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Complete Response to Stage IV Colorectal Adenocarcinoma with Disease-free Survival at 24 Months: Case Report and Overview of the Literature

Madison N. Crank 6746693

Arslan Iqbal

Michael Abdelmasseh

Mohamed Alsharedi

Doreen Griswold

See next page for additional authors

Author Affiliations

Madison N. Crank (*Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia*)

Arslan Iqbal (*Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia*)

Michael Abdelmasseh (*Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia*)

Mohamed Alsharedi (*Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia*)

Doreen Griswold (*Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia*)

Alysia Browne (*Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia*)

Juan R. Sanabria (*Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia*)

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Corresponding Author
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Juan Sanabria MD
1600 Medical Center Drive Suite 2500
Huntington, West Virginia
Email: sanabriaj@marshall.edu

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Complete response to stage IV colorectal adenocarcinoma with disease-free survival at 24 months: case report and overview of the literature

Abstract

Over 150,000 new cases of colon cancer were diagnosed in the US in 2019. Stage and age at diagnosis are important prognostic factors for overall survival (OS). For the age group 70-79, the OS for females with poorly differentiated stage IV colon cancer at 1, 2 and 5 years after surgery is 39%, 15%, and 2%, respectively. We present a case of a 77-year-old female with significant cardiac history. She was diagnosed with stage IV colorectal cancer complicated with enteric fistula. Due to her initial performance status and comorbidities, she was not a candidate for surgery or systemic chemotherapy. Nonetheless, and given her tumor was microsatellite unstable, she was treated with neo-adjuvant immunotherapy. She achieved complete pathological remission with no evidence of disease found upon surgical resection, for which she eventually qualified due to improvement of performance status. The patient is alive and free of disease twenty-four months after the operation.

Keywords

colon cancer, immunotherapy, complete response, disease-free survival

Introduction

Colorectal cancer (CRC) is the third most common malignancy in the US with more than 150,000 newly diagnosed cases per year.[1] Policies for early detection have been developed. However, due to poor compliance, more than 50% of the newly diagnosed CRC is still locally advanced or at a metastatic stage.[1] Risk factors for CRC include age, geography, family history, and genetic background.[4] Most CRCs follow the adenoma-carcinoma sequence from a spontaneous mutation (>80%), with a growing load of tumor microsatellite instability mutations described as part of the Lynch Syndrome.[5] In addition, a reduced yet significant number of patients carry germline mutations. The best described is the polyposis coli syndrome, where a germ mutation in chromosome 5 favors the development of colon cancer in nearly all carriers by age 20.[5] Once CRC is diagnosed by biopsy at colonoscopy, imaging is ordered to stage the disease based on tumor, node, metastasis (TNM) classification.

While CT scans of the chest, abdomen, and pelvis are preferred for colon cancer, MRI of the pelvis is rapidly replacing rectal ultrasound for rectal malignancies.[6,7] Despite these screening and staging techniques, the survival rate for stage IV colon cancer one year postoperatively is only 39%, dropping to 2% by year 5.[3] The introduction of chemotherapeutic agents, i.e. FOLFOX (5-Fluorouracil (5-FU), leucovorin, oxaliplatin), FOLFIRI (5-FU, Leucovorin, Irinotecan), and FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin), in combination with immunotherapy and individual targeted point inhibitors, have changed the prognosis of CRC.[8] We present a 77-year-old female with multiple comorbidities and stage IV CRC that, after medical treatment with complete response, underwent surgery and remains free of disease at 24 months.

Case Report

A 77-year-old white female was admitted for abdominal pain, chronic constipation, and anemia. She had a history of coronary artery disease, chronic obstructive pulmonary disease, type 2 diabetes mellitus, heart failure, hypertension, gastroesophageal reflux disease, and tobacco use. Imaging evaluation with a CT scan revealed a large mass originating from the ascending colon with near-complete obstruction and invasion of the third portion of the duodenum (Figure 1). Findings were confirmed at colonoscopy and esophagogastroduodenoscopy (EGD). Biopsies were positive for poorly differentiated adenocarcinoma of the colon (Figure 2A). The CT scan of the chest was clear with no evidence of metastatic disease.

