World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4251/wjgo.v5.i11.198

World J Gastrointest Oncol 2013 November 15; 5(11): 198-203
ISSN 1948-5204 (online)

CASE REPORT

Striking similarities in genetic aberrations between a rectal tumor and its lung recurrence

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Received: August 16, 2013 Revised: October 9, 2013
Accepted: November 2, 2013
Published online: November 15, 2013

Abstract

We are reporting on a colorectal cancer patient with the longest disease-free interval ever published, where chromosomal microarray analysis was used to confirm the link between the primary and metastatic lesions. This rare case reports on a patient with late recurrence of colorectal cancer in the lung 19 years after its initial diagnosis. We used high-resolution array CGH (aCGH) to analyze the genetic aberrations of both the primary rectal and the recurrent metastatic lung lesions. Interestingly, we found striking similarities between the two lesions, despite the 19 years disease-free interval. In addition, most of the genes that were previously reported to be associated with a high recurrence score showed copy number gains by aCGH in one or both lesions. Our findings suggest that aCGH may be a helpful tool in analyzing the origin of metastases and reflect the need for a better understanding of the characteristics of the rectal tumors with a late recurrence potential.

Key words: Colorectal cancer; Genetic aberrations; Delayed; Recurrence; High-resolution array CGH.

Core tip: The role of genetic profiling in determining the risk of recurrence in colorectal cancer has been under serious investigation. This case report not only represents the longest rectal cancer disease-free interval in the literature, but also applies genetic analysis as a tool to confirm the similarity of the original and metastatic tumor and to predict the risk of recurrence.

Rahma OE, Burotto M, Do Canto LM, Germanos AA, Haddad BR, Marshall JL. Striking similarities in genetic aberrations between a rectal tumor and its lung recurrence. *World J Gastrointest Oncol* 2013; 5(11): 198-203 Available from: URL: http://www.wjgnet.com/1948-5204/full/v5/i11/198.htm DOI: http://dx.doi.org/10.4251/wjgo.v5.i11.198

INTRODUCTION

Colorectal cancer (CRC) has a high incidence worldwide with more than 1.2 million new cases diagnosed in 2008[1]. The 5-year overall survival in the United States for all stages is 61%[2]. Rectal cancer accounts for approximately 30% of CRC cases[3]. The treatment of

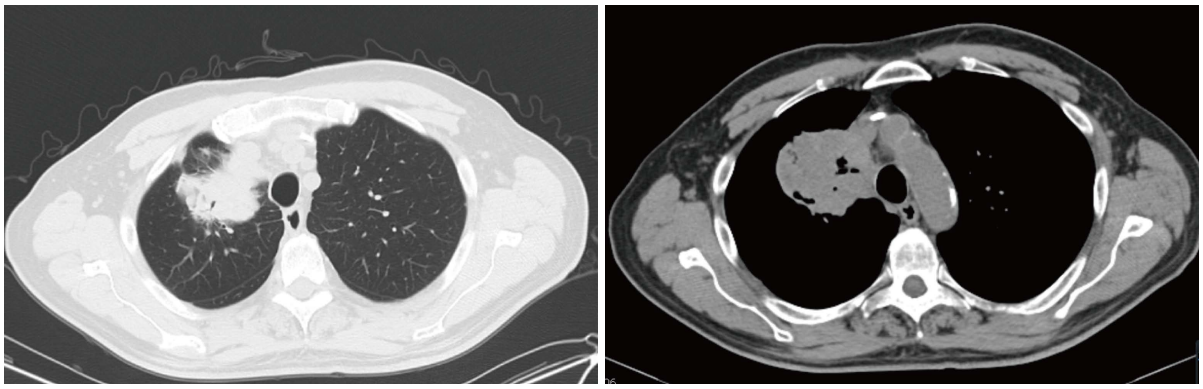

Figure 1 Chest computed tomography-scan demonstrating 7.9 × 7.8 cm mass in the right upper lobe and right sided mediastinal and hilar lymphadenopathy.

localized rectal tumors differs from colon tumors in that it involves a multidisciplinary approach that includes surgery, radiation and chemotherapy[4]. The goal of neoadjuvant or adjuvant treatment is to decrease local and distant recurrence of the disease[5]. As of today, we do not have predictive biomarkers that indicate when a particular patient will benefit from systemic chemotherapy or, more importantly, in which cases the tumor will recur. Preliminary molecular tools have been developed to help predict which patient is more likely to experience disease recurrence and eventually die from the disease[6,7]. Despite these efforts we only partially understand the complexity of rectal cancer, clonal evolution and dormancy of micro-metastatic disease[8,9]. In this report we present the case of a long term survivor of CRC with a delayed recurrence almost two decades later.

