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CASE REPORT OPEN ACCESS

# DUODENAL PAPILLA NEUROENDOCRINE TUMOR - CASE REPORT

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## ABSTRACT

**Objetivo:** Os tumores neuroendócrinos (TNEs) surgem das células endócrinas do trato gastrointestinal (GI); que são células enterocromafins derivadas das criptas de Lieberkühn, encontradas na mucosa e submucosa. Na papila duodenal, esses tumores são raros, portanto, sua história natural não está bem estabelecida. Dessa forma, protocolos para o manejo adequado devem ser feitos. **Metodologia:** Foi realizada revisão do prontuário do paciente, bem como extensa pesquisa bibliográfica sobre os tumores neuroendócrinos da papila duodenal, com estudo detalhado de sua etiologia, fisiopatologia, diagnóstico e tratamento. As correlações entre o caso e os achados da literatura também são apresentadas. **Caso clínico:** Homem de 73 anos, com icterícia há uma semana, sem colúria ou hipocolia fecal. A colangiopancreatografia retrógrada endoscópica (CPRE) mostrou edema da papila e ausência de cálculo. Uma biópsia mostrou tumor neuroendócrino grau 1 em 3 da papila duodenal. O paciente foi submetido a procedimento para colocação de prótese biliar plástica para alívio sintomático. O paciente faleceu dois anos após o diagnóstico. **Conclusão:** O potencial maligno do carcinoma papilífero neuroendócrino é alto, por isso é muito importante reconhecer as características clínicas, histológicas e imuno-histoquímicas desta entidade para uma melhor proposta de tratamento.



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# INTRODUCTION

The term "neuroendocrine" is used to describe cells with neurological and endocrinological properties; as for the neurological property, it is due to the identification of dense-core granules, a hallmark of the neurosecretory cell phenotype found, for example, in serotonergic neurons; the endocrinological property refers to its capacity to synthesize and secrete substances. Such neuroendocrine cells can be found in endocrine glands, but also in exocrine tissues, such as the digestive and respiratory tracts (Oronsky et al, 2017). In the gastrointestinal (GI) tract, neuroendocrine tumors (NETs) derive from enterochromaffin cells in Lieberkühn's crypts, found in the mucosa and submucosa (Dias et al, 2017).

Approximately 73.7% of these tumors are found in the gastrointestinal tract, 25.1% in the bronchopulmonary system, and they are rarely found in ovaries and kidneys. Within the GI system, the most frequently affected organs are the small intestine (28.7%), appendix (18.9%), and rectum (12.6%) (Matli et al, 2022). In the duodenal papilla, these tumors are rare, therefore, their natural history is not well established (Seo & Choi, 2018). They correspond to 2% of malignant periampullary neoplasms and less than 1% of gastrointestinal NETs (Galetti et al, 2021). These tumors are somatostatin producers and often obstruct the duodenal ampulla leading to jaundice or pancreatitis. Functional somatostatinoma syndromes occur very rarely (Sato et al, 2016). They usually have a good prognosis, although a small portion may present with local invasion or distant metastasis (Attili et al, 2014). The reported case is a neuroendocrine tumor of the duodenal papilla that was diagnosed in the investigation of extrahepatic cholestasis.

The patient presented with jaundice and the tumor was diagnosed in an advanced stage, treated in a palliative way, with the use of a biliary prosthesis. The importance of this case report is that it is a rare tumor. As more case reports of this type of tumor are published, we will be able to better understand both the natural history of the disease and the approaches to managing the disease. In this way, protocols for proper management should be made.

