—Case Reports—

A Rapidly Growing Small-Intestinal Metastasis from Lung Cancer

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Small-intestinal metastasis from lung cancer, although relatively rare, often causes intestinal obstruction, gastrointestinal perforation, and gastrointestinal bleeding, making it an oncological emergency. Many patients have undergone emergency surgery for treatment of rapid progression of an intestinal metastatic lesion; however, information on changes in such metastases is lacking. We analyzed data from 4 patients with small-intestinal metastases from lung cancer who were treated during a 10-year period (January 2011 to December 2020) and for whom data on change in tumor diameter were available. The average rate of growth in tumor volume was 1.48-fold (range, 1.31- to 1.78-fold) during a median observation period of 22 (4-39) days, a rapid increase. Histopathological analysis showed that, in patients with a high degree of primary tumor atypia, rapid tumor growth may be caused by intratumoral hemorrhage, which was the reason for the rapid increase in tumor volume.
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Key words: metastasis, small intestine, lung cancer, oncologic emergency, tumor volume

Introduction

Lung cancer is one of the most common cancers worldwide[1]. Small-intestinal metastasis from lung cancer is relatively rare and can cause intestinal obstruction, gastrointestinal perforation, and gastrointestinal bleeding[2,3], all of which require urgent intervention. While emergency surgery is sometimes required for such intestinal metastases, no study has investigated changes that occur in such lesions over time. Herein, we describe a patient with one of the fastest growing intestinal metastases from lung cancer reported to date. Additionally, we report the characteristics of other patients with lung cancer who underwent surgery at our hospital for small-intestinal metastases.

Case Presentation

Primary Patient

A 53-year-old man was diagnosed as having primary lung cancer and brain metastasis. Computed tomography (CT) scans to determine the cause of anemia revealed a small-intestinal mass (**Fig. 1A**). Subsequent double-balloon endoscopy revealed a growth protruding into the lumen of the small intestine. The patient had no symptoms of melena but had severe anemia (hemoglobin level, 6.8 g/dL) that required frequent blood transfusions. Therefore, we decided to perform a partial resection of the small intestine. However, on the day after double-balloon endoscopy, he suddenly reported abdominal pain. On physical examination, the patient was pale, diaphoretic, and distressed owing to continuous lower abdominal tenderness without recoil pain. He had a temperature of 37.2°C, heart rate of 71 beats per minute, and blood pressure of 102/58 mmHg. Laboratory examination revealed a hemoglobin level of 8.4 g/dL, white blood cell count of 10,400 /μL, and C-reactive protein level of 9.14 mg/dL. Reevaluation with CT showed a marked increase in the size of the tumor in the small intestine, as compared with 4 days previously (**Fig. 1B**). No perforation or

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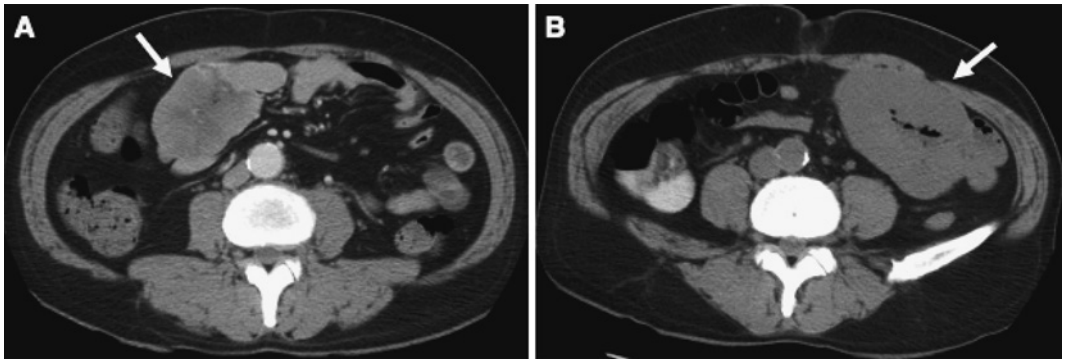


Fig. 1 Abdominal computed tomography scan showing a small-intestinal tumor (arrow) (**A**). The tumor continued to grow while the patient experienced abdominal pain (arrow) (**B**).

