ADAMIEC, Dominika Karolina, GONCIARZ, Marta Justyna, DĄBROWSKA, Anna, ZALIWSKA, Dominika, KIENANH DO , Monika, STROJNY, Agnieszka Aleksandra, PADUSZYŃSKA, Natalia, KRASZKIEWICZ, Adrianna, KAMIŃSKA, Monika Anna and CZACH, Magdalena. Pancreatic neuroendocrine tumors: classification, diagnosis and treatment – A review of the most frequent neuroendocrine tumors. Quality in Sport. 2024;19:53611. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.19.53611
https://apcz.umk.pl/QS/article/view/53611

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.07.2024. Revised: 06.08.2024. Accepted: 12.08.2024. Published: 17.08.2024.

Pancreatic neuroendocrine tumors: classification, diagnosis and treatment – A reviev of the most frequent neuroendocrine tumors

1. Dominika Karolina Adamiec [DKA], dominikaa.adamiec@gmail.com
Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland
https://orcid.org/0009-0008-5975-3927
2. Marta Justyna Gonciarz [MJG], marta.gonciarz1@gmail.com
Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland
https://orcid.org/0009-0006-7746-1237
3. Anna Dąbrowska [AD], annaalicjadabrowska06@gmail.com
Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland
https://orcid.org/0009-0003-2289-5909
4. Dominika Zaliwska [DZ], dzaliwska@gmail.com
University Clinical Hospital in Poznań, Przybyszewskiego 49, 60-355 Poznań, Poland
https://orcid.org/0009-0009-1423-7918
5. Monika Kienanh Do [MKD], mkienanh@gmail.com
Independent Public Complex of Health Care Facilities, Marshal Józef Piłsudski in Płońsk, Henryka Sienkiewicz 7, 09-100 Płońsk
https://orcid.org/0009-0000-3155-0513
6. Agnieszka Aleksandra Strojny [AAS], agnieszkastrojny@icloud.com
Saint Sophia Hospital, Żelazna 90, 01-004 Warsaw, Poland
https://orcid.org/0000-0003-0893-1881

7. Natalia Paduszyńska [NP], natalia_paduszynska@onet.eu
Dr Anna Gostynska Wolski Hospital, Independent Public Health Care Institution, Marcina Kasprzaka 17, 01-211 Warsaw, Poland
https://orcid.org/0000-0001-9953-662X
8. Adrianna Kraszkiewicz [AK], ada.kraszkiewicz@gmail.com
University Clinical Hospital in Poznań, Przybyszewskiego 49, 60-355 Poznań, Poland
https://orcid.org/0009-0008-4746-903X
9. Monika Anna Kamińska [MAK], monika.anna.kaminska1@gmail.com
Independent Public Clinical Hospital Witolda Orłowskiego, Czerniakowska 231, 00-416 Warsaw, Poland
https://orcid.org/0009-0004-3955-4710
10. Magdalena Czach [MC], magdalena.czach@op.pl
LUX MED Sp. z.o.o., Postępu 21C, 02-676 Warsaw, Poland
https://orcid.org/0009-0009-3786-5706

Corresponding author: Dominika Karolina Adamiec dominikaa.adamiec@gmail.com

ABSTRACT
Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originating from cells of the dispersed endocrine system. They vary in their degree of differentiation and malignancy. They are primarily located in the gastrointestinal tract, pancreas, and lungs. This article will present the most common pancreatic neuroendocrine tumors, their specific characteristics, diagnostic methods including imaging diagnostics, and treatment options. NETs account for approximately 0.5% of all malignant tumors. Pancreatic neuroendocrine tumors include insulinoma, gastrinoma, glucagonoma, vipoma, and somatostatinoma. They secrete hormones specific to each type, chromogranins, and pancreatic polypeptide. However, only some of these tumors have a secretory function. They are usually well-differentiated tumors. Neuroendocrine tumors are difficult to diagnose due to their specific nature. They are typically diagnosed at an advanced stage, except for insulinoma. The most commonly used imaging methods are CT, MRI, PET, and SPECT. Treatment is extremely challenging due to symptoms caused by excessive hormone secretion. Usually, the first step in treatment is to alleviate symptoms. The only curative option is the removal of the tumor and its metastases. Unfortunately, this option is not available for many patients due to the late detection of the disease. Currently, many methods are used to slow the progression of tumors, including peptide receptor radionuclide therapy, mTOR inhibitors (everolimus), sunitinib, and chemotherapy. Detection and treatment are extremely difficult due to the specific nature of this group of tumors.
Material and methods
To research information about neuroendocrine neoplasm, characteristic, ways of imaging and treatment we conducted an exhaustive literature review using PubMed and Google Scholar. Our search included specific key terms including: “neuroendocrine neoplasms”, “glucagonoma”, “insulinoma”, “vipoma”, “somatostatinoma” and “gastrinoma”.

KEY WORDS: neuroendocrine tumors, insulinoma, glucagonoma, gastrinoma, vipoma, somatostatinoma

Introduction

Neuroendocrine tumors (NET) are tumors that develop from cells of the dispersed endocrine system. Most of them are located in pancreas and gastrointestinal tract - GEP (gastro-entero-pancreatic (62-67%) and lungs (22-27%). These tumors can be hormonally active - secreting hormones or hormonally inactive (1, 6) Neuroendocrine tumors of the gastrointestinal tract and pancreas occur relatively rarely. Until recently, this heterogeneous group of tumors was considered a uniform disease entity, masking their diversity. The greatest achievement of recent decades has been the awareness of this diversity. NET account for approximately 0,5% of all malignant tumors with dominate the woman. Hormonally active tumors are less frequent, accounting for about one-third of GEP neuroendocrine tumors. These neuroendocrine neoplasms are characterized by specific clinical symptoms defined by unregulated hormonal production. The progenitor cells of NETs are cells of the diffuse endocrine system that can form certain endocrine glands (e.g., the adenohypophysis, parathyroids, adrenal medulla), groups (e.g., pancreatic islets), smaller clusters, or appear individually among other cells (especially within the gastrointestinal tract and CNS). (2) Their common feature is the expression of similar genes, which is related to their similar microscopic and immunohistochemical appearance. The term "neuroendocrine tumors" refers to a wide range of tumors with varying degrees of differentiation - from highly differentiated (G1 to G3) to poorly differentiated neuroendocrine carcinomas (NEC) with a high degree of malignancy. According to WHO (2010), all NENs are malignant, but they can differ in their degree of differentiation and malignancy. In recent decades, there has been an observed increase in the incidence of neuroendocrine tumors, which is a result of improved detection. In most cases, neuroendocrine tumors occur as independent tumors, but they can sometimes be associated with hereditary syndromes, such as multiple endocrine neoplasia (MEN I, II), Carney syndrome, von Hippel-Lindau syndrome, and neurofibromatosis. Unfortunately, NENs are often diagnosed with significant delay due to the variable degree of their secretory activity and very diverse localization. Increasingly, NENs must be considered in the differential diagnosis of many diseases. In Poland, the Endocrinology and Neuroendocrine Tumors Clinic of the Medical University of Silesia in Katowice and the National Institute of Oncology Department in Gliwice have been designated as ENETS

Centers of Excellence. The Endocrinology and Neuroendocrine Tumors Clinic in Katowice offers doctors from across the country the possibility of remote patient consultations via the TELENEN Tumor Board online platform.(8)
Depending on the degree of differentiation and histological maturity, determined based on the percentage of cells with the Ki-67 antigen and/or the mitotic index, the classification according to WHO 2017 is as follows(5):
1)Well- differentiated NENs:
a) NEN G1 – neuroendocrine tumors G1 (Ki-67 <3% or <2 mitoses per 10 high power fields (HPF))
b) NEN G2 – neuroendocrine tumors G2 (Ki-67 3–20% or 2–20 mitoses per 10 HPF)
c) NEN G3 – neuroendocrine tumors G3 (Ki-67 >20%(usually ≤55%)or >20 mitoses per 10 HPF); features of well-differentiated cells
2)Poorly differentiated NENs – neuroendocrine carcinomas (NEC; Ki-67 >20% (usually >55%) or >20 mitoses per 10 HPF):
a) Small cell carcinomas
b) Large cell carcinomas.

