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Colorectal Cancer With Multiple Metachronous Metastasis Achieving Complete Remission 14 Years After Surgical Resection: Report of a Case

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A 63-year-old man underwent a colectomy for sigmoid colon cancer in 1997. The upper lobe of his left lung and his left adrenal gland were resected because of metachronous metastases, 7 and 10 years after the initial surgery, respectively. Recurrence of metastases to the middle lobe of the right lung and left adrenal gland were sequentially detected in 2007, and a multimodal therapy, consisting of the combination of radiotherapy and chemotherapy, was conducted since 2007. The chemotherapy included drugs such as FOLFOX, FOLFIRI, bevacizumab, capecitabine, and cetuximab. In 2011, the complete response of all metastatic lesions could be achieved, and no recurrence was detected for more than 1 year. In spite of repeated recurrences, by the combination of surgical resection, chemotherapy, and radiotherapy, the complete response could be achieved 14 years after the initial surgical resection, which can be attributed to the development of new treatment modalities and new agents for colorectal cancer.

Key words: Colorectal cancer – Multimodal treatment – Long-term survival

Worldwide, colorectal cancer is the third most commonly diagnosed cancer in men and the second in women, causing about 61,000 deaths every year.[1] In recent decades, great progress has been achieved in the management of colorectal cancer, especially on the development of new chemotherapeutic agents. The combination therapy of 5-fluorouracil (5-FU) and leucovorin, which was developed in 1987, greatly contributed for the improvement of the treatment (5-FU alone versus 5-FU/ leucovorin; 10%–11% versus 26%–48%, respectively).[2,3] In 2000, the effectiveness of oxaliplatin or irinotecan for the treatment of colorectal cancer have been demonstrated. Molecular target drugs, such as bevacizumab, cetuximab, and panitumumab, have been developed in addition to oral anticancer drugs such as tegafur, fluorouracil, and capecitabine. As a result, the response rate was

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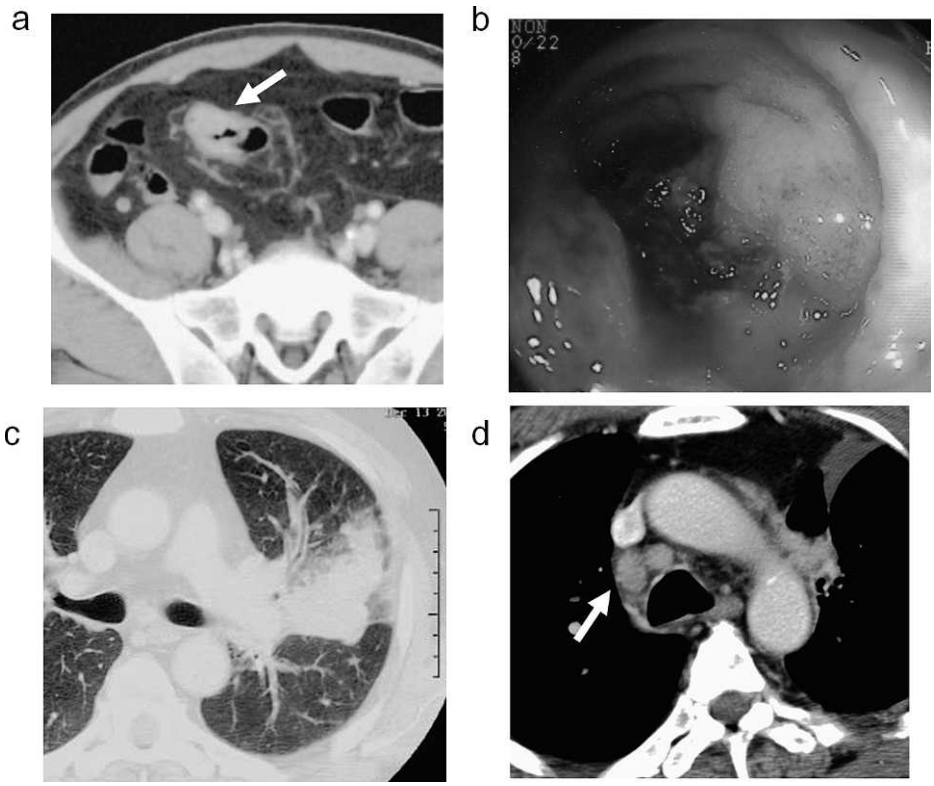

