Neoadjuvant Treatment in a Locally Advanced Pancreatic Neuroendocrine Tumor: Case Report

https://doi.org/10.32635/2176-9745.RBC.2026v72n2.5661EN

Tratamento Neoadjuvante em Tumor Neuroendócrino Pancreático Localmente Avançado: Relato de Caso

Tratamiento Neoadyuvante en Tumor Neuroendocrino Pancreático Localmente Avanzado: Informe de Caso

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ABSTRACT

Introduction: Pancreatic neuroendocrine tumors (pNETs) originate from the endocrine cells of the islets of Langerhans in the pancreas. These are neoplasms with heterogeneous clinical behavior and variable prognosis, whose therapeutic approach includes chemotherapy, targeted therapies, arterial embolization, somatostatin analogues, peptide receptor radionuclide therapy, and surgical resection – the latter considered the only potentially curative treatment. **Case report:** A 38-year-old patient, previously asymptomatic, was diagnosed with a pancreatic mass in the body of the pancreas, measuring 5.0 x 5.7 x 4.7 cm, with characteristics of a locally advanced and unresectable tumor. Pancreatic biopsy, together with anatomopathological and immunohistochemical examinations, confirmed the diagnosis of grade 2 (G2) pNET of intermediate grade. The patient was submitted to neoadjuvant treatment with two cycles of capecitabine and temozolomide, which resulted in sufficient tumor regression to enable complete surgical resection by distal pancreatectomy with splenectomy. **Conclusion:** The use of neoadjuvant chemotherapy may be an effective strategy in the management of locally advanced and initially unresectable pNET. Although there is still no consensus on the ideal neoadjuvant regimen for G2 pNETs, CAPTEM therapy enabled sufficient tumor reduction for complete surgical resection with good postoperative outcomes. Continuous clinical and radiological follow-up remains essential due to the risk of late recurrence.

Key words: Pancreatic Neoplasms/diagnosis; Neoadjuvant Therapy/methods; Pancreatectomy/methods; Case Reports.

RESUMO

Introdução: Os tumores neuroendócrinos pancreáticos (pNET) originam-se das células endócrinas das Ilhotas de Langerhans no pâncreas. Trata-se de neoplasias de comportamento clínico heterogêneo e prognóstico variável, cuja abordagem terapêutica inclui quimioterapia, terapias-alvo, embolização arterial, análogos de somatostatina, terapia com radionuclídeos receptores peptídicos e ressecção cirúrgica – esta última considerada o único tratamento potencialmente curativo. **Relato do caso:** Paciente de 38 anos, previamente assintomática, diagnosticada com uma massa pancreática em topografia de corpo de pâncreas, medindo 5,0 x 5,7 x 4,7 cm, com características de tumor localmente avançado e irressecável. A biópsia pancreática, juntamente com os exames anatomopatológico e imuno-histoquímico, confirmou o diagnóstico de pNET grau 2 (G2), de grau intermediário. A paciente foi então submetida a tratamento neoadjuvante com dois ciclos de capecitabina e temozolomida, que resultaram em regressão tumoral suficiente para viabilizar a ressecção cirúrgica completa por meio de pancreatectomia distal com esplenectomia. **Conclusão:** O uso da quimioterapia neoadjuvante pode ser uma estratégia eficaz no manejo de pNET localmente avançados e inicialmente irressecáveis. Apesar de ainda não existir consenso sobre o esquema ideal de neoadjuvância para pNET G2, a terapia com o CAPTEM possibilitou redução tumoral suficiente para a ressecção cirúrgica completa, com boa evolução pós-operatória. O seguimento clínico e radiológico contínuo permanece essencial pelo risco de recorrência tardia.

Palavras-chave: Neoplasias Pancreáticas/diagnóstico; Terapia Neoadjuvante/métodos; Pancreatectomia/métodos; Relatos de Casos.