CASE REPORT

An 81-years-old Caucasian male initially presented with rectal bleeding in 1991. He underwent a colonoscopy with biopsy that was later tested and revealed a wild type K-ras moderately differentiated adenocarcinoma. The patient was diagnosed with stage ⅢB (T3N1M0) rectal cancer and treated with surgical resection and colostomy followed by chemoradiation with fluorouracil (5-FU) and leucovorin. He subsequently underwent a colostomy reversal and remained in remission with no evidence of disease until 2011 when he developed cough and was found to have a lung mass in the right upper lobe (RUL) and right sided mediastinal and hilar lymphadenopathy (Figure 1). A PET scan showed the RUL mass to be 8.2 cm × 7.3 cm with SUV of 14.5, and confirmed the right-sided mediastinal and hilar lymphadenopathy, in addition to a 1.2 cm nodule in the left costophrenic angle with no FDG activity. He underwent bronchoscopy and biopsy that revealed a wild type K-ras adenocarcinoma of colonic primary, CDX2/CK20 positive and TTF1/CK7/CD58 negative. The tumor characteristics were consistent with the primary tumor. The patient had a colonoscopy that only showed friable rectal mucosa with no evidence of malignancy. Accordingly, the patient was treated with FOLFOX (5-FU, oxaliplatin and leucovorin) in combination with bevacizumab for his recurrent metastatic rectal cancer. He received 10 cycles of FOLFOX/bevacizumab. The oxaliplatin was stopped due to cumulative neuropathy and he was switched to capecitabine and bevacizumab. The patient had a good response to chemotherapy by PET scan that showed a decrease in the RUL mass size (from 8.2 to 6.6 cm) and SUV (from 14.5 to 4.6), in addition to a decrease in the bilateral hilar and subcarinal lymph nodes' uptake. Given the patient good response to chemotherapy he subsequently underwent right upper and middle lobectomies in July 2012. His pathology showed metastatic adenocarcinoma with extensive necrosis consistent with his known primary colorectal carcinoma. Given the dormancy of his disease for so many years, the options were presented to the patient including watchful waiting versus maintenance chemotherapy with capecitabine for 1-2 years. The patient opted not to proceed with more treatment and to be monitored with regular CT-scans.

Genetic aberrations in the metastatic lung lesion compared to the primary rectal carcinoma

In order to compare the DNA copy number changes in the metastatic lung lesion to the changes in the primary tumor, we evaluated both lesions by high-resolution aCGH analysis using an Agilent® platform (SurePrint G3 Human CGH Microarray Kit 8x60K, Agilent, Santa Clara, CA). Genomic DNA was isolated from formalin-fixed paraffin embedded tumor tissues using a standard phenol-chloroform laboratory protocol and cleaned with a MinElute® Reaction Cleanup Kit (Qiagen, Valencia, CA). Commercially available, pooled, normal control DNA (Promega, Madison, WI) was used as a reference DNA. aCGH experiments were performed according to the manufacturer's protocol with minor modifications. In brief, tumor and reference DNA were labeled using enzymatic labeling (Agilent, Santa Clara, CA), hybridized for 40 h at 65 ℃, washed, and immediately scanned using Agilent Scanner (G2505C). Data were extracted using Agilent Feature Extraction 10.7.3.1 software, and analyzed with Agilent Workbench 7.0 software. High-

Table 1 Genetic aberrations in the primary rectal tumor, the metastatic lung lesion, and both lesions by array comparative genomic hybridization analysis

