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Single Case

Duodenal Papillary Metastasis of Lung Cancer with Bleeding Controlled by Endoscopic Treatment and Systemic Osimertinib Therapy: Case Report

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Keywords
Duodenal papillary metastasis · Lung adenocarcinoma · Tumor hemorrhage · TTF-1

Abstract
Introduction: Solid organ malignancies rarely metastasize to the duodenal papilla. We describe a case of primary lung cancer with duodenal papillary metastasis in a patient who presented with melena. To the best of our knowledge, this is only the second report of duodenal papillary metastasis from lung cancer. ***Case Presentation:*** A 65-year-old woman presented with complaints of anorexia, weight loss, and black stool. Imaging studies led to a clinical diagnosis of stage IVB lung cancer, and anticoagulants were initiated to treat pulmonary artery thrombosis. However, endoscopic hemostasis was challenging because of bleeding from a duodenal papillary tumor. Fortunately, the patient was positive for the plasma epidermal growth factor receptor (EGFR) gene mutation, and osimertinib, an EGFR tyrosine kinase inhibitor, was administered, successfully achieving hemostasis. Subsequently, endoscopic ultrasonography-guided transbronchial needle aspiration of an enlarged mediastinal lymph node and duodenal papillary tumor biopsy confirmed duodenal papillary metastasis of the primary lung adenocarcinoma. ***Conclusion:*** Although duodenal papillary metastasis is extremely rare, a good clinical outcome was achieved in this case by considering duodenal papillary metastasis from lung cancer as the differential diagnosis and administering systemic osimertinib therapy.

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Introduction

Solid organ malignancies rarely metastasize to the duodenal papilla, with renal cell carcinoma (34%), malignant melanoma (31%), and breast cancer (13%) being the most commonly implicated tumors [1]. To our knowledge, only 1 case of duodenal papillary metastasis from lung cancer has been reported in the English literature [2]. Here, we report a case of primary lung cancer with duodenal papillary metastasis in a patient who presented with melena complicated by right pulmonary artery thrombosis. In this educational case, refractory bleeding from a duodenal papillary tumor posed a treatment dilemma; however, hemostasis was achieved through endoscopic intervention and systemic therapy by differentiating duodenal papillary metastasis from lung cancer.

Case Report

A 65-year-old woman with anorexia, weight loss, and black stools visited her primary care physician. She was referred to our hospital for assessment of malignancy because of a high carcinoembryonic antigen level (659.2 ng/mL) and abdominal ultrasonography revealing a dilated common bile duct and multiple liver masses. She had a history of hypertension, dyslipidemia, and smoking (0.5 pack-years). Blood test results revealed anemia (hemoglobin, 8.2 g/dL) and increased coagulation/fibrinolysis (fibrin degradation products, 60.3 μg/mL; D-dimer, 21.7 μg/mL), although liver function tests were normal. Carcinoembryonic antigen (458.0 ng/mL), sialyl Lewis-x antigen (170.0 U/mL), cytokeratin 19 fragment (4.8 ng/mL), gastrin-releasing peptide (proGRP, 138.0 pg/mL), and nerve-specific enolase (24 ng/mL) levels were high; however, squamous cell carcinoma-associated antigen and carbohydrate antigen 19–9 levels were within normal limits.

Thoracic and abdominal contrast-enhanced computed tomography (CT) revealed a 34-mm spiculated lesion in the lower S6 lobe of the right lung, an irregular mass with pleural depression, suspected multiple metastases in the bilateral lungs, multiple lymph node metastases in the contralateral mediastinum and upper abdomen, multiple liver metastases, and bilateral adrenal metastases. Additional CT findings included right pulmonary artery involvement due to right hilar lymph node metastasis and multiple peripheral pulmonary artery thrombi showing poor contrast (shown in Fig. 1a, b). Duodenal papillary swelling, a dilated common bile duct, and an enlarged gallbladder were also observed (shown in Fig. 2a). Contrast-enhanced magnetic resonance imaging of the head showed multiple brain metastases. Therefore, the condition was diagnosed as lung cancer cT4N3M1c, stage IVB. Anticoagulation with calcium heparin was initiated to treat the pulmonary artery thrombi.