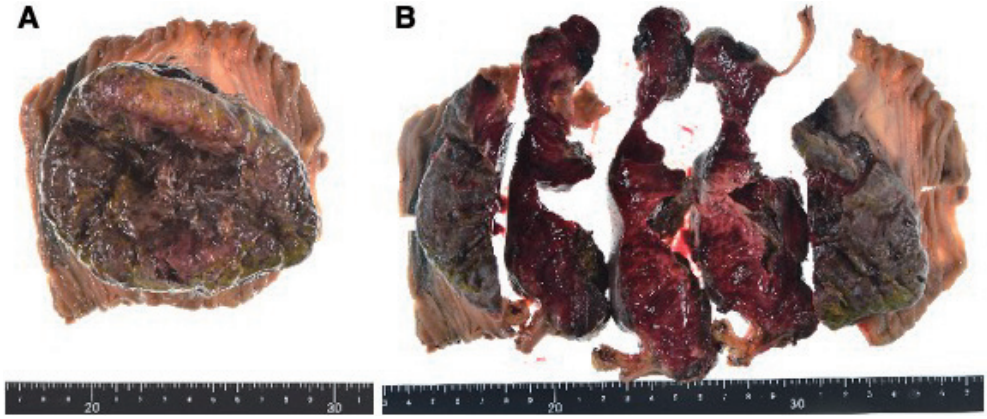


Fig. 2 Gross tumor findings. Macroscopically, the bulging lesion in the resected small intestine measured 110 × 80 mm (**A**), and cut sections showed a tumorous mass with massive bleeding (**B**).

intestinal obstruction was observed, and the patient was prescribed analgesics. Six days later, laparoscopic partial resection of the small intestine was performed; the resected specimen measured 110 × 80 mm.

Grossly, the mucosal surface bulged into the intestinal lumen (**Fig. 2A**); sectioning revealed a tumorous mass with hemorrhaging in the submucosal area (**Fig. 2B**). Histopathological examination showed tumor cell proliferation, with severe atypia in the submucosal area (**Fig. 3 A**), and hemorrhage (**Fig. 3B**). The histological features of the lesion were similar to those of the primary lung tumor (**Fig. 3C and D**), which confirmed the presence of metastasis.

Immunohistochemically, the Ki-67 proliferative index was approximately 40% (**Fig. 4A**). Staining with CD34, a marker of endothelial cells, revealed destruction of the vascular structure from tumor invasion of the vascular lumen (**Fig. 4B**). The postoperative course was uneventful, and the patient was discharged 25 days after the surgery. He is alive at this writing, 14 months later.

Review of Other Patients

Among the 56 patients with small-intestinal tumors surgically treated at our hospital between January 2010 and December 2020, the clinicopathological factors of the 7 patients with lung cancer with small-intestinal metastases were examined (including the present patient). In the 4 patients for whom tumor diameter could be traced over time, the region of interest was set using a 5-mm abdominal CT slice to determine tumor volume. Tumor growth rate was determined by using a previously reported formula: $v_{(t)} = v_{(0)}e^{TG \cdot t}$, where v = volume, TG = tumor growth rate, and t = time in days[4].

Clinicopathological Factors

All patients were men (median age, 70 years; range, 53-76 years). The symptoms at presentation were anemia, melena, and intestinal obstruction in 3, 1, and 3, patients respectively. All patients had adenocarcinoma; Union of International Cancer Control stage I/II/III/IV disease was noted in 1 patient each. Epidermal growth factor receptor (EGFR) and Anaplastic lymphoma kinase (ALK) were negative in all cases, PD-L1 was positive in 3 cases,

