Clinical Case Report

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Metastatic spread of solid subtype lung adenocarcinoma to the small intestine with anemia and melena

A case report

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Abstract

Rationale: Metastasis to the small intestine from a primary lung cancer is rare, and is associated with a poor prognosis. Early diagnosis of small intestine metastasis is difficult because of the low incidence of clinically apparent symptoms.

Patient concerns: Clinical data and treatment of a 59-year-old man with small intestine metastasis from primary solid subtype lung adenocarcinoma are summarized.

Diagnoses: A man who was previously diagnosed with stage IIIA (T3N2M0) lung adenocarcinoma (solid subtype) came to our hospital for postoperative radiotherapy. Laboratory tests indicated anemia and melena. The patient was initially believed to have digestive ulcer and was treated with omeprazole, which proved to be ineffective. We conducted an abdominal computed tomography (CT) contrast scan and discovered a mass in the small intestine mass. Further positron emission tomography–computed tomography (PET-CT) imaging indicated the small intestine mass with fluorodeoxyglucose uptake.

Interventions: The patient underwent an enterectomy and anastomosis. Pathological analysis confirmed the diagnosis of small intestinal metastasis from lung cancer with concomitant mesenteric lymph node metastasis.

Outcomes: One month after the operation, hemoglobin levels became normal, and the patient had good quality of life. However, 3 months after the operation, the patient suffered from anemia again. An abdominal CT scan indicated a new small intestine mass. Progression continued rapidly, and the patient died of hemorrhagic shock 5.5 months after the resection of the small intestine mass.

Lessons: Although uncommon, if lung cancer patients present with anemia and melena, enteric metastasis should be part of the differential diagnosis. Abdominal CT scans and PET-CT are effective for early diagnosis. The prognosis of metastatic spread of solid subtype lung adenocarcinoma to the small intestine with mesenteric lymph node metastasis is poor. Subgroups of patients benefitting from metastasectomy and more effective systemic therapy need to be further investigated.

Abbreviations: CT = computed tomography, EGFR = epidermal growth factor receptor, FDG = fluorodeoxyglucose, Hb = hemoglobin, MET = mesenchymal-epithelial transition, MRI = magnetic resonance imaging, NSCLC = non-small cell lung cancer, PCK = pan cytokeratin, PET-CT = positron emission tomography-computed tomography, TTF-1 = thyroid transcription factor-1.

Keywords: anemia, lung adenocarcinoma, metastasis, small intestine, solid subtype

1. Introduction

Lung cancer is a major cause of death worldwide. Most commonly, distant metastases from lung cancer are found in the adrenal glands, bone, liver, brain, and contralateral lung.[1] Clinically apparent gastrointestinal metastases of lung cancer are considered uncommon.[2] Nevertheless, intestinal metastases may induce symptoms such as abdominal pain, obstruction, perforation, bleeding, and intussusceptions, which may be life-threatening and may necessitate emergency surgery.[3] The prognosis of patients with small intestinal metastases secondary to lung cancer is generally very poor, with an estimated survival

Editor: Emmanuel Melloul.

XY and MW contributed equally to this work.

Funding information: This current study was supported by Applied Basic Research Program in Wuhan (grant no. 2015060101010054) and Natural Science Foundation of Hubei Province (grant no. 2016CFC737).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:34(e7768)

Received: 10 November 2016 / Received in final form: 19 April 2017 / Accepted: 20 July 2017

http://dx.doi.org/10.1097/MD.0000000000007768

time ranging from days to a few months, whereas select patients may survive longer after appropriate treatment.[4]

Herein, we present a rare case of a patient with primary lung adenocarcinoma (solid subtype) that developed small intestine metastasis. Clinicopathological features, management, and the importance of the differential diagnosis are discussed, along with a review of the literature, with an emphasis on the early detection of the small intestine metastatic tumor.

