

## Ileal neuroendocrine tumor: diagnosis by endoscopic capsule

### Tumor neuroendocrino ileal: diagnóstico por cápsula endoscópica

Matheus Dantas Gomes Gonçalves<sup>1</sup>, Vinicius Grigolli<sup>1</sup>, Nataliê Almeida Silva<sup>1</sup>, Lister Arruda Modesto dos Santos<sup>1</sup>,  
Lucimara Sonja Villela<sup>2</sup>, Vitorino Modesto dos Santos<sup>3</sup>

#### Abstract

The diagnosis of neuroendocrine tumors of the small intestine is usually challenging. They are infrequent, and the clinical course is insidious with nonspecific manifestations. Routine endoscopic and abdominal imaging studies are more often unremarkable. Therefore, distant metastases are frequently detected at the time of diagnosis. The tumor markers chromogranin A, synaptophysin, and neuron-specific enolase, and capsule endoscopy, and device-assisted enteroscopy are useful resources to establish a diagnosis. The aim was to present a case of neuroendocrine tumor of small intestine diagnosed with base in findings of the capsule endoscopy and further open surgery.

**Keywords:** capsule endoscopy; diagnosis; gastrointestinal; neuroendocrine tumors; small-intestine; surgery.

#### Resumen

El diagnóstico de tumores neuroendocrinos del intestino delgado suele ser un desafío. Son infrecuentes y el curso clínico es insidioso con manifestaciones inespecíficas. Los estudios de imágenes endoscópicas y abdominales de rutina suelen ser anodinos. Por tanto, las metástasis a distancia se detectan con frecuencia en el momento del diagnóstico. Los marcadores tumorales cromogranina A, sinaptofisina y enolasa neuronal específica, y la cápsula endoscópica y la enteroscopia asistida por dispositivo son recursos útiles para establecer un diagnóstico. El objetivo de este trabajo fue presentar un caso de tumor neuroendocrino de intestino delgado diagnosticado con base en hallazgos de la cápsula endoscópica y de una nueva cirugía abierta.

**Palabras clave:** cápsula endoscópica; diagnóstico; gastrointestinal; tumores neuroendocrinos; intestine delgado; cirugía

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#### Introduction

Neuroendocrine tumors (NETs) origin in enterochromaffin cells of the gastrointestinal (GI) tract, and small intestinal NETs (SI-NETs) arise from the submucosal crypts (Ahmed, 2020). Even with a slow growth, they usually have metastases at the time of diagnosis (Deguelte et al., 2020; Folkestad et al., 2020, Levy et al., 2020). There is a genetic influence in their etiology associated with deleting of the tumor suppressor gene  $PLC\beta 3$  that causes uncontrolled growth of the neuroendocrine cells (Kamei et al., 2020). The diagnosis depends on laboratory, radiology, endoscopy, and histopathology. We report the case of a patient with episodes of obscure intestinal hemorrhage. Being uncommon, with nonspecific symptoms, SINETs cause diagnostic pitfalls, but images by capsule

endoscopy (CE) and enteroscopy allow early diagnosis (Kim et al., 2020; Perez-Cuadrado-Robles et al., 2020; Rondonotti et al., 2020; Vasilakakis et al., 2020; Yoo et al., 2020). Intestinal bleeding of unknown origin is a common symptom of adenocarcinoma and gastrointestinal stromal tumors (GISTs), which may propitiate diagnostic challenges or misdiagnosis with NETs (Yoo et al., 2020). Currently, both the CE and the device-assisted enteroscopy have been employed in several medical centers and can optimize the timely diagnosis and treatment of the SI-NETs. The images of the SI-lumen obtained by swallowing a small digital camera, and the associated enteroscopy can take tissue samples and also perform local interventions.

