Neuroendocrine gastric carcinoma in a young patient

Neuroendokrini karcinom želuca kod mlađeg bolesnika

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Abstract

Background. Neuroendocrine tumors cover a spectrum of neoplasms showing wide variations in their clinicopathological and pathogenetic features, as well as prognosis. They may develop throughout the whole gastrointestinal tract. **Case report.** We described a case of gastric neuroendocrine carcinoma in a 29-year-old male. The patient presented with chronic continuous abdominal pain and weight loss over a 6-month period. Preoperative diagnosis, operative findings, histology and immunohistochemistry of the tumor confirmed the diagnosis of the rare neuroendocrine gastric carcinoma, stage T2N1. **Conclusion.** Case reports of this rare tumor are important, because of the paucity of studies noted in the gastrointestinal literature as a result of poor identification prior to the advent of modern immunohistochemistry. Significance of accurately diagnosing gastrointestinal neuroendocrine tumors is crucial for an appropriate treatment.

Key words:
neurosecretory systems; neoplasms; stomach; immunohistochemistry; gastrectomy.

Apstrakt

Uvod. Neuroendokrini tumori (NET) karakterišu se mnogobrojnim varijacijama u kliničkopatološkoj i patogenetskoj slici, kao i prognozi. **Prikaz slučaja.** Prikazali smo bolesnika, starog 29 godina, sa neuroendokrinim karcinomom želuca. U kliničkoj slici dominirali su hronični stalni bol u predelu stomaka koji je bio praćen gubitkom telesne mase u trajanju od šest meseci. Preoperativna dijagnostika, operativni nalaz, histološke i imunohistohemijske analize tumora potvrdile su dijagnozu retkog neuroendokrinog karcinoma želuca stadijuma T2N1. **Zaključak.** Prikazi slučajeva ovog retkog tumora veoma su važni, jer su bili retki u ranijoj gastroenterološkoj literaturi pre pojave moderne imunohistohemijske dijagnostike. Blagovremeno dijagnostikovanje NET odlučujuće je za adekvatno lečenje i prognozu bolesti.

Ključne reči:
neurosekretorni sistem; neoplazme; želudac; imunohistohemija; gastrektomija.

Introduction

Distinguishing between neuroendocrine carcinoma and adenocarcinoma may be difficult. According to the World Health Organization (WHO) classification of 2000, gastric neuroendocrine tumors (NETs) are classified as well-differentiated NETs with benign or uncertain malignant potential (classic carcinoids), well-differentiated NETs with low-grade malignant behaviour (malignant carcinoids), and poorly differentiated NECs with high-grade malignant behaviour, which can be subdivided into small cell and large cell variants based on morphological characteristics [1,2]. It was recognized that gastric neuroendocrine tumors cover a spectrum of neoplasms showing wide variations in their clinicopathological features, prognosis and pathogenetic mechanisms [3,4]. According to the literature, they usually develop in the seventh decade [5]. We reported a case of large cell neuroendocrine carcinoma diagnosed in a young patient.

Case report

A 29-year-old male presented to our hospital due to continuous epigastric pain and a weight loss of 15 kg. At the time of referral, he had been symptomatic for approximately 6 months. His medical history revealed duodenal ulcer disease with hemorrhage and hemorrhagic shock four years ago. Physical examination demonstrated pallor, distress and discomfort with epigastric palpation. Laboratory testing consisting of complete blood count, biochemistry, and tumor markers showed no abnormalities, iron defficiency, anemia (hemoglo-

