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TAKASHI IWATA, KIYOTOSHI INOUE, SACHIKO KIRIIKE et al. Hemorrhagic Small Intestine Cancer with Solitary Pulmonary Metastasis Initially Presented as Suspected Primary Lung Cancer: An Autopsy Report. Osaka City Medical Journal. 2007, 53, 109-116

Osaka City Med. J. Vol. 53, 109-116, 2007

Hemorrhagic Small Intestine Cancer with Solitary Pulmonary Metastasis Initially Presented as Suspected Primary Lung Cancer: An Autopsy Report

Takashi Iwata[1)], Kiyotoshi Inoue[1)], Sachiko Kiriike[1)], Nobuhiro Izumi[1)], Shinjiro Mizuguchi[1)], Takuma Tsukioka[1)], Ryuhei Morita[1)], Noritoshi Nishiyama[1)], Masashi Takemura[2)], Harusi Osugi[2)], Kenichi Wakasa[3)], and Shigefumi Suehiro[4)]

Departments of Thoracic Surgery[1)], Gastroenterological Surgery[2)], Pathology[3)], and Cardiovascular Surgery[4)], Osaka City University Hospital

Abstract

Cancer of the small intestine presenting with a solitary pulmonary metastasis is rare. Diagnosis and treatment of hemorrhagic small intestinal disease is clinically problematic due to its anatomic aspect, especially after multiple laparotomies. The case that we present here was a 79-year-old man who was initially diagnosed with suspected T2N2M0 lung cancer. After non-diagnostic results on two bronchoscopic biopsies and computed tomography-guided needle biopsy, he was admitted for thoracoscopic biopsy and possible curative operation. The patient had a history of multiple laparotomies for gastric ulcer and had no abdominal symptoms. A fecal occult blood test was positive; this was thought to be because of persistent bloody sputum. During the preoperative evaluation period, massive intestinal hemorrhage occurred. Intestinal tumor was identified by double-balloon enteroscopy and emergency laparotomy was performed to control the bleeding. The histopathological diagnosis was metastatic adenocarcinoma. However, intestinal bleeding started again. His systemic status deteriorated progressively, resulting in death. Autopsy revealed a large polypoid tumor with hemorrhagic necrosis in the jejunum that was histologically and immunohistochemically diagnosed as primary poorly differentiated adenocarcinoma in the small intestine. Multiple small submucosal tumors with central ulceration were confirmed as intramural metastases. A lung mass in the right lower lobe was diagnosed as a metastatic lesion. In the diagnosis and treatment of the disease, we faced several clinically difficult problems. We here describe in detail the clinical course and the diagnostic and therapeutic difficulties of this rare case, with some references to the literature.

Key Words: Adult; Gastrointestinal hemorrhage; Jejunal neoplasms; Lung neoplasms

Received August 4, 2006; accepted January 9, 2007.

Correspondence to: Takashi Iwata, MD.
Department of Thoracic Surgery, Osaka City University, Graduate School of Medicine,
1-4-3, Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3841; Fax: +81-6-6646-6057
E-mail: taiwata@med.osaka-cu.ac.jp

Introduction

Cancer of the small intestine diagnosed by the presence of a metastatic lung tumor is extremely rare. We could not find any reports in the literature. In the diagnosis and treatment of this disease, we faced several clinical difficulties. We present here the clinical course and some suggestive findings from this autopsy case of primary small intestine cancer with multiple intestinal metastases and a solitary metastatic pulmonary tumor that was initially diagnosed as suspected primary lung cancer with multiple metastatic disease in the small intestine.

Case report

Case history

A 79-year-old man, with a history of distal gastrectomy with Bilroth **II** reconstruction for gastric ulcer and two laparotomies for postoperative complications 26 years ago, presented with bloody sputum at a local clinic in January 2004. A right lung mass was observed on a chest radiograph. The patient was transferred to the respiratory medicine outpatient clinic of our hospital for further evaluation and treatment on February 2.

Both bronchoscopic biopsy (undertaken twice) and percutaneous computed tomography (CT)-guided biopsy of the lung mass were non-diagnostic. The tumor was hemorrhagic and accompanied by mild secondary inflammatory change in the surrounding lung tissue. The failure to make a correct diagnosis at this time was probably due to the presence of the inflammatory tissue around the tumor. Bone scintigraphy, and brain and abdominal CT revealed no metastatic disease. Although the lung mass showed no evidence of malignancy at the time, the patient was followed-up carefully. On follow-up CT on April 28, the lung mass had increased in size and hilar and mediastinal lymph nodes were newly swollen. The patient was suspected to have T2N2M0 lung cancer and admitted to our department for thoracoscopic biopsy and surgical treatment on May 10.