(1) *Advanced General Surgery, State Worker's Hospital, São Paulo-SP, Brazil.*

(2) *Pathologic Anatomy, State Worker's Hospital, São Paulo-SP, Brazil.*

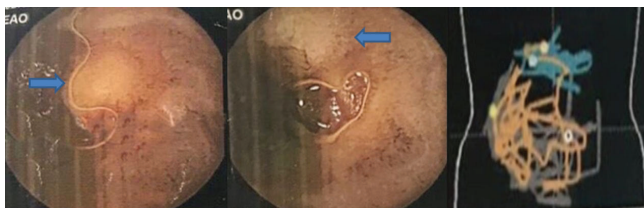
(3) *Department of Medicine, Armed Forces Hospital and Catholic University of Brasília-DF, Brazil.*

Correspondant author: [vitorinomodesto@gmail.com](mailto:vitorinomodesto@gmail.com)

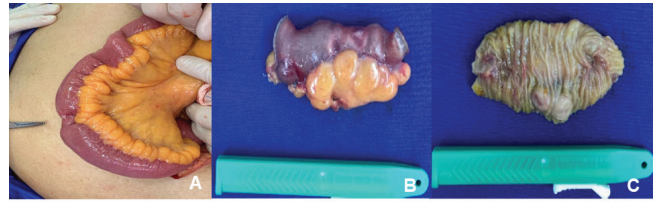


## Case report

A 54-year-old woman came to the hospital complaining of intestinal bleeding with clots starting one day ago, without abdominal pain, nausea, vomiting, or general weakness. Routine laboratory tests did not show any changes, except for hemoglobin 8.8 g/dL (in the previous month: 12.3 g/dL). Episodes of intermittent gastrointestinal bleeding occurred about two years ago, some with hemodynamic instability but without etiological clarification. There was a personal history of arterial hypertension, diabetes mellitus, dyslipidemia, hypothyroidism, and two cesarean sections. She denied smoking, alcohol drinking, and use of drugs. The initial investigation included upper digestive endoscopy, angiotomography, enterotomography, and colonoscopy, which revealed no changes. Therefore, she underwent CE (Figure 1) that detected a submucosal rounded lesion, presenting a slight vascular alteration, with the probable site in the jejunum, suggesting a diagnosis of GIST. Surgical exploration revealed a lesion 70 cm away from the ileocecal valve, whitish in appearance, and not adhered to deep structures. The option was a segmental latero-lateral enterectomy anastomosis in two planes. Anatomopathological study of the surgical specimen revealed a neuroendocrine tumor (NET) with infiltration, including the visceral serosa (Figures 2A and B), pT4, histological grade 1. The immunohistochemical evaluation showed chromogranin A (CgA), synaptophysin (SYP), and AE1/AE3 positive, in addition to KI-67 positive (1% of cells). Taken together, the morphological findings and the immunohistochemical profile were consistent with the diagnosis of NET. Therefore, enlargement of the surgical margin in addition to lymphadenectomy was necessary. During the evaluation of the second surgical specimen (Figure 2C), we found another 0.8 mm NET, besides 4 of 11 lymph nodes affected by the histological grade 1 tumor. Postoperative evolution was satisfactory, and the asymptomatic patient remains under an outpatient follow-up at the Surgical Oncology Service.



**Figure 1:** Images of the capsule endoscopy study indicate a submucosal lesion with a probable jejunal location.



**Figure 2:** Image of the small intestine during laparotomy (A); excised segment 5.5 cm long, smooth brownish serosa and adjacent yellowish fatty tissue of lobed aspect (B); opened intestine with brownish wall 0.3 cm thick, mucosa with preserved folds, and a vegetative lesion (2.2 cm x 0.8 cm x 0.3 cm) distant 1.8 cm from surgical margins (C).

