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Contents

Thrice Monthly Volume 9 Number 27 September 26, 2021

EDITORIAL

7963 *Exophiala dermatitidis*

Usuda D, Higashikawa T, Hotchi Y, Usami K, Shimozaawa S, Tokunaga S, Osugi I, Katou R, Ito S, Yoshizawa T, Asako S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M

REVIEW

7973 Gastric neuroendocrine neoplasms: A review

Köseoglu H, Duzenli T, Sezikli M

MINIREVIEWS

7986 Coronavirus disease 2019 and renal transplantation

Nassar M, Nso N, Ariyaratnam J, Sandhu J, Mohamed M, Baraka B, Ibrahim A, Alfshawy M, Zheng D, Bhangoo H, Soliman KM, Li M, Rizzo V, Daoud A

7998 Impact of COVID-19 on liver

Su YJ, Chang CW, Chen MJ, Lai YC

ORIGINAL ARTICLE

Case Control Study

8008 Association of gestational anemia with pregnancy conditions and outcomes: A nested case-control study

Sun Y, Shen ZZ, Huang FL, Jiang Y, Wang YW, Zhang SH, Ma S, Liu JT, Zhan YL, Lin H, Chen YL, Shi YJ, Ma LK

Retrospective Cohort Study

8020 Clinical stages of recurrent hepatocellular carcinoma: A retrospective cohort study

Yao SY, Liang B, Chen YY, Tang YT, Dong XF, Liu TQ

Retrospective Study

8027 Accuracy of ultrasonography in diagnosis of fetal central nervous system malformation

Pang B, Pan JJ, Li Q, Zhang X

8035 Analysis of ocular structural parameters and higher-order aberrations in Chinese children with myopia

Li X, Hu Q, Wang QR, Feng ZQ, Yang F, Du CY

8044 Radial nerve recovery following closed nailing of humeral shaft fractures without radial nerve exploration: A retrospective study

Yeh KL, Liaw CK, Wu TY, Chen CP

8051 Bridging therapy and direct mechanical thrombectomy in the treatment of cardiogenic cerebral infarction with anterior circulation macrovascular occlusion

Ding HJ, Ma C, Ye FP, Zhang JF

- 8061** Endu combined with concurrent chemotherapy and radiotherapy for stage IIB-IVA cervical squamous cell carcinoma patients

Zhao FJ, Su Q, Zhang W, Yang WC, Zhao L, Gao LY

CASE REPORT

- 8071** Primary pancreatic paraganglioma harboring lymph node metastasis: A case report

Jiang CN, Cheng X, Shan J, Yang M, Xiao YQ

- 8082** Retraction of lumbar disc herniation achieved by noninvasive techniques: A case report

Wang P, Chen C, Zhang QH, Sun GD, Wang CA, Li W

- 8090** Mixed neuroendocrine carcinoma of the gastric stump: A case report

Zhu H, Zhang MY, Sun WL, Chen G

- 8097** Diploic vein as a newly treatable cause of pulsatile tinnitus: A case report

Zhao PF, Zeng R, Qiu XY, Ding HY, Lv H, Li XS, Wang GP, Li D, Gong SS, Wang ZC

- 8104** Acute myocardial infarction and extensive systemic thrombosis in thrombotic thrombocytopenic purpura: A case report and review of literature

Şalaru DL, Adam CA, Marcu DTM, Şimon IV, Macovei L, Ambrosie L, Chirita E, Sascau RA, Statescu C

- 8114** Limited thoracoplasty and free musculocutaneous flap transposition for postpneumonectomy empyema: A case report

Huang QQ, He ZL, Wu YY, Liu ZJ

- 8120** Paraneoplastic focal segmental glomerulosclerosis associated with gastrointestinal stromal tumor with cutaneous metastasis: A case report

Zhou J, Yang Z, Yang CS, Lin H

- 8127** Acute coronary syndrome with severe atherosclerotic and hyperthyroidism: A case report

Zhu HM, Zhang Y, Tang Y, Yuan H, Li ZX, Long Y

- 8135** Gastric cancer with calcifications: A case report

Lin YH, Yao W, Fei Q, Wang Y

- 8142** Value of eosinophil count in bronchoalveolar lavage fluid for diagnosis of allergic bronchopulmonary aspergillosis: A case report

