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Teaching Case

FANCD2 Mutation in a Patient With Early Rectal Cancer Receiving Definitive Chemoradiation

Jordan McDonald, BA,[a] Chine-Yu Chuang, BA,[a] J. Kevin Hicks, PharmD, PhD,[b] Darcy K. Berry, MS, CGC,[b] Iman Imanirad, MD,[c] Anupam Rishi, MD,[d] Jessica M. Frakes, MD,[d] Sarah E. Hoffe, MD,[d] and Seth Felder, MD[e,*]

[a]USF Health Morsani College of Medicine; [b]Departments of Individualized Cancer Management; [c]Gastrointestinal Oncology; [d]Radiation Oncology; [e]Surgical Oncology, Moffitt Cancer Center, Tampa, Florida

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Introduction

The standard of care for locally advanced rectal cancer (clinical T3/4N0 or T any N+) has evolved from upfront surgery followed by postoperative adjuvant therapy to a paradigm delivering neoadjuvant chemoradiation (CRT). More recently, the sequence of therapies has been re-examined, delivering all treatment (CRT and chemotherapy) in a total neoadjuvant approach. Subgroups of patients with locally advanced or earlier stage disease may achieve a clinical complete response, allowing highly selected patients to defer or avoid major pelvic surgery, managed by a rectal-preserving nonoperative management strategy. In rare instances, early and severe toxicity may occur during CRT, which can be associated with genetic alterations that disrupt DNA damage response pathways. In this case report, we highlight the clinical course of a patient with T2N0 rectal cancer who declined abdominoperineal resection and subsequently experienced early toxicity during treatment and who was ultimately discovered to be a carrier for Fanconi anemia after broad panel testing for hereditary cancer.

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*Corresponding author: Seth Felder, MD; E-mail: Seth.felder@moffitt.org

Case Background

In accordance with our institutional review board approved protocol to retrospectively review patients treated with radiation for rectal cancer, we present the case of a 69-year-old man with no significant medical history who was diagnosed with a palpable 3-cm rectal moderately differentiated adenocarcinoma, microsatellite stable, magnetic resonance imaging (MRI) staged T2N0, 3 cm from the anal verge (Fig 1). Before diagnosis, he had only noticed intermittent low volume bright red blood per rectum that was not associated with any changes in the caliber of his stool, pain, or diarrhea. A former smoker (2-year pack history >10 years before diagnosis), he was otherwise healthy except for hypertension and a remote history of a quadruple bypass; he had an excellent Karnofsky Performance Status of 90%. The patient was offered radical oncologic resection for which sphincter-preservation was not feasible, necessitating an abdominoperineal resection (APR). To avoid a permanent colostomy, the patient elected to pursue a definitive chemoradiation (CRT) strategy with subsequent transanal local excision or nonoperative management (NOM) depending on tumor response.

The patient was simulated in the prone position on a belly board and planned for 45 Gy at 1.8 Gy per fraction to the pelvis followed by at least a 5.4 Gy boost at 1.8 Gy per fraction with helical 3-dimensional conformal radiation therapy (RT) (Fig 2A,B). Diagnostic MRI images were fused to the treatment

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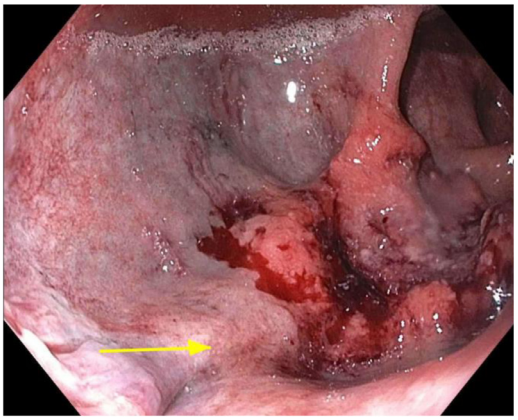


Figure 1 Endoscopic visualization of tumor at diagnosis before any treatment. Arrow indicates the dentate line.

planning computed tomography to facilitate delineation of the gross tumor volume (Fig 2C). As per Radiation Therapy Oncology Group consensus contouring guidelines, the clinical target volume was delineated to include the internal iliac nodes, presacral nodes, and mesorectal nodes[1,2]. The anal canal was included in the RT field because the tumor was within 6 cm of the anal verge. Although this was a low lying tumor, elective irradiation of the inguinal nodes was not indicated.[1]An interval MRI was planned at 30.6 Gy to assess tumor response and tailor the final radiation boost/volume planning. As a radiation sensitizer, the patient received 5-flurouracil (5-FU) in the oral capecitabine formulation.