RESUMEN

Introducción: Los tumores neuroendocrinos pancreáticos (TNE-P) se originan en las células endocrinas de los islotes de Langerhans, en el páncreas. Se trata de neoplasias de comportamiento clínico heterogéneo y pronóstico variable, cuyo enfoque terapéutico incluye quimioterapia, terapias dirigidas, embolización arterial, análogos de la somatostatina, terapia con radionúclidos receptores peptídicos y resección quirúrgica –esta última considerada el único tratamiento potencialmente curativo. **Informe del caso:** Paciente de 38 años, previamente asintomática, fue diagnosticada con una masa pancreática en la topografía del cuerpo del páncreas, de 5,0 x 5,7 x 4,7 cm, con características de tumor localmente avanzado e irresecable. La biopsia pancreática, junto con los exámenes anatomopatológico e inmunohistoquímico, confirmaron el diagnóstico de TNET-P de grado 2 (G2), de grado intermedio. A continuación, la paciente se sometió a un tratamiento neoadyuvante con dos ciclos de capecitabina y temozolomida, que dieron como resultado una regresión tumoral suficiente para permitir la resección quirúrgica completa mediante pancreatectomía distal con esplenectomía. **Conclusión:** El uso de la quimioterapia neoadyuvante puede ser una estrategia eficaz en el tratamiento de TNE-P localmente avanzados e inicialmente irresecables. Aunque todavía no existe consenso sobre el esquema ideal de neoadyuvancia para los TNE-P de G2, la terapia con CAPTEM permitió una reducción tumoral suficiente para la resección quirúrgica completa, con una buena evolución posoperatoria. El seguimiento clínico y radiológico continuo sigue siendo esencial debido al riesgo de recidiva tardía.

Palabras clave: Neoplasias Pancreáticas/diagnóstico; Terapia Neoadyuvante/métodos; Pancreatectomía/métodos; Informes de Casos.

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INTRODUCTION

Pancreatic neuroendocrine tumors (pNET) are rare neoplasms that arise from the islets of Langerhans, accounting for nearly 5% of all pancreatic tumors. These tumors are categorized as functional, producing hormones as insulin, glucagon, gastrin, vasoactive intestinal peptide and somatostatin whose symptoms associated facilitate their early detection[1,2] and nonfunctional, which are typically asymptomatic in 60% to 90% of the cases and diagnosed at advanced stages as inoperable tumor masses[1,3].

The approximate incidence of pNET is one case in 100,000 persons/year and prevalence from 1% to 5%[4]. They are more common in the fifth decade of life and predominantly malignant, except insulinoma, benign in 90% of the cases. At diagnosis, nearly 60% of these tumors are already metastatic[4,5].

Complete surgical resection (R0) continues to be the best action for localized pNET[1,2,4,5]. However, many patients have tumors with suspicious margins or locally advanced, making immediate surgery difficult. Neoadjuvancy can increase the odds of R0 or turning initially inoperable tumors, operable[6]. Neoadjuvant therapies, according to The North American Neuroendocrine Tumor Society Consensus (NANETS)[1] of 2020 include cytotoxic chemotherapy, standing out capecitabine + temozolomide (CAPTEM), peptide receptors radionuclides therapy (PRRT) with radioanalogues of somatostatin and, in selected cases, analogues of somatostatin or target-therapy as everolimus. However, there is still no defined standard due to the lack of large-scale randomized studies[1,6].

The objective of this report is to stimulate the discussion in the scientific community given the relevance of the theme and scarce literature available.

The Ethics Committee of "*Faculdade de Medicina de São José do Rio Preto*" approved the study, report number 7714420 (CAAE (submission for ethical review) 89198125.8.0000.5415) in compliance with the Declaration of Helsinki and Directives 466/2012[7] and 510/2016[8] of the National Health Council (CNS).

CASE REPORT

Female patient, 38 years, attended the emergency complaining of cramp-like left flank pain, irradiated to the pelvis, with dysuria, pollakiuria, episodes of vomits, fever and recurring urinary infections not improving with nitrofurantoin, ceftriaxone and tamsulosin. She had type 2 diabetes *mellitus* for one year and hypothyroidism for 13 years, using gliclazide 60 mg, metformin XR 1g and levothyroxine 100 mg. No smoker and non-alcohol user. Received common analgesics (dipyrone and non-steroidal anti-inflammatory) to manage the symptoms and was admitted for two weeks for medical investigation.