Upper gastrointestinal endoscopy (GIF-H290T; Olympus Medical Systems, Tokyo, Japan) performed to investigate anemia and melena revealed a mass lesion with fresh blood in the duodenal papilla. Side-viewing duodenoscopy (TJF-Q290V; Olympus Medical Systems, Tokyo, Japan) showed exudative bleeding on the cranial side of the ulceration (shown in Fig. 2b), which was endoscopically treated using clipping (SureClip; MC Medical, Tokyo, Japan) and application of PuraStat® (3D Matrix, Tokyo, Japan) (shown in Fig. 2c). Due to concerns about rebleeding from the duodenal papillary tumors, heparin calcium was discontinued.

Unfortunately, melena was observed again 3 days after the endoscopic hemostasis was achieved. Blood test results showed no worsening of anemia, but white blood cell count, total bilirubin, and aspartate transaminase/alanine transaminase levels were 16,500/μL, 3.8 mg/dL, and 385/258 IU/L, respectively, indicating obstructive jaundice and moderate acute cholangitis according to the Tokyo Guidelines 2018 criteria [3]. Endoscopic assessment using duodenoscopy revealed exudative bleeding on the inferior side of the ulcer at the duodenal

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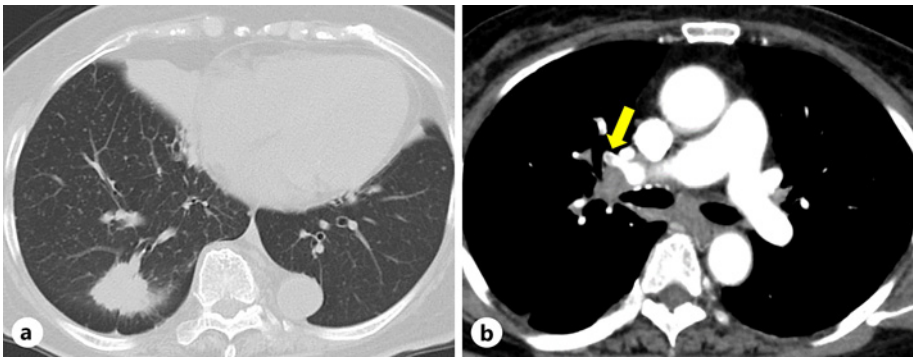

Fig. 1. CT. **a** Image showing a 34-mm spiculated lesion in the S6 lower lobe of the right lung with pleural depression. **b** Image showing right pulmonary artery involvement and multiple pulmonary artery thrombi (arrow) due to right hilar lymph node metastasis.

papilla (different from the site of the previous bleeding), which was treated with clipping. Subsequently, endoscopic treatment of the obstructive jaundice and acute cholangitis was attempted, but transpapillary bile duct cannulation was unsuccessful because the mass obstructed the bile duct orifice. Thereafter, bile duct cannulation was achieved by precut fistulotomy performed using a needle knife, and a fully covered biliary stent (10 mm diameter, 6 cm long, BONASTENT; Medico's Hirata, Osaka, Japan) was successfully placed for bile drainage (shown in Fig. 2d, e), thus improving obstructive jaundice and acute cholangitis.

Meanwhile, the patient tested positive for the epidermal growth factor receptor (EGFR) gene mutation (exon 19 deletion) on plasma EGFR gene mutation analysis. Based on this information, we considered that the ulcerated lesion in the duodenal papilla was due to metastasis from non-small-cell lung cancer (NSCLC) with the EGFR exon 19 deletion and that administration of systemic therapy for NSCLC could result in hemostasis. Hence, osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), was initiated 4 days after the initial hemostasis by upper gastrointestinal endoscopy, despite the lack of a histopathological diagnosis.

