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## Huge recurrent gastric neuroendocrine tumor: a second-line chemotherapeutic dilemma

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### ABSTRACT

Chemotherapy is considered “state of the art” for the treatment of poorly differentiated neuroendocrine neoplasms. Unfortunately, there is no standard effective post-first-line treatment for relapsing high-grade gastroenteropancreatic neuroendocrine neoplasms. We report the case of a patient with a gastric neuroendocrine carcinoma stage IV, with massive gastrointestinal bleeding at diagnosis. After the first line of platin-based chemotherapy a major tumoral response was documented, but the patient relapsed after 4 months. A second line of chemotherapy treatment was given, with the FOLFOX regimen, and the patient has been free of progression for almost 2 years. There is no second-line standard treatment accepted for this type of carcinoma, but 5-fluorouracil combined with oxaliplatin showed interesting antitumor activity.

### Keywords

Carcinoma; Neuroendocrine; Stomach Neoplasms; Neoplasm Metastases; Medical Oncology

### INTRODUCTION

Neuroendocrine neoplasms (NENs), which arise from the gastroenteropancreatic (GEP) system, define a group of heterogeneous diseases with a growing incidence.<sup>1,2</sup> According to histopathological characteristics, NENs can be classified in neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). NECs usually show more aggressive behavior, and patients are usually diagnosed with metastatic disease.<sup>2,3</sup> The European guidelines recommends that systemic chemotherapy should be the treatment of choice for metastatic poorly differentiated NECs.<sup>2,4</sup> We present the case of a poorly differentiated gastric neuroendocrine carcinoma that had a sustained major

response to a second line of chemotherapy with 5-fluorouracil (5-FU) combined with oxaliplatin.

### CASE REPORT

A 63-year-old male with no previous significant medical history was admitted to our department after hemorrhagic shock. He complained of dysphagia and asthenia for 2 weeks followed by abdominal pain and melena over the past 3 days. On physical examination, he presented with pale skin, blood pressure of 99/69 mmHg and tachycardia of 110 bpm. There were no palpable masses on the abdomen. The laboratory

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tests showed a hemoglobin level of 6.8 g/dL (reference value [RV]: 14-17.5 g/dL), a hematocrit of 20.5% (RV: 40-54%), and a normal platelet count. The liver function tests, renal function tests, and coagulation results were normal. The electrocardiogram, and the chest and abdominal x-rays showed no abnormal findings. A gastroesophageal transit and an upper abdominal endoscopy were performed; an important ulcerated tumor was seen, which involved the esophagogastric junction and the gastric fundus with active bleeding (Figure 1A).

A computed tomography (CT) scan (Figure 1B) was also performed and revealed extensive gastric wall thickening extending from the cardia through the minor curvature. Large masses in the gastrohepatic ligament and celiac trunk were also described, which were consistent with a conglomerate of lymph nodes. The size of the primary tumor was around 10.6 × 7.8 × 8.4 cm, and the left gastric artery was invaded. The CT also showed several enlarged lymph nodes in the retroperitoneum, a 20 mm mass in segment VII of the liver, nodules of 16 mm and 10 mm in the right adrenal gland, and 12 mm in the left adrenal gland, which were consistent with metastases.

The gastric tumor was biopsied. Microscopic examination showed malignant epithelial proliferation forming nests of large cells, with no glandular differentiation. Immunohistochemistry disclosed diffuse cytokeratin AE1/AE3 and diffuse synaptophysin staining,

focal chromogranin positivity and Ki-67 proliferation index of 90%. Histopathological diagnosis was gastric carcinoma with neuroendocrine differentiation, grade 3.

