Showa Univ J Med Sci **27**(4), 285～289, December 2015

Case Report

A Case of Krukenberg Tumor Metastasized from Colon Cancer Subsequent to Synchronous Multiple Liver Metastasis

Takahiro UMEMOTO*[1)], Nobuyuki OHIKE[2)], Kazuhiro KIJIMA[1)], Masatsugu NAGAHAMA[3)], Takashi KATO[1)], Hiroshi TAKAHASHI[3)] and Jun-ichi TANAKA[1)]

Abstract: A 34-year-old woman with synchronous, multiple liver metastases of stage IV, T4N2M0H2P0 descending colon cancer was referred to our hospital. The lesion was considered unresectable because of insufficient estimated future remnant liver volume resulting from invasion of three hepatic veins and the hepatic hilum, and she underwent laparoscopic left hemicolectomy. The patient underwent 14 courses of mFOLFOX6 (5-flurouracil, leucovorin and oxaliplatin) and 21 cetuximab administrations as first-line chemotherapy, which allowed her to maintain a complete response for 6 months despite adverse reactions such as mild neutropenia and thrombocytopenia. However, abdominal computed tomography (CT) revealed a large ovarian mass 6 months after chemotherapy cessation. A bilateral adnexectomy at another hospital revealed involvement of both ovaries, and immunohistochemistry revealed that the tumor was CK7− and CK20+, compatible with a colon cancer origin. The ovarian lesions were histologically diagnosed as Krukenberg tumor metastasized from the colon cancer. This case highlights the possibility of metastatic tumor development from colon cancer.

Key words: Krukenberg tumor, colon cancer, chemotherapy

Introduction

Recently, targeted therapies have proven effective for the treatment of colon cancer. In some cases, intensive systemic chemotherapy may even facilitate tumor resection in patients with previously unresectable liver metastases. For example, the anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab have improved the survival of patients with metastatic colon cancer; accordingly, these agents are considered a standard component of therapy[1-3)]. However, anti-EGFR therapeutic resistance has been reported. We report here a case of metastatic Krukenberg tumor that developed following chemotherapeutic treatment including cetuximab in a patient with colon cancer and synchronous multiple liver metastases.

[1)] *Department of Gastroenterological and General Surgery, Showa University Fujigaoka Hospital,* 1-30 Fujigaoka, Aoba-ku, Yokohama 227-8501, Japan.
[2)] *Department of Diagnostic Pathology, Showa University Fujigaoka Hospital.*
[3)] *Department of Gastroenterology, Showa University Fujigaoka Hospital.*
* To whom corresponding should be addressed.

Case Report

A 34-year-old woman with synchronous, multiple liver metastases of colon cancer was referred to our hospital with the following vital signs : temperature 36.7°C, pulse rate 66 beats / min, and blood pressure 104 / 64 mmHg. Abdominal examination revealed abdominal distension, decreased bowel sounds, and tenderness with rebound tenderness. Laboratory tests revealed a hemoglobin level of 13.9 g / dl, leukocyte count of 8,800 cells / cm^3, and serum C-reactive protein level of 0.25 mg / dl. Abdominal computed tomography (CT) revealed multiple liver tumors and a large concentric mass involving the descending colon that extended 6 cm in length and caused narrowing of the colon but not complete obstruction. Colonoscopy revealed a large, friable, ulcerated, circumferential tumor in the descending colon that had almost completely obstructed the organ. A pathological tumor evaluation revealed moderately differentiated adenocarcinoma. However, the multiple metastatic lesions in the liver were deemed unresectable because the estimated future remnant liver volume was insufficient due to tumor invasion of three hepatic veins and the hepatic hilum. The patient's disease was classified as stage IV [cT4N2M0H2P0 according to the Union of International Cancer Control (UICC) TNM classification].

The patient underwent laparoscopic left hemicolectomy to treat the descending colon cancer. There were no postoperative complications, and oral intake was initiated 3 days after surgery. She was discharged from the hospital on postoperative day 14. We obtained her consent to undergo v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation analysis, which revealed the presence of wild-type alleles. Six weeks after surgery, she received the first administration of cetuximab alone, resulting in a high rate of early liver metastasis shrinkage (Fig. 1A, 1B). Next, she underwent 14 courses of mFOLFOX6 (5-flurouracil, leucovorin, and oxaliplatin) and 21 administrations of cetuximab as a first-line chemotherapeutic regimen.

