Case Report

An ALK-positive lung adenocarcinoma with gastric and skin metastasis: a case report and literature review

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Abstract: Primary lung cancer with gastric metastasis is rare to see in the world, little is known about its characteristics. Here, we describe the first case of primary lung adenocarcinoma with gastric and skin metastases along with a review of literature to help clinical decision making. A 49-year-old woman admitted to our department for abdominal distension. The immunohistochemistry staining for the biopsy in the gastric fundus, back and lung showed positive for CK5/6, TTF-1, Napsin A and CK7, but negative for CK20, which strongly indicated all of them were homologous and might originate from lung adenocarcinoma. Chromosome mutation analysis presented an EML4-ALK fusion gene. Brain metastases occurred after 6 months with crizotinib treatment. More than two months later, intracranial lesions became more and larger as she persisted in taking crizotinib plus whole-brain radiotherapy (WBRT). Hence, alectinib was performed due to the continuous growth of brain lesions. When reexamined three months later, the craniocerebral lesions were significantly reduced and all tumor markers were up to normal level. This review comprised 42 published case reports in total. Generally, the average morbidity age was 62 years old, and male with smoking history were more prone to it. It could be found that squamous cell carcinoma (17/38) accounts for a high proportion of gastrointestinal metastases pathology, most of which were poorly differentiated. Surgical excision of the lesions was supposed to improve long-term prognosis, mitigate associated complications, decrease patients' pain, and enhance the quality of life. Gastric metastasis of lung cancer is apt to metastasize to the brain, and the prognosis is inferior. Crizotinib with preventive WBRT may be the optimal choice for NSCLC patients harboring ALK mutation in the initial treatment of gastric metastasis. However, If the lesion in the brain keep on going, timely replacement to alectinib is an appropriate choice.

Keywords: Lung cancer; gastric metastasis; ALK-positive; case report

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Introduction

For both sexes combined, lung cancer is the most commonly diagnosed cancer and time leading cause of cancer death (1). Half of patients have metastatic diseases at the time of diagnosis, with survival rates of 20% at 1 year and 1% at 5 years (2). The most common site of extra pulmonary spread included liver (35%), bones (25%), adrenals (22%), kidneys (10–15%) and heart pericardium (20%) (3). Gastric metastasis of lung cancer is rare in clinic, and there are few reports in literature. The actual incidence of gastric metastasis from lung cancer is hard to calculate as patients suffered it are asymptomatic which are easily to be ignored. It seems to be some controversy in the diagnosis of gastric metastasis from lung cancer, let alone have some recommendations for treatment and established prognosis.

In this paper, we report a case of lung adenocarcinoma with EML4-ALK-positive that metastasized to gastric and skin, and systematically review previous case reports for better understanding of its clinicopathological features,

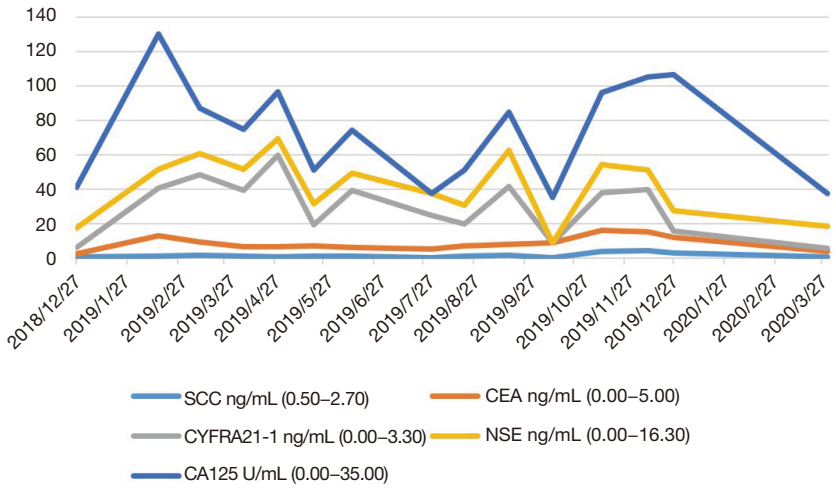

Figure 1 Changes in tumor markers during treatment. It seems that all tumor markers would change more or less over the duration of treatment. Among them, the values SCC and NSE were within standard ranges. A majority of CEA values were mostly higher than the normal. Cyfra21-1 values were all above the normal range, with a significant upward trend in January, April, June, September. CA-125 values were mostly below the normal, however, it increased significantly in January and November. SCC, squamous cell carcinoma; NSE, neuron-specific enolase; CEA, Carcinoembryonic antigen.

prognosis and optimal treatment strategy.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1025).

