Clinicopathological features, endoscopic features, and treatment analysis of gastric neuroendocrine neoplasms

Ju Huang[1], Xi Wu[2], Tianming Xu[2], Jingnan Li[2]

[1]Peking Union Medical College, Chinese Academy of Medical Science, Beijing 100730, China;
[2]Department of Gastroenterology, Peking Union Medical College Hospital, Beijing 100730, China.

To the Editor: Gastric neuroendocrine neoplasms (gNENs) are highly heterogeneous tumors derived from different neuroendocrine cells in the stomach. Recent epidemiological evidence has indicated that gNENs account for 0.3% to 1.8% of all gastric malignancies.[1] However, few research data are available on gNENs in Chinese patients, but Chinese doctors need to improve their knowledge about this disease.

Patients with gNENs diagnosed using endoscopy and pathological biopsy in Peking Union Medical College Hospital from November 2015 to October 2021 were enrolled for retrospective analysis. The following data were collected and analyzed: general information (gender, age, and clinical symptoms), endoscopic manifestations (lesion location, number, size, shape, and whether accompanied by signs of endoscopic mucosal atrophy), pathological features (pathological grading and immunohistochemical markers of tumors), and treatment (endoscopic treatment, somatostatin analog treatment, and surgical treatment). The follow-up period was the time interval from the initial diagnosis of gNENs to the last follow-up. The risks and benefits of the subjects are reasonable and they signed the informed consent. The ethic committee of Peking Union Medical College Hospital approved the study protocol (No. B483).

Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). A normal distribution test was conducted for measurement data. The normally distributed data were expressed as mean ± standard deviation, and a *t*-test was conducted for comparison between groups. A P value of <0.05 was considered statistically significant.

This study included 45 patients with gNENs. Their ages ranged from 29 to 73 years (53 ± 11 years). The patients comprised 15 (33.3%) men and 30 (66.7%) women, with a male-to-female ratio of 0.5:1.0. The most common symptoms were abdominal distension in 12 (26.7%) patients, abdominal pain in nine (20.0%), heartburn in five (11.1%), and fatigue in four (8.9%). Thirty (66.7%) patients showed endoscopic features of multiple nodules or polypus, with a lesion size of 0.2–1.2 cm and an average diameter of 0.6 cm. Three (6.7%) patients showed endoscopic protuberant and ulcerative lesions, all of which were single lesion, and the tumor size was 1.5 to 2.5 cm.

According to the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines, gNENs are divided into three subtypes based on their clinicopathological features. Types I and II gNENs are derived from enterochromaffin-like (ECL) cells of the stomach and are closely associated with hypergastrinemia, while type III are sporadic and not linked to underlying gastric mucosal abnormality. Grading was assessed according to the ENETS grading system: grade 1 (G1), Ki-67 index <3%; grade 2 (G2), Ki-67 index between 3% and 20%; and grade 3 (G3), Ki-67 index >20%. Among the 45 patients, 39 (86.7%) had type I gNENs, three (6.7%) had type II, and another three (6.7%) had type III; additionally, 34 (75.6%) had G1 of gNENs, ten (22.2%) had G2, and one (2.2%) had G3. Immunohistochemical staining showed positive result in 44 (97.8%) cases for chromogranin A (CgA), 44 (97.8%) for synaptophysin (Syn), and 34 (75.6%) for neural cell adhesion molecule (CD56).

Thirty-three (73.3%) patients were diagnosed with atrophic gastritis and autoimmune atrophic gastritis by pathological biopsy. In these patients, endoscopy showed mucosal thinning with white-dominant and submucosal vascular penetration, and pathological biopsy showed signs of intestinal metaplasia, intrinsic glands, and decreased oxyntic glands. Among these 33 patients, 32 (97.0%) had type I gNENs, while one (3.0%) had type II;

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002437

Correspondence to: Jingnan Li, Department of Gastroenterology, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Dongcheng District, Beijing 100730, China
E-Mail: lijin2008@126.com

Chinese Medical Journal 2022;135(20)

Received: 10-07-2022; **Online:** 09-12-2022 **Edited by:** Rongman Jia and Xiuyuan Hao

additionally, 27 (81.8%) had G1 gNENs, six (18.2%) had G2, and none had G3.

