SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 14: 3697-3700, 2017

Benefit of rebiopsy for deciding treatment strategy in rectal cancer: A case report

KENTA KAWASAKI[1], YASUO HAMAMOTO[2], TAKESHI SUZUKI[1], KENRO HIRATA[1], YASUTAKA SUKAWA[1], AKIYOSHI KASUGA[1], YUICHIRO HAYASHI[3], HIROMASA TAKAISHI[2], KAORI KAMEYAMA[3] and TAKANORI KANAI[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine; [2]Keio Cancer Center; [3]Division of Diagnostic Pathology, Keio University School of Medicine, Tokyo 160-8582, Japan

Received January 11, 2016; Accepted March 23, 2017

DOI: 10.3892/ol.2017.6601

Abstract. Rebiopsy is considered an option for specific types of cancer, such as breast, non-small cell lung, and prostate cancer, in clinical trials and in practice. The benefit of rebiopsy comes from the selection of a new treatment strategy based on the genetic profile of the cells, which may reflect the development of drug resistance or hormonal changes. For colorectal cancer, the presence of different genomic mutations between the primary tumor and its metastases is rare, and rebiopsy is therefore not generally performed. The present study reports the case of a 68-year-old man who was initially diagnosed with metastatic adenocarcinoma from a primary colorectal cancer, but was subsequently rediagnosed with metastatic neuroendocrine carcinoma based on the pathological rebiopsy results. The patient responded well to cisplatin and etoposide treatment, after not responding to initial FOLFOX treatment. In this case, rebiopsy resulted in a change in treatment regimen and improved the patient's quality of life and his long-term survival. This case indicates that, when a colorectal cancer patient is unresponsive to standard treatment, it may be beneficial for the clinician to suspect an atypical histological type, and to consider rebiopsy.

Introduction

Rebiopsy is considered an option for specific cancer types, such as breast cancer, non-small cell lung cancer (NSCLC), and prostate cancer, due to the ability of gene profiling to detect hormonal changes (1-3). However, rebiopsy is not usually considered in the treatment of colorectal cancer (4,5).

The present study reports a case of a 68-year-old man who was initially diagnosed with metastatic adenocarcinoma, but was subsequently rediagnosed with metastatic neuroendocrine carcinoma (NEC) from a primary rectal cancer following rebiopsy. The patient was unresponsive to the standard chemotherapy regimen of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), but responsive to the treatment for NEC.

NEC is an atypical type of colorectal cancer that accounts for <1% of all colorectal cancer cases (6). The 5-year survival rate of stage IV colorectal NEC is poor, at ~3% (7). While colorectal adenocarcinoma is usually treated with the FOLFOX or 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) regimens, colorectal NEC is treated with cisplatin (CDDP)/carboplatin and etoposide (VP-16). In the current case report, the clinical significance of rebiopsy as it applied to the treatment of this colorectal cancer patient is discussed. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Case report

A 68-year-old man was diagnosed with colorectal cancer and underwent lower anterior resection and D3 lymph node dissection with ileostomy at a public hospital in Nagasaki, Japan in October 2013. The pathological stage was IIIB (T2N2M0), and the tumor was determined to be a moderately differentiated tubular adenocarcinoma with positive G12A *KRAS* mutation (Fig. 1A-C). The lymph node metastasis exhibited the same adenocarcinoma histology as the primary lesion. The patient received modified FOLFOX6 [400 mg/m^2 bolus 5-fluorouracil (day 1 of each cycle); 200 mg/m^2 leucovorin (day 1 of each cycle); 100 mg/m^2 oxaliplatin (day 1 of each cycle); 2,400 mg/m^2 continuous 5-fluorouracil (day 1-2 of each cycle); all intravenously administered every 2 weeks] as post-operative chemotherapy; however, after receiving two cycles, the patient was found to be suffering from liver dysfunction. A subsequent computed tomography (CT) scan showed several large masses in the liver (Fig. 2A). Relapse of rectal cancer was considered; however, the elevated neuron-specific enolase (NSE) level (155.2 ng/ml) and non-elevated carbohydrate antigen 19-9 (12 U/ml) and carcinoembryonic antigen levels (3.6 ng/ml), together with the cancer's resistance to FOLFOX treatment, indicated a more unusual type of rectal cancer. Therefore, a liver biopsy was performed.