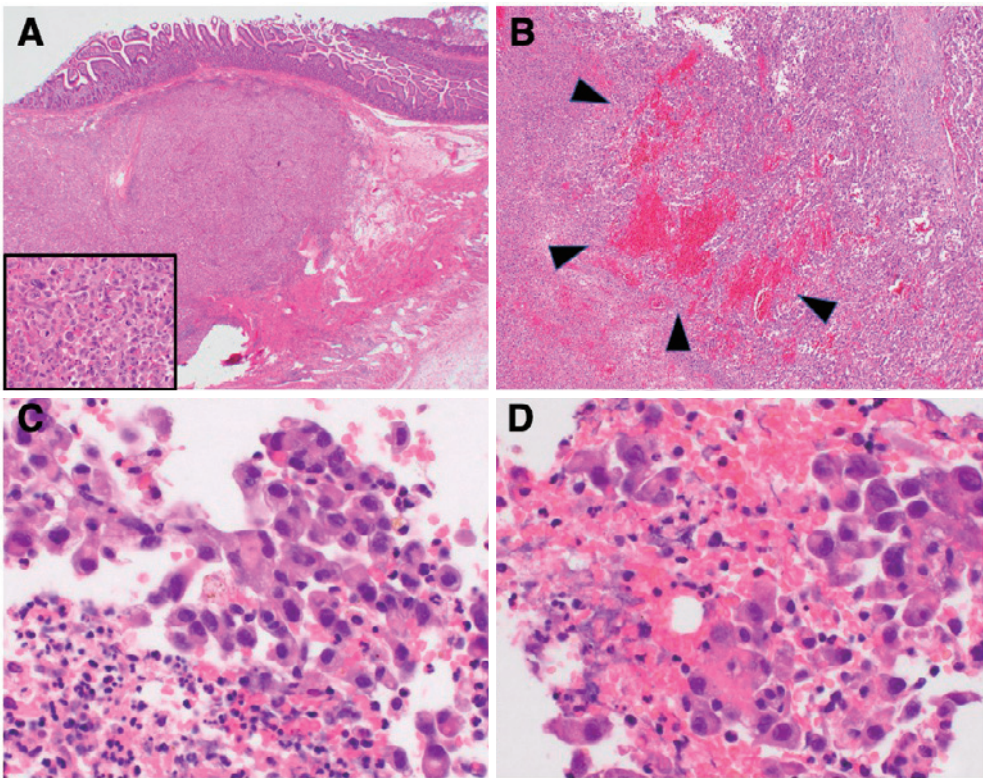


Fig. 3 Microscopic findings of the small-intestinal metastasis from lung cancer (hematoxylin and eosin staining). Tumor cells infiltrating below the intestinal mucosa (magnification ×2) (**A**) had severe nuclear atypia and pleomorphism (×40) (**A** inset). The tumor exhibited significant bleeding (×4) (**B**). The histological features of the lesion are identical to those of the primary lung tumor, confirming the presence of metastasis (×60) (**C, D**).

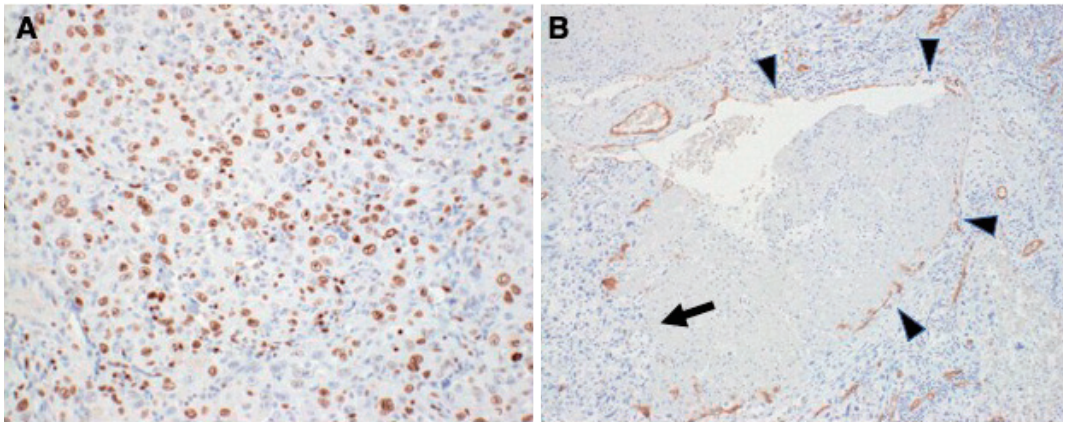


Fig. 4 The Ki-67 proliferation index of tumor cells was approximately 40% (magnification ×20) (**A**). Within the tumor component, the vascular lumen, as indicated by CD34-positive endothelial cells (arrowheads), was destroyed by invading tumor cells (arrow), likely causing intratumoral bleeding (×10) (**B**).

and preoperative chemotherapy was administered in 3 cases. Three patients had synchronous metastases, while 4 had metachronous metastases. Six patients had a single metastasis and 1 had multiple lesions; the site of intestinal metastasis was the jejunum in 5 patients and ileum in 2 patients. The mean interval between diagnosis and surgery was 37.7 (8-120) days; there were no postoperative complications, and the duration of follow-up after surgery was 27.4 (14-50) months. Intratumoral bleeding was observed in all 4 patients for whom tumor diameters were recorded (**Table 1**).

