LONG-TERM SURVIVAL OF A METASTATIC COLON CANCER PATIENT WITH LYNCH SYNDROME: MOLECULAR PROFILING DEMONSTRATED HIGH MUTATION BURDEN AND MULTIPLE ACTIONABLE GENETIC ALTERATIONS

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Received: April 22, 2016; **Accepted:** May 16, 2016; **Published:** May 16, 2016

ABSTRACT

Introduction: The occurrence of cutaneous and testicular metastatic disease from colorectal cancer is uncommon and typically signifies widespread disease with poor prognosis. We herein report a case of such patient that was successfully treated with a multimodal strategy that combines surgical interventions and multi-agent chemotherapies.

Case presentation: In December 2004, the patient initially underwent right hemicolectomy and resection of right lower quadrant abdominal wall metastases for T4, N0, M1 mucinous adenocarcinoma of the cecum. In addition to multiple courses of chemotherapy, he underwent three metastasectoies for repeated recurrences in 2013-2015. He remain disease free at the time of last follow up. Next-Generation sequencing of tumor sample revealed 24 gene alterations and 53 variants of unknown significance [VUS] abnormality.

Conclusion: Multidisciplinary management is imperative to achieve the optimal outcome in our patient. Surgical resection of subcutaneous or testicular metastases may be worthwhile in selected patients with mCRC. The genomic alterations in the tumor of this patient with Lynch syndrome (LS) may serve as the potential targets for future immunotherapy and target therapy.

Keywords: Metastatic colon cancer, Lynch syndrome, Recurrence, Multimodal treatment, Long-term survival, Metastasectomy, Next-Generation sequencing, Genomic alterations

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer related mortality in the USA, with an estimated 132,700 new cases and 49,700 deaths in 2015[1]. Despite developments in diagnosis and treatment, 20% of CRC patients present with metastatic disease and 30% of cases recur after curative surgery[2]. With the advent of combination cytotoxic chemotherapy options (FOLFOX, FOLFIRI) and the availability of biologic therapies[3] including anti-EGFR antibodies, cetuximab and panitumumab, and VEGF inhibitors, bevacizumab, ramucirumab, and AFLIBERCEPT, survival in metastatic colorectal cancer (mCRC) has more than doubled. Surgery now plays an increasing important role in the treatment of patients with limited metastatic disease of mCRC. Long term survival is reported in highly selected patients with oligometastatic disease who underwent

surgery. The therapeutic objectives in patients with mCRC and resectable metastases have shifted from palliation to maximization of the chance of resection by applying systemic bio-chemotherapy[4]. Over the past several decades, resection of low-volume hepatic and isolated pulmonary metastases has been shown to offer long-term survival in carefully selected patients. However, the clinical benefit of resection of metastases to more unusual sites such as subcutaneous or testicular metastases are not reported.

In this article, we report a case of metastatic cecum cancer with subcutaneous or testicular metastases who was successfully treated with multimodal therapies including chemotherapy and repeated metastasectomies.

CASE REPORT

In Dec 2004, a 32-year-old white male developed symptoms of cramping abdominal pain and bowel movement changes. A colonoscopy revealed a constrictive lesion of the cecum. Biopsy of cecum mass was consistent with poorly differentiated mucinous adenocarcinoma.

His family history is notable for Lynch syndrome (LS) and colon cancer. One of his brothers died in his 30s from metastatic colon cancer. Another brother was diagnosed with pancreatic cancer in his 30s.

He underwent right hemicolectomy and en block resection of right lower quadrant posterior abdominal wall for T4, N0, M1 mucinous adenocarcinoma of the cecum. Following surgery, he received chemoradiation therapy with fluorouracil (5-FU) as a radiosensitizer and subsequently received adjuvant chemotherapy with oxaliplatin with fluorouracil (5FU) and folinic acid chemotherapy (FOLFOX).

In March 2013, he developed pain in his right inguinal region, and physical examination revealed enlarged right scrotum and right inguinal lymph node. Testicular ultrasound indicated a testicular mass. Serum CEA, bHCG and AFP levels were normal. Right inguinal lymph node biopsy showed metastatic mucinous carcinoma. DNA Mismatch repair immunohistochemistry showed normal expression in HMLH-1 and HPMS2, while the expression HMSH-2 and HSH-6 were abnormal (Table 1). He underwent lymph node dissection and right radical orchiectomy. Metastatic mucinous adenocarcinoma was found involving right spermatic cord, testis, and soft tissue adjacent to vas deferens. The tumor was CK20-positive, CK7-negative and support colonic origin. Molecular analysis showed wide type Nras and Kras. Subsequently, he was treated with chemotherapy FOLFOX/bevacizumab after surgery.

In August 2014, he underwent resection of metastatic lesions involving right lower quadrant abdominal wall, the right inguinal canal and right retroperitoneal nodes. Surgical pathology showed metastatic mucinous carcinoma. Post surgically, he was then treated with twelve cycles of cetuximab/irinotecan.

In June, 2015, he underwent surgical resection of peritoneal nodule, abdominal wall skin, interaortocaval lymph node and suprapubic abdominal wall nodule. Surgical pathology showed metastatic mucinous carcinoma. Additional chemotherapy was offered, however, he decided to pursue surveillance. The patient remains asymptomatic and work full time at the time of last follow up.