After confirming that the clinical symptoms had stabilized on day 7 since starting EGFR TKI, endoscopic ultrasonography-guided transbronchial needle aspiration (BF-UC290F; Olympus, Tokyo, Japan) was performed on the mediastinal lymph nodes. The analysis revealed adenocarcinoma by hematoxylin and eosin staining, thyroid transcription factor-1 (TTF-1), and napsin A positivity by immunohistochemistry (shown in Fig. 3a–c); this confirmed the diagnosis of primary lung adenocarcinoma.

After confirming the absence of rebleeding on day 9 since EGFR TKI initiation, a biopsy was performed on the duodenal papillary tumors (shown in Fig. 2f). The biopsy results showed adenocarcinoma by hematoxylin and eosin staining and TTF-1 and AE1/AE3 positivity by immunohistochemistry (shown in Fig. 3d–f). The final diagnosis was duodenal papillary metastasis from primary lung adenocarcinoma.

Twenty-one months after initiating EGFR TKI, no rebleeding from the duodenal papillary metastasis was observed. Both primary tumor and metastases had radiological responses on CT, the right peripheral pulmonary artery thrombi were absent on sequential imaging indicating treatment response, and the patient was still receiving EGFR TKI for lung adenocarcinoma. The CARE Checklist has been completed for this case report and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537778).

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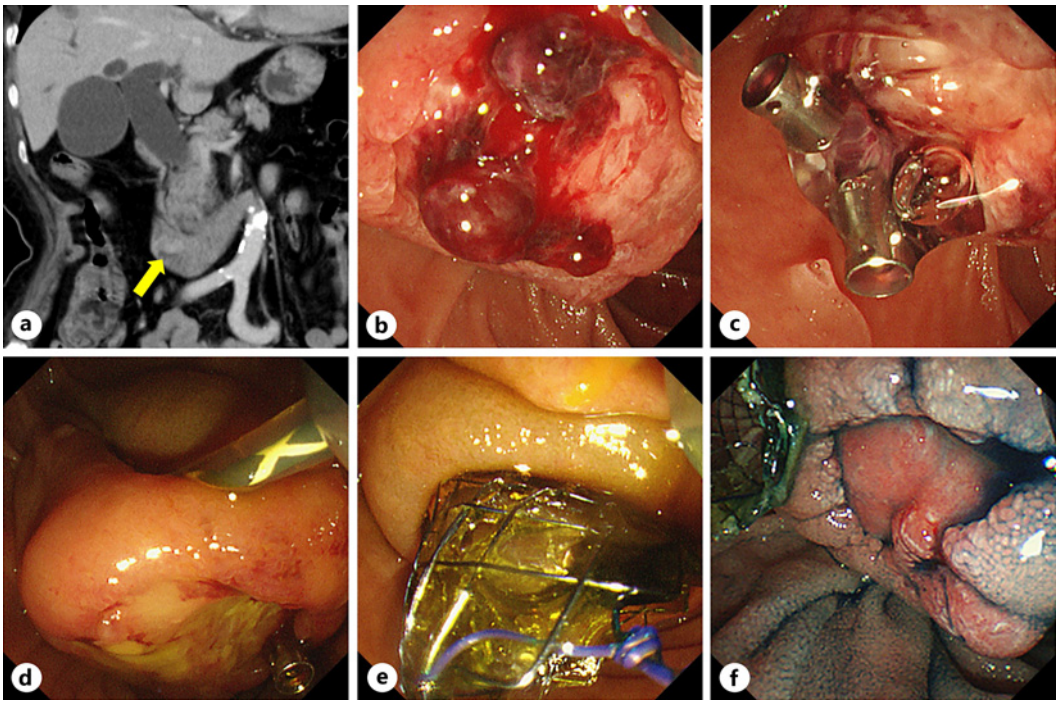