Fig. 1 Computed tomography (CT) scan (a) and endoscopic findings (b) of primary tumor. Left lung metastasis was detected in 2004 (c) and the mediastinal lymph node metastasis in 2005 (d).

significantly improved, reaching up to 46.9%, and the complete response to chemotherapy or chemoradiotherapy could be achieved in some patients.[4,5]

Here, we report a case of a 63-year-old man with sigmoid colon cancer in whom complete remission was achieved 14 years after the initial surgical resection of the primary cancer, and the subsequent control of the repeated metastatic recurrences by multimodal treatments.

Case Report

A 63-year-old man, diagnosed with well-differentiated adenocarcinoma of the sigmoid colon (Fig. 1a and 1b), presented to our surgical department for the surgical treatment. The preoperative laboratory data, including the serum level of carcinoembryonic antigen (CEA) (4.3 ng/mL), showed no abnormality. A sigmoid colectomy with a regional lymph node resection was performed in November 1997, and the histology revealed a well-differentiated adenocarcinoma perforating to the visceral peritoneum. No apparent distant metastasis was detected in the preoperative computed tomography (CT) or in intraoperative macroscopic examination, but the histologic examination revealed metastatic involvement in 2 of 13 dissected lymph nodes. The final stage was T4aN1bM0 stage IIIB according to Union for International Cancer Control. After surgical treatment, oral adjuvant chemotherapy (5-FU) was given for 2 years. During the 7-year follow-up, no recurrence occurred.

Seven years (December 2004) after the initial operation, an abnormal shadow was detected in the upper lobe of his left lung, and with the diagnosis of primary lung cancer (Fig. 1c), a left upper lobectomy was indicated. The histologic examination, however, revealed metastatic adenocarcinoma from the previously resected sigmoid colon cancer. Thus, the adjuvant chemotherapy, consisting of tegafur-uracil and leucovorin, was given for 3 months.

In March 2005, the CT scan revealed lymph node metastases in the mediastinum (Fig. 1d), and radiation therapy (50 Gy/25 Fr) was chosen as the treatment modality. The mediastinal metastatic lesion completely regressed with the radiation