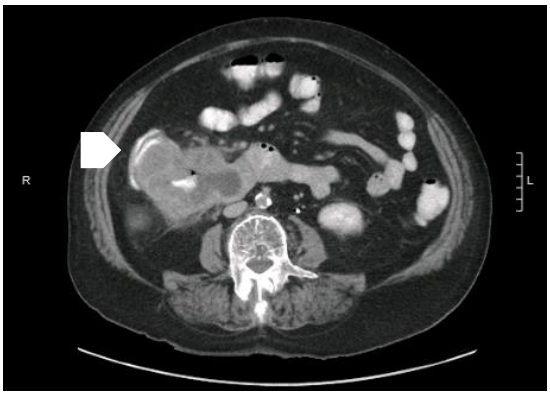
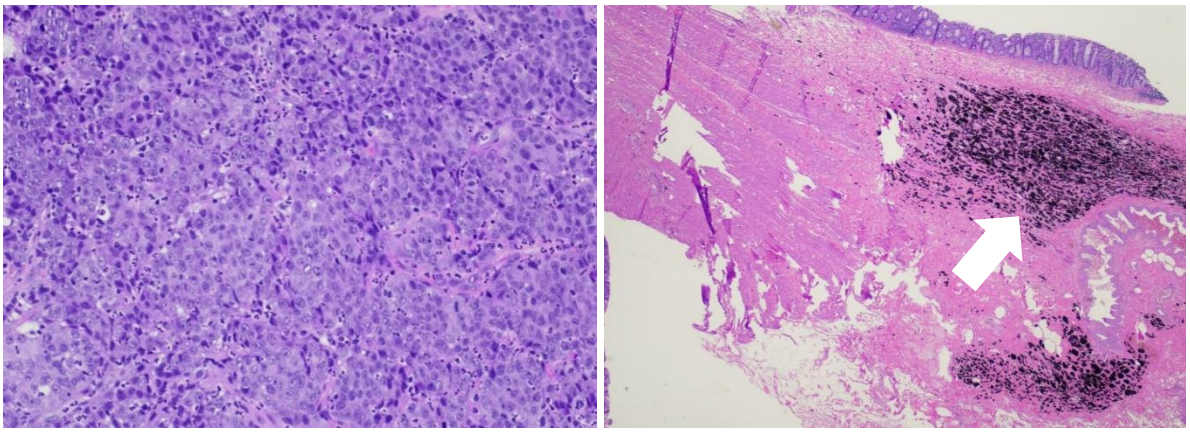


Figure 1. CT abdomen and pelvis with IV contrast revealed a 6.5x7.9cm mass (white arrow), originating from the ascending colon at the hepatic flexure and producing near-complete obstruction of the colonic lumen.



A) **B)** **⟷ 20µm**

Figure 2. A) Evaluation of the endoscopic biopsy from the mass showing ulcerated poorly differentiated carcinoma (by Hematoxylin and Eosin x20.) B) Evaluation of the surgical specimen inked tattoo (white arrow) showing significant surrounding fibrosis and paucity of malignant cells.

The case was reviewed by our multidisciplinary gastrointestinal tumor board, which recommended systemic chemotherapy with FOLFOX with diversion surgery. Accordingly, the patient underwent laparoscopic loop diverting ileostomy. Her postoperative course was complicated with acute coronary syndrome which necessitated an urgent cardiac assessment and

stent placement. She was considered for palliative care after multiple admissions complicated by colo-duodenal fistulae and acute kidney injury. The patient was not a candidate for systemic chemotherapy due to poor performance status and severe protein-calorie malnutrition. First-line chemotherapy used in CRC consists of cytotoxic agents, which are usually associated with systemic side effects (not limited to renal failure, hematological toxicities, infection, and generalized fatigue). Recently, the use of immunotherapy or checkpoint inhibitors has emerged as a new form of cancer therapy. In general, immunotherapy is a quite tolerable systemic therapy with no significant side effects apart from immune-related adverse events (most common are skin rashes, diarrhea, and damage to hair, nails, and oral mucosa).[24] Therefore, the tumor board recommended the use of off-label immunotherapy, given her tumor's microsatellite instability. On a compassionate use basis, she was started on Pembrolizumab even though her performance status was poor with Eastern Cooperative Oncology Group (ECOG) of 3, a BMI of <20 kg/m^2, and albumin of <2g/dl.

The patient tolerated and responded well to treatment and had a significant nutritional recovery. Three months after being on therapy, her overall general condition had a significant improvement that included nutritional recovery and better performance status. Tumor board re-evaluation reached a consensus for further aggressive therapy, including bowel resection. At surgery, she was found to have a significant amount of fibrosis but no evidence of malignancy. A right extended hemicolectomy was performed with resection of the duodenal fistulae which was sealed by a jejunal-serosa patch with temporal duodenal diversion. The patient recovered uneventfully. She re-started immunotherapy four months after surgery, and she remains disease-free twenty-four months after surgery. The pathology specimen showed complete response with fibrosis but no identifiable malignant cells (Figure 2B).

