

# Gastrointestinal hemorrhage caused by duodenal metastasis from a primary lung adenocarcinoma: A case report

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**Abstract.** The present case study reported a rare case of duodenal metastasis from a lung adenocarcinoma. A 62-year-old male, who underwent radical lung cancer surgery two years ago, was readmitted to Guangzhou Red Cross Hospital complaining of epigastric pain. The esophagogastroduodenoscopy identified a 2.5x3.5 cm ulcerative lesion at the duodenum. Histopathological and immunohistochemical staining results confirmed that the lung adenocarcinoma had metastasized to the duodenum. The tumor cells were positive for cytokeratin-7, thyroid transcription factor-1 and napsin-A expression, but negative for caudal-related homeobox 2 expression. Prior to the second cycle of targeted treatment with anlotinib, the patient reported severe hematochezia. Therefore, an angiography and artery embolization were subsequently performed. However, the patient succumbed to acute kidney injury three days after the operation. The metastasis of lung cancer to the gastrointestinal tract is extremely rare and usually asymptomatic. However, when treating patients with lung cancer presenting with digestive symptoms or other distant metastatic sites, clinicians should consider the possibility of gastrointestinal metastasis so that it can be identified in a timely manner. If lesions exist, doctors should locate these and perform biopsies to conduct histopathological and immunohistochemical examinations to make a clear diagnosis.

## Introduction

Primary lung cancer is common and often malignant, and is accompanied with a high mortality rate (1). Distant metastases caused by primary lung cancer are frequently identified in the brain, liver, adrenal glands and bones, while the gastrointestinal tract is a relatively unusual site for metastases to occur (2).

The incidence of gastrointestinal metastases of lung cancer was <2% a previous clinical study, which was much lower compared with its prevalence identified during autopsies (3). The low clinical incidence of gastrointestinal metastasis may be due to the fact the metastasis is usually asymptomatic (4). The clinical incidence and associated mortality rate of lung cancer are low and the lack of symptoms may cause studies to be difficult to organize (4). However, in recent years, an increased number of cases of primary lung cancer have been reported to metastasize to the gastrointestinal tract, which indicated that the prevalence of gastrointestinal metastasis may be more frequent (3). In addition, numerous retrospective studies have reported that the gastrointestinal metastasis of lung cancer was an indicator of poor prognosis, demonstrating a median survival time of 69-130.3 days (3-7). The present case study reported a patient with upper gastrointestinal bleeding caused by the duodenal metastasis of a primary lung adenocarcinoma, which is an extremely rare complication in the history of the occurrence and development of lung cancer.

## Case report

A 62-year-old male, who had experienced a cough and hoarseness for 1 month, was admitted to our hospital in June 2017. He had a history of duodenal ulcers and bleeding, diabetes mellitus and hypertension. He was also an active ex-smoker and had a family history of different types of cancer; his father had lung cancer, his elder brother had colon cancer and his two younger sisters had uterine and breast cancer, respectively. A CT scan revealed the presence of a mass in the left upper lobe of the chest. Therefore, a thoracoscopic lobectomy was performed on the left upper lobe and the posterior segment of the left lower lobe. In addition, the patient was discovered to have both hilar and mediastinal lymphadenopathy and biopsies were taken. The histopathological examination revealed a well-differentiated adenocarcinoma with lymph node metastasis and partial infiltration into the pulmonary membrane (T4N2M1) (Figs. 1 and 2). The patient received six cycles of chemotherapy with liposomal paclitaxel and cisplatin, six cycles of chemotherapy with pemetrexed, and five cycles of chemotherapy with pemetrexed and carboplatin.

After complaining of abdominal pain for 3 days, the patient was readmitted to our hospital in July 2019. While conducting physical examinations, the doctors noted that the patient was

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mildly pale and that there was mild tenderness in the epigastrium, but recorded no signs of rigidity or rebound tenderness. Laboratory investigations revealed that the patient had anemia, with hemoglobin levels of 104 g/l and a carcinoembryonic antigen (CEA) level of 113.2  $\mu\text{g/l}$ . The stool test for the presence of occult blood returned positive. CT-positron emission tomography (CT-PET) and an abdominal CT scan revealed that the patient had brain, bone and hepatic metastases. The patient underwent esophagogastroduodenoscopy, which confirmed the presence of a 2.5x3.5 cm malignant ulcer accompanied by the whitish center due to the thick layers of skin cells and bloody discharge in the junction between the bulb and descending portions of the duodenum (Fig. 3). The results of the histopathological examination of the duodenal mucosal biopsy specimen demonstrated that the mucosa was denatured and necrotic, with a heteromorphic epithelioid cell infiltration consisting of solitary cells, or cells arranged in sheets, microglandular duct and/or papillary formations (Fig. 4). The results of the immunohistochemical staining of the lesion illustrated that the tumor cells were positive for cytokeratin-7, thyroid transcription factor-1 and napsin-A expression, but negative for caudal-related homeobox 2 expression (Fig. 5), which confirmed the diagnosis of duodenal metastasis from a primary lung adenocarcinoma. Therefore, the patient received targeted treatment with anlotinib.