In this research, all patients had non-functional gNENs with various clinical manifestations, including abdominal distension, abdominal pain, heartburn, and fatigue. Since the clinical manifestations of gNENs are diverse and lack specificity, early diagnosis and treatment are rendered difficult. Endoscopic direct-vision observation of the tumor or the gastric mucosa around polyps, combined with pathological biopsy, is the most important approach for the diagnosis of gNENs. In the clinical setting, many endoscopists consider that most polyposis in the body and fundus of the stomach are benign fundic gland polyps and thus neglect to perform biopsy, which may lead to missed diagnosis of some gNENs.

Clinically, some patients with gNENs are symptomatic, and the tumors of 11 (24.4%) patients in this study were incidentally found by endoscopy. The typical histological manifestations of autoimmune atrophic gastritis by gastroscopic pathological biopsy include focal intestinal metaplasia, focal and nodular ECL cell hyperplasia, and oxyntic mucosa with mucosal atrophy. Endoscopists and pathologists should be vigilant for these abnormalities.

Pathologic examination is the gold standard for the diagnosis of gNENs, and immunohistochemical staining provides the most favorable evidence for the diagnosis of gNENs combined with microscopic observation of the morphology of tumor cells. CgA, Syn, and CD56 are the most useful markers to examine. A definite diagnosis can be made when CgA, Syn, and CD56 are all positive. CgA is expressed inconsistently or not expressed in the cytoplasm of neuroendocrine tumor (NET) cells. Syn is widely expressed in the cytoplasm of NET cells and is diffusely positive. In the present study, the positive rates of CgA and Syn in 45 patients were both 97.8%, and the positive rate of CD56 was 75.6%; these findings demonstrated that CgA, Syn, and CD56 had strong specificity and sensitivity to diagnose gNENs. These markers should be combined to improve the accuracy of diagnosis.

Type I gNENs were the most common in the present study, of which 30 (76.9%) occurred in the gastric corpus. Ultrasound gastroscopy showed that the lesions were confined to the muscularis mucosa or submucosa, and they were hypoechoic or isoechoic lesions with regular edges and an average diameter of 0.6 cm. The ENETS recommends that gNENs of $\leq$1 cm can be resected endoscopically or followed up for observation; while those $>$1 cm can be treated by endoscopic resection or surgery depending on the depth of invasion and lymph node metastasis.[1] For non-advanced tumors, endoscopic resection is recommended as the initial treatment. In this study, 20 (44.4%) patients underwent endoscopic submucosal dissection (ESD), among which, the postoperative histopathological grading showed 16 (80.0%) cases of G1 and four (20.0%) cases of G2. There were no residual tumor cells at the horizontal and vertical resection margins. Gastroscopy was performed every six to twelve months after the operation, with a median follow-up time of 27 months, and the survival rate was 100%; however, local recurrence was found in two (10.0%) patients. In a prospective study, Esposito *et al*[2] performed endoscopic resection in 65 patients with gNENs; 37 patients (56.9%) had disease recurrence after a median follow-up of ten months. Among the above 37 patients, 18 (48.6%) were removed by biopsy forceps, 12 (32.4%) were removed by endoscopic mucosal resection (EMR), six (16.2%) were removed by cold snare polypectomy, one (2.8%) were removed by ESD. In the present study, the recurrence rate of 10.0% was relatively low, and was considered possibly related to ESD. Li *et al*[3] analyzed 24 patients with gNENs who received endoscopic treatment and found that ESD was safer and more effective than EMR. Moreover, ESD had a better resection effect. Type I gNENs can be completely removed by ESD, but six to twelve months of endoscopic follow-up are required to prevent recurrence.

The 39 patients with type I gNENs and three patients with type II gNENs included in this study had significantly elevated fasting serum gastrin levels. In a prospective study by Massironi *et al*,[4] 25 patients with recurrent type I gNENs, with mean serum gastrin and CgA levels of 802 pg/mL and 33 U/L, respectively, received somatostatin analogue (SSA) treatment for 12 months. At the end of the treatment, the mean serum gastrin and CgA levels had decreased to 299 pg/mL and 15.6 U/L, respectively. After a median follow-up of 12 months, the tumors disappeared. Octreotide acetate microspheres, a type of long-acting SSA, can specifically bind to the somatostatin receptor. SSAs were effective in reducing the serum gastrin level, inhibiting tumor growth, and controlling the uncomfortable symptoms caused by tumor-related hormones. In this study, 19 (42.2%) patients with type I multifocal ($\geq$6 lesions) gNENs received intramuscular injection of 20 mg octreotide acetate microspheres every four weeks [Figure 1]. The median follow-up was 20 months. The mean serum gastrin level decreased from 1584 pg/mL to 532 pg/mL; no tumor progression was found in endoscopic follow-up, and the survival rate was 100%. No obvious side effects or adverse reactions were found in any of the 19 patients during treatment or follow-up, suggesting that SSA is safe and effective in the treatment of gNENs. However, there are currently no definite recommendations for the treatment cycle and medication interval, and large-scale clinical studies are expected in the future.