Case presentation

The patient, a 41-year-old female, was admitted to our department on December 27, 2018 with chief complain of abdominal distension for 2 months. She was neither a smoker nor a drinker. She has not seen at any other hospital before. There was no cancer history or any other certain diseases history in her family. A tough lump on the back with 9.2 cm × 5.6 cm in size was detected during the physical examination. The lump underneath the skin was moveable, painless and the shape was regular.

Laboratory examinations were as follows: Cytokeratin 19 fragment (CYFRA21-1): 3.98 ng/mL (normal range, 0.00–3.30 ng/mL); Carbohydrate antigen199 (CA199): 143.20 U/mL (normal range, 0.00–39.00 U/mL); Carbohydrate antigen-125 (CA-125): 23.8 U/mL (normal range, 0.00–35.00 U/mL); Carcinoembryonic antigen (CEA): 1.70 ng/mL (normal range, 0.00–3.40 ng/mL) (*Figure 1*). The patient underwent ultrasound-guided percutaneous biopsy of the skin to obtain the histological examination specimen, which indicated a poorly differentiated adenocarcinoma. Immunohistochemical staining showed positive expression in cytokeratin 5/6 (CK5/6), thyroid transcription factor-1 (TTF-1) and cytokeratin 7 (CK7), but negative expression in Napsin A(-), and cytokeratin 20 (CK20). Gastroscopy revealed two protruding lesions in the gastric fundus whose biopsy indicating a poorly differentiated metastatic adenocarcinoma (*Figure 2*). We have a consultation with the pathologist to make a definite diagnosis. The pathology department thought that there was a high homology between the gastric fundus and dorsal biopsy, both of which may originate from lung adenocarcinoma. Chest computed tomography was performed, which revealed a mass measuring 4cm next to the right lung hilum (*Figure 3*). A CT-guided percutaneous transthoracic needle aspiration biopsy of the mass was carried out, revealing a poorly differentiated adenocarcinoma. Immunohistochemical stained CK5/6, TTF-1, Napsin A and CK7 positive, while stained CK20 negative, which confirming the diagnosis of gastric metastasis from lung adenocarcinoma. The patient had an echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene.

Therefore, oral treatment with crizotinib (250 mg, twice a day) started on January 20, 2019. Diarrhea and mild increase in liver enzymes occurred during targeted therapy, but became resistant after symptomatic support therapy.

