



# Multidisciplinary diagnosis and treatment of undifferentiated gastric cancer with a specific morphology: a case report

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**Background:** Due to ongoing research on digestive endoscopy, early gastric cancer has become a popular topic. Based on macro-research on morphology using the Paris endoscopic classification system and micro-explorations of histopathology under endoscopy, several researchers have organically combined endoscopy with pathology and surgery. This multidisciplinary combination of digestive endoscopy could improve the diagnosis rate and cure rate of early gastric cancer.

**Case Description:** A 45-year-old female patient underwent gastroscopy for the treatment of intermittent upper abdominal pain, which she had been experiencing for a year. A diagnosis of a submucosal tumor (SMT) was made after several preoperative examinations. An endoscopic submucosal dissection (ESD) was performed to remove the lesion, and the specimens were then fixed to conduct the pathologic examination. The results led to the diagnosis of undifferentiated gastric adenocarcinoma with the following general classification: type 0-IIa, a lesion of 2.7 cm × 2.0 cm × 0.5 cm, and no vascular tumor thrombus or nerve invasion. The surrounding mucosa showed mild chronic non-atrophic gastritis. The tumor tissue reached the vertical cutting edge, and no residual cancer tissue was found at the horizontal cutting edge. The immunohistochemistry results showed poorly differentiated adenocarcinoma. Based on the results, the patient underwent distal gastrectomy and abdominal lymph node dissection. Our combined multidisciplinary diagnostic processes and treatments can now be used as a reference for endoscopists.

**Conclusions:** ESD plays an essential role in the diagnosis and treatment of undifferentiated gastric cancer, and provides a reference for endoscopists.

**Keywords:** Undifferentiated gastric cancer with specific morphology; Paris classification; elevated type (0-IIa); endoscopic submucosal dissection (ESD); case report

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## Introduction

Gastric carcinoma is a malignant tumor with high incidence and mortality rates worldwide (1). Study has shown that gastric cancer is the second most malignant tumor in China, and its incidence and mortality rates are second only to those of lung cancer (2). Due to continuous enhancements in medical technology, high-definition endoscopy has

improved the diagnosis of early gastric cancer, but it still has a miss rate of 20–25%. Magnification endoscopy with narrow-band imaging (NBI) can be used to further characterize the histology of early gastric cancer (3–5). There are several research directions and perspectives on early gastric cancer. Therapeutic indications can be investigated based on changes observed in the surrounding mucosa, size, tone, morphology, microvessels and

microstructure, the nature of lesions, and the depth of invasion. However, the manifestations of some “cunning” lesions are atypical and highly occult. Early cancer with a special differentiation type can be missed even after multiple examinations. We need to ensure that such lesions can be identified. In addition to being familiar with the performance of various types of endoscopes, it is critical that awareness of the benefits of early cancer screening is increased.

Currently, the Paris classification system is mainly used to evaluate the morphology of lesions revealed by performing an endoscopy. The Paris classification system was developed for the systematic evaluation of superficial lesions in the esophagus, stomach, and colon. Superficial carcinomas are defined as lesions extending through the mucosa and submucosa of the digestive tract (6). Superficial gastric cancer (type 0) is divided into protuberant lesions (0–I), flat lesions (0–II), and ulcerated lesions (0–III). Type 0–I lesions are divided into pedicled type (0–Ip), sessile type (0–Is), and semi-pedunculated type (0–Isp) lesions. Type 0–II lesions are divided into the following 3 subtypes: elevated type (0–IIa), flat type (0–IIb), and depressed type (0–IIc) lesions (6). Most undifferentiated gastric cancers are faded and have depressed (0–IIc) lesions with cliff-like changes at the edge. Undifferentiated gastric cancer infiltrates and proliferates horizontally in the glandular neck, resulting in the fragmentation of the original glandular duct. The lack of glandular support leads to overall collapse, and the capillaries in the lamina propria of mucosa decrease, resulting in discoloration and clear margins (7). According to a report, undifferentiated elevated type 0–IIa gastric cancer is rare, and accounts for only 5.6% of gastric cancers (8).

