

Neuroendocrine tumors: Preface

This section contains the reports of the meeting on neuroendocrine tumors held in Milan (May 2010). Neuroendocrine tumors are commonly considered a rare pathology. In the last years, the clinical approach to these tumors has changed considerably, following the improvements in diagnostic tools (histology and immunohistochemistry, imaging), radiometabolic therapies and surgical techniques. More recently, biological targeted therapies, tailoring intracellular signaling pathways, provided us with new promising therapeutics weapons. The purpose of this meeting consists in put-

ting together all the specialists involved in the management of the patients affected by neuroendocrine tumors, especially pulmonary and GI tumors, representing the most frequent ones.

This represents an important opportunity to compare different centers worldwide recognized in this field, regarding the state-of-the-art and new perspectives of such a disease that unfortunately is still relatively unknown and underestimated.

Kjell Öberg and Emilio Bajetta

1. Neuroendocrine tumors (NETs): historical overview and epidemiology

Kjell Öberg

Department of Endocrine Oncology, University Hospital, Uppsala, Sweden

ABSTRACT

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms which take origin from the neuroendocrine cell system and are characterized by embryological, biological and histopathological differences. Traditionally considered as a rare and “niche” pathology, over the last decades they have gained significant attention from the scientific community, even because of their increasing incidence and prevalence probably imputable to the availability of more sensitive diagnostic tools and to the development of higher awareness among clinicians. This paper retraces the key events that led to the discovery, characterization and classification of NETs as well as to the development of adequate treatment strategies. Incidence and epidemiology are also addressed. Free full text available at www.tumorionline.it

Introduction

NETs were described for the first time more than 100 years ago and considered to show indolent behaviour compared with typical adenocarcinomas, but the broad heterogeneity characterizing NETs has always posed problems regarding their correct classification and, consequently, the selection of the appropriate therapeutic approach. However, the clinical approach to these tumors has changed considerably over the last years, opening new intriguing diagnostic and therapeutic perspectives for their clinical management. This paper retraces the key events that led to the discovery, characterization and classification of NETs as well as to the development of adequate treatment strategies. Incidence and epidemiology are also addressed.

Historical overview

The history of neuroendocrine tumors (NETs) traces its origin back to the 19th century, when T. Langhans (1839-1915), O. Lubarsch (1860-1933) and W.B. Ransom (1860-1909) described for the first time unusual tumors in the small bowel¹⁻³. In particular, in 1888 O. Lubarsch, while working at the Pathological Institute of Gissen, Breslau, provided a detailed pathological characterization of these tumor entities reporting multiple ileal tumors at autopsy in two male patients. However, all these first descriptions failed to adequately investigate these new cancer entities. The person who really started the discussion about what we call now gastroenteropancreatic neuroendocrine tumors (GEP NETs) was the pathologist Siegfried Oberndorfer (1876-1944) of the University of Munich. Oberndorfer was the first to clearly distinguish these tumors from other forms of cancer. More specifically, he reported descriptions of multiple “benign carcinomas” of the small intestine at the German Pathological Society meeting of 1907 in Dresden and, four months after this initial presentation, he published his work in the *Frankfurt Journal of Pathology* and coined the term “karzinoide” (carcinoma-like)⁴. He felt this term best described the “presumably harmless” and anomalous nature of the tumors, which appeared to be “carcinomatous” but behaved more like benign lesions. Despite the initial characterization of karzinoide as tumors benign, in 1929 Oberndorfer modified his description and thereafter conceptually embraced the

malignant potential of the disease. In 1914, the introduction of the eponymous trichome stain by Pierre Masson (1880-1959) allowed him and Andre Gosset (1872-1944) to demonstrate the argentaffin staining properties of carcinoid tumors. They suggested that the Kulchitsky or enterochromaffin (EC) cells in the gut, which had been described in 1897 by Nikolai Kulchitsky within the crypts of Lieberkühn in the intestinal mucosa, formed a diffuse endocrine organ. In 1928 they described these cells as being of neural origin, and proposed that they were the progenitors of neuroendocrine tumors of the gut (carcinoids)⁵. In 1938 Friederich Feyrter (1895-1973) while working at the Medical Academy of Danzig published his seminal manuscript that described *Hellen Zellen* (clear cells) in the ducts of the pancreas and mucous membrane of the gastrointestinal tract⁶. This text enunciated the widespread regulatory role of these cells. Feyrter proposed that the syncytium of these cells comprised a novel entity that he proposed should be considered as constituting a diffuse neuroendocrine system in the gastrointestinal tract, but also in the lung and everywhere.