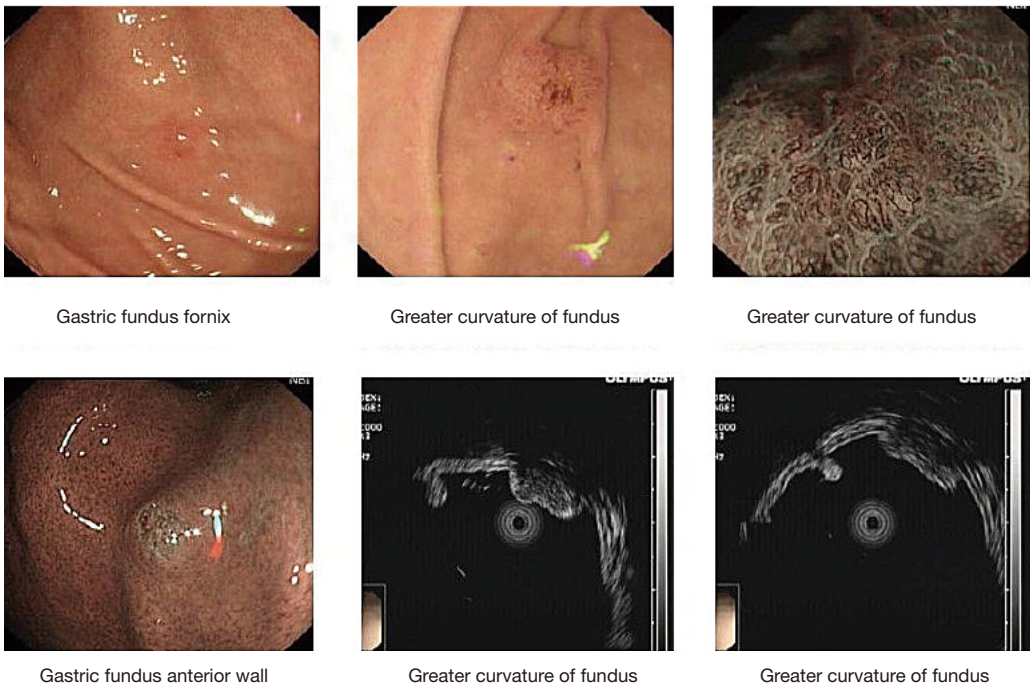

Figure 2 Gastroscopy revealed two protruding lesions in the fundus. One in the greater curvature measuring 1.0 cm × 1.0 cm with mucosa erosion and hyperemia and the other in the fundus fornix of stomach with 0.3 cm × 0.4 cm in size.

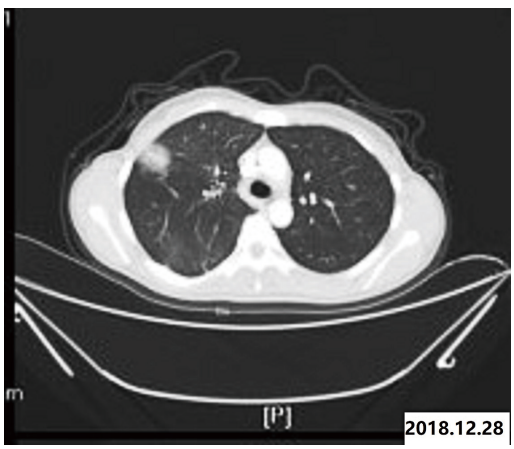

Figure 3 Enhanced CT scan of the chest. It demonstrates a solitary round mass next to the right lung hilum measuring 3.8 cm × 4.0 cm with a blurry margin, spiculation sign.

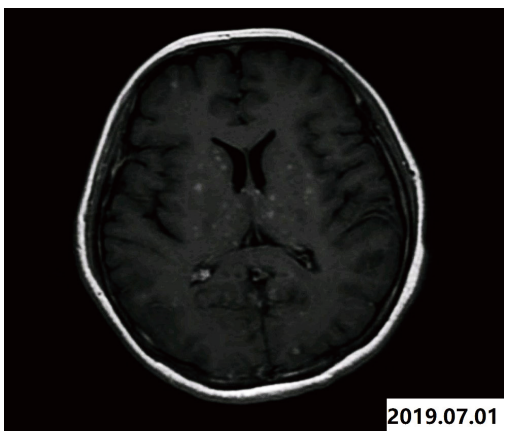

Figure 4 Magnetic imaging of the brain. It revealed multiple spotted abnormal signal shadows in the cerebellum and brainstem.

Two months later, comparing with the former image of chest CT, the mass size in the right lung hilum was slightly smaller than before. The lesions were considered to be stable, which proved that molecular targeted therapies could be effective in this disease. The chest CT on July 1, 2019 (compared with on February 18, 2019) showed a reduction in the volume of the mass in the right hilum of the lung. Almost at the same time, multiple nodules in the brain were found by magnetic resonance imaging (MRI), which was considered to be the occurrence of brain metastasis (*Figure 4*). The patient's primary lesion was reduced and intracranial metastasis was observed. According to RECIST 1.1 criteria (4), it can be identified as progressive disease