Wang WY, Wan SH, Zheng YL, Zhou LM, Zhang H, Jiang LB

- 8147** Asymptomatic gastric adenomyoma and heterotopic pancreas in a patient with pancreatic cancer: A case report and review of the literature

Li K, Xu Y, Liu NB, Shi BM

- 8157** Successful treatment of gastrointestinal infection-induced septic shock using the oXiris® hemofilter: A case report

Li Y, Ji XJ, Jing DY, Huang ZH, Duan ML

- 8164** Streptococcal pneumonia-associated hemolytic uremic syndrome treated by T-antibody-negative plasma exchange in children: Two case reports
Wang XL, Du Y, Zhao CG, Wu YB, Yang N, Pei L, Wang LJ, Wang QS
- 8171** Subclavian steal syndrome associated with Sjogren's syndrome: A case report
Hao LJ, Zhang J, Naveed M, Chen KY, Xiao PX
- 8177** Metachronous mixed cellularity classical Hodgkin's lymphoma and T-cell leukemia/lymphoma: A case report
Dong Y, Deng LJ, Li MM
- 8186** Duodenal perforation after organophosphorus poisoning: A case report
Lu YL, Hu J, Zhang LY, Cen XY, Yang DH, Yu AY
- 8192** Surgical treatment of abnormal systemic artery to the left lower lobe: A case report
Zhang YY, Gu XY, Li JL, Liu Z, Lv GY
- 8199** Madelung's disease with alcoholic liver disease and acute kidney injury: A case report
Wu L, Jiang T, Zhang Y, Tang AQ, Wu LH, Liu Y, Li MQ, Zhao LB
- 8207** Anesthetic technique for awake artery malformation clipping with motor evoked potential and somatosensory evoked potential: A case report
Zhou HY, Chen HY, Li Y
- 8214** Multiple hidden vessels in walled-off necrosis with high-risk bleeding: Report of two cases
Xu N, Zhai YQ, Li LS, Chai NL
- 8220** Non-small-cell lung cancer with epidermal growth factor receptor L861Q-L833F compound mutation benefits from both afatinib and osimertinib: A case report
Zhang Y, Shen JQ, Shao L, Chen Y, Lei L, Wang JL
- 8226** Successful removal of two magnets in the small intestine by laparoscopy and colonoscopy: A case report
Oh RG, Lee CG, Park YN, Lee YM
- 8232** Acute lower extremity arterial thrombosis after intraocular foreign body removal under general anesthesia: A case report and review of literature
Jeon S, Hong JM, Lee HJ, Kim E, Lee H, Kim Y, Ri HS, Lee JJ
- 8242** Low-intensity extracorporeal shock wave therapy for midshaft clavicular delayed union: A case report and review of literature
Yue L, Chen H, Feng TH, Wang R, Sun HL
- 8249** Treatment of bilateral granulomatous lobular mastitis during lactation with traditional Chinese medicine: A case report
Li ZY, Sun XM, Li JW, Liu XF, Sun ZY, Chen HH, Dong YL, Sun XH
- 8260** Early acute fat embolism syndrome caused by femoral fracture: A case report
Yang J, Cui ZN, Dong JN, Lin WB, Jin JT, Tang XJ, Guo XB, Cui SB, Sun M, Ji CC

- 8268** Combined fascia iliaca compartment block and monitored anesthesia care for geriatric patients with hip fracture: Two case reports
Zhan L, Zhang YJ, Wang JX
- 8274** Bell's palsy after inactivated COVID-19 vaccination in a patient with history of recurrent Bell's palsy: A case report
Yu BY, Cen LS, Chen T, Yang TH

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Gastric neuroendocrine neoplasms: A review

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Abstract

Gastric neuroendocrine neoplasms (g-NENs) or neuroendocrine tumors are generally slow-growing tumors with increasing incidence. They arise from enterochromaffin like cells and are divided into four types according to clinical characteristic features. Type 1 and 2 are gastrin dependent, whereas type 3 and 4 are sporadic. The reason for hypergastrinemia is atrophic gastritis in type 1, and gastrin releasing tumor (gastrinoma) in type 2 g-NEN. The diagnosis of g-NENs needs histopathological investigation taken by upper gastrointestinal endoscopy. g-NENs are positively stained with chromogranin A and synaptophysin. Grading is made with mitotic index and ki-67 proliferation index on histopathological analysis. It is crucial to discriminate between types of g-NENs, because the management, treatment and prognosis differ significantly between subtypes. Treatment options for g-NENs include endoscopic resection, surgical resection with or without antrectomy, medical treatment with somatostatin analogues, netazepide or chemotherapy regimens. Follow-up without excision is another option in appropriate cases. The prognosis of type 1 and 2 g-NENs are good, whereas the prognosis of type 3 and 4 g-NENs are close to the prognosis of gastric adenocancer.

