# Endoscopic manifestations and treatment outcomes of asymptomatic gastric metastases from primary lung adenocarcinoma: Report of two cases

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**Abstract.** Metastatic spread of lung adenocarcinoma to the stomach is rare and most gastric metastases are discovered at the advanced stage due to certain symptoms. The present study reported two cases of asymptomatic gastric metastases from lung adenocarcinoma presenting as diminutive nodules or erosion endoscopically. The manifestations were also visualized under magnifying endoscopy with blue laser imaging (BLI-ME), the two cases share certain common characteristics under BLI-ME, such as an obviously widened intervening part and extended subepithelial capillary network, which indicated that lesions developed beneath the superficial epithelium. Target biopsy and further immunohistochemical staining confirmed that the gastric lesions were metastatic from primary lung cancer. None of the two patients were candidates for surgery due to multiple distant metastases, but the gastric metastases regressed to scars after systemic anticancer therapy. These two cases were presented in order to improve the current understanding of the endoscopic manifestations of early gastric metastases from lung cancer, and the outcomes may demonstrate that systemic treatment is effective for eliminating early gastric metastatic lesions.

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## Introduction

Lung cancer is one of the most common malignancies worldwide and its incidence and mortality rate are both the highest among cancers in China (1). Approximately half of all patients with lung cancer suffer from metastatic disease at the time of diagnosis, with the most common metastatic regions being lymph nodes, liver, adrenal gland, bone and brain (2). However, gastric metastasis is uncommon with a prevalence of 0.1-6.8% according to clinical and autoptic results (3-5). In most cases, gastric metastases are discovered at an advanced stage when patients experience symptoms, such as abdominal pain, anemia or vomiting, due to perforation, bleeding or obstruction caused by the metastatic mass (6,7), which usually predict poor prognosis; the average time between discovery of gastrointestinal metastasis and death ranges from 96.5 to 130.3 days, as reported in certain case series (8,9). Asymptomatic and diminutive gastric metastases are rarely found in the clinic and the manifestations of gastric metastases from lung cancer under chromoendoscopy and magnifying endoscopy have not been reported in the literature, to the best of our knowledge; furthermore, although there are certain reports regarding the systemic treatment outcome of primary lung cancer with gastric metastasis, which mainly focus on the therapeutic effect of primary tumor treatment (10,11), the effect of systemic treatment on gastric metastatic lesions is not well documented. In the two cases presented in the current study, the gastric metastases from lung adenocarcinoma manifested as diminutive nodules or erosion endoscopically and had certain common characteristics under magnifying endoscopy with blue laser imaging (BLI-ME). After systemic anticancer therapy, the gastric metastases had effectively regressed to scars in both cases.

## Case reports

Case 1. A 66-year-old female patient complained of shortness of breath for >10 days. The chest computed tomography (CT) scan at the local hospital indicated a pulmonary nodular lesion