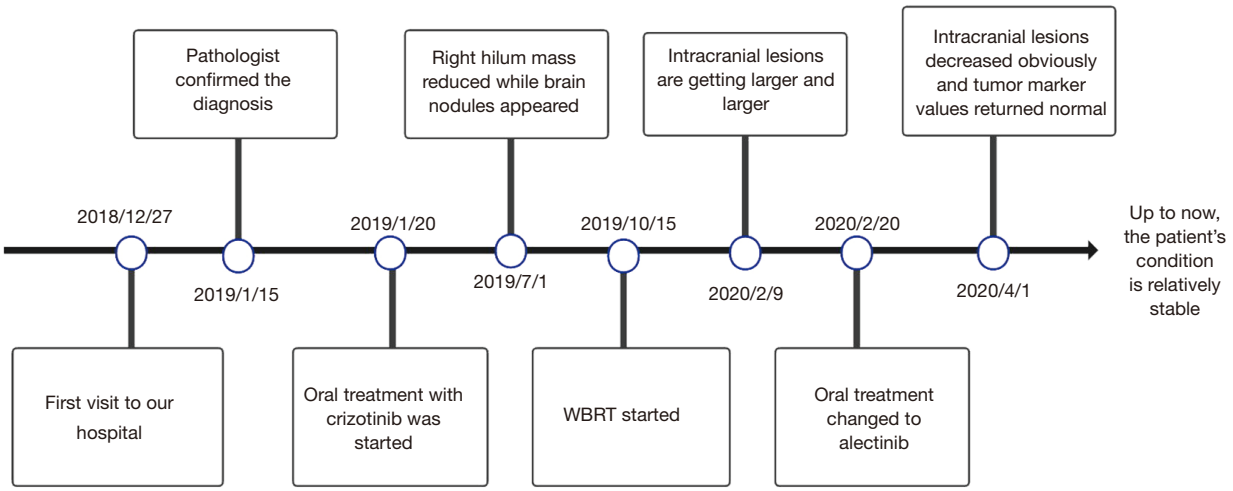

Figure 5 Timeline. It demonstrates the diagnosis, treatment and prognosis of our case report succinctly. WBRT, whole-brain radiotherapy.

(PD). It was difficult to determine whether to continue local radiotherapy with crizotinib or to change to alectinib directly. Global brain radiation therapy (WBRT) started on October 15, 2019 (30 Gy/10 times) due to the patient's refusal to use alectinib for personal reasons. After 7 months, there was no significant change in primary lung lesions. Whereas, the intracranial lesions on the enhanced brain MRI images are getting larger and larger compared with that on July 9, 2019. Finally, the patient agreed to take alectinib (600 mg, twice a day) as a follow-up treatment. On April 1, 2020, intracranial lesions decreased obviously and all tumor marker values returned to the normal range. Up to now, the patient's condition is relatively stable. For a better idea of this case, a timeline figure is established (*Figure 5*). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). All treatments were performed with the consent of the patient. Written informed consent was obtained from the patient for publication of this study and any accompanying images.

Systematic review. After searching for all possible eligible case reports and their references in PubMed and CNKI (China National Knowledge Infrastructure), combined with our case, a systematic review was conducted. *Table 1* summarized the patients' clinical characteristics, and *Table 2* showed the tumors' pathology, treatment and prognosis. We collected 42 patients with an average age of 62 years (ranged, 39–90 years), comprised of 35 males (83.3%) and 7 females (16.7%). Twenty-five of these cases have a definite smoking history and six cases with no smoking history. Although the location of lung cancer is varied, the upper lobe has a predominance to be involved. Squamous cell carcinoma (17/38) attribute to the main pathology type, followed by adenocarcinoma (15/42), small cell lung cancer (5/38), large cell carcinoma (3/38) and polymorphic cell carcinoma (2/38). Most of them are undifferentiated or poorly differentiated. The initial symptom that metastasized to the gastrointestinal tract in the review mostly was epigastric pain. Signs of gastrointestinal bleeding including hematemesis, melena, and chronic anemia. Different cancer treatment strategies would lead to a completely distinct response and prognosis. The interval for the diagnosis of gastric metastasis subsequent to the primary tumor ranged from 0 to 36 months with 3.9 months in average. Twenty-thee patients had lung cancer and gastric cancer at the same time, which were later confirmed to be lung-cancer related by immunohistochemistry. There are 60% (25/42) of patients accompanied by other clinically detectable metastatic lesions like liver, bone, brain and skin at the diagnosis of the gastric metastases. Ten patients underwent palliative treatment after gastric metastasis and 12 underwent an operation to improve their survival. On account of final results and follow-up time were not mentioned in 33.3% of previous cases, the overall survival, 1-year post-metastasis survival rate as long as 5-year post-metastasis survival rate could not be calculated correctly.