Key Words: Gastric neuroendocrine tumors; Gastric neuroendocrine neoplasm; Gastric neuroendocrine carcinoma; Hypergastrinemia; Carcinoid; Somatostatin receptor imaging

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Core Tip: Gastric neuroendocrine neoplasm is an indolent tumor, which is more commonly seen with time. It has 4 subtypes with different clinical characteristics, and diagnostic management and treatment depends on subtypes. This article reviews the

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INTRODUCTION

The term “carcinoid” was firstly used in 1907 to define a slowly progressing tumor somewhere between adenoma and carcinoma[1]. When it was first described, the main features of carcinoids were determined as follows: (1) Usually small and multiple; (2) Surrounded by an undifferentiated tissue; (3) Potentially invasive but they do not metastasize; and (4) Grow slowly and therefore considered as harmless[2]. After the first description, various definitions and classifications have been used over years, which illustrates the complex biological nature of these tumors. In 1963 Williams and Sandler classified carcinoid tumors as foregut, midgut and hindgut according to embryological development sites[3]. Later, Soga and Tazawa classified carcinoids according to histological features as A, B, C, D and mixed type[4]. Capella *et al*[5] stated that the term neuroendocrine tumor (NET) would be more appropriate instead of carcinoid and proposed a new classification system. They classified NETs of the stomach as benign, benign or low-grade malignant, low-grade malignant and high-grade malignant.

The World Health Organization (WHO) classified neuroendocrine neoplasms (NENs) as Grade 1, 2 and 3 according to Ki-67 proliferation index and mitotic activity in 2010[6]. In 2017 this classification was changed and NENs were divided into NET and neuroendocrine carcinoma (NEC) according to tumor grade, independently where the tumor arises[7]. A less common type is mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN), which includes both neuroendocrine tumor and non-neuroendocrine tumor components (each neoplasms constitute more than 30% of the entire tumor)[8]. The proposed classification and staging criteria for NENs of the gastrointestinal tract according to 2017 WHO classification is summarized in Table 1 [7].

EPIDEMIOLOGY AND TYPES OF NENS OF THE STOMACH

NENs of the digestive system may arise from the pancreas and the digestive tract. Gastric NENs (g-NENs) are uncommon disorders, and represent 5% to 23% of all digestive NENs in various trials[9-14]. The incidence of g-NENs increases nearly 15-fold with time, probable because of the expanding use of upper gastrointestinal endoscopy[9,15]. A recent study showed that the incidence of g-NENs increased from 0.309 to 6.149 per 1000000 persons in the last 40 years[16]. Similar incidence results were reported in a study from Japan with an adjusted incidence of 4.82 per 1000000 population[17].

Rindi *et al*[18] defined three different subtypes of g-NENs. They showed that some patients had atrophic gastritis and hypergastrinemia along with non-metastatic lesions, some patients had hypertrophic gastropathy and hypergastrinemia due to multiple endocrine neoplasia (MEN) and Zollinger-Ellison syndrome and finally some NENs were sporadic which showed invasion and metastasis[18]. This classification is still in use and with further knowledge the three types of g-NENs may be summarized as followed, along with a newly defined fourth type (Table 2).

Type 1 g-NEN

Type 1 is the most common type and represents 70-80% of g-NENs[9,19]. It is commonly seen in patients with 60-70 years of age and a slight female dominance is present[20,21]. Chronic atrophic gastritis is present along with elevated gastrin levels. The elevated gastrin level due to chronic atrophic gastritis has a trophic effect on enterochromaffin-like (ECL) cells, with ECL cell hypertrophy and hyperplasia as the

Table 1 Classification of neuroendocrine neoplasms according to World Health Organization criteria

	Mitotic rate (mitoses/mm ²)	Ki-67 index	Differentiation
Neuroendocrine tumor, Grade 1	< 2	< 3%	Well
Neuroendocrine tumor, Grade 2	2-20	3%-20%	Well
Neuroendocrine tumor, Grade 3	> 20	> 20%	Well
Neuroendocrine carcinoma, small-cell type	> 20	> 20%	Poor
Neuroendocrine carcinoma, large-cell type	> 20	> 20%	Poor
Mixed neuroendocrine–non-neuroendocrine neoplasm	Variable	Variable	Variable