Two months later, the patient reported the occurrence of hematochezia on three occasions, with 200 ml of blood lost each time, prior to receiving the second cycle of the targeted treatment in our hospital. In order to prevent gastrointestinal bleeding, he underwent superior mesentery artery and coeliac artery arteriography, and transcatheter gastroduodenal and left gastric arterial embolization. However, the patient died of acute kidney injury three days after the operation.

Immunohistochemical analysis was performed on 10% neutral formalin-fixed with neutral resin mounting medium specimens. Thickness of sections was 1  $\mu\text{m}$ . Three percent UV inhibitor (24 h in 37°C; Roche Diagnostics) were used as the blocking reagent. Cytokeratin-7 (CK7; IR619; 32 min in 37°C; Dako), Thyroid transcription factor-1 (TTF-1; 790-4756; 32 min in 37°C; Roche Diagnostics), Napsin-A (CNM-0012; 32 min in 37°C; Celnovte), p53 (IR616; 32 min in 37°C; Dako), and caudal-related homeobox 2 (CDX-2; IR080; 32 min in 37°C; Dako) antibodies were used as the primary antibodies. Ready-to-use antibodies (760-500; 4-12 min in 37°C; Roche Diagnostics) were used as the secondary antibodies. For staining, we used an automated stainer (Dako) according to the manufacturer's protocol. ChemMate EnVision (Dako) methods were used for detection and Olympus BX51 biological microscope (magnification, x100 or x200) was used for observation.

## Discussion

The gastrointestinal tract is considered a rare site for the metastasis of primary lung cancer. According to clinical statistics, the odds of metastasis is <2% (3). Although the small intestine was described as the most common gastrointestinal metastatic site in previous studies (4,8,9), the proportion of the cases of primary lung cancer metastasizing to the duodenum only accounts for 15.8% of small bowel metastases (6). Usually, the gastrointestinal metastasis of primary

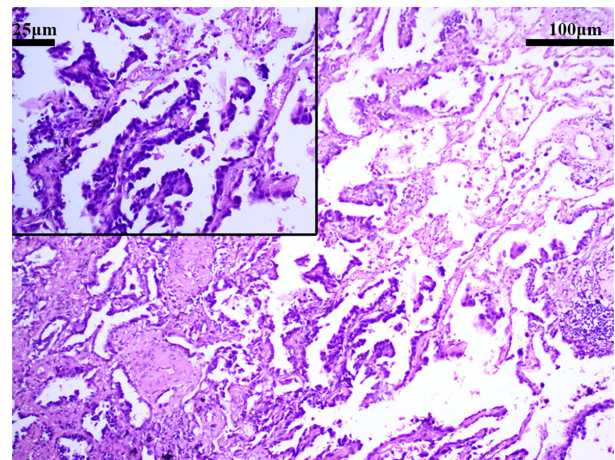


Figure 1. Histopathological staining of the resected lesions of the left lobe. Sections demonstrated a papillary adenocarcinoma.

lung cancer is asymptomatic. Numerous previous studies have reported that perforation is the most common symptom of small bowel metastasis (5,6,9). In reports where patients presented with symptoms, the most commonly experienced symptoms were abdominal pain, melena and anemia, while other symptoms included weight loss, jaundice and pyrosis, amongst others (4,5,8,10,11). Therefore, the symptoms that we discussed above have been suggested to be associated with different organs and incubation times (3,10).

In a retrospective study by Hu *et al* (3), >3/4 of the incidences of gastrointestinal metastases of lung cancer cases analyzed were squamous cell carcinomas, adenocarcinomas and large cell carcinomas. In a published series of 423 autopsies, in which 58 patients presented with gastrointestinal tract secondary lesions from lung cancer, the most frequently encountered histological types were squamous cell (33%), large cell (29%) and oat cell (19%) (12). As squamous cell carcinoma and adenocarcinoma are common types of primary lung cancer, the conclusions drawn may have selection bias. Further studies are required to estimate whether a strong association between the histopathology and gastrointestinal tract metastases exists.

