Case report

# Duodenal large-cell neuroendocrine carcinoma as unusual cause of acute pancreatitis

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**Abstract**

Early identification of acute pancreatitis etiology is essential for choosing the best therapeutic management. The main causes are cholelithiasis and alcohol consumption. Tumors that obstruct the main pancreatic duct are uncommon causes of acute pancreatitis. Duodenal neuroendocrine tumors are rare entities and may be exceptional causes of acute pancreatitis. A 57-year-old male, with associated severe cardiovascular pathology, was admitted with clinical and biological picture of acute pancreatitis. Biliary and alcoholic causes were excluded. Abdominal contrast-enhanced computed tomography scan identified circumferential wall thickening of the second segment of the duodenum with peri-ampullary and papillary nodular non-homogenous contrast enhancement aspect. Upper gastrointestinal endoscopy described irregular hypertrophic duodenal mucosal folds and biopsies were performed. The histopathological diagnosis after immunohistochemistry tests was duodenal large-cell neuroendocrine carcinoma. The patient was referred to the oncology clinic and palliative treatment was initiated. The evolution was marked by additional complications due to the tumor evolution – upper gastrointestinal bleeding and obstructive jaundice, conservatory treated and, respectively, by interventional radiology technique. This case illustrates that, although often obvious, etiological diagnosis approach of acute pancreatitis can be sometimes challenging. Tumor cause is infrequent and requires thorough work-up, as the treatment is different. Although extremely rare and sometimes with mild clinical presentation, duodenal neuroendocrine carcinomas may have dramatic onset and evolution, involving extensive therapeutic resources.

**Keywords:** *acute pancreatitis; neuroendocrine neoplasm; duodenum; large-cell neuroendocrine carcinoma.*

## Introduction

Duodenal neuroendocrine neoplasms (D-NENs) are extremely rare malignancies derived from the neuroendocrine cell system, representing up to 3% of all duodenal tumors [1] and about 2% of gastrointestinal (GI) neuroendocrine neoplasms (NENs) [2]. There is an increase in the incidence over the past 3 decades, with 1.1/100.000 diagnosed annually in the United States [3]. They are commonly arising in first or second part of the duodenum, often being incidentally diagnosed at upper gastrointestinal endoscopy (UGE) examination, while the ampullary region is involved in about 20% of cases [4].

Based on histological findings, D-NENs are defined as well-differentiated neuroendocrine tumors (NETs) (50-70%), poorly differentiated small-cell neuroendocrine carcinomas (SC-NECs) or large-cell neuroendocrine carcinomas (LC-NECs) (less than 3%), and mixed neuroendocrine/non-neuroendocrine neoplasms (MiNEN), with different disease prognostic according to mitotic count and Ki-67 index values [5, 6].

Received: February 2020; Accepted after review: April 2020; Published: April 2020.

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Clinical presentation is related to the localization, size, functional status and differentiation grade. More often, 90% of D-NENs are asymptomatic non-functional tumors [7], while in other cases they may present with dyspepsia, epigastric pain, weight loss, jaundice, nausea, gastrointestinal bleeding, diarrhea or duodenal obstruction. In the case of ampullary or peri-ampullary localization, vomiting, diarrhea and bile duct dilatation are more frequent [8].

We present a case of advanced duodenal LC-NEC revealed by acute pancreatitis as first local complication, with subsequent evolution involving various palliative resources.

## Case report

A 57-year-old non-alcoholic male patient, associating important cardiovascular pathology and insulin-treated type 2 diabetes, was admitted for acute upper abdominal pain, nausea and vomiting.

Laboratory tests showed inflammatory syndrome, hyperlipasemia (1734 U/L) and hyperamylasemia (380 U/L), iron deficiency anemia, hepatic cytolysis, enzymatic cholestasis and elevated tumor markers (CA 19-9 = 220.81 U/mL, Carcinoembryonic Antigen = 9.87 ng/mL).

On clinical and biological grounds, a diagnosis of acute pancreatitis was made. Initially, an abdominal ultrasound exam was performed, showing a dilated main biliary duct and no cholelithiasis. Afterwards, an abdominal contrast-enhanced computed tomography (CECT) scan was performed, describing circumferential wall thickening of the second segment of the duodenum up to the inferior duodenal flexure, para-ampullary and papillary nodular aspect with non-homogenous contrast enhancement, irregular margins, with no separation limit from the pancreatic parenchyma (Figure 1). The CECT scan also identified a nodular hepatic lesion, enlarged abdominal lymph glands and nodular lesions in the inferior pulmonary lobes, with associated hilum and mediastinal adenopathies (confirmed by a subsequent thoracic CECT) (Figure 2). Broncho-alveolar lavage results were inconclusive. Upper gastrointestinal endoscopy (UGE) described irregular hypertrophic duodenal mucosal folds suggestive for tumor infiltration (Figure 3) and biopsies were performed.

