

Neuroendocrine carcinoma of the esophagogastric junction: a case report

G. PAPPALARDO¹, G. POILLUCCI¹, A. TORNESE², F.M. FRATTAROLI¹,
P. LIBERATORE¹, F. FRANCIONI¹

SUMMARY: Neuroendocrine carcinoma of the esophagogastric junction: a case report.

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Gastrointestinal neuroendocrine neoplasms are extremely rare. EsophagoGastric Junction (EGJ) is exceptionally struck by these neoplasms. The prognosis of these tumors is poor owing to their aggressive malignancy. A 77-year-old man was admitted with epigastric pain and dysphagia due to an ulcerative lesion of the EGJ, initially diagnosed by endoscopic biopsy as a moderately differentiated

adenocarcinoma.

Computed tomography scan revealed full thickness invasion of the EGJ and two abnormal lymph nodes along the lesser curvature of the stomach (cT2 N1 M0). An esophagectomy and partial gastrectomy with mediastinal and lesser curvature lymphadenectomy was performed. A cervical esophagogastric anastomosis completed the surgical procedure. The patient was discharge on the 11th postoperative day. Histology revealed a high grade neuroendocrine carcinoma combined with an adenocarcinoma of the EGJ (pT2 pN1 G3). The rarity of these tumors and the particularity of their heterogeneous cellular origin determine a diagnostic and therapeutic challenge not yet completely addressed.

KEY WORDS: Neuroendocrine carcinoma - Neuroendocrine tumor - Esophagogastric junction.

Introduction

The incidence of EsophagoGastric Junction (EGJ) carcinoma has dramatically increased world-wide, partly owing to widespread occurrence of gastroesophageal reflux, Barrett's esophagus and Helicobacter pilory infection (1). Although EGJ tumors may comprise any histological type, the majority are adenocarcinomas (2). Adenocarcinomas of EGJ are commonly classified into three categories according to Siewert's classification (3, 4). Among GastroIntestinal NeuroEndocrine Neoplasms (GINENs), which are very rare tumors, localization at EGJ is even rarer (0.04% of all GINENs) (5). In 2010 World Health Organization (WHO) Classification of Tumors of the Digestive System revised the de-

nomination and classification of GINENs by dividing these neoplasms into five categories based on their mitotic rate and Ki-67 labeling index (6). The WHO definition of NeuroEndocrine Carcinoma (NEC) requires positive endocrine markers such as chromogranin A, synaptophysin and CD56. Owing to the rarity and heterogeneous cellular origin of these neoplasms, guidelines on treatment of these neoplasms are still lacking.

Case presentation

A 77-year-old man came to our department with a five-month history of epigastric pain resistant to Proton-Pump Inhibitors and subsequent progressive dysphagia. He had had a radical prostatectomy one year earlier without evidence of recurrence.

An oeso-gastro-duodenoscopy revealed an ulcerative lesion of the EGJ extending 3 cm above the Z-line (Siewert Type 1). The biopsy result was

¹ Department of Surgery "Paride Stefanini", University of Rome "La Sapienza", Rome, Italy

² Department of Radiological Sciences, Oncology and Pathological Anatomy, "La Sapienza" University and "Umberto I" Polyclinic of Rome, Rome, Italy

Corresponding author: Gaetano Poillucci, e-mail: gaetano.poillucci@gmail.com

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diagnostic for moderately differentiated adenocarcinoma.

Computed Tomography (CT) showed abnormal thickening of the EGJ wall (Figure 1), without signs of adipose tissue invasion and two lymph nodes of 18mm and 12mm along the lesser gastric curvature (Figure 2), without evidence of liver or lung

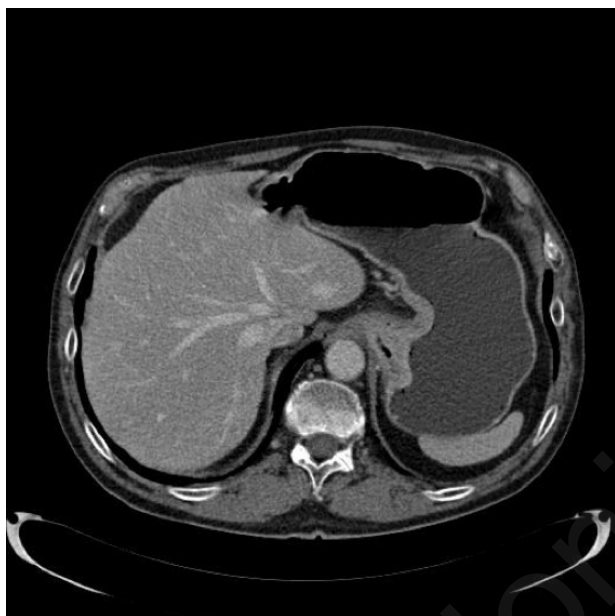


Figure 1 - CT scan shows thickening of the EGJ wall.