Table 2 Characteristics of the subtypes of neuroendocrine neoplasms of the stomach

	Type 1	Type 2	Type 3	Type 4
Approximate Proportion	70%-80%	5%	10%-25%	Rarely
Pathogenesis	Increased gastrin levels due to atrophic gastritis. ECL origin	Increased gastrin levels due to gastrinoma. ECL origin	Not known. Mostly ECL origin	Not known. Non-ECL origin
Location and characteristics	Gastric body and fundus. Often small and multiple	Gastric body and fundus. Often small and multiple	Anywhere. Large and solitary	Anywhere. Large (often larger than type 3)
Gastrin level	Increased	Increased	Normal	Increased or normal
Prognosis	Excellent	Good	Bad	Bad
Treatment	Surveillance without resection, Endoscopic resection, surgery	Endoscopic or surgical resection, resection of gastrinoma	Gastrectomy and regional lymphadenectomy, systemic chemotherapy	Gastrectomy and regional lymphadenectomy, systemic chemotherapy

result[22]. Annual risk of development of g-NENs among patients with chronic atrophic gastritis is around 0.4%-0.7% [23,24]. Most of the lesions in type 1 g-NENs are multiple and are around 1-2 cm. The lymph node metastasis potential of type 1 g-NENs is low and only few cases of distant metastasis have been reported to date[25, 26]. The prognosis is good and the expected 5 year survival is over 95% [27,28].

Type 2 g-NEN

Type 2 g-NEN constitutes 5% of g-NENs[25,29]. Hypergastrinemia is also present in these patients, but it is due to ectopic gastrin producing neoplasia (gastrinoma), which is also named as Zollinger-Ellison syndrome[25,29,30]. Among patients with MEN 1 and gastrinoma, 20% of patients will develop type 2 g-NEN[31]. Although type 2 g-NENs may present with metastasis for up to 30%, the prognosis is still good with tumor-related deaths under 10% [9,32].

Type 3 g-NEN

This type of g-NEN is not associated with hypergastrinemia, and is therefore accepted as sporadic[33]. Type 3 g-NENs represents 15%-25% of g-NENs[9]. The lesion is commonly single and large with a high metastasis potential and high grade compared to type 1 and 2 g-NENs[21,34,35].

Type 4 g-NEN

Type 4 g-NEN is a more recently defined type, which is the rarest subtype. They are not originated from ECL cells and their growth is independent from gastrin. Mostly the lesion presents as a large polypoid lesion localized anywhere in the stomach. Type 4 g-NENs are aggressive tumors with high invasion and metastasis potential[36].

Trinh *et al* [37] investigated patients without atrophic gastritis or gastrinoma according to long term PPI use, and they showed that this group of NENs had some different clinical characteristics than type 3 g-NEN, including better prognosis. They suggested to classify g-NENS arising in moderate hypergastrinemia in patients who were treated continuously for a long period with PPI, without autoimmune chronic atrophic gastritis, gastrinoma, and MEN1 syndrome as a new group of g-NEN[37]. This suggestion needs further investigations.

PATHOGENESIS OF NENS OF THE STOMACH

It is known for years that elevated gastrin levels, which results commonly due to gastric acid inhibition, are associated with the hyperplasia, dysplasia and neoplasia development in ECL cells[38]. Furthermore the gastrin level was found to be correlated with the severity of hyperplasia[39]. Elevated serum gastrin levels are associated with type 1 and 2 g-NENs, with different mechanisms for hypergastrinemia.

Many factors and cells are involved in the physiological acid secretion. After food consumption, G cells which are placed in the gastric antrum release gastrin. Elevated gastrin levels stimulates ECL cells to produce histamine, and histamine stimulates parietal cells to produce acid. Normally, increased acid levels inhibits gastrin levels primarily *via* somatostatin, which is released from D cells placed in the gastric antrum [25].

