Neuroendocrine tumours of rare location

Guzy neuroendokrynne o rzadkiej lokalizacji

Alicja Hubalewska-Dydejczyk[1], Małgorzata Trofimiuk[1], Anna Sowa-Staszczak[1], Aleksandra Gilis-Januszewska[1], Ewelina Baczyńska[1], Piotr Szybiński[2], Ryszard Anielski[3], Maciej Matłok[4], Wiesław Bonicki[5], Jolanta Kunikowska[6]

[1]Chair and Department of Endocrinology, Jagiellonian University, Medical College, Kraków
[2]Gastrointestinal and General Surgery Department, Jagiellonian University, Medical College, Kraków
[3]Endocrine Surgery Department, Jagiellonian University, Medical College, Kraków
[4]Endoscopic Surgery Department, Jagiellonian University, Medical College, Kraków
[5]Department of Central Nervous System Neoplasms, Oncology Centre — Maria Skłodowska-Curie Institute, Warszawa
[6]Nuclear Medicine Department, Medical University of Warsaw, Warszawa

Abstract

Neuroendocrine tumours (NETs) arising from dispersed endocrine system may originate from almost every location, although they are most commonly found in the gastrointestinal tract and respiratory system. NETs are considered as particularly rare if they constitute less than 1% of all neuroendocrine tumours.
The aim of the paper is to present ten rare NETs from the database of the Endocrinology Department of the Jagiellonian University, Medical College: 4 NETs of the ampulla of Vater, 2 of the gallbladder, and 1 of the ovary, sphenoid sinus, Meckel's diverticulum, and epiglottis. The clinical presentation of such tumours and their management are discussed. **(Pol J Endocrinol 2010; 61 (3): 322–327)**

Key words: neuroendocrine tumours, uncommon location of NET, diagnosis, carcinoid

Streszczenie

Guzy neuroendokrynne (NET) wywodzące się z rozproszonego układu komórek endokrynnych mogą lokalizować się nieomal w każdym narządzie i tkance ludzkiego ciała, najczęściej jednak powstają w obrębie układu pokarmowego i oddechowego. Guzy neuroendokrynne uważane są za szczególnie rzadkie, jeżeli ich częstość występowania nie przekracza 1% wszystkich nowotworów neuroendokrynnych. Celem pracy było przedstawienie rzadkich NET z rejestru Katedry i Kliniki Endokrynologii Uniwersytetu Jagiellońskiego *Collegium Medicum*: 4 NET wywodzących się z brodawki Vatera, 2 z pęcherzyka żółciowego, 1 z jajnika, zatoki klinowej, uchyłka Meckela i nagłośni; oraz sposobu postępowania w takich przypadkach.
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Słowa kluczowe: guzy neuroendokrynne, rzadka lokalizacja NET, diagnostyka, rakowiak

Neuroendocrine tumours (NETs) arise from neuroendocrine cells (NECs). NECs are defined as cells 1) with the ability to produce neurotransmitters, neuromodulators, or neuropeptide hormones, 2) containing dense core secretory granules, 3) and lacking axons and synapses [1]. Since NECs form some of the classic endocrine glands, tumours of parathyroids, adrenal medulla, and medullary thyroid cancer are sometimes also classified as NETs. Most of NECs are, however, dispersed in the mucosa of gastric and respiratory tracts, forming one of the largest endocrine "organs" of the human body. NECs are found in all solid organs, skin, and mucous membranes; as a result, NETs can originate from almost every location [2] .

The incidence of NETs is as high as 5.25 cases per 100000 population per year [3], and is probably underestimated. Unsurprisingly, the most common location of NETs is the gastrointestinal tract (about 70% of cases), followed by the respiratory tract (about 25%), other locations being extremely rare. However, in some parts of the digestive tract or airways, NETs are a very unusual finding, either because of NECs density (gallbladder, biliary tract, oesophagus, larynx) or uncommon presentation of the organ (Meckel's diverticulum) [4–5].

✉ Małgorzata Trofimiuk M.D., Ph.D., Endocrinology Department, Jagiellonian University, Medical College, Kopernika St. 17, 31–501 Kraków, tel.: +48 12 424 75 00, fax: +48 12 424 73 99, e-mail: mtrofimiuk@gmail.com

The aim of the study is to present and discuss the clinical cases of NETs originating from unusual locations.