Both active (usually highly differentiated, G1 or G2) and inactive NENs can be highly differentiated, while poorly differentiated NENs lose their secretory function (their immunohistochemical markers are nonspecific – chromogranin A (CgA), in insulinoma – chromogranin B(CgB) is not routinely assessed, synaptophysin, or neuron-specific enolase [NSE]). (2) Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) – in the clinical presentation of an active tumor, symptoms typically predominate due to excess secretion of hormones (e.g., insulin, gastrin, glucagon, vip. somatostatin) or biogenic amines (e.g., serotonin - causing carcinoid syndrome), while the tumor size may be small, making it difficult to locate. Neuroendocrine features of clinically inactive tumors are often detectable only through immunohistochemical examination.(7,10) The most common gastrointestinal NETs typically occur around the 5th to 6th decade of life, often presenting asymptomatically and proving difficult to diagnose. They are usually incidentally detected during surgery for another reason if they cause nonspecific symptoms. Gastrointestinal NETs are divided into two categories: gastrointestinal carcinoid tumors and pancreatic NETs.(5)

In this reviev, we'll focus on the characteristics of pancreatic neuroendocrine tumors.

Pancreatic NETs originate from pancreatic islet cells: insulinoma, gastrinoma, glucagonoma, pancreatic polypeptide-secreting tumors, VIPoma and somatostatinoma. Insulinoma arises from pancreatic β-cells. It's the most common gastrointestinal NET responsible for excessive insulin secretion, leading to symptoms of hypoglycemia and hypokalemia. Gastrinoma is the second most common gastrointestinal NET. It's typically located in the pancreas and duodenum and predominantly occurs in older men. VIPoma is a type of NET that autonomously secretes vasoactive intestinal peptide (VIP), leading to Werner-Morrison syndrome or WDHA (watery diarrhea, hypokalemia, achlorhydria). Glucagonoma is an exceptionally rare pancreatic tumor that excessively produces glucagon. Glucagonoma syndrome is a paraneoplastic phenomenon characterized by the presence of the "4 Ds": diabetes, dermatitis (necrolytic migratory erythema), deep vein thrombosis, and depression. Somatostatinoma is the rarest pancreatic NET. They secrete somatostatin, which inhibits pancreatic, biliary, gastric, and intestinal secretions and gallbladder motility. Somatostatinoma syndrome is characterized by a triad of symptoms: cholelithiasis, hyperglycemia, and steatorrhea.(3,7) NETs of the gastrointestinal tract also include carcinoid tumors, which secrete serotonin. They mainly occur in the small intestine and the duodenum. However, this present study focuses on pancreatic tumors.

Diagnosis

Depending on the suspected type of NET, specific marker levels can be measured: for insulinoma (insulin/glucose, proinsulin, C-peptide), gastrinoma (gastrin, gastric pH), glucagonoma (glucagon), VIPoma (VIP), and somatostatinoma (somatostatin). Nonspecific markers of NETs include chromogranins A, B, C, which are produced in the secretory granules of NET cells. Chromogranin A measurement has found the most significance in practice, although some tumors, such as insulinoma, only secrete chromogranin B. Another marker is neuron-specific enolase and synaptophysin, which are present in the cytoplasm of NET cells.(2) The next step in diagnosis, depending on the suspected type of NET, may involve performing specific functional tests. Fasting test for suspected insulinoma. During fasting, blood glucose and insulin levels are measured. Approximately 30% of individuals with this tumor experience hypoglycemia after 12 hours, 67% after 24 hours, and 95% after 48 hours. It should be noted that after 48 hours of fasting, hypoglycemia (<45 mg/dl) may occur in healthy individuals, but insulin levels are very low or undetectable. In patients with insulinoma, insulin levels are inadequate for hypoglycemia and often remain within the

normal range. (3) C-peptide suppression test - exogenous insulin does not suppress C-peptide secretion in patients with insulinoma. Selective arterial stimulation with calcium gluconate to induce insulin and gastrin secretion, followed by sampling blood from the splenic vein and superior mesenteric vein. Secretin test - involves measuring gastrin at baseline, then administering secretin at 2 IU/kg body weight intravenously and measuring gastrin levels at 2, 5, 10, and 20 minutes. Samples are considered positive if gastrin levels exceed 95 pmol/l in any of the samples. To ensure the reliability of the test, proton pump inhibitor use should be discontinued for 3 weeks before the examination.

Imaging studies

In the diagnosis of NET, both anatomical and functional imaging methods are used. For non-functioning NENs, the basis of diagnosis is spiral multiphase CT or MRI. Hormonally active neuroendocrine tumors are diagnosed based on characteristic symptoms, followed by imaging studies. Tumors secreting hormones are usually very small, making them difficult to locate. Intraoperative ultrasound is performed to locate pancreatic tumors and liver metastases, while abdominal ultrasound is typically used for initial detection of liver metastases. EUS (endoscopic ultrasound) is also useful in patients suspected of having pancreatic NETs. EUS is widley applied in diagnosis of pancreatic neuroendocrine tumors located in head and corpus. CT is more often applied to recognise the metastates. Due to the presence of somatostatin receptors on the cell membranes of tumors, scintigraphy can be used to image small tumors.

Radioisotope diagnostics are conducted using somatostatin analogs labeled with 111In or technetium (99mTc). In both cases, the highest sensitivity is achieved by performing the examination using the SPECT technique. It allows to recognize the tumor and evaluate the extent of the tumor. Currently, PET-CT or SPECT-CT scans are the standard. Unfortunately, NEC is characterized by a lack of somatostatin receptors, so this imaging is useless for them. Neuroendocrine tumors often lose the ability to express somatostatin receptors, so SPECT imaging may not visualize them.(4) The highest utility in functional diagnostics is with PET (in stage G1 and G2) – using radiotracers with positron emitters 68Ga DotaTOC, 68Ga DOTANOC. In diagnosing rapidly growing and aggressive NEC (WHO grade 3), positron emission tomography with fluorodeoxyglucose is used. Other methods used include gastroscopy, colonoscopy, enteroscopy, and capsule endoscopy.