In previous studies, results from autopsies have revealed that the rate of gastrointestinal metastases from lung cancer was 4.7-14.0% (13-15), which is notably higher compared with clinical statistics. The reasons for these differences are as follows: Firstly, the majority of patients who presented with gastrointestinal metastasis following lung cancer had no specific signs and symptoms; secondly, the gastrointestinal tract is not a typical metastatic site for primary lung cancer, thus it is rarely considered as a priority when the clinicians are making a differential diagnosis; thirdly, even if patients present with gastrointestinal symptoms, it is very likely that the symptoms will be mistaken to be due to the common gastrointestinal disturbances experienced following chemotherapy and other benign lesions, such as peptic ulcer and intestinal polyposis; and finally, although laboratory examinations, CT and MRI scans, and CT-PET can help to diagnose gastrointestinal metastasis, there still remains the risk that these techniques will miss the presence of the lesions. Histopathology and immunohistochemistry are vital methods required for the diagnosis (3,8).

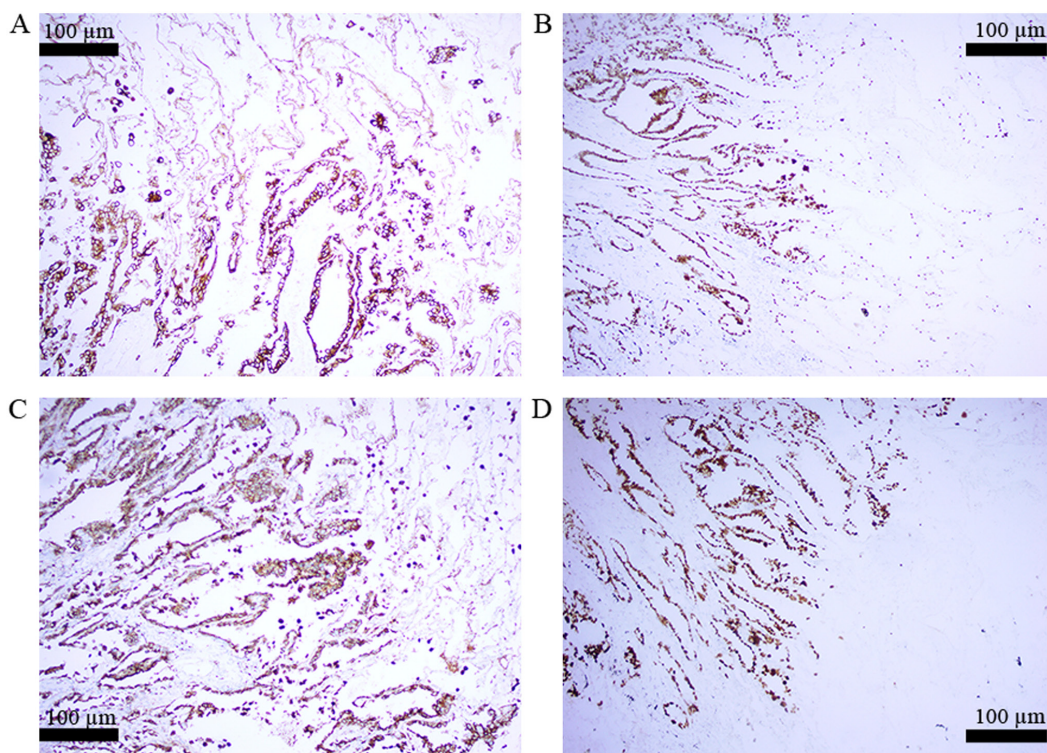


Figure 2. Immunohistochemical analysis of the resected specimens of the left lobe revealed that the tumor cells were positive for (A) cyokeratin-7, (B) thyroid transcription factor-1 and (C) napsin-A expression. (D) p53 expression was strongly positive (+++). CK7, cyokeratin-7; TTF-1, thyroid transcription factor-1.