Fig. 2. CT, esophagogastroduodenoscopy, and endoscopic retrograde cholangiopancreatography (ERCP). **a** CT showing an enlarged duodenal papilla (arrow) and gallbladder and a dilated common bile duct. **b** Esophagogastroduodenoscopy showing an ulcerated lesion on the main duodenal papilla with exudative bleeding from the cranial side of the ulcer base. **c** Endoscopic hemostasis is performed with clipping and PuraStat® application. **d**, **e** In ERCP, precut fistulotomy is performed on an oral ridge that appeared to be a dilated bile duct, and bile outflow is confirmed. Images of successful endoscopic biliary drainage with fully covered self-expandable metallic stent. **f** Dye endoscopy with indigo carmine, 9 days after EGFR TKI initiation, clearly showing an ulcerated tumor in the main duodenal papilla without bleeding.

Discussion

Lung cancer can often result in distant metastasis to the nervous system, bones, liver, and adrenal glands (reported metastasis rates of 39%, 34%, 20%, and 8%, respectively) [4]. However, the number of reported cases of biliary metastasis of lung cancer is low [5], and notably, this is only the second documented instance of duodenal papillary metastasis in the English literature [2].

In a previous report summarizing secondary duodenal papillary metastases, tumors from renal cell carcinoma, malignant melanoma, and breast cancer accounted for approximately three-quarters of all primary metastases. Secondary duodenal papillary metastases are often heterochronous. The average time to reveal duodenal papillary metastasis with renal cell carcinoma (most frequent primary tumor), malignant melanoma, and breast cancer (second-most frequent) is approximately 8.8, 2.5, and 2.5 years, respectively. Furthermore, among duodenal papillary metastases of malignant tumors, only 38% of all cases have a single metastasis and 62% of cases have duodenal papillary metastases as one of the systemic metastases. The physiological reason for metastasis to the duodenal papillary region is not clear, but the prognosis in terms of survival after the diagnosis of duodenal papillary metastasis is poor [1]. In the present case, distant metastases to the liver, adrenal gland, and brain were present at the time of NSCLC diagnosis, and concurrent metastasis to the duodenal papilla was also detected. However, the response to systemic therapy for NSCLC was favorable.

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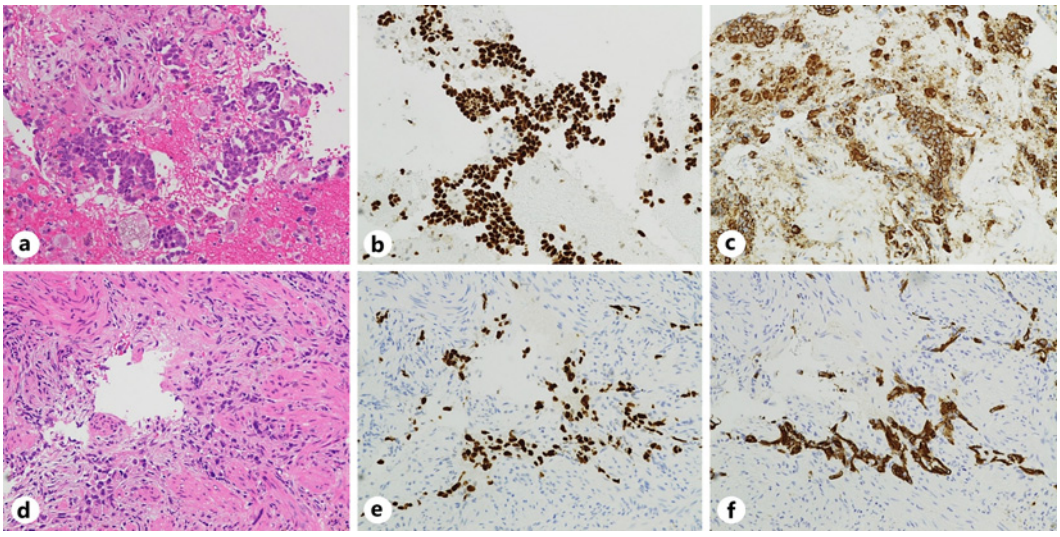

Fig. 3. Hematoxylin and eosin staining of biopsy of mediastinal lymph nodes showing adenocarcinoma (**a**: ×200). Immunohistochemistry showing tumor cells positive for TTF-1 (**b**: ×200) and napsin A (**c**: ×200). Hematoxylin and eosin staining of the duodenal papillary tumor biopsy showing adenocarcinoma by histopathological analysis (**d**: ×200). Immunohistochemistry showing tumor cells positive for TTF-1 (**e**: ×200) and AE1/AE3 (**f**: ×200).