Treatment

The treatment of choice is the radical surgical removal of the tumor. If complete resection of the lesion is not possible, palliative procedures are performed to improve quality of life and reduce symptoms. The treatment of liver metastases includes methods such as surgical resection, selective chemoembolization, local ablative radiotherapy, radioembolization, cryosurgery, laser therapy, and orthotopic liver transplantation. Pharmacological treatment includes the use of somatostatin analogs, which are considered the gold standard for hormonally active tumors. These drugs bind to somatostatin receptors, showing the greatest affinity for subtype 2 and 5 receptors. Somatostatin analogs come in two forms: short-acting and long-acting. The short-acting – octreotide, can be administered subcutaneously or intravenously, which in practice is used to quickly control symptoms and in perioperative treatment. Long-acting preparations used chronically are octreotide and lanreotide. They are used in the treatment of glucagonoma and VIPoma but are not the first choice in the treatment of insulinoma and gastrinoma. Only 50% of insulinomas have SSTR2 receptors, while proton pump inhibitors are used in gastrinoma. Somatostatin analogs are also used in the treatment of progressive neuroendocrine tumors regardless of their secretory activity – their antiproliferative action is utilized here. Unfortunately, during long-term use of SST analogs, tachyphylaxis occurs, which is a significant decrease in response to the drug or even its absence. Another treatment method is the use of everolimus (mTOR inhibitor) and sunitinib (tyrosine kinase inhibitor). Both drugs have been registered in the European Union for the treatment of inoperable or metastatic well- and moderately-differentiated pancreatic NETs. For the treatment of advanced NETs in highly differentiated tumors after exhausting other treatment methods and as primary treatment in poorly differentiated tumors, chemotherapy is used. Multi-drug regimens are more effective than single-drug ones. Combinations of fluorouracil, doxorubicin, and streptozocin are used. In patients whose NETs show high expression of the SSTR2 receptor, treatment with radiolabeled isotopes (90Y, 177Lu) combined with somatostatin analogs is used. This method is applicable for patients with inoperable tumors and distant metastases who are in good overall condition.

Characteristic

Insulinoma

Insulinoma - an insulin-producing tumor originating from the pancreatic B cells. The majority, approximately 99%, are located in the pancreas. They are extremely rarely described in other locations such as the lungs, duodenum, small intestine, splenic hilum, and gastric inlet. Insulinoma accounts for approximately 25% of all pancreatic NEN (11). Incidence of this type of tumor is approximately 1-3 per million per year. Around 90% of cases present as solitary tumors (<2 cm), well-vascularized and encapsulated, located in the head, body, or tail of the pancreas (similar frequency)(9). Only 8-10% of tumors exhibit malignant behavior with local invasiveness and metastases to para-aortic lymph nodes and the liver. Insulinoma can also be part of MEN1 syndrome (multiple endocrine neoplasia) (11, 43), a genetic disorder associated with tumors of the pituitary, parathyroid, and enteropancreatic regions. In cases where insulinomas are associated with MEN1, a mutation in the MEN1 gene on chromosome 11q13 is typically observed.

The etiology of solitary insulinoma remains unclear. The most common symptom of insulinoma is hypoglycemia, occurring in approximately 73% of patients while fasting, and in about 20% of patients both fasting and postprandially. It often occurs after physical exertion or prolonged fasting and can also happen spontaneously without any triggers. Symptoms of hypoglycemia may resemble alcohol intoxication or mimic epileptic seizures (neuroglycopenia), accompanied by palpitations, tremors, and excessive sweating. Memory loss of hypoglycemic events is also common. The clinical symptoms of insulinoma are characterized by the Whipple triad: Occur during fasting, associated with a decrease in blood glucose levels, resolve upon administration of carbohydrates.(9, 43) The presence of hypoglycemic symptoms with fulfillment of the following criteria is diagnostic of insulinoma: blood glucose level 2.5 mmol/L or lower, insulin level 6 units/mL or higher, C-peptide level 0.2 nmol/L or higher, plasma proinsulin level 0.5 nmol/L or higher, plasma beta-hydroxybutyrate 2.7 mmol/L or lower, change in blood glucose of 0.25 g/L or higher at 30 min after 1 mg intravenous glucagon, and a negative sulphonylurea screen in the plasma and/or urine. (11,12) Non-invasive imaging methods for tumor visualization include abdominal ultrasound, including EUS (endoscopic ultrasound) (13), computed tomography (CT), and magnetic resonance imaging (MRI). However, the sensitivity of transabdominal ultrasound is low. MRI has an advantage over CT, but technical advancements have improved the quality of CT scans. A recent study showed that multi-detector CT can detect 94.4% of these tumors. CT is currently accepted as the first-line imaging modality for visualizing insulinomas. Like CT, MRI is safe, non-invasive, rapid, and facilitates the detection of

metastases. However, limitations in the use of MRI in detecting insulinomas include standard contraindications to MRI. (11) If the tumor is not visualized in the above-mentioned imaging studies, selective arterial angiography or arterial stimulation with calcium gluconate (ASVS), receptor scintigraphy, or PET using a somatostatin analogue can be performed. However, these methods detect only 46% of tumors, as not all tumors possess somatostatin receptors. The next step may involve performing scintigraphy using a labeled GLP-1 analogue. After identifying an insulinoma, the recommended treatment is surgical removal of the tumor. The choice of procedure will depend on tumor characteristics such as type, size, and location. Laparoscopic methods are preferred for benign, small-sized tumors located in the body or tail of the pancreas due to their less invasive nature compared to traditional surgery. (18) Patients recover faster and have shorter hospital stays. In cases with a very high risk of surgical intervention and high mortality associated with surgical treatment of these tumors, alcohol ablation and RFA (radiofrequency ablation) can be performed (14). These methods have been recognized as minimally invasive in the treatment of primary liver tumors and liver metastases. Radical pancreatic resection should be considered for patients with tumors that are not solitary, poorly encapsulated, > 4 cm in diameter, and affect or are located near the main pancreatic duct. The goal of treatment is complete removal of the tumor and any metastases. Within 3 years, approximately 60% of patients with G2 stage tumors experience recurrence. Attempts have been made to treat G2 stage tumors with somatostatin receptor radioisotopic analogues labeled with indium or lutetium. Clinical practitioners may attempt pharmacological treatment before surgery in cases of recurrent or malignant tumors. Initial steps may include dietary modification, diazoxide (the most effective drug for preventing hypoglycemic episodes), everolimus. Other strategies, including glucagon pens, somatostatin analogues, and steroids, are also considered. If the tumor is inoperable, the patient has metastases, or if they are a poor candidate for surgery, diazoxide is an option. However, taking it in large doses can lead to edema, kidney failure, and hirsutism. Approximately 60% of patients become symptom-free. The efficacy of octreotide in patients with resistant hypoglycemia is less predictable but remains an option for patients who do not respond to diazoxide (15, 16). For patients with resistant symptoms and stable tumor volume, adjusting the octreotide dose or performing surgical resection may be considered. (17) For patients with resistant symptoms and increasing tumor volume, oncological treatment is recommended with referral to specialized centers. Targeted therapy (everolimus or sunitinib) is recommended for patients with well-differentiated pancreatic neuroendocrine tumors.