# METHODOLOGY

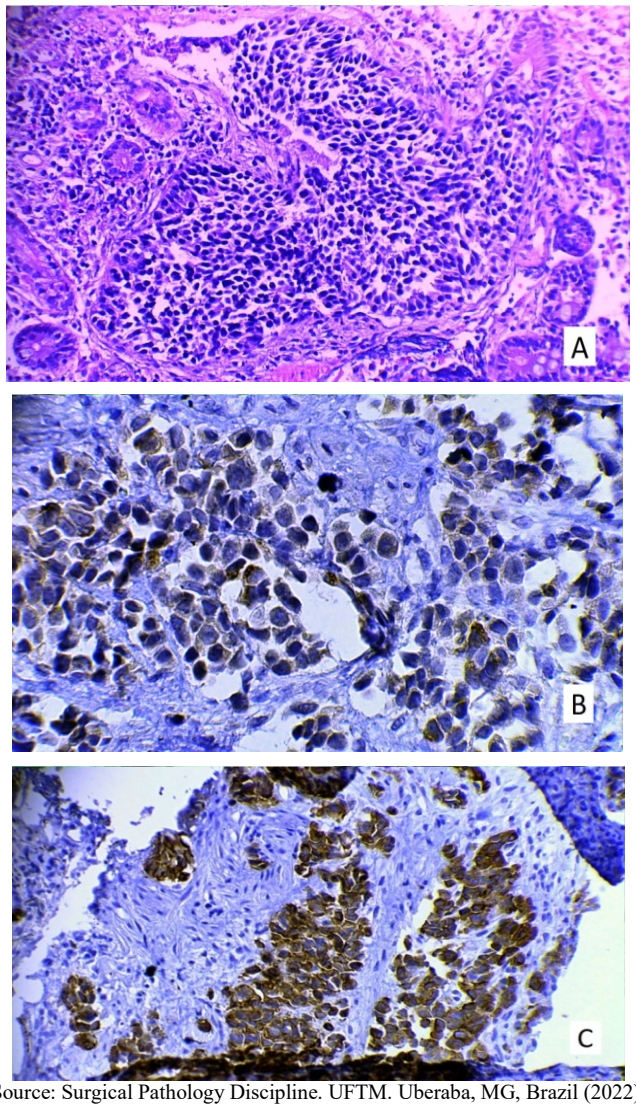
The present report is a retrospective study of the clinical case of a patient undergoing outpatient follow-up at the Hospital de Clínicas, Universidade Federal do Triângulo Mineiro. The study was conducted in accordance with current bioethical standards and was submitted to the Research Ethics Committee for analysis and prior approval (CAAE: 59936922.6.0000.8667; Approval No. 5.529.666). After the necessary instructions and clarifications were provided, the patient signed a Free and Informed Consent Form. The methodology of the report and case study was divided into four phases: 1) analysis of the patient's chart and data collection of clinical findings; 2) evaluation of complementary examinations and review of tomographic images by the radiology and vascular surgery team; 3) bibliographic review with the establishment of the main findings related to the patient's pathology, its prevalence, signs and symptoms, diagnosis, and treatment; and 4) analysis and correlation of findings found in cases with those described in the literature. The authors were divided into two groups: one was responsible for reviewing the medical records, collecting data, and evaluating the complementary exams, while the other was responsible for the literature review. Subsequently, correlations were made between the patient's clinical condition and the findings described in the literature; these were interpreted and elaborated on for publication of the case report.

# CASE REPORT

A 73-year-old male, with a one-week jaundice, without choluria or fecal hypocholia. Laboratory tests showed total bilirubin (BT) 8.22 mg/dL (RV: <1,2 mg/dL), at the expense of the direct fraction (BD) 7.18 mg/dL (RV: <0,4 mg/dL), gamma glutamyltransferase (GGT) 1228 U/L (RV: <60 U/L), alkaline phosphatase (FA) 282 U/L (RV: 40-129 U/L), alanine aminotransferase (ALT) 194 U/L (RV: <41 U/L) and aspartate aminotransferase (AST) 128 U/L (VR: <40 U/L). Endoscopic retrograde cholangiopancreatography (ERCP) showed edema of the papilla and no stone. A biopsy showed grade 1 in 3 neuroendocrine tumor of the duodenal papilla (Figure 1).