Table 1 Clinical features of patients with gastric metastasis from lung cancer in the literature

Author	Case	Age (y/o)	Sex	Smoking history	Clinical presentation of gastric cancer	Primary lung location	Gastric location	Other metastatic sites
Fushi Wei (5)	1	60	M	NM	Abdominal distension	NM	Fundus	Liver
Zuoyou Wang (6)	2	55	M	Y	Melena	Left lobe	Body	Bone, liver
Yuyan Wang (7)	3	71	M	Y	Fecal occult blood positive	LRL	Fundus	None
Yanping Liu (8)	4	74	M	NM	Abdominal pain	NM	Body	None
Hs Kim (9)	5	68	M	Y	NM	ULL	Body	Brain
Song Gao (10)	6	66	M	NM	NM	RH	Body	Liver
Qingyuan Huang (11)	7	61	F	N	Epigastric discomfort	LRL	Cardia	None
Min Hee Lee (12)	8	77	M	NM	Abdominal pain	URL	Antrum	NM
Ryota Okazaki (13)	9	68	M	Y	Abdominal pain	LRL	Body	Brain, bone
Giovanni Casella (14)	10	63	M	Y	Abdominal pain	LH	Body	Liver, brain, bone
Keiju Aokage (15)	11	69	M	NM	Anemia	URL	Body	None
Keiju Aokage (15)	12	62	M	NM	NM	ULL	Body	None
Ciğdem Ozdilekcan (3)	13	43	M	Y	Abdominal distension	URL	Body	None
Engin Altintas (16)	14	55	M	NM	Melena	NM	Body	Brain, bone, skin
Ibrahim Azar (17)	15	90	M	NM	Melena	ULL	Body	Liver
Our case	16	41	F	N	Abdominal distension	RH	Fundus	Skin, brain
Hs Kim (9)	17	66	M	Y	Abdominal pain	ULL	Body, Fundus	Bone
Yenmin Huang (18)	18	41	F	Y	Abdominal pain, abdominal distension	LLL	Body	Brain, bone, rectum
Michael Del Rosario (2)	19	77	F	N	NM	Left lobe	Body	NM
Yong Il Kim (19)	20	71	M	Y	Anemia	LRL	Body	Spleen, mediastinum, pancreas
Motoharu Hamatake (20)	21	65	M	Y	Acute hematemesis	LLL	Body	NM
Miyazaki J (21)	22	54	M	Y	Abdominal pain, anemia	URL	Antrum	Cecum, liver
Alpar S (22)	23	66	M	Y	NM	NM	NM	NM
Ying He (23)	24	61	M	Y	Dysphagia	LLL	Fundus	None
Stamatis Katsenos (24)	25	61	M	Y	Melena	ULL	Body	Liver, bone, brain
Takayuki Jujo (25)	26	73	M	NM	None	URL	Body	Liver, bone
Ihab I. El Hajj (26)	27	59	M	NM	Nausea, abdominal pain	URL	Fundus	Pancreas, splenic vein
Mohammad Esmadi (27)	28	62	F	Y	Abdominal pain, melena	LH	NM	Adrenal glands, bone, soft tissue
Ayman Qasrawi (28)	29	69	F	N	Melena	ULL	Body	Brain
Tsung I Hung (29)	30	47	M	Y	None	URL	Body	Left adrenal gland,

Table 1 (*continued*)

Table 1 (*continued*)

