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CASE REPORT

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Durable complete response in a patient with metastatic left-sided colon cancer treated with 5-fluorouracil, folinic acid, and irinotecan (FOLFIRI) and panitumumab: A case report

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Abstract

There are rare patients with metastatic colon cancer who experience dramatic and durable responses. Primary tumor location is a prognostic and potentially predictive factor and should be taken into consideration when deciding on the optimal first-line therapy to be used in combination with chemotherapy.

KEYWORDS

chemotherapy, colon cancer, complete response, metastatic, panitumumab, radiologic

1 | INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancer diagnoses worldwide,[1] and approximately 20% of new diagnoses are metastatic at presentation.[2] The majority of cases of metastatic colorectal cancer (mCRC) are incurable. First-line therapy consists of chemotherapy in combination with targeted agents such as bevacizumab or an anti-epidermal growth factor receptor (EGFR) therapy. The optimal targeted therapy in the first-line setting is unclear; however, recent evidence suggests that sidedness of the primary tumor may be prognostic and predictive for response to bevacizumab or an epidermal growth factor receptor inhibitor. The median survival with optimal therapy is now almost 3 years.[3-5] Despite improvements in systemic therapy for mCRC, long-term survival and complete radiologic responses remain rare.[6] We present the case of a 36-year-old female with no family history of colorectal cancer who presented with two synchronous adenocarcinomas of the sigmoid colon and metastatic retroperitoneal lymphadenopathy. She received palliative chemotherapy with FOLFIRI and panitumumab, experienced a radiologic complete response, and continues to have no radiologic evidence of disease after over 40 cycles of chemotherapy.Durable complete response is rare in metastatic colon cancer. Given the evolving data regarding the prognostic and predictive significance of tumor sidedness, cases of complete response to chemotherapy plus targeted agents should be reported, as these may represent durable responses, and rarely cure.

2 | CASE

We present the case of a 36-year-old previously healthy Caucasian female who presented with hematochezia, abdominal pain, and cramping.

She underwent colonoscopic examination in January 2016. Four benign polyps were removed, and three suspicious lesions at 10, 20, and 30 centimeters (cm) from the anal verge were biopsied. A pedunculated lesion at 10 cm was a tubulovillous adenoma with no high-grade dysplasia.

The ulcerating lesion at 20 cm and the fungating tumor at 30 cm both showed adenomatous mucosa with high-grade dysplasia.

A staging computed tomography (CT) scan of the chest, abdomen, and pelvis showed colonic wall thickening. There was no evidence of distant metastatic disease, although nonspecific subcentimeter lymph nodes were noted in the retroperitoneum and mesentery (Figure S1).

The patient underwent a segmental colectomy in February 2016. Pathology revealed two synchronous adenocarcinomas of the sigmoid colon, one of which invaded the subserosal muscularis propria (T3), and the other of which invaded the muscularis propria (T2), with 9 of 16 regional lymph nodes positive for metastatic disease. Lymphovascular invasion was present, and surgical margins were negative. Multiple benign tubular adenomas were identified within the surgical specimen. Further molecular testing revealed intact mismatch repair (MMR) protein expression, microsatellite stable, BRAF wild-type (WT), and all RAS WT disease. There was no mutation in the *adenomatous polyposis coli* gene. Postoperative CEA and CA 19-9 were normal (2.2 and 8, respectively).

Upon receiving her diagnosis, the patient made a number of dietary alterations on her own discretion, including increasing intake of fruits and vegetables and reducing carbohydrate intake. She also started using Chaga mushroom extract, frankincense oil, cannabis oil, and vitamin D.

Postoperatively, the patient was referred to medical oncology and started adjuvant chemotherapy with 5-fluorouracil, folinic acid, and oxaliplatin (FOLFOX). Because of her high-risk disease, a repeat CT scan was done in March 2016 (Figure 1A), which showed progression of retroperitoneal lymphadenopathy, extending from the level of the renal vessels to the aortic bifurcation and left common iliac region, concerning for metastatic disease. The largest lymph node mass now measured 1.8 cm in short-axis dimension.

Chemotherapy was changed to FOLFIRI, the first-line option of choice for patients with mCRC in Canada, and panitumumab was added. Toxicity consisted of grade one constipation, grade one fatigue, and grade two skin rash. After 6 months of therapy, a CT scan showed calcification and complete resolution of the metastatic retroperitoneal lymphadenopathy (Figure 1B).

Given the complete radiologic response, the case was discussed at a multidisciplinary case conference, which included medical oncology, radiation oncology, surgical oncology, radiology, and pathology. The consensus recommendation was that the patient should receive six more months of chemotherapy, and if there was still no evidence of disease, treatment would be discontinued, and the patient would be monitored closely for recurrence. After 9 months of a treatment break, her CEA rose from 1.4 to 5.3 and imaging showed disease recurrence in the retroperitoneal lymph nodes.

