Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medical Oncology

Gastric Metastatic Grade 3 Well-Differentiated Neuroendocrine Tumor: A Case Report

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DOI: 10.36347/sjams.2022.v10i02.012 | **Received:** 06.01.2022 | **Accepted:** 10.02.2022 | **Published:** 13.02.2022

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Abstract **Case Report**

Background: Neuroendocrine neoplasms (NENs) are rare tumors .They are defined by the expression of specific biomarkers. Progress in pathological diagnosis has allowed a better identification and classification of these tumors. The 2019-revised World Health Organization (WHO) classification of tumors of endocrine organs classifies grade 3 gastroenteropancreatic neuroendocrine neoplasm (GEP-NENs) into well-differentiated neuroendocrine tumors (NET G3) and poorly differentiated neuroendocrine carcinomas (NEC G3). There are few reported cases of NET G3 occurring in the stomach. ***Case presentation:*** A 63-year- man who suffers from dysphagia and Melaena. Fibroscopy revealed a ulcero-budding process of the cardia. Pathologic examination concluded on NET well-differentiated grade 3. Surgical exploration showed peritoneal carcinomatosis and histologically confirmed liver metastases. He underwent chemotherapy with modified folfox 4 protocol for 3 months with satisfactory clinico-morphological response. ***Conclusion***: A definite diagnosis of NET G3 or NEC G3 must be made to determine the appropriate treatment strategy for patients with GEP-NEN G3. the efficacy of treatments for G3 NETs appear modest, as evidenced by the short PFS observed, therefore, more effective therapies are needed with Further case reports and case series. Keywords: Neuroendocrine tumor G3, stomach, modified FOLFOX 4.

Keywords: Gastric, Neuroendocrine Tumor.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare tumors .They are defined by the expression of specific biomarkers, such as synaptophysin and chromogranin A (CGA), which can be absent in high-grade NEN [1–4]. They are are most often located in the lung and in the digestive tract. Neuroendocrine neoplasms (NEN) of the digestive tract are rare tumors with a rising incidence due to diagnostic improvement [5]. Progress in pathological diagnosis has allowed a better identification and classification of these tumors. The 2019-revised World Health Organization (WHO) classification of tumors of endocrine organs classifies grade 3 gastroenteropancreatic neuroendocrine neoplasm (GEP-NENs) into well-differentiated neuroendocrine tumors (NET G3) and poorly differentiated neuroendocrine carcinomas (NEC G3) table 1. The concept of NET G3 was first described in the WHO 2017 classification of pancreatic tumors related to multiple endocrine neoplasia (MEN) syndromes. Cell differentiation is a major prognostic marker of neuroendocrine neoplasms [7, 8].Indeed, regardless of the stage or the location of the primary tumor, it has been highlighted [6] that well-differentiated lesions have a better prognosis than poorly differentiated ones [7, 9–11]. Therefore, NET G−3 should benefit from a different therapeutic approach but more studies are needed to validate their precise management [12]. There are few reported cases of NET G3 occurring in the stomach, and there are currently no data on antitumor therapy for patients with metastatic gastric NET G3.

Table-1: The 2019 World Health Organization (WHO) classification for neuroendocrine neoplasms (NEN) of the digestive tract.

Well-Differentiated NEN [1]	Ki-67 Index (%)	Mitotic Index (HPF [2]/10 HPF)
NET [3] G-1 (low-grade)	<3	<2/10
NET G-2 (intermediate-grade)	3–20	2–20/10
NET G-3 (high-grade)	>20	>20/10
Poorly differentiated NEN		
NEC [4] G-3 Small-cell type, Large-cell type	>20	>20/10
Mixed neuroendocrine–nonneuroendocrine neoplasm (MiNEN)		

[1] NEN: neuroendocrine neoplasm; [2] HPF: high-power field; [3] NET: neuroendocrine tumor; [4] NEC: neuroendocrine carcinoma.

CASE REPORT

A 63-year-old Moroccan man with no particular history, especially no family history of MEN, who consults for dysphagia and melaenas. Gastric fibroscopy revealed a non-stenosing ulcero-budding process of the cardia, then the patient was referred to our hospital. Laboratory analysis revealed a total peripheral leukocyte count of 6500/mm3, with normal tumor markers (carcinoembryonic antigen [CEA], 2 ng/mL; cancer antigen 19-9 [CA 19-9], 11 U/ mL). His height was 177 cm, and his weight was 65 kg. Computed tomography revealed a locally advanced gastric tumor with regional adenopathies with no suspicious distant lesions **(Fig. 1).** The anatomopathological examination of a biopsy specimen gave a clear diagnosis of well-differentiated grade 3 (Immunohistochemically staining revealed that diffuse staining for synaptophysin and chromogranin A, and focal staining for CD56 and index MIB-1 were greater than 20% Protein CK7, CK20 and S-100 results were negative The patient's Ki67 index was 30%) **(Fig. 2).** The chormogranin A and 5HIAA biological assays came back negative. The patient was then referred for surgery. The intraoperative examination after a midline laparotomy revealed the presence of peritoneal nodules and suspicious liver lesions, therefore oncological surgery was not retained. The anatomopathological examination of the biopsies was in favor of secondary localizations of the known primary. We judged liver and peritoneal metastases to be unresectable. The patient was discharged on the sixth postoperative day. Two months after surgery, the patient started chemotherapy with the modified folfox4 oxaliplatin (85 mg/m2), calcium folinate (400 mg/m2) plus 5FU (2500 mg/m2) every 15 days. The morphological evaluation of his disease revealed lesion stability according to RECIST 1-1 criteria (7% reduction in the size of the gastric tumor). The clinical evaluation was in favor of a clinical benefit comparing to the initial digestive symptomatology.