	Chr	Cytoband	Base pair		Aber
			Start	Stop	
Recurrent metastatic lung lesion	chr1	p34.2-p34.1	40022181	45250726	G
	chr1	q21.1- q44	143700072	245804497	G
	chr2	p25.3-p11.2	32444	89387655	G
	chr2	q11.2-q37.3	96143358	241478888	G
	chr4	q32.1- q35.1	156452014	186681608	L
	chr6	p25.3-p11.1	200350	58722020	G
	chr7	p12.3-p11.1	49282714	57498383	G
	chr7	q11.21-q22.1	62291739	99905860	G
	chr7	q36.1-q36.3	150049339	158781397	G
	chr8	p23.1- p12	12627630	32499834	L
	chr8	p12-p11.21	32882718	42971936	G
	chr8	q11.21-q24.3	48549253	146250824	G
	chr9	q33.2-q34.3	124984647	139633014	G
	chr10	q22.3-q24.2	80370579	101360302	L
	chr10	q26.3	131868597	134682710	L
	chr11	p15.5-p11.12	974637	48986659	G
	chr13	q12.11-q34	18556982	113766081	G
	chr15	q25.3-q26.3	83411251	96875147	G
	chr19	p13.3-p13.11	318892	19154766	G
	chr20	q11.21-q13.33	29436537	62320720	G
	chrX	p11.23-p11.1	48639378	57116899	G
	chrX	q11.1-q28	61980262	154886101	G
	chrY	p11.31-p11.2	2716461	8521949	L
	chrY	q11.21-q11.221	13208776	17558012	L
Primary rectal lesion	chr1	q21.1-q44	143700072	243198779	G
	chr2	p25.3-p11.2	698239	89387655	G
	chr2	q11.1-q37.3	95562654	241301905	G
	chr3	p26.3-p11.1	134711	90336752	G
	chr3	q11.2-q29	95063426	197289184	G
	chr6	q11.1-q27	63002508	170700061	G
	chr7	p22.3-p11.2	524935	55936992	G
	chr7	q11.21-q36.3	62291739	158602499	G
	chr8	p23.3-p12	369418	32621998	L
	chr8	p12-p11.21	32705506	42971936	G
	chr8	q11.1-q24.3	47800500	146024209	G
	chr9	p24.3-p13.2	319684	37451026	G
	chr11	p15.5-p11.2	2121540	46490960	G
	chr13	q11-q34	18361637	113964366	G
	chr20	q11.21-q13.33	29352138	62343283	G
	chrX	p22.33-p11.1	2719027	58068490	G
	chrX	q11.1-q28	61848414	154561665	G
	chrY	p11.31-p11.2	2716461	10511314	L
	chrY	q11.21-q11.23	12593244	27176992	L
Common aberrations between the two lesions	chr1	q21.1-q44	143700072	243198779	G
	chr2	p25.3-p11.2	698239	89387655	G
	chr2	q11.2-q37.3	96143358	241301905	G
	chr7	p12.3-p11.2	49282714	55936992	G
	chr7	q11.21-q22.1	62291739	99905860	G
	chr7	q36.1- q36.3	150049339	158602499	G
	chr8	p23.1- p12	12627630	32499834	L
	chr8	p12-p11.21	32882718	42971936	G
	chr8	q11.21-q24.3	48549253	146024209	G
	chr11	p15.5-p11.2	2121540	46490960	G
	chr13	q12.11-q34	18556982	113766081	G
	chr20	q11.21-q13.33	29436537	62320720	G
	chrX	p11.23-p11.1	48639378	57116899	G
	chrX	q11.1-q28	61980262	154561665	G
	chrY	p11.31-p11.2	2716461	8521949	L
	chrY	q11.21-q11.221	13208776	17558012	L

Chr: Chromosomes; Aber: Aberrations; G: Gain; L: Loss.

resolution aCGH analysis showed that both lesions share a large number of similar aberrations (Table 1 and Figure 2). Review of these aberrations revealed that many of them have been reported to be very common in colorectal cancers (*e.g.*, segments with copy number increase on chromosomes 13, 7, 8q, and 20q)[9,10], thus supporting the conclusion that the lung lesion is a recurrent metastasis from the primary rectal lesion.

DISCUSSION

This case represents an atypical course of rectal cancer with prolonged disease-free survival of about 19 years prior to the manifestation of disease recurrence in the form of metastatic disease to the lung.

Our aCGH results are consistent with other studies showing similar patterns of chromosomal imbalances in primary colorectal tumors and their corresponding pulmonary metastasis[11,12]. While we realize that aCGH analysis reveals the DNA copy number changes in tumor cells and not the exact origin of these cells, specific trends and patterns of genetic aberrations have been reported to be associated with specific tumor sites and types[10,13].

O'Connell *et al*[14] identified a recurrence risk score based on the expression of 12 genes (seven cancer-related genes and five reference genes). Six of the seven cancer-related genes were grouped into two biological pathways: cell cycle control (KI-67, C-MYC, MYBL2) and stromal response (BGN, FAP, INHBA), and the seventh gene (GADD45B) may regulate the activity of the stromal response genes. Interestingly, while we have not evaluated the expression of these genes in the primary rectal tumor or the recurrent lung metastatic lesion, we have noticed that most of those genes show copy number gains by aCGH in one or both lesions. Specifically, BGN (Xq28), FAP (2q24.2), C-MYC (8q24.21), and MYBL2 (20q13.12) have copy number gain in both the rectal and lung lesions; INHBA (7p14.1) has copy number gain in the rectal lesion; GADD45B (19p13.3) has copy number gain in the lung lesion; and KI-67 (10q26.2) has no changes in the copy number in either lesions.

