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Case Report

Concomitant Primary Lung Cancer and Metastatic Pulmonary Colorectal Cancer that Responded to Gemcitabine/Cisplatin/ Bevacizumab Combination Therapy

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Abstract.

The incidence of double primary malignancy in colorectal cancer is rare (approximately 1-6%), and synchronous double primary malignancy is even rarer for cases involving colorectal cancer. Indeed, its incidence is estimated to be less than 1%. The probability of concurrent colorectal cancer and lung cancer, in particular, is extremely low (approximately 0.1%). In this report, we present such a case of synchronous primary lung cancer and pulmonary metastatic colorectal cancer, which was mistaken for primary lung cancer with lung-to-lung metastasis. Tumors were identified in the upper and lower lobes of right lung. After the patient received a lung cancer chemotherapy, gemcitabine/cisplatin/bevacizumab, the right upper lobe tumor was stable in size, and the right lower lobe tumor regressed. Surprisingly, the right lower lobe tumor was proven to be metastatic colorectal cancer after surgical resection. A primary rectal tumor was then identified through colonoscopy. Subsequently, the patient underwent surgical resection of the primary rectal cancer and chemotherapy. She has now remained disease-free for more than two years.

Keywords **:** bevacizumab, colorectal cancer, double primary cancer, gemcitabine, lung cancer

病例報告

併存原發性肺癌及轉移性結腸直腸癌在接受 Gemcitabine/Cisplatin/ Bevacizumab 治療後獲得改善

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中文摘要

結腸直腸癌相關之雙重惡性腫瘤發生率約為百分之一至六，而同時產生結腸直腸癌及另一原發性惡性腫瘤的發生率更是少於百分之一，其中同時合併原發結腸直腸癌以及肺癌約為百分之零點一。在這篇文章裡，我們呈現一位罕見病例同時產生原發性肺癌以及肺部轉移性結腸直腸癌；起初腫瘤位於肺部右上葉及右下葉，在經過 gemcitabine/cisplatin/bevacizumab 合併之化學治療後，右上葉腫瘤為穩定狀態而右下葉腫瘤明顯縮小，術後切片證實右下葉腫瘤為轉移性腺癌，並經結腸鏡檢查證實為直腸癌合併肺轉移。病患接受原發直腸癌切除術併化學治療後， 超過兩年仍無病存活。

***關鍵字*:** bevacizumab、結腸直腸癌、雙重惡性腫瘤、gemcitabine、肺癌

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide [1]. After treating CRC with curative resection, the liver is the most common site of metastatic recurrence, followed by the lungs [2]. Pulmonary metastases of CRC usually present as multiple tumors; however, approximately 10% consist of a solitary pulmonary nodule [3]. For patients who have a solitary pulmonary nodule, surgical resection and subsequent pathological examination of the tumor may be necessary to distinguish metastatic CRC from primary lung cancer, because the therapeutic strategies for these diseases are different. In rare cases, however, patients may developed synchronous CRC and lung cancer [4-6]. Here we report a case with concomitant primary lung cancer and metastatic pulmonary CRC, which responded to gemcitabine/cisplatin/bevacizumab combination therapy.

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CASE REPORT

A 48-year-old woman began to suffer from a cough with scanty sputum in May 2007. She had never smoked and had no known family history of cancer. The patient visited a local hospital where a computed tomography (CT) scan of the chest showed two tumors: one in the right upper lobe (RUL) and the other over the right lower lobe (RLL) (Figure 1A,1B). CT guided-biopsy of the RLL tumor revealed adenocarcinoma. However, immunohistochemical (IHC) stain was not done. She was referred to our hospital with a suspected diagnosis of primary lung cancer with lung-to-lung metastasis.

In our hospital, another CT scan of the chest revealed one nodular lesion of the RUL 0.5 x 0.5 cm in size and the other mass lesion of the RLL 4.4 x 4.2 cm in size. The carcinoembryonic antigen (CEA) was 4.3 ng/ml (normal range: < 5 ng/ml). Treatment was given under the diagnosis of primary lung adenocarcinoma with lung-to-lung metastasis【clinical stage: T2N0M1, American Joint Committee on Cancer (AJCC), 6th edition】, and she received a regimen of gemcitabine/cisplatin/bevacizumab (cemcitabine: 1250 mg/m^2 on day 1 and day 8; cisplatin: 80 mg/m^2 on day 1; and bevacizumab: 7.5 mg/kgw on day 1; GCB-G regimen) every three weeks for four courses.