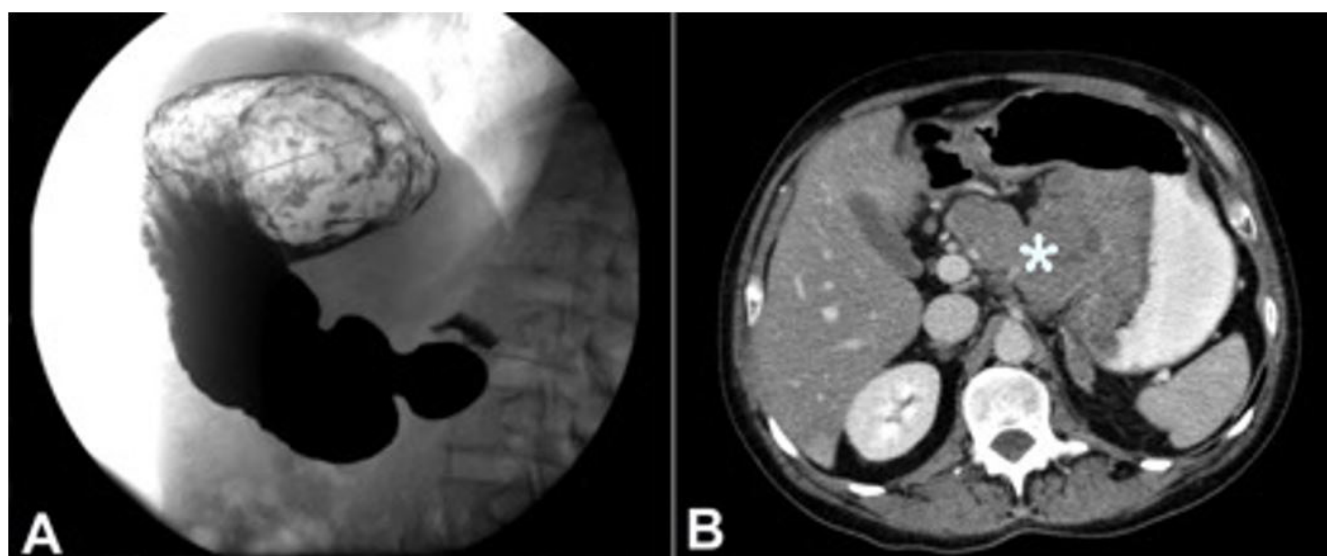
(Figure 2). As the biopsy was taken by endoscopy, the mitotic index could not be established in 10 high-power fields (HPF). However, in an isolated HPF, four mitotic figures were found.

The extended laboratory blood work-up showed an elevated chromogranin A of 586 ng/mL (RV: <36.4 ng/mL) and enolase of 94.8 ng/mL (RV: ≤15 ng/mL).

The clinical staging was cT4N1M1, stage IV, according to the tumor, node, and metastasis (TNM) classification for gastric endocrine tumors (European Neuroendocrine Tumor Society).<sup>5-7</sup> The case was presented at the hospital multidisciplinary tumor board and systemic treatment was initiated with carboplatin (AUC5, at day 1) and etoposide (100 mg/m<sup>2</sup> at days 1, 2, and 3). The patient was discharged after the first cycle of chemotherapy; he was clinically steady, tolerating oral diet and without any signs of bleeding.