Chronic atrophic gastritis is involved in the pathogenesis of type 1 g-NEN. If chronic atrophic gastritis is associated with parietal cell or intrinsic factor antibodies the condition is named as pernicious anemia, and this is commonly present in patients with type 1 g-NEN[25]. Achlorhydria, which occurs in chronic atrophic gastritis, leads to D cell suppression and hypergastrinemia due to G cell hyperplasia. This hypergastrinemia is actually a physiological response to achlorhydria, but has also trophic effect on ECL cells, resulting in ECL cell hypertrophy and hyperplasia[22]. This alteration leads finally to the development of NEN[40]. Long term proton pump inhibitor use enhances the development of g-NEN in animal studies and case reports[41,42], but various studies showed that chronic proton pump inhibitor use or vagotomy has no effect on g-NEN development[29,43]. This fact proves that hypergastrinemia is essential for type 1 g-NEN development but is not sufficient.

Type 2 g-NEN develops similar to type 1 due to hypergastrinemia. Conversely, hypergastrinemia and excess acid production is due to an ectopic gastrin-producing G cell neoplasia (gastrinoma). The neoplasia is located commonly in the duodenum or pancreas. In the case of gastrinoma the normal inhibitory feedback of hyperacidity on gastrin production is inadequate[25,30]. Patients with gastrinomas without NEN may not develop NEN, but they showed nevertheless a 168% increase of ECL cell volume compared to normal population[44]. Gastrinoma may or may not be a component of MEN-1. Compared to non-MEN 1 related gastrinomas, the potential of the development of g-NENs is increased in patients with MEN-1 induced gastrinomas[45].

In patients with type 3 g-NEN the gastrin and acid production are in normal ranges. The exact pathogenesis of type 3 g-NEN is not well known. Mutations of the p53 gene may have probable role in the pathogenesis of type 3 g-NEN[46,47].

The fact that g-NEN develops only in a minority of patients with chronic atrophic gastritis[24] suggests that other pathogenic factors than hypergastrinemia is involved in the development of g-NENs. Expression of glycoprotein hormone alpha-subunit, production of basic fibroblast growth factor and mutations of Reglalpha gene are examples for accused factors for g-NEN development[48-50]. MEN-1 associated gastrinoma is commonly related to type-2 g-NEN. But even patients with NEN without MEN-1 syndrome may have loss of heterozygosity (LOH) at the MEN-1 gene locus at 11q13. In a study LOH was detected in 50% of patients with type-1 g-NEN, and 75% of patients with type-2 g-NEN without MEN-1 syndrome[51]. *Helicobacter pylori* (*H. pylori*) may also have an effect on the development of g-NENs[52,53].

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of g-NENs are not specific and they are usually diagnosed during upper gastrointestinal endoscopy for upper gastrointestinal tract symptoms such as abdominal pain, nausea, bleeding or anemia[19,28]. Bleeding has been reported more commonly in type 3 g-NENs[54]. Carcinoid syndrome may be seen in patients with gastrointestinal NENs, but it is rarely detected in patients with g-NENs [55,56]. If carcinoid syndrome develops in g-NENs, it shows a different presentation than carcinoid syndromes that develop from midgut and hindgut, which is termed as atypical carcinoid syndrome. In this type of carcinoid syndrome, the rashes are more diffuse, the surrounding area is prominent and serpiginous and the lesions are very itchy. Diarrhea and cardiac symptoms are usually absent[19,55,57].

Diagnosis of g-NENs are made by upper gastrointestinal endoscopy. Generally small polyps are detected on endoscopy. Type 1 and 2 Lesions are often located in multiple areas outside the antrum, while type 3 and 4 NENs are usually single and can

be detected in all parts of the stomach[29]. In type 3 g-NENs the gastric mucosa except for polyps is detected normal. It is commonly atrophic in type 1 g-NENs and peptic ulcers may accompany in especially type 2 g-NENs[29].