Results

In the NETs database of the Department of Endocrinology of the Jagiellonian University, Medical College, comprising 244 patients mostly from the south-eastern part of Poland, 10 tumours of unusual origin have been registered so far. They are: 4 NETs of Vater's ampulla, 2 NETs of the gallbladder, 1 NET of Meckel's diverticulum, 1 ovarian NET, 1 epiglottic NET, and 1 NET arising from the sphenoid sinus. A short description of a few chosen cases, confirmed histopathologically by positive chromogranin A and synaptophysin immunostaining, is given below.

Case 1 — epiglottic NET

A 54-year-old male, tobacco smoker, with hoarse voice, dyspnoe, swallowing problems, and enlarged neck lymph nodes, underwent a horizontal laryngeal dissection with bilateral neck dissection due to the suspicion of laryngeal cancer. The histopathological evaluation revealed a poorly differentiated intermediate cell neuroendocrine carcinoma with multiple mitotic figures of 3 cm in diameter with loco regional lymph node metastases (WHO/ENETS group 3). Subsequent irradiation of the postsurgical lodge and loco regional lymph nodes was performed. The post-therapeutic scintigraphy with [99mTc-EDDA/HYNIC] octreotate (SRS, somatostatin receptor scintigraphy) confirmed multiple nodal and bone metastases (Fig. 1A and B). One year later, the patient received one cycle of palliative peptide receptor radionuclide therapy (PRRT) with mixed ^{177}Lu/^{90}Y-DOTA-TATE. Due to progression of the disease with evolving superior caval vain syndrome, the further therapy was stopped and the patient died 1.5 years after initial diagnosis.

Case 2 — Meckel's diverticulum NET

A 16-year-old male underwent surgery due to acute appendicitis. In the muscular and serous layers of the apparently unchanged Meckel's diverticulum, which was also removed during the laparotomy, small lesions of well differentiated neuroendocrine tumour were found. The margins of resection were tumour-free and no angioinvasion was found (WHO/ENETS group 1B). Postsurgical abdominal and chest CT scans, bronchoscopy, digestive tract endoscopies, as well as repeated SRS revealed no abnormalities. Chromogranin A and urinary 5-OH-indole-acetic acid levels were within the normal range. The patient is being followed up in the Outpatient Clinic of the Endocrinology Department and 2 years and 2 months after surgery is disease-free.

Cases 3–4 — gallbladder NETs

A 46-year-old male with a history of acute pancreatitis was admitted to the Surgery Department because of acute abdominal symptoms. Gallbladder hydrops was suspected and the patient underwent surgery. On histopathological examination, a neuroendocrine carcinoma of 1 cm in diameter with focal infiltration of the adipose tissue was discovered (WHO/ENETS group 2). The patient received 6 cycles of chemotherapy with 5-FU. The SRS performed post therapy was negative. The patient was lost for further follow up after 8 months of observation.

A 47-year-old female with symptoms related to cholelithiasis was referred for cholecystectomy. On histopathological examination, a neuroendocrine tumour of the gallbladder neck with low mitotic index was discovered (WHO/ENETS group 1B). She was followed with serial abdominal CTs and SRS. Ten years after the surgery she is disease-free.

Case 5 — sphenoid sinus NET

A 51-year-old male with chronic headaches was diagnosed with a 4 cm pituitary mass. No other tumour-related signs and symptoms were present. On head MR the intra and extrasellar pituitary tumour was found involving the sphenoid sinus and ethmoidal sinuses. Lab tests confirmed hypogonadotropic hypogonadism. He was operated on twice by transsphenoidal approach. During the first procedure, a sphenoid sinus tumour was removed and diagnosed immunohistochemically as a well differentiated neuroendocrine tumour with low MIB index (WHO/ENETS group 1B). During second surgery, a silent corticotropinoma of the pituitary was sub-totally excised. Postsurgical SRS was negative, and CgA levels were within normal limits. The post-surgery pituitary function test results were normal. After surgery, the patient was diagnosed with benign, non-functioning left adrenal gland adenoma. The patient has been followed up for 1 year and 8 months.