Next-Generation sequencing of sample from metastasectomy revealed wild type NRAS, KRAS and BRAF genes, 24 gene alterations (Table 2) including multiple tumor suppressor genes and DNA repair genes were identified, many of which are potentially druggable targets. In addition, 53 variants of unknown significance (VUS) abnormalities were detected in this patient's tumor.

Table 1
Mismatch repair immunohistochemistry (IHC) testing results.

Gene	Antibody used	Result
MLH1	G168-15	Normal expression
PMS2	A16-4	Normal expression
MSH6	BC/44	Loss of expression
MSH2	FE11	Loss of expression

Table 2 Next-Generation Sequencing revealed 24 gene alterations.	
MSH2	N115fs*2
PTCH1	R1308fs*64
ATM	N3044fs*15+, R1489H
FBXW7	G477S
RNF43	Q283*, R371*
TP53	R158C
ARID1A	D1850fs*4, Q372fs*19, S1985fS*13
ASXL1	G645fs*58
BCORL1	P1681fs*20
BLM	N515fs*16
CYLD	1769fs*7
FGF14	T229M
FLCN	H429fs*
MLL2	P2354fs*30, T4629fs*11
MLL3	K2797fs*26
PAX5	V26G
SOX9	P360fs*23, V306fs*77
TNFAI P3	K759fs*10

DISCUSSION

Several clinical features of this case are quite unique and worth to report. First of all, only few reports have documented long-term survival in patients with mCRC. Remarkably, our patient remains alive without disease recurrence 11 years after initial diagnosis of metastatic disease. Secondly, recurrence of CRC at cutaneous, testicular and spermatic cords is a rare and poorly studied phenomenon. Particularly, the long term clinical benefit of resection of metastases at these sites remain unclear. Thirdly, molecular investigation of tumor samples suggested actionable molecular targets and open up new possibility of intervention.

It is now recognized that multidisciplinary management is imperative to achieve an optimal treatment outcome of mCRC patients. The therapeutic objectives in patients with mCRC and resectable metastases have shifted from palliation to maximization of the chance of resection by applying systemic bio-chemotherapy[4]. With improvement of systemic chemotherapy and surgical approach, more patients are likely to benefit from extended survival that not achievable previously.

Metastatic disease in the abdominal wall from a primary CRC is a poorly studied and understood phenomenon. Ledesma et al.[5] report surgical treatment of isolated abdominal wall metastasis in 22 CRC patients. Koea[6] identified 31 patients with recurrent disease in the abdominal wall were managed surgically at the Memorial Sloan-Kettering Cancer Center, between 1986 and 1998. The authors concluded that abdominal wall metastases are often indicators of recurrent intra-abdominal cancer; aggressive resection in patients with disease restricted to the abdominal wall and associated adherent viscera can result in local disease control with little morbidity and no mortality.

mCRC metastasizing to the testis is even rarer. There have been less than 40 reported cases in the published literature[7-13]. The mechanism of metastasis from the colon to testis remains unknown. Several theories including arterial tumor emboli, retrograde venous spread, and retrograde lymphatic spread have been proposed[13]. Most of the patients with testicular metastases of colonic origin were found to have peritoneal disease with a short survival (averaged 6-12 months) regardless of therapy[7-13].

Resection of metastases to concurrent subcutaneous or testicular metastases has not been reported. In this article, we report such a case with successful management with a combination of chemotherapy and metastasectomies. Literature and our experiences suggest surgical resection of multiple recurrences may be

worthwhile in selected patients, not only as a means of local control, but also as a strategy for long term disease control, without the burden of long term drug therapy.

Because our patient has had repeated recurrences, the possibility of a new recurrence in the future still remains. At that time, hopefully new therapeutic drugs or modalities will be available. Molecular profiling has the potential to revolutionize cancer therapy by helping clinicians select treatments based on the genomic characteristics of each patient's tumor. In the past two decades, comprehensive analyses such as that of The Cancer Genome Atlas have provided important clues into carcinogenesis and discerned additional potentially druggable targets for mCRC[14]. However, considering the numbers of somatic mutations identified in our patient, focusing on a single mutational target alone is unlikely to result in significant clinical impact.

Defects in DNA mismatch repair (MMR) commonly lead to microsatellite instability (MSI), which can be found in most cancers, including a majority of patients with hereditary nonpolyposis CRC (Lynch syndrome, LS)[15]. LS is inherited autosomal dominant and is caused by inactivating germline mutations in MMR genes, including MLH1, MSH2, and more rarely MSH6 and PMS2[16]. It has been hypothesized that the higher level of neo antigens in MSI should facilitate immune eradication and contributes to better survival[17,18]. A proof-of-principle study recently showed that MMR status predicted clinical benefit of immune checkpoint blockade with pembrolizumab[19].

CONCLUSION

Multidisciplinary management was imperative in achieving the optimal outcome in our patient. Surgical resection of recurrences at unusual sites, such as subcutaneous or testicular metastases may be worthwhile in selected patients with mCRC, not only as a means of local control, but also as a strategy for long term disease control by removing potentially drug-resistant residual disease after systemic chemotherapy. Finally, the multiple genomic alterations in this patient's tumor may serve as the potential targets for future immunotherapy and target therapy.

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