The definitive diagnosis of g-NEN is made on histopathological examination. Biopsy samples should be obtained from both the gastric mucosa and the polyps in order to examine the condition of the underlying mucosa and to detect microscopic NENs[56]. Four samples from the corpus and two samples from the antrum should be taken for histopathological examination[58]. In histopathological examination of g-NENs, the tumor cells are usually uniform with round-oval nuclei, coarse chromatin and fine granular cytoplasm. On immunohistochemical staining the cells are positively stained with Chromogranin A (CgA) and Synaptophysin[58]. CgA may be absent in type 4 g-NENs[36]. It is crucial to determine the tumor grade during pathological examination with proliferative indices such as mitotic activity and Ki-67 index. Mitotic activity is determined by examining 10 fields at 40 × magnification and counting the active cells in these areas. Although the amounts of mitotic activity used in determining the tumor grade level are not clearly defined, mitotic activity of 2 is accepted by WHO to distinguish grade 1 from grade 2, and 20 to distinguish grade 2 from grade 3 NEN. But mitotic activity index may be misleading in determining the grade of the tumor, especially in the distinction in grade 1 from grade 2 NENs. Ki-67 is another proliferation index, which was first described by Gerdes *et al*[59] in 1991. Studies have shown that Ki-67 is present in proliferation phases of the cell cycle, but not in the quiescent or resting cells, which makes it possible to use as a proliferation marker effectively in many cancers[60]. Different cut-off levels of Ki-67 indexes were suggested for differentiating grade 1 from grade 2 NEN, but the cut-off level of 3% was accepted for this differentiation[7,61,62]. Although the 10% level was suggested for grade 3 definition, this limit was changed to 20% in the following studies and WHO recommendation[7]. It is not clear whether mitotic index or Ki-67 proliferation index is better in determining the tumor grade. But it is recommended that both indexes should be measured and the higher parameter should be selected if there is a discrepancy between them[7]. Since Ki-67 index is a method that gives the ratio of cells with positive staining, it has the advantage of having the ability to study also in small tissue samples. Whereas the advantage of mitotic index is that it does not need immunohistochemical staining[63].

INITIAL MANAGEMENT OF GASTRIC NENS

After g-NEN is diagnosed, it is necessary to determine the tumor type, spread and stage of the disease, and to detect the presence of metastasis. While upper gastrointestinal endoscopy is performed, the whole mucosa should be examined properly, and the number of the lesions and the size of the largest polyp should be recorded[64]. If gastrinoma is present, the localization of the tumor should also be made.

The discrimination between g-NEN types is of great importance, because the therapy and follow-up differs among types. Serum gastrin levels are elevated in type 1 and 2 g-NENs, whereas it is normal in patients with type 3 and 4 g-NENs. Before the measurement of gastrin, the use of proton pump inhibitors should be withdrawn. But in patients with type 2 g-NENs the withdrawal of antisecretory therapy is with the risk of rebound acid secretion, which may lead to peptic ulcer and bleeding[65]. For differential diagnosis of type 1 and 2 g-NENs, biopsy samples outside the lesions should be investigated to detect whether atrophy is present. Atrophic mucosa indicates type-1 g-NENs, whereas normal mucosa is detected in patients with type 2 g-NEN. Another tool for differential diagnosis may be gastric acid measurement. In cases with hypergastrinemia, gastric pH is generally above 4 in type-1 g-NEN, while it is less than 2 in type 2 g-NEN[29]. If type 2 g-NEN is detected, additional testing for MEN-1 syndrome should be performed. Vitamin B12 Level should be tested along with anti-parietal cell and anti-intrinsic factor antibodies, if indicated. Addison disease and hypothyroidism should also be screened in suspected cases[25]. Serum CgA level is usually elevated in patients with g-NENs, but its specificity is low[66]. Serum CgA measurement may be also used in the follow up to predict response to chemotherapy and predict prognosis[19]. Somatostatin analogues (SSA) and proton pump inhibitors may alter the level of serum CgA, which should be taken into account in interpreting the results[29].

Several imaging modalities are used to evaluate the spread and stage of the disease. Endoscopic ultrasonography (EUS) plays an important role in the diagnostic workup

of g-NENs. EUS helps to detect tumor invasion to the deeper layers of the gastric wall, and also to determine lymph node metastasis with the advantage of ability of histological confirmation by fine needle aspiration[58,67]. Cross sectional imaging modalities like computerized tomography (CT) and magnetic resonance imaging (MRI) may be needed to determine disease staging and metastasis for advanced neoplasms and especially type 3 g-NEN[9]. Liver metastases rapidly enhance contrast after contrast material injection on CT and a wash-out is observed in the portal venous phase[68]. Somatostatin receptor imaging (SRI) modalities (somatostatin receptor scintigraphy or 68 Ga-PET-DOTANOC) are rarely useful for type 1 g-NENs which are generally small and indolent, but they can be useful in type 2 and 3 g-NENs as part of the overall staging and perhaps choosing therapy[28,69,70].

