Clinical characteristics of early neuroendocrine carcinoma in stomach
A case report and review of literature
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Abstract

Introduction: Gastric neuroendocrine carcinoma (NEC) is rare. It is considered to be aggressive and has a poor prognosis since the diagnosis is usually made at its advanced stage. However, the survival rate is increased in some early gastric NECs. This study showed a case and reviewed the clinical characteristics of early NECs in stomach.

Patient concerns: A 38-year-old man displayed no symptoms and underwent the gastric endoscopy test for his health examination, which showed a red slightly depressed lesion 1.0 cm in size on the lesser curvature of gastric cardia. Magnifying endoscopy with narrow-band imaging (NBI) revealed a clear demarcation and an irregular mesh in vessels within the depressed area. The background mucosa was negative for atrophic gastritis and Helicobacter Pylori infection. A contrast-enhanced computed tomography (CT) scan disclosed no obvious thickening of stomach and lymphadenopathy. Blood tests and physical examination were unremarkable. He had not received any surgical treatment and denied a family history of cancer and any genetic disorders. The pathologic result of biopsy from the lesion was suspicious of superficial carcinoma. Then endoscopic submucosal dissection (ESD) was performed.

Diagnosis: Gastric NEC G3 in the early stage (T1aN0M0).

Interventions: Concerning this patient’s situation, we considered the ESD as a curable treatment. And no radical surgery or adjuvant chemotherapy was arranged.

Outcomes: The patient is doing well and displays no recurrence for 11 months, who is still in follow-up.

Lessons subsections as per style: The early diagnosis and effective treatment by endoscopy would contribute to improve the prognosis of gastric NECs.

Abbreviations: AC = adenocarcinoma, CgA = chromogranin A, CT = computed tomography, ECL = enterochromafin-like, ESD = endoscopic submucosal dissection, FDG-PET = fluorodeoxyglucose-positron emission tomography, GEP-NEN = gastro-enteropancreatic neuroendocrine neoplasm, MANEC = mixed adenoneuroendocrine carcinoma, NBI = narrow-band imaging, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, SRS = somatostatin receptor scintigraphy, Syn = synaptophysin, WHO = World Health Organization, ZES = Zollinger–Ellison syndrome.

Keywords: early gastric neuroendocrine carcinoma, endoscopic submucosal dissection, mixed adenoneuroendocrine carcinoma, prognosis, upper gastrointestinal endoscopy

1. Introduction

Stomach is one of the most common primary sites of gastroenteropancreatic neuroendocrine neoplasm (GEP-NENs), although the incidence of gastric NENs account for only 2%–6% of gastrointestinal NENs. Gastrointestinal NENs are classified into neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC), and mixed adenoneuroendocrine carcinoma (MANEC) based on the criteria of Ki67

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The written consent of patient was obtained for publication of this case report and accompanying images.

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index, mitotic count, and adenocarcinoma (AC) component in the World Health Organization (WHO) 2010. NET is considered to be well differentiated and has a good prognosis. In contrast, NECs with or without AC component are more aggressive and have lower 5-year survival than NET, which are diagnosed at advanced stages with lymph node or distant metastasis in most cases.

Thank to endoscopic technologies, the prognosis of gastric NETs have been much improved due to the early detection and subsequently better therapies, especially for those tumors with features of small size, limited within mucosa and no lymphovascular invasion. Recently there are a few reports that mentioned the discovery and therapeutic strategies of gastric NECs in early stage, some of which had an unexpectedly good prognosis. It was supported by Kubota et al who stated that the 5-year survival rate of gastric NEC in pathological stage I was 100%.

2. Case report

A 38-year-old man displayed no symptoms and underwent the gastric endoscopy test for his health examination, which showed a red slightly depressed lesion 1.0 cm in size on the lesser curvature of gastric cardia (Fig. 1A). Magnifying endoscopy with narrow-band imaging (NBI) revealed a clear demarcation and an irregular mesh in vessels within the depressed area (Fig. 1B). The background mucosa was negative for atrophic gastritis and Helicobacter Pylori infection. A contrast-enhanced computed tomography (CT) scan disclosed no obvious thickening of stomach and lymphadenopathy. Blood tests and physical examination were unremarkable. He had not received any surgical treatment and denied a family history of cancer and any genetic disorders. The pathologic result of biopsy from the lesion was suspicious of superficial carcinoma. Then endoscopic submucosal dissection (ESD) was performed. Microscopic examination showed the tumor was composed by uniform cells for size and features organized in insular and glandular shape.