Usually, undifferentiated gastric cancer presents with white moss on the protuberance, an uneven nodular surface, and discoloration. Protuberant mucosa tends to form an erosion or ulcer with a deeper infiltration of the mucosa and submucosa.

In recent years, endoscopic submucosal dissection (ESD) has been widely used for the treatment of early gastric cancers with a negligible risk of lymph node metastasis. However, currently, only limited data are available on the long-term outcomes of ESD for undifferentiated gastric cancer. In this study, we aim to improve the diagnostic and therapeutic evidence for patients with undifferentiated gastric cancer, describing a rare undifferentiated gastric cancer case for which elevated type 0–IIa was the main form. We performed the multidisciplinary diagnostic

processes and treatments, hoping to provide a new reference for endoscopists in the clinic. We present the following case in accordance with the CARE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-344/rc>).

## Case presentation

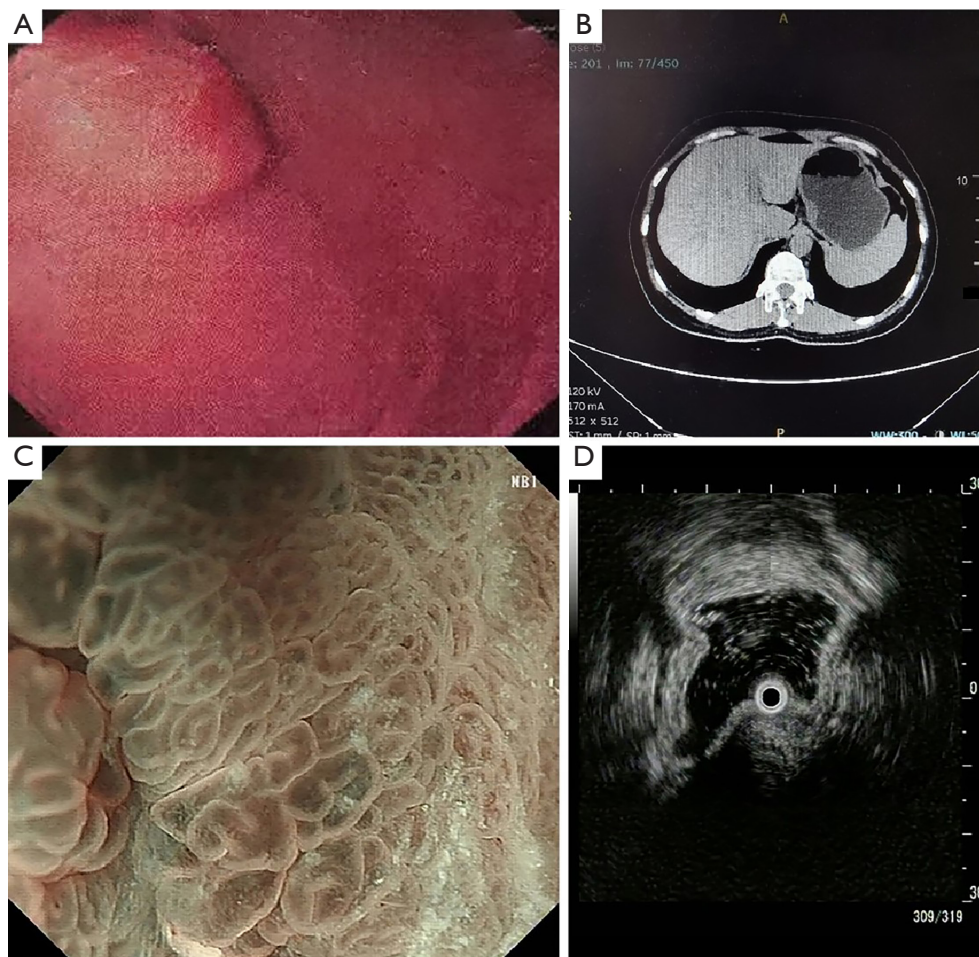
A 45-year-old female patient underwent a gastroscopy at Affiliated Hospital of Nanjing University of Chinese Medicine (Jiangsu Province Hospital of Chinese Medicine) in Nanjing in February 2021 to treat intermittent upper abdominal pain, which she had experienced for a year. The resulting imaging indicated a submucosal protuberance of approximately 2.0 cm × 1.8 cm on the anterior wall of the gastric antrum, and local surface congestion (see *Figure 1A*). The pathological results showed moderate chronic superficial gastritis with a small amount of granulation hyperplasia. In March 2021, the patient was hospitalized at the Gastrointestinal Endoscopy Center at the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine to undergo an endoscopy. The patient had no history of chronic cardiovascular and cerebrovascular diseases, infectious diseases, or drug and food allergies. The patient’s mother and 2 aunts had died of gastric cancer. The patient’s sister and brother were in good health. In 2004, the patient had a son through cesarean section, who was in good health. In 2015, she underwent right thyroid papillary carcinoma resection, and currently takes Euthyrox orally. All procedures performed in this study were in accordance with the ethical standards of the Affiliated Hospital of Nanjing University of Chinese Medicine research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Physical examination