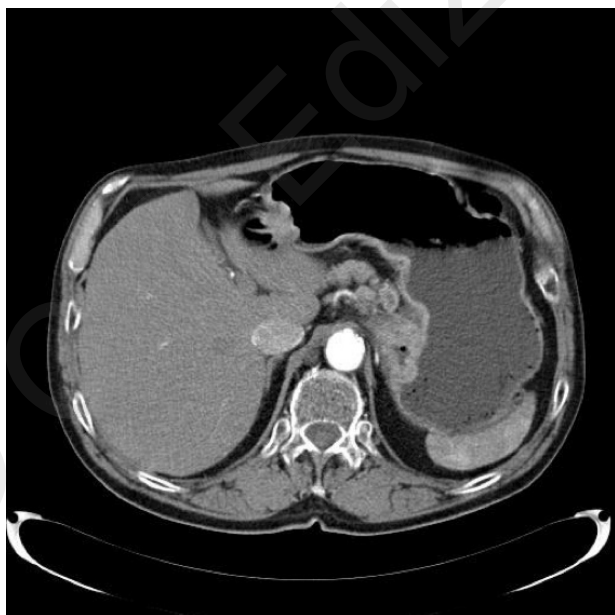


Figure 2 - CT scan shows two metastatic lymph nodes along the lesser gastric curvature.

metastases (cT2 N1 M0). Based on preoperative diagnosis and staging (Siewert 1 adenocarcinoma T2 N1 M0), the patient underwent total esophagectomy and upper partial gastrectomy. A gastric conduit was constructed along the greater curvature and transposed to the neck for esophagogastric anastomosis through a left cervical incision. A mediastinal and lesser curvature lymphadenectomy was performed.

A barium swallow study was performed on the 5th postoperative day and no stenosis or leaks were observed. The patient had an uneventful postoperative course and was discharged in good condition on the 11th postoperative day.

Histopathological examination showed a neoplasm with two distinct components: a well-differentiated adenocarcinoma (10% of cellularity) with glandular or cribriform pattern and low-grade cytological abnormalities coexisting with a neuroendocrine carcinoma (90% of cellularity). The tumor showed a full-thickness wall invasion involving up to 3 cm of the distal oesophagus and the EGJ without extension to periesophageal tissue.

On immunohistochemical study, the neoplasm presented synaptophysin and CD56 immun-expression (Figure 3). The Ki-67 proliferation rate was 70% (Figure 4).

Of the twenty-seven lymph nodes removed, two nodes along the lesser curvature of the stomach were metastatic (Figure 5).

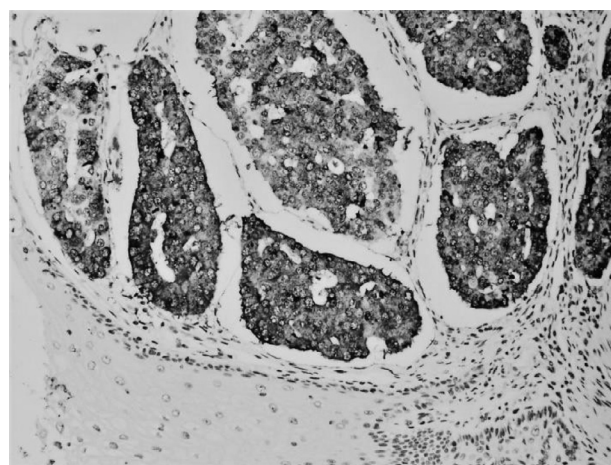


Figure 3 - Cytoplasmic positivity with synaptophysin immunostaining shows neuroendocrine differentiation.

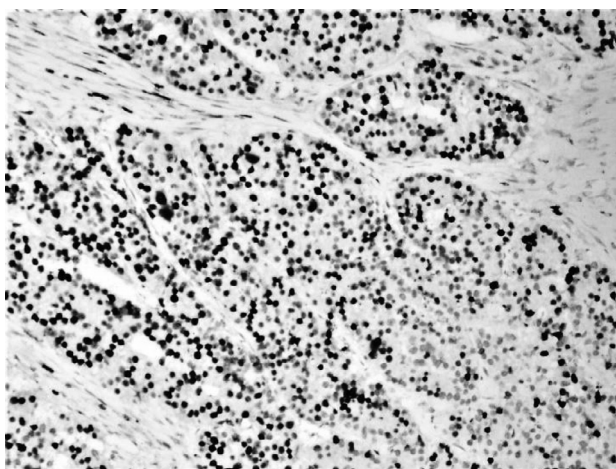


Figure 4 - Ki67 expression shows high cellular proliferation rate.