CT scans were obtained every 2-3 months throughout the treatment course (Fig. 1A-D) ; these revealed a partial response of liver metastases after 3 months (Fig. 1C) and decreases in the tumor sizes at each scan. Complete response was observed after 6 months (Fig. 1D). Magnetic resonance imaging (MRI) at 10 months after the start of chemotherapy revealed significant decreases and reduced activity in all liver metastatic areas when compared with pretreatment findings (Fig. 2A, 2B).

Despite adverse reactions such as mild neutropenia and thrombocytopenia, chemotherapy maintained the complete response for 6 months. However, 13 months after surgery (6 months after chemotherapy cessation), abdominal CT revealed a large ovarian mass and ascites (Fig. 3A, 3B), and the patient underwent bilateral adnexectomy at another hospital. Although we were unable to acquire a specimen of the resected tumor, the pathological examination report indicated a mass measuring 9 cm × 5 cm × 3.5 cm and affecting both ovaries. Immunohistochemistry determined that the tumor was cytokeratin (CK)7− and CK20+, compatible with a colon cancer origin. The ovarian lesions were diagnosed following histological analysis as Krukenberg tumor with metastatic signet ring cell adenocarcinomas of the ovary, originating from colon cancer. The patient remains symptom-free after surgery and additional chemotherapy.

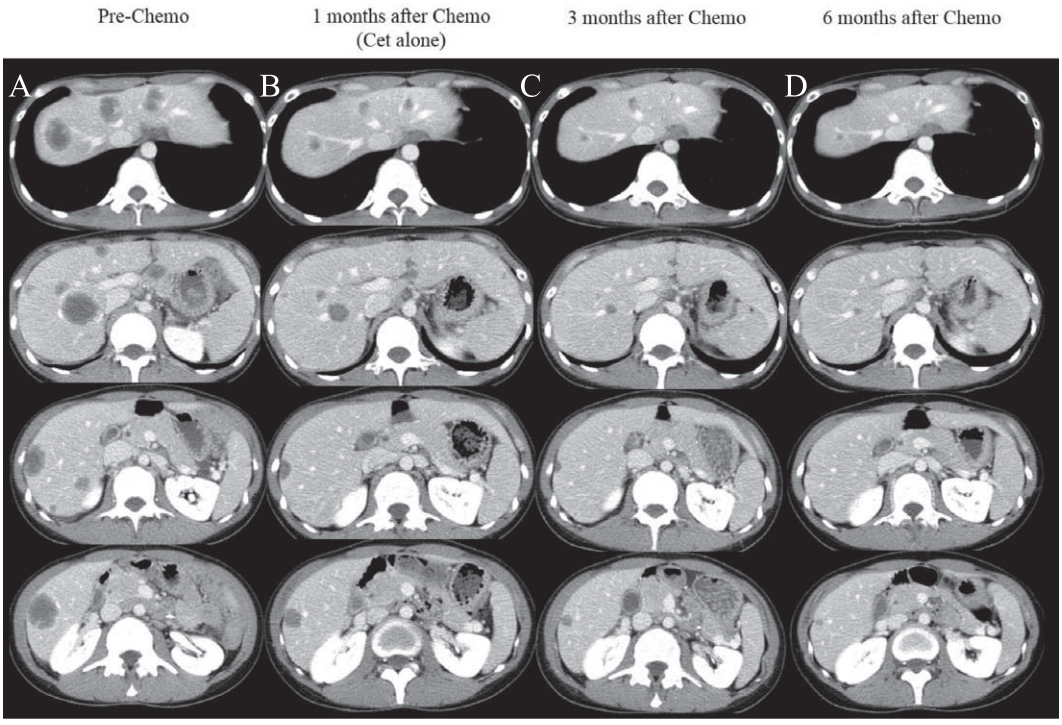

Fig. 1. Computed Tomography
CT of the liver metastases revealed a high rate of early tumor shrinkage (1A, 1B), with a partial response after 3 months (Fig. 1C). Subsequent CT revealed continuous tumor shrinkage, with a complete response after 6 months (Fig. 1D).