Author	Case	Age (y/o)	Sex	Smoking history	Clinical presentation of gastric cancer	Primary lung location	Gastric location	Other metastatic sites
Mariko Nemoto (30)	31	64	M	Y	Epigastric pain and progressive dysphagia	LRL	Cardia	Liver
Xinyu Li (31)	32	61	M	N	Abdominal distention	LRL	Body	None
Richa Bhardwaj (32)	33	39	F	Y	Dizziness and black tarry stools	LRL	Fundus	Bone and lymph nodes
Punit Sharma (33)	34	59	M	N	None	URL	Body	None
Charlotte Bouzbib (34)	35	64	M	Y	Acute anemia	LLL	Fundus	None
Jian-Bin Hu (35)	36	54	M	Y	Dysphagia	RH	Body	Lymph node
Stamatis Katsenos (24)	37	61	M	Y	Melena	ULL	Body	Brain, bone
Ciğdem Ozdilekcan (3)	38	46	M	Y	Dysphagia and epigastric pain	URL	Body	None
Masaya Tamura (36)	39	67	M	Y	Hematemesis	URL	Body	None
E. Guérin (37)	40	72	M	NM	Epigastric, pain, heartburn	LH	NM	Adrenal gland, slenic hilum, skin
Cornelia Nitipir (38)	41	66	M	Y	Abdominal pain	Left lobe	Fundus	Liver, kidneys, bones, brain
Naoki Hasegawa (39)	42	74	M	Y	None	URL	Body	None

M, male; F, female; Y, yes; N, no; NM, not mentioned; ULL, upper left lobe; URL, upper right lobe; LRL, lower right lobe; LLL, lower left lobe; RH, right hilum; LH, left hilum.

Discussion

The incidence of gastric metastasis from lung carcinoma has been reported to range from 0.19–5.1% [4] (19). While the rate of gastric metastasis incidence was significantly higher in the autopsy reaching 2–14% (17,40). Under this circumstance, we can reasonably speculate that the occurrence of gastrointestinal metastases may represent a poor prognosis. Lung cancer with gastric metastasis is more likely to occur in the old, and male patients are more susceptible. Whether stomach ailments history worked in the tumor progress or not was unclear, as little previous cases contain the history of gastropathy.

In review of previous cases, the most common histopathological type of metastasis to the gastrointestinal tract was underdetermined as previous studies about it varied in their findings. Our study showed that squamous cell carcinoma was prone to cause gastric metastasis, which is consistent with previous studies (41). However, there were still other certain studies and autopsy series had shown adenocarcinoma to be prominent (31). At present, the cause of gastric metastasis is not clear. It is suspected that some cytokines may affect the organ specificity of blood metastasis (40). Metastatic gastric cancer generally occurred in the gastric body, while the vast majority of primary gastric cancer present in the gastric antrum (5). However, it is still visible in the gastric body and gastric fundus. Therefore, immunohistochemistry is a reliable method to distinguish primary from metastatic gastric cancer. The commonly used markers for subtyping non-small cell lung cancer included TTF-1, CK7, Napsin A for adenocarcinoma, and p63, CK5/6, CK34βE12/CK903 for SCC (38). TTF-1 is highly specific for adenocarcinomas of pulmonary origin exhibiting a positive predictive value of 100% (2,13). Also, primary lung carcinomas usually express the immunophenotype of CK7+/CK20-, while gastrointestinal carcinomas have the CK7−/CK20+ pattern (2). Since CK7+/CK20- immunophenotype still could be observed in 45% of patients with gastrointestinal cancers such as primary rectal or small bowel adenocarcinomas, using TTF-1 in combination with CK7 and CK20 could differentiate primary gastric tumor from metastatic gastric tumor with reasonable degree of certainty (24). Gastric

Table 2 Pathological features, treatment and prognosis of secondary gastric cancer