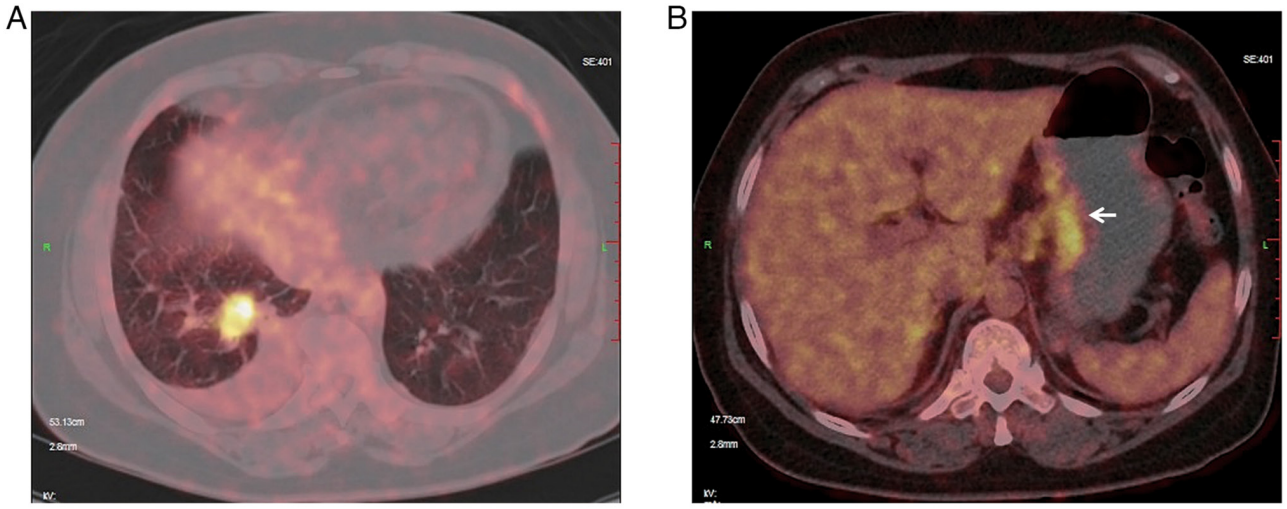


Figure 1. PET/CT of case 1. (A) PET/CT indicating a pulmonary nodular lesion in the right lower lobe with high FDG uptake. (B) PET/CT indicating a highly FDG-uptaking lesion in the gastric lesser curvature (arrow). PET/CT, positron emission tomography/computed tomography; FDG, fluorodeoxyglucose.

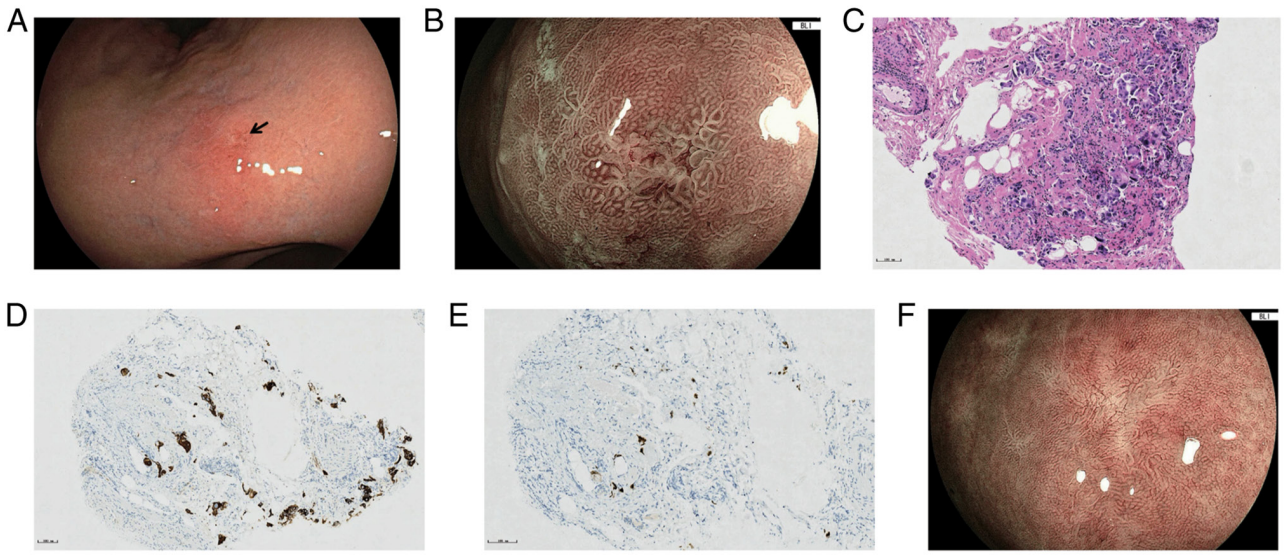


Figure 2. Endoscopic and pathologic data of case 1. (A) Esophagogastroduodenoscopy in May 2021 revealed a diminutive erosion sized 5x4 mm in the gastric lesser curvature with slight swelling and redness of the surrounding mucosa. The arrow indicates the location of the erosion. (B) Magnifying endoscopy with blue laser imaging revealed heterogeneous morphology of marginal crypt epithelium and a widened intervening part; the subepithelial capillary network became extended and a demarcation line may be seen between the erosion and background mucosa. (C) Hematoxylin-and-eosin staining of the biopsied tissues revealed poorly differentiated carcinoma-cell infiltration. (D) Cytokeratin 7-positive staining of the cancerous gastric lesion. (E) Thyroid transcriptional factor-1-positive staining of the cancerous gastric lesion (magnification, x40; scale bars, 100 $\mu$m). (F) The metastatic lesion had regressed to a scar under non-magnifying endoscopy with blue laser imaging after 4 cycles of chemotherapy in September 2021.