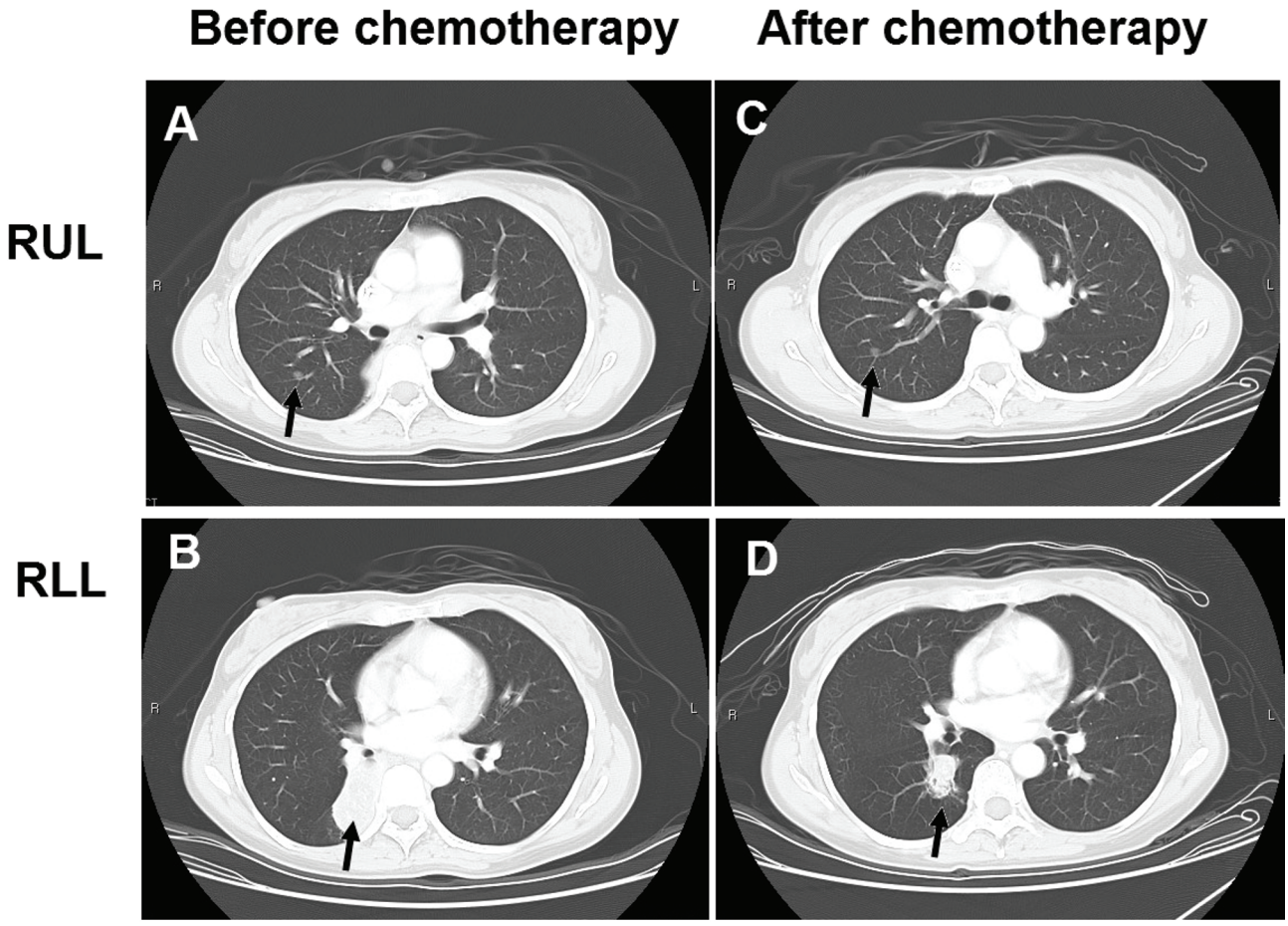

Figure 1. CT scan of chest before (A,B) and after (C,D) chemotherapy. Arrows indicate the tumor. Significant regression was seen in RLL tumor after chemotherapy. RUL: right upper lobe, RLL: right lower lobe

Subsequently, a CT scan showed no change in the RUL tumor and regression of the RLL tumor (Figure 1C,1D). The size of the RLL tumor decreased to 2,1 x 1 cm. Thereafter, she received video-assisted thoracoscopic surgery (VATS) for wedge resection of the RUL nodule and RLL lobectomy with lymph node dissection. No tumor cells could be found in the lymph node samples. IHC stains of the RUL nodule were positive for cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1), and negative for cytokeratin 20 (CK20) and caudal type homeobox 2 (CDX2) (Figure 2, right lane). These findings were consistent with a primary adenocarcinoma. In contrast, IHC stains of the RLL tumor revealed an opposite pattern (Figure 2, left lane), suggesting metastatic CRC [7-9]. Consequently, the patient underwent a colonoscopy, which revealed an annular tumor of the rectum, 10 cm from the anal verge. Examination of the biopsy specimen indicated rectal adenocarcinoma.