One of the first descriptions of the carcinoid syndrome ("carcinoidosis") was published in 1952 in the *American Heart Journal* by Gunnar Biörck (1916-1996) and his Swedish group of Stockholm⁷. They described a patient that was dying from a very peculiar clinical syndrome presenting as a constellation of symptoms including flushing, diarrhea, edema, wheezing, and right-sided heart failure. The latter was ascribed to the deposition of fibrotic subendocardial plaques, that constitute the basis of the clinical condition referred to as "carcinoid heart disease". In 1953 E. Lembeck established that enterochromaffin cells synthesized and secreted serotonin⁸, and during the 1950's and 1960's there were the first descriptions of the Zollinger-Ellison syndrome, the glaucomatoma syndrome and the Verner-Morrison syndrome in pancreatic NETs. Most importantly, in 1961 appeared in *Cancer* the first characterization of the unique relationship between carcinoids of the small intestine and fibrosis by Charles Moertel (1927-1994) and his colleagues of the Mayo Clinic⁹. They reported that once carcinoid tumors become invasive, they seemed to stimulate a considerable fibroblastic reaction within the peritoneum, mesentery, and retroperitoneum, as well as in the lungs and cardiac valves. The precise biological basis for this phenomenon remains unclear but is associated with either the fibroblastic effects of serotonin or growth factors such as connective tissue growth factor (CTGF).

The first proposal of a classification of carcinoid tumors was published in *The Lancet* by E.D. Williams and M. Sandler¹⁰. This classification was based on the embryonic site of origin and distinguished between carcinoids arising in the foregut (respiratory tract, stomach, duodenum, biliary tree, pancreas), midgut (small intestine, appendix, right colon, ovary testis) and hindgut (transverse colon, left colon, rectum), with tumors within each subgroup sharing distinct histological features,

metabolism and secretory products. This classification system remained in use for many years and has been replaced only during the last 4-5 years.

In 1969 Anthony Pearse (1916-2003) introduced the histochemically derived APUD (amine precursor uptake and decarboxylation) concept, which drew on Feyrter's original anatomical description of *Hellen Zellen*¹¹. Pearse based his proposal on the observation that the majority of endocrine cells shared a series of biochemical and immunostaining characteristics regardless of their location, suggesting that they had both a common origin and were part of an integrated, albeit dispersed functional system. This characterization led to the introduction of the term "apudoma" by Ilona Szijj to describe the neoplastic lesions of the system.

A revised classification of carcinoid tumors based purely on histological features was formulated in 1971 by Jun Soga and Kenji Tazawa from Niigata, Japan¹². This classification system subdivided carcinoid tumors according to their dominant growth pattern: insular, trabecular, glandular, mixed or undifferentiated. So, while "midgut" carcinoids display mostly an "insular pattern", "foregut" and "hindgut" tumors typically show a trabecular form. Also this classification, which recognized that these types of tumors cannot be considered as one entity, has been extremely important for the understanding of NETs.

One of the most important events in the diagnosis and treatment of NETs was the discovery of chromogranin A in endocrine tumors by DT O'Connor and LJ Deftos in 1986¹³, followed by the establishment of the first chromogranin A assays in Europe in 1988. Chromogranin A is a water-soluble acidic glycoprotein stored in the secretory granules of neuroendocrine cells, and actually is the best biochemical marker we have for most types of NETs. Its detection by immunohistochemistry or plasma assay can be used as a general tumor marker for GEP-NETs as well as for "non-functioning" tumors. In addition to its diagnostic value (99% sensitivity, <50% specificity) as a NET marker, secretion of chromogranin A also correlates with tumor volume and burden and nowadays it is widely used also to follow NETs treatment. Overexpression of chromogranin A mRNA can identify micrometastases with greater sensitivity than conventional histochemical and immunohistochemical techniques.

In 2000 the World Health Organization (WHO) produced an important classification of NETs that served as a basis for all subsequent classifications¹⁴. Endocrine tumors had been already classified by the WHO in 1980. According to this initial classification, the term carcinoid was applied to most neuroendocrine tumors resulting in misunderstandings between pathologists and clinicians, since the former applied the term to all tumors with neuroendocrine features, whereas clinicians considered the term to refer to a serotonin-producing tumor with carcinoid syndrome. The revised WHO classification produced by Gunter Klöppel in 2000 modified this system by removing the term "carcinoid" from the nomencla-

ture and introducing the neutral and inclusive terms neuroendocrine tumor and neuroendocrine carcinoma. This allowed to distinguish between well-differentiated neuroendocrine tumors, which show benign behavior or uncertain malignant potential, well-differentiated neuroendocrine carcinomas, which are characterized by low-grade malignancy, and poorly differentiated (usually small cell) neuroendocrine carcinomas of high-grade malignancy. However, only the recent introduction of the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines and classification system, which applies the TNM staging and grading system to these tumors, made it possible to get definitively away from lumping together all these tumors into one group and to improve significantly the understanding of NETs^{15,16}.