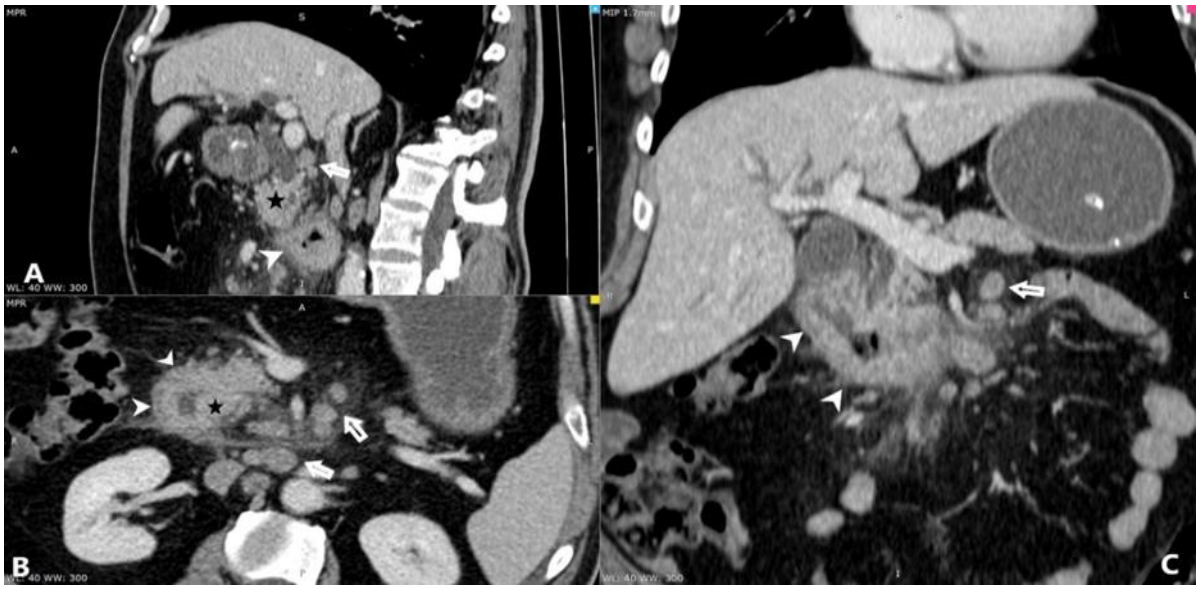


**Fig. 1.** CECT of the abdomen, venous phase: sagittal (A), axial (B), coronal (C) views, showing duodenal wall thickening both above and beyond papilla (white arrowheads) with nodular aspect at para-ampullary level (*); biliary tree is mildly dilated; adenopathies (arrows) and fat stranding around them as well as peri-duodenal are also present. *CECT: Contrast-enhanced computed tomography*