2. Case report

2.1. Clinical features

A 59-year-old man who was previously diagnosed with stage IIIA (T3N2M0) lung adenocarcinoma (solid subtype) came to our hospital for postoperative radiotherapy. The patient had well-controlled hypertension for 10 years, treated with antihypertensive medications. The patient did not have coronary heart disease, diabetes, emphysema, or any other chronic diseases. He complained of melena at the time. Laboratory data showed the hemoglobin (Hb) level was 84 g/L (normal 110–170 g/L), and fecal occult blood testing was positive, but the patient did not present with abdominal pain or vomiting. No lesion could be palpated on clinical examination. He received a right lower lobectomy and mediastinal lymph node dissection 4 months before, followed by 4 cycles of adjuvant therapy (pemetrexed/cisplatin). During the 4th adjuvant therapy, he suffered from anemia and melena. He was initially suspected to have a digestive ulcer and was treated with omeprazole. However, the anemia and melena continued.

2.2. Diagnostic assessment

As the anemia and melena continued, we tried to determine the reason for the anemia. Coagulation testing and platelet counts were normal at the time. An abdominal contrast-enhanced computed tomography (CT) scan revealed a mass in the small intestine (Fig. 1), along with mesenteric lymphadenopathy (maximum short-axis dimension of 8 mm), without other suspicious lesions. Contrast-enhanced chest CT and brain magnetic resonance imaging were also negative for metastatic disease. Furthermore, whole body positron emission tomography–computed tomography (PET-CT) imaging indicated the small intestine mass with fluorodeoxyglucose (FDG) uptake (SUVmax 15.6) (Fig. 2), which was suspicious for metastatic disease, whereas no other abnormal FDG uptake was present. Colonoscopy did not find a bleeding site or tumor mass. Multidisciplinary team evaluation suggested that the small intestine mass could be a primary tumor versus metastasis (the latter was considered more likely given the history of lung cancer and may be an oligometastatic tumor). It was suggested that pathological diagnosis could be accomplished by enteroscopic biopsy versus resection of the small intestinal mass. The patient and relatives opted to receive resection. The patient then underwent a second surgery consisting of an enterectomy and anastomosis. A $5 \times 5 \times 6$ cm tumor mass was found in the

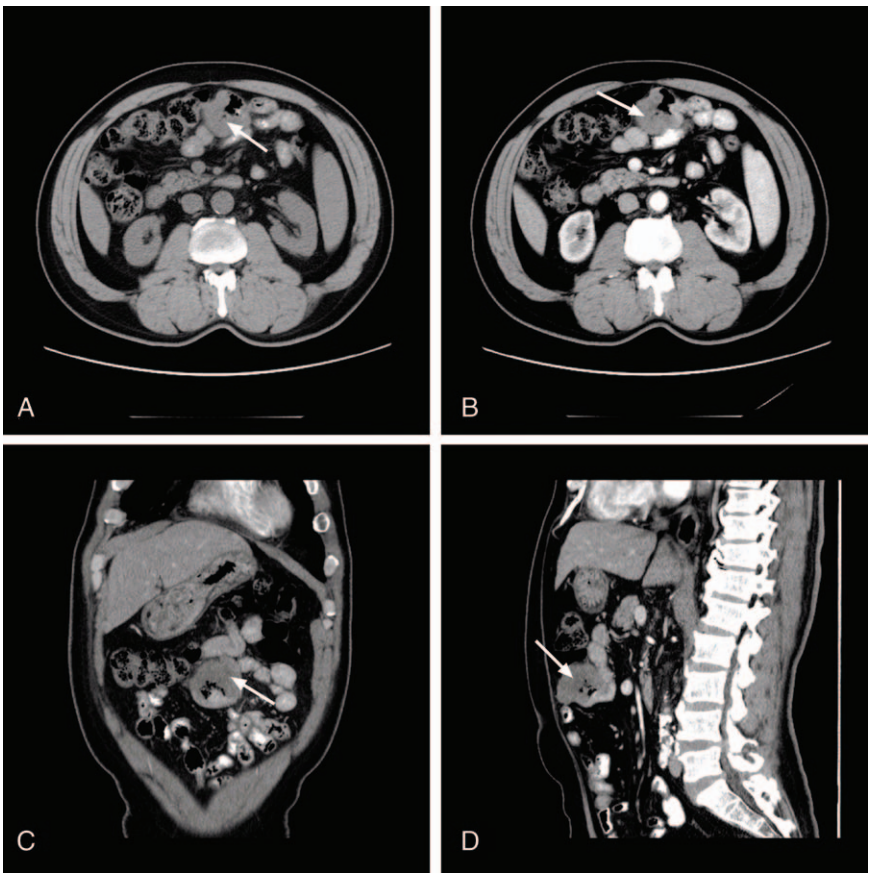

Figure 1. Abdominal contrast-enhanced computed tomography (CT) revealed a small intestine mass in the middle abdomen. (A) Axial imagine of the mass without CT contrast medium. (B) Axial imagine by contrast-enhanced CT. (C and D) Coronal and sagittal plane CT images of the tumor mass. CT = computed tomography.

