or Medicine in 1977. Some years after, a somatostatin analogue, octreotide acetate, was developed and used to control carcinoid syndrome, and its use was approved in Europe in 1988 and in the USA in 1989. After that, the FDA approved a new type of preparation, a longer acting octreotide acetate (octreotide long acting repeatable, LAR) following the publication of Joseph Rubin and colleagues, regarding the positive trial results of this drug [32]. Somatostatin compounds also played a role in the diagnostic phase when the Swiss pathologist Jean Claude Reubi and colleagues discovered different somatostatin receptor subtypes and the methods to detect or visualize them for the diagnosis of these types of tumors. OctreoScan® was the first product which became available in 1994, and more recently, 68Gallium (Ga)-DOTATOC and 68Ga-DOTATE were developed as PET (positron emission tomography) traces for somatostatin receptor imaging [33].

1.3 Conclusion

Neuroendocrine neoplasms are a rare family of tumors arising from various different epithelial cells with patterns of neuroendocrine differentiation. They share similar histopathological features, but, at the same time, these tumors vary greatly in their biological behavior and clinical characteristics. Although they are rare tumors, neuroendocrine neoplasms have a very long clinical history (Fig. 1.1) involving various medical figures, from surgeons to pathologists, oncologists, gastroenterologists, radiologists, nuclear physicians, and endocrinologists. Still today they are the subject of discussion and study. Proof of this is the continuous search to classify them in order to better diagnose and treat these rare and, at the same time, fascinating tumors.

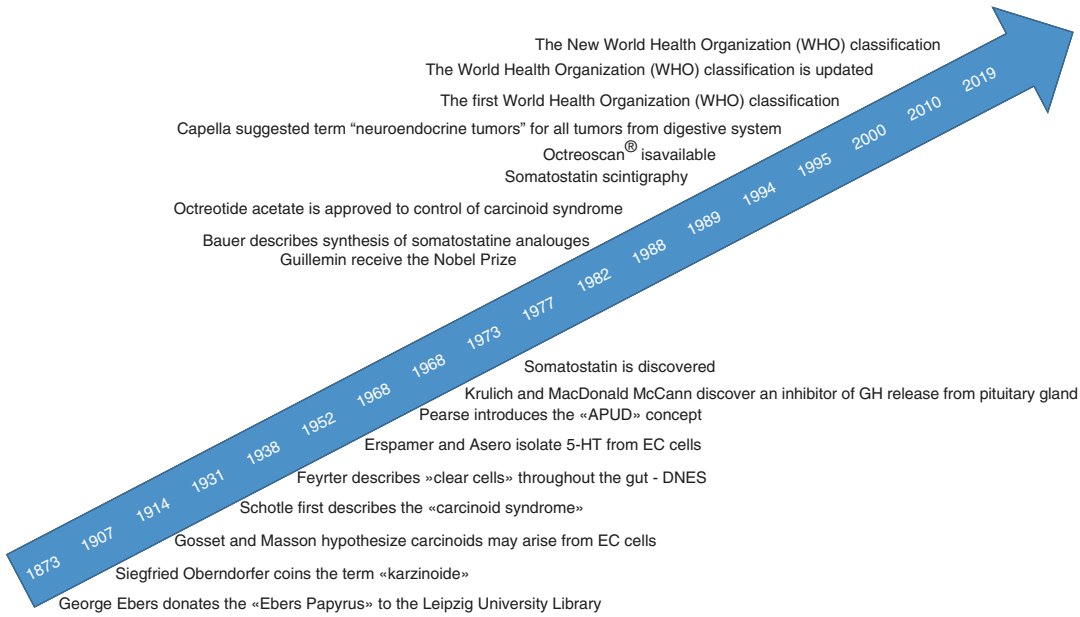

Fig. 1.1 The timeline of neuroendocrine neoplasms (adapted from Modlin IM et al. A century of advances in neuroendocrine tumor biology and treatment: a tribute to Siegfried Oberndorfer. Felsenstein CCCP 2007)