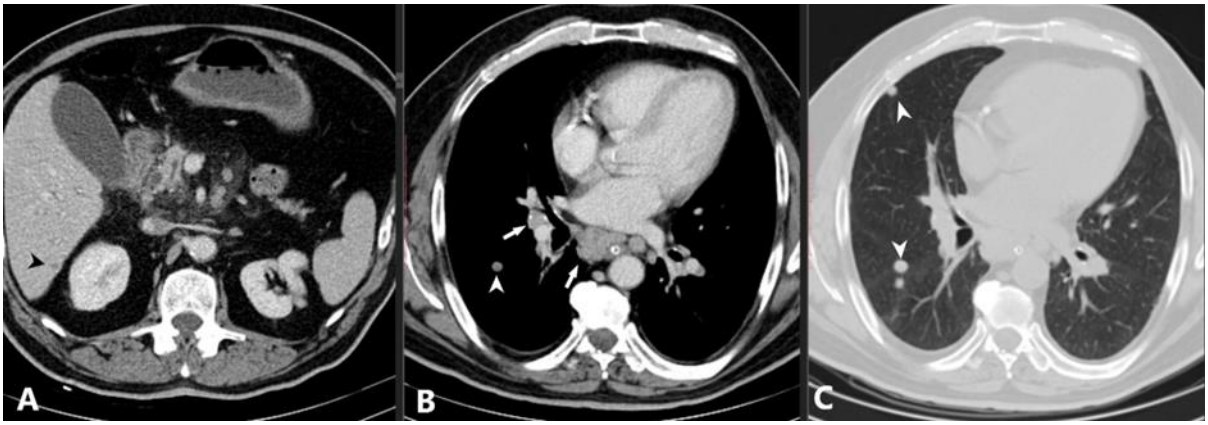


**Fig. 2.** CECT of the abdomen and thorax, venous phase: abdomen axial (A), axial thorax, chest window (B) and lung window (C) showing single liver metastasis (black arrowhead), mediastinal and interlobar adenopathies (arrows), lung metastasis at the lungs base (white arrowheads).

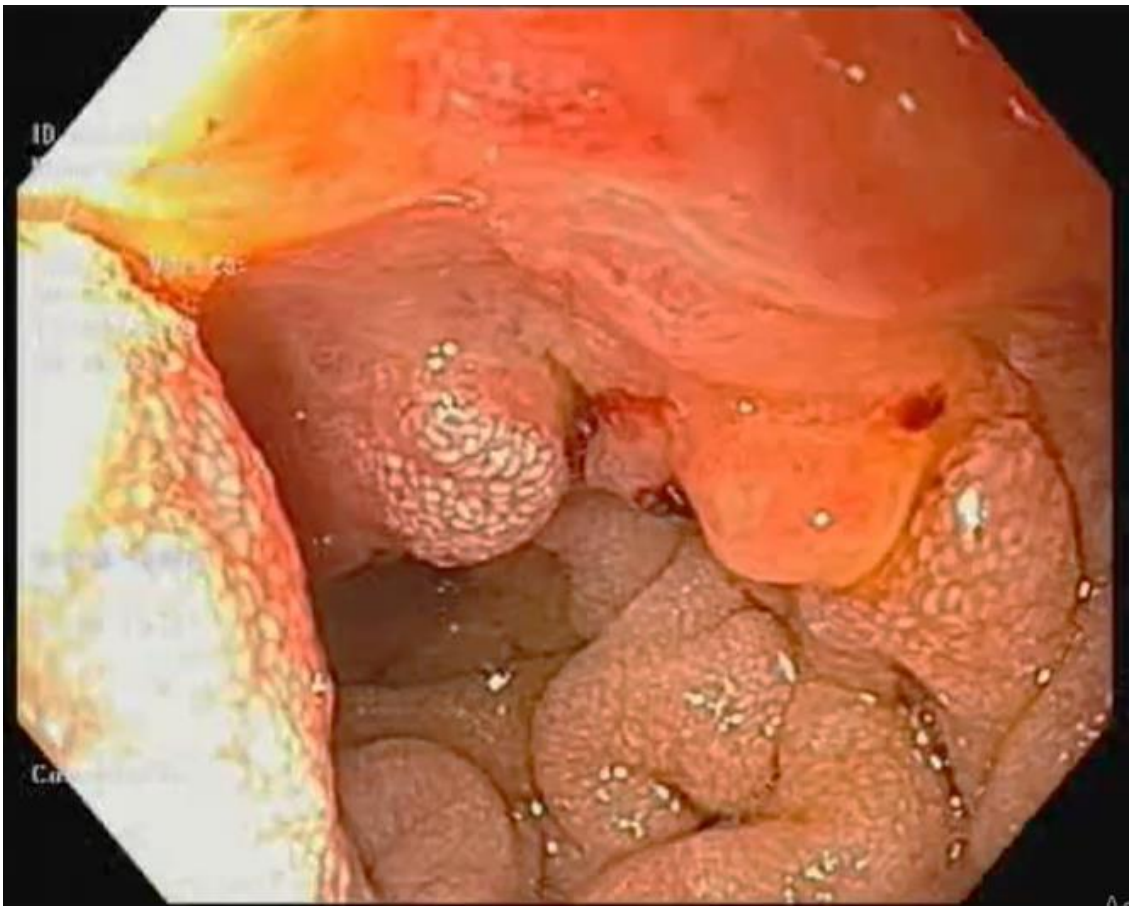

**Fig. 3.** Irregular hypertrophic duodenal mucosal folds suggestive for tumoral infiltration – endoscopic view

Histological examination using routine technique showed isles of large, polygonal tumor cells in *lamina propria* and submucosa, and numerous tumor emboli in vascular spaces (Figure 4.A). Immunohistochemical (IHC) tests were positive for cytokeratin CK7 (Figure 4.B) and synaptophysin in the tumor cells (Figure 4.C), and negative for chromogranin; Ki-67 proliferation index was 80% (Figure 4.D). The histopathological diagnosis after immunohistochemistry tests was duodenal large-cell neuroendocrine carcinoma.