Correspondence to: Dr Hiromasa Takaishi, Keio Cancer Center, Keio University School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan
E-mail: takaishi@z6.keio.jp

Key words: biopsy, colorectal cancer, neuroendocrine cancer

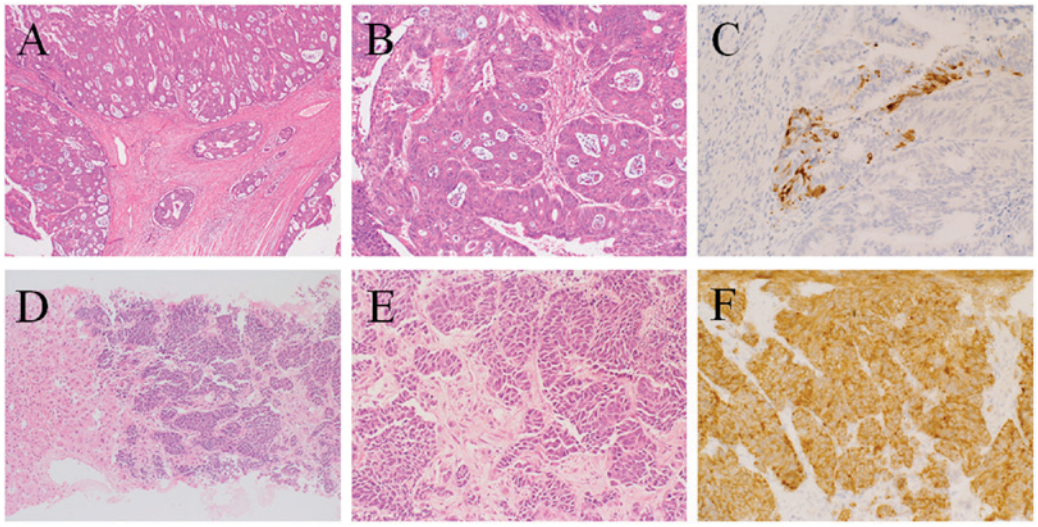

Figure 1. Histology of the primary cancer and liver metastasis. H&E staining at (A) magnification, x2 and (B) x4 of the primary rectal adenocarcinoma. Moderately differentiated tubular adenocarcinoma was observed, with ductal formation and mucus production. (C) Synaptophysin staining of the primary rectal adenocarcinoma. Sporadic synaptophysin-positive cells were confirmed in the primary adenocarcinoma. Magnification, x10. H&E staining at (D) magnification, x4 and (E) x10, and (F) synaptophysin staining (magnification, x10) of the liver metastasis. Ductal formation and mucus production were not observed, and the lesion was positive for synaptophysin. H&E, hematoxylin and eosin.

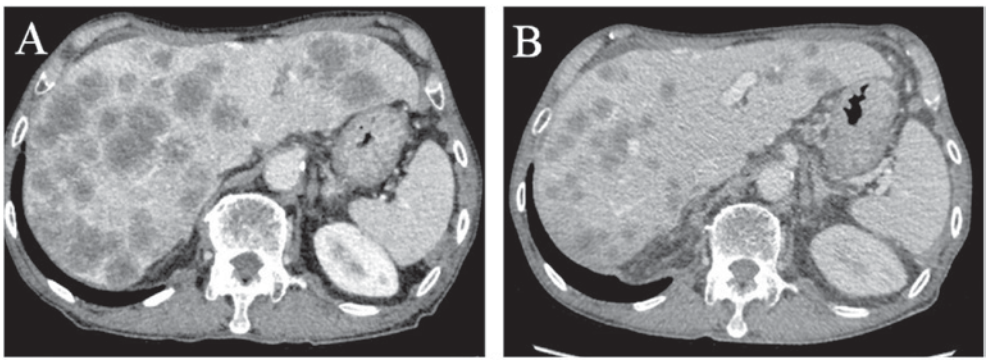

Figure 2. CT scan pre- and post-chemotherapy. (A) CT image of multiple liver metastases following two cycles of 5-fluorouracil, leucovorin, and oxaliplatin. (B) Multiple liver metastases exhibited a marked decrease of 45.1% (Response Evaluation Criteria In Solid Tumors, version 1.1) following treatment with cisplatin and etoposide. CT, computed tomography.