Case	Cancer cell type	Histology	Time span (months)	Time interval (months)	Treatment protocols		Outcome	Overall survival
					Lung	Stomach		
1	AC	NM	36	NM	Lung cancer resection	Radical gastrectomy and chemotherapy	Alive	>39
2	SCC	PD	<12	4	Pulmonary lobectomy	Supporting therapy	Died	16
3	AC	PD	>4	NM	Chemotherapy, targeted therapy	Chemotherapy, targeted therapy	Alive	>15
4	SCLC	UN	NM	NM	Chemotherapy	Chemotherapy	Died	12
5	SCC	PD	0	NM	NM	NM	NM	NM
6	SCLC	UN	14	3	Chemotherapy	Chemotherapy	Died	17
7	AC	PD	4	NM	Right lower lobectomy and, complete mediastinal lymph node dissection	Partial gastrectomy	Alive	>19
8	AC	PD	0	NM	Right upper lobectomy	Subtotal gastrectomy	NM	NM
9	AC	PD	0	12	Right lower lobectomy	Chemotherapy	Died	12
10	SCLC	PD	0	1	Supportive care	Supportive care	Died	1
11	PC	NM	>5	NM	Lung lobectomy	Distal gastrectomy	Alive	>60
12	PC	NM	0	NM	Left upper lobectomy and lymph node dissection	Partial gastrectomy	Alive	>48
13	SCC	PD	<1	NM	NM	NM	NM	NM
14	AC	PD	11	<1	Chemotherapy	Supportive care	Died	14
15	SCC	NM	5	<2	Supportive care	Supportive care	Died	7
16	AC	PD	0	NM	Targeted therapy	Targeted therapy	Alive	>15
17	SCLC	UN	0	NM	NM	NM	NM	NM
18	AC	NM	0	15	Chemotherapy	Chemotherapy	Died	15
19	AC	PD	0	NM	Targeted therapy	Targeted therapy	NM	NM
20	AC	NM	0	11	None	Total gastrectomy	Died	>12
21	SCC	PD	0	5	Left lower lobectomy with a partial resection of the lingual segment and combined resection of the chest wall	Total gastrectomy	Died	5

Table 2 (*continued*)

Table 2 (*continued*)

Case	Cancer cell type	Histology	Time span (months)	Time interval (months)	Treatment protocols		Outcome	Overall survival
					Lung	Stomach		
22	AC	PD	0	NM	Right upper lobectomy, chemotherapy	NM	NM	NM
23	SCC	NM	1	NM	Chemotherapy	NM	NM	NM
24	SCC	MD	0	NM	Left lower lobe resection	Cardia resection with anastomosis of the esophagus and stomach below the aortic arch	Alive	NM
25	SCC	NM	0	7	Chemotherapy	Chemotherapy	Died	10
26	AC	NM	0	NM	NM	NM	Died	NM
27	SCC	NM	24	NM	Supportive care	Supportive care	NM	NM
28	LCC	PD	NM	NM	Supportive care	Supportive care	NM	NM
29	LCC	PD	<1	<1	Radiotherapy	Supportive care	NM	NM
30	SCC	NM	NM	NM	Radiotherapy	Wedge resection of the gastric cancer, chemotherapy	NM	NM
31	SCC	NM	12	12	Thoracoscopic lower lobectomy and adjuvant chemotherapy	Proximal gastrectomy, nivolumab therapy, chemotherapy	Died	24
32	SCC	MD	0	7	Chemotherapy	Laparotomy with curative gastrectomy	Died	7
33	SCC	PD	<2	>13	Nivolumab	Radiation	Died	>15
34	AC	NM	0	>3	Chemotherapy	Chemotherapy	Alive	>3
35	AC	NM	0	1	Radiotherapy, chemotherapy	Radiotherapy, Chemotherapy	Died	1
36	SCC	MD	7	2	Right-middle lobectomy, chemotherapy	Supportive care	Died	10
37	AC	NM	0	10	Chemotherapy	Supportive care	Died	10
38	SCC	PD	0	2	Radiotherapy	Supportive care	Died	2
39	SCC	PD	12	6	Segmentations	Total gastrectomy	Died	18
40	SCLC	NM	0	8	Chemotherapy	Chemotherapy	Died	8
41	SCC	NM	0	>5	Chemotherapy, radiotherapy	Chemotherapy, radiotherapy	Died	>5
42	LCC	PD	0	NM	Chemotherapy	Chemotherapy	Alive	NM

Time span: time interval between diagnosis of primary lung cancer and gastric metastasis (months); time interval: the time from the discovery of gastric metastases to the death; SCC, squamous cell carcinoma; AC, adenocarcinoma; SCLC, small cell lung cancer; PC, pleomorphic carcinoma; LCC, large cell carcinoma; UN, undifferentiated; PD, poorly differentiated; MD, moderately differentiated; NM, not mentioned.