Literature Overview

In the Western world, CRC is the third most common malignancy in males and the second most common cancer in females.[25] Detection at early stages through screening colonoscopies and better multimodality treatments has increased overall survival.[9] Although CRC tends to be a disease of the elderly (median age of 68 for men and 72 for women), it can be present in subjects at an early age, especially in patients with a family history of colon cancer or genetic background.[9] Clinical presentation varies from progressive changes in bowel habits, to bloody stools, to large bowel obstruction with or without perforation. Weight loss occurs at a late stage.[9] Right-sided cancers typically cause bleeding, i.e. producing anemia, and tend to be more aggressive, whereas left-sided lesions tend to cause obstruction.[10] Tumor grade and degree of bowel wall invasion, rather than sidedness or size, tend to influence malignant cell migration to regional nodes, following vascular basins, where cells commonly graft into the liver, or less frequently, into the lungs, bone, or brain.[1] Such line of thought is followed by the tumor (T), nodes (N), and metastases (M) classification. At stage 0, colon cancer has not grown beyond the mucosa of the colon or rectum. The cancer invades the submucosa through the muscularis mucosa during stage I but has not spread to lymph nodes. Stages IIa, IIb, and IIc are reached once the cancer grows into and possibly through the wall of the colon or rectum to invade nearby tissues, sparing the lymph nodes. Stage IIIa, IIIb, and IIIc are designated based on growth through the colon or rectum and spread to lymph nodes, sparing any nearby organs or distant sites. Stage IV colon cancers have spread to distant organs such as the liver or lung and may

reach the peritoneum.[13] According to the TNM classification, CRC ranges from stages 1 to 4, a grading that predicts OS. In general, N+/M+ (positive metastases disease, i.e. liver, lung, bones) CRC is considered a systemic disease.[13]

Screening for CRC should begin at age 50 unless the patient has a first-degree relative with CRC or an advanced adenoma before the age of 60. In the latter cases, screening should begin at age 40, or 10 years prior to the earliest age at diagnosis in the family. Other factors to induce earlier screening include the diagnosis of CRC in a family member under the age of 50 or three relatives with CRC regardless of the age.[11] Initial screening colonoscopy provides visualization of the colon, identification of occult lesions, and biopsy of the tissue. CT of the abdomen and pelvis is used to stage patients with GI cancer found on colonoscopy due to its sensitivity for revealing metastases. [6] Depending on CT findings, other staging procedures, such as laparoscopy, chest x-ray, endoscopic ultrasound, or PET may be performed. MRI is more useful for rectal and anal cancer staging due to its higher sensitivity to reveal positive lymph nodes.[7] The pathologic stage at presentation is the primary indicator of overall survival (OS) after surgical resection in colorectal cancer.[12] After its removal, CRC is staged based on histology, where by far the most common variety is adenocarcinoma, that follows the TNM classification.

Treatment of CRC involves a multidisciplinary team (physicians of oncology, surgical oncology, intervention radiology, radiation oncology, and pathology, as well as nurses and social workers). Upon a complete evaluation of the histological type and stage of the disease, as well as the general health of the patient, including but not limited to comorbidities, general performance, nutritional status, and family support, this team makes treatment recommendations. Guidelines have been enunciated from several societies and institutes, including the American College of Surgery and the National Cancer Institute (NCI). Surgical resection through a minimally invasive or standard open approach offers a more robust pathological staging and the intent to cure. Depending on the disease stage, adjuvant chemotherapy is offered. Special consideration is given to rectal malignancy and liver metastases. Neoadjuvant therapy, consisting of chemo-radiation for rectal disease and chemotherapy for liver disease, offers survival advantage in responsive patients. In fact, for rectal disease, neoadjuvant therapy significantly reduces the risk of recurrent local disease. In liver disease, neoadjuvant therapy causes tumor size reduction, allowing for liver sparing resections.[14] In addition and sadly not infrequently, patients with advanced disease are referred for palliative interventions.[12] Adjuvant chemotherapy is recommended for high-risk patients to eliminate micro-metastases and increase OS.[12]

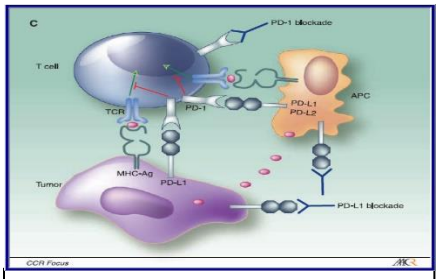


Figure 3. PD-1 ligand on T-cells and its relation with both PDL-1 receptors on malignant cells and APC cells.