Cytotoxic therapies such as 5-FU or temozolomide may be considered for patients with advanced pNET as palliative therapy. Some studies suggest neoadjuvant therapy, including peptide receptor radionuclide therapy (PRRT), in patients with inoperable or marginally resectable pNET due to survival benefits. PRRT may also control hypoglycemia in malignant insulinomas, but its role in insulinoma treatment still requires further research. (19,20, 21)

Gastrinoma

Gastrinoma is a tumor classified under NEN (neuroendocrine neoplasms), originating from cells that secrete gastrin. It is the second most common neuroendocrine tumor (after insulinoma). It is primarily located in the duodenum (70%), the head of the pancreas (25%), and rarely in other locations (5%), including the stomach, liver, ovary, and lungs.(22) Duodenal gastrinomas are usually less than 1 cm in length, are multiple, occur mainly in the first part of the duodenum, and constitute about 50-88% of sporadic ZES-related gastrinomas and 70-100% of MEN 1-related gastrinomas. (24,25)Pancreatic gastrinomas are larger than their duodenal counterparts, can occur in any part of the pancreas, and account for 25% of these tumors. They are commonly diagnosed between the ages of 20 and 50, slightly more often in men. Gastrinomas are slow-growing tumors, but about 60% of them are malignant and metastasize at the time of diagnosis. (23) Gastrinomas arise from G cells. They secrete gastrin, which causes excessive production of stomach acid, leading to severe peptic ulcer disease of the stomach and esophagus, known as Zollinger-Ellison syndrome (ZES). The terms gastrinoma and ZES are often used interchangeably, although gastrinoma refers to a gastrin-secreting NEN, while ZES refers to the clinical manifestations of the disease. The annual incidence is about 0.5-3/million. (23) Gastrinoma secretes excessive amounts of gastrin, a hormone that causes hyperplasia of the parietal cells in the gastric fundus and increases basal gastric acid secretion, which disrupts the protective mechanisms of the gastric and duodenal mucosa, causing ulcers in atypical locations, even in the jejunum, and peptic changes in the esophagus. Excess hydrochloric acid stimulates secretin secretion in the duodenum, causing diarrhea and dyspeptic symptoms. Additionally, the diarrhea mechanism includes inactivation of pancreatic enzymes due to excess hydrochloric acid, resulting in malabsorption of fats. High levels of gastrin can inhibit sodium and water absorption by the

intestinal epithelium, contributing to the secretory component of diarrhea. (24) These symptoms usually resolve with the use of proton pump inhibitors (PPIs), which significantly delay the correct diagnosis, often due to their widespread use. The most common clinical symptoms are abdominal pain, chronic diarrhea, heartburn, gastrointestinal bleeding, and weight loss. Endoscopic symptoms are also non-specific and may include erosions and ulcers, but in patients with ZES, multiple ulcers in atypical locations and enlarged gastric folds may occur in over 90% of patients with ZES, whereas gastric ulcers are rare. Patients with gastrinoma associated with MEN 1 are usually younger (32-35 years). Zollinger-Ellison syndrome symptoms precede hyperparathyroidism symptoms. Diagnosis of ZES requires confirmation of fasting hypergastrinemia with concurrent HCl hypersecretion or a gastric pH <2.0. Gastrin measurement requires discontinuation of PPIs for at least 10-14 days before the test. If PPIs cannot be discontinued, endoscopy, EUS, gastric juice pH measurement obtained during endoscopy, and somatostatin receptor imaging with SPECT/CT are proposed. Hypergastrinemia associated with gastrinoma is also indicated by elevated serum chromogranin A levels. Chromogranin A is a non-specific biomarker of neuroendocrine tumors in serum, correlating with tumor volume, providing prognostic information, and being useful in monitoring. Chromogranin A should be measured fasting, and physical exertion should be avoided before the test. (23) If fasting gastrin levels are elevated <10 times and gastric pH is ≤2, a secretin test is recommended. Before the test, atrophic gastritis should be ruled out, and a 24-hour pH-metry and basal acid output (BAO) should be performed. The test is conducted fasting; secretin is administered at 2 U/kg IV, and gastrin is measured at -15, -1, 2, 5, 10, 15, 20, and 30 minutes. Most authors consider a positive result with a serum gastrin concentration increase of > 110 pg/mL. (26) A second-line test is the calcium stimulation test, with food stimulation also used. Basal (BAO) and maximal (MAO) HCl secretion after pentagastrin stimulation are also measured, though rarely due to low availability.(27) Imaging diagnostics are similar to insulinoma, utilizing US, EUS, CT, MRI, and isotope methods, including gastrointestinal endoscopy. Multiphase CT, MRI, nuclear medicine imaging with somatostatin receptor scintigraphy using SPECT/CT, and PET-CT imaging with gallium and somatostatin analogs are non-invasive methods that can locate the tumor and assess metastasis spread. Enlarged peripancreatic lymph nodes or liver metastases suggest malignancy. CT is relatively insensitive to small liver lesions, where MRI is superior. Endoscopy with endoscopic ultrasound is useful for small tumors that might be missed, with the added advantage of fine-needle aspiration for histological purposes. Due to low proliferation activity,

FDG-PET is not useful. (23) Various intraoperative techniques are also used to determine lesion location, as preoperative imaging may be unsuccessful in about 30% of cases. Some tumors can only be localized during laparotomy through direct palpation by the surgeon or intraoperative ultrasound (IOUS), intraoperative transillumination, or duodenotomy. A physician can confirm the diagnosis based on elevated fasting serum gastrin levels associated with increased basal gastric acid secretion and/or low gastric pH. Normal fasting serum gastrin levels exclude ZES. Hypergastrinemia can also occur in patients on PPI, with hypercalcemia, atrophic gastritis, or gastric outlet obstruction, making gastric acid secretion analysis useful. In most patients with gastrinoma, gastrin levels are less than 10 times the upper limit of normal, necessitating confirmatory testing. Stimulation tests can differentiate gastrinoma from other causes, but access to secretin is limited. All patients with ZES should be evaluated for MEN 1 based on history (hypercalcemia, kidney stones, pituitary tumors), including family history and biochemical assessment, including serum ionized calcium, parathyroid hormone, and prolactin levels. Treatment aims to control symptoms and prevent peptic ulcer disease complications. The preferred treatment method is high-dose proton pump inhibitors (PPIs). PPIs are superior to H2 receptor blockers due to their greater potency and longer duration of action. The only effective treatment for gastrinoma and other NETs is surgery. Candidates for surgery are those without unresectable metastases. Conservative therapy is the current standard of care for most patients with MEN1-related ZES due to the multiplicity of tumors, extrapancreatic location, coexisting metastatic disease, and low likelihood of surgical cure. Metastases and their spread extent are the most important mortality determinants. Surgery aims to excise the primary tumor to potentially cure and reduce distant metastasis risk and improve survival. In non-metastatic pancreatic gastrinoma, surgical excision/enucleation is often effective. Duodenal gastrinomas are often multiple and may require duodenectomy but have a better prognosis than pancreatic gastrinoma. Regional lymph nodes should be systematically sampled. Annual monitoring includes fasting serum gastrin and chromogranin A levels, and imaging if needed post-resection. Conservative PPI treatment is recommended for non-surgical candidates or patients with extensive metastases. Current treatments for metastatic disease have limited efficacy. Chemotherapy is an option for extensive metastases, with first-line treatment being streptozotocin and 5-fluorouracil or doxorubicin. However, these treatments show limited responses and significant toxicity. Hormonal therapy with octreotide or lanreotide, human somatostatin analogs, reduces gastric acid secretion but has no anti-tumor effect. In pancreatic NETs, targeted therapies such as

anti-angiogenic strategies, multikinase or mTOR inhibition, which specifically inhibit growth factor receptors and related signaling pathways, offer promising new approaches with significant clinical benefits in several phase III clinical trials, delaying tumor progression, but await large-scale application and further clinical studies. Other treatments include hepatic artery embolization for liver metastases and human leukocyte interferon administration. Radiotherapy is generally not recommended. Patients undergoing complete tumor resection can expect over 90% survival at 5-10 years. Incomplete tumor removal has a 5-year survival rate of 43% and a 10-year survival chance of just 25%. (28)