## Discussion

The 54-year-old woman herein reported had an SI-NET diagnosed with base in data of the CE and underwent an uneventful open surgery with curative intent. She only claimed episodic gastrointestinal bleeding with clots causing a drop in the hemoglobin level, but previous routine imaging studies did not detect the etiology. Despite the various techniques for evaluating the small intestine, in patients with small lesions, routine exams including CT, MR enteroclysis, and CE often give negative results in preoperative work-up. Besides, none of them can replace the manual bowel palpation at the surgery's time for detection of the small lesions (Deguelte et al., 2020). Studying 56 patients with preoperative CT scans and 47 with SRS, CT localized a primary NET of small bowel in 27 of 56 (48 %) and nodal metastases in 33 of 56 (79 %). At the same time, SRS showed intra-abdominal uptake in 35 of 47 (74 %) cases. However, 10% to 15 % of the tumors are preoperatively unsuspected by both imaging exams. The authors concluded that surgical exploration still plays an important role in the diagnosis of these tumors (Dahdaleh et al., 2013). A retrospective study of 194 patients with SI-NET and preoperative CT imaging of metastases in abdominal lymph nodes, liver, and extra-abdominal metastases revealed the pattern of suggestive hypervascular lesions (tumor in the intestinal wall; mesenterium mass with unsharp borders and calcification; enlarged mesenterium lymph nodes; and liver metastases). Patients with a preoperatively confirmed diagnosis had longer median overall survival than those with an unknown diagnosis before surgery (10.2 years vs. 7.3 years). The authors highlighted the role of preoperative diagnosis and elective surgery on better outcomes (Folkestad et al., 2020). An initial concern was about GI adenocarcinoma or GIST (Kim et al., 2020; Yoo et al., 2020). Besides, metastases from melanoma, lung cancer, breast cancer, cervical cancer, sarcoma, and colon cancer are more common than primary tumors (Kim et al., 2020). Because the upper digestive endoscopy, angiotomography, abdominal tomography,

and colonoscopy of control did not show any change, we performed the CE, utilized since 2001 to visualize the small bowel and its mucosa by high-quality images. Currently, it is a standard method with a higher diagnostic accuracy and sensitivity than other radiologic tools, allowing earlier diagnosis and treatment of tumors (Rodrigues et al., 2017). With good diagnostic resolution and as the first-line therapeutic procedure for small intestine diseases DAE depends on CE's previous evaluations (Pérez-Cuadrado-Martínez et al., 2020). This useful noninvasive initial approach for small-bowel tumors allows the exam of the entire small bowel, aids in determining the extent of tumor involvement and monitors the response to treatment and can help the decision on the initial approach route for a DAE procedure. Besides, CE can have a better diagnostic yield than other routine imaging modalities to detect of smaller jejunoileal polyps (Kim et al., 2020). The concern about CE was related to eventual difficulty of distinguishing submucosal lesions from innocent bulges. However, the criteria and scores proved to be accurate to distinguish these changes, such as the smooth, protruding lesion index on CE score – SPICE (Rodrigues et al., 2017). Another possible concern is the difficulty of CE to measure with needed accuracy the lesion size. The 3D CE device has a similar performance as the conventional CE, with tools of reconstruction and size measurement, optimizing the characterization of the small subepithelial tumors. Thirty one patients, 20 males and a mean age of 44.5 years, underwent the procedure for visualization of the small bowel; completion rate was 77.4%, and the detection rate was 64.5%. Subepithelial tumor diagnosis is the main promising of the 3D CE (Nam et al., 2020). With the known site of an intestinal lesion, the histopathological study of tumor samples showed CgA, SYP, and AE1 /AE3 positive, establishing the final SI-NET diagnosis. After a careful revision of the small bowel diseases small bowel diseases excised tumor with the loco-regional lymph nodes, the patient underwent an enlargement of the surgical margin and lymphadenectomy. NETs were considered rare; however, with the advancement and availability of new diagnostic modalities such as the endoscopic capsule, an increasing number of this neoplasia has been diagnosed (Ahmed, 2020; Deguelte et al., 2020; Folkestad et al., 2020; Levy et al., 2020). The majority of NETs are found in the GI and bronchopulmonary locations (Ahmed, 2020). The small intestine is not the most frequent area of NETs but is the most common primary site giving origin to distant metastases (Ahmed, 2020; Deguelte et al., 2020). The majority of tumors are non-functioning and usual manifestations are abdominal pain, partial intestinal obstruction, and hemorrhage (Ahmed, 2020; Deguelte et al., 2020; Folkestad et al., 2020; Kamei et al., 2020). In accordance with the WHO, the well-differentiated NETs are classified by Ki-67 index (%) and mitotic index/10 HPF, as grade 1 (< 3% and < 2); grade 2 (3-20% and 2-20); and grade 3 (> 20% and > 20). The poorly differentiated are grade 3, small cell