The tumor cells had abundant and eosinophilic cytoplasm. Ovoid nuclei were with salt and pepper chromatin as well as inapparent nucleoli. Mitoses were 18/10HPF. No evidence of tumor necrosis was observed. Immunohistochemistry analyses revealed neoplastic cells were positive for synaptophysin (Syn), chromogranin A (CgA) and CD56, and Ki-67 proliferation index was 50%. Combining above typical morphology for neuroendocrine architecture with the immunopositive pattern, the diagnosis was NEC G3. Tumor cells were restricted to the mucosal layer. No evidence for lymphovascular invasion was found. Concerning this patient’s situation, we boldly attempted to use ESD as a curable treatment. And no radical surgery or adjuvant chemotherapy was arranged. He is doing well and displays no recurrence for 11 months.

3. Discussion

This case inspired us to review the clinical characteristics of early NECs in stomach which might provide the valuable information for the medical treatment and research.

4. Methods

Early gastric carcinoma is generally defined as the tumor confined to the mucosa and/or submucosa without consideration of lymphoid involvement and tumor size. A PubMed search was performed to obtain articles on the diagnosis of early NECs in stomach from 2000. Search queries were described by using key words including “early”/T1/mucosal/submucosal,” “gastric/stomach,” and “neuroendocrine carcinoma.” Papers that did not match the following conditions were excluded: firstly, NECs were primary in stomach; secondly, tumor invasion was not deeper than the submucosal layer; thirdly, complete information of the medical process of patient was included. In addition, only English literatures or abstracts were reviewed. This study was approved by the Ethical Committees of Shandong Provincial Hospital Affiliated to Shandong University (LCY): NO. 2018-052).
5. Results

5.1. Demography and symptomatology

Based on the search criteria, eleven cases were brought into the review (Table 1). Most patients were elderly male. Nine males and 2 females were at a mean age of 70.9 years (range, 60–80 years).

Before the diagnosis of tumor, more than 60% patients were asymptomatic and had no remarkable abnormalities in blood tests. Two of them experienced a history of gastric cancer, which was treated by ESD and partial gastrectomy respectively. One patient underwent a surgery of Roux-en-Y gastric bypass for severe obesity. The gastric NECs were unexpectedly discovered during the follow-up process after former operations.

Only three patients complained the abdominal discomfort including nausea, bloating or epigastralgia, which were not specific symptoms for gastric NECs. Although there was one male having high serum gastrin, he took orally the proton pump inhibitor for over ten years.

5.2. Endoscopic and pathologic features

Upper gastrointestinal endoscopy was the preferred and effective examination for detecting tumor in all these cases, except for one case in which the abnormality was firstly found by gastric fluoroscopy and then checked by endoscopy. There were two common characteristics for these early NECs described as follow: firstly, tumors were presented as superficial lesions with slightly elevated or depressed changes and secondly, tumors were small and solitary, localized in any part of the stomach.

The coincidence rate of pathological diagnosis between biopsy and specimen was only ≈9% (1/11 cases). Most of these NECs were companied with AC component. Interestingly, the part of NEC but not AC in tumors was more easily omitted in biopsy. Early gastric NECs were 13.3 mm in mean diameter. There was no lymph node metastasis or lymphovascular invasion if the tumor was confined in the mucosal layer or smaller than 10 mm in size. But in the cases that tumors were beyond the mucosa in depth and larger (>10 mm) in diameter, six in seven patients had lymphovascular invasion.

5.3. Treatment and prognosis

Of 10 patients, no one was died related to the gastric NECs during the follow-up period. ESD treatment was performed alone for two patients with carcinoma cells limited to the mucosa, and they had a good prognosis without neoplasm recurrence for at least more than 7 months. Other 9 patients received surgery treatments and two of them were also combined with chemotherapy, whose outcomes were two patients with hepatic metastasis and one patient with tumor recurrence.
Table 1