During the investigation, an IV contrast computed tomography (CT) (Figure 1) incidentally revealed a mass in the head and body of the pancreas, with heterogenous enhancement, measuring approximately 5 x 5.7 x 4.7 cm, causing abrupt interruption of the main pancreatic duct. Close contact with portal vein (>180°), 90° angle with liver and splenic arteries and proximity with the posterior wall of the pyloric canal, gastric body and lower border of the liver.

Lab tests evaluated the tumor markers CA 19-9 as 41.59 U/mL, and carcinoembryonic antigen (CEA) as 3.30 ng/mL. The anatomopathological test from the pancreatic biopsy confirmed the presence of an epithelial neoplasm. The immunohistochemistry was compatible with well-differentiated, histological grade 2 (G2) pancreatic neuroendocrine tumor.

Neoadjuvant chemotherapy was selected with CAPTEM, capecitabine 1,200 mg/m²/day, from day 1 to 14 and temozolomide 200 mg/m²/day, from day 10 to day 14, repeated after a 14-day pause due to the locally advanced lesion in two cycles (52 days) followed by restaging with imaging exams and evaluation of resectability. Figure 2 shows abdominal restaging CT with reduction of the mass to 4.6 x 3.5 x 3.2 cm mainly at the head of the pancreas, its epicenter was in the pancreatic neck. Presented cleavage plane in relation to the liver, splenic and mesenchymal upper arteries, in addition to contact of nearly 180° with the mesentery-portal junction.

A body-caudal pancreatectomy with splenectomy was performed without complications. The patient was hospitalized for one week, hemodynamically stable, asymptomatic with antibiotic prophylaxis and serial exams. The anatomopathological and immunohistochemistry of the surgical piece (Figure 3) confirmed well-defined G2 pancreatic neuroendocrine tumor with free margins and without lymphovascular or perineural invasion.

The patient recovered quite well and after hospital discharge, attended outpatient visit in two weeks, complaining of sharp-like moderate pain according to visual analogue scale in the epigastric that ceased spontaneously. Adapted well to insulin with few episodes of hypoglycemia without other complaints. Was asymptomatic in continuous outpatient follow-up in 2025.

DISCUSSION

pNET are rare tumors arising from the endocrine portion of the pancreas and usually do not metastasize

rapidly[1]. According to the World Health Organization (WHO), pNET can be well-differentiated, low grade (G1) or intermediate grade (G2) or poorly differentiated high grade (G3), with distinguished clinical, pathological and prognostic characteristics[9].

Due to the remarkable advances and improvement of imaging tests, diagnosis of pNET is increasing with incidence of one case or more per 100,000 individuals/year[3,9]. In addition, only 5% of pNET holds relation with family history, being 95% of them sporadic[1]. Definitive diagnosis is performed through anatomopathological and immunohistochemistry exams[5].

These tumors present heterogeneous behavior and variable prognosis with multiple therapeutic options: chemotherapy, target-therapy, analogues of somatostatin, peptide receptors radionuclides therapy, arterial embolization

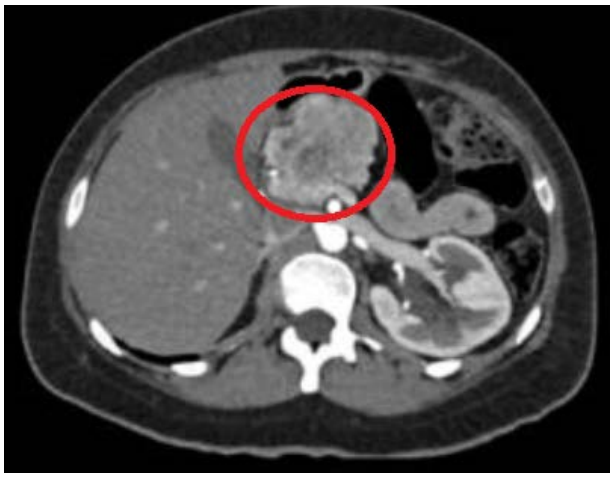

Figure 1. Axial abdominal CT with IV contrast
Note: Localized heterogeneous mass at the head of the pancreas, 5.0 x 5.7 x 4.7 cm.