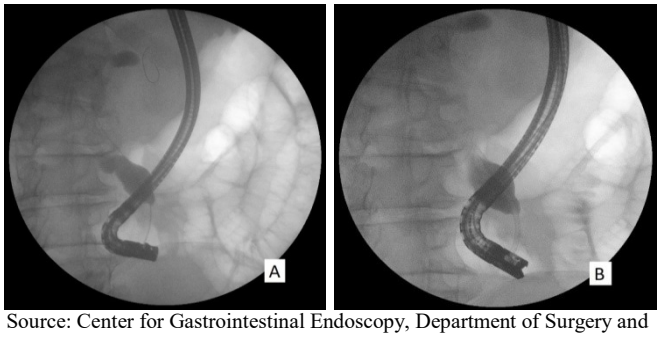
During the evolution of the condition, there was the appearance of fecal hypocholia, choluria and intense pruritus. In the upper-left image (A), grade 1 neuroendocrine tumor, solid epithelial neoplasm, without glandular differentiation. The neoplasm infiltrates the mucosal stroma and the smooth muscle layer of the major duodenal papilla and measures 1.69 x 0.38 mm in the histological section. Their nuclei are small, ovoid, without visible nucleoli. Their cytoplasms are moderately abundant and pale. There are no mitotic figures or necrosis, hematoxylin and eosin (200x). On the right (B), Chromogranin A (400x). In the lower image (C), Synaptophysin (200x). After 40 days, the patient underwent a procedure for placement of a plastic biliary prosthesis for symptomatic relief (Figure 2) and a second biopsy of the lesion was performed.

In the image above, stenosis of the distal common bile duct was observed (A); thus, a plastic biliary prosthesis was placed (B).The anatomopathological result was a well-differentiated neuroendocrine tumor, grade 3 (NETG3) in the duodenal mucosa. Immunohistochemical profile showed positivity in neoplastic cells for synaptophysin (focal), chromogranin (diffuse) and CD56 (focal). Cell proliferation index estimated by KI-67/MIB-1 around 30% (Figures 3 and 4). There was a need to change the plastic prosthesis for the metallic one (Figure 5).




Source: Surgical Pathology Discipline. UFTM. Uberaba, MG, Brazil (2022)

**Figure 1. Anatomopathological result of the biopsy performed on 12.18.2020**

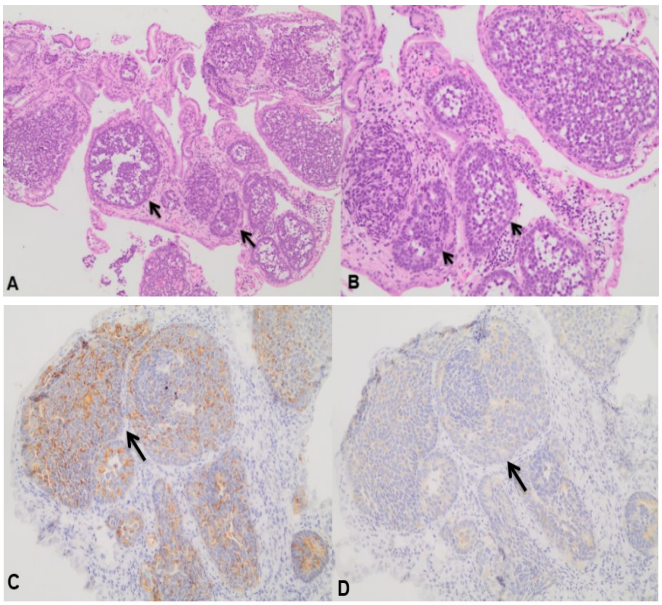



Source: Center for Gastrointestinal Endoscopy, Department of Surgery and Anatomy, FMRP/USP, Ribeirão Preto, SP, Brazil (2022)