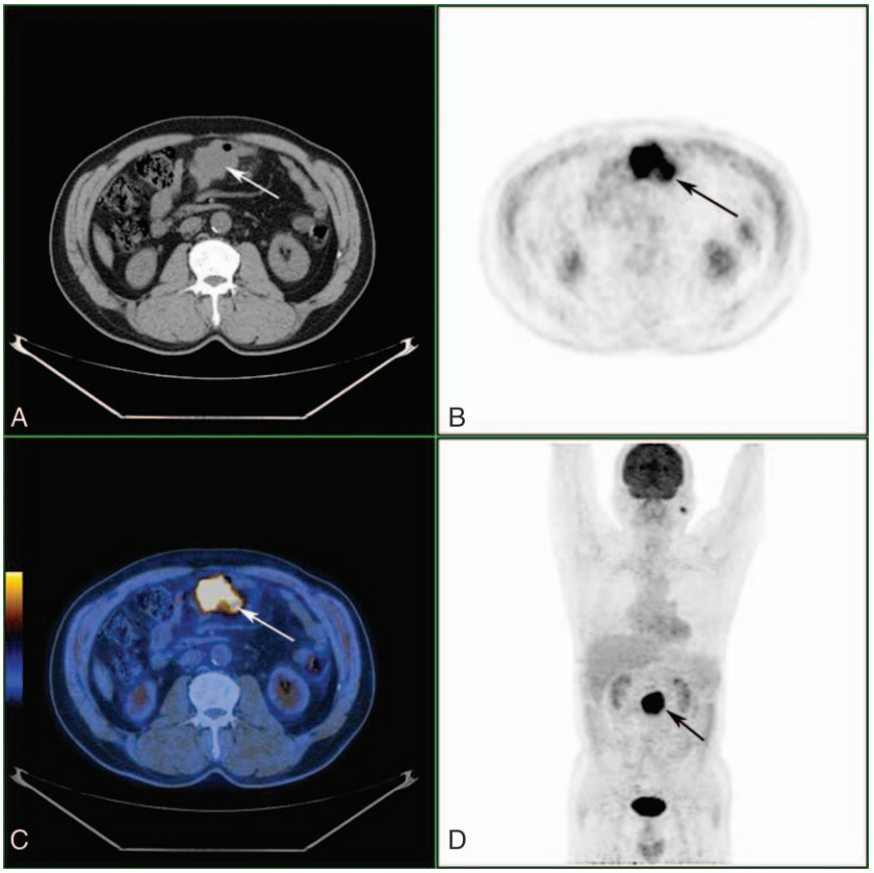

Figure 2. Positron emission tomography-computed tomography (PET-CT) indicated increased fluorodeoxyglucose (FDG) uptake in the small intestine. (A) Transaxial CT slices indicated a mass in the jejunum. (B) Axial FDG PET image at the corresponding level demonstrated marked FDG uptake by the mass. (C) Fusion of the transaxial CT and PET image at the same level revealed a small intestine mass measuring 5.5 by 5.5 cm with FDG uptake (SUVmax 15.6). (D) Maximum intensity projection image of PET-CT showing increased FDG uptake in the upper abdomen. CT = computed tomography, FDG = fluorodeoxyglucose, PET-CT = positron emission tomography-computed tomography.

jejunum. Hematoxylin-eosin staining showed that the characteristic morphological features of the tumor cells from the small intestine mass were similar to tumor cells from a primary lung lesion. Immunohistochemical staining indicated that the small intestine tumor cells were positive for thyroid transcription factor-1, vimentin, and pan cytokeratin but negative for cytokeratin 20 and villin, along with a ki-67 positive rate of 90% (Fig. 3). Additionally, 9 of 14 sampled mesenteric lymph nodes showed metastases and lymphovascular invasion was found. Molecular testing revealed negative epidermal growth factor receptor (EGFR) mutations and ALK rearrangement; however, Met gene amplification was observed (16% of tumor cells with >5 copies of Mesenchymal-epithelial transition [MET]). Accordingly, a diagnosis of small intestine metastasis from the primary solid subtype adenocarcinoma was achieved.