Case 6 — ovary NET

A 68-year-old female with carcinoid syndrome symptoms (cachexia, stomach aches, diarrhoea, mild flushes) underwent the bilateral salpingoovariectomy because of the tumour. Histopathological examination revealed a neuroendocrine carcinoma probably arising from the ovary (WHO/ENETS group 2). SRS confirmed the neoplasm dissemination. The patient developed heart failure due to carcinoid heart valve disease. She was treated with cold somatostatin analogues, followed by one cycle of ^{90}Y-DOTA-TATE therapy. She died before completing the PRRT because of heart failure 6 months after initial diagnosis.

Figure 1. *SRS results of a patient with epiglottic NET (case 1): **A.** Chest SPECT; **B.** Whole body. Nodal and bone metastases marked with arrows*

Rycina 1. *Wyniki badania SRS (scyntygrafia receptorów somatostatynowych) u pacjenta z NET nagłośni (przypadek 1): **A.** SPECT klatki piersiowej. **B**. Całe ciało. Strzałki wskazują przerzuty do węzłów chłonnych i kości*

Cases 7–10 — ampulla of Vater NETs

A 48-year-old female presented with jaundice. On ERCP examination tumour of Vater's ampulla was found. Surgical excision of the duodenum, pancreatic head, and loco-regional lymph nodes was performed. Immuno-histochemical evaluation of the tumour specimens confirmed 0.7 cm diameter, poorly differentiated neuroen-docrine carcinoma with high proliferation index — Ki67

— 60%; the lymph nodes were negative for metastases (WHO/ENETS group 3). The patient is being followed up with imaging (SRS, abdominal and chest CT) and CgA. One year after surgery she is free from disease.

A 67-year-old male was admitted to the surgery department due to jaundice. On ultrasound examination, liver metastases were found. Pancreatoduodenectomy with pancreatogastrostomy followed by partial liver resection were performed. On histopathology, 1.5 cm poorly differentiated neuroendocrine carcinoma of the ampulla of Vater with high Ki-67 (20%) index was found (WHO/ENETS group 3). The tumour was positive for chromogranin A and cytokeratin, and negative for somatostatin and other specific hormones. The somatostatin receptors expression in tumour tissues was negligible. On SRS, only weakly increased radiopharmaceutical uptake was seen in the 6th liver segment, making PRRT inapplicable. The patient received two cycles of chemotherapy with: cisplatin, farmorubicin, 5-fluorouracil and leucovorin. The therapy was stopped because of disease progression. Serial abdominal CT imaging revealed progressive liver and nodal metastases. The patient has been observed for 3 years and 1 month from initial diagnosis.

A 62-year-old female was evaluated because of weight loss (8 kilos during 3 months). She denied other symptoms and was negative for hyperbilirubinaemia. A duodenal tumour was found on imaging and the patient was referred for pancreatoduodenectomy. Histopathological examination revealed well differentiated neuroendocrine carcinoma of the ampulla of Vater (Ki-67 — 2.4%), infiltrating the duodenal wall and ductus choledochus (WHO/ENETS group 2). The postsurgical SRS and abdominal CT were negative. Chromogranin A levels were within normal range. Two years after surgery the patient is disease-free.

A 42-year-old female underwent upper gastric tract endoscopy due to abdominal pain and jaundice. A 2 cm well differentiated neuroendocrine carcinoma of the ampulla of Vater positive for somatostatin was found and surgically removed (Ki-67 — 6%; WHO/ENETS group 2). The postsurgical course was complicated by fungal sepsis and intra-abdominal abscess. No local recurrence was noted on conventional imaging one year after the procedure. SRS performed two years after surgery revealed weak non-specific tracer uptake in the epigastric area. Chromogranin A was negative. Last abdominal CT revealed infiltration of the right peri-renal area — the patient was referred for surgical treatment 2.5 years after initial diagnostic procedures.

Discussion

Modlin et al. have defined NETs as rare if they constitute less than 1% of all neuroendocrine tumours [5]. So far,

about 110 cases of Vater's ampulla NETs, 150 cases of gallbladder NETs, 170 Meckel's diverticulum NETs, 280 cases of laryngeal NETs, 500 ovarian NETs, and only about 30 NETs of paranasal sinuses have been reported (the patient presented as Case 5 being the third description of a neuroendocrine tumour located in the sphenoid sinus, and probably the first of such NETs coexisting with pituitary adenoma) [5–11]. There are some known risk factors of NETs such as: smoking for laryngeal NETs and irradiation for sino-nasal tract NETs [12–14]. Twenty-five per cent of ampulla of Vater NETs are associated with von Recklinghausen disease [15], although none of the four patients in our group had been diagnosed with neurofibromas.

