

Title:

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Large cell neuroendocrine carcinoma at the esophagogastric junction. An extremely rare entity

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Dear Editor,

Esophageal neuroendocrine tumors (NETs) account for 0.04-1 % of all gastroenteropancreatic NETs and 0.03-0.05 % of all malignant esophageal tumors. Within esophageal NETs, small cell neuroendocrine carcinoma accounts for more than 90 % of cases, with well-differentiated NETs, large cell neuroendocrine carcinoma (LCNEC) and mixed neuroendocrine neoplasms being much less frequent (1). Specifically, LCNEC accounts for 1 % of esophageal NETs (2). Due to the infrequency of this condition, we describe the case of a patient with an LCNEC at the level of the esophagogastric junction (EGJ).

Case report

A 65-year-old male, ex-smoker with chronic obstructive pulmonary disease, consulted due to epigastric pain of two months duration, associated with constitutional syndrome. An upper gastrointestinal endoscopy was performed and a friable, ulcerated tumor was identified at the level of the esophagogastric junction, and a biopsy was taken. As the biopsy was compatible with LCNEC of the EGJ (Siewert II), the study was completed with echoendoscopy and computed tomography, without finding locoregional adenopathies or distant metastases (cT2N0M0). Total gastrectomy with distal esophagectomy and associated lymphadenectomy was performed. Finally, histopathological analysis revealed a 2.5 cm LCNEC with involvement down to the submucosa, with positive expression of CDX2, CD56 and synaptophysin, Ki67 of 70 % and associated intestinal metaplasia in the distal esophagus. The resection margins were free of disease and there was no evidence of metastatic adenopathy in the 16 isolated nodes (pT1bN0M0). After six months of follow-up, the patient is asymptomatic and free of disease.

Discussion

LCNEC of the intestinal tract occurs in the EGJ in 9.7 % of cases (3). Thus, five cases of LCNEC of the EGJ have been documented in the scientific literature, two described (2,4) (Table 1) and three reported in a retrospective study (3).

LCNEC from the intestinal tract is positive for chromogranin A in 71 %, synaptophysin in 94 % and CD56 in 54 %. However, 100 % of patients will have chromogranin or synaptophysin, or at least one of these three markers. In turn, 78 % will have lymphovascular invasion and 26 % perineural invasion (3). Only 11 % of patients will have stage I-II (3), which implies an aggressive course and worse prognosis (2-4). Finally, it should be noted that distal esophageal and EGJ NETs can be associated with intestinal metaplasia (Barrett's esophagus) (2,5).

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Table 1. Cases of large cell neuroendocrine carcinoma of the esophagogastric junction described in the scientific literature

	<i>Fukuchi M et al.</i> (2015) (4)	<i>Ichimata S et al.</i> (2019) (2)	<i>García-Redondo M et al.</i> (2023)
Age (years)	65	81	65
Sex	Male	Male	Male
Clinic	Heartburn for 5 months	Constitutional syndrome	Epigastric pain and constitutional syndrome for 2 months
Macroscopic appearance	Ulcerated tumor	Ulcerated tumor	Ulcerated tumor
Surgery	Distal esophagectomy, total gastrectomy, and lymphadenectomy (levels 1-11, 19, 20, 110, and 111)	Subtotal esophagectomy	Distal esophagectomy, total gastrectomy and lymphadenectomy (levels 1-9, 11, 12, 19, 20, 110 and 111)
Approach	Open	Thoracoscopy	Laparoscopic
Size (maximum diameter) (cm)	5.5	4	2.5
Invasion	Subserosa	Submucosa	Submucosa
Metastatic adenopathy	6 of 30 isolated	Yes	0 of 16 isolated
Synaptophysin	+	+	+
Chromogranin A	+	-	-
CD56	+	-	+
Intestinal metaplasia	No	Yes	Yes
TNM	T3N2M0	T1bN1M0	T1bN0M0
Adjuvant	Chemotherapy	No	No



Follow-up (months)	9	18	6
Recidivism	Liver metastases	No	No
Mortality	Yes	No	No

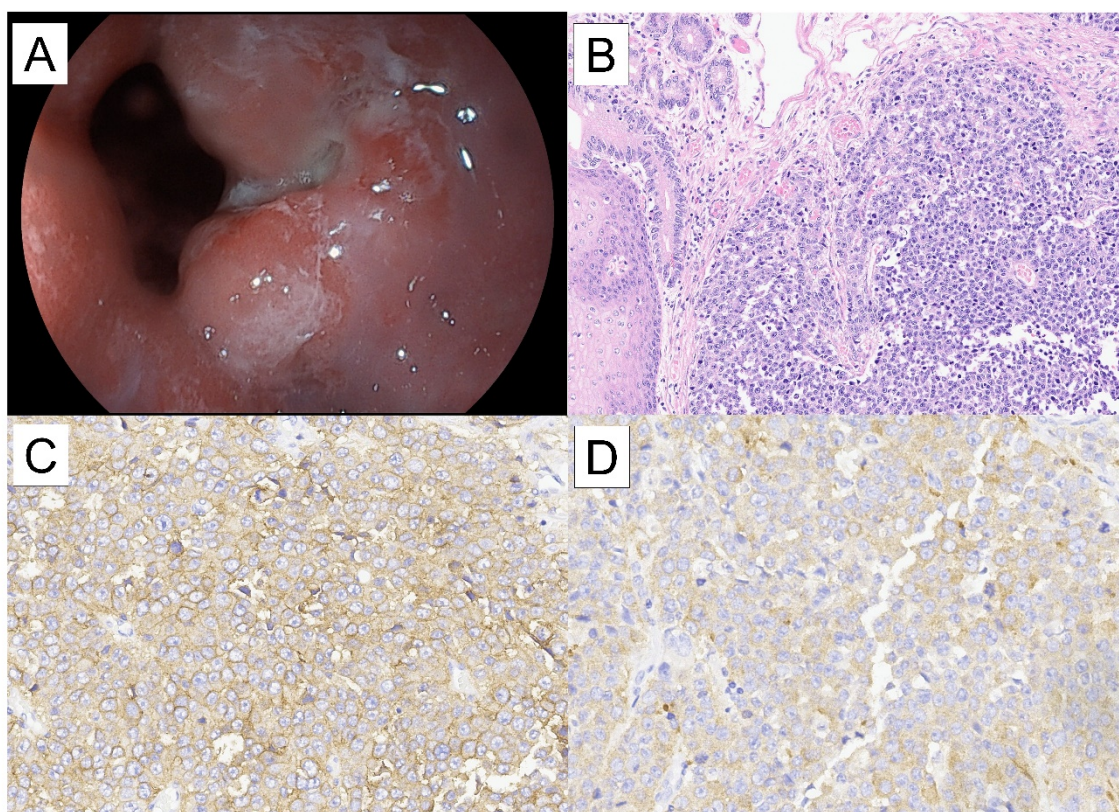


Fig. 1. A. Upper gastrointestinal endoscopy showing a tumor at the esophagogastric junction with an ulcerated surface. B. Histological section showing large cell neuroendocrine carcinoma (LCNEC) infiltration adjacent to the esophagogastric junction mucosa (x20 hematoxylin-eosin). C. Immunohistochemistry: diffuse positivity of tumor cells for CD56 (40x). D. Immunohistochemistry: heterogeneous positivity in tumor cells for synaptophysin (40x).