

DIAGNOSIS AND MANAGEMENT OF A PANCREATIC NEUROENDOCRINE TUMOR: A CLINICAL CASE REPORT

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Summary

Pancreatic neuroendocrine tumors (PNETs) are rare cancers of pancreatic islet cells, comprising 1–2% of pancreatic neoplasms with a rising incidence. Their presentation depends on tumor growth hormone secretion; most are nonfunctioning, while functioning tumors produce hormones such as insulin. Treatment remains challenging and the role of immunotherapy in well-differentiated PNETs is not yet established.

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms arising from pancreatic islet cells, accounting for 1–2% of pancreatic cancers, with an incidence of ≤ 1 per 100,000 per year that is steadily increasing. Their clinical presentation varies based on tumor growth and hormone secretion. PNETs are classified as functioning or nonfunctioning; most (60–90%) are nonfunctioning and asymptomatic, while functioning tumors secrete hormones such as insulin, gastrin or glucagon [1,2]. Management remains challenging and although immunotherapy has shown promise in other cancers, its effectiveness in well-differentiated PNETs is still unclear [3].

This case report evaluates treatment efficacy in a 52-year-old patient with insulinoma.

Research objects and methods

A clinical case study was performed. The subject is a patient of the Gastroenterology Clinic of the Kaunas Clinics Hospital of the Lithuanian University of Health Sciences who was diagnosed with insulinoma. Data were collected from the medical history.

Clinical case

A 52-year-old male patient presented to the Emergency

Department with abdominal pain, weakness and dizziness. On January 14, 2014, a computed tomography (CT) scan of the abdomen and pelvis revealed a mass in the tail of the pancreas with multiple liver lesions consistent with metastasis. A liver biopsy was performed at LSMU Kaunas Clinics on January 9, 2014 and was confirmed histologically on January 13, 2014. It demonstrated metastatic PNET.

The diagnosis was established as PNET, cT4N0M1, stage IV, with multiple liver metastases. Histology showed a well-differentiated PNET, Ki-67 up to 4%, consistent with G2 NET, synaptophysin-positive and chromogranin A-negative.

Magnetic resonance imaging (MRI) of the liver and pancreas was performed on January 21, 2014 and it demonstrated extensive metastatic involvement of all liver lobes with hepatomegaly and a cystic lesion in the pancreatic tail consistent with the primary tumor. The largest liver lesion (segment 7/8) measured 10×9.4 cm and the pancreatic tail lesion measured 4 cm. Positron emission tomography with a computed tomography (PET-CT) scan showed no extrahepatic spread. The case was discussed in a multidisciplinary team (MDT) meeting on January 30, 2014, where surgical treatment was deemed not feasible and palliative systemic therapy was recommended.

The patient received 8 cycles of temozolomide and capecitabine (CAPTEM). MRI in April 2014 showed a response after 3 cycles, with further response noted in July 2014 after 6 cycles. Chemotherapy was discontinued in October 2014 due to rising chromogranin A levels and elevated total bilirubin ($56 \mu\text{mol/L}$). MRI in November 2014 showed further minor response and the pancreatic primary lesion was no longer visible, indicating a positive treatment response. Positive disease dynamics were observed during follow-up in 2015–2016.

In December 2017 MRI of the liver demonstrated disease progression with increasing liver metastases. Restart of the systemic therapy (sunitinib or everolimus) or initiation of somatostatin analogue therapy (lanreotide) was recom-

mended. In February 2018, due to disease progression and the patient's refusal of chemotherapy because of its side effects, treatment with lanreotide 120 mg every 4 weeks was initiated.

In September 2018, updated MRI and blood tests showed worsening liver function tests (AST 53 U/L, ALT 79 U/L, ALP 276 U/L, GGT 314 U/L). Imaging demonstrated progression of liver metastases, although the disease was described as relatively stable. Initiation of everolimus was recommended by a medical oncologist at The Christie Private Care, Manchester.

MRI performed at LSMU Kaunas Clinics on August 30, 2018, showed >20% growth of liver metastases according to RECIST 1.1, with chromogranin A level of 200. A liver metastasis biopsy was recommended, along with repeat chromogranin A and neuron-specific enolase testing after changing somatostatin analogues. Treatment was switched from lanreotide to octreotide 30 mg every 4 weeks. MRI on October 19, 2018, showed stable pancreatic disease; however, chromogranin A levels continued to rise (up to 267.42 µg/L).

On November 30, 2018, disease progression was confirmed during treatment with somatostatin analogues and MDT decided to start treatment with everolimus 10 mg daily. Peptide receptor radionuclide therapy (PRRT) was also recommended.

The patient underwent 4 cycles PRRT with lutetium-177 in Uppsala University Hospital, Sweden. He was also treated with interferon, without clinical benefit. Due to further disease progression, additional PRRT cycles were administered in 2023 (March 5, May 26, August 14 and October 24) in Uppsala, Sweden, resulting in clinical improvement.

Despite treatment, the patient continued to experience weakness during hypoglycemic episodes, although hypoglycemia became less frequent. Follow-up CT scans showed negative dynamics: enlargement of existing liver lesions, development of new lesions, free fluid in the parahepatic and pelvic regions, and increased density of mesenteric fat, raising suspicion of carcinomatosis. Everolimus was continued, with dose adjustment to 5 mg daily for hypoglycemia control.