**Figure 2. Endoscopic retrograde cholangiopancreatography of 1.28.2021**

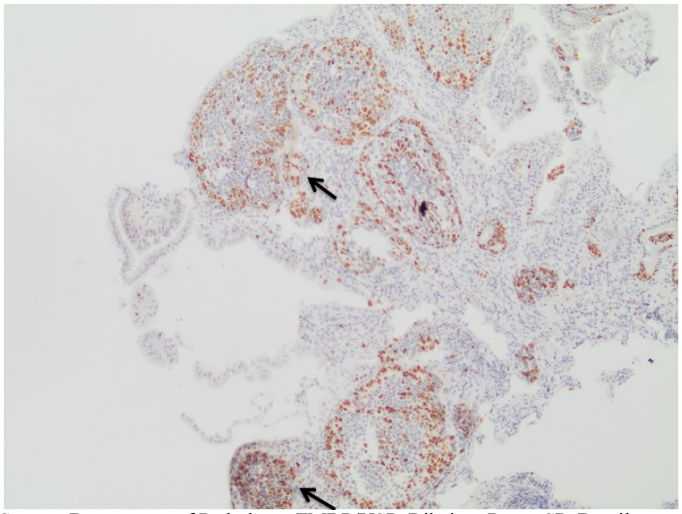
In the top image, duodenal mucosa showing nests of round tumor cells distributed in the lamina propria (blacks arrows). H&E.(A) 100X original magnification. (B) 200X original magnification. In the bottom image, immunohistochemical staining for neuroendocrine markers chromogranin A (C) and synaptophysin (D) shows diffuse cytoplasm immunoreactivity in the tumor cells. Chromogranin and synaptophysin IHC, 200x original magnification.

In the image above, Ki-67 proliferation index showing nuclear immunoreactivity in 30% of the tumor cells (black arrows). Ki-67 IHC, 100x original magnification.



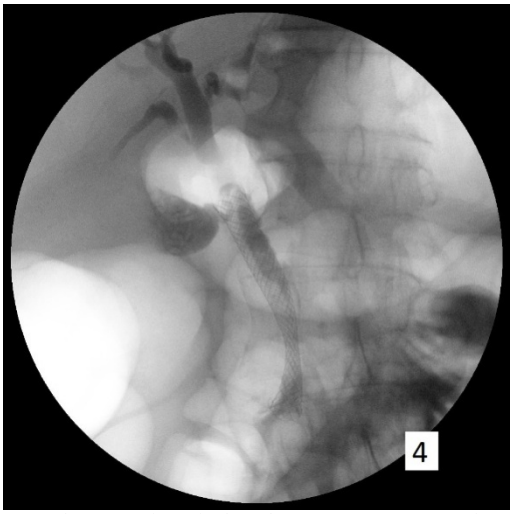

Source: Department of Pathology, FMRP/USP, Ribeirão Preto, SP, Brazil

**Figure 3: Anatomopathological result of the biopsy performed on 1.28.2021**



Source: Department of Pathology, FMRP/USP, Ribeirão Preto, SP, Brazil

**Figure 4. Anatomopathological result of the biopsy performed on 1.28.2021**




Source: Center for Gastrointestinal Endoscopy, Department of Surgery and Anatomy, FMRP/USP, Ribeirão Preto, SP, Brazil (2022)

**Figure 5. Endoscopic retrograde cholangiopancreatography of 11.26.2021**

In the image above, the metallic prosthesis was positioned. The patient evolved with several clinical complications, including worsening of the cholestatic syndrome, poor general condition and sepsis of urinary focus, requiring several hospitalizations. In the last hospitalization, the patient was already in palliative care, dying two years after the diagnosis.

# DISCUSSION

Neuroendocrine cells correspond to 1% of the intestinal mucosa, 1-2% of the pancreas, and they are also present in the extrahepatic bile duct mucosa (Kim & Hong, 2016). Physiologically, they assist in digestive and metabolic functions – such as intestinal motility and glucose storage – through substances' secretion. Any of these neuroendocrine cells are subject to carcinogenesis' process and, therefore, NETs may arise along the gastrointestinal tract. Such tumors can be classified as functioning or non-functioning. Nonfunctioning ones are typically asymptomatic in early stages, and when they become large enough to obstruct the GI tract or extrahepatic bile duct, they may lead to bowel obstruction and jaundice, respectively; functional ones, on the other hand, may generate clinical conditions resulting from the secreted hormone's excess, in addition to the compressive symptoms already mentioned. For example, serotonin-producing NETs may present with diarrhea and sudden skin flushing; and insulinomas typically present with hypoglycemia, leading to symptoms as tremor, sweating and fatigue (Bonds & Rocha, 2020), (Takagi et al, 2021). Usually, gastrointestinal NETs do not manifest with symptoms due to the excess of hormone secreted, with the exception of duodenal NETs (gastrinoma, somatostatinoma) and jejunal/ileal NETs that metastasize to the liver (Gonzalez, 2020). Neuroendocrine tumors (NET) of the gastroenteropancreatic system, although rare, represent 20% of all gastrointestinal tumors (Sivero et al, 2016). In the duodenum they represent approximately 5% of tumors (Dasari et al, 2018) and in the duodenal papilla, they are even rarer, corresponding to <2% of periampullary malignancies and <1% of gastrointestinal NETs (Galetti et al, 2021). Its prevalence is higher in females 2.2:1, with the highest prevalence at the fifth decade of life (Vanoli et al, 2019). It was believed that NETs had a more indolent nature, having been previously called carcinoids, but with more studies, it was seen that they have a great malignant potential. (Iwasaki et al, 2016).