Given that even in cases of a typical carcinoid, diagnosis is usually delayed by 5–7 years due to non-characteristic symptoms, oligosymptomatic course of the disease, or an inadequate awareness among physicians [16], these very rare neoplasms are a real challenge for clinicians.

The NETs are usually diagnosed because of 1) symptoms related to the overproduction of hormones by the tumours, 2) complaints related to the presence of the pathological mass, or 3) as an incidental finding during imaging due to other diseases, in surgical specimens (*i.e.* carcinoid tumours of the appendix) or even during autopsy [17]. The hormone secretion-related syndromes seem to develop less frequently in patients with rare NETs. The ampulla of Vater NETs usually are manifested by symptoms of biliary obstruction, particularly jaundice and itching [18–21], but also as gastrointestinal bleeding [22]. They may be asymptomatic and found incidentally [23], even if the immunohistochemical staining for hormones is positive [24]. Symptoms (*i.e.* diarrhoea) related to the somatostatin oversecretion were also observed [25]. Gallbladder NETs are often found incidentally during cholecystectomy, usually preceded by symptoms mimicking cholecystitis or cholelithiasis, sometimes accompanied by jaundice [26––29], rarely they cause syndromes related to excessive hormones secretion, *i.e.* hyperinsulinaemic hypoglycaemia [30]. Patients with laryngeal NETs usually complain of dysphagia, throat pain, dyspnea, and hoarseness [5, 31], there are only a few reports of carcinoid syndrome associated with laryngeal tumours [13]. Clinical manifestations of sphenoid sinus neuroendocrine tumours include headaches, epistaxis, and cranial nerve palsies [32]. Most of the patients with ovary NETs present local symptoms (pain, acute abdomen, pressure with defecation); however, due to direct venous drainage of the ovaries to the inferior caval vein, up to 38.9% cases — depending on tumour histopathology — develop carcinoid syndrome, including carcinoid heart disease [6, 9, 33]. Constipation, seen in many patients with ovarian NETs, may be related to peptide YY production [5].

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Although NETs of rare origin are frequently non-functioning, expression of active peptides and amines are to be found on immunohistochemical staining of the tumour, for example serotonin and somatostatin in the ampulla of Vater NETs [15]. NETs may coexist, although infrequently, with other neoplasms; adenocarcinomas have been reported in patients with gallbladder andampulla of Vater NETs [34–35].

Because the diagnosis of rare NETs is usually made retrospectively, after obtaining the results of histopathological evaluation of primary tumour or metastases, the imaging is usually used for disease staging and further therapy planning. Somatostatin receptor nuclear imaging, using either SPECT or PET modalities, seems particularly effective in localizing the primary tumour and its metastases [36–37].

Surgery remains the best method of treatment for NETs, regardless their localization. For localized disease it provides the only possibility for complete remission [4–5]. However, metastases to the regional lymph nodes or distant metastases may be present at the time of surgery, *i.e.* they are found in about 10% of patients with gall bladder NETs, in up to 30% with ovarian NETs, and in up to 70% with laryngeal NETs [4, 13]. The effectiveness of adjuvant therapy with chemotherapy or radiotherapy in rare disseminated NETs has not been evaluated. For such patients, therapy with somatostatin analogues has been proposed [37–38], particularly for carcinoid heart disease [39]. A radionuclide therapy ([90]Yttrium or [177]Lutetium- labelled analogues, ^{131}I-MIBG) may also be considered as the palliative one [40].

The prognosis and long-term survival in rare NETs are related to the histopathological typing, the staging at the time of the diagnosis, and the type and completeness of the intervention. For localized and well differentiated tumours treated with complete surgical resection, 5-year survival approaches 90% for ovary NETs and 83% for Meckel's diverticulum NETs [4, 41]. For atypical carcinoids, the survival drops significantly: for example 50% of patients with atypical laryngeal carcinoid and only 5% with small cell cancers are alive after 5 years [12].

Conclusions

The NETs of rare location are usually diagnosed because of local symptoms or incidentally. They very rarely cause syndromes related to hormone overexpression. Surgical treatment, if applicable, provides the possibility for complete remission. The prognosis in rare NETs is related less to the primary lesion location than the tumour grading, local invasion, presence of metastases, and time of presentation.

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