The abdomen was flat, and soft on palpitation without apparent tenderness or rebound pain. There were no other positive physical examination indications.

## Laboratory examination

The patient had total cholesterol (TC) of 5.48 mmol/L,



**Figure 1** Preoperative assessment. (A) Endoscopic white light showing elevated type 0-IIa (other hospitals); (B) upper abdomen CT showing a slightly thickened gastric wall at the gastric antrum; (C) NBI-ME: DL (-), IMVP (-), IP widening, MCE fusion; (D) mini-probe EUS: a mixed-echo mass with an uneven internal echo mainly characterized by a low echo. The mass had a clear margin and originated from the submucosa, and the far-field echo was not clear. NBI-ME, narrow-band imaging-magnifying endoscopy; DL, demarcation line; IMVP, irregular microvascular pattern; IP, intervening parts; MCE, marginal crypt epithelium; EUS, endoscopic ultrasound.

and a low-density lipoprotein-cholesterol (LDL-C) level of 3.17 mmol/L. Upper abdominal computed tomography (CT) showed a slightly thickened gastric wall at the gastric antrum (see *Figure 1B*). After excluding relevant contraindications, the preoperative microscopic evaluation was completed by Dr. Yu at our Center. Endoscopic imaging revealed a gentle slope protuberant change of about 2.0 cm × 1.8 cm at the anterior wall of the junction of the gastric antrum and gastric body with a tough texture. The lesion was generally smooth and flat, with local flushing, erosion, and scarring at the top. The NBI-magnifying endoscopy (NBI-ME) results were as follow: demarcation line (DL) (-), irregular microvascular pattern (IMVP)

(-), intervening parts (IP) widening, and marginal crypt epithelium (MCE) fusion (see *Figure 1C*). The patient had a scar from previous pathological biopsies at other hospitals. Mini-probe endoscopic ultrasonography (VP-7000 Fujifilm, Japan) showed a mixed-echo mass with an uneven internal echo, mainly characterized by a low echo. The mass had a clear margin and originated from the submucosa, and the far-field echo was not clear (see *Figure 1D*). Lesion morphology and small probe ultrasound findings and the microvascular structure indicated a possible diagnosis of a submucosal tumor (SMT). ESD diagnosis and treatment were considered after obtaining consent from the patient and her family.

## Final diagnosis

The patient was diagnosed with undifferentiated gastric cancer (type 0–IIa).

## Treatment

ESD treatment was performed by Professor Xiao at our Center. The patient was anesthetized and intubated. The endoscope reached the anterior wall of the gastric antrum and gastric body junction with the assistance of the transparent cap (see *Figure 2A*). A dual-knife was used to mark the tissue about 0.5 cm away from the lesion, and an epinephrine and methylene blue suspension was injected under the mucosa with fair lifting (see *Figure 2B,2C*). A dual-knife was used to dissect the lesion layer-by-layer along the mark (see *Figure 2D,2E*). There were abundant blood vessels at the root of the lesion. In case of bleeding from the small blood vessels or wound, the exposed blood vessels were treated with hot biopsy forceps, and the lesion was completely dissected (see *Figure 2F*). Finally, the separated specimens were fixed *in-vitro* (see *Figure 2G-2I*).