measuring 2.9x2.7 cm in the right lower lobe, with mediastinal and bilateral hilar enlarged lymph nodes. The patient was admitted to the Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences (Shenzhen, China) in May 2021. The common bronchoscopy was normal, but endobronchial ultrasound-guided transbronchial needle aspiration from lymph nodes of the 11R and 7 regions confirmed pulmonary adenocarcinoma. In addition to the pulmonary tumor, positron emission tomography (PET)/CT revealed a highly fluorodeoxyglucose (FDG)-up-taking lesion in the gastric lesser curvature (Fig. 1). Furthermore, lymph node and bone metastases were considered due to high FDG uptake. Although the patient denied any abdominal complaints, esophagogastroduodenoscopy (EGD) was recommended and a diminutive erosion sized 5x4 mm was identified in the gastric lesser curvature with slight swelling and redness of the surrounding mucosa (Fig. 2A). BLI-ME revealed heterogeneous morphology of the marginal crypt epithelium and a widened intervening part (IP), the subepithelial capillary network (SECN) was extended and a demarcation line was recognized between the erosion and background mucosa (Fig. 2B). Biopsies were taken on the erosion and hematoxylin-and-eosin (H&E) staining of the tissues (according to standard procedures, the biopsy specimens were fixed in 10% neutral-buffered formalin solution, embedded in paraffin, serially cut into 3-4 mm-thick sections and stained with H&E) revealed poorly differentiated carcinoma infiltration

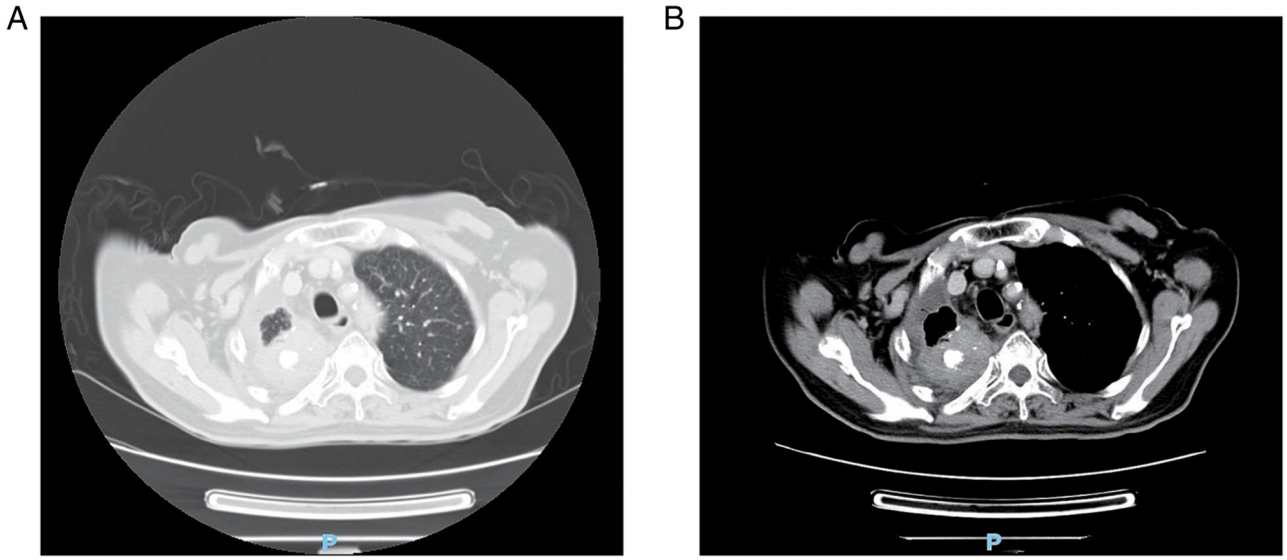


Figure 3. Chest computed tomography of case 2 in July 2021. (A) A pulmonary irregular tumor mass with calcification in the right upper lobe with a diameter of 5.0 cm (lung window), (B) A pulmonary irregular tumor mass with calcification in the right upper lobe with a diameter of 5.0 cm (mediastinal window).