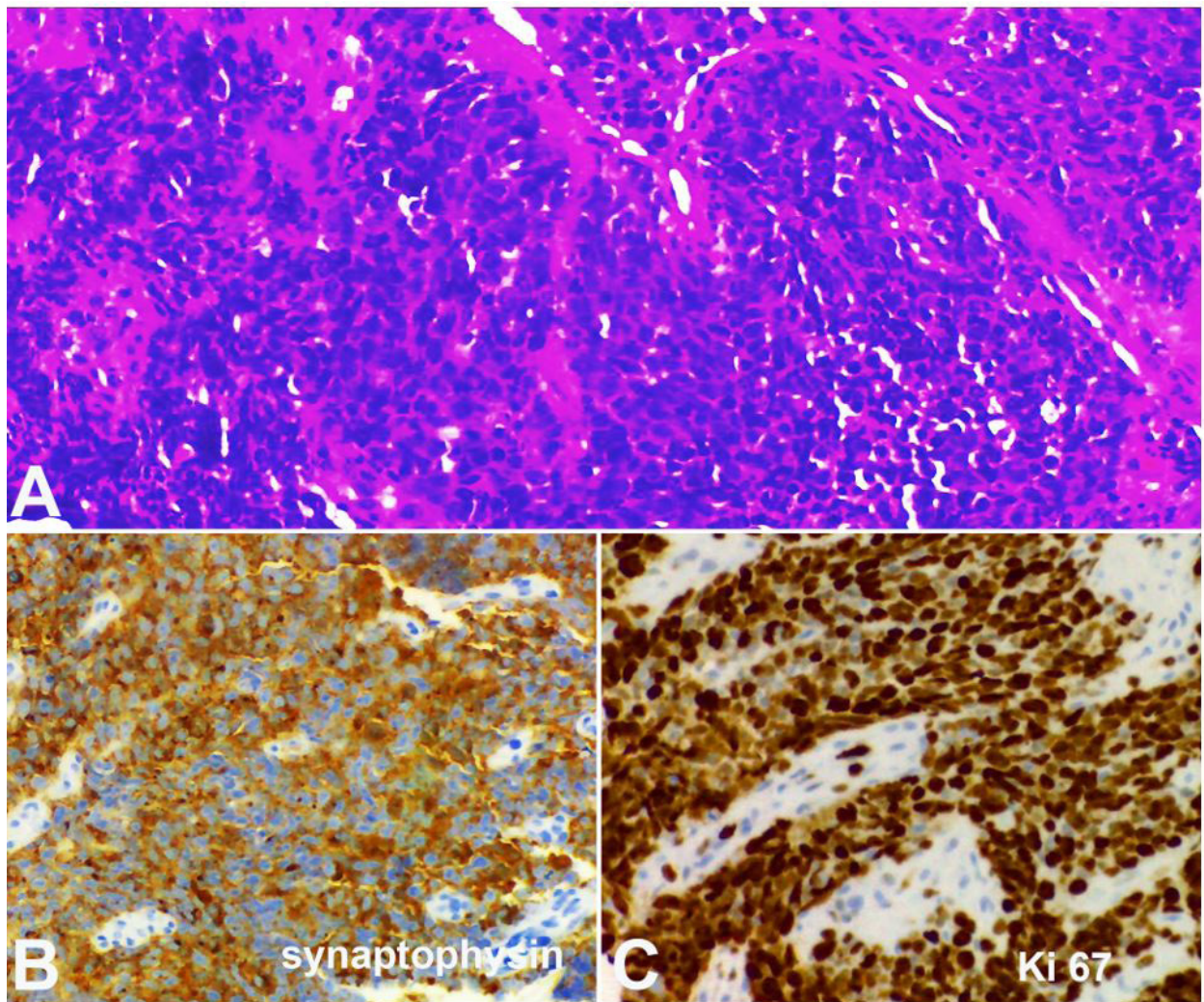
After the end of six cycles of chemotherapy, a control CT scan (Figures 3A and 3B) revealed a partial tumoral response, with almost complete recovery of the gastric wall; however, a lymph node of 20 mm remained in the celiac axis.

On the fourth month of follow-up, a new CT scan (Figure 4A) showed a 70 mm mass in the gastrohepatic ligament.