At a dose of 10.8 Gy, he experienced Common Terminology Criteria for Adverse Events grade 1 diarrhea and fecal urgency, which increased in severity to grade 3 diarrhea along with mild perianal erythema at 19.8 Gy.[2] After 16 fractions (28.8 Gy), the patient developed urinary hesitancy and severe tenesmus and complained of intermittent lower abdominal spasms. Medications including tamsulosin for the urinary symptoms and dicyclomine for the spasms were administered with a 3-day treatment break from CRT. At 30.6 Gy, an interval rectal protocoled MRI with diffusion weighted imaging showed no viable tumor; however, severe proctocolitis and perirectal edema were present (Fig 3). Despite another treatment break his symptoms worsened, requiring hospital admission. Chemoradiation was discontinued given the intolerance to therapy as well as the absence of radiographically measurable viable tumor. With supportive care, the patient's symptoms resolved over the subsequent weeks. Approximately 6 weeks after discontinuation of CRT, flexible sigmoidoscopy demonstrated a flat, white scar with no apparent residual disease, endoscopically consistent with a clinical complete response (Fig 4).

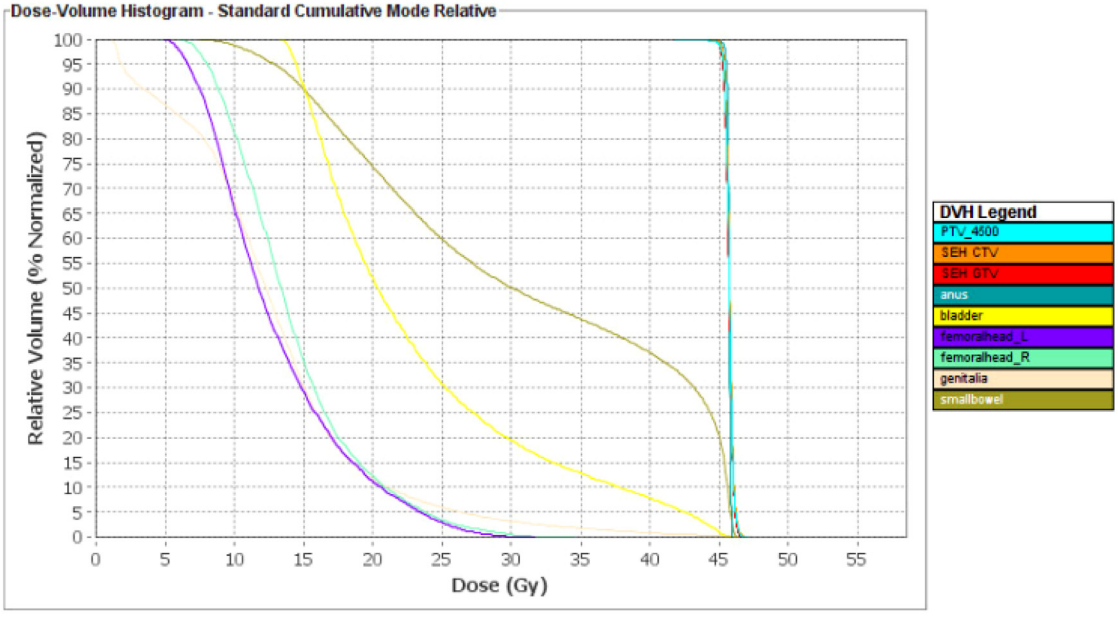
Because the patient was strongly averse to an APR and demonstrated radiographic and endoscopic findings consistent with a complete clinical response (cCR), he was observed under a high intensity surveillance protocol, despite incomplete CRT.[3] However, interval endoscopic examination approximately 6 months from last fraction of radiation demonstrated a nodule, consistent with a local regrowth (Fig 5). Restaging showed no distant disease, and immediate resection was advised. The patient inquired whether pursuing additional radiation was an option rather than pursuing an APR. The patient was referred for genetic counseling and a broad genetic testing panel was ordered that included a total of 72 genes associated with hereditary colorectal cancer as well as sensitivity to ionizing radiation (Table E1), including the Fanconi anemia complementation group.[4] The results revealed a heterozygous germline pathogenic variant *FANCD2* c.707_708del (p.Ile236Argfs*19). Given his increased sensitivity to RT, definitive surgery was recommended for curative intent treatment. APR was thus performed with final pathology ypT2N0, American Joint Committee on Cancer Tumor Regression grade 1 (near complete response). Since his surgery, the patient has been doing well. No further therapy was required given his pathologic findings and he entered into surveillance. At his last colonoscopy through his stoma, 26 months from diagnosis, he was found to have no evidence of disease, with a serum carcinoembryonic antigen of 1.9 ng/dL.