Glucagonoma

Glucagonoma is a neuroendocrine tumor originating from the alpha cells of the pancreas that secrete glucagon. It is relatively rare, with an annual incidence of 0.01 to 0.1 new cases per 100,000 people. Glucagonomas are typically large tumors (over 3 cm) and are primarily located in the tail or body of the pancreas. Metastases are often present at the time of diagnosis, and symptoms typically appear in the fifth to sixth decade of life, occurring with similar frequency in both men and women. (30) Glucagonoma belongs to the group of neuroendocrine tumors and is derived from alpha cells of the pancreas that secrete glucagon. Most glucagonomas occur as solitary tumors. However, less than 10% of them are associated with multiple endocrine neoplasia type 1 (MEN1) syndrome. (29) The annual incidence is between 0.01 to 0.1 new cases per 100,000. They are usually large (over 3 cm) and are predominantly located in the tail or body of the pancreas due to the high prevalence of alpha cells in these areas. More than 50% of patients have metastases at the time of diagnosis. The incidence of glucagonoma is similar in men and women, and most patients with glucagonoma are in their fifth to sixth decade of life. Glucagon is a hormone composed of a 29 amino acid polypeptide. (30) It regulates blood glucose levels and is also involved in lipid metabolism. It acts in the liver, increasing glycogenolysis and gluconeogenesis through the stimulation of the cAMP pathway, leading to elevated plasma glucose levels. Glucagon secretion is inhibited by hyperglycemia, insulin, somatostatin, and GLP-1. It also causes relaxation of the smooth muscles of the stomach, duodenum, small intestine, and colon. Other actions of glucagon include stimulating lipolysis. The classic glucagonoma syndrome includes weight loss,

necrolytic migratory erythema (NME), diabetes, and mucosal abnormalities, such as stomatitis, cheilitis, and glossitis. Diabetes symptoms occur in about 70% of patients, weight loss in 60%. Glucagon is a catabolic hormone often associated with diarrhea (15%). Symptoms that may accompany glucagonoma also include painful glossitis, cheilitis, and angular stomatitis (41%), onychodystrophy in females, deep vein thrombosis, and pulmonary embolism, normochromic and normocytic anemia (50%), hypoaminoacidemia, and low zinc levels. Depression may affect about 50% of patients. (29) Another, though rare, autosomal recessive syndrome associated with hyperglucagonemia is glucagon cell hyperplasia and neoplasia (GCHN) of the pancreatic endocrine system (Mahvash syndrome). Diagnosis of glucagonoma includes measuring fasting glucagon levels, which are usually above 500 pg/ml (N<150 pg/ml). It is important to note that different glucagon assays may show variable cross-reactivity with different glucagon isoforms, not all of which are biologically active (about 70%). Measurements should be performed using the same assay. Additionally, serum amino acid and zinc levels should be measured, and a complete blood count should be performed to assess anemia. (30) Serum levels of parathyroid hormone, gastrin, insulin, pancreatic polypeptide, serotonin, vasoactive intestinal peptide (VIP), prolactin, and ACTH are important as glucagonoma may be associated with MEN1 syndrome. A skin biopsy of the NME lesion shows psoriasiform epidermal hyperplasia, pallor of keratinocytes, vacuolization or dyskeratosis of keratinocytes, upper epidermal necrosis, and perivascular inflammation. (30) Small blisters consist of acantholytic epidermal cells with lymphocytic and neutrophilic infiltrate. The dermis contains a perivascular lymphocytic infiltrate with intact epidermis. As with other neuroendocrine neoplasms (NENs), spiral multiphase computed tomography (CT) is performed to visualize the tumor's location. MRI is used if CT does not provide conclusive results. Compared to other NENs, glucagonoma is characterized by a high number of somatostatin receptors. Currently, positron emission tomography (PET)-CT with somatostatin analogs (SSA) labeled with 68 Ga (DOTATATE, DOTANOC, DOTATOC) has the highest sensitivity for detecting metastases of pancreatic neuroendocrine tumors G1-2 and some G3. To confirm the diagnosis and assess the stage, a biopsy is recommended. (30) Treatment, as in other NENs, primarily involves surgical removal of the tumor. This is the only option for a complete cure. Depending on the location and local invasion, enucleation, distal pancreatectomy with or without splenectomy, central pancreatectomy, pancreaticoduodenectomy, or total pancreatectomy can be performed. Postoperatively, glucagonoma syndrome symptoms typically resolve within a few weeks. For selected patients

with a limited number of liver metastases, extended surgical resection can be considered. One form of supportive treatment includes nutritional therapy, such as total parenteral nutrition, amino acid supplementation, and zinc supplementation. This helps to reverse the effects of malnutrition and the catabolic effects of weight loss. (32) Somatostatin analogs, such as octreotide and lanreotide, help reverse the effects of excess glucagon and inhibit glucagon secretion. Octreotide LAR and lanreotide have been reported to significantly extend the time to tumor progression. They also improve NME, diabetes, diarrhea, and neurological symptoms. (31, 33) Prophylactic anticoagulant therapy, such as heparin, to prevent deep vein thrombosis is mandatory for all patients in the perioperative period. For unresectable metastases, treatment focuses on tumor stabilization and symptom relief by reducing glucagon secretion. Guidelines from ENETS, NANETS, and ESMO describe the selection and sequencing of SSA, targeted therapy, peptide receptor radionuclide therapy (PRRT) with radioactively labeled SSA, and cytotoxic chemotherapy. (29) The most common site of metastasis is the liver. Hepatic resection is recommended for patients without extensive liver involvement, widespread extrahepatic metastases, and liver dysfunction. This approach leads to a reduction in glucagon levels and significant improvement in NME. (31) Another method is hepatic artery embolization with or without selective hepatic artery chemotherapy infusion, a palliative treatment used for patients with symptomatic liver metastases who are not candidates for resection. Radiofrequency ablation is also performed, usually for lesions smaller than 3 cm, and is less invasive than liver resection or hepatic artery embolization. For patients with large tumors and enlarging metastases, combination chemotherapy with streptozocin, 5-fluorouracil, or temozolomide is used, often in combination with a somatostatin analog. Systemic chemotherapy is limited to patients with advanced disease. (31) Molecularly targeted drugs, such as sunitinib, a tyrosine kinase inhibitor, and everolimus, an mTOR inhibitor, have been approved in the United States for the treatment of advanced, well-differentiated pancreatic neuroendocrine tumors, including glucagonoma. Peptide receptor radionuclide therapy z 177 LuDOTATATE (PRRT), also known as radioisotope therapy, is a novel method used to treat neuroendocrine tumors. The high expression of somatostatin receptors in glucagonoma presents an opportunity for PRRT use. (34,35)