type, and large cell type, while mixed NETs have at least 30% of other components as acinar or squamous cell carcinoma (Ahmed, 2020). The SINETs have a higher incidence than the small bowel adenocarcinomas, being the most frequent primary small bowel malignancy, representing 25% of the GI-NETs (Ahmed, 2020). The annual incidence of jejunoileal NETs is from 1 to 2 per 100000 persons-years, and over 60% are in the terminal ileum and up to 60 cm of the ileocecal valve (Ahmed, 2020; Deguelte et al., 2020; Folkestad et al., 2020; Kamei et al., 2020). The mean age at diagnosis is in the 6th and 7th decades, without gender difference (Ahmed, 2020). SI-NETs more often develop as slow-growing and multifocal ileal lesions (89%); significant is the tendency to invasion of *muscularis propria* at diagnosis (70%), implants to regional lymph nodes, and hepatic metastasis (50%), whatever the tumor size (Ahmed, 2020; Deguelte et al., 2020; Folkestad et al., 2020; Kamei et al., 2020). Therefore, the earliest diagnosis is established best is the outcome. More useful diagnostic resources include determination of CgA, SYP, neuron-specific enolase (NSE), and 5-hydroxy indole acetic acid (in cases of carcinoid syndrome); CE and balloon-assisted or spiral endoscopy; and imaging study as SRS (Octreoscan), Ga-DOTATATE PET/CT or 111In-TPA-Octreotide scan (Ahmed, 2020; Deguelte et al., 2020; Levy et al., 2020; Pérez-Cuadrado-Robles et al., 2020). Promisors in monitoring the disease are circulating tumor cells or tumor transcripts (Kim et al., 2020). The estimated detection rate of small-bowel tumors by capsule is from 2% to 9%, and capsule retention is rare (up to 2.6% of cases), more often in intestinal obstruction (Levy et al., 2020). Folkestad et al., reviewed data of 186 patients with SI-NETs and median age of 68 years, 54.3% men, and most of them underwent surgery for curative purposes or to prolong overall survival. Their median overall survival was 9.7 years, and 36 of 120 (30%) patients presented recurrence of disease after a median follow-up time of 5.5 years (Folkestad et al., 2020). Nine of 23 (39.1%) patients with SI-NET had other synchronous abdominal cancer. Tumor stage, carcinoid heart disease, synchronous cancer, preoperatively known SI-NET, elective surgery, curative surgery, and age were all associated with survival (Folkestad et al., 2020). The first treatment option is tumor resection with regional lymphadenectomy (Ahmed, 2020; Deguelte et al., 2020; Folkestad et al., 2020; Kamei et al., 2020); chemotherapy does not improve well-differentiated jejunoileal NETs, while capecitabine and temozolomide are utilized to treat metastatic poorly differentiated tumors (Ahmed, 2020; Deguelte et al., 2020; Folkestad et al., 2020; Kamei et al., 2020). The 5-year survival rate drops from 60% to 18% in the presence of liver metastases, and these implants can be managed with octreotide, transarterial embolization, radiotherapy with yttrium 90- or 177-lutetium-DOTA-lanreotide, TACE, and radiofrequency (Ahmed, 2020; Deguelte

et al., 2020). NETs in advanced phases may have an increase in estimated survival time if submitted to cytoreductive surgery in association with multidisciplinary management (Deguelte et al., 2020; Kamei et al., 2020). Although with the inherent weaknesses of a single case study, the authors believe that this report may enhance the knowledge about novel diagnostic modalities.

## Conclusion

NETs are currently growing in number in daily practice, mainly due to the best knowledge about the biological mechanisms of these tumors and advanced resources for diagnosing this condition. SI-NETs should be among the possible causes of an occult digestive bleeding, and the use of the CE has been of great value to establish the diagnosis.

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