But looking back in time another major contribution to the study of NETs came from J. C. Reubi of Bern, who identified in 1982 the cellular location of somatostatin receptors on neuroendocrine cells and tumors by using both radiolabeled somatostatin and immunohistochemical antibody techniques¹⁷. The further delineation of the distribution and binding characteristics of

the individual 5 somatostatin receptor subtypes as well as the presence of somatostatin and somatostatin receptors on neuroendocrine tumors provided the scientific basis for the development of both diagnostic and therapeutic strategies to treat somatostatin receptor expressing lesions. Among these there was the introduction of somatostatin scintigraphy in 1989, which paved the way to the subsequent development of other more sophisticated imaging techniques in use nowadays, such as positron emission tomography/computed tomography (PET/CT) with ⁶⁸Ga-DOTA-otcretotide. But if we look over the last few decades, other key events deserve particular attention: Bauer's synthesis of the first available somatostatin analog octreotide in 1982; the introduction of Ind¹¹¹-labeled radiopeptide therapy in 1994 by professor E. Krenning of Rotterdam; the development of the long-acting somatostatin analog, Sandostatin LAR, which has been so important for the management of some functioning tumors; the PROMID study, which will be treated in details elsewhere in this number of "Tumori". Figure 1 summarizes the principal events in the research on NETs over the centuries.