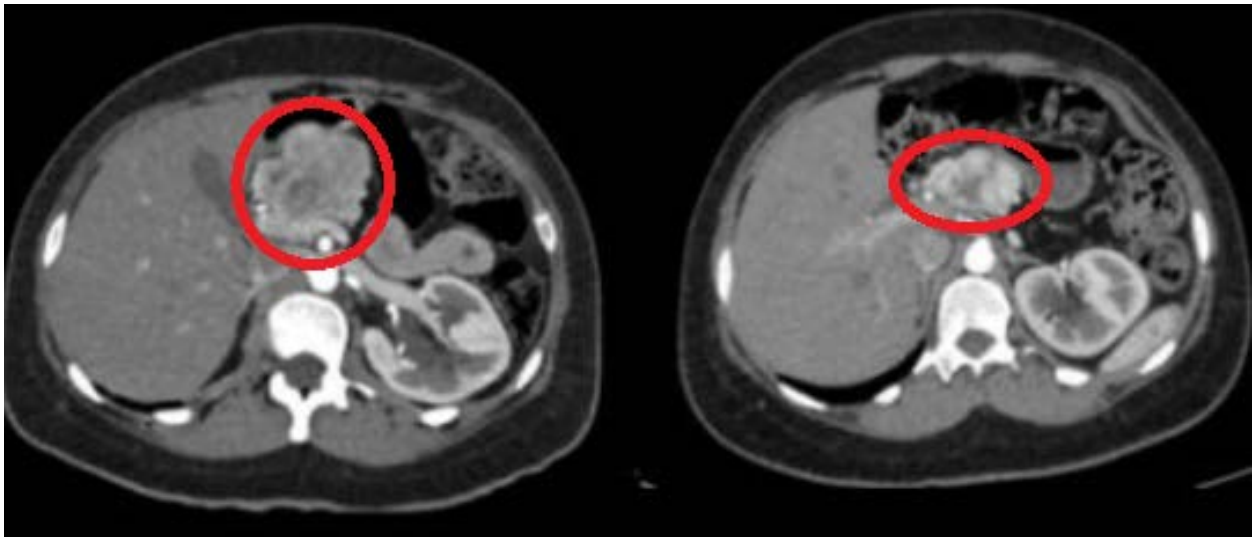

Figure 2. Axial abdominal CT with IV contrast
Note: The image shows the pancreatic mass before and after the neoadjuvant treatment with two cycles of CAPEM respectively.