2.3. Interventions and outcome

One month after the operation, the hemoglobin level became normal, and the patient had a good quality of life. Two cycles of docetaxel were thereafter administered without influence on the hemoglobin level, as indicated by routine blood count. However, 3 months after the operation, the patient suffered from anemia again. An abdominal CT scan indicated a new small intestine mass of 3 cm in diameter. Crizotinib (250 mg orally, twice daily) was commenced to control the tumor. Unfortunately, the small intestine mass continued to grow rapidly to approximately 16 cm in diameter in 2 months. No tumor relapse or other organ metastasis was found at the same time, as indicated by a chest CT scan, brain magnetic resonance imaging (MRI), and bone single photon emission computed tomography. The patient's condition continued to deteriorate, and he was hospitalized with supportive medical care. He died of hemorrhagic shock 5.5 months after the resection of the small intestine mass.

2.4. Ethical statement

Ethical approval of this case report was granted by our institutional ethic committee (Hubei Cancer Hospital). Since this is a retrospective case report, patient consent was waived by our institutional ethic committee.

3. Discussion

Although small intestinal metastasis from lung cancer is rare, it warrants further study owing to a poor prognosis and potentially life-threatening consequences if untreated. Hence, it must be part of the differential diagnosis of patients with a history of lung cancer that present with anemia and melena.

Previous case reports regarding small intestine metastasis from lung adenocarcinoma have not examined associations with histologic subtype. The new International Association for the