The patient then underwent a laparoscopic low anterior resection in December 2007. The final pathological staging of the rectal cancer was pT3N1M1. AJCC 6th edition. *KRAS* sequencing revealed a mutation in codon 12. Because fluorouracil (5-FU) based regimen was still a main therapy in metastatic CRC, she received combination chemotherapy consisting of FOLFOX (fluorouracil (5-FU), leucovorin (LV), and oxaliplatin). FOLFOX was administered for 11 courses between January and July 2008.

Subsequently, the disease recurred on two separate

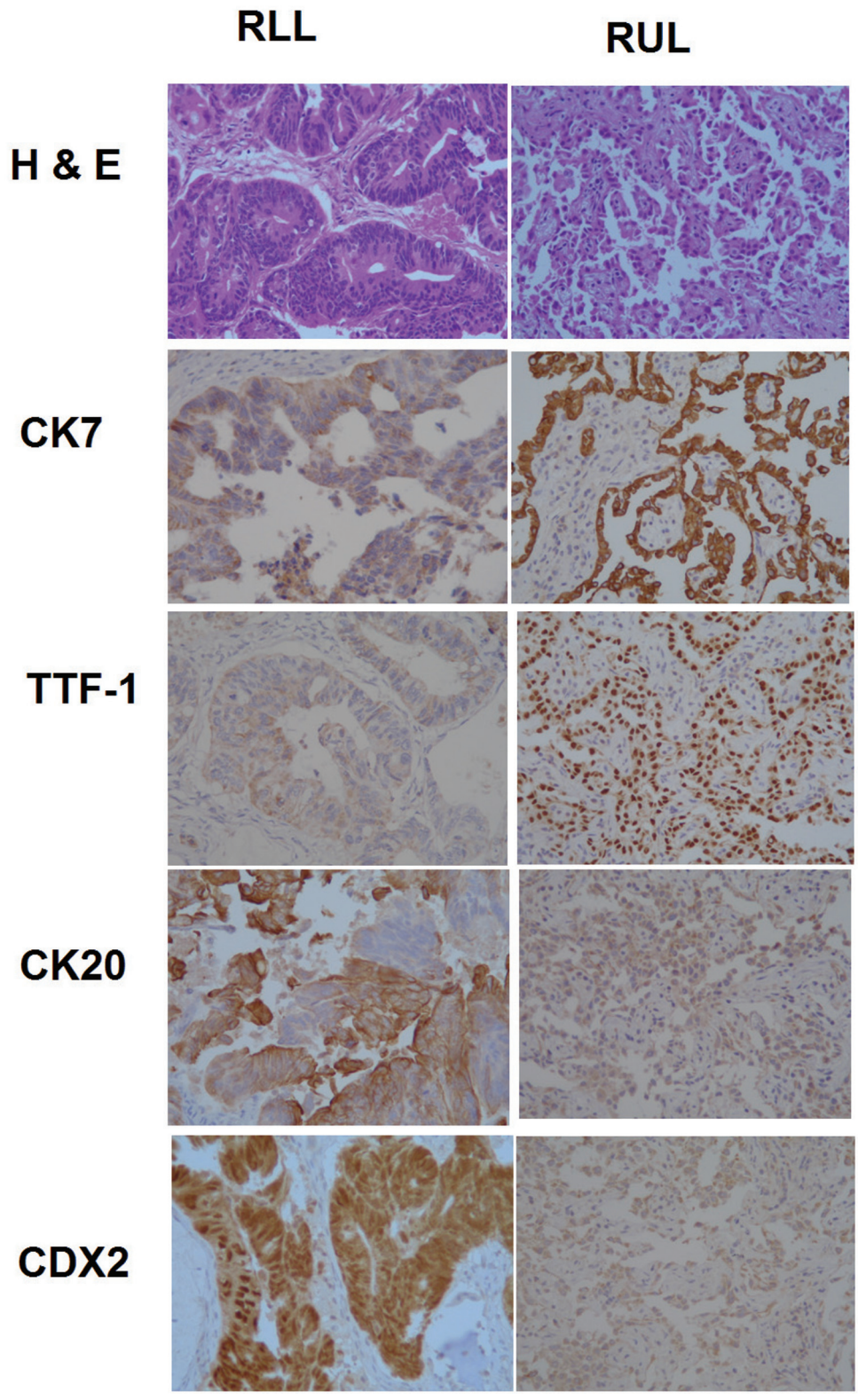

Figure 2. H&E and IHC staining of right lower lobe (left lane) and upper lobe (right lane) tumors. Complete opposite patterns were noted. RUL: right upper lobe, RLL: right lower lobe. H&E : Hematoxylin and eosin stain; CK7: cytokeratin 7; TTF-1: thyroid transcription factor-1; CK20: cytokeratin 20; CDX2: caudal type homeobox 2