Table 1 Review of 7 patients with small-intestinal metastases from lung cancer

Patient number	Age (y)/sex	Symptom at presentation	Histology	Stage (UICC 8th ed.)	EGFR/ALK/PD-L1	Preoperative chemotherapy	Timing of metastasis	Number of metastatic lesions	Site of intestinal metastasis	Interval from diagnosis to surgery (days)	Intratumoral hemorrhage	Outcome, time since surgery
1	65/M	Anemia	Adeno	IIIA	(–)/(–)/TPS<1%	(+)	Heterochronous	1	Jejunum	18	(+)	Dead, 19 months
2	74/M	Melena	Adeno	IA2	(–)/(–)/TPS<1%	(–)	Heterochronous	1	Ileum	61	(+)	Alive, 16 months
3	76/M	Intestinal obstruction	Adeno	IIB	(–)/(–)/TPS<1%	(–)	Heterochronous	1	Jejunum	8	Unknown	Alive, 30 months
4	55/M	Intestinal obstruction	Adeno	IVA	(–)/(–)/TPS<1%	(+)	Heterochronous	2	Jejunum	120	(–)	Dead, 50 months
5	70/M	Intestinal obstruction	Adeno	IVB	(–)/(–)/TPS<50%	(+)	Synchronous	1	Ileum	24	Unknown	Alive, 45 months
6	53/M	Anemia	Adeno	IVB	(–)/(–)/TPS>90%	(–)	Synchronous	1	Jejunum	15	(+)	Alive, 14 months
7	73/M	Anemia	Adeno	IVA	(–)/(–)/TPS>50%	(–)	Synchronous	1	Jejunum	18	(+)	Alive, 18 months

Adeno: adenocarcinoma; UICC: Union of International Cancer Control.

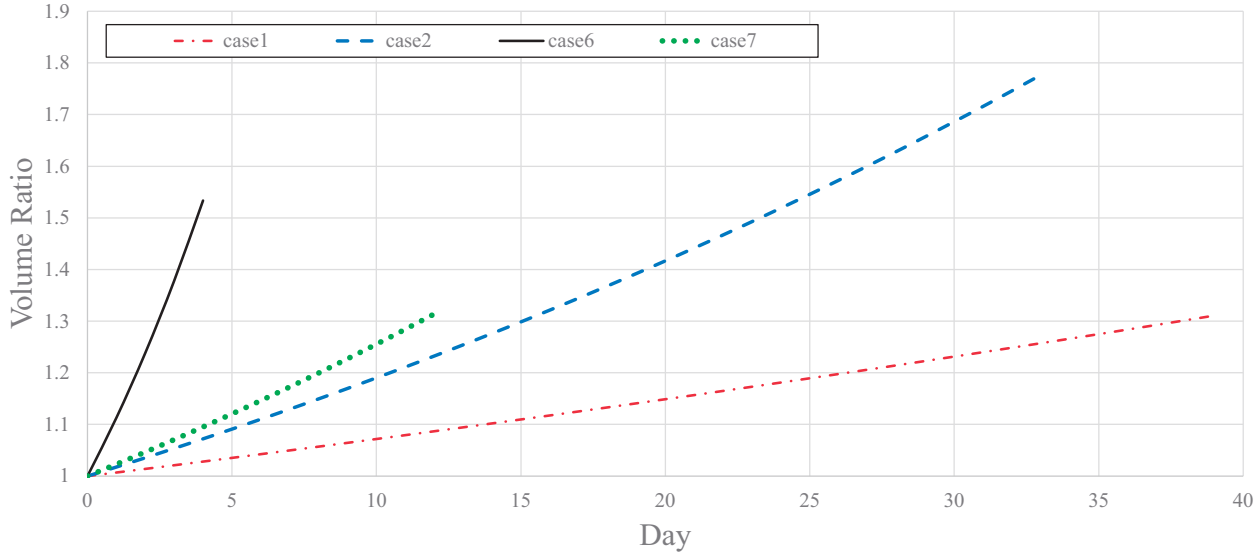
Growth Rate

The average growth rate of tumor diameter in the 4 of the 7 patients with available data was 1.48-fold (1.31- to 1.78-fold) during a median observation period of 22 (4-39) days. The most rapidly growing tumor was that of our primary patient described above (patient #6), which increased by 1.53-fold in just 4 days (**Fig. 5**).