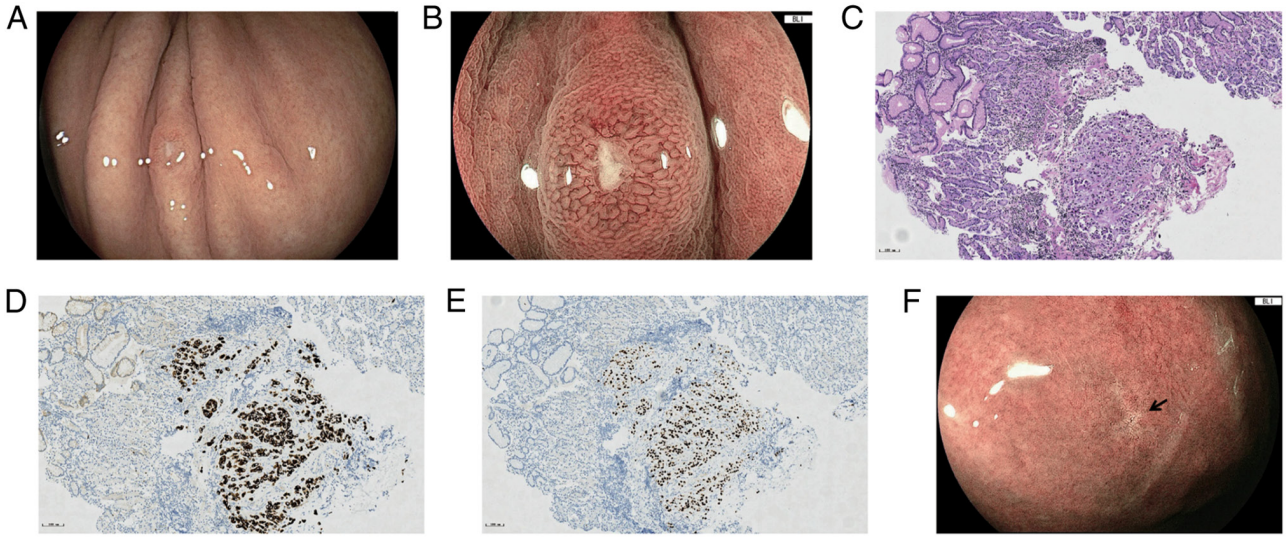


Figure 4. Endoscopic and pathologic presentation of case 2. (A) Esophagogastroduodenoscopy revealed a diminutive nodule sized 4x3 mm in the upper greater curvature of the stomach with central depression in July 2021. (B) Magnifying endoscopy with blue laser imaging revealed a widened intervening part and extended subepithelial capillary network around the depression; the demarcation line between the nodule and background was unclear, and within the depression, the microvascular and microsurface structures were absent. (C) Hematoxylin-and-eosin staining of the biopsied tissues revealed poor differentiation carcinoma cell infiltration. (D) Cytokeratin 7-positive staining in the cancerous gastric lesion. (E) Thyroid transcriptional factor-1-positive staining in the cancerous gastric lesion (magnification, x40; scale bars, 100 $\mu$m). (F) The metastatic lesion had regressed to a scar after 4 months of systemic treatment under non-magnifying endoscopy with blue laser imaging. The arrow indicates the location of the scar.

(Fig. 2C). Further immunohistochemical staining performed with the Benchmark XT Staining Instrument (Ventana Medical Systems, Inc.) indicated positivity for cytokeratin 7 (CK7; rabbit monoclonal antibody; cat. no. 790-4462) and thyroid transcriptional factor-1 (TTF-1; rabbit monoclonal; cat. no. 790-4756) (Fig. 2D and E), and negativity for cytokeratin 7 (CK20; rabbit monoclonal; cat. no. 790-4431) and caudal-related homeobox 2 (CDX-2; rabbit monoclonal; cat. no. 760-4380; all from Ventana Medical Systems, Inc.), which confirmed the pulmonary origin. Before the genetic test results came out, the patient started the AP chemotherapy regimen [Pemetrexed 0.8 g day (d)1, cisplatin 40 mg d1-3, every 3 weeks]. After 4 cycles of chemotherapy, the follow-up CT revealed shrinkage of the primary lung tumor and lymph nodes, and EGD also found that the gastric lesion had regressed to a white scar (Fig. 2F). However, MRI revealed newly emerged brain metastases at the same time, and on the account of a V600E mutation in the BRAF gene and PD-L1 TC-positive (80%) results of genetic testing, the therapeutic strategy was switched to targeted therapy and immunotherapy, and whole-brain radiotherapy was also performed due to enlarged brain metastases in January 2022. At the time of writing, the patient was still under targeted therapy (bevacizumab 400 mg, every 3 weeks) with regular follow-up every month.