The classification and terminology of gastroenteropancreatic neuroendocrine neoplasms have been revised and changed throughout history. In 2010, the World Health Organization (WHO) classified neuroendocrine tumors of the gastrointestinal tract into low-grade (G) or intermediate (G1 and G2) and high-grade poorly differentiated NETs (histologically divided into large or small cells). In 2017, the well-differentiated high grade G3 category was added. Most duodenal gastrointestinal neuroendocrine tumors are well-differentiated. They arise in the first or second portions of the duodenum (Mollazadegan et al, 2021). They can also be classified as ampullary and non-ampular. Ampoules account for about 20% of duodenal NETs (Iwasaki et al, 2016). In the case presented here, the lesion was classified in the first biopsy as G1 and G3 after ten months. Ki67 immunohistochemical reaction was available only for the second biopsy. Therefore, it may actually have been grade 3 at the first biopsy. The diagnosis is established through Upper Digestive Endoscopy and biopsy, as was the case with the patient, the subject of this report. Computed tomography helps complete the staging (Zhang et al, 2015). The NET incidence has been increasing due to higher rates for endoscopic screening (Dasari et al, 2018). They may appear endoscopically as polypoid formations, nodules, masses, ulcers or strictures, with sizes ranging from a few millimeters to several centimeters, and may be single or multiple (Sivero et al, 2016). The reported case presented as a mass of about 3 cm, raising into the lumen of the duodenum. Tumor treatment is based on the extent and resectability of the disease, in addition to its proliferative activity (Mollazadegan et al, 2021). The optimal treatment strategy for NETs in the second portion of the duodenum has not been well established (Kato et al, 2016). The therapeutic possibilities are minimally invasive or endoscopic

resection, operative local resection with primary repair of the duodenum or duodenopancreatectomy (Dasari et al, 2018). As recommended by the European Neuroendocrine Tumor Society (ENETS), endoscopic resection should be the first choice for G1 neuroendocrine tumors, confined to the submucosal layer, up to 1 cm in diameter, without lymph node metastasis on imaging. It should be noted that, for tumors smaller than 1 cm, there is a risk for difficult to diagnose metastasis on CT. The surgeon can use tools such as frozen sections of swollen/suspected lymph nodes to assess the need to expand the resection margin (Iwasaki et al, 2016). However, presence of lesions >2 cm or lymph node metastases should be treated with surgical resection (Tamburrino et al, 2016). The case reported here presented as a lesion with infiltration of the mucosal stroma and the smooth muscle layer of the duodenal papilla, and underwent ERCP and placement of a biliary prosthesis. Radical resection with pancreatoduodenectomy may also be chosen as a first-line strategy, due to the malignant potential. In a literature review, a large number of lymph node metastases were found in tumors smaller than 1 cm. Minimally invasive pancreatoduodenectomy may be optional given the safety and oncologic efficacy of the procedure. In contrast, local surgical or endoscopic excision should not be recommended as a curative treatment, but may be an alternative for the relief of obstruction (Takagi et al, 2021). High-risk features, such as large tumor size and advanced disease, are contraindications to surgery. Such patients should be considered for systemic therapy, providing palliative relief. First-line chemotherapy for NET is cisplatin/etoposide or carboplatin/etoposide, with no second-line treatment proposed (Mollazadegan et al, 2021).

# CONCLUSION

In conclusion, the malignant potential of neuroendocrine papillary carcinoma is high, so it is very important to recognize the clinical, histological and immunohistochemical characteristics of this entity for a better treatment proposal (Suzuki et al, 2006).

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