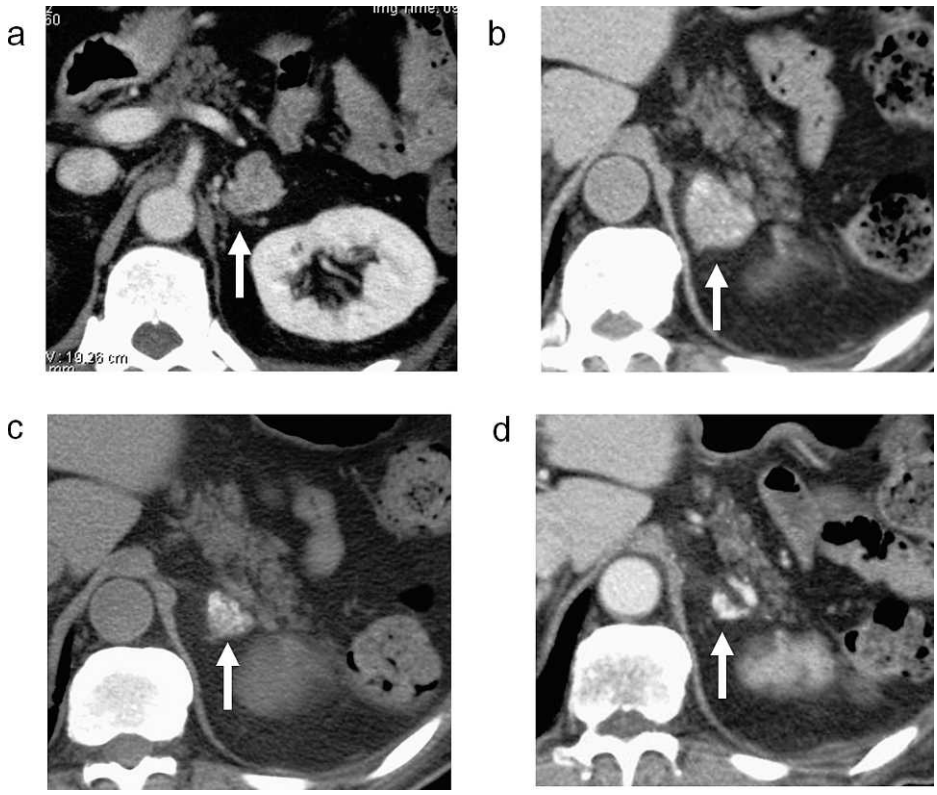

Fig. 2 Computed tomography (CT) scan of left adrenal gland. (a) Left adrenal gland metastasis was detected in 2007. (b) Regrowth of the resected adrenal metastasis in 2008. (c) Cetuximab therapy achieved significant reduction of metastasis in 2010. (d) The tumor was replaced by calcification after radiotherapy in 2011.

therapy, which was considered a complete response. Additional adjuvant chemotherapy with TS-1 (tegafur, gimeracil, and oteracil potassium) was given for 1 year.

In July 2007, significant elevation of the serum CEA level (96.1 ng/mL) was observed, and the CT scan revealed a metastatic lesion in the left adrenal gland (Fig. 2a). The left adrenal gland was resected, and the histologic examination confirmed metastatic adenocarcinoma of colorectal cancer.

In November 2007, recurrent metastasis in the middle lobe of the right lung was detected, with concomitant elevation of the serum CEA level (14.8 ng/mL) (Fig. 3a). Because of respiratory function impairment, dependent on the previous left upper lobectomy and the mediastinal irradiation, the systemic chemotherapy was chosen as the subsequent treatment modality. Although partial regression of the lung metastatic tumor could be achieved with FOLFOX (Fig. 3b), but in November 2008, stump recurrence of left adrenal gland was diagnosed (Fig. 2b), and the treatment regimen was changed to FOLFIRI. Thereafter, in November 2009, the stereotactic body radiation (48 Gy/4 Fr) of the right lung was indicated for the control of the progression of the lung metastatic lesion. The patient developed radiation-associated pneumonitis in the left middle lobe, which finally progressed to complete atelectasis of the middle lobe, making difficult the analysis of the metastatic tumor (Fig. 3c). The subsequent sequential treatment of the left adrenal gland metastasis with bevacizumab, capecitabine, and cetuximab resulted in only partial response. Unfortunately, complete response could not be achieved by the single use of each of these drugs (Fig. 2c). The changes of the patient's serum CEA level during the whole treatment period and the available systemic chemotherapeutic agents with the corresponding periods are shown in Fig. 4. In July 2011, the stereotactic body radiation therapy (48 Gy/4 Fr) was indicated for the treatment of the metastatic lesion of the left adrenal gland. The serum CEA level normalized after the radiation and the recurrent tumor of the left adrenal gland was