## Outcome and follow-up

The ESD postoperative pathology results revealed an undifferentiated gastric adenocarcinoma (P<sub>or</sub>2 > Sig). Most of the cancerous tissue was located in the submucosa, but a small part was found in the mucosal layer (the front of the tumor had invaded an area 3 mm away from the mucosal muscle, SM2). The general classification was as follows: type 0–IIa, a lesion of 2.7 cm × 2.0 cm × 0.5 cm, and no vascular tumor thrombus or nerve invasion. The surrounding mucosa showed mild chronic non-atrophic gastritis. The tumor tissue reached the vertical cutting edge, and no residual cancer tissue was found at the horizontal cutting edge (see *Figure 2J,2K*). The immunohistochemistry results showed poorly differentiated adenocarcinoma. The tumor cells expressed cytokeratin-positive (CK-P) (+), carcinoembryonic antigen (CEA) local (+), Ki67 about 15% (+), human epithelial growth factor receptor 2 (HER2) (–), CD68 (–), CD117 (–), gastrointestinal stromal tumor 1 (–), and CD34 vessel (+) (see *Figure 2L*).

As the character, size, and depth of the lesion exceeded the ESD curative resection standard, the patient was transferred to the Surgical Department of our hospital. The patient underwent distal gastrectomy and abdominal lymph node dissection. The patient's postoperative

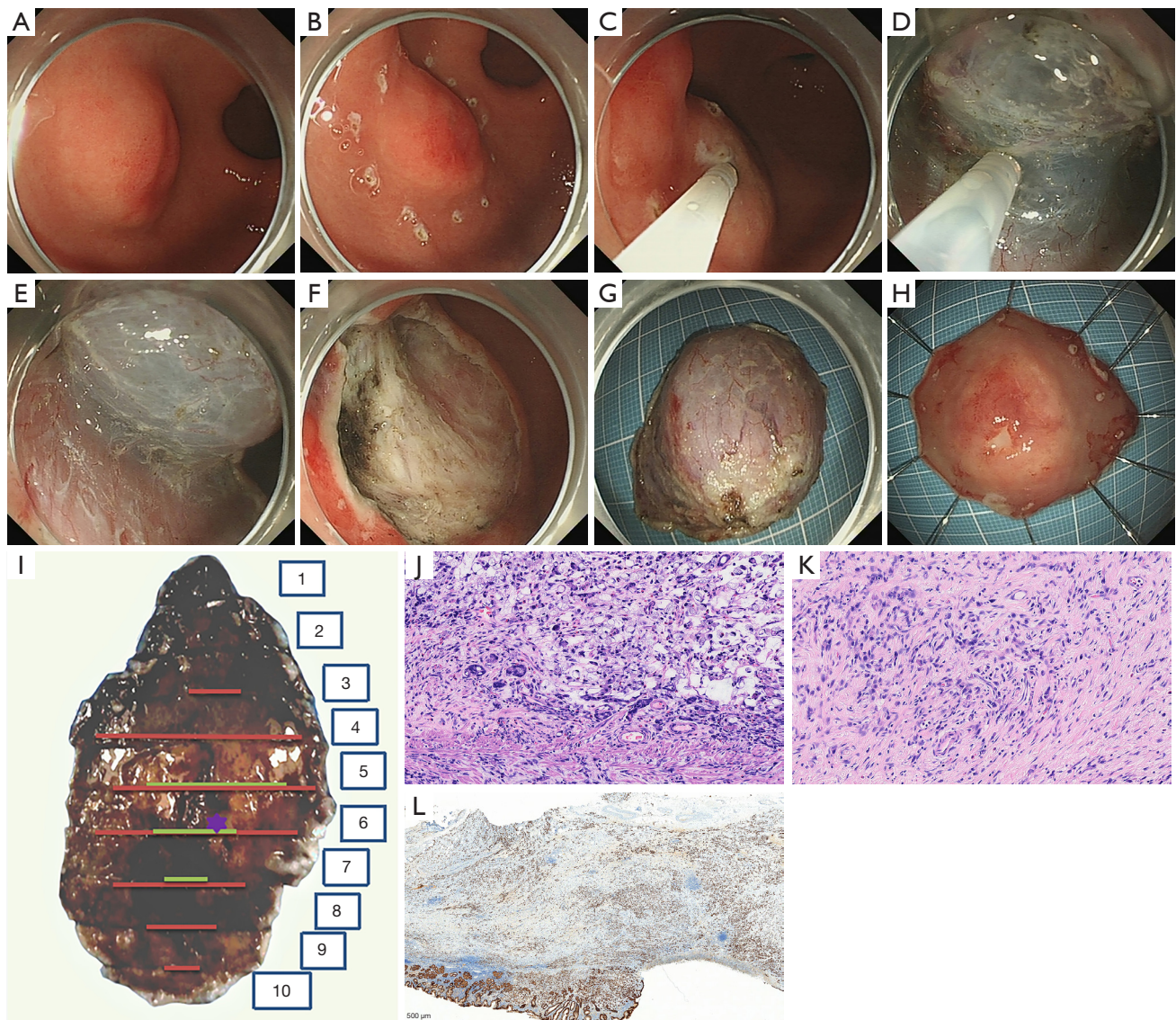
pathology results were as follows: (I) post ESD for gastric adenocarcinoma with wound ulcer formation; (II) no residual cancer tissues at the upper and lower cutting edges, and omental tissues were not invaded by tumors; and (III) 20 and 11 lymph nodes of the lesser and greater curvature of the stomach, respectively. A total of 31 lymph nodes were not invaded by tumors (0/31). Based on the postsurgical pathology results, the patient did not require radiotherapy and chemotherapy after the operation. Thereafter, the regular follow-up plan was followed.