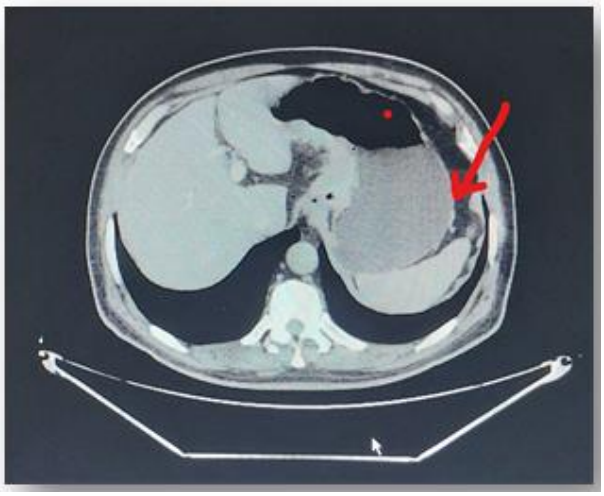

Fig-1: Abdominal section of a CT scan showing a process of the gastric wall which originates at the cardia level and which infiltrates the lesser omentum and the locoregional lymph nodes classified cT4aN3aM0

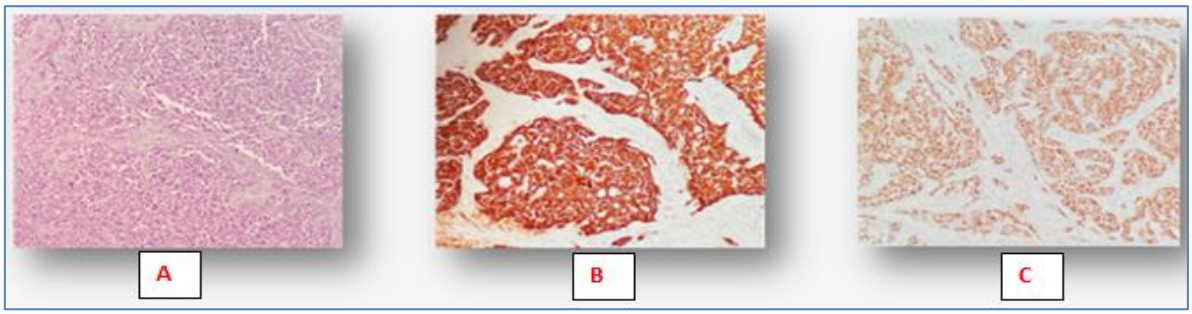

Fig-2: The anatomopathological examination showing a clear diagnosis of well-differentiated grade 3(A= tumor proliferation with neuroendocrine differentiation (HE, Gx400), B= strong and diffuse labeling of the anti-synaptophysin antibody, C= Diffuse expression of anti-chromogranin A antibody)

DISCUSSION

The incidence of neuroendocrine tumor was 1.09 per 100,000 persons in 1973, increasing to 6.98 per 100, 000 persons by 2012 in the USA [13].Studies show that NET G-3 are more often found in the pancreas with a frequency ranging from 10% to 65% [14,15]. Other main tumor sites are the colon/rectum and stomach, with frequencies ranging from 8% to 24% and 8% to 29%, respectively [15].

Specific biomarkers such as plasma CGA, plasma neuron specific enolase (NSE) and urinary 5-hydroxyindoleacetic acid (5-HIAA) are frequently used in NEN management. Plasma CGA helps monitor evolution and treatment response in well-differentiated NET [16-18] whereas NSE is more frequently assessed in high-grade NEN [19,20].In various works, the overall survival (OS) for NET G-3 patients was longer than for NEC patients: median survival ranged from 41–99 months versus (vs.) 5.3–17 months [21].