Discussion

Increased risk of radiation toxicity may be associated with comorbidities such as diabetes, hypertension, and collagen/vascular disorders.[5] However, a small proportion of patients possess genetic abnormalities that result in heightened radiosensitivity and are treatment-limiting. (Table E1). Early toxicity can be associated with genetic alterations in DNA damage response genes, with genetic causes estimated to account for up to 80% of observed cases of severe acute toxicity.[5] The majority of patients are unaware of a pre-existing genetic mutation, and for those experiencing severe and acute toxicity, genetic testing can be performed to identify potential causes of radiosensitivity. Referral to specialized genetic services such as genetic counselors can help identify appropriate genetic testing options, interpret test results, and educate patients regarding the effect results may hold for their families. Genetic results may assist in guiding additional treatment considerations, provide insight regarding additional primary cancer risk, and provide information regarding increased cancer risk for family members.

For this case, genetic testing revealed a *FANCD2* variant. Fanconi anemia (FA) is an autosomal recessive disease known to affect about 1 in 136,000 individuals.[6] The FA pathway is comprised of at least 17 known Fanconi

(A)



(B) Regions at Risk Statistics

Name	Blocked	Max Dose [Gy]	Min Dose [Gy]	Median Dose [Gy]	Avg Dose [Gy]	StdDev Dose [Gy]	Physical Vol [cc]
anus	None	45.94	43.42	45.73	45.71	0.16	15.39
bladder	None	46.34	13.34	20.32	23.21	8.46	129.32
femoralhead_L	None	31.69	4.87	11.71	12.96	5.09	122.89
femoralhead_R	None	34.52	6.00	13.36	14.17	4.76	115.53
genitalia	None	45.74	1.08	12.25	12.86	7.29	354.49
smallbowel	None	46.37	7.52	30.07	30.96	12.17	460.69
external	None	47.04	0.26	8.24	12.12	13.25	25,301.48
ring	None	46.06	2.45	27.68	27.04	9.92	3,527.60
blk bowel	DIRECTIONAL	38.47	7.92	16.52	17.24	5.40	210.19
blk femora	DIRECTIONAL	14.98	5.87	10.89	10.84	1.80	16.39

(C)

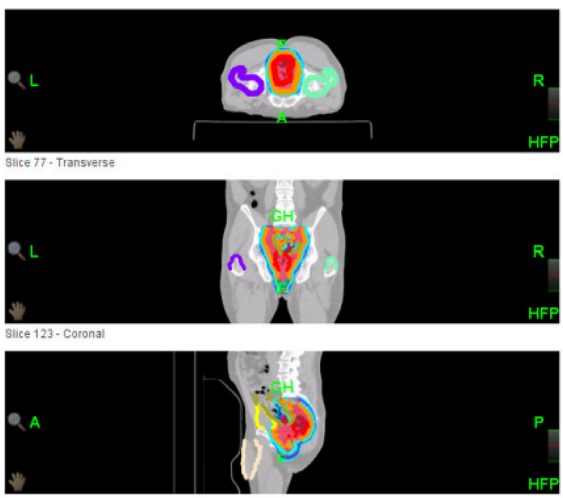


Figure 2 (A) Dose-volume histogram for the treatment plan for this patient. (B) Dose-volume histogram statistics for the patient's treatment plan. (C) Axial, coronal, and sagittal views of radiation treatment plan for this patient.