After admission, bloody sputum was produced several times per day. Fine crackles were audible in the right chest. The patient was anemic, but did not complain of any abdominal symptoms. The abdomen was flat and soft and no mass was palpable. The patient had smoked 30 cigarettes per day for 30 years, but had quit 3 months ago. Blood chemistry showed a red blood cell count of $235\times10^4/\mu L$, hemoglobin 8.0 g/dL, hematocrit 25.1%, C-reactive protein 0.2 mg/dL, and carcinoembryonic antigen 8.7 ng/mL (<5.0 ng/mL). The other blood chemical data were normal. A fecal occult blood test was positive.

Chest radiography showed a mass lesion in the right lower lung field surrounded by a reticular shadow (Fig. 1). Chest CT showed a mass of approximately 2.5 cm diameter in the apical segment of the right lower lobe (Fig. 2a) and swelling of the hilar lymph nodes (Fig. 2b).

Further preoperative evaluation showed severe hypothyroidism (triiodothyronine 1.9 ng/dL, thyroxine 0.4 μg/dL, and thyroid-stimulating hormone 190 μg/mL). Therefore, the patient needed oral hormone replacement therapy before surgical treatment of the lung. During this period, a small amount of bloody sputum persisted and the anemia increased. Hormone replacement therapy and examination and correction of the acutely progressing anemia were undertaken simultaneously. Both colonoscopy and gastroscopy were performed twice, but we could not find any bleeding lesions. A massive tarry stool was suddenly observed for the first

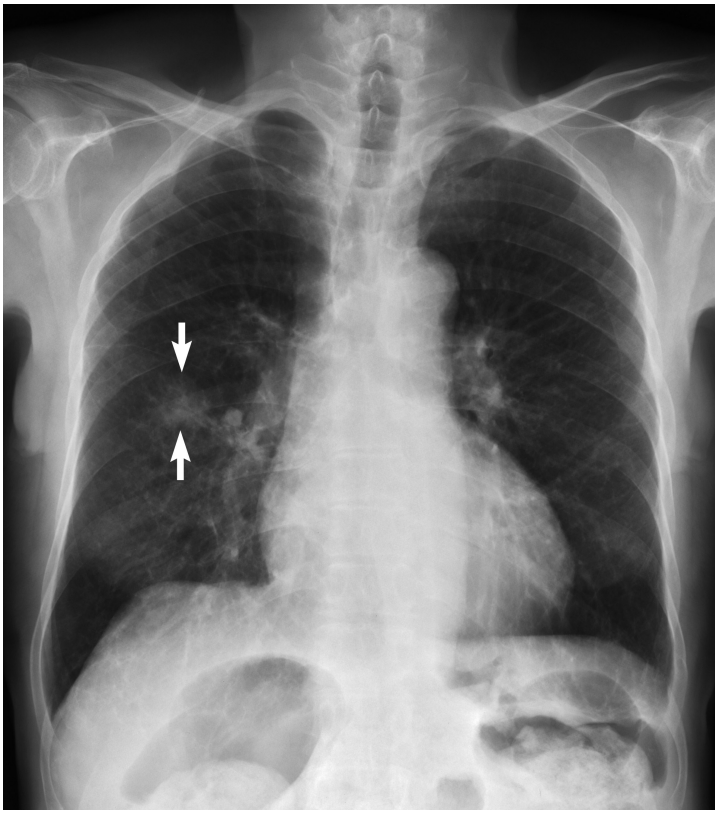

Figure 1. Chest radiography shows an unclear mass lesion in the right lower lung field (arrows), surrounded by reticular shadow.