The evolution of chemotherapy in the last two decades has been significant and has changed the OS and the free of disease survival (FDS) of patients with advanced CRC. 5-FU/ Leucovorin was the standard protocol for decades until the introduction of FOLFOX and FOLFIRI protocols that doubled the patient's 5-year OS. In addition, targeted therapies based on genetic mutations have made a further survival impact. Targets include vascular endothelial growth factor (VEGF) targeted by anti-angiogenic drugs such as bevacizumab, epidermal growth factor receptor targeted by cetuximab, or programmed cell death protein 1(PD-1)

antagonized by the monoclonal antibody pembrolizumab. PD-1 is a receptor on T-lymphocytes that attaches to the PDL-1 receptor localized on tumor cells. In association with a signal from the MSH proteins, PD-1 causes the T-cells to recognize the malignant cells as "self," preventing lymphocytes from attacking the tumor. Blockade of PD-1 enhances tumor detection by the immune system (Figure 3).[14] Microsatellite instability, present in our patient, reflects a deficiency of mismatch repair enzymes and predicts a poor response to fluoropyrimidine therapy.[8] Therefore, we chose to utilize the immune checkpoint inhibitor pembrolizumab (200mg every 3 weeks for up to 2 years) since it is approved for advanced microsatellite instability-high colorectal cancer that has progressed after a trial of conventional chemotherapy.[17] In the present case, the patient was not a good candidate for a standard chemotherapy protocol. Also, due to her multiple comorbidities, the possibilities of further therapy were limited.[4, 8, 15]

Family history must be taken into account for any patient with CRC to advise the subject about genetic counseling and the detection of hereditary mutations and to decide whether or not to screen family members.[16] Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is one of the most common inherited cancer syndromes due to mutations in genes involved in DNA mismatch repair. Individuals with Lynch syndrome have an increased risk for CRC (15 to 60%) and endometrial cancer (10 to 80%). The Amsterdam criteria to clinically suspect Lynch syndrome include 3 relatives with at least one instance of colorectal, endometrial, small bowel, ureter, or renal pelvis cancer; one relative should be a first-degree relative and one relative should be less than fifty years old at diagnosis. Cancer must affect two successive generations and be verified by pathology. Another hereditary CRC includes the relatively frequent familial adenomatous polyposis (FAP), a condition that segregates in families due to its germline mutation in the APC gene with an autosomal dominant phenotype.[18] Other conditions associated with FAP include congenital hypertrophy of the retinal pigment epithelium (CHRPE) and Gardener syndrome involving multiple bone and fibrous tumors, i.e. desmoids.[6] More importantly, patients may present at an early age with thousands of colonic polyps and, if not treated, will develop CRC before the age of twenty. Thus, patients with FAP are recommended to have a total colectomy before malignancy arrives with lifelong follow up. Patients after colectomy may develop duodenal polyposis and adenocarcinoma, the most common cause of mortality for patients with FAP.[6] The European Organization for Research and Treatment of Cancer endorses that undergoing neoadjuvant chemoradiotherapy improves outcomes, so a short course of radiotherapy is standard preoperatively for rectal adenocarcinomas. Moreover, neoadjuvant chemotherapy, in conjunction with adjuvant immunotherapy, improves local control of the tumor and reduces the incidence of toxicity.[19, 20]

A controversial issue is the timing of surgery after neoadjuvant therapy. In general, surgical stomas are recommended before systemic therapy in lesions producing near or complete obstruction. A diverting procedure decreases the chance of perforation and enhances nutritional recovery. Right-sided lesions can be managed in this way due to low bacterial counts in the right and transverse colon. However, ileostomies are performed less often with left-sided lesions due to the high bacterial load present.[21] Surgery is indicated when a good response is documented by imaging and the condition of the patient is optimized. In the case of rectal tumors, surgical resection is currently recommended between weeks seven and ten after completion of chemoradiation. Waiting beyond eight weeks does not improve overall survival.[22] In fact, in the GRECCAR-6 trial, higher complication rates were observed in patients who waited for eleven

weeks, rather than seven weeks after chemotherapy.[23] Our patient, in contrast, did not undergo any chemotherapy, just immunotherapy.

Brief Summary of Case and Conclusion

A 77-year-old female with stage IV colon cancer and multiple comorbid conditions, including a significant cardiac history, underwent a temporary diverting ileostomy, multiple coronary stents, and a short course of radiation. Due to poor standard chemotherapy tolerance, she was treated with immunotherapy alone followed by surgical resection once her performance status improved. Remarkably, her poorly differentiated adenocarcinoma, despite facing a 12% two-year OS rate, showed a complete response to immunotherapy. Today, twenty-four months after treatment, the patient is alive, free of disease, and doing normal activities.

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