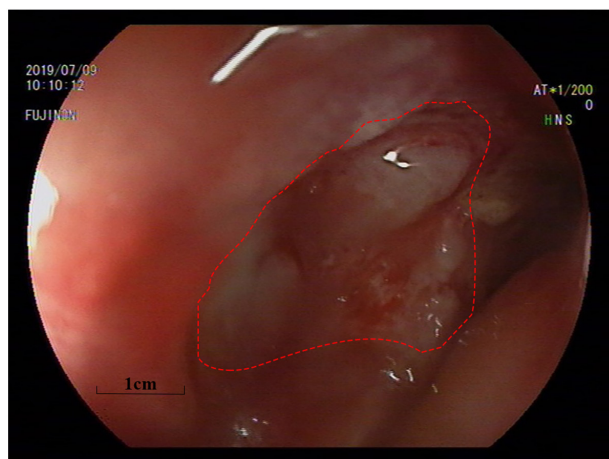


Figure 3. Esophagogastroduodenoscopy revealed the presence of a 2.5x3.5 cm malignant ulcer in the junction between the bulb and descending portions of the duodenum (presented as the red dotted line circled).

The route by which lung cancer metastasizes to the gastrointestinal tract is currently unknown, but both hematogenous and lymphatic routes are considered to be involved (4,5,12). The patient in the present case report had diabetes, which could block the immunological surveillance of cancer cells and may cause unusual metastases (16). However, there are several limitations to this report. For example, when the patient first complained of the abdominal pain, the endoscopy was not immediately scheduled because his previous esophagogastroduodenoscopy indicated that he had Barrett's esophagus and duodenal ulcers with bleeding. In addition, there was no evidence of gastrointestinal metastasis on the CT or PET/CT

scan. In fact, the initial diagnosis was a peptic ulcer. However, the symptoms of the patient had not improved following the treatment with omeprazole. Therefore, an endoscopy was performed and specimens were obtained to perform pathological and immunohistochemical examinations. The results confirmed the diagnosis of duodenal metastasis from a primary lung adenocarcinoma. It is worth mentioning that the laboratory findings of anemia with hemoglobin levels of 103 g/l in April 2019 may be crucial indicators. However, at the time, it was thought that these results were due to a reduction in iron intake that caused iron deficiency anemia, and the possibility of occult gastrointestinal bleeding was ignored at the time. Therefore, upon encountering patients who have primary lung cancer with gastrointestinal symptoms or anemia, it is vital that doctors consider whether gastrointestinal metastases may have occurred and perform further examinations to confirm.

For the majority of patients who have gastrointestinal metastasis with no particular symptoms, one must determine the presence of metastatic lesions in other organs. In a study by McNeill *et al* (14), it was reported that 46 patients with small bowel metastases had  $\geq 1$  other metastatic site, with an average of 4.8 sites. Yoshimoto *et al* (15) suggested that gastrointestinal metastasis should be considered when patients had adrenal gland, kidney and abdominal lymph node metastases. Therefore, further investigations into the occurrence of gastrointestinal metastasis following lung cancer must be appropriately investigated if distant metastasis has occurred at other sites. It is of vital importance to perform these appropriate examinations as soon as possible. According to the research by Kim *et al* (17), 93% of patients with gastrointestinal metastases from lung cancer had positive findings on the CT scan, which included wall thickening, an intraluminal

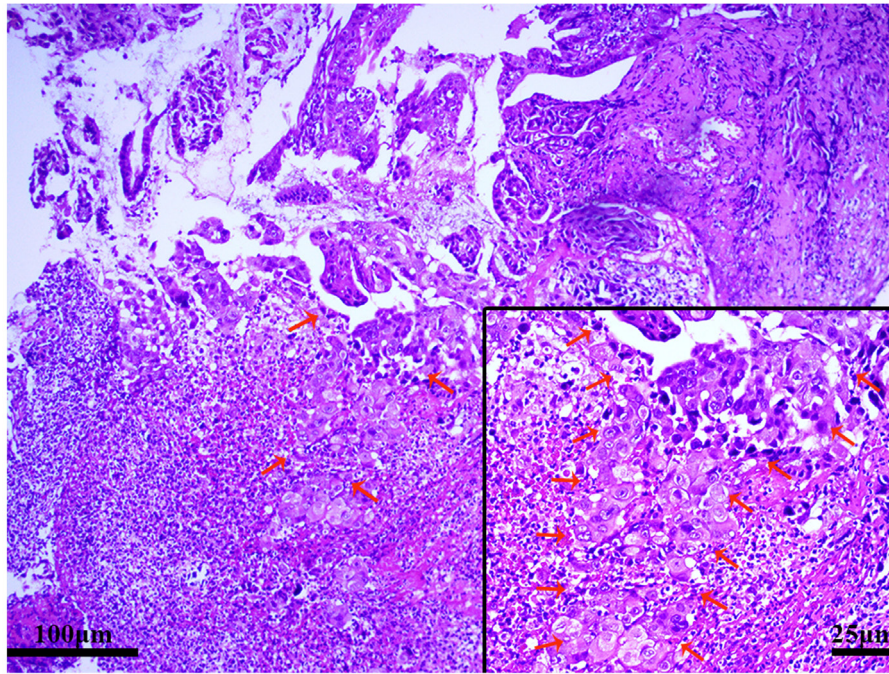


Figure 4. Histopathological analysis of the duodenal mucosal biopsy specimen demonstrated that the mucosa was denatured and necrotic, with signs of heteromorphic epithelioid cells infiltration consisting of solitary cells, or cells arranged in sheets, microglandular duct and/or papillary formations (red arrow indicators).