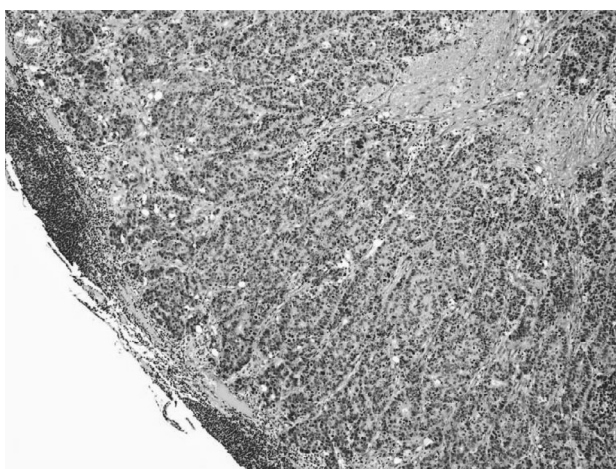


Figure 5 - Lymphnode neoplastic localization along the lesser curvature of the stomach.

According to the current WHO criteria (6), the final pathological diagnosis was NEC of the EGJ (pT2 pN1 G3).

Despite the high risk of recurrence, the oncologist did not consider adjuvant chemotherapy necessary, based on patient's age, risk factors and associated diseases, recommending only a follow-up every four months with CT scan and tumor marker evaluation.

Endoscopic control at 3 months showed no evidence of residual or recurrent disease.

Discussion

The incidence of EGJ adenocarcinoma has in-

creased rapidly over the last few decades, especially in Western countries (7); the overall proportion of adenocarcinoma of the EGJ increased from 2.3% (1962-1965) to 10.0% (2001-2005) of all gastric adenocarcinomas (8).

Siewert's classification divides these tumors into three types. Siewert type I: tumors located 1-5 cm above the EGJ, usually arising from an area of intestinal metaplasia in the distal oesophagus (i.e. Barrett's esophagus); Siewert type II: tumors located from 1 cm above to 2 cm below the EGJ (they represent true adenocarcinomas of the EGJ) arising from the epithelium of the cardia or from short segments of intestinal metaplasia at the EGJ; Siewert type III: subcardial gastric cancer located 2-5 cm below the EGJ with invasion of the distal esophagus (3, 4).

Of all tumors of EGJ, neuroendocrine ones are very rare. Primary NEC of the esophagus and stomach have an incidence ranging from 0.01 to 0.08 cases per 100.000 persons per year; the prevalence of esophageal NEC ranges between 0.01 and 1.4% and gastric NEC between 2 and 3% of all gastroenteropancreatic neuroendocrine tumors (9).

NECs are prevalent in the male sex, incidence increases progressively after 45-50 years, patients presenting with symptoms owing to effects of the mass and an EGJ tumor location were similar to features of conventional adenocarcinomas of the esophagus (10).

The classification of GINENs is difficult due to their heterogeneity and rarity. In 2010, WHO issued a new classification of these neoplasms.

GINENs were divided based on their mitotic rate (HPF, high-power field) and Ki-67 labeling index (6-11) (Table 1):

- 1) NeuroEndocrine Tumor (NET) G1 (mitotic count $<2/10$ HPF and/or $\leq 2\%$ Ki-67 index);
- 2) NET G2 (mitotic count 2-20/10 HPF and/or 3-20% Ki-67 index);
- 3) NEC (mitotic count $>20/10$ HPF and/or $>20\%$ Ki-67 index);
- 4) Mixed AdenoNeuroEndocrine Carcinoma (MANEC) where at least 30% of either component should be identified to qualify for this definition;
- 5) Hyperplastic and preneoplastic lesions.

The WHO definition for NEC requires positive

TABLE 1 - TRANSITION SCHEME FOR THE NEW CLASSIFICATION (WHO 2010) INCLUDING PREVIOUS DEFINITION FOR NEUROENDOCRINE NEOPLASMS OF THE DIGESTIVE SYSTEM (WHO 1980 AND 2000) (6).

WHO 1980	WHO 2000	WHO 2010
I Carcinoid	1. Well-differentiated endocrine tumour (WDET) ^a 2. Well-differentiated endocrine carcinoma (WDEC) ^a 3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	1. NET G1 (carcinoid) ^b 2. NET G2 ^b 3. NEC (large cell or small cell type) ^{b,c}
II Mucocarcinoid	4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
III Mixed forms	carcinoid- adenocarcinoma	
IV Pseudotumour lesions	5. Tumour-like lesions (TLL)	5. Hyperplastic and paraneoplastic lesions

G, grade (for definition); NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour.