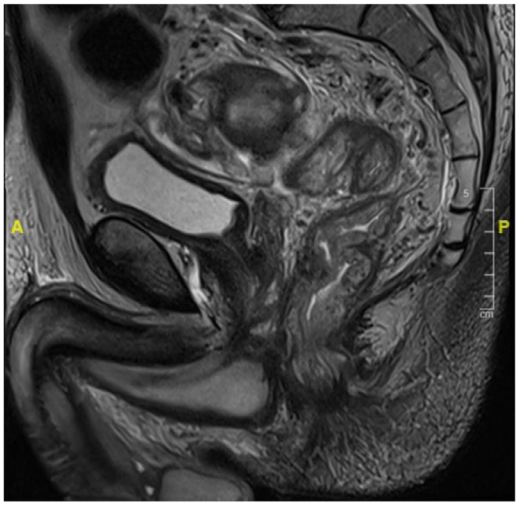


Figure 3 Magnetic resonance imaging after chemoradiation demonstrates no residual mass (mrT0N0) with proctocolitis and perirectal edema.

anemia genes (Table E1),[6] with *FANCA* pathogenic variants being the most common cause of FA (66%).[7] FA genes are involved in DNA repair and are implicated in carcinogenesis as well as toxicity to antineoplastic therapies (radiation toxicity and chemotherapy). This patient carried a pathogenic heterozygous *FANCD2* variant that resulted in loss of protein function. *FANCD2* has a prominent role in the FA pathway. In response to DNA damage, *FANCD2* undergoes monoubiquitination and localizes to the damage sites serving as a molecular platform for recruitment of other DNA repair proteins, as shown in Figure 6.[8] Loss of *FANCD2* can impair the ability to repair single or double-stranded DNA breaks[7] after radiation exposure,[9] but the influence of heterozygous *FANCD2* loss on severe, early onset radiation toxicity has not yet been fully elucidated. A prior case report described acute hypersensitivity to chemoradiation in a

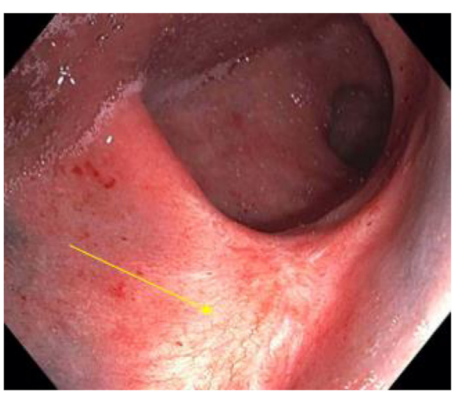


Figure 4 Endoscopic view approximately 6 weeks after discontinuation of chemoradiation secondary to severe acute toxicity. The arrow points to a flat, white scar with telangiectasia consistent with an endoscopic clinical complete response.

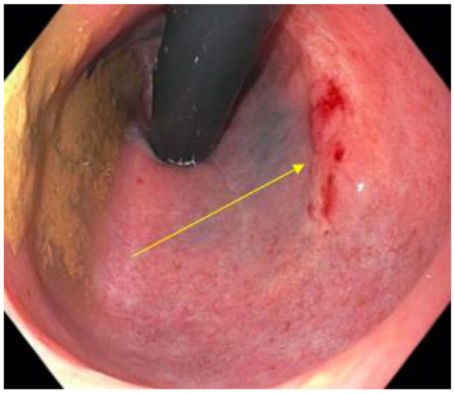


Figure 5 Retroflexed endoscopic view showing a mucosal irregularity with superficial ulceration, which is delineated by the arrow. Blue tattoo is noted just distal.

patient heterozygous for a *FANCA* mutation, proposing that FA heterozygotes may have an increased risk for chemoradiation toxicities.[10]