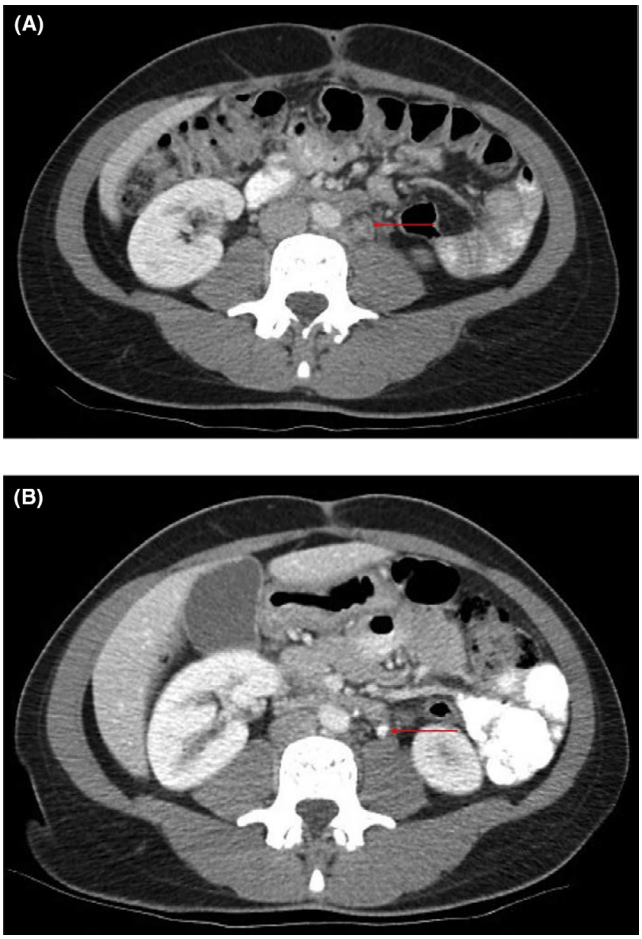

FIGURE 1 A, Baseline postoperative CT scan showing metastatic retroperitoneal lymphadenopathy. B, CT scan 1 y after starting treatment, showing calcification and complete resolution of metastatic lymphadenopathy

A PET CT showed hypermetabolic periaortic and left common iliac retroperitoneal lymphadenopathy with a SUV max of 6.2. She was started back on FOLFIRI and panitumumab and again had an excellent response with shrinking of the retroperitoneal lymph nodes with calcification suggestive of chemotherapy response. After a year of ongoing systemic therapy with no radiologic evidence of disease, she was taken to the operating room for a retroperitoneal lymphadenectomy. Pathology revealed the presence of metastatic disease in 38 of 43 resected lymph nodes.

3 | DISCUSSION

Metastatic CRC usually represents an incurable situation, for which systemic chemotherapy in combination with targeted therapy is the treatment of choice.[7,8] Recent studies have shown that there is a role for EGFR inhibitors such as cetuximab and panitumumab along with chemotherapy in the first-line setting.[3,9,10] The CRYSTAL trial revealed

a progression-free survival (PFS) and overall survival (OS) benefit in patients treated with FOLFIRI plus cetuximab compared to FOLFIRI alone, a benefit which was even greater when assessed in patients with RAS WT tumors.[11,12] The PRIME study showed an improvement in PFS when panitumumab was added to FOLFOX in patients with RAS WT mCRC.[4] The median survival with an EFGR inhibitor plus chemotherapy approaches 3 years; however, complete radiologic responses and long-term survival are rare.

Whether bevacizumab or an EGFR inhibitor is the preferred targeted agent in combination with chemotherapy in the first-line setting is an area of ongoing study. The phase II PEAK trial randomized patients to first-line FOLFOX plus panitumumab or bevacizumab, and the use of panitumumab was associated with a numerically increased OS.[3] In the FIRE-3 trial, patients with mCRC who received cetuximab with chemotherapy had an improved OS compared to those who received bevacizumab with chemotherapy.[5] It should be noted that this study did not meet its primary endpoint of improvement in overall response rate. The CALGB/SWOG 80405 trial has since attempted to add clarity to the question of the optimal targeted therapy in the first-line setting. There was no difference in OS or PFS whether patients received cetuximab or bevacizumab in addition to first-line chemotherapy. A retrospective analysis, however, showed that patients with left-sided primary tumors had a better OS compared to those with right-sided tumors.[13] In those with left-sided tumors, OS was better for those who received cetuximab in combination with chemotherapy, whereas those with right-sided primary tumors had a better OS with bevacizumab and chemotherapy compared to cetuximab and chemotherapy.

The prognostic and predictive significance of tumor sidedness may be pertinent to the case that we present. Our patient had a left-sided, RAS WT colon cancer, and experienced an excellent response with first-line chemotherapy plus an EGFR inhibitor, consistent with what has been reported in the CALGB/SWOG 80405 study. A meta-analysis which included data from the CRYSTAL, PRIME, PEAK, FIRE-3, and CALGB/SWOG 80405 trials has investigated the relationship between primary tumor location and first-line targeted therapy[14] and has suggested that patients with left-sided tumors do indeed experience greater benefit from an EGFR inhibitor in combination with chemotherapy.