TTF-1 is a gene regulatory protein found in the thyroid, lungs, and brain [6]. In normal lung tissue, it maintains homeostasis by promoting transcription of surfactant protein genes in type II alveolar cells and club cells [7]. TTF-1 is a highly specific marker for adenocarcinoma of lung origin, with a sensitivity of 54–75% and specificity of 97–100% [8]. It is useful for differentiating adenocarcinomas of lung origin from those arising from non-lung sites [9]. In this case, biopsy specimens from the mediastinal lymph node and duodenal papillary tumors were positive for TTF-1, leading to the diagnosis of duodenal papillary metastasis from primary lung adenocarcinoma.

Selective biliary cannulation was unsuccessful at the time of the initial endoscopic retrograde cholangiopancreatography before the onset of cholangitis. Therefore, precut fistulotomy was chosen at the onset of moderate cholangitis and bile duct cannulation, and the patient was treated with endoscopic biliary stenting. However, bleeding from duodenal papillary tumors was a clinical problem in our case. In a previous report, 33% of patients with primary cancer of other organs with duodenal papillary metastasis had bleeding from duodenal papillary tumors [1]. In situations where concomitant antithrombotic drugs for pulmonary artery thrombosis are desirable, as in the present case, the risk of tumor bleeding increases further [10]. Therefore, the risk-benefit balance should be analyzed, taking measures such as discontinuing anticoagulants, devising endoscopic hemostatic procedures, and therapeutic intervention for the primary cancer.

PuraStat®, a novel self-assembling peptide hemostatic hydrogel, is an effective and safe rescue therapy for acute upper and lower gastrointestinal bleeding, including tumor bleeding [11]. It is also used as a prophylaxis for bleeding after endoscopic mucosal resection and submucosal dissection [12], not only in the field of surgery but also in gastrointestinal endoscopy. In our case, the bleeding was temporarily treated hemostatically using clipping and PuraStat®. However, 3 days later, despite discontinuing anticoagulant therapy, the patient experienced duodenal papillary tumor rebleeding. The reason for the lack of effect on tumor hemorrhage in this case is unknown.

Although no diagnosis was made initially as to whether the duodenal papillary tumors were caused by distant metastasis from lung cancer, EGFR TKI was introduced early presuming that treating lung cancer with EGFR mutation-positive tumors could potentially reduce bleeding from the papillary duodenal tumor. Subsequently, both primary lung tumors and metastases decreased in size, and no recurrence of bleeding was observed.

Although extremely rare, we encountered a case in which bleeding from a duodenal papillary metastasis of lung cancer was stopped by early therapeutic intervention. A good clinical outcome was achieved, citing duodenal papillary metastasis as the differential diagnosis.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethics approval was not required in accordance with our national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Taiyo Hirata and Shinya Kawaguchi made substantial contributions to the study concept, data analysis, and interpretation. Taisuke Akamatsu, Atsuko Inagawa, Tomoki Hikichi, Kohei Ohkawa, Kazuhisa Asahara, Tatsunori Satoh, Shinya Endo, Makoto Suzuki, and Kazuya Ohno drafted the manuscript and revised it critically for important intellectual content. Taiyo Hirata, Shinya Kawaguchi, Taisuke Akamatsu, Atsuko Inagawa, Tomoki Hikichi, Kohei Ohkawa, Kazuhisa Asahara, Tatsunori Satoh, Shinya Endo, Makoto Suzuki, and Kazuya Ohno approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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