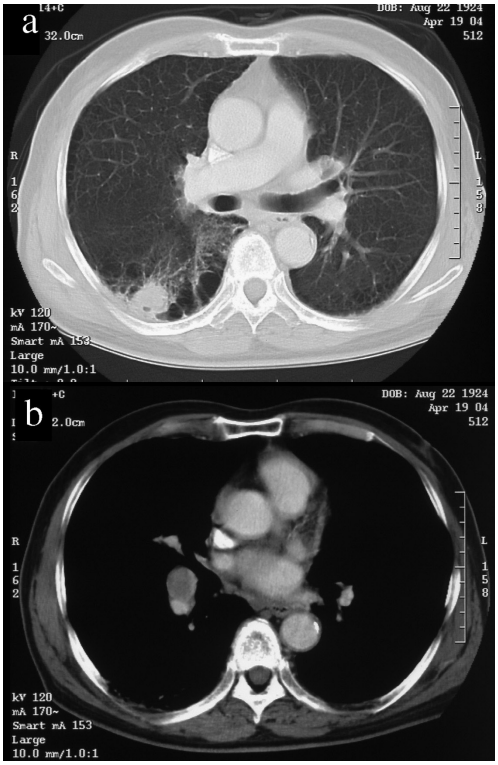

Figure 2. Chest computed tomography shows a lung tumor in the apical region of the right lower lobe (a). Secondary change is obvious surrounding the tumor due to repeated hemorrhage. Hilar lymph node swelling is seen (b).

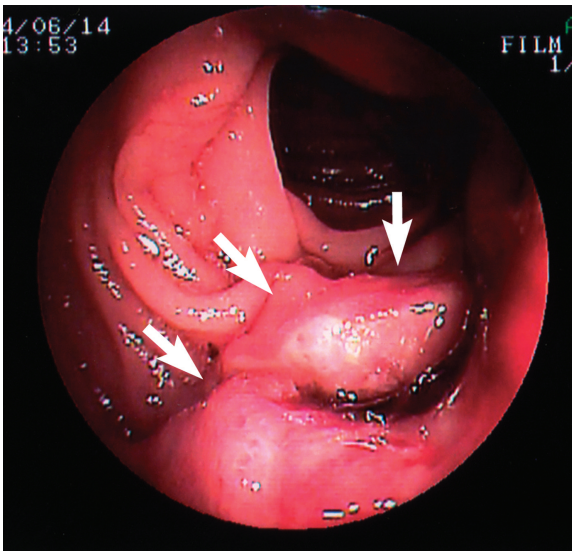

Figure 3. Double-balloon enteroscopy shows submucosal tumors in the middle part of the jejunum with bleeding ulceration in the center of the lesion near Braun's anastomosis (arrows).

time on June 5. Emergency abdominal angiography was performed; however, we could not find the point of bleeding. Gastrointestinal bleeding scintigraphy using technetium-99m diethylene-triamine-pentaacetic acid human serum albumin (^{99m}Tc-DTPA-HSA) revealed leakage of the isotope into the proximal half of the jejunum. Double-balloon enteroscopy revealed Braun's anastomosis and two submucosal tumors in the middle part of the jejunum, with clotting ulceration in the center of the lesion (Fig. 3). The bleeding from the tumor was thought to be not

continuous, and active bleeding was not demonstrated at the time. The precise extent of the lesion was almost impossible to determine on double-balloon enteroscopy, because the small intestine was extremely stretchy. The approximate extent was determined by simultaneous radiological guidance with intraluminal contrast medium.

Exploratory laparotomy was performed to control the bleeding on June 18, after 9600 mL of blood transfusion since admission. The abdominal cavity had severe adhesions due to the previous multiple laparotomies. An elastic soft tumor was palpated in the jejunum, 40 cm anal to the gastrojejunal anastomosis. The tumor was approximately 2.0 cm in diameter. Two similar lesions were palpated in the jejunum 15 cm and 35 cm anal to the main lesion; these were approximately 1.0 cm and 1.5 cm in size. Partial resection of the jejunum was performed and reconstruction was undertaken by functional end-to-end anastomosis. The gross specimen revealed three submucosal tumors with central ulceration. The largest lesion had a blood clot on the ulceration. The other lesions were smaller but similar to the main lesion. The histopathological diagnosis was metastatic adenocarcinoma in the small intestine and mesenteric lymph nodes. These findings suggested that the patient had multiple metastatic intestinal tumors from primary lung cancer.

Tarry stool was observed again with biliary vomit on the 8th postoperative day. Enteroscopy revealed multiple ulcerative lesions in the oral half of the jejunum and gastrojejunal anastomosis that had not been seen on the previous enteroscopy. Each lesion was bleeding or had blood clots. The anemia increased rapidly despite massive blood transfusion. Repeat surgical treatment was decided to be inappropriate due to the acute progression of the disease, and the patient was considered unable to endure massive resection of the small intestine. The patient died of disseminated intravascular coagulation 40 days after the laparotomy.