If smaller than 1 cm type 1 g-NEN is detected, no further evaluation is required. Although the exact cut-off level of lesion size for EUS is not defined, EUS should be performed if the lesion is greater than 1 cm to assess invasion[9,58]. CT scan and MRI techniques are not indicated in most type 1 g-NENs[58]. SRI techniques do not make extra contribution compared to imaging methods, but they can be performed for treatment response evaluation if SSA therapy is planned[71]. *H. pylori* should be assessed in these patients. Serum CgA and gastrin levels should be tested, and the patients should also be evaluated for autoimmune diseases with anti-parietal cell and anti-intrinsic factor autoantibodies, thyroid functional tests and anti-thyroperoxidase antibodies[58].

Because locally advanced disease and metastasis is seen more commonly in type 2 g-NEN compared to type 1, imaging modalities are more commonly used for patients with especially larger type 2 g-NEN lesions. CT, MRI and SRI modalities are used to determine for disease stage and to find the gastrinoma lesions' origin[58]. SRI modalities and EUS may detect gastrinoma lesions more effectively than CT or MRI [72,73]. It is recommended to perform genetic testing for MEN-1 and screen for associated tumors in the pituitary gland and pancreas[22]. Serum gastrin and CgA levels should also be tested in these patients[58].

Type 3 and 4 g-NENs behave similar to gastric adenocarcinoma, and the staging and diagnostic modalities should be performed like adenocarcinoma[64]. CT, MRI or SRI modalities (especially 68 Ga-PET-DOTANOC) are needed for disease staging, but SRI tests may be false negative in poorly differentiated patients[9,64].

TREATMENT

The treatment options of g-NENs depends on the tumor type, lesion number and size, disease extent and the differentiation of the tumor. Follow up without excision, endoscopic resection, surgical resection and medical therapies are treatment options for g-NENs.

Type 1

The metastasis risk of type 1 g-NEN is low, and therefore conservative management strategies are commonly preferred in small lesions[9,74]. Some authors suggested to resect all visible lesions larger than 5 mm[67,75], but this approach is not widely accepted. In a study performed by Sato *et al*[76], 25 patients were followed up without resection, and after an average of 7 years, no significant rapid growth, metastasis or invasion of the tumor was detected in any patient, and no disease-related death was reported. ENETS suggested to remove all lesions in their guideline in 2013, but they changed this recommendation in 2016 and recommended to remove lesions greater than 10 mm with close follow-up[9,58]. Similarly, NANETS recommends that surveillance without excision and endoscopic removal may be chosen for lesions smaller than 10 mm[74]. They recommended endoscopic resection or close follow up with less than 6 Lesions between 1 to 2 cm diameter, and endoscopic or surgical resection in patients with more than 6 Lesions[74]. Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) may be used for endoscopic resection. ESD has the advantage of en bloc resection for complete histological analysis [9,77]. Preferably EUS should be performed for lesions greater than 10 mm to assess tumor invasion, and endoscopic resection should be done when it is possible[58,74].

Surgical treatment is the option for lesions which are predicted to be T2 or lesions with positive margins. Surgical antrectomy may be added to the surgical procedure to suppress gastrin secretion, with questionable efficacy[9]. Although it is stated that performing antrectomy after surgical or endoscopic removal of the lesion provides tumor regression and reduces recurrence[78,79], there are also publications reporting

that it does not reduce metastasis and recurrence[80]. It has been shown in a study that performing antrectomy requires less often endoscopies in the follow-up time period, lowers the risk of recurrence and it may reduce the anxiety of patients for malignancy development[81]. Another method to suppress gastrin levels is SSAs. SSAs have the advantage of regression of tumors, but this has not been compared to other treatment strategies, and it is not widely accepted for routine use. SSAs may be useful for multiple small lesions which are not possible for endoscopic resection[82]. The use of SSAs (both lanreotide and octreotide) may be an option for inoperable patients and for metastatic diseases[9,83,84]. Netazepide is a gastrin receptor antagonist, which has favorable effects on type 1 g-NENs[85-88], but its use needs further studies for clear recommendation. It also should be kept in mind that the tumors will grow after the withdrawal of netazepide[25].

Type 2

The preferred treatment of type 2 g-NEN is local excision[58]. Endoscopic treatment for noninvasive tumors and surgical resection for invasive or metastatic lesions should be chosen. Another important issue is to search for the gastrinoma lesions and perform surgical resection for it[64]. Because the cause of hyperacidity is not antral G cells, antrectomy has no favorable effect. Proton pump inhibitors should be used for hyperacidity and to reduce the risk of peptic ulcer. No evidence is present for the treatment of type 2 g-NEN with netazepide.