Despite improved OS with the use of EGFR inhibitors in combination with chemotherapy, complete responses to systemic therapy remain rare. In the PEAK trial, 2% of patients had a complete radiologic response.[3] In the second-line setting, FOLFIRI and panitumumab resulted in a complete response in only one patient.[15] Further details regarding durability of response and sidedness of the primary tumor in these studies are not known; however, achieving a complete response is nonetheless a rare occurrence in patients with mCRC treated with palliative intent chemotherapy and panitumumab.

A literature review confirms that durable complete responses in patients with mCRC are rare. Two case reports of long-term disease-free survival were identified from Japan.

The first case was of a 67-year-old male with KRAS WT adenocarcinoma of the sigmoid colon with bladder invasion. Surgical resection was not possible; therefore, the patient was treated with FOLFOX and panitumumab. The patient had a partial response and underwent laparoscopic sigmoidectomy and partial cystectomy and was disease-free for 36 months at the time of publication.[16]

The second report was of a 54-year-old male with unresectable KRAS WT sigmoid cancer with bladder invasion. He underwent a diverting ileostomy and received three cycles of FOLFOX and panitumumab and experienced remarkable tumor regression on CT scan. A sigmoidectomy and partial cystectomy were performed, followed by adjuvant chemotherapy. The patient was disease-free for 9 months at the time of report publication.[17] In both of these cases, panitumumab and chemotherapy were used in a neoadjuvant fashion for locally advanced and not metastatic disease.

Although our patient had metastatic disease identified in a large number of lymph nodes at lymphadenectomy and therefore likely has a very high risk of recurrence, she has now survived over 3 years from the time of her initial diagnosis and currently has no radiologic evidence of disease. Her CT scans under-represented the extent of her disease, and the radiologic response did not represent a pathologic complete response. Nonetheless, she has had an excellent response to first-line therapy and has many further systemic therapy options available if her disease recurs in the future. As far as we are aware, there are no published case reports of durable complete responses with the use of a first-line EGFR inhibitor and chemotherapy in mCRC.

4 | CONCLUSION

We present the case of a young patient with RAS WT left-sided colon cancer and metastatic retroperitoneal lymphadenopathy who had a complete radiologic response with palliative intent FOLFIRI and panitumumab. She has undergone lymphadenectomy and had a higher burden of disease than what was represented on imaging. She continues to have no radiologic evidence of disease 3 years after diagnosis. Given the evolving understanding of the importance of tumor sidedness, primary tumor location should be taken into consideration when deciding on the optimal targeted therapy to be used in combination with chemotherapy in the first-line setting. Cases of mCRC with durable complete responses in response to systemic therapy should be reported.

CONFLICT OF INTEREST

Dr Esther Kim and Dr Graham H. Bay declare that they have no conflict of interest. Dr Christina A. Kim has a research grant from Celgene, Inc.

AUTHOR CONTRIBUTION

EK and CAK: performed the literature search, and designed and drafted the manuscript. EK and GHB: prepared the figures. EK, GHB, and CAK: edited and revised the manuscript, and approved the final version of the manuscript.

ETHICS APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the University of Manitoba.

INFORMED CONSENT

Informed consent was obtained from the patient included in the study.

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REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2016;66(1):7-30.
3. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal. *J Clin Oncol*. 2014;32(21):2240-2247.
4. Douillard J-Y, 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(31):4697-4705.
5. Stintzing S, Modest DP, Rossius L, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol*. 2016;17(10):1426-1434.
6. Dy GK, Hobday TJ, Nelson G, et al. Long-term survivors of metastatic colorectal cancer treated with systemic chemotherapy alone: a North Central Cancer Treatment Group review of 3811 patients, N0144. *Clin Colorectal Cancer*. 2009;8(2):88-93.
7. Papamichael D, Audisio RA, Glimelius B, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. *Ann Oncol*. 2015;26(3):463-476.
8. Edwards MS, Chadda SD, Zhao Z, Barber BL, Sykes DP. A systematic review of treatment guidelines for metastatic colorectal cancer. *Colorectal Dis*. 2012;14(2):31-47.
9. Elez E, Argilés G, Tabernero J. First-line treatment of metastatic colorectal cancer: interpreting FIRE-3, PEAK, and CALGB/SWOG 80405. *Curr Treat Options Oncol*. 2015;16(11):52.
10. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol*. 2014;25(7):1346-1355.
11. Van Cutsem E, Köhne C-H, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360(14):1408-1417.
12. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011;29(15):2011-2019.
13. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol*. 2016;34(15_suppl):3504.
14. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur J Cancer*. 2017;70:87-98.
15. 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(31):4706-4713.
16. Tomizawa K, Miura Y, Fukui Y, et al. Curative resection for locally advanced sigmoid colon cancer using neoadjuvant chemotherapy with FOLFOX plus panitumumab: a case report. *Int J Surg Case Rep*. 2017;31:128-131.
17. Yukawa Y, Uchima Y, Kawamura M, et al. A case of advanced rectal cancer resected successfully after induction chemotherapy with modified FOLFOX6 plus panitumumab. *Gan To Kagaku Ryoho*. 2016;43(5):641-644.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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