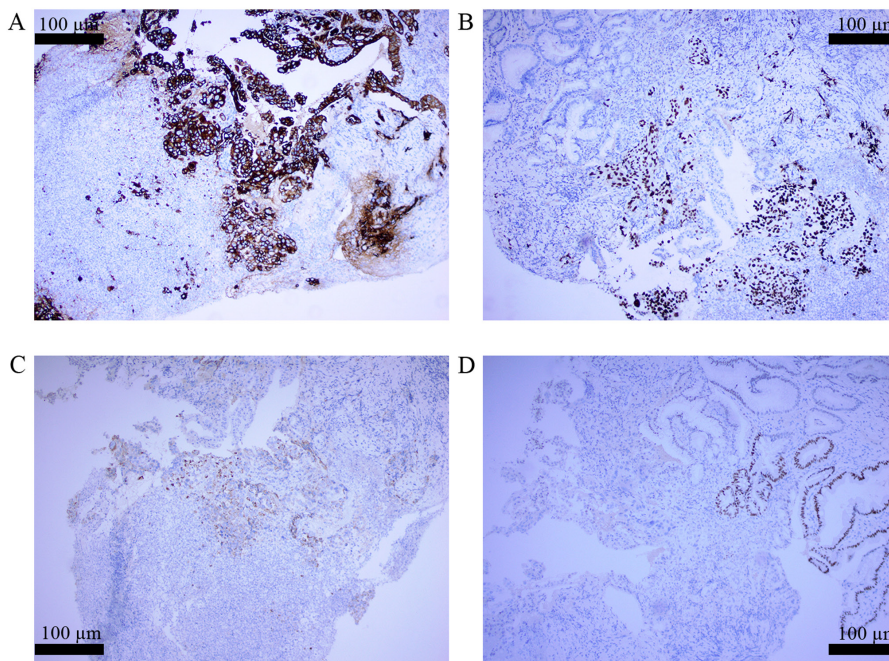


Figure 5. Immunohistochemical analysis of the duodenal lesion identified that the tumor cells were positive for (A) CK7, (B) TTF-1 and (C) napsin-A expression, but negative for (D) CDX-2 expression. CK7, cytokerin-7; TTF-1, thyroid transcription factor-1; CDX-2, caudal-related homeobox 2.

mass and a protruding lump. PET/CT may also be helpful in diagnosing the gastrointestinal metastasis of lung cancer (3). However, due to the high cost and shortage of clinical cases, the necessity of using PET-CT for the diagnosis of the gastrointestinal metastasis of lung cancer remains controversial (5,6,11). For example, certain patients who had confirmed gastrointestinal metastases exhibited no signs on either the PET scan or through endoscopy, and presented with possible mucosal edema, hyperemia, multiple nodules with or without

mucosal ulcerations, or even as a single ‘volcano-like’ lesion imitating a primary gastrointestinal tumor (8). Therefore, histopathological and immunohistochemical examinations are considered the only method to confirm whether the lung carcinoma has metastasized to the gastrointestinal tract (3,8,10).

In conclusion, although the gastrointestinal tract is a rare site of metastasis for primary lung cancer, on account of the increasing incidence of primary lung cancer and the development of medical technology for the diagnosis and

treatment of the disease, an increasing number of cases of gastrointestinal metastases from lung cancer have been reported. Therefore, clinicians should pay more attention to the infrequent metastatic sites of primary lung cancer and consider the possibility of gastrointestinal metastasis if digestive symptoms are experienced or if other distant metastasis sites are present in patients who have been diagnosed with lung cancer, so that the lesions can be located to obtain a biopsy for histopathological and immunohistochemical examinations in a timely manner.

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### Availability of data and materials

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

### Authors' contributions

MZ, JS and XL collected the patient's data. LL and QW analyzed the data and performed reference search. MZ, JS and XL drafted the manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### Competing interests

The authors declare that they have no competing interests.

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