*Case 2*. A 76-year-old female experienced weight loss of 10 kg within half a year, falling below the normal Body Mass Index range, accompanied by chest tightness and cough, without any abdominal complaints. PET/CT at the local hospital indicated a pulmonary mass in the right upper lobe with high FDG uptake, together with multiple enlarged hilar and mediastinal lymph nodes, and ilium and sigmoid colon metastases were also suspected. The patient was admitted to the Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences (Shenzhen, China) in July 2021. CT indicated a pulmonary irregular mass with calcification in the right upper lobe (maximum diameter, 5.0 cm) (Fig. 3) and adenocarcinoma was confirmed by CT-guided percutaneous lung biopsy. For colonic lesions suspected by PET/CT, the patient received upper and lower gastrointestinal endoscopy. The colonoscopy was unremarkable, whereas EGD found a diminutive nodule with central depression sized 4x3 mm in the upper greater curvature of the stomach (Fig. 4A). BLI-ME revealed a homogeneously extended SECN and widened IP around the depression, and within the depression, the microvascular and microsurface structures were absent, and the demarcation line between the nodule and background was unclear (Fig. 4B). Biopsy of the nodule revealed poorly differentiated carcinoma cells (Fig. 4C), and immunohistochemical staining was positive for CK7 and TTF-1 (Fig. 4D and E) but negative for CK20 and CDX-2, which confirmed the pulmonary origin. Since gene tests of the lung lesion indicated a positive L858R mutation in exon 21, the patient received targeted therapy (gefitinib 250 mg, every day, bevacizumab 600 mg, every 3 weeks). The follow-up EGD indicated that the gastric lesion had regressed to a scar after 3 months of treatment (Fig. 4F), and the pulmonary tumor remained stable. Due to drug-induced liver injury and a rash, the patient stopped taking medicine for 5 months on her own account, and repeated CT indicated that the lung tumor had grown to a size larger than that at the first presentation. The targeted agent was then switched to Almonertinib (110 mg, qd) in May 2022 and the patient tolerated it well, the last chest CT showed no enlargement of the pulmonary tumor in October 2022.

## Discussion

Gastric metastasis is uncommon for lung cancer in the clinic. Metastatic lesions may develop at any site of the stomach, mainly locating in the middle and upper thirds (11,12), and solitary gastric metastases are more common than multiple metastases (13). The endoscopic manifestations of gastric metastases may be diverse and the most common endoscopic appearance is submucosal mass with or without ulceration, and the ulceration at the apex of the submucosal mass usually be described as volcano-like or umbilicated (7,11). Apart from that, multiple nodules, polypoid lesions or an infiltrating 'linitis plastica' pattern have also been reported (14,15).

The two cases reported in the present study are gastric metastasis from lung adenocarcinoma without any related symptoms. They presented as diminutive nodules or erosion under conventional white-light endoscopy, which is different from the common endoscopic appearance of gastric metastasis (6,10). In addition, most of the literature only describes the manifestations of gastric metastasis from lung cancer under white-light endoscopy (6,14). The present study further reported the characteristics of small gastric metastases under BLI-ME; the microvascular and microsurface patterns of the covering mucosa may be regular or irregular, and the demarcation line between lesion and normal mucosa may exist or not correspond to the development stage of metastases; however, in the present study, certain common characteristics between the two cases were found under BLI-ME, such as an obviously widened IP and extended SECN, indicating that lesions developed beneath the superficial epithelium. These above endoscopic characteristics may be explained by the growth pattern of metastasis from a distant primary cancer; cancerous cells traveling through the blood or lymph system usually disseminate into the gastric submucosal layer first and then develop as a submucosal lesion (12,16), with further growth it may break through the covered epithelium and present as a central defection of the mucosa, or even erosion and ulcer. Endoscopic ultrasonography (EUS) has been widely used in the diagnosis and management of gastrointestinal neoplasms, particularly in gastric subepithelial lesions due to its excellent capability in evaluating the originating layer, echo level and internal echo pattern (17). As for gastric metastases, EUS may identify the hypoechoic and demarcated mass originating from the muscular or submucosal layer (12,18), EUS-guided tissue acquisition and the following immunohistochemical examination may provide a reliable method to identify gastric metastases (19,20).