occasions. The first recurrence became evident in October 2010, when a newly developed nodular lesion was found in the RUL of the lung. The patient received VATS with wedge resection of the RUL tumor in December 2010. Pathological examination indicated metastatic CRC. She then received 12 cycles of chemotherapy, consisting of an LV, 5-FU, and irinotecan (FOLFIRI) regimen, which was followed by capecitabine maintenance therapy. The second relapse occurred in April 2013, when CT scanning revealed another tumor in the RUL. VATS with wedge resection of the RUL tumor was performed in May 2013. Pathological examination also indicated metastatic CRC. Currently the patient is receiving bevacizumab plus mFOLFOX6 therapy.

DISCUSSION

Double primary malignancy (DPM) is not unusual in cases that involve CRC. Yu et al. analyzed more than 2000 cases of CRC in which the patients underwent curative resection. Of these patients, 145 (6.4%) developed DPM during follow-up [5]. On the other hand, two large case series from Taiwan (each of which included more than 1000 cases) found DPM in less than 2% of cases involving primary CRC [6,10]. Synchronous DPM and CRC is even rarer, with an estimated incidence of less than 1% [5,6]. For CRC, the common sites of the other primary malignancy include the stomach, lung, urinary system, and liver [5,6]. The incidence of concurrent CRC and lung cancer, in particular, is only 0.1% [5]. Therefore, this combination may easily be overlooked because of its rarity.

How to detect the hiding secondary malignancy in time is therefore an important issue. Quint et al suggested some methods to distinguish a primary lung cancer from metastasis from other sites [11]. One of the methods is radiological morphology. With a smooth margin, the nodular lesion is more likely to be benign or metastatic. In contrast, the diagnosis may be a primary lung cancer if the nodule has an irregular or blurred margin. As to our patient, the lesion of the RUL showed an irregular margin, and the one of the RLL a regular margin on the CT. Therefore, the radiological finding of our patient appeared to be compatible with the conclusion of Quint et al.

It is quite challenging to treat patients who have concurrent double primary malignancies. Surgical excision is always an option, if both diseases are confirmed to small areas. For CRC with pulmonary metastases, several studies have also shown that surgical resection of the lung metastatic tumors can greatly improve patients' long-term survival to 20-30% [12-14]. However, chemotherapy should be considered for advanced disease and patients who are not suitable enough for surgery. Kaneki et al. reported a case with concurrent non-small cell lung cancer (NSCLC) and CRC, which was successfully treated using irinotecan in combination with cisplatin [15]. However, we treated our patient with a GCB-G protocol, because we thought that her cancer was a lung adenocarcinoma only. The gemcitabine-cisplatin (GC) doublet has been demonstrated to be efficacious for locally advanced NSCLC [16], and the combination of GC with bevacizumab has also been shown to improve progression-free survival for patients with metastatic NSCLC [17]. Therefore, this combination was a reasonable made of treatment for our patient. Surprisingly, the metastatic CRC tumor showed a good response to this regimen. In combination with chemotherapy, bevacizumab has been used to treat advanced CRC with considerable efficacy [18]. However, a few studies have suggested that the GC doublet is an effective regimen for CRC. In a pre-clinical study, the combination of gemcitabine with oxaliplatin or cisplatin was effective in suppressing the growth of colon cancer cell lines although the cytotoxic effects of GC were worse than gemcitabine-oxaliplatin combination [19]. Additionally, in a phase II trial, 19 patients who failed first-line 5-FU-based regimens received 5-FU plus LV followed by GC as a second-line treatment. Although a partial response was achieved in only one

patient (5%), stable disease status was maintained in eight (42%) [20]. In this study, the GC doublet had only modest activity for pre-treated advanced CRC. Therefore, in our case, the efficacy of GCB-G regimen may have greatly contributed to gemcitabine and the combination with bevacizumab.

In summary, we have reported an unusual case of concurrent primary lung cancer and pulmonary metastatic CRC. Moreover, the metastatic CRC tumor showed an unexpectedly good response to a GCB-G regimen, suggesting that this lung cancer chemotherapy regimen may have potential for treating CRC. However, because of its modest effects and lack of large randomized controlled trials, we still recommend this regimen as a salvage therapy after the failure of 5-Fluorouracil, oxaliplatin or irinotecan-based chemotherapy. Our patient has now remained disease-free for over two years after surgical resection of both the metastatic and primary rectal tumors, followed by chemotherapy. Biopsy and detailed immunohistochemical staining are necessary for correctly diagnosing lung tumors.

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