In this study, three patients had type II gNENs, including two with gastrinomas and one with multiple endocrine neoplasia type-1 (MEN-1). Three patients had type III gNENs with endoscopic manifestations of protrusive and ulcerative lesions, and all of them were single lesion. The tumors were located in the gastric fundus, gastric body, and gastric antrum, respectively and the size ranged from 1.5 to 2.5 cm. After surgery, six (13.3%) patients were followed up for a median of 24 months. One patient with type III and G3 liver metastasis and lymph node metastasis died, and the survival rate was 83.3%. Type III gNENs have always been considered to be invasive tumors. In a retrospective analysis of 77 patients with type III gNENs, Li *et al*[5] found lymph node metastases and distant metastases in ten (13.0%) patients with G2 gNENs, and 24 (31.2%) patients with G3 gNENs. In this study, two

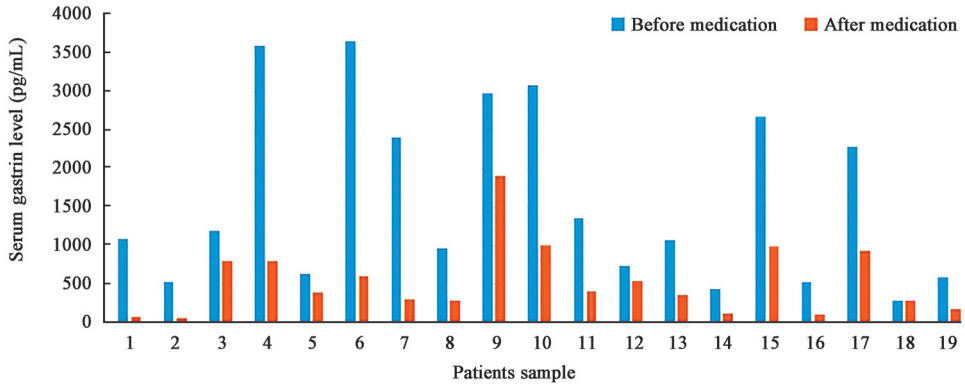

Figure 1: Changes in serum gastrin levels in 19 patients with type I multifocal (≥6 lesions) gastric neuroendocrine neoplasms before and after intramuscular injection of 20 mg octreotide acetate microspheres every four weeks.

patients with type III gNENs were found to have liver metastases, including one case of G2 and one case of G3. Most patients with type II gNENs have gastrinomas secondary to the duodenum or pancreas or related to MEN-1. The tumor secretes gastrin, which promotes an increase in gastric acid secretion and results in typical Zollinger–Ellison syndrome. Surgical tumor resection can not only eliminate the root cause of hypergastrinemia, but also prevent continuous proliferation of ECL cells and avoid the recurrence of refractory ulcers in the upper gastrointestinal tract. Type III gNENs are highly invasive and associated with a risk of lymph node metastasis and distant metastasis. Surgical tumor resection combined with regional lymph node dissection and even radical resection of metastatic organs can be performed. Surgical resection is the recommended treatment for patients with type II and III gNENs.

In conclusion, the key to a definitive diagnosis of gNENs is to improve endoscopists' awareness, attach importance to endoscopic biopsy of lesions, increase pathologists' attention, and combine diagnostic procedures with immunohistochemical staining. Tumors can be completely removed by ESD, and SSA is safe and effective in the treatment of gNENs. Accurate classification, graded diagnosis, individualized treatment, and regular follow-up are necessary.

Conflicts of interest

None.

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How to cite this article: Huang J, Wu X, Xu T, Li J. Clinicopathological features, endoscopic features, and treatment analysis of gastric neuroendocrine neoplasms. Chin Med J 2022;135:2497–2499. doi: 10.1097/CM9.0000000000002437