On July 8, 2024, the patient presented to LSMU Kaunas Clinics with severe, nearly continuous hypoglycemia and was hospitalized in the endocrinology department due to suspected PNET progression. In October 2024, he represented with increasing abdominal girth and persistent hypoglycemia. Due to the need for repeated paracenteses, he was admitted to the gastroenterology department, where ascites and pleural effusion were diagnosed.

Multiple therapeutic procedures were performed, including paracentesis, drainage and treatment with antibiotics,

albumin, diuretics and supportive care. Despite these measures, the patient's condition progressively worsened, with increasing fluid accumulation, development of spontaneous bacterial peritonitis, profound weakness, edema, hypotension and hypoalbuminemia.

Ultimately, despite intensive medical management, the patient's condition continued to deteriorate and clinical death was pronounced on October 25, 2024.

Discussion

Pancreatic neuroendocrine carcinomas are extremely rare, representing about 2–3% of all pancreatic neuroendocrine neoplasms, but they are highly aggressive, with most patients developing metastatic disease [4]. These tumors occur across a wide age range, most commonly between the third and sixth decades of life, with a mean age at diagnosis of 50–56 years and equal incidence in men and women. Risk factors such as age, smoking, diabetes and obesity may contribute to their development. Insulinomas are characterized by inappropriate insulin secretion causing hypoglycemia and are classically identified by Whipple's triad: hypoglycemic symptoms, low blood glucose and symptom relief after glucose administration [5–7].

Diagnosis of neuroendocrine tumors is challenging and relies on both imaging and laboratory tests. Contrast-enhanced CT scan is the most common initial imaging modality, typically showing hypervascular, round, solid pancreatic lesions, though about 10% appear cystic with peripheral enhancement. CT scan has a sensitivity of 63–82% and specificity of 83–100% for tumors larger than 2 cm. MRI is usually a second-line option, offering higher sensitivity and better detection of small tumors and liver metastases, but with lower specificity [8].

Laboratory evaluation of PNETs includes general biomarkers and hormone assays for functional tumors. Chromogranin A, a common neuroendocrine marker, is elevated in 50–100% of patients and correlates with tumor burden and metastasis, but its low specificity and sensitivity limits its use for treatment monitoring [9]. Definitive classification requires tissue biopsy to assess tumor morphology and proliferation markers such as Ki-67 and mitotic index. Most PNETs (80–100%), except insulinomas (50–70%), express somatostatin receptors, enabling functional imaging with indium-111 somatostatin receptor scintigraphy or gallium-68 PET-CT scan using radiolabeled somatostatin analogs [9,10].

Management of PNETs requires a multidisciplinary approach, including surgery, somatostatin analogs, targeted therapies, chemotherapy and radionuclide therapy. Surgery remains the cornerstone of treatment and can be curative in localized disease, while selected patients with metastatic,

well-differentiated tumors may benefit from surgical debulking for symptom control and survival. Tumors larger than 2 cm and all functional PNETs should be resected. For hepatic metastases, options include ablation, hepatic artery embolization or liver transplantation in carefully selected patients [11].

For metastatic disease, long-acting somatostatin analogs are first-line therapy due to their antiproliferative effects and favorable safety profile. Targeted agents such as sunitinib and everolimus are commonly used as second-line treatments. The CAPTEM regimen has emerged as an effective and well-tolerated chemotherapy option. Additionally, PRRT has shown significant improvement in progression-free survival in metastatic NETs [11,12].

Conclusions

1. This case highlights the complex and prolonged clinical course of a well-differentiated, metastatic pancreatic neuroendocrine tumor with insulin secretion. Despite the indolent histology (G2, Ki-67 $\leq 4\%$), the disease demonstrated progressive behavior over time, requiring multiple lines of systemic therapy.

2. A multidisciplinary approach, including chemotherapy, somatostatin analogs, targeted therapy and PRRT, achieved periods of disease control and symptom relief. However, long-term progression with treatment resistance ultimately led to severe complications and poor outcome.

3. This case underscores the challenges in managing advanced PNETs and the need for individualized, multimodal treatment strategies and close long-term monitoring.

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KASOS NEUROENDOKRININIS NAVIKAS. KLINIKINIS ATVEJIS

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Raktažodžiai: kasos neuroendokrininiai navikai, insulinoma. Santrauka

Kasos neuroendokrininiai navikai (KNN) yra retai pasitaikantys, kilę iš kasos salelių ląstelių ir sudarantys 1–2 % visų kasos navikų, o jų sergamumo rodikliai nuolat didėja. Klinikinė ligos eiga priklauso nuo naviko diferenciacijos, augimo pobūdžio ir hormonų sekrecijos: dauguma navikų yra nefunkcionuojantys, tačiau funkcionuojantys navikai gali išskirti hormonus, tokius kaip insulinas. Gydymas išlieka sudėtingas, o imunoterapijos vaidmuo gydant gerai diferencijuotus KNN dar nėra aiškiai nustatytas. Šiame straipsnyje pristatomas 52 metų paciento, sergančio insulinoma, klinikinis atvejis ir gydymo rezultatai.

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