## Discussion

We reported a rare case of undifferentiated gastric cancer for which elevated type 0–IIa was the main form. Multidisciplinary diagnostic processes and treatments were carried out. Undifferentiated-type early gastric cancers account for a large proportion of gastric cancers in younger patients; thus, the prognoses of younger patients following endoscopic resection need to be improved.

This case provides further evidence on the endoscopic diagnosis of undifferentiated gastric cancer. The morphology and tone of undifferentiated early carcinoma in the context of non-atrophic gastritis were not typical or 0–IIc. Indeed, the patient had an extremely rare elevated 0–IIa lesion. The tone of the lesion was not significantly different to that of the surrounding mucosa, and the overall shape of the lesion was regular. The surface showed no apparent ulcers. No typical thunder signs or wavy and corkscrew patterns were observed using ME, which might be a limitation of the VS theory in evaluating undifferentiated gastric cancer. There was insufficient evidence of a malignant tumor during the preoperative evaluation, and the lesion could have easily been confused with a benign SMT. Most of the tumor tissues were located in the submucosa, leading to an upward shift of the mucosa and mucosal muscle layers. Further, the growth mode did not cause damage to the surface structure. The lesion showed SMT-like changes and was difficult to diagnose clinically.

Due to the complexity and difficulty of the diagnoses and treatment in gastric cancer, the multidisciplinary team (MDT) model is becoming increasingly important, which can improve the diagnosis and treatment quality of gastric cancer, thus enhancing the prognosis of patients with gastric cancer. MDT refers to the cooperation among more than two disciplines, setting as a settled work team in charge of one disease through the regular meeting to make the optimal treatment strategy for patients. First,