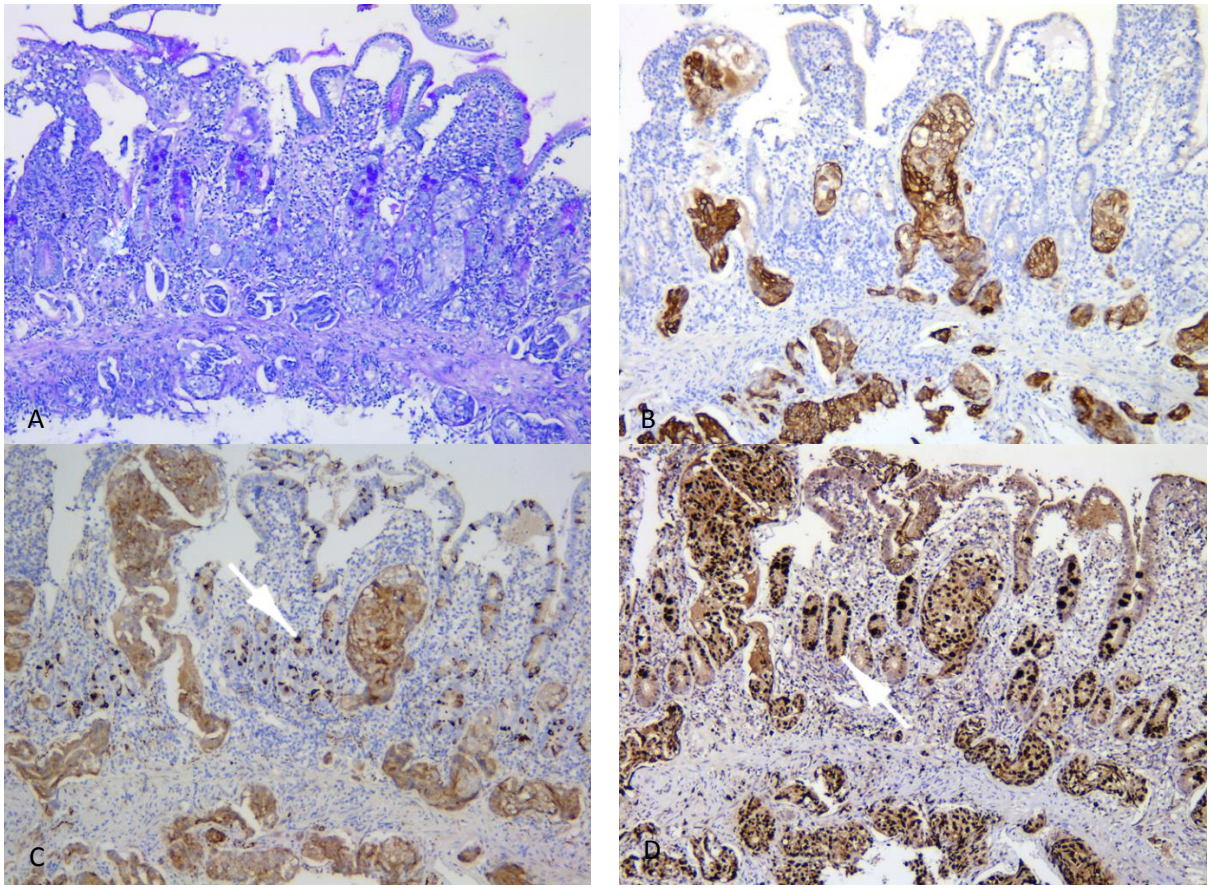


**Fig. 4.** Duodenal large-cell neuroendocrine carcinoma: **A)** Isles of large, polygonal tumor cells in *lamina propria* and submucosa; numerous tumor emboli in vascular spaces (PAS, x100); **B)** Tumor cells are positive for Cytokeratin 7 (IHC, anti-CK7 Ab, x100); **C)** Synaptophysin is positive in tumor cells and normal enterochromaphin duodenal cells (arrow) (IHC, anti-Synaptophysin Ab, x100); **D)** Ki-67 positive in 80% of tumor cells and in proliferative compartment of duodenal crypts (arrow) (IHC, anti-Ki-67 Ab, x100).