Autopsy findings

In the jejunum near Braun's anastomosis, we found a polypoid mass lesion 4 cm in diameter with hemorrhagic necrosis, which had invaded into the subserosal layer (Fig. 4a). The cleavage plane showed a polypoid tumor invading the submucosal layer (Fig. 4b). Histopathology revealed poorly differentiated adenocarcinoma in the small intestine (Fig. 4c). Intravascular invasion was also shown (Fig. 4d). Multiple small submucosal tumors with central ulceration were found and diagnosed as intramural metastases. Multiple mesenteric lymph node metastases were also seen.

In the apical segment of the lower lobe of the right lung, there was a mass lesion 4 cm in diameter (Fig. 5a). Macroscopically, the tumor margin was clear and surrounded by hemorrhagic lung tissue (Fig. 5b). In the tumor tissue, alveolar cells were hardly identifiable, as in typical primary adenocarcinoma of the lung. Cancer cells were observed to develop mainly from the lung mesenchyma, compressing the surrounding hemorrhagic alveolar structure, as shown in the left quarter of Figure 5b, and indicating hematogenous metastasis from the small intestine cancer. These pathological findings suggested that the lung tumor was metastatic from the small intestine. Thus, the histological diagnosis of the lung mass was metastatic poorly differentiated adenocarcinoma. Neither hilar nor mediastinal lymph node metastasis was observed.

Immunohistochemistry revealed negative thyroid transcription factor (TTF)-1 staining in both