Vipoma

A VIPoma is a tumor belonging to the NEN (neuroendocrine neoplasms) group that secretes vasoactive intestinal peptide (VIP). This hormone is a neurotransmitter found in the central

nervous system, intestinal neurons, lungs, adrenal glands, pancreas, liver, and neuroendocrine cells of the pancreas. It is mainly produced in the duodenum and delta-2 pancreatic islet cells. VIPomas primarily occur in the pancreas, producing high levels of VIP. (37) VIPomas are rare tumors, occurring with a frequency ranging from 0.05% to 2.0%, and can be found in both children and adults. The average age of patients is around 50 years.(37). They usually present as isolated tumors, but in about 5% of cases, they may be part of the MEN1 (multiple endocrine neoplasia type 1) syndrome. VIPoma is also known as Verner-Morrison syndrome, named after its discoverers Verner and Morrison, or WDHA syndrome, an acronym derived from its main symptoms (watery diarrhea, hypokalemia, and achlorhydria). The most common symptom is watery diarrhea (secretory), which persists despite 48 hours of fasting. Patients can excrete from 700 ml to up to 8 liters of stool daily in severe cases. The stools are usually odorless and tea-colored. Due to the nature of the diarrhea, electrolyte imbalances occur, such as hypokalemia, dehydration, and metabolic acidosis. Other symptoms include flushing (in 8-20% of patients), nausea, vomiting, muscle weakness, and cramps due to dehydration and hypokalemia. Seizures caused by hypomagnesemia have also been reported. Severe fluid and electrolyte loss can lead to cardiac arrhythmias, myopathy, tetany, and hypovolemic shock. (36,37) VIP has structural homology with secretin, glucagon, and GIP, which may be responsible for increased pancreatic enzyme secretion, inhibition of gastric acid secretion, and glycogenolysis. VIPoma is typically diagnosed in patients with significant diarrhea (> 3 liters/day). Measuring VIP levels in serum is challenging due to its short half-life, requiring multiple tests to avoid false negatives. Stool in patients suspected of VIPoma has a low osmotic gap, less than 50 mOsm/kg. Moderately elevated plasma VIP levels can also result from gastrointestinal ischemia, renal failure, or congestive heart failure. Electrolyte disturbances include hypokalemia, hypochlorhydria, hypomagnesemia, hyperglycemia, and hypercalcemia. Hypochlorhydria occurs secondary to the direct action of VIP inhibiting gastric acid secretion. Hypercalcemia can be caused by dehydration, incidental MEN1 syndrome, or tumor secretion of a calcitropic peptide. Hyperglycemia results from increased glycogenolytic activity of VIP. (36,37) As with other NEN cases, a spiral triphasic CT or MRI should be performed. Additionally, positron emission tomography (PET)-CT/MRI using somatostatin analogs labeled with 68 Ga (DOTATATE, DOTANOC, DOTATOC) is recommended to detect or exclude metastases, often useful in locating small metastases not visible in other tests. Endoscopic ultrasonography can evaluate invasiveness and allow biopsy of the tumor for histopathological assessment. The initial treatment phase for patients with

VIPoma involves correcting electrolyte imbalances and adequate hydration. Administering somatostatin analogs (SSA) can reduce secretory diarrhea and help restore fluid-electrolyte balance. In acute states, SSA like octreotide can be given subcutaneously or by continuous intravenous infusion. After initial stabilization, surgical resection of the lesion should be performed. Surgical resection is considered the only therapy for a tumor without metastases. The five-year overall survival rate after surgery for patients with localized VIPoma is >90%. Following complete tumor resection in patients eligible for surgical resection, symptoms of VIPoma syndrome completely resolved. In selected patients with a limited number of liver metastases, extended surgical resection, including the liver, can be considered if there is no diffuse involvement of both lobes, liver function deterioration, or extrahepatic metastases. Ablation and cryoablation using radiofrequency are also chosen as methods for treating small liver metastases less than 3 cm. Hepatic artery embolization is a palliative treatment method for patients with unresectable liver metastases. In patients with unresectable tumors, treatment focuses on stabilizing the tumor and controlling excessive VIP secretion and its associated symptoms. Unfortunately, in 60% of cases, metastases are detected at the time of VIPoma diagnosis. Metastases most commonly occur in the liver, lymph nodes, bones, and kidneys. Treatment involves the administration of somatostatin analogs (SSA). It is recommended to continue SSA use to control symptoms after introducing subsequent lines of treatment. Approximately 65-85% of patients experience a reduction in the frequency and volume of diarrhea when taking SSA. Systemic chemotherapy is a treatment method used for patients with large, bulky tumors or patients with extrahepatic metastases. Combination regimens with streptozocin or temozolomide have been attempted. The overall response to systemic chemotherapy is not encouraging. Streptozotocin (STZ) and 5-FU have been used in patients with well-differentiated and moderately differentiated pancreatic NEN for several decades. STZ and its combinations are described as beneficial in inhibiting oncological tumor growth and controlling hormonal symptoms. Other combinations of 5-FU with immunomodulatory drugs, such as interferon-alpha, have also been described as effective in both tumor growth and hormonal symptom control. However, interferon-alpha treatment is not recommended due to the frequency of side effects. The median survival and overall response to systemic chemotherapy are not encouraging. The antisecretory effect of chemotherapy is limited and often delayed. For patients who are not candidates for surgery and for whom other antisecretory drugs have not worked, chemotherapy may be an option. New drugs, such as sunitinib and everolimus, have been approved in the United States for the treatment of

advanced, well-differentiated pancreatic neuroendocrine tumors, including VIPoma. According to reports, they prolong progression-free survival. Peptide receptor radionuclide therapy (PRRT) is a newly introduced treatment method for patients with NEN. It is targeted therapy for somatostatin receptors 2 and 5, which are present on the surface of tumor cells. Treatment with 177 Lu-Dotatate has resulted in significantly longer progression-free survival and a significantly higher response rate compared to high-dose octreotide LAR in patients with metastatic neuroendocrine tumors of the small intestine. Due to the remarkable objective response rate, PRRT can reduce tumor burden and subsequently hormone-dependent clinical symptoms, ultimately making it a potentially valuable therapeutic option for patients with VIPoma. (39)

Somatostatinoma

A somatostatinoma is a tumor classified as a neuroendocrine neoplasm (NEN), originating from pancreatic cells but also from the duodenum, which secretes somatostatin. Somatostatin is a tetradecapeptide that inhibits almost all gut hormones, including insulin, glucagon, gastrin, secretin, and gastric inhibitory polypeptide (GIP). It also inhibits gastric acid and pancreatic enzyme secretion, affects gastrointestinal transit time, intestinal motility, and the absorption of nutrients from the small intestine. Pancreatic δ cells exert a paracrine effect on β and α cells, particularly to regulate glucose levels. In the nervous system, somatostatin acts as a neurotransmitter or neuromodulator. Somatostatin receptors are widely distributed in the brain, and their activation is associated with the regulation of food and water intake. Recently, they have been linked to the pathogenesis of obesity. Given that obesity is an increasingly prevalent civilization disease, innovative approaches to its treatment are being developed, including anti-obesity injections containing hormone analogs, such as somatostatin or ghrelin. (39, 40, 41, 42) Somatostatinoma is a relatively rare tumor, with an incidence of 1 in 40 million people, constituting less than 5% of pancreatic NENs. It is most commonly located in the head of the pancreas, less frequently in the body and tail, and sporadically in the duodenum, ampulla of Vater, and small intestine. It can also be part of MEN1 syndrome, neurofibromatosis type 1 (NF1), and von Hippel-Lindau syndrome. It usually occurs between the ages of 40 and 60. Somatostatinoma is a tumor that secretes somatostatin. Fasting serum somatostatin levels are three times above normal (>60 pg/ml). Non-secreting tumors do not exhibit typical somatostatinoma syndrome symptoms and are most commonly located in the ampulla of Vater and the duodenum. The symptoms of these tumors usually result from the