metastases initially occurred in the submucosal layer and only when the metastatic lesions grow and cause obstruction or ulceration could patients develop symptoms (13). The clinical manifestations of gastric metastatic carcinoma are not peculiar. Most of the complaints were epigastric pain or distension, which was easy to be ignored. Consequently, little could be seen of it in clinic. For patients with a history of the primary tumor, gastrointestinal reactions should not only be considered as adverse reactions caused by chemotherapy, but also the possibility of metastasis. Timely endoscopic examination should be made to clarify the pathology. The use of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) was very useful to detect gastrointestinal metastasis of lung cancer, as it could identify occult metastases of primary cancer prior to several diagnostic methods including gastroduodenoscopy, colonoscopy, abdominal CT and small bowel series (42).

At present, there is no unified treatment plan for patients with gastric metastasis of lung cancer and optimal treatment would be made according to pathology and patients' condition. Due to the dismal outcomes, a summary of previous case reports shows that 24% of the patients have chosen palliative care treatment. In the management of gastric metastasis, instead of chemotherapy or just supporting alone, combined with palliative operation may lead to a more favorable outcome. For instance, two patients with gastric metastasis of lung cancer who underwent subtotal gastrectomy had a long-term survival time of more than 4 years (15). Aokage *et al.* (15) thought pathologic stage I patients with a solitary recurrence after complete non-small cell lung cancer resection can prolong the survival time, while it doesn't suit for the stage II/III patient. However, since digestive tract tumors are prone to perforation, obstruction and bleeding, early and less invasive intervention such as palliative resection or bypass surgery may be needed to prevent or control severe complications (15).

Our patient had an EML4-ALK-positive gene. ALK gene rearrangements are detected in 3–7% of NSCLC patients (43). Compared with chemotherapy, ALK inhibitors significantly prolonged progression-free survival and overall survival in patients with ALK-positive in advanced NSCLC (44). After 6 months of treatment with crizotinib, there is a progression of the disease. Our patients had a shorter progression-free survival, in sharp contrast to 11.5 months mentioned in clinical study PROFILE 1014 about the efficacy of crizotinib treatment (44). CNS was a frequent site of acquiring resistance to crizotinib. It was reasonable to suppose that ALK-positive lung cancer with gastric metastasis was more likely to occur brain metastases and was worse prognosis than others organ metastasis. For them, crizotinib combined with local treatment might be related to the clinical efficacy and would prolong the progression free survival in the initial treatment. Retrospective data showed that alectinib treatment after crizotinib failure can improve sustained control and overall survival in patients with ALK rearrangement of NSCLC (45). After brain metastasis, the replacement of alectinib in time, rather than the persistence of combination of crizotinib and local radiotherapy, may achieve more encouraging results. However, we switched crizotinib to alectinib only when the brain lesions had progressed.

This study systematically summarized the clinical characteristics, treatment and prognosis of gastric metastasis of lung cancer, in order to provide a better reference for clinical decision-making. We also proposed a feasible therapy for EML4-ALK-positive lung cancer, and summarized some experience. The limitation of the study is that the feature data we summarized may not fully represent the real feature data due to the selection bias. The cases included in our study only come from the literature available in PubMed. There still are many suitable cases that haven't been reported or even be misdiagnosed fail to be enrolled.

In conclusion, though less occurrence of lung cancer with gastric metastasis, attention should be paid when gastrointestinal symptoms occurred for patients with lung cancer. Timely detection of gastric metastases and initiation of appropriate treatment could improve the quality of life and prolong survival. There was no clinical study on whether to continue using crizotinib combined with local radiotherapy, or to use alectinib when brain metastasis occurs. In comparison with other site metastasis, the occurrence of gastric metastases of ALK-positive lung cancer was seemed to accelerate the process of brain metastasis. Hence, it could be speculated that the combination use of crizotinib and prophylactic whole brain radiotherapy simultaneously was the optimal treatment at the beginning of the intervention. In our cases, timely replacement was appropriate when intracranial lesions were gradually increased.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1025

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1025). 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 studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). All treatments were performed with the consent of the patient. Written informed consent was obtained from the patient for publication of this study and any accompanying images.

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