From the biopsy, the patient was rediagnosed with NEC that was synaptophysin-positive, chromogranin A-positive, CD56-positive, and Ki-67-positive (>80% of cells) (Fig. 1D-F). Pathologically, ductal formation and mucus production were not observed. On positron emission tomography (PET), extrahepatic lesions, which could have been considered primary cancer, were not observed. Therefore, liver metastasis from primary rectal cancer was diagnosed. To confirm this, immunostaining was performed, which revealed sporadic synaptophysin-positive cells in the primary adenocarcinoma of the rectum (Fig. 1C). Based on this diagnosis, the chemotherapy regimen was changed from FOLFOX to CDDP (80 mg/m^2 on day 1 of each cycle) and VP-16 (100 mg/m^2 on day 1-3 of each cycle), which were intravenously administered every 3 weeks.

After the first cycle in March 2014, the patient was admitted to Keio University Hospital (Tokyo, Japan) with febrile neutropenia. A CT scan was performed to investigate the site of the infection, and a remarkable decrease of 45.1% [Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1; Fig. 2B] (8) was observed, which was associated with a decrease in the serum concentration of NSE (Fig. 3). The patient was then evaluated as having a partial response (RECIST, version 1.1) (8). Following four cycles of chemotherapy, an ileostomy closure was performed. Within 6 months, the metastatic lesions had enlarged and the patient was treated with 40 mg/m^2 amrubicin, which was intravenously administered every 3 weeks (day 1-3 of each cycle) for seven cycles before he was reevaluated as having progressive disease (PD). The patient opted for best supportive care; however, the patient succumbed in June 2015.

Discussion

The present study reports the case of a FOLFOX-resistant metastatic rectal cancer, which was diagnosed as NEC from rebiopsy. According to the National Comprehensive Cancer Network (NCCN) guidelines, for metachronous unresectable metastases, as in this case, continuation of intensive chemotherapy for colorectal cancer is recommended (4,5). Thus, rebiopsy was not indicated for this patient, and he would be

Table I. Indications for rebiopsy in different cancer types according to various guidelines.

Indication	Breast cancer	Non-small cell lung cancer	Prostate cancer	Colorectal cancer
NCCN guidelines	First recurrence of disease should be biopsied (1)	Consider rebiopsy if appropriate (2)	Consider biopsy if small cell carcinoma is suspected (3)	None
ASCO guidelines	Based on the discordance of results between primary and metastatic tissues, rebiopsy is recommended (15)	None	None	None
ESMO guidelines	Biopsy of metastasis should be performed (16)	Rebiopsy at disease progression may be considered (26)	None	None
Clinical benefit	Change in hormonal status in 5-40% of patients (13,14)	Different molecular mutation and resistance in 30-50% of patients (17,18)	Small cell carcinoma can be detected in 0.5-2% of patients (27)	Unknown

NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

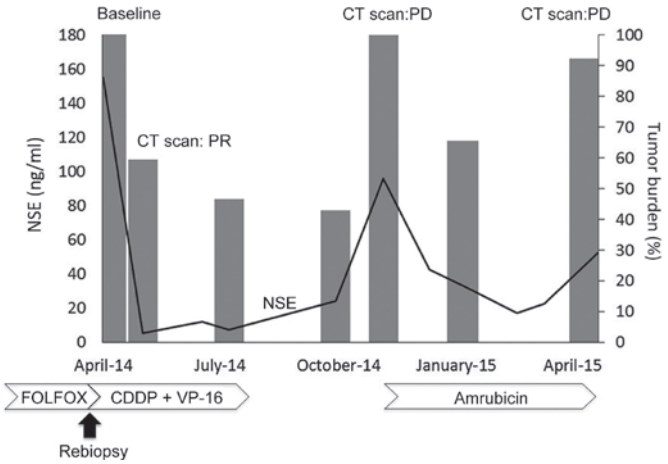

Figure 3. Time course of the patient, including NSE, tumor burden and treatment. Tumor burden, shown as a bar graph, was calculated as the sum of two metastatic liver lesions according to the Response Evaluation Criteria In Solid Tumors, version 1.1. The line graph shows the NSE levels over time. NSE, neuron-specific enolase; CT, computed tomography; PR, partial response; PD, progressive disease; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; CDDP, cisplatin; VP-16, carboplatin and etoposide.

characterized as having PD (4,5). However, rebiopsy was undertaken and revealed the existence of NEC in the metastatic lesion. It is notable that the primary cancer was an adenocarcinoma which had a completely different pathological status compared with the metastatic site. The result of the PET scan revealed no other primary sites. It is possible that the pathological analysis results from the primary adenocarcinoma were not representative of the whole tumor. As shown in Fig. 1C, sporadic synaptophysin-positive cells were detected in the primary adenocarcinoma, and these sporadic cells may have been the origin of the liver metastasis. Another possibility is that the adenocarcinoma changed into NEC subsequent to the initial diagnosis. One previous report has shown that neuroendocrine differentiation is more frequently observed in metastatic cancers compared with primary site tumors (9), whereas other reports have described cases wherein chemotherapy was shown to cause histological conversions (10,11). This phenomenon has also been observed in cases of prostate cancer and NSCLC, but the underlying mechanism is unknown (12).

Rebiopsy is indicated in the NCCN guidelines for NSCLC, breast and prostate cancers in clinical trials and in practice (Table I). With regard to clinical benefit, an alteration in the gene profile of the tumor may arise from the development of drug resistance, or from hormonal changes (13,14). For breast cancer, the NCCN, the American Society of Clinical Oncology, and the European Society for Medical Oncology guidelines all recommend rebiopsy of the metastasis (1,15,16). The guidelines are supported by a number of reports that indicate that rebiopsy can reveal changes in the tumor for 14-20% of patients (13,14). This is determined from the hormonal status of the tumor and any differences between the primary tumor and its distant metastases (13,14). For NSCLC, tumor rebiopsy is recommended if deemed suitable (17), and in clinical practice it has been reported that >80% of patients undergo rebiopsy (18). Recently, drug-resistant cell lines derived from rebiopsy specimens have been established (19). This strategy can be used in directing the selection of the most appropriate treatment, which has been demonstrated to be important in the treatment of NSCLC (19). The NCCN guidelines also recommend rebiopsy of prostate cancer, but only in cases where small cell prostate cancer has been suspected (3). Treatment-related NEC has been reported, and the necessity for rebiopsy has been clearly demonstrated in numerous cases (12,20). The prevalence of prostate NEC is <2% of all prostate malignancies, which is similar to that of colorectal NEC (20).

For colorectal cancer, rebiopsy is not indicated for metachronous metastases (4,5) and the clinical benefit is unknown. Rebiopsy is supported where there is evidence of differing genetic mutations between the primary tumor and

the metastasis, including those in *KRAS*, *BRAF*, *PTEN* and *PIK3CA* (21-24).

When considering rebiopsy, it is important to determine whether it will improve the patient's quality of life and overall survival compared with the burden and the potential risks associated with additional biopsy (25). From the present case study, we consider rebiopsy to have been beneficial for the patient, as the correct diagnosis resulted in the selection of a treatment regimen that produced a better response.

In conclusion, for cases in which a patient with colorectal cancer is unresponsive to a standard treatment, it may be beneficial to consider an atypical histological type, and, if appropriate, to perform rebiopsy.

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