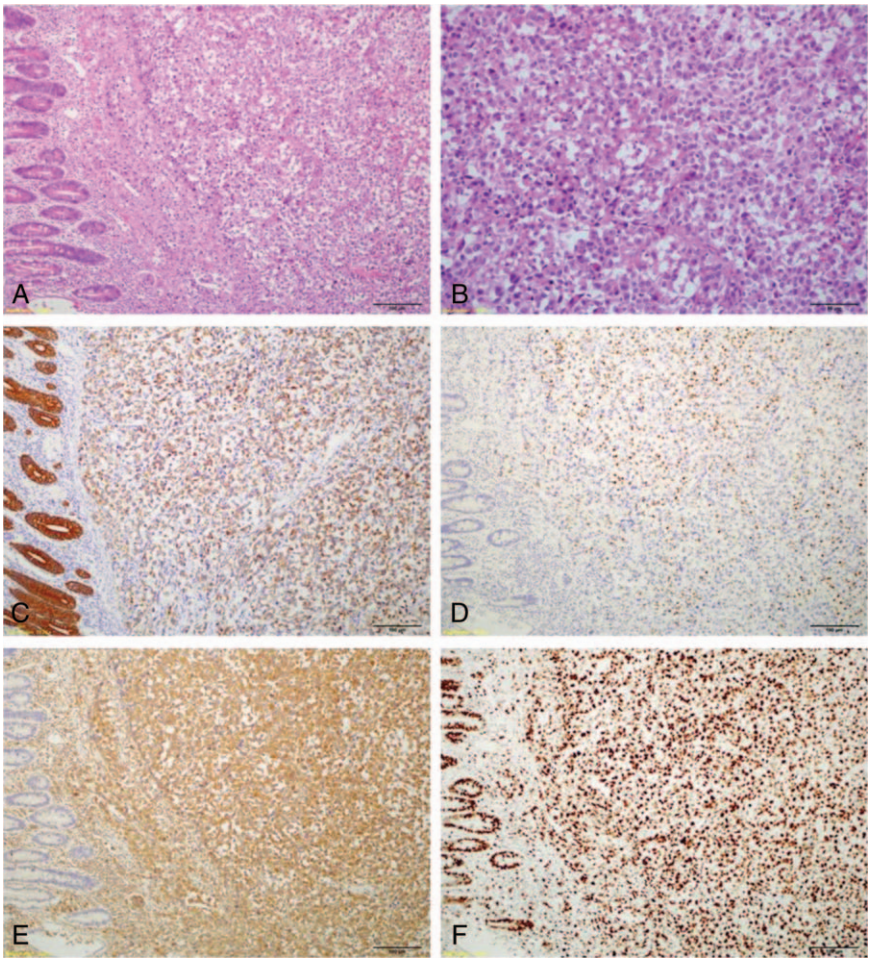

Figure 3. Pathological findings of the small intestine tumor. (A) Hematoxylin–eosin staining of small intestine metastatic tumor cells. (B) The tumor cells were round or polygonal and diffusely arranged. Immunohistochemical analysis indicated the small intestine tumor cells were positive for PCK (C), thyroid transcription factor (TTF)-1 (D), and vimentin (E). More than 90% of the tumor cells were positive for Ki-67 (F), indicating its aggressive phenotype. The magnification for images A and C–F is ×100, whereas image B is ×200. PCK = pan cytokeratin, TTF-1 = thyroid transcription factor-1.

Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system pathologically classified adenocarcinoma according to the predominant histologic features: lepidic, papillary, acinar, micropapillary, and solid patterns. This is important because it is becoming increasingly accepted that histologic patterns drive the biologic behavior of the tumor.[5] As reported by Hung et al,[6] micropapillary/solid predominant subtypes (versus acinar/papillary) were significant poor prognostic factors for postrecurrence survival in resected lung adenocarcinoma. In our case, further immunohistochemistry analysis of the small intestine mass showed the Ki-67 proliferation rate to be approximately 90%, along with lymph node metastasis and lymphovascular invasion, thus revealing its invasive characteristics. Additionally, the small intestine tumor was also positive for vimentin, which was consistent with a report that vimentin expression levels were significantly higher in the solid subtype component than in other histologic components.[7]

In our case, the patient continued to present with anemia and melena, which was initially regarded as digestive ulcer with no response to antacids. Further abdominal contrast-enhanced CT scan and a PET-CT scan indicated a small intestine mass with FDG uptake. For other cases, PET-CT has been shown to be an effective method for the detection of occult distant metastasis.[8] However, because of the high cost of PET-CT scans, they may not be affordable for all patients. In our case, an abdominal contrast CT scan also discovered the small intestine mass, indicating the value of the CT scan, which is more cost-effective in uncovering the disease. For patients with solid-predominant subtype lung adenocarcinoma, we could consider regular CT scanning of their abdomens for distant disease because it is more likely to recur distantly. In addition, the patient's Hb level changed with the progression of the disease; anemia occurred when the small intestine metastasis was diagnosed, disappeared after the resection of the small intestine mass, and recurred with the recurrence of the small intestine mass. This indicates that monitoring the level of Hb may be a useful way to facilitate evaluating the tumor status. Anemia may be because of the chronic hemorrhage of the metastatic tumor. An incidence of 0.5% producing clinical symptoms in patients with small bowel metastases of a primary carcinoma was reported,[2] whereas Jansen et al reported that hemorrhage was the most unusual complication.[9]

The prognosis of a patient with small intestinal metastases secondary to lung cancer is generally very poor, with an estimated survival time ranging from days to a few months, whereas select patients may survive longer after appropriate treatment.[4] In a

comprehensive evaluation of the literature, around 100 cases with small intestinal metastasis from primary lung cancer were found (data not shown). Of these, 18 cases survived for <1 month and 15 cases for >6 months, among which only 5 cases survived for >1 year. As most cases with <1-year survival (median survival time 2.3 months) were summarized in the review by Zhong et al,[10] this was not repeated herein. Because the focus of this review was patients experiencing long-term survival, only patients with survival for >1 year were shown in Table 1.[9,11,12] Although surgical management is the most common treatment option for these patients, not all patients may benefit from surgery. No extraintestinal metastasis may be associated with longer survival from resection, which is consistent with the report from Zhong et al.[10] In our case, the patient's prognosis was relatively poor, possibly because of mesenteric lymph node metastasis, which indicated that the tumor may have already disseminated before the time of surgery. Whether these patients benefit from metastasectomy needs further investigation. We suppose that patients with small intestine metastasis achieving a longer survival may be in an oligometastatic state, which could be controlled by local ablative therapy.