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bin 90 g/L, Fe^{2+} 3 μmol/L), as well as serum normal gastrin levels. The patient subsequently underwent a routine gastrointestinal work-up. Ultrasonography demonstrated a "pseudo kidney" sign in the epigastrium. According to the radiographic examination, a ventricular ulcer disease was diagnosed. Esophagogastroduodenoscopy revealed a large ulcerovegetating tumor on the lesser gastric curvature to the posterior wall, which was covered with necrotic detritus and hemorrhage, callous and rigid. Tissue samples for patohistology examination were taken. Endoscopic ultrasound revealed involvement and thickening of the mucosa, submucosa and muscularis propria, while the serosa was preserved (T2 stage) in posterior wall of the stomach body. The regional lymph nodes were markedly enlarged (N1stage) (Figures 1 and 2).
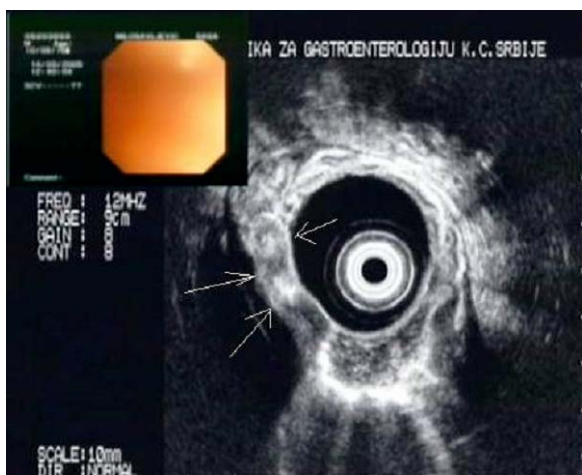

Fig. 1 – Ultrasound image: T2 tumor of the stomach wall

Fig. 2 – Ultrasound image of enlarged lymph nodes around the tumor (see white arrows)

With the exception of the apparent thickening of the gastric wall in the antral region, no other abnormalities were detected on computerized tomography. Explorative laparotomy was appropriately performed. A mass lesion located corporally within the gastric wall was easily identified. This was consistent with preoperative findings. Following exploration, total gastrectomy was performed. Histology evaluation demonstrated trabecula and islet of round cells with rare

eosinophilic cytoplasm. The nuclei were atypical, hyperchromatic, moderately pleomorphic, without prominent nucleolus. The stroma was edematous. Vascular invasion in mucosa and submucosa was detected (Figure 3). Cytological immunophenotypes included: marked and diffuse immunoreactivity in the
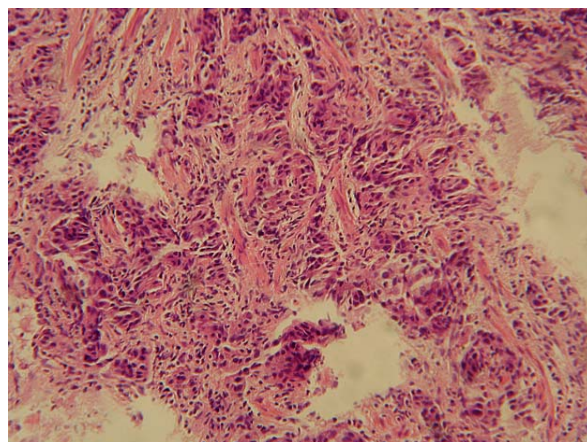

Fig. 3 – Vascular invasion in gastric mucosa and submucosa (HE, ×400)

majority of the cells to neuron specific-enolase (NSE), chromogranin A and synaptophysin (Figures 4 and 5). Immunore-
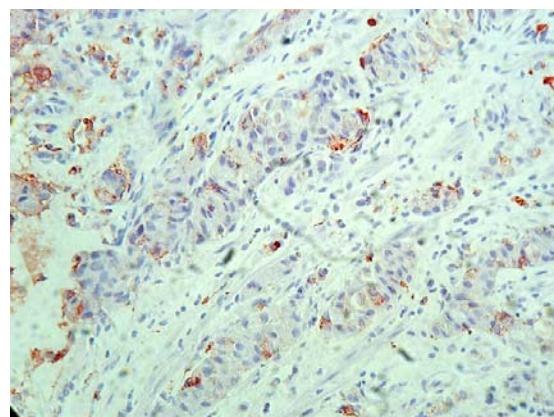

Fig. 4 – Neuroendocrine tumor cells of the stomach wall immunostaining – neuron-specific enolase (LSAB+, ×200)
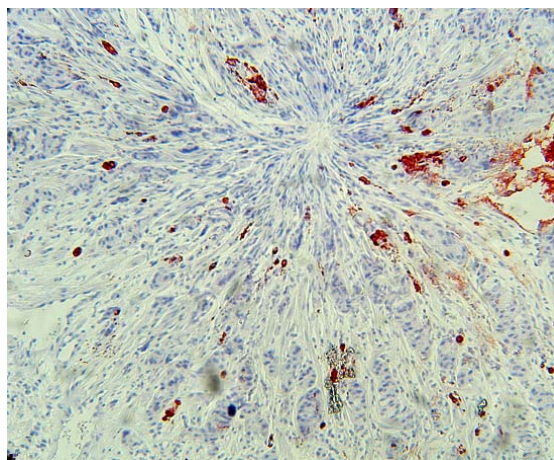

Fig. 5 – Neuroendocrine tumor cells of the stomach wall immunostaining - chromogranin A (LSAB+ , ×200)

activity to other markers was not significant. The mitotic index was 1/10 per microscopic High Power Field (HPF). Our pathologist diagnosed neuroendocrine gastric carcinoma – a large cell type.