According to the TNM classification, the tumor was $T_3N_1M_1$ and stage IV [5]. A surgical cure was excluded and the patient was referred to the oncology clinic with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 2, where palliative chemotherapy (Cisplatin and Etoposide) was started. Due to the bleeding potential of the duodenal neoplasia, the patient also underwent hemostatic radiotherapy. After the third cycle of chemotherapy, the patient returned in our service with ECOG-PS 3, important cholestatic jaundice, GI intolerance and self-limited upper GI bleeding manifested as melena, with no active bleeding at UGE. Blood transfusions were made. Because the endoscopic approach of the papilla was impossible due to the tumor extension, an interventional radiology procedure was performed as palliation for the biliary obstruction. Internal-external biliary drainage was placed percutaneously by left hepatic lobe approach (Figure 5), with good immediate evolution and fully functional drainage afterwards. Unfortunately, tumor progression was recorded, as showed by a recent thoraco-abdominal CECT examination (Figure 6).

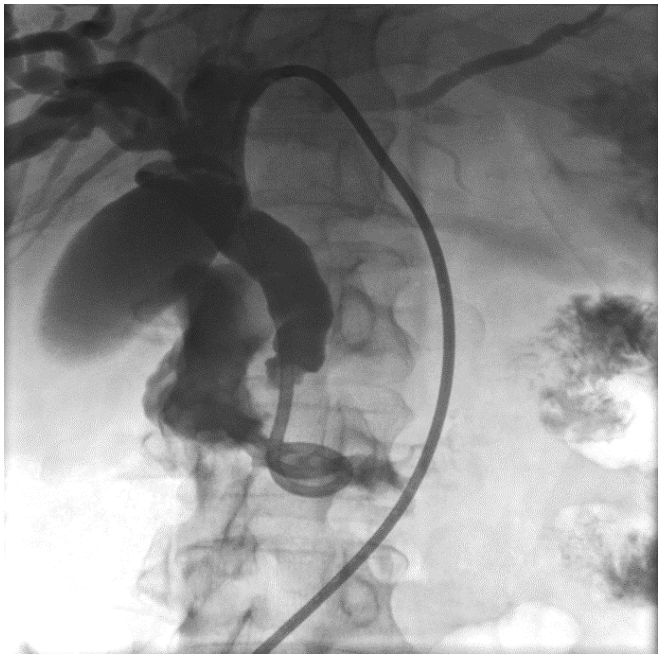

**Fig. 5.** Internal-external percutaneous biliary drainage, left side approach

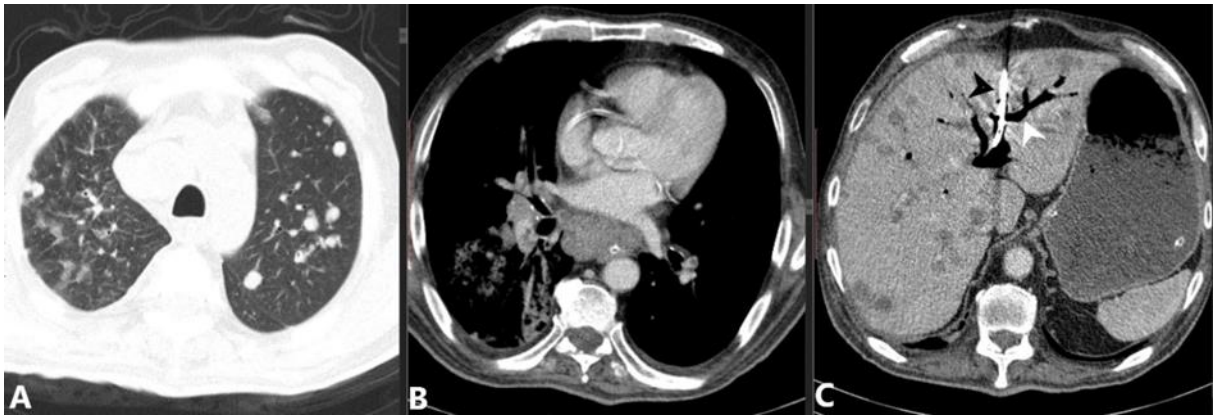


**Fig. 6.** CECT of the abdomen and thorax 6 months later: axial lung upper regions (A), axial chest window at the base of the lungs (B), axial abdomen, liver (C). Lung metastasis are present also in upper lungs, increased size of mediastinal adenophaties, and multiple liver metastasis; functional percutaneous internal-external biliary drainage (black arrowhead) – aerobilia (white arrowhead)