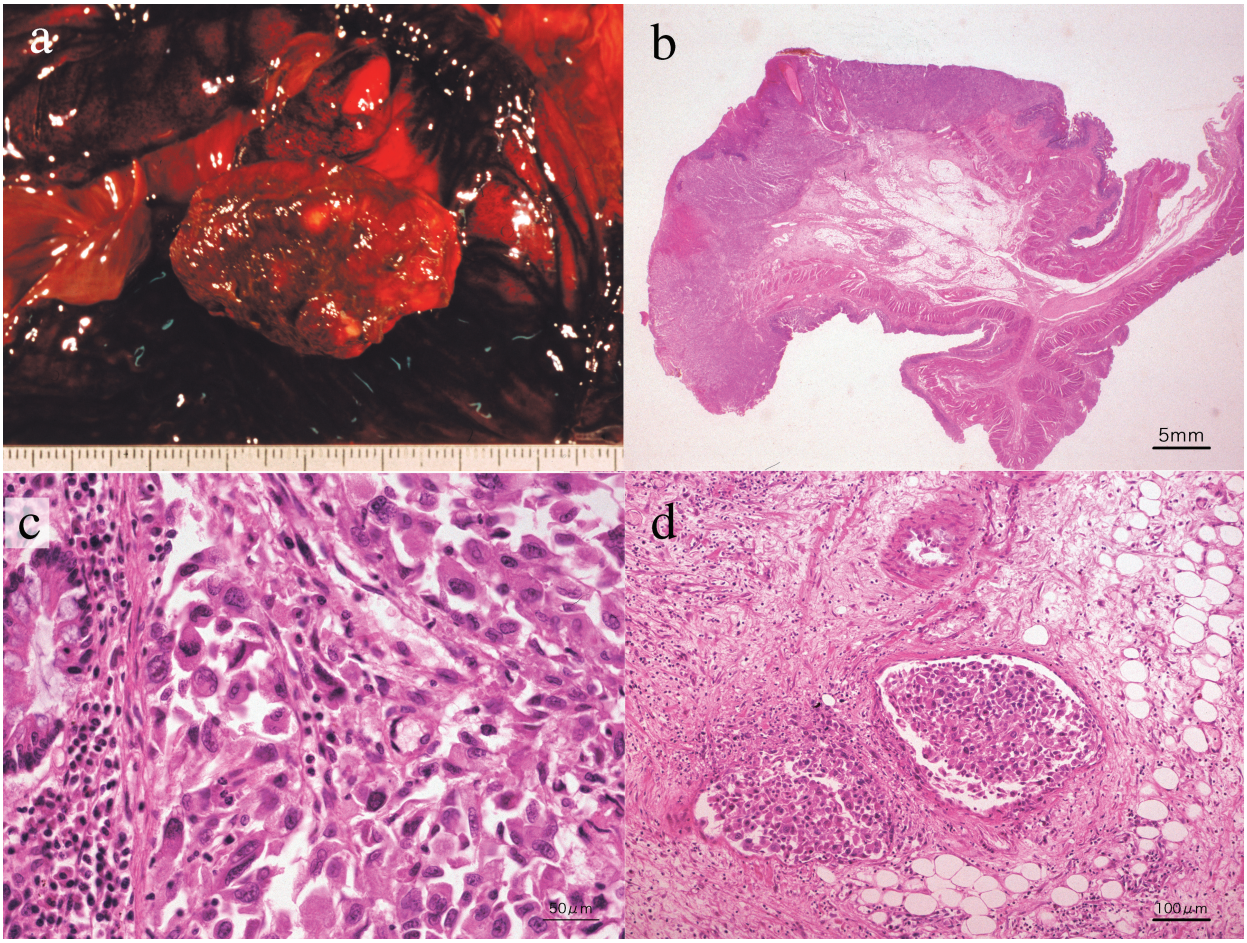

Figure 4. Gross specimen of a polypoid lesion in the ileum taken at autopsy (a). All of the other multiple lesions in the ileum were submucosal and ulcerative. Microscope image of the cut surface of the specimen (b). (Hematoxylin and eosin stain.) The pathological diagnosis was a poorly differentiated adenocarcinoma of the small intestine (c). Intravascular invasion is also seen (d).

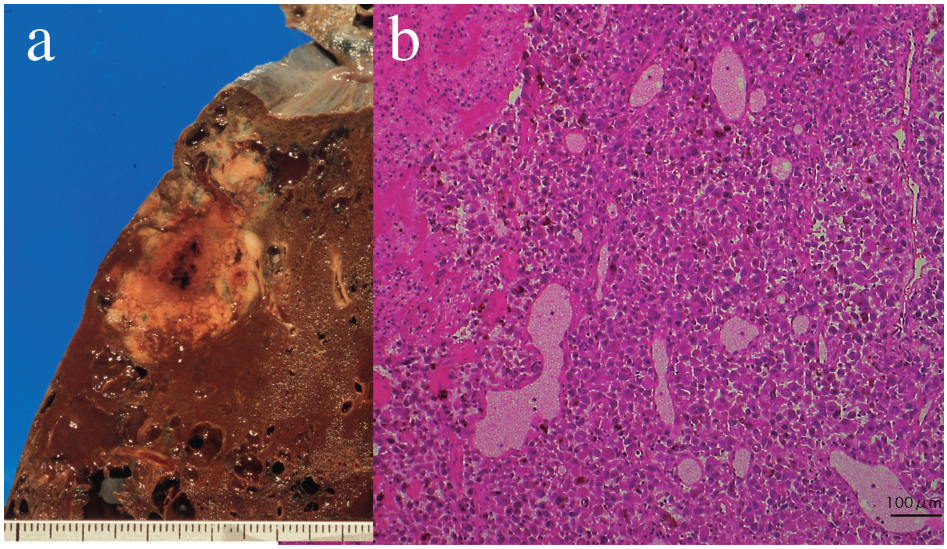

Figure 5. Gross specimen of the lung tumor (a). Macroscopically, the tumor margin is clear and surrounded by hemorrhagic lung tissue. Pathology reveals poorly differentiated adenocarcinoma tissue compressing the surrounding hemorrhagic alveolar structure, as shown in the left upper part of the figure (b).

the lung and the small intestinal lesions. This result confirmed that the disease was not primary lung cancer but an intestinal lesion.

Small intestine cancer (poorly differentiated adenocarcinoma) with multiple intramural and mesenteric lymph node metastases and a solitary pulmonary metastasis was finally diagnosed macroscopically, histopathologically, and immunohistochemically on the autopsy findings.

Discussion

In this case, the difficulty of preoperative diagnosis was due to the following reasons. 1) Clinically, small intestine cancer with a solitary lung metastasis is very rare. Primary lung cancer with small intestinal metastasis was more likely. 2) Although the occult blood test was positive, lack of abdominal symptoms and persistent bloody sputum from the lung tumor meant that exploration of the small intestine was delayed. 3) Because the lung tumor was bleeding and surrounded by inflammatory tissues, precise sampling was difficult by both bronchoscopy and needle biopsy. 4) Detection of all of the multiple intestinal lesions was difficult endoscopically and surgically, especially as the path of the digestive tract had been altered by repeated laparotomies. In addition, the main polypoid lesion and the other metastatic lesions were soft and difficult to be palpated during laparotomy.