The patient denied any postoperative treatment and died six months after the operation.

Discussion

Since Hamperl [6] described argentaffin or argyrophil cells in gastric adenocarcinomas in 1927, neuroendocrine differentiation in gastric carcinomas has been repeatedly reported [7–15]. However, the prevalence of neuroendocrine differentiation in gastric carcinomas still remains undefined.

As already mentioned, these tumors are usually diagnosed in the seventh decade, but we recognized it in this case much earlier (29-year-old patient). There is no significant sex prevalence. Neuroendocrine (NE) gastric carcinomas are generally large (mean size 4.2 cm), fungating or annular lesions, found most frequently in the body/fundus, as it was in our presented case. At the time of diagnosis, most of the tumors were already in advanced stage. Presenting symptoms (weight loss, vomiting, abdominal pain, loss of appetite) were similar to those seen in our patient [16].

Neuroendocrine tumors are neoplasms that consist of relatively uniform cells. Histologically, NE carcinomas are solid, organoid, trabecular, pseudoglandular, spindle cell, or rosette-like [3]. The tumor of the patient related in this report was composed of malignant cells having a moderately pleomorphic aspect and exhibiting vascular and perineural invasion as detected in practically all NE carcinomas [2]. Based on both cell size and morphologic features, Matsui et al. [3] subdivided NE carcinomas into two variants, namely, small and large cell NE carcinoma. Comparing with small cell NE carcinomas, large cell NE carcinomas have a higher mitotic index, larger polygonal cells, a decreased nuclear-cytoplasmic ratio, coarser nuclear chromatin, and more frequently conspicuous nucleoli. In relation to small cell NE carcinoma, large cell NE carcinoma, as presented in this case report, is a more aggressive tumor with a very poor prognosis.

Four types of "pure" NETs can be distinguished in the stomach. Type 1 is the most common, occurring in 70–80% of all cases. In most cases, type 2 NETs of the stomach are small (0.1–1 cm in diameter), multifocal tumors, mainly limited to the mucosa and submucosa, with no metastasis, affecting women more than men, and always occurring in the background of chronic atrophic gastritis. Type 3 (sporadic and solitary) is the second most common NET of the stomach, not associated with any significant clinicopathological condition; these tumors have mostly solitary growth, or are larger than type 1 and type 2 in size, and are deeply invasive with metastase, whereas types 2 (occurring in association with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1) and 4 (undifferentiated solid neuroendocrine carcinoma) are considered rare [1]. According to this, we classified our patient's tumor into NET type 3.

The main immunohistological feature of NETs are cells strongly positive for endocrine markers in the major part of the tumor (> 50%). In this case, neoplastic cells expressed immunoreactivity to chromogranin A, synaptophysin, and neuron-specific enolase. Neuron-specific enolase and chromogranin A are most frequently expressed. Several reports have shown that the most useful immunohistochemical marker of NE differentiation is chromogranin A, followed by Leu-7 and synaptophysin. Other authors have suggested that neuron-specific enolase could be unreliable because it also stains in up to 60% of non-NETs. Use of panel rather than a single NE marker appeared to be more valuable [3, 17, 18].

Although rare, gastric NE carcinomas deserve particular attention, as they are aggressive and have an extremely poor prognosis. Surgical resection is the most appropriate form of treatment for this type. The usefulness of multi-drug chemotherapy remains to be evaluated in larger clinical studies [3]. Mean survival rates of 6.5–14.9 months have been reported with a 1-year survival rate of 58% [16, 19]. As the patient reported in this study, the majority of the patients die due to extensive metastatic disease [20].

Conclusion

Neuroendocrine tumors of the stomach cover a spectrum of neoplasms showing wide variations in their clinicopathological features, prognosis, and pathogenetic mechanisms. It can, however, appear in much younger age as we described, than previously reported.

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