## Discussion

NENs are rare and heterogeneous, representing 2% of all digestive malignancies [2]. The most common primary tumor sites are the GI tract and the lungs; D-NENs are infrequent, comprising up to 3% of all duodenal tumors [1]. The duodenal poor-differentiated NECs are the less frequent, 3% from all NENs. Most D-NENs are developing in the first or second part of the duodenum. Because 90% are not functional, they are often incidentally discovered during UGE [7]. Other diagnostic circumstances are related to hormonal secretion (for instance, gastrinoma may be revealed by Zollinger-Ellison syndrome, or carcinoid syndrome in serotonin-secreting tumors) or tumor's evolution or complications [9].

The association between D-NENs and acute pancreatitis is extremely rare. The leading causes of acute pancreatitis are represented by gallstones (28-38%) and alcohol consumption (19-41%), followed by

hypertriglyceridemia (1-3%), while less common causes are surgical or endoscopic procedures, genetic mutations, adverse drug reactions, trauma, infections, hypercalcemia or neoplasia, mostly intraductal papillary mucinous neoplasms [10]. Based on neoplastic etiology, frequently involved are exocrine pancreatic tumors or metastatic dissemination from other organs, NENs being a rare cause [11, 12].

UGE and endoscopic ultrasound with biopsy sampling play a key role in the diagnosis and management of D-NENs. Additionally, CECT or magnetic resonance imaging scan are recommended for tumor staging. Tumor size, histological grading, presence of immunohistochemical neuroendocrine markers such as synaptophysin and/or chromogranin A, mitotic index and Ki-67 values, as well as detection of peptide hormones in functional tumors are determinant for diagnosis and treatment strategy and overall survival rate [13]. Also, NETs have a distinct set of mutated genes, represented by MEN1, DAXX and ATRX, while NECs present mutation in TP53 and RB1 genes, but these are not part of routine diagnostic investigations [14].

While for well-differentiated NETs, endoscopic or surgical resection may be curative and specific medical treatment may successfully control symptoms, poorly differentiated NECs are far more aggressive and carry an unfavorable prognosis. Fifty percent of patients present metastatic disease at the time of diagnosis with overall survival of 10 months, making a surgical approach in this advanced stage impossible [13, 15]. Mainly, these tumors are non-functional, lacking symptoms in the early stages of the disease, making them more difficult to diagnose [15]. In these circumstances, palliative management is required, using a multidisciplinary approach. Platinum based chemotherapy drugs (cisplatin or carboplatin) in association with etoposide represent the first-line chemotherapy in advanced NECs [13]. Palliative procedure can be required when tumor localization, size and/or progression cause specific complications. Thus, palliative radiotherapy for hemostasis in unresectable tumors can be performed with success in about 88% of cases when medical or endoscopic therapy has failed [16]. In our case, the patient started with an ECOG-PS of 2, making chemotherapy possible, after hemostatic radiotherapy. He was strictly monitored for complications such as nausea and vomiting, low blood cell count and kidney toxicity. After three cycles of chemotherapy, the ECOG-PS of the patient worsened to 3, with severe anemia and digestive intolerance, so chemotherapy was ceased. Also, the advanced local stage of the tumor determined obstructive jaundice that needed palliation, by biliary stent through retrograde endoscopic approach or, alternatively, interventional radiology. In our case, tumor type and localization made impossible the endoscopic approach, therefore biliary internal-external drainage was placed.

## Conclusions

We reported a case of advanced duodenal large-cell neuroendocrine carcinoma revealed by acute pancreatitis as tumor complication. Since the tumor cause of acute pancreatitis is infrequent and moreover NENs and, especially, NECs are extremely rare, this case illustrates how sometimes etiological diagnosis approach of acute pancreatitis can be very challenging, requiring thorough work-up. At the same time, although sometimes with mild clinical presentation, D-NECs may have dramatic onset and evolution. This may involve, as in our case, extensive therapeutic resources, especially in this particular situation of advanced stage at the diagnosis and aggressive evolution.

### Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Competing interests

The author(s) declare that they have no competing interests.

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