References

1. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3:1335–42.
2. Ferrari L, Bajetta R, Gevorgyan A. Epidemiologia e storia dei tumori neuroendocrini. In: Bajetta E, editor. La famiglia dei carcinoidi. Elsevier Masson; 2007. p. 1–3.
3. Langhans T. Uber einen Drüsenpolyp im ileum. Arch für Pathol Anat Physiol für Klin Med. 1867;38:559–60.
4. Lubarsch O. Über den primarën Krebs des ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberkulose. Arch für Pathol Anat Physiol für Klin Med. 1888;111:280–317.
5. Ransom WB. A case of primary carcinoma of the ileum. Lancet. 1890;136:1020–3.
6. Notthafft A. Über die Entstehung der carcinoma. Dtsch Arch für Klin Med. 1895;54:555–87.
7. Heidenhain R. Untersuchungen über den Bau der Labdrüsen. Arch für Mikrosk Anat. 1870;6:368–406.
8. Kultschitzky N. Zur Frage über den Bau des Darmcanals. Arch für Mikrosk Anat. 1897;49:7–35.
9. Rosai J. The origin of neuroendocrine tumors and the neural crest saga. Moder Pathol. 2011;24:553–7.
10. Masson P. La glande endocrine de l’intestin chez l’homme. C R Acad Sci Paris. 1914;158:52–61.
11. Gosset A, Masson P. Tumeurs endocrines de l’appendice. Presse Med. 1914;25:237–8.
12. Oberndorfer S. Karzinoide Tumoren des Dunndarms. Frankf Z für Pathol. 1907:426–9.
13. Modlin IM, Shapiro M, Kidd M, Drozdov I, Gustafsson B. Siegfried Oberndorfer and the origins of carcinoid tumors. In: A century of advances in neuroendocrine tumor biology and treatment: a tribute to Siegfried Oberndorfer. Felsenstein CCCP; 2007. p. 22–37.
14. Feyrter F. Uber diffuse endokrine epitheliale organe. Zentralbl Innere Med. 1938;545:31–41.
15. Erspamer V, Asero B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. Nature. 1952;169:800–1.
16. Williams ED, Sandler M. The classification of carcinoid tumours. Lancet. 1963;1:238–9.
17. Pearse AG. The APUD cell concept and its implications in pathology. Pathol Annu. 1974;9:27–41.
18. Modlin IM, Champaneri MC, Bornschein J, Kidd M. Evolution of the diffuse neuroendocrine system: clear cells and cloudy origins. Endocrinology. 2006;84:69–82.
19. Percopo V. Neuroendocrine tumors general aspects. In: GEP and multiple neuroendocrine tumors. Percopo V, Kaplan EL. Padova: Piccin 1996. p. 3–19.
20. Capella C, Heitz PU, Hofler H, Solcia E, Klöppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. Virchows Arch. 1995;425:547–60.
21. Solcia E, Klöppel G, Sobin LH. Histological typing of endocrine tumours. Berlin, Heidelberg, New York: Springer; 2000.

22. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. International Agency Research Cancer, WHO; 2010.
23. Kim JY, Hong SM, Ro JY. Recent updates on grading and classification of neuroendocrine tumors. Ann Diagn Pathol. 2017;29:11–6.
24. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76:182–8.
25. Scholte A. Ein fall von angioma teleangiectaticum cutis mit chronischer endocarditis und malignem dünndarmacarcinoid. Beitr Pathol Anat. 1931;86:440–3.
26. Thorson A, Biorck G, Bjorkman G, Waldenstrom J. Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. Am Heart J. 1954;47:795–817.
27. Pernow B, Waldenström J. Paroxysmal flushing and other symptoms caused by 5-hydroxytryptamine and histamine in patients with malignant tumours. Lancet. 1954;267:951.
28. Oates J, Melmon K, Sjoerdsma A. Release of a kinin peptide in the carcinoid syndrome. Lancet. 1964;18:514–7.
29. Moertel C, Sauer W, Dockerty M. Life history of the carcinoid tumor of the small intestine. Cancer. 1961;14:901–12.
30. Krulich L, Dhariwal AP, McCann SM. Stimulatory and inhibitory effects of purified hypothalamic extracts on growth hormone release from rat pituitary in vitro. Endocrinology. 1968;83:783–90.
31. Brazeau P, Vale W, Burgus R, Ling R, Butcher M, Rivier J, et al. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science. 1973;179:77–9.
32. Rubin J, Ajani J, Schirmer W, Venook AP, Bukowski R, Pommier R, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. J Clin Oncol. 1999;17:600–6.
33. Bodei L, Sundin A, Kidd A, Prasad V, Modlin IM. The status of neuroendocrine tumor imaging: from darkness to light? Neuroendocrinology. 2015;101:1–17.