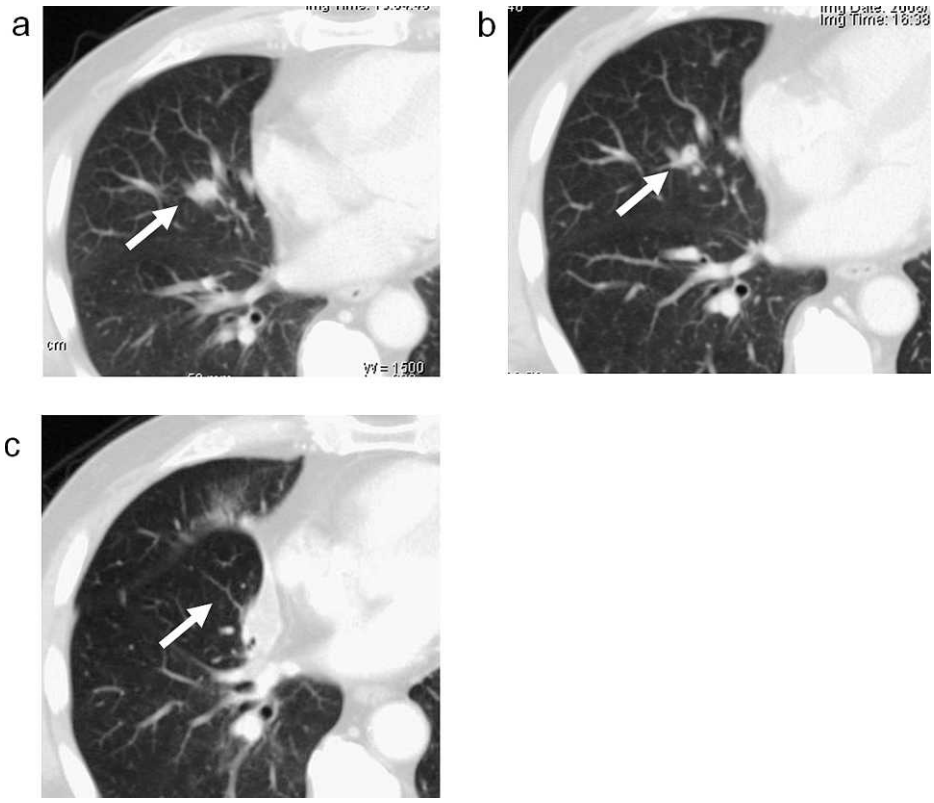

Fig. 3 Computed tomography (CT) scan of the right lung. (a) Right lung metastasis was diagnosed in 2007. (b) FOLFOX therapy achieved partial response in 2008. (c) Radiotherapy resulted in the complete disappearance of lung metastasis in 2011.

replaced by a calcification (Fig. 2d), which meant complete control of all metastatic lesions. The treatment protocol with cetuximab was continued thereafter to prevent new recurrences. Nearly 1 year has passed since the last irradiation and no recurrence has been detected so far.

Discussion

Although even at present, surgical resection is the dominant therapeutic modality for colorectal cancer, in recent decades a rapid progress of the therapeutic modalities for colorectal cancer, including chemotherapy, radiofrequency ablation, and heavy particle radiotherapy, have increased the choice, and consequently the improvement of the prognosis after surgery.

In Fig. 4, the chemotherapeutic agents available in Japan with the corresponding periods are shown. TS-1 is available since 1999, oxaliplatin since 2005, capecitabine since 2007, bevacizumab since 2007, cetuximab since 2008, and panitumumab since 2010. As a result of these significant advances in the clinically available chemotherapeutic agents, the median survival period of patients with colorectal cancer improved significantly, with up to 24 months improvement in a recently published report.[4] On the other hand, the survival period of those cases receiving best supportive care remained unchanged (about 6 months).[6]

In the present case, sigmoidectomy for primary cancer was performed in 1997. At that time, the adjuvant chemotherapy available was limited to 5-FU and leucovorin, which failed to prevent the metastatic recurrence 7 years after the initial surgery.[7] However, during this period, the repeated recurrences were treated with resection or irradiation, and various new agents have been developed for the treatment of colorectal cancer. FOLFOX and FOLFIRI were available since 2000,[8,9] capecitabine since 2001,[10] and the additional effect of bevacizumab and cetuximab was proven in 2004.[11,12] Cetuximab alone and panitumumab have been used since 2007.[13,14] By implementation of a multimodal therapy, consisting of the combination of surgical