A recent study reported that solid-predominant adenocarcinoma was a poor predictor for tumor response in patients undergoing adjuvant chemotherapy.[13] In our case, a very poor response to chemotherapy was observed using pemetrexed and cisplatin with second-line docetaxel. Another study showed that the relatively lower frequency of EGFR mutations in solid-predominant adenocarcinoma, as exemplified by our patient, conferred less opportunity to receive targeted therapies.[14] The patient had MET amplification, which has been reported to be associated with the pathogenesis of non-small cell lung cancer (NSCLC).[15] De-novo MET amplification has also been associated with poor prognosis.[16] Crizotinib has been reported to have significant MET inhibitory activity *in vitro*.[17] In a randomized phase II trial that combined MET inhibitors with erlotinib vs erlotinib alone in NSCLC patients, a retrospective analysis showed that progression-free survival improved most in patients with >5 MET copies, whose MET amplification criteria are consistent with our study.[18] Crizotinib has been reported to have antitumor activity in NSCLC patients with de-novo MET amplification but without ALK rearrangement in 2 other studies,[19–20] whose criteria for MET amplification were MET/CEP7 ratio >5.0 and MET/CEP7 ratio >2.2, respectively. In our case, crizotinib was administered in an attempt to control tumor growth. Unfortunately, the patient experienced disease progression during treatment. Guidelines for MET amplification criteria and indicators predicting the activity of crizotinib in solid subtype lung adenocarcinoma still need to be investigated.[21]

There are some limitations for this case report. One limitation is mesenteric lymphadenopathy was indicated by our preoperative abdominal contrast-enhanced CT; further PET-CT did not show abnormal FDG uptake for the lymph node, so we supposed the lymphadenopathy was negative for metastasis. However, as shown by the pathological analysis for the resected lymph nodes, this mesenteric lymphadenopathy was positive for metastasis. It indicated that we should be cautious about the mesenteric lymphadenopathy for patients with history of malignancy.[22] Another one is a new small intestine tumor was discovered 3 months later after the operation. It is possible that this tumor already existed at the time of small intestine mass operation, which is so small that it was not discovered by preoperative abdominal CT and our surgeon. Preoperative enteroscopy may

Table 1

Reported cases of the survival time from discovery of small intestine metastasis to death for >1 year.

Reference	Age, y	Pathological diagnosis of primary cancer	Initial staging	*Time interval, mo	Clinical presentation	Diagnostic procedure	Extraintestine metastasis	Treatment for metastatic small intestine tumor	†Survival time, mo
Jansen et al,[9] 2004	73	Pleiomorphic	NA	NA	Anemia	Labeled erythrocyte scintigraphy	NA	Surgery	14+
Kim et al,[11] 2009	61	Large cell Adenocarcinoma	T3/N2/M0; IIIa	3.4	Abdominal pain	NA	Abdominal LN, Adrenal gland	Operation	33+
	62	Sarcomatoid	T2/N2/M1; IV	0	Abdominal pain, Melena	NA	None	Operation	63+
Fujiwara et al,[12] 2011	68	Large cell	IIIB	9.5	Anemia	NA	None	Surgery	>84
	62	Adenocarcinoma	T1N0	14.7	Abdominal pain	Upper GI	None	Partial resection, drainage	24.7

NA = not available, Upper GI = upper GI series, LN = lymph nodes.
* Time interval (months) between diagnosis of lung tumor and intestine metastasis.
† Survival time from discovery of intestine metastasis to death (months).

be a good option for detection of small, multifocal small intestine lesions along with diagnostic biopsy.[23]

4. Conclusion

Small intestine metastasis from lung cancer is rare, but clinicians should keep it in the differential diagnosis when patients with a history of lung cancer present with anemia and melena. Abdominal CT scan and PET-CT are effective for early diagnosis. The prognosis of metastatic spread of solid subtype lung adenocarcinoma to the small intestine with mesenteric lymph node metastasis is poor. Subgroups of patients benefitting from metastasectomy and more effective systemic therapy need to be further investigated.

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