Malignancy of the small intestine is rare, accounting for only 1-2% of malignant neoplasms in the gastrointestinal tract[1-3]. The major histological type is adenocarcinoma (40-50%). Other histological types include malignant lymphoma (approximately 15%; most cases are non-Hodgkin's lymphoma), sarcoma (15%, including gastrointestinal stromal tumors, commonly leiomyosarcoma), carcinoid (20%), and metastatic disease. In a Japanese autopsy series of 195092 cases, 3846 cases (1.97%) of small bowel malignancy were found. Of these, 453 (11.8%) were primary small bowel malignancy and 3393 (88.2%) were metastatic disease[4]. Primary small intestine carcinomas are located in the duodenum and jejunum more commonly than in the ileum. Synchronous or metachronous multiple occurrences in these sites are common.

We could find only one reported case of lung metastasis from primary small intestine cancer in Japanese literature[5]. Small intestine cancer is highly malignant, and patients may not survive long enough to develop clinically problematic lung metastases.

In contrast, lung cancer is one of the most common causes of cancer death in Japan. Common metastatic sites are lung, bone, liver, adrenal gland, and brain. Intestinal metastasis is likely to occur in the terminal stage of the disease; thus, metastatic lesions in the small intestine are rarely a clinical problem, especially if they are asymptomatic. In a series of Japanese lung cancer autopsy cases in 1990, 200 (5.0%) of 4019 had metastatic disease in the small intestine[6]. In another autopsy series, 10 (4.6%) of 218 non-small cell lung cancer patients had intestinal involvement[7]. However, as there has been recent rapid progress in chemotherapy for lung cancer, the number of the patients with intestinal metastasis is predicted to increase.

Most primary and metastatic small bowel cancers are thought to be asymptomatic, and detection of such small bowel neoplasms is extremely rare, according to the findings of a previous autopsy series[4]. Symptomatic cases are rare, but in both small intestine cancer[8] and intestinal metastasis of lung cancer[6,7,9-13], the common symptoms are non-specific, such as abdominal pain, vomiting, and nausea related to gastrointestinal bleeding, obstruction (intussusception), or perforation.

Diagnoses are usually made by macroscopic and histological findings from resected specimens obtained by surgical treatment. Preoperative diagnosis is difficult because the small intestine is difficult to access by endoscopy due to its anatomy, especially when the patient has a history of multiple laparotomies, as in our case. Even if the bleeding from a small intestine tumor is massive, detection of the site of hemorrhage is difficult when the bleeding is sporadic rather than continuous. Gastrointestinal bleeding scintigraphy using ^{99m}Tc-DTPA-HSA was useful in our case. However, it is still difficult to find the exact part of the intestinal lesion.

Double-balloon enteroscopy was useful in our case to detect multiple lesions in the small intestine. This technique is a recently developed diagnostic method that can explore deeply in the small intestine. Its usefulness in the examination of intestinal bleeding was reported recently[14,15]. However, with a surgically altered intestinal pathway, as in our case, total exploration of the small intestine would be difficult.

The pathological findings from the lung specimen suggested that the lung tumor was metastatic from small intestine cancer. Immunohistochemistry confirmed that the disease was of intestinal origin, with negative expression of TTF-1. TTF-1 is a sensitive marker for thyroid and pulmonary adenocarcinoma, and is useful in determining the origin of lung tumors[16,17]. In our case, the histopathological findings strongly suggested that the lung cancer was metastatic, and negative TTF-1 staining proved the diagnosis. Routine TTF-1 staining of bronchoscopically and/or surgically obtained specimens is needed in the diagnosis of lung tumors in patients with a history of gastrointestinal or colorectal cancer, or a positive occult blood test as in our case.

During the preoperative evaluation period, massive intestinal hemorrhage occurred, and the systemic status of the patient deteriorated progressively during further examination, resulting in death despite our efforts in the diagnosis and treatment of acute intestinal bleeding. Evaluation of the post-reconstruction intestine is another difficult problem, and advances in diagnostic methods are expected.

These difficulties in diagnosis could have led to a relative delay of treatment. However, considering the rapid progression of the disease and the patient's deterioration, and the presence of metastatic disease, the use of extended surgical treatment such as massive small bowel resection to control bleeding is doubtful. Without a definite histopathological diagnosis, chemotherapy would also have been problematic. Furthermore, the patient would have been at risk of perforation of the intestinal lesion during chemotherapy.

Acknowledgements

We thank Ms Yukiko Wakita for preparing this manuscript.

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