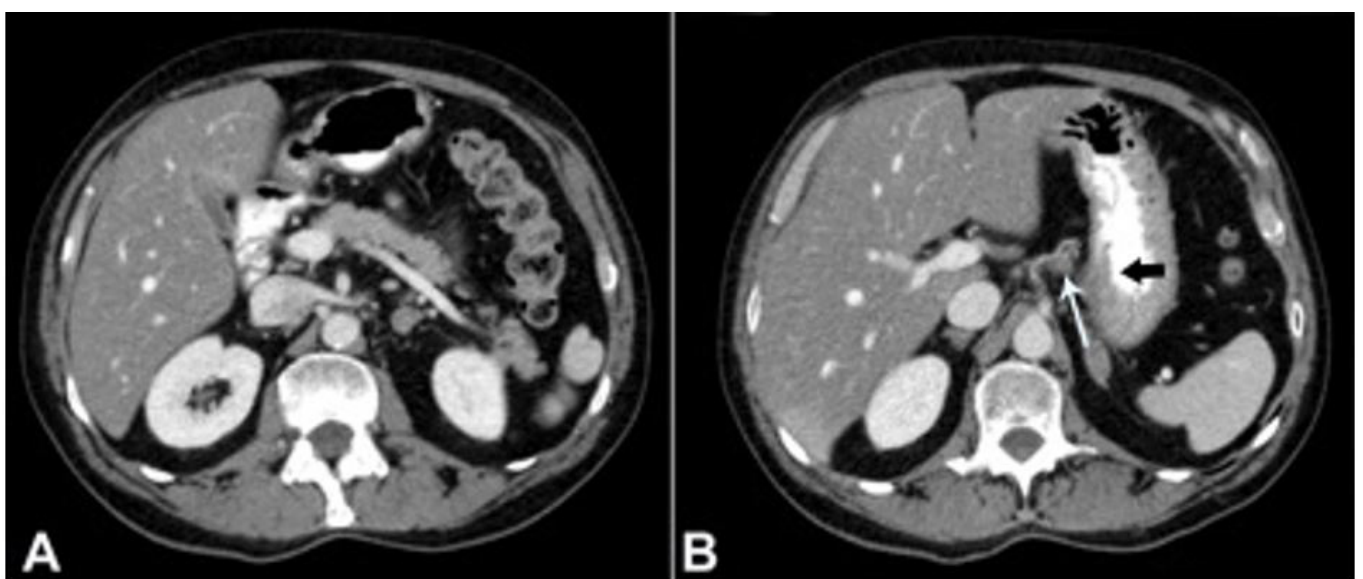


**Figure 1. A** – Gastroesophageal transit showing a huge mass involving the esophagogastric junction and the gastric fundus; **B** – CT scan showing an exophytic mass in the lesser gastric curvature referring to the known gastric cancer (asterisk).

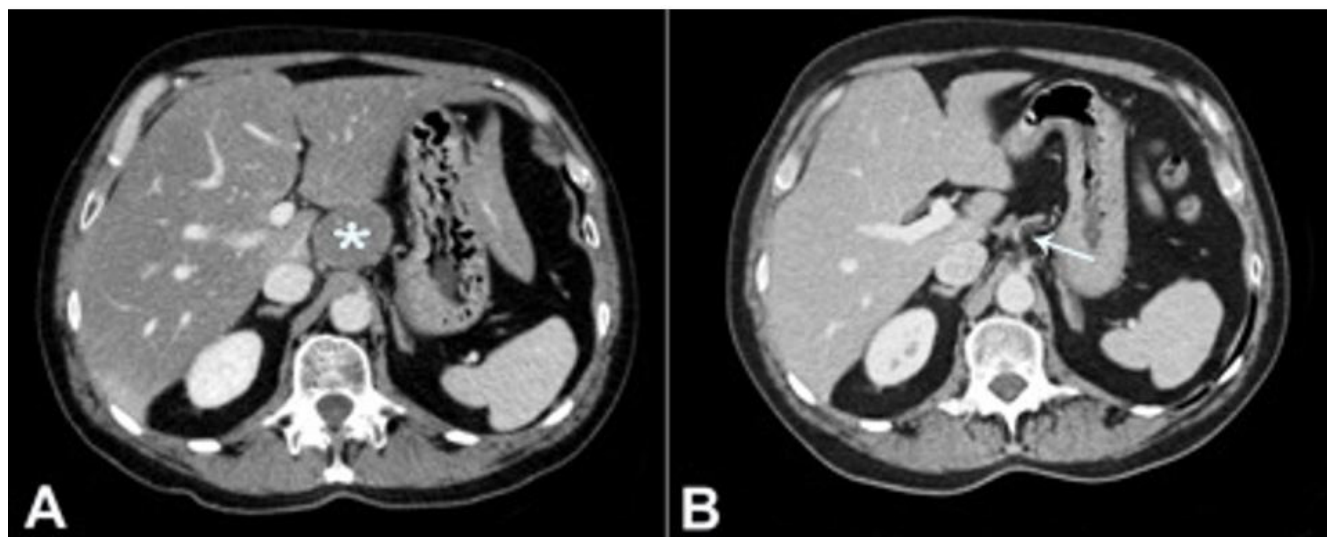




**Figure 2.** Photomicrography of the gastric biopsy. **A** – Nests of a poorly differentiated carcinoma stained with hematoxylin-eosin; **B** – Diffuse cytoplasmic synaptophysin immunostaining; **C** – High cell proliferation index, showing 90% of Ki-67 positive cells.



**Figure 3.** **A** and **B** – CT-scans revealing a major tumoral response, with almost complete recovery of the gastric wall (black arrow), but a lymph node of 20 mm remained in the celiac axis (white arrow).



**Figure 4.** **A** – CT scan showing local relapse (asterisk); **B** – The sustained major tumoral response after the 44th cycle of chemotherapy (arrow).