Discussion

The most common sites for metastasis of primary lung cancer are the lymph nodes (48%), liver (45%), adrenal glands (41%), bones (31%), and brain (25%). Metastases to the digestive system are relatively rare: 0.2% and 1.7% in 2 previous studies[5,6]. However, such metastases were observed in 4.6%, 11.9%, and 14.0% of autopsied patients in 3 other studies[2,7,8]. Small-intestinal metastases from lung cancer are more common in men; indeed, all of the present patients were male. Most intestinal metastases arising from lung cancer are found after patients develop acute abdominal symptoms and are very rarely asymptomatic and incidental. Lui et al. reported that clinical symptoms caused by small-intestinal metastasis include perforation, obstruction, and bleeding[9]; however, none of our patients presented with perforation. As described by Leidich and Rudolf, tumor cells deposited in the small intestine exhibit varying growth morphologies[10]. For example, tumors that form in the submucosa and muscular layer can grow toward the intestinal lumen and cause obstruction. Additionally, an extensive section of the bowel wall may be replaced by tumor cells, leading to malabsorption. Ulceration of the tumor can also cause bleeding, whereas a necrotic tumor can lead to perforation. Although none of our patients experienced extensive necrosis, intratumoral bleeding was present. There is no study of the lung cancer tissue type that is most likely to bleed, making comparison difficult. Regarding the effect of chemotherapy, it is unlikely that chemotherapy was administered preoperatively for only 1 of the 4 patients that had an increased tumor size. We searched PubMed using the terms ”small intestinal metastasis” and ”bleeding” to determine whether bleeding frequency was associated with the primary lesion, but our analysis was limited by the small number of case reports identified in the search, and there were no data on bleeding rate. This subject should be investigated in future studies.

All of our patients had adenocarcinomas. In contrast, Yang et al. reported that squamous cell carcinoma was the most frequent histological type for primary lesions in their patients[11], and Yoshimoto et al. and McNeil et al.



Case	1st CT (㎜³)	2nd CT (㎜³)	Inspection interval(days)	Growth rate(×100%)
1	4501.75	5900.87	39	1.31
2	2524.47	4485.34	33	1.78
6	32192.71	49367.42	4	1.53
7	23090.35	30338.04	12	1.31

Fig. 5 Tumor diameter was measured over time in 4 of the 7 patients. The average rate of growth was 1.54-fold (range, 1.31- to 1.78-fold). The average observation period was 25.3 (4–39) days. The most rapid tumor growth—1.53-fold in 4 days—was seen in patient #6.
CT, computed tomography

both reported a large proportion of patients with large-cell carcinomas[7,12]. In a study by Hu et al., the rate of small-intestinal perforation caused by metastases was highest for those originating from large-cell carcinomas and lowest for those originating from adenocarcinomas[13]. Moreover, they reported a median overall survival of 2.8 months in patients with gastrointestinal metastases from lung cancer and that 53.4% of their patients died of the disease within 3 months of detection of gastrointestinal metastases[13]. These survival rates were better than those reported by Garwood et al.; however, outcomes were nevertheless poor[14]. The median survival time of our patients significantly exceeded that in the aforementioned studies, probably because our patients were in better general condition during the perioperative period and had no perforations.

Because it is difficult to detect lung cancer metastases to the small intestine when a patient is asymptomatic, most reported patients presented with perforation. Moreover, some reports described a rapid increase in tumor volume owing to intratumoral hemorrhage, as in our case. Although perforation was not present in any of our 7 patients, we were able to track tumor diameter over time in 4 of them. It was difficult to accurately measure tumor volume using CT in the remaining 3, owing to intussusception or intestinal obstruction. The average tumor growth rate in the 4 patients with complete data was 1.48-fold, and the tumor for patient #6 grew by 1.53-fold over 4 days. Intratumoral hemorrhage was observed in all 4 of these patients, suggesting that such bleeding is an important reason for the increase in tumor diameter. Intratumoral hemorrhage was likely attributable to the fact that the degree of primary tumor atypia was extremely high, which led to venous wall destruction.

Conclusion

The findings for our patient with lung cancer and a rapidly growing small-intestinal metastasis highlight the need for urgent intervention for this rare condition. Because tumor growth resulting from intratumoral hemorrhage may be rapid in patients with a high degree of primary tumor atypia, surgery should be considered as soon as this condition is detected.

Conflict of Interest: The authors declare no conflict of interest and received no external funding.

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