mass effect (biliary obstruction, gastrointestinal bleeding). Secreting tumors cause somatostatinoma syndrome, which includes diabetes, diarrhea, and gallstones. Less commonly, other symptoms such as hypochlorhydria/achlorhydria, dyspepsia, and weight loss are observed. These symptoms are caused by the inhibitory action of somatostatin on other pancreatic hormones, including insulin, or by inhibiting gastric acid secretion and cholecystokinin. (39, 40, 41, 42) Somatostatinoma symptoms are often subtle and appear late, so they are usually detected incidentally during imaging studies such as computed tomography (CT) or MRI performed for other non-specific gastrointestinal complaints. The imaging diagnostics are the same as for other pancreatic NENs and include triphasic CT, MRI, endoscopic ultrasound (EUS) with biopsy, and PET-CT with 68Ga, which is the preferred study for detecting metastases. Due to their nature, somatostatinomas are usually detected late, often at the stage of metastasis, most commonly to regional lymph nodes and the liver. The treatment of somatostatinoma is also similar to other pancreatic NENs, encompassing the management of excessive somatostatin production, surgical and/or radiological interventions, and, if necessary, cytotoxic treatment. The only option for a complete cure is the radical removal of the tumor and any potential liver metastases (partial resection, mild embolization, radioembolization, radiofrequency ablation (RFU), microwaves, cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy, irreversible electroporation (IRE), laser-induced thermotherapy, transcatheter arterial chemoembolization (TACE), selective internal radiation therapy (SIRT)), depending on local availability. For unresectable metastases, treatment focuses on tumor stabilization and symptom relief by reducing somatostatin secretion. Somatostatin analogs are typically used to alleviate clinical symptoms, especially diarrhea and weight loss in patients with somatostatinoma. Somatostatin analogs are the first-line palliative treatment to control somatostatin secretion and tumor growth. Another therapeutic option for patients with widespread disease is peptide receptor radionuclide therapy (PRRT). PRRT with 177 Lu-DOTATATE has been approved for treating grade 1-2 pancreatic NETs. The side effects of this treatment result from subacute toxicity, mainly including nausea, vomiting, and reduced hematological parameters. Hematological parameters normalize in 70% of patients with toxicity, but 1% of patients treated with PRRT develop acute leukemia, and 2% develop myelodysplastic syndrome. Another drug used in treatment is everolimus (an mTOR inhibitor). It may exacerbate diabetes by reducing insulin secretion from the pancreas and causing insulin resistance; its impact on the treatment of patients with somatostatinoma is still unclear. Sunitinib is currently one of the remaining treatment options

for grade 1-2 pancreatic NETs that progress during treatment with first-generation long-acting somatostatin analogs. However, data on its use in patients with somatostatinoma are minimal. Chemotherapy is also effective in treating pancreatic NENs, but no detailed data on somatostatinoma are available.(39, 40, 41, 42)

Conclusion

Neuroendocrine noeplams (NEN) are rare tumors. They localised the most often in pacnreas nad gastrointestinal tract. The sypmtpoms are nonspecyfic which means delayed deteced. The symptoms are often nonspecific, which frequently leads to delayed diagnosis. To locate the tumor and its metastases, various techniques are employed, including ultrasound (US), endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI), SPECT-CT, and PET-CT. The only method of cure is the complete surgical removal of the tumor. With the development of new techniques, it is also possible to remove liver metastases, thereby extending patients' survival. In advanced and metastatic stages, the prognosis is significantly more serious. Due to the nature of the tumor and the fact that poorly differentiated tumors lose somatostatin receptors, treatment options are highly limited. Research is ongoing with the use of everolimus, sunitinib, PRRT (Peptide Receptor Radionuclide Therapy), and chemotherapy. In my opinion, the key lies in introducing new therapies for the treatment of neuroendocrine neoplasms (NENs), because even advancements in diagnostics and imaging methods may not yield the expected results in improving early detection due to their nonspecific symptoms or even absence of symptoms (if they do not secrete hormones) and often challenging locations.

Disclosure

Author`s Contribution Statement

Conceptualization, Dominika Karolina Adamiec and Marta Justyna Gonciarz; Methodology, Anna Dąbrowska; Software, Agnieszka Aleksandra Strojny and Adrianna Karaszkiewicz; Check, Dominika Zaliwska and Monika Kienanh Do; Formal analysys, Anna Dąbrowska and Adrianna Karaszkiewicz; Investigation, Magdalena Czach and Dominika Zaliwska; Resources, Monika Anna Kamińska and Monika Kienanh Do and Monika Anna Kamińska; Data curation, Natalia Paduszyńska; Writing rough preparation, Magdalena Czach and Monika Anna Kamińska; Writing review and editing, Dominika Karolina Adamiec and Marta

Justyna Gonciarz; Visualization, Natalia Paduszyńska and Agnieszka Aleksandra Strojny; Supervision, Dominika Karolina Adamiec; Project administration, Marta Justyna Gonciarz;

All authors have read and agreed with the published version of the manuscript.

Conflict of interest statement: The authors report no conflict of interest.

Founding statement: The study did not receive any funding.

Institutional Review Board Statement: Not applicable.

Data availability Statement: Not applicable.

References

1) Inzani F, Rindi G. Introduction to neuroendocrine neoplasms of the digestive system: definition and classification. Pathologica. 2021;113(1):1-4. doi:10.32074/1591-951X-227

2) Lila AR, Memon SS. Neuroendocrine neoplasm: Current understanding. J Postgrad Med. 2023;69(2):65-67. doi:10.4103/jpgm.jpgm_51_23

3) Hofland J, Falconi M, Christ E, et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. J Neuroendocrinol. 2023;35(8):e13318. doi:10.1111/jne.13318

4) Ichikawa Y, Kobayashi N, Takano S, Kato I, Endo K, Inoue T. Neuroendocrine tumor theranostics. Cancer Sci. 2022;113(6):1930-1938. doi:10.1111/cas.15327

5) Cives M, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors. CA Cancer J Clin. 2018;68(6):471-487. doi:10.3322/caac.21493

6) Taal BG, Visser O. Epidemiology of neuroendocrine tumours. Neuroendocrinology. 2004;80 Suppl 1:3-7. doi:10.1159/000080731

7) Fang JM, Li J, Shi J. An update on the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. World J Gastroenterol. 2022;28(10):1009-1023. doi:10.3748/wjg.v28.i10.1009

8) Kunikowska J, Zemczak A, Górska M, et al. TeleNEN as a telemedicine model for neuroendocrine neoplasm management in case of Meckel's diverticulum NET. Endokrynol Pol. 2018;69(3):313-317. doi:10.5603/EP.2018.0033