Since the endoscopic manifestations of gastric metastasis may be diverse, it is at times difficult to differentiate it from other gastric neoplasms; when the metastatic lesions manifest as linitis plastica-like tumor or submucosal tumor, it is easily confused with primary gastric cancer or gastric gastrointestinal stromal tumor (GIST) (15,18). In the two cases of the present study, the metastases were small and less obvious, and they required to be differentiated from early gastric cancer (EGC) and small submucosal tumors. EGC usually demonstrates slight changes in color and surface morphology under white-light endoscopy in the very early stage. Magnifying endoscopy may contribute to improving diagnostic accuracy; according to the 'VS classification system' proposed by Yao *et al* (21), an irregular microvascular pattern and/or an irregular microsurface pattern together with a clear demarcation line under magnifying endoscopy are the hallmarks of EGC. When considering a different origin, the 'VS classification system' may not be applied to the diagnosis of gastric metastasis. Gastric GIST is the common submucosal tumor of the stomach, which usually has a smooth overlying mucosal surface under white-light endoscopy without any microvascular or microsurface changes under magnifying endoscopy; on EUS, it typically appears as hypoechoic solid lesions arising from the muscle layer with a well-demarcated border (22). Another kind of gastric submucosal tumor is neuroendocrine tumors (NETs), which generally present as multifocal polypoid protrusions or sporadic nodular subepithelial lesions endoscopically, and on EUS, gastric NETs appear as mucosal and/or submucosal well-edged isoecho or hypoecho lesions (23). Further differentiation may require histologic examination by biopsy or EUS-guided tissue acquisition.

Target biopsy and further immunohistochemical staining is the gold standard for distinguishing primary from metastatic gastric tumor. The coordinated expression of CK7 and

CK20 in tumor cells is useful for distinguishing the origin of carcinomas, and 90% of lung adenocarcinomas demonstrate a CK7+/CK20-immunoprofile. On the other hand, intestinal carcinomas generally have an CK7-/CK20+ immunophenotype (24). Other specific markers may further aid the diagnosis: TTF-1 is positive in lung and thyroid cancer but negative in gastric cancer, and it is accepted as a specific marker for primary lung cancer (25,26). CDX-2 is commonly expressed in intestinal-type adenocarcinomas from the gastrointestinal tract and negative staining for CDX-2 further supports the presence of metastasis from an extra-intestinal tumor (27).

The correct diagnosis of distant gastric metastasis may facilitate accurate staging of the primary tumor and earlier detection may affect the treatment strategy. With the development of targeted therapy and immunotherapy, the 5-year survival rate of lung cancer has increased (28); furthermore, with the rising popularization of gastrointestinal endoscopy, more asymptomatic stomach metastases may be detected early and prior to the appearance of related symptoms, which may help physicians to comprehensively treat this condition and avoid life-threatening events, such as severe bleeding or perforation due to metastasis. According to the literature, certain patients with solitary gastric metastasis may get a survival benefit from surgery (4). However, when gastric metastasis is identified, most patients may exhibit metastatic lesions in other organs, and systemic treatments, including chemotherapy, targeted therapy and immunotherapy, are major strategies to manage them. In the two cases presented in the current study, EGD revealed that the gastric metastatic lesions had regressed to scars after systemic anticancer therapy. The systemic treatment outcomes of primary lung cancer with gastric metastasis have been previously reported, but the focus was on the therapeutic effect on the primary tumor rather than the gastric metastatic lesions (10). To the best of our knowledge, only one previous study reported the systemic treatment outcomes of gastric metastasis from lung cancer; the gastric metastasis exhibited complete regression after 3 months of oral treatment with Osimertinib (12). This is in accordance with the cases of the present study and it may suggest that gastric metastases respond well to systemic treatment.

In conclusion, clinicians should direct their attention to small nodules or erosion in gastric mucosa of patients with confirmed primary cancer. Careful observation under white-light endoscopy, chromoendoscopy combined with magnifying endoscopy, may identify certain characteristics indicating a lesion originates in the subepithelial layer. Target biopsy or EUS-guided tissue acquisition in conjunction with further immunohistochemical staining is the gold standard for distinguishing primary lesions from metastases. Comprehensive anticancer treatment may be effective for eliminating gastric metastatic lesions.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors' contributions**

MW conceived the study and drafted the manuscript. WZ, CF and JG analyzed and interpreted the data. XN and FY interpreted the data and critically revised the article. MW and FY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Written informed consent for the publication of any associated data and accompanying images was obtained from both patients.

**Competing interests**

The authors declare that they have no competing interests.

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