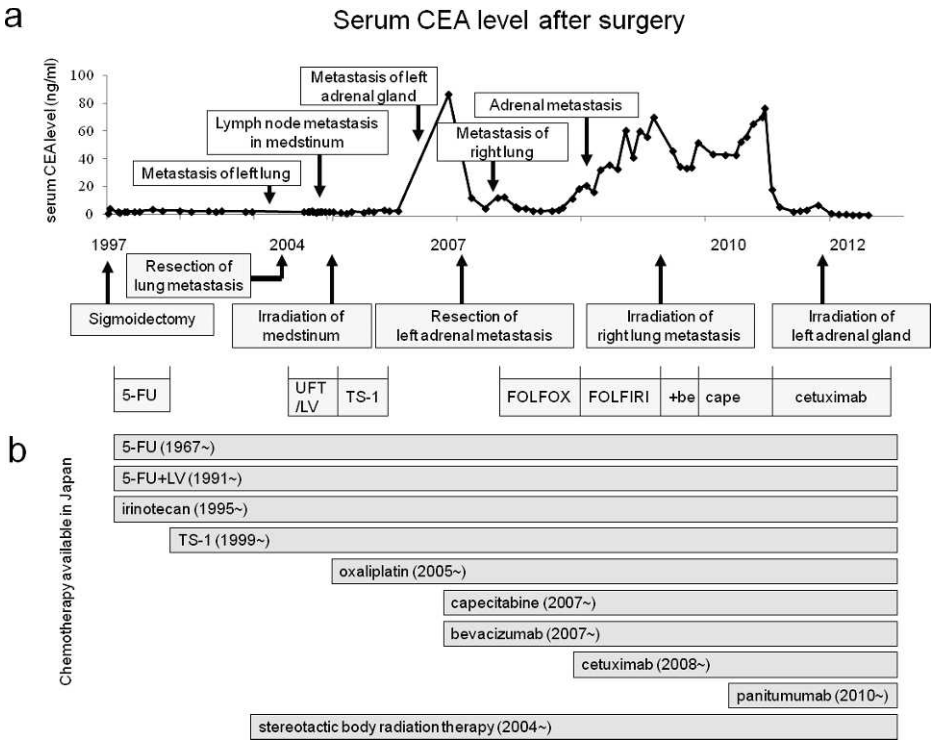

Fig. 4 (a) Clinical course of the patient, the changes in the serum carcinoembryonic antigen (CEA) level after the resection of colorectal cancer. (b) The chemotherapeutic agents available in Japan for colorectal cancer therapy since 1967. The bars in the lower part of the figure represent the drugs available in Japan and the corresponding periods. UFT, tegafur-uracil; LV, leucovorin; FOLFOX, 5-fluolouracil, leucovorin, oxaliplatin; FOLFIRI, 5-fluolouracil, leucovorin, irinotecan; Be, bevacizumab; Cape, capeciatabine.

resection, chemotherapy, especially cetuximab, and radiotherapy, complete response could be achieved 14 years after the first surgery, in spite of the repeated recurrences in the left lung, mediastinal lymph node, left adrenal gland, and right lung. In the present case the first recurrence occurred several years after the surgical resection, suggestive of a slow growing tumor, and finally complete remission could be achieved because during this period, new therapeutic agents and modalities became available for the treatment of colorectal cancer. We are confident that with the rapid advancement of the therapeutic modalities, an increasing number of colorectal cancer patients with uncontrollable metastasis at the time of diagnosis will be able to achieve a cancer-free state in the near future.

Because our patient has had repeated recurrences, the possibility of a new recurrence in the future still remains. At that time, possibly new therapeutic drugs or modalities will be available. The development of further new therapy is desired.

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