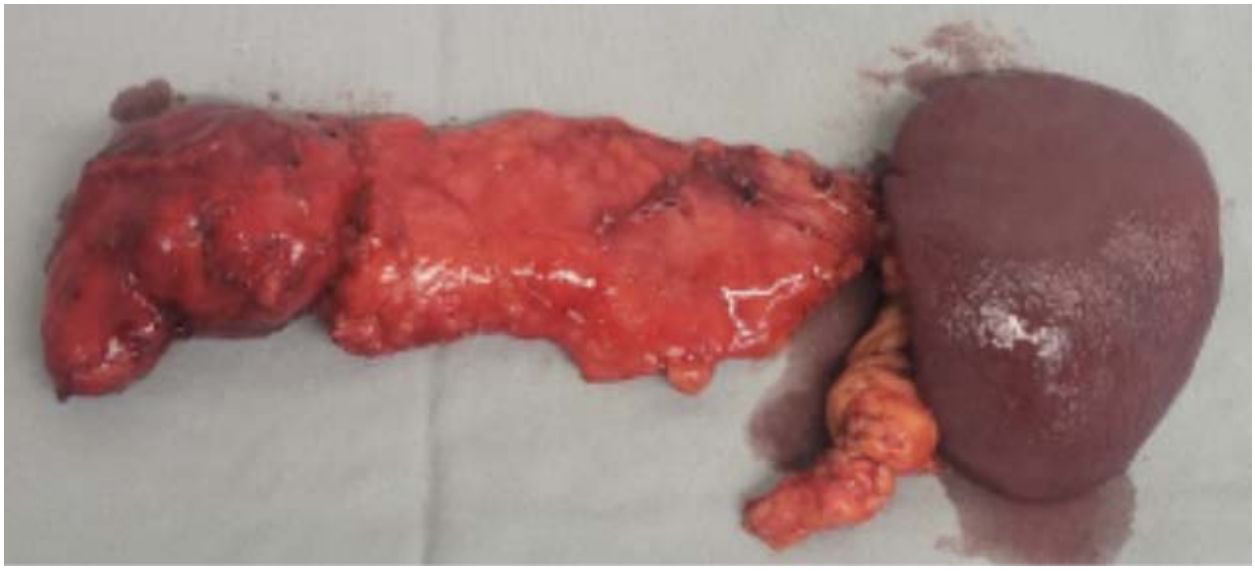

Figure 3. Surgical piece of body-caudal pancreatectomy and splenectomy

or a combination of these approaches[3,10]. The choice depends on the local and classification of the tumor, disease extent, involvement of proximal structures and comorbidities[1].

Neoadjuvant chemotherapy was the choice for the present case even without consensus about the best regimen for G2 pNET[9]. Neoadjuvancy attempts to reduce the tumor mass of advanced and irresectable pNET making them surgically resectable[4,11]. In addition, it optimizes the selection of candidates for the surgery, reduces post-operative complications, avoids resection in patients with aggressive disease and increases survival[1].

The therapy with CAPTEM was well tolerated and effective in clinical trials and retrospective studies in reducing locally advanced and irresectable pNET, making full resection possible (R0). Devata et al. reported a case of pNET with partial response after CAPTEM which led to R0 resection and 3-month survival after the surgery[12].

A randomized, multicenter, prospective, phase II clinical trial conducted by Kunz et al.[13] compared CAPTEM with temozolomide isolate in neoadjuvancy. The response rate was 39.7% and higher mean survival with CAPTEM (22.7 months *vs.* 14.4 months). Therefore, the combination CAPTEM was recommended as standard treatment option for well-differentiated advanced pNET, especially G2 when tumor reduction is necessary to facilitate curative resection[11,13].

After neoadjuvancy, surgical resection was the choice to control the symptoms and reduction of the neoplasm, the only curative resection for localized pNET[3,4,11,12]. However, although with best prognosis, pancreatic surgery is associated with high morbimortality and significant risk of formation of pancreatic fistula in case of pNET[11].

For localized pNET, surgical options include distal pancreatectomy with or without splenectomy for tumors in the body or tail of the pancreas; pancreatoduodenectomy for tumors at the head of the pancreas and enucleation for non-invasive tumors[5]. 5-year survival varies from 50% in locally advanced tumors to more than 90% in non-metastatic[10,11]. However, less than 30% of malignant pNET are resectable with curative intent. Surgery should include regional lymphadenectomy because more than 50% of tumors > 2cm present lymph node metastasis, increasing the risk of recurrence[5].

In face of the clinical scenario with >2cm pNET in the body of the pancreas, distal pancreatectomy with splenectomy was preferred due to low mortality (1-3%) and morbidity around 30%, most of all due to endocrine pancreatic insufficiency with risk of post-operative diabetes between 10% and 35%. Usually, splenectomy is necessary because of the anatomical and vascular proximity with the pancreas, but increases the risk of long-term infections and malignancies[10,11].

After curative surgical resection possible in less than 30% of the cases of malignant pNET, recurrence can exceed 75% in 15 years, emphasizing the importance of post-operative monitoring[9]. 5-year survival rate is higher than 80%[14]. Follow-up should last between three and six months post-surgery and continue from six to 12 months for at least seven years due to potential late relapse[5].

CONCLUSION

Neoadjuvant chemotherapy is an effective strategy to manage locally advanced and initially irresectable pNET. Although there is no consensus on the ideal neoadjuvancy regimen for G2 pNET, therapy with CAPTEM allowed sufficient tumor reduction for full R0 resection with good post-operative evolution. Continuous clinical and radiologic follow-up remains essential due to risk of late recurrence.

CONTRIBUTIONS

All the authors contributed substantially to the conception and design of the study, acquisition, analysis and interpretation of the data, writing and critical review. They approved the final version for publication.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE

The authors utilized Artificial Intelligence (AI) – Chat GPT and DeepL Translate – to support the writing of the article. They are the sole responsible for the analysis, interpretation or synthesis of the results without AI intervention.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

All the content underlying the text is contained in the manuscript.

FUNDING SOURCES

None.

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Recebido em 5/1/2026
Aprovado em 26/2/2026

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