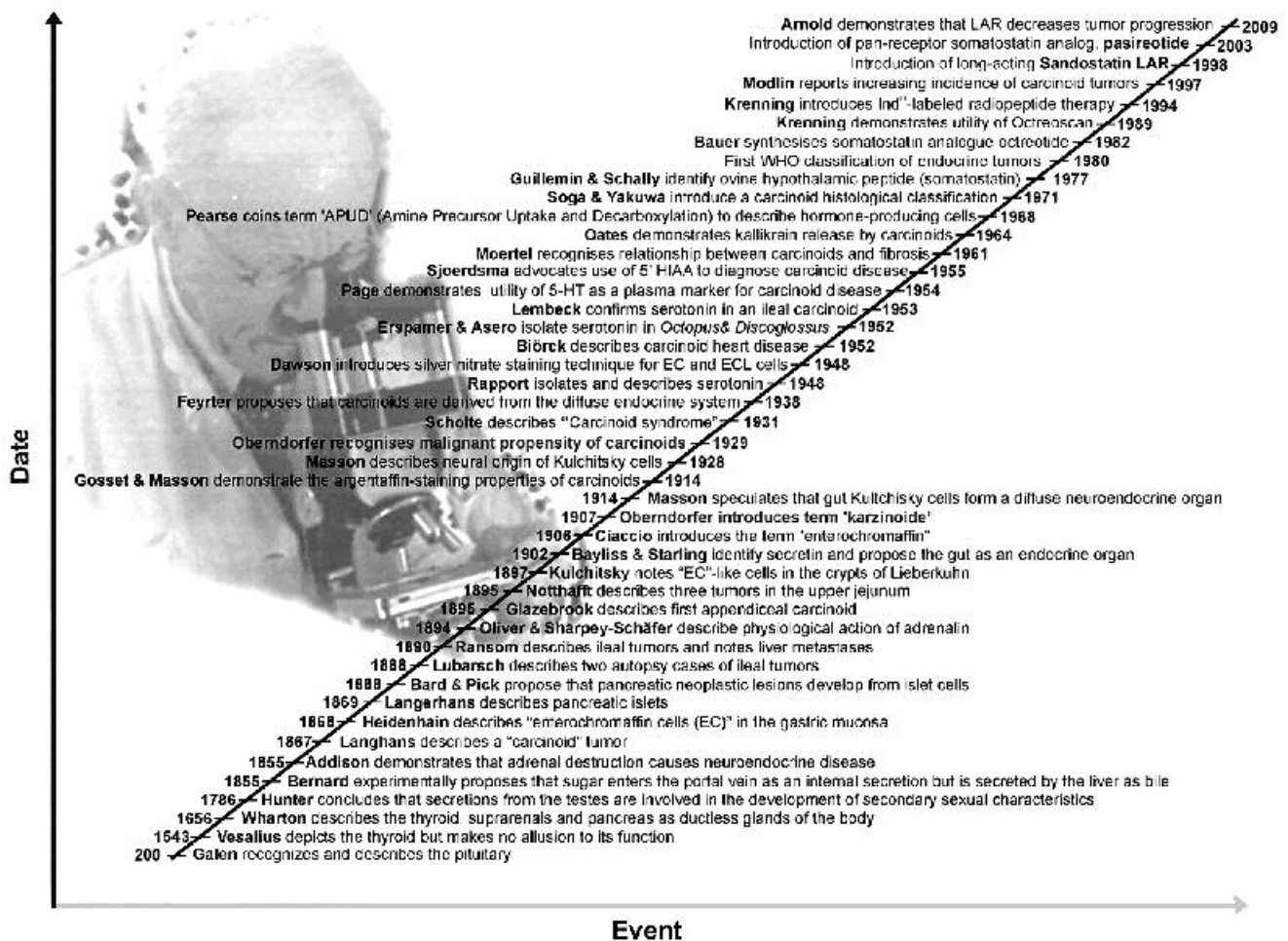


Figure 1 - Major events in the history of NETs over the centuries.

In the last decades considerable advances have been made also in medical treatment of NETs. During the so-called cytotoxic era, i.e. the 1960's and 1970's, the cornerstone for the management of most types of NETs were combinations of streptozotocin plus 5-fluorouracil or doxorubicin. These cytotoxic drugs worked rather well for endocrine pancreatic tumors, with response rates of 50-60%, but performed much worse for patients with carcinoid tumors, which showed very low response rates between 0% and 30%. Median survival for malignant metastatic midgut carcinoid tumors was only 12 months in 1979-80 compared with more than 12 years today. During the 1980's, with the development of somatostatin analogs octreotide (SMS 201 995) and α -interferon biotherapy by out group, the first specific treatment for these types of tumors became available. Then, in 2000's, targeted therapy was introduced, thanks to E. Krenning, J. Yao and M. Kulke among others, with peptide receptor radionuclide therapy (PRRT), m-TOR inhibitors, vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (TKIs), allowing to improve considerably the outcome of medical therapy in these patients. Finally, the increasing awareness that successful treatment of NETs requires a multimodal approach has led over the last 4-5 years to the introduction of multidisciplinary management teams. These teams are of paramount importance to provide optimal balance of diagnostic and therapeutic strategies, thus ensuring maximally effective management of NETs. They can include gastroenterologists, endocrinologists, radiologists, nuclear medicine specialists, oncologists, pathologists, surgeons and often a transplant team.

Epidemiology

Although until recently NETs were regarded as rare diseases, the incidence and prevalence not only of gastroenteropancreatic (GEP), but also of lung NETs have significantly increased over the last decades. Data reported by Modlin IM and coworkers from the Surveillance, Epidemiology, and End Results (SEER) Program registries have indicated a incidence of 2.5-5.0 cases/100,000 inhabitants in the period 1974-2005¹⁸.

Similarly, data reported by Yao and colleagues for the same period from 1973 to 2004 confirmed increased incidence of NETs and increased survival durations over time, suggesting that these tumors are more prevalent than previously referred¹⁹. More specifically, the authors observed a significant increase in the reported annual age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000), as well as an estimated prevalence of 103,312 cases (35/100,000) in the United States. Taken together, these data clearly indicate that these tumors should no longer be considered as rare diseases. Actually GEPs are the most common tumor type of the gastroin-

testinal tract after colorectal cancers and is far more common than gastric, pancreatic, esophageal and hepatobiliary cancers. The overall 5-year survival for pancreatic NETs varies from 97% for benign insulinomas to 30% for non-functioning tumors. The overall 5-year survival for carcinoid tumors of the small intestine is about 60%, a proportion that has not significantly changed over the last three decades. The increase in incidence is in great part due to the introduction of more sensitive diagnostic tools as well as an overall increased awareness among physicians. The increased prevalence is mainly related to improved management of NETs including more active surgery, new biological and cytotoxic treatment and recently also PRRT.

Conclusions

In the last decades NETs have gained significant consideration from the scientific community, even because of their increasing incidence and prevalence. Since the first observations of these tumors in the 19th century, considerable efforts have been made to improve our knowledge of these tumors and to develop effective diagnostic tools and therapeutic strategies for the management of NET patients. However, to further ameliorate the diagnosis and treatment of this disease it will be of paramount importance to have new more sensitive biomarkers, to improve molecular imaging also with the availability on new and more sophisticated tracers, to improve NET's classification, to develop new targeted treatments and possibly, to consider the development of vaccines and nanoparticles.

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