Discussion

Krukenberg tumors are uncommon, and account for 1-2% of all ovarian tumors. In most cases involving Krukenberg tumors (70%), gastric cancer is the primary tumor, with colon, appendix, and breast (mainly invasive lobular carcinoma) cancers also common primary sites[4]. In the present case, the resected ovarian lesions were diagnosed by histological analysis as Krukenberg metastatic tumors to ovary.

Unresectable liver metastases of stage IV colon cancer were until recently treated with palliative chemotherapy, resulting in a median survival of <24 months[5]. With recent advances in chemotherapy, such as the development of anti-EGFR antibodies (e.g., cetuximab and panitumumab), the survival of patients with inoperable metastases of colorectal cancer (CRC) has been prolonged, and these agents are now considered a standard component of therapy[1-3, 6]. However, in the management of liver metastases of stage IV CRC, whether to operate first or administer chemotherapy first remains under debate[7].

In addition, liver resection has recently become more feasible following a response to intensive systemic chemotherapy in some patients with unresectable liver metastases, with clinical anti-EGFR treatment a common and effective component of such conversion therapy. In this context, KRAS mutation testing is highlighted because of its demonstrated importance in predicting

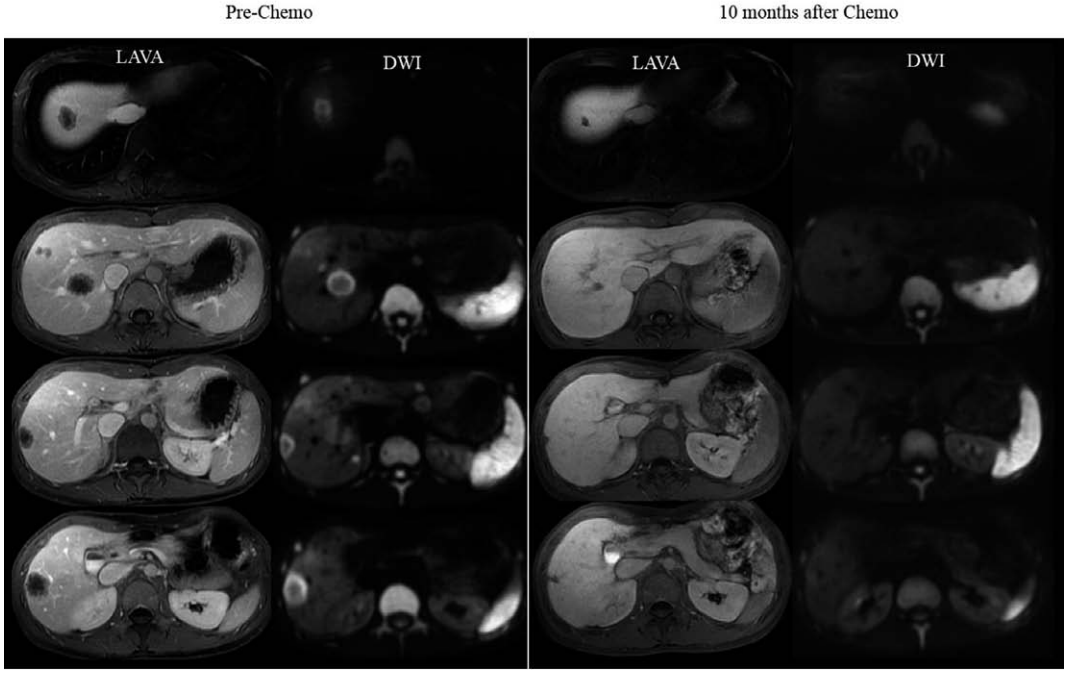

Fig. 2. Magnetic Resonance Imaging
A comparison of MRI performed before and 10 months after chemotherapy revealed significant decreases in the lesions and low activity in all liver metastatic areas.