| Author          | Sex | Age  | Initial examination/diagnosis | Location                     | Specimen diagnosis | Size (mm) | Treatment                  | Outcome                              |
|-----------------|-----|------|--------------------------------|------------------------------|--------------------|-----------|----------------------------|--------------------------------------|
| Yamaguch et al. | F   | 60   | Endoscopy type 0-IIc/AC        | Lesser curvature, lower gastric body | MANEC SM 8          | 8         | ESD, surgery               | 18 mo, no recurrence                  |
| Scherubl et al. | M   | 63   | Gastric fluoroscopy irregularity/AC | Greater curvature, gastric antrum | MANEC SM 22        | 10 x 9     | ESD, Surgery               | 9 mo, no recurrence                   |
| Sato            | M   | 77   | Partial gastrectomy           | Gastric body                 | MANEC SM 7          | 10 x 6     | Surgery                    | 15 mo, no recurrence                  |
| Solcia et al.   | M   | 67   | Unknown                       | Lesser curvature, lower gastric body | MANEC SM 15        | 15        | Surgery, chemotherapy      | 3 yr, no recurrence                   |
| Bordi et al.    | M   | 61   | RYGBP                          | Upper gastric polyp          | MANEC SM 12         | 12        | ESD, Surgery               | 15 mo, no recurrence                  |
| Hakanson et al. | M   | 75   | Abdominal bloating            | Lesser curvature, gastric antrum | MANEC SM 15        | 15        | ESD, Surgery               | 15 mo, no recurrence                  |

Ac—adenomatous; EGD—endoscopic gastritis; GEP—gastric enteroendocrine neoplasms; MANEC—mixed adenoneuroendocrine carcinoma; NEC—neuroendocrine carcinoma; RYGBP— Roux-en-Y gastric bypass; SM—submucosa, type 0-

6. Conclusion

Gastric NENs are a heterogeneous group of rare tumors. Among them, patients with NECs are commonly considered to have an extremely poor prognosis because of the aggressive biological behavior and frequent lymphovascular metastasis of the tumors.[25] However, this consequence might be greatly improved if the tumors are diagnosed in their early stages. Based on the literature and our review of 11 cases, we compared main clinical characteristics of early NECs with that of NETs and advanced NECs in stomach (Table 2).[26–29]

According to the serum gastrin level and clinical features, gastric NENs are divided into four types.[29] The main clinical characteristics were showed in Table 3.[3,15,16,30] Both type I and type II are associated with enterochromaffin-like (ECL) cell hyperplasia and hypergastrinemia, of which tumors are usually situated in the fundus or corpus of stomach.[31–33] However, type III and type IV are not accompanied with high gastrin in blood and specific tumor location but have been regarded as the more malignancy.[34–37] Although elderly patients were the most population in all types of gastric NENs, males were dominant in the aggressive groups. It has been convinced by Borch et al that sex but not age differed significantly between the subtypes of gastric NENs.[29]

Some GEP-NENs belong to the functional neoplasm if they cause symptoms related to the hormone release, also named carcinoid syndrome, including dry flushing, diarrhea, intermittent abdominal pain, lacrimation, and rhinorrhea.[38] Most gastric NENs are nonfunctioning. But in rare situations gastric NETs may induce the atypical carcinoid syndrome, a purplish prolonged flushing on extremities, and trunk,[39–41] and Zollinger–Ellison syndrome (ZES), a kind of digestive discomfort evoked by reflux, recurrent ulcers, and chronic diarrhea.[42]

Regard to advanced NECs in stomach, it is not too difficult to be aware of tumors because patients have the tumor-related features such as obstruction, bleeding, weight loss, and pain from infiltration or hepatic metastasis.[26] Unfortunately, patients with early gastric NECs were either asymptomatic or with nonspecific symptoms, who were accidentally recognized through a routine upper gastrointestinal endoscopy examination for other indications such as anemia, abdominal pain, dyspepsia, or follow-up for former tumors. This could be the most important reason why early gastric NECs are not easily perceived. As for blood test, it has been mentioned that plasma CgA as well as the gastrin level is elevation of plasma CgA is also present in patients with chronic gastritis. Therefore, it may not be a good marker for screening early gastric NECs. Fransen et al had implied that approximately 25% patients did not have alarm symptoms at the time of diagnosis of upper digestive cancer.[44]

There is no doubt that endoscopy is the first choice of examination for detecting gastric NENs, especially for tumors at the early stage.[29,45] On account of the growth pattern of neuroendocrine cells, which prefer to extend downward in mucosa, the early NENs are generally superficial with or without erosion compared to the advanced ones.[46] Hence, these neoplasms are not so remarkable that can be easily discovered by endoscopic doctors unless some gastric NETs are in polyp shape.[47] It was consistent with our result that cases described the early gastric NECs as a reddish area with slightly elevated or
depressed changes and irregular margins. Besides, there are other methods that would be performed in consideration of endoscopic results. For example, endoscopic ultrasound is the examination for determining tumor size, invasive depth, and regional lymphadenopathy.\(^{26,47}\) CT or MRI is useful for evaluating the radiological stage about regional spread and metastasis.\(^{10,46}\) Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning is more sensitive than somatostatin receptor scintigraphy (SRS) for detecting the metastasis induced by poorly differentiated neuroendocrine carcinomas, where the expression of somatostatin receptor is low.\(^{46,48}\)