Type 3 and type 4

If type 3 g-NEN is detected, the optimal treatment strategy is surgical treatment as the procedure for gastric adenocarcinoma (partial or total gastrectomy with lymph node dissection)[9,74]. Although some authors cited that endoscopic resection would be sufficient in small lesions without invasion, this is not a widely accepted approach [89]. Similarly, the treatment of localized type 4 g-NEN is gastrectomy and lymph node dissection.

Metastatic disease

Surgery, local methods and systemic treatment are included in the treatment options of liver metastasis due to g-NENs. Treatment options for patients with metastases of g-NENs are not specific for gastric lesions, and the options are based on recommendations for liver metastases of NETs. The appropriate method for liver metastases of grade 1 and 2 g-NENs is surgical removal of the metastatic lesions. Although surgery is not commonly recommended for grade 3 tumors, single and suitable lesions may be surgically removed[90]. Primary tumor resection is suggested in patients with advanced resectable disease, but the role of primary tumor resection in patients with unresectable metastases is debated[74,91]. Recently published studies showed that resection of primary gastrointestinal neuroendocrine tumors among patients with metastases (with and without liver treatment) has survival advantage, but improved survival could not be achieved in patients with g-NENs[92,93]. Liver transplantation may be done after surgical removal of the primary focus, especially in selected low-grade patients with extensive liver metastasis[94,95]. Transarterial embolization, chemoembolization and radioembolization and radiofrequency ablation may be effectively used as local treatment options of liver metastasis[90,96]. Systemic chemotherapy with etoposide and cisplatin is recommended in grade 3 and metastatic patients[58,97]. Peptide receptor radionuclide therapy targeting somatostatin receptors may also an alternative treatment approach for gastrointestinal NENs, but its use in metastatic g-NEN is not widely studied[98,99].

Carcinoid syndrome

Carcinoid syndrome is seldom seen in patients with g-NENs. But it is more commonly seen in patients with liver metastasis. If carcinoid syndrome is present, it should be treated with SSAs, along with symptomatic treatment if indicated[74]. In addition, SSAs should be given for prophylaxis before surgical and local treatment methods[90].

PROGNOSIS

The prognosis of g-NENs depends on tumor type, grade and tumor stage. In general, tumor size, histological grade, type 3 NEN, mitotic index and Ki-67 index, tumor depth, lymph node involvement and presence of metastasis are defined as poor prognosis criteria for g-NENs. Type 1 g-NENs have usually excellent prognosis with

around 100% of survival even in untreated patients[27,28,100]. Type 2 g-NENs have almost similar prognosis to type 1 and are generally detected at early stages, which shows good survival rates. But patients with type 2 g-NEN may have MEN-1, and when MEN-1 is present patients may die with metastatic diseases from other organs (especially pancreas and thymus) than the stomach[101]. Type 3 g-NEN shows the worst prognosis with similar survival rates with gastric adenocarcinoma, which displays the crucial role of the differential diagnosis among g-NENs[35]. The tumor-related annual mortality rate of g-NENs was calculated as 1.07%, but this rate gradually increases in grade 2 and 3 and reaches 57% in grade 3 g-NENs[102].

CONCLUSION

g-NENs or neuroendocrine tumors are tumors with increasing incidence. The pathogenesis, clinical characteristics, prognosis and treatment options differs apparently between subgroups of g-NENS. Type 1 and 2 are gastrin dependent, whereas type 3 and 4 are considered as sporadic. The reason for hypergastrinemia is atrophic gastritis and gastrinoma in type 1 and type 2 g-NEN, respectively. New data is emerging recently about new subgroups, which should be evaluated with further studies. It is crucial to differentiate tumors between these subgroups for further management and treatment. Treatment options for g-NENs include endoscopic resection, surgical resection with or without antrectomy, medical treatment with somatostatin analogues, netazepide or chemotherapy regimens. Also follow-up without endoscopic or surgical excision is another option in appropriate cases. The prognosis of type 1 and 2 g-NENs are good, whereas the prognosis of type 3 and 4 g-NENs are worse. Despite it took decades after the definition of carcinoid or NET, new data and evidences still change the management of g-NENs in recent years.

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