The patient started second-line treatment with mFOLFOX6 (oxaliplatin 85 mg/m<sup>2</sup>; folinic acid 200 mg/m<sup>2</sup>; 5-FU 400 mg/m<sup>2</sup>; and an infusion of 2 400 mg/m<sup>2</sup> for 46 hours), every 14 days. Three months after, on re-evaluation of the first CT scan, there was a partial tumoral response. The patient presented with grade 3 neuropathy, which led to the discontinuation of oxaliplatin on the 16th cycle, while the CT scans showed a sustained partial response, and continued with the *De Gramont* scheme (folinic acid 200 mg/m<sup>2</sup>; 5-FU 400 mg/m<sup>2</sup>; and an infusion of 2 400 mg/m<sup>2</sup> for 46 hours, every 14 days). The patient has been free of tumor progression for 24 months, on the 44th cycle of the *De Gramont* scheme and the last CT scan (Figure 4B) documented a sustained major tumoral response.

The patient signed an informed consent and the case report is in accordance with the institution's ethics committee.

## DISCUSSION

The classification for GEP NENs was recently revised. The World Health Organization defines grade 3 GEP carcinomas according to a Ki-67 greater than 20% and/or mitosis greater than 20/HPF. The recommended therapeutic regimen for grade 3 neuroendocrine tumors is the systemic chemotherapy with platinum plus etoposide.<sup>2,4,8</sup> Grade 3 carcinomas show diverse responses and outcomes to chemotherapy.

Some studies have shown a correlation between Ki-67 and the response to a platinum-based chemotherapy, while others have shown longer survival rates with lower Ki-67 values.<sup>9-11</sup> A new sub-classification, which was recently proposed by Fazio and Milione,<sup>12</sup> uses the term "tumor" for morphological well-differentiated neoplasms, and "carcinoma" for poorly differentiated neoplasms, and classified GEP NENs according to the Ki67 index. In this setting, they suggest using an alkylating-based or oxaliplatin-based chemotherapy for poorly differentiated GEP NET G3, with a Ki-67 inferior to 55%, while the poorly-differentiated GEP NECs with a Ki-67 superior to 55% should be treated with cisplatin/carboplatin plus etoposide.<sup>12</sup>

Treatment with first-line chemotherapy usually results in response rates around 42%; the median duration of response is approximately 9.2 months.<sup>11</sup> However, our patient responded well to the platin-etoposide chemotherapeutic regimen, but relapsed within 4 months. There is no standard second-line therapy established for GEP tumors. The European Society for Medical Oncology guidelines refer to promising results regarding a fluoropyrimidine drug associated with oxaliplatin or irinotecan.<sup>2</sup> The response rate with irinotecan is known to be around 31%, with disease stabilization also around 31%, and a median progression free survival (PFS) of 4 months.<sup>13</sup> Alternatively, Hadoux et al.<sup>14</sup> evaluated the antitumor activity of 5-FU and oxaliplatin (FOLFOX) chemotherapy in poorly differentiated



grade 3 neuroendocrine carcinomas that relapsed after the cisplatin-based regimen. This French retrospective study revised 17 patients—all with distant metastases—in which 11 patients (64%) had a stable disease/partial response with FOLFOX; the median PFS was 4.5 months. An Italian Group<sup>15</sup> also analyzed the response to the oxaliplatin-based scheme (n = 78) and documented a PFS of 8 months. After receiving 16 cycles (approximately 8 months) of FOLFOX, our patient is still on the *De Gramont* scheme with good tolerability, showing a PFS (until now) superior to the aforementioned studies.

The activity of other chemotherapy regimens has been evaluated only in small retrospective studies for poorly differentiated tumors. Welin et al.<sup>16</sup> tested temozolomide alone or in combination with bevacizumab and capecitabine, in patients who had a platinum failure, achieving a median overall survival of 22 months. Other approaches, such as monotherapy docetaxel, or FOLFIRI, showed similar results.<sup>13,17</sup>

## CONCLUSION

The prognosis for grade 3 NECs is dismal.<sup>6,10</sup> Evidence on what should be the second line of chemotherapy is still lacking. Our patient presents an excellent response to the FOLFOX regimen as a second line of chemotherapy; nevertheless, further larger, prospective studies and guidelines are needed to establish an optimal second-line treatment.

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