Neuroendocrine neoplasms – think about it and choose the most appropriate diagnostic and therapeutic steps

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We are pleased to present the second issue on neuroendocrine neoplasms (NEN). Often, NEN are also referred to as “zebras” because of their rarity, and we would like to expand this thought into “black swans,” a term that is based on an ancient perception that presumed black swans did not exist, but had to be changed once they were discovered in nature. This should teach us that any system of thought should constantly be re-evaluated. It is understandable that humans usually harbor some anxiety towards the unknown and that this angst is more pronounced in more conservative communities than in progressive ones. Discoveries are usually made by thinking “outside of the box.” For instance, excessively high serum calcitonin levels could be alarming for an existing NEN. The odds of a possible NEN would call for a neck examination to search for medullary thyroid carcinoma and in some cases thyroidectomy would be performed without identifying any tumor [1], because calcitonin secretion occurs ectopically from an unsuspected NEN [2–8]. More recently, the presence of macrocalcitonin as a pitfall in the endocrine laboratory assessment has been discovered [9]. Similar to other macrohormones such as macroprolactin, a macro-thyroid stimulating hormone, macrocalcitonin has neglectable biological activity [9–11].

The first article is a report on rare locations of NEN including kidney, lung, and heart/ileum [12]. Solitary fibrous tumors of the pleura can demonstrate increased tracer uptake at 68Ga-DOTATOC positron emission tomography imaging [13]. In addition, we present a 17-year-old young man with multifocal

pheochromocytoma/paraganglioma syndrome in von Hippel Lindau (VHL) disease who during a 9 year follow-up remained in remission. According to a recent study of 272 patients with malignant pheochromocytoma/paraganglioma over 55 years, the clinical course of these patients is very variable [14]. Predictors of rapid progression in that study included males, older age at diagnosis, larger tumor size, synchronous metastases, and not undergoing resection of primary tumor. For unresectable pheochromocytomas/paragangliomas associated with uncontrolled endocrine hypertension, peptide receptor radionuclide therapy with 177Lu-DOTA-octreotate can lead to worthwhile clinical and biochemical responses in selected patients [15]. Treating patients with VHL disease and growing and/or unresectable lesions with pazopanib may reduce tumor size [16, 17]. It is both challenging and yet necessary to make NEN visible. Functional imaging modalities have resolution limits and usually cannot depict lesions smaller than 4 mm in size. In addition, uptake in areas that are not typically NEN can occur and are often referred to as “false positive uptake.” This problem will be discussed in the article concerning nuclear medicine by Professor Vani Vijayakumar and colleagues [18]. Typically, functional imaging technologies in NEN should be used in combination with conventional imaging modalities, if resolution limits permit. Often this task is directed by skilled radiologists. However, for small, pancreatic NEN, an endocrinologist or gastroenterologist, highly skilled in conducting endosonography, may localize NEN better than magnetic resonance imaging, as demonstrated in the article by Professor Kann [19].

Once a NEN is discovered, the question arises of what the next steps should be in its management. This is especially important in family members of hereditary tumor syndromes [17]. For instance, Pieterman and colleagues [20] in a retrospective longitudinal observational cohort study of patients with small (<2 cm) nonfunctional pancreatic NEN from the Dutch national multiple endocrine neoplasia type 1 database, found that the growth rate of 115 NEN from 99 patients was 0.4 mm per year, irrespective of the underlying MEN1 genotype [20]. Moreover, Ariotti and colleagues [21] provide a review on how incidentally

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discovered gastrointestinal and pancreatic NEN should be followed. If the decision is made to perform surgery on a patient with NEN, a multidisciplinary team should discuss the perioperative proceedings including an effective prophylaxis against an intraoperative carcinoid crisis, supportive therapy, and nutrition [7, 8, 22]. Psychosocial support, expert nursing, nutritional support and management of cancer related pain will be reviewed by the groups, Auernhammer and Spitzweg, as well as the group, Faggiano, Colao, Muscogiuri and colleagues [23, 24].

Furthermore, Professor Goretzki and colleagues, review curative and palliative surgery in patients with neuroendocrine tumors of the gastro-entero-pancreatic (GEP) tract with excellent case illustrations [25]. Lastly, this issue is concluded with an article by Professor Castaño and his group demonstrating once more the heterogeneity of NEN and underscoring the critical importance for all health care providers involved in the care of NEN patients to have an interest in and understanding of the pathogenesis of these rare, but not so uncommon tumor entities [26].

Compliance with ethical standards

Conflict of interest Prof. Christian Koch declares no direct conflict with this article. He has served on the Advisory Board of Novartis on the topic acromegaly and has participated in educational conferences on the topics neuroendocrine tumors and acromegaly sponsored by Novartis and Ipsen.

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