**Figure 2** Surgical process and postoperative pathology. (A) An auxiliary transparent cap was installed at the tip of the endoscope to expose the operative field (D-20I-11804, Olympus Optical, Japan). The equipment was a single channel therapeutic endoscope (GIF-Q260J, Olympus Optical, Japan); (B) a dual-knife (KD-650L, Olympus Optical, Japan) was used to mark the boundary; (C) a mixture of methylene blue (0.04 mg/mL) and adrenaline hydrochloride (0.02 mg/mL) was injected. The liquid pad formed by loose connective tissue in the submucosa fully separated the submucosa from the muscularis propria, facilitating submucosal dissection. The lesion was lifted using a submucosal injection needle (25G, Olympus Optical, Japan); (D,E) a dual-knife was used for the incision and submucosal dissection; (F) hemostatic forceps, Coagrasper (FD-410LR, Olympus Optical, Japan), were used to stop bleeding under endoscopy. The thicker exposed blood vessels and wound were treated for hemostasis; (G,H) the dorsal side of the resected specimen was intact and the specimen was fixed *in vitro*; (I) specimen restoration: the red lines indicate the submucous layer, the green lines indicate the mucous layer, and the purple star indicates the deepest infiltrated part of the whole lesion; (J,K) postoperative pathology: gastric adenocarcinoma, undifferentiated (Por2 > Sig), hematoxylin-eosin (HE) staining, magnification  $\times 200$ ; (L) immunohistochemistry: Keratin CK, magnification  $\times 40$ .

MDT discussion makes diagnosis more accurate. Second, MDT meetings can promote better communication and information sharing among experts from different departments, and supervise the consistency of treatment for gastric cancer patients as scheduled. Third, MDT model can establish a more reasonable therapeutic process, which is conducive to introducing the new technologies, it is helpful to reduce hospital costs and unnecessary waste; Finally, MDT discussions provide more learning opportunities for young doctors. Recently, a single-center cohort study performed in West China Hospital of Sichuan University found that through the implementation of standardized surgical treatment technology and multidisciplinary treatment model, the quality of surgery treatment and overall survival (OS) increase, and prognosis of gastric cancer patients has been improved (10).

In recent years, ESD has begun to be generally applied in differentiated gastric cancer. Additionally, due to the high risk of lymph node metastasis, ESD has also begun to be used as an investigational treatment approach for patients with undifferentiated gastric cancer, such as poorly differentiated adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma. Jeon *et al.* (11) performed a retrospective analysis of 66 patients who underwent ESD for undifferentiated-type early gastric cancer, all 26 patients with more than 1 year of follow-up after curative resection survived without any evidence of local or distant recurrences over a median follow-up period of 36 months, and the OS, disease-specific survival (DSS), and recurrence-free survival (RFS) rates of patients with curative ESD were 93.8%, 100%, and 100%, respectively, indicating ESD may have favorable long-term outcomes in patients with undifferentiated-type gastric cancer at an early stage after curative resection. Japan Clinical Oncology Group (12) conducted a nonrandomized, single-arm confirmatory trial of expanded endoscopic submucosal dissection indication for undifferentiated early gastric cancer, they demonstrated that ESD can be a curative and less invasive treatment for undifferentiated early gastric cancer for patients meeting the eligibility criteria. However, it is limited to patients with undifferentiated gastric cancer at an early stage. Besides, although ESD seems to be technically feasible, inaccurate prediction of lateral or vertical margin leads to lower curative resection rate, thus the application of more strict indication is needed for gastric cancer—mixed-type histology (13). In this case, the lesion was removed with the help of the Pathology and Surgery Departments, which also reflects the advantages of a multidisciplinary

diagnosis and treatment. Based on the familial history of malignancy provided by the patient, germline gene testing was recommended to predict the patient's predisposition to the disease. The patient refused to undergo any further examinations for personal reasons, and is currently being followed up. The authors hope that this case report will provide a reference for endoscopists in the clinical diagnosis and treatment of gastric cancer, and thus improve diagnoses by differentiating between the morphological diversities commonly observed in gastric cancer.

## Conclusions

We reported a rare case of undifferentiated gastric cancer for which elevated type 0–IIa was the main form. Multidisciplinary diagnostic processes and treatments were performed to improve the prognosis of this patient. This case showed that ESD plays an essential role in the diagnosis and treatment of undifferentiated gastric cancer. We hope that this case can provide evidence and a reference in diagnosis and treatment of undifferentiated gastric cancer for endoscopists.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-344/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-344/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Affiliated Hospital of Nanjing University of Chinese Medicine research committee and with the Helsinki Declaration (as revised in 2013). Written informed

consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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