The difference between WDET and WDEC was defined based on staging features in the WHO 2000 classification. G2 NET does not necessarily translate into WDEC of the WHO 2000 classification.

Definition in parentheses for the International Classification of Diseases for Oncology (ICD-O) coding.

“NET G3” has been used for this category but is not advised, since NETs are by definition well-differentiated.

endocrine markers such as chromogranin A, synaptophysin and CD56 (12). A Ki67 or mitotic index of 20% or more is also necessary for diagnosing NEC, because the tumors with less than 20% Ki67 positivity are diagnosed as NET (G1-G2) (12).

Many EGJ adenocarcinomas have a neuroendocrine differentiation (neuroendocrine component less than 30% of cellularity), but NECs (neuroendocrine component more than 30%) are extremely uncommon (13). Most reported cases are NECs with a frequent (43%) admixed component of squamous cell carcinoma or adenocarcinoma (14).

Diagnosis of NEC is usually obtained from endoscopic biopsies. In our case, endoscopic biopsies showed an adenocarcinoma, while the diagnosis of NEC was obtained only with histological and histochemical examination after surgery. Considering that these tumors are often characterized by heterogeneous cellularity (13, 14), it is not surprising that all biopsies were taken from adenocarcinoma tissue. But would a different histological diagnosis lead to wrong therapeutic choices? The answer is affirmative because current guidelines on the treatment of EGJ adenocarcinomas suggest preoperative chemoradiation to approach neoplasms staged as cT2 N1 M0 and subsequent esophagectomy (not indicated if unresectable or metastatic disease after preoperative chemoradiation is present) (15), while for NEC of the EGJ surgery treatment for resectable tumor and chemo(radio) therapy postoperative is recommended (16).

In our case, after an analysis of the patient's performance status of patient and his preferences we decided to perform only surgery. This choice allowed the patient to receive adequate treatment compliant with international recommendations and at the same time avoid preoperative chemotherapy treatment recommended for EGJ adenocarcinomas based on 2 cycles of fluorouracil and cisplatin (17). However, evidence for treatment recommendations in NEC of the EGJ is limited to mainly retrospective series and a few non-controlled small trials and patients are often treated analogously to the more common small cell lung cancer (18) and surgery is the only curative option (19).

Prognosis of these rare tumors is poor; it appears to correlate with grade and stage of the disease and the tumor is often at an advanced stage when diagnosed.

Conclusions

Treatment of NEC of the EGJ remains controversial. There are currently no treatment guidelines for these neoplasms and surgery is often the only cure. Thus, NECs of the EG are treated surgically as adenocarcinomas and the surgical approach is based on Siewert's classification. The importance of surgery has been accepted and multidisciplinary treatment modalities, including surgical treatment and postoperative adjuvant chemotherapy, are receiving more and more attention.

Highlights

- Neuroendocrine carcinoma (NEC) of the esophagogastric junction is a very rare tumor with aggressive behavior.
- Diagnosis of NEC requires histochemical positivity of endocrine markers such as chromogranin A, synaptophysin, CD56 and Ki67 of 20% or more.
- There are no validated guidelines for treatment of these neoplasms.

Abbreviations

EGJ: EsophagoGastric Junction

GINEN: GastroIntestinal NeuroEndocrine Neoplasms WHO: World Health Organization

NEC: NeuroEndocrine Carcinoma CT: Computed Tomography

HPF: High Power Field

NET: NeuroEndocrine Tumor

Declarations

Informed consent

Written informed consent was obtained from the patient for the publication of this report.

Conflicts-of-interest

The Authors declare no conflicts of interest.

Acknowledgement

This case report conforms to the SCARE criteria (20).

Competing interests

All Authors report no competing interests.

This manuscript was prepared in accordance with the SCARE guidelines (20).

All Authors have reviewed and approved the final manuscript.

Authors' Contributions

Giuseppe Pappalardo, MD, FACS and Professor of General Surgery, contributed to revision of the paper critically for important intellectual contents. Gaetano Poillucci, MD, contributed to conception, design, writing the paper and doing literature review. Andrea Tornese, MD, contributed to writing the paper. Fabrizio Maria Frattaroli, MD and Associate Professor of General Surgery, contributed to revision of the paper critically for important intellectual contents. Piero Liberatore, MD, contributed to conception, design, writing the paper and doing literature review. Federico Francioni, MD and Associate Professor of Thoracic Surgery, contributed to revision of the paper critically for important intellectual contents.

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Conflicts of interest

All Authors report no conflicts of interest or competing interests regarding the publication of this paper.

Ethical Approval

This study was not conducted with research intervention; thus ethics committee approval was not necessary.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Registration of Research Studies

Not applicable.

Guarantor

Giuseppe Pappalardo MD, FACS, Professor of General Surgery.

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