The diagnostic rate of gastric NECs by endoscopic biopsy is \(11\%–27\%.\)\(^{49,53}\) It was even lower in our study. Notably, of 11 cases, tumors from 10 cases were composed by NEC and AC components. Nishikura et al\(^{61}\) demonstrated the similar phenomenon that AC localized in the mucosa/submucosa was found in 70.6% of gastric NEC cases. If both histological parts are not less than 30%, it is classified into MANEC according to 2010 WHO. Although the canceration course of MANCE is unclear, two hypotheses are mainly proposed. One is that both NEC and AC have respective origins, which coincidentally exist in the same tumor.\(^{52}\) The other one is that NEC and AC have respective origins, which coincidentally exist in the same tumor.\(^{209}\) Anyhow, gastric NEC arises more early and develops faster than AC component, and then infiltrates rapidly into the submucosal and deeper layers.\(^{51}\) It might explain the reason that most diagnosis of superficial biopsies for MANEC was AC in cases from our review.

Treatment strategies are made for gastric NENs based upon the type, size, pathologic grade, and TNM stage. Gastric type I and II NENs, having lower metastatic incidence, are recommended for endoscopic resection unless tumors are accompanied with risk factors including angioinvasion, high histological grade (G2 or G3), clinical grade (cT2), enlarged regional lymph nodes, or tumor size \(\geq 2\,\text{cm}.\)\(^{10,29,39,54,55}\) Surgery is suggested for patients with type III gastric NENs, as it is more aggressive than former types. However, it is still controversial if endoscopic management is a reliable option for small and well differentiated type III gastric NENs.\(^{10,29,39,54,55}\) For gastric NECs, surgery should be performed if the tumor can be resected safely.\(^{53,56}\) In the case with distant metastasis, chemotherapy is even advised.\(^{48,57}\) Saka et al emphasized that endoscopic therapy was not adequate for NECs even if in rare condition the tumor was just in clinical T1 stage.\(^{58}\) In our review, ESD treatment was tentatively used as a curative therapy for two patients with early gastric NECs, in which tumors were approximate 10 mm in diameter, limited in mucosa and lymphovascular invasion negative.

Even though gastric NETs have the incidence of recurrence and metastasis, the prognosis is good, with 5-year survival rate higher than 60%.\(^{151}\) In contrast most gastric NECs with or without AC are diagnosed at an advanced stage and half of patients die of the disease within 12 months, a 25%–33% survival at 5 years.\(^{48,57,59}\) Compared with that, the patients with

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### Table 2

| Characteristic | Type I | Type II | Type III | Type IV |
|---------------|--------|---------|----------|---------|
| Tumor number and size | Multiple, small (<1–2 cm) | Multiple, small (<1–2 cm) | Unique, large (>2 cm) | Unique, large (>2 cm) |
| WHO classification | NET | NET | NET | NEC |
| Serum gastrin levels | High | High | Normal | Normal |
| Gastric pH | High | Low | Normal | Normal |
| Associated conditions | Chronic atrophic gastritis | ZES/MEN1 | No | No |
| Tumor origin | ECL cells | ECL cells | ECL cells | Diversity |

ECL = enterochromaffin-like; GNE = gastric neuroendocrine neoplasms; MEN = multiple endocrine neoplasia; NEC = neuroendocrine carcinoma; NET = neuroendocrine tumor; WHO = the World Health Organization; ZES = Zollinger–Ellison Syndrome

1. Tumors with secretion of serotonin, gastrin, or adrenocorticotropic hormone (ACTH), poorly differentiated neuroendocrine carcinomas, and mixed adrenocortical carcinoma.
early gastric NECs in this review presented better prognosis with no one dying related to the tumor and only two having hepatic metastasis or recurrence.

In conclusion, the outcome of gastric NECs might be dramatically improved through early detection and proper therapy options. Although the more information need further investigated in multicentric cohorts, based on our study, the following precautions could be the key points: firstly, paying attention to the possibility of NECs existing, when gastric endoscopy screening implies a superficial lesion and suspects the early carcinoma in elder male population; secondly, making the pathologic diagnosis accurate in biopsy by using immunochemistry and neuroendocrine antibodies if necessary; thirdly, evaluating the aggressive risk of tumor comprehensively with multiple imaging methods; fourthly, planning a proper therapeutic treatment by experienced doctors from multidisciplinary treatment.

Author contributions

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