Approximately 30% of patients with colorectal carcinoma who undergo primary curative surgical resection experience recurrent disease[15,16]. Several predictive factors for recurrence have been reported including: primary site (rectum *vs* colon), advanced stage, invasion of contiguous organs, and presence of perforation[16]. The most frequent sites of recurrence are liver and lungs (33% and 22%, respectively), with the majority of these recurrences occurring in the first two years after surgery[17]. In a retrospective study by Galandiuk *et al*[18], the median time to recurrence for patients who had undergone curative resection for stage Ⅲ colorectal cancer was 16.7 mo. Likewise, another retrospective study by Obrand *et al*[17] reported an average time for distant recurrence of 22.9 mo.

It was established in the early 90's that adjuvant

Figure 2 Common aberrations between the rectal tumor and the lung metastasis. The abnormalities are summarized by the colored bars (blue for the colon tumor and orange for the lung metastasis). The bar is to the right of the tracing when there is DNA gain and to the left of the tracing when there is DNA loss. The length of the bar delineates the area of the chromosome involved.

therapy with fluorouracil and radiation in rectal cancer patients with locally invasive or regional nodal involvement reduces the risk of cancer recurrence and improves the overall survival[18]. More recently the German Rectal Cancer Trial established preoperative chemoradiotherapy as the standard of care in locally advanced rectal cancer showing a lower pelvic relapse rate (6% *vs* 13%) with no change in 10-years disease-free survival (68%) or overall survival (60%) compared to postoperative chemoradiation treatment[19]. Our patient was treated prior to the era of preoperative chemoradiation therapy and therefore received postoperative chemoradiation therapy. It would be difficult to determine whether the prolonged time in remission in this case is due to the administration of adjuvant chemoradiation therapy or simply due to this patient's unique tumor biology.

Late recurrence of colorectal cancer has been reported in small series. Recently, Ishii *et al*[21] reviewed 16 cases of colorectal cancer recurrence after a disease-free interval of 5 years or more. The median disease-free interval was 10 years with a range of 5-16 years. Shimoda *et al*[22] reported the longest recurrence interval in the literature of 16 years in a rectal cancer patient who had recurrent solitary metastatic ileal tumor. To our knowledge, the case we are reporting here represents the longest disease-free survival of 19 years in recurrent colorectal cancer after surgical resection.

The 5-years survival of patients with untreated metastatic disease is less than 5%[22]. Pulmonary metastasectomy in selected group of patients has a positive effect on survival (5-year survival rate of up to 50%)[23]. Accordingly, recurrent disease in this case was treated with preoperative chemotherapy followed by surgical resection. Whether patients with metastasectomies should receive perioperative chemotherapy remains controversial[24].

This case identified striking similarities in genetic aberrations between a primary rectal tumor and its lung recurrence after long disease-free survival. Indeed, it reflects a lack of our full understanding of the tumor microenvironment. The mechanism responsible for recurrence following years of "dormancy" of the cancer cells deserves further investigation, in order to identify a subgroup of colorectal cancer patients that should be treated differently and, perhaps, should have prolonged surveillance. Focusing research efforts on outliers such as this case may help identify fundamental biologic patterns that would also help in more traditional patients.

COMMENTS

Case characteristics

An 81-years-old male with a history of resected rectal cancer presented with cough.

Clinical diagnosis

Dullness to percussion and decrease breath sounds over the upper lobe of the right lung.

Differential diagnosis

Lung mass, lung abscess, pneumonia.

Laboratory diagnosis

WBC 8.20 k/uL; HGB 12.10 gm/dL; CEA 1.20 ng/mL; metabolic panel and liver function test were within normal limits.

Imaging diagnosis

CT/PET scan showed right upper lobe mass (8.2 cm × 7.3 cm) with SUV of 14.5, and right-sided mediastinal and hilar lymphadenopathy, in addition to a 1.2 cm nodule in the left costophrenic angle with no FDG activity.

Pathological diagnosis

Bronchoscopy and biopsy revealed a wild type K-ras adenocarcinoma of colonic primary, CDX2/CK20 positive and TTF1/CK7/CD58 negative.

Treatment

The patient was treated with FOLFOX (5-FU, oxaliplatin and leucovorin) in combination with bevacizumab.

Related reports

The tumor biology of colorectal cancer of is not very well understood and we do not have predictive biomarkers that indicate when a particular patient tumor will recur.

Term explanation

High-resolution array CGH is a molecular cytogenetic method that is used for analyzing DNA copy number aberrations which is applied to detect genomic abnormalities in cancer.

Experiences and lessons

This case report not only represents the longest rectal cancer disease-free interval in the literature, but also applies genetic analysis as a tool to confirm the similarity of the original and metastatic tumor and to predict the risk of recurrence.

Peer review

This article applies genetic analysis to confirm the origin of a recurrent rectal tumor and to predict the risk of recurrence.

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P- Reviewer: Chetty R, Cardinale V, Wongkham S, Zoli W
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