9) Okabayashi T, Shima Y, Sumiyoshi T, et al. Diagnosis and management of insulinoma. World J Gastroenterol. 2013;19(6):829-837. doi:10.3748/wjg.v19.i6.829

10) Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. Dig Dis Sci. 1991;36(7):933-942. doi:10.1007/BF01297144

11) Abboud B, Boujaoude J. Occult sporadic insulinoma: localization and surgical strategy. World J Gastroenterol. 2008;14(5):657-665. doi:10.3748/wjg.14.657

12) de Herder WW. Biochemistry of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab. 2007;21(1):33-41. doi:10.1016/j.beem.2006.12.002

13) Sotoudehmanesh R, Hedayat A, Shirazian N, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine. 2007;31(3):238-241. doi:10.1007/s12020-007-0045-4

14) Rott G, Biggemann M, Pfohl M. Embolization of an insulinoma of the pancreas with trisacryl gelatin microspheres as definitive treatment. Cardiovasc Intervent Radiol. 2008;31(3):659-662. doi:10.1007/s00270-007-9185-4

15) Kishikawa H, Okada Y, Hirose A, Tanikawa T, Kanda K, Tanaka Y. Successful treatment of insulinoma by a single daily dose of octreotide in two elderly female patients. Endocr J. 2006;53(1):79-85. doi:10.1507/endocrj.53.79

16) Katabami T, Kato H, Shirai N, Naito S, Saito N. Successful long-term treatment with once-daily injection of low-dose octreotide in an aged patient with insulinoma. Endocr J. 2005;52(5):629-634. doi:10.1507/endocrj.52.629

17) Falconi M, Bettini R, Boninsegna L, Crippa S, Butturini G, Pederzoli P. Surgical strategy in the treatment of pancreatic neuroendocrine tumors. JOP. 2006;7(1):150-156. Published 2006 Jan 11.

18) Giannis D, Moris D, Karachaliou GS, et al. Insulinomas: from diagnosis to treatment. A review of the literature. J BUON. 2020;25(3):1302-1314.

19) Walker MP, Shenoy V, Metz DC, et al. Case presentation of 8-year follow up of recurrent malignant duodenal Insulinoma and lymph node metastases and literature review of malignant

Insulinoma management. BMC Endocr Disord. 2022;22(1):310. Published 2022 Dec 9. doi:10.1186/s12902-022-01219-9

20) Davi MV, Pia A, Guarnotta V, et al. The treatment of hyperinsulinemic hypoglycaemia in adults: an update. J Endocrinol Invest. 2017;40(1):9-20. doi:10.1007/s40618-016-0536-3

21) Sorbye H, Kong G, Grozinsky-Glasberg S. PRRT in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3). Endocr Relat Cancer. 2020;27(3):R67-R77. doi:10.1530/ERC-19-0400

22) Rossi RE, Elvevi A, Citterio D, et al. Gastrinoma and Zollinger Ellison syndrome: A roadmap for the management between new and old therapies. World J Gastroenterol. 2021;27(35):5890-5907. doi:10.3748/wjg.v27.i35.5890

23) Jensen RT, Ito T. Gastrinoma. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; September 27, 2023.

24) Norton JA, Foster DS, Ito T, Jensen RT. Gastrinomas: Medical or Surgical Treatment. Endocrinol Metab Clin North Am. 2018;47(3):577-601. doi:10.1016/j.ecl.2018.04.009

25) Pieterman CRC, van Leeuwaarde RS, van den Broek MFM, van Nesselrooij BPM, Valk GD. Multiple Endocrine Neoplasia Type 1. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; December 22, 2021.

26) Metz DC, Buchanan M, Purich E, Fein S. A randomized controlled crossover study comparing synthetic porcine and human secretins with biologically derived porcine secretin to diagnose Zollinger-Ellison Syndrome. Aliment Pharmacol Ther. 2001;15(5):669-676. doi:10.1046/j.1365-2036.2001.00976.x

27) Metz DC, Cadiot G, Poitras P, Ito T, Jensen RT. Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. Int J Endocr Oncol. 2017;4(4):167-185. doi:10.2217/ije-2017-0018

28)Cingam SR, Botejue M, Hoilat GJ, Karanchi H. Gastrinoma. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 28, 2023.

29) de Herder WW, Hofland J. Glucagon & Glucagonoma Syndrome. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; April 7, 2023.

30) Sandhu S, Jialal I. Glucagonoma Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 4, 2023.

31) Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: advances. Best Pract Res Clin Gastroenterol. 2012;26(6):737-753. doi:10.1016/j.bpg.2012.12.00

32)Jin XF, Spampatti MP, Spitzweg C, Auernhammer CJ. Supportive therapy in gastroenteropancreatic neuroendocrine tumors: Often forgotten but important. Rev Endocr Metab Disord. 2018;19(2):145-158. doi:10.1007/s11154-018-9443-6

33) Grozinsky-Glasberg S, Shimon I, Korbonits M, Grossman AB. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer. 2008;15(3):701-720. doi:10.1677/ERC-07-0288

34) Makis W, McCann K, Riauka TA, McEwan AJ. Glucagonoma Pancreatic Neuroendocrine Tumor Treated With 177Lu DOTATATE Induction and Maintenance Peptide Receptor Radionuclide Therapy. Clin Nucl Med. 2015;40(11):877-879. doi:10.1097/RLU.0000000000000891

35) Hofland J, Brabander T, Verburg FA, Feelders RA, de Herder WW. Peptide Receptor Radionuclide Therapy. J Clin Endocrinol Metab. 2022;107(12):3199-3208. doi:10.1210/clinem/dgac574

36) Sandhu S, Jialal I. ViPoma. In: StatPearls. Treasure Island (FL): StatPearls Publishing; June 12, 2023.

37) de Herder WW, Hofland J. Vasoactive Intestinal Peptide-Secreting Tumor (VIPoma). In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; April 5, 2023.

38) Azizian A, König A, Ghadimi M. Treatment options of metastatic and nonmetastatic VIPoma: a review. Langenbecks Arch Surg. 2022;407(7):2629-2636. doi:10.1007/s00423-022-02620-7

39) de Herder WW, Hofland J. Somatostatinoma. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; April 12, 2023.

40) Elangovan A, Mathias PM, Zulfiqar H. Somatostatinoma. In: StatPearls. Treasure Island (FL): StatPearls Publishing; June 25, 2023.

41) Zakaria A, Hammad N, Vakhariya C, Raphael M. Somatostatinoma Presented as Double-Duct Sign. Case Rep Gastrointest Med. 2019;2019:9506405. Published 2019 May 9. doi:10.1155/2019/9506405

42) Popoviciu MS, Paduraru L, Nutas RM, et al. Diabetes Mellitus Secondary to Endocrine Diseases: An Update of Diagnostic and Treatment Particularities. Int J Mol Sci. 2023;24(16):12676. Published 2023 Aug 11. doi:10.3390/ijms241612676

43)Sapuła, K., Remjasz, K., Siedlecki, W., Fabiś, M., Kuchnicka, J., Aleksandrowicz, J., & Zielińska, M. (2022). Insulinoma - review of characteristics, diagnosis and treatment. Journal of Education, Health and Sport, 12(9), 446–453. doi.org/10.12775/JEHS.2022.12.09.051