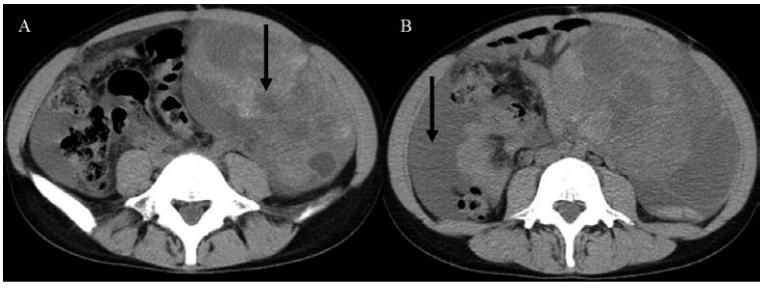

Fig. 3. Computed Tomography
CT at 6 months after chemotherapy cessation revealed a large ovarian mass (A) and ascites (B).

resistance to cetuximab chemotherapy in patients with metastatic CRC[8]. The present case harbored no KRAS mutation, and her liver metastasis exhibited a high rate of early tumor shrinkage (ETS) (Fig. 1B), leading to a complete response that was maintained with chemotherapy.

Giessen *et al*[9] defined ETS as a ≥20% decrease in the maximum tumor diameter between the baseline and 7 weeks of treatment and found that patients with ETS had a more favorable outcome in terms of progression-free survival (PFS) (9.9 months *vs*. 6.1 months, $P = 0.029$) and overall survival (OS) (27.5 months *vs*. 17.8 months, $P = 0.002$). Modest *et al*[10] observed ETS according to the above definition in 59% of patients with KRAS wild-type tumors and indicated that these patients exhibited increases in their overall response rate (82% *vs*. 19%, $P < 0.001$),

as well as PFS (8.9 months *vs*. 4.7 months, $P < 0.001$) and OS (31.6 months *vs*. 15.8 months, $P = 0.005$). These studies suggest that ETS is an effective predictor of the success of conversion therapy. The long-term survival of our patient with Krukenberg tumors of CRC, and other similar patients, is therefore supported by improvements in systemic chemotherapy, the introduction of anti-angiogenic agents, and the utilization of advanced surgical strategies and equipment[11-13].

In conclusion, in patients with a history of colon cancer, a rare ovarian mass must be diagnosed correctly with CT and MRI to ensure early detection of ovarian metastasis.

References

1) Van Cutsem E, Kohne CH, Hitre E, *et al*. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;**360**:1408-1417.
2) Peeters M, Price TJ, Cervantes A, *et al*. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;**28**:4706-4713.
3) Douillard JY, Siena S, Cassidy J, *et al*. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;**28**:4697-4705.
4) Al-Agha OM, Nicastri AD. An in-depth look at Krukenberg tumor: an overview. *Arch Pathol Lab Med*. 2006;**130**:1725-1730.
5) Giacchetti S, Itzhaki M, Gruia G, *et al*. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol*. 1999;**10**:663-669.
6) Hurwitz H, Fehrenbacher L, Novotny W, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;**350**:2335-2342.
7) Stillwell AP, Buettner PG, Ho YH. Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. *World J Surg*. 2010;**34**:797-807.
8) Lievre A, Bachet JB, Le Corre D, *et al*. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res*. 2006;**66**:3992-3995.
9) Giessen C, Laubender RP, Fischer von Weikersthal L, *et al*. Early tumor shrinkage in metastatic colorectal cancer: retrospective analysis from an irinotecan-based randomized first-line trial. *Cancer Sci*. 2013;**104**:718-724.
10) Modest DP, Laubender RP, Stintzing S, *et al*. Early tumor shrinkage in patients with metastatic colorectal cancer receiving first-line treatment with cetuximab combined with either CAPIRI or CAPOX: an analysis of the German AIO KRK 0104 trial. *Acta Oncol*. 2013;**52**:956-962.
11) Wang CC, Li J. An update on chemotherapy of colorectal liver metastases. *World J Gastroenterol*. 2012;**18**:25-33.
12) Padman S, Padbury R, Beeke C, *et al*. Liver only metastatic disease in patients with metastatic colorectal cancer: impact of surgery and chemotherapy. *Acta Oncol*. 2013;**52**:1699-1706.
13) Donati M, Stavrou GA, Oldhafer KJ. Current position of ALPPS in the surgical landscape of CRLM treatment proposals. *World J Gastroenterol*. 2013;**19**:6548-6554.

[Received June 22, 2015 : Accepted August 13, 2015]