The 2019 revised WHO classification of tumors of endocrine organs classifies grade 3 GEP-NENs into NET G3 and NEC G3 categories, indicating well- or poorly differentiated neoplasms, respectively. Cytologically, neuroendocrine tumors usually have abundant granular cytoplasm, which results in a low nuclear to cytoplasmic (N/C) ratio, and stippled chromatin. Cells of NEC G3 neoplasms have a lesser amount of granular cytoplasm and a higher N/C ratio [23, 24]. Immunohistochemically, both NET G3 and NEC G3 have a Ki-67 index of greater than 20% and an amitotic index of greater than 20 per 10 high-power fields. There are some differences in their pathologic characteristics. The rate of positive chromogranin A is 100% in NET G3 and 88.6% in NEC G3, with positive synaptophysin rates of 95.2% and 93.8%, median Ki67-LI values of 28.5% and 80.0%, loss of retinoblastoma protein (Rb) expression in 0% and 54.5%, presence of a KRAS gene mutation in 0% and 48.7%, loss of Rb expression with a KRAS mutation in 0% and 30%, and p53 expression in 0% and 75%, respectively [25, 26]. The expression of Rb and p53 is particularly useful especially in patients who are difficult to differentiate between NET G3 and NEC G3 because the expression rate is high in NEC G3, but neither is expressed in NET G3. 18F-Fluorodesoxyglucose (18F-FDG) PET-CT is recommended to help in NEC diagnosis and often indicates poor prognosis when positive in well-differentiated NEN [27-29].

The primary treatment for GEP-NEN G3 is surgery. The high-grade malignancies NET G3 and NEC G3 have already developed distant metastases by the time of the primary resection, and even if the primary lesions are completely removed, they can recur on a long-term basis. Liver-directed therapies can be performed alone or in combination with surgery. Indeed, they have shown good clinical and morphological responses for well-differentiated G-1 and G-2 NET, especially when liver burden is important or in the presence of a secretory syndrome. To date, there is no specific data for this therapeutic approach in NET G-3 [30, 31]. Both PROMID and CLARINET prospective trials have validated the anti-proliferative effect of somatostatine analogues (SST) in GEP-NET G-1 and G-2 [32–34]. They are mainly used for indolent well-differentiated NET in the first-line setting and for treatment of the secretory syndrome [35, 36]. Both studies also showed that SST has a higher efficacy in tumors with low Ki-67 index, low hepatic load and slow pretreatment growth [37–39]. There were no G-3 lesions included in these trials so the use of SST in this population should be limited and only considered with a close monitoring for its effect on the secretory syndrome. In a large retrospective cohort of G3 NETs treated at a single institution, somatostatin analogues SST are indicated for patients with symptomatic carcinoid syndrome, which appears to be rare in this population. However, some cases may show disease control after treatment with long progression-free survival [40].

Chemotherapy is a key treatment in metastatic PanNET irrespective of grade. In gastric net or other non-pancreatic net there is no standard of care regarding chemotherapy. Various regimens have been evaluated with studies showing low response rates, especially with alkylant-based treatments [41–43]. In metastatic NET G-3 the efficacy of platinum-based chemotherapy seems limited, with response rates ranging from 0% to 10% Furthermore, a monocentric study on G-2 and G-3 NEN from various sites (including 11 NET G-3 patients) evaluated the effect of capecitabine-temozolomide (CAPTEM) with 22% patients treated in the first line setting [44]. There was a trend towards improved median PFS in patients with NET G-3 and Ki-67 index. In a recent retrospective study of patients treated at Mayo Clinic for NET G3, CAP TEM was found to be the most commonly used treatment with reasonable efficacy and disease control. FOLFOX was found to be an acceptable treatment option with the longest PFS. The etoposide platinum protocol could be considered early in patients with clinically aggressive G3 TEN, particularly if there are concerns about a poorly differentiated component [45].

In the era of immunotherapy, data from prospective phase I or II clinical trials and retrospective studies, all with small sample sizes, on the role of immunotherapies on G3 GEP-NET conclude that ICI monotherapy (pembrolizumab, spartalizumab and avelumab). Only toripalimab showed moderate clinical activity on NEN with Ki-67 ≥ 10%, PD-L1 expression ≥ 10% or elevated TMB. However, none of these diets is recognized as a treatment option in this context. While the nivolumab ipilimumab combination may represent an extremely promising treatment option for G3 NET. It is therefore necessary to conduct prospective clinical trials with a large sample of

pathologically confirmed G3-NETs to assess the efficacy of the above immunotherapies [46].

In our patient, with symptomatic gastric cancer, the choice of chemotherapy was justified. The FOLFOX 4m protocol as in the literature seems to be effective during the first 3 cycles.

CONCLUSIONS

NET well-differentiated G-3 is rare tumors showing specific features of clinical interest. Their prognosis seems closer to that of NET G-2 rather than that of NEC, but with a worse OS. If in doubt, pathologic reassessment by a NEN expert should be easily proposed. The efficacy of treatments for G3 NETs appear modest, as evidenced by the short PFS, therefore, more effective therapies are needed.

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