Additionally, the patient was treated with 5-FU, which sensitizes to RT.[11] Fluoropyrimidines have effectively been used in gastrointestinal malignancies as radiosensitizing agents, with a number of proposed mechanisms of action, including downregulation of NAD+-dependent deacetylase sirtuin-7.[12] Given that the patient's FA mutation is known to induce sensitivity to radiation in the homozygous setting, this heterozygous *FANCD2* mutation may have contributed to the patient's treatment-limiting toxicity. Further research into FA mutation-carriers may determine whether they are at increased risk for severe radiation toxicity, which could also be exacerbated by the concurrent administration of 5-FU. Consistent with our patient's presentation, patients possessing a heterozygous FA genetic mutation (that is, carriers of FA) do not possess the characteristic phenotypic manifestations associated with the syndrome (eg, small or absent distal

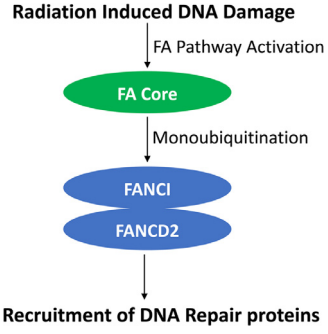


Figure 6 A simplified cartoon of the Fanconi anemia pathway and role of *FANCD2*. Radiation-induced damage can cause DNA conformational changes that activate the Fanconi anemia pathway. The FANCI and *FANCD2* complex undergoes monoubiquitination, localizes to DNA damage sites, and recruits other DNA repair proteins.

radius or thumb, short stature, endocrine anomalies, and diabetes with hyperinsulinemia). If early radiation toxicity is identified, additional treatment should be withheld and alternative approaches considered, as was done in this case.[7]

In retrospect, given the pathologic findings, the patient had likely experienced a complete response of gross disease at 30.6 Gy but still had residual microscopic disease remaining. It may have been possible to pursue a boost dose of RT to the site of small volume initial disease to a microscopic disease dose of 45 to 50.4 Gy once the patient's acute symptoms had resolved. This would have decreased the volume irradiated, significantly limiting the extent of rectal/small bowel mucosa exposed to further dose and potential complications. It is not clear, however, whether the patient could have tolerated such focused RT and whether increasing the dose would have resulted in a durable cCR.

This case raises the question of how best to optimize the radiation dose for the individual patient, which remains an active area of investigation. In the TIMING trial for locally advanced rectal cancer with higher doses of RT to the 54 Gy range, the pathologic complete response (pCR) rate was highest (38%) when the CRT was delivered followed by 6 cycles of fluorouracil, leucovorin, oxaliplatin chemotherapy.[13] This is far higher than the 8% pCR rate reported in the landmark German Rectal Cancer trial, in which 50.4 Gy CRT alone was delivered. The substantial increase in tumor regression, as reflected by higher pCR rates, suggests neoadjuvant systemic chemotherapy administered sequentially to CRT expands the proportion of patients who may be considered for a rectal organ preservation approach. In patients with early stage rectal cancer, neoadjuvant CRT results in significant tumor response, with low reported local recurrence rates after either transanal excision or NOM.[14] In the phase 2 American College of Surgeons Oncology Group Z6041, 49% of clinical T2N0 patients treated with neoadjuvant CRT had a ypT0 or ypTis tumor determined by local excision, with 4% (3 of 79 patients) of the study population experiencing local recurrence at 3 years, resulting in 91% of the patients with preserved rectum at the end of follow-up.[15] Both the CApecitabine, Radiotherapy and Tem Surgery and French Research Group of Rectal Cancer Surgery-2 studies similarly reported good long-term local recurrence oncologic outcomes for early stage rectal cancers treated with neoadjuvant CRT and organ-preserving transanal local excision.[14,16] With MRI-guided RT, it may become possible in the future to assess tumor response with more sophisticated tools during therapy, such as radiomic measurements, such that the boost dose can be better optimized to enhance response.[17]

As we approach wider adoption of total neoadjuvant therapy with improved response rates, more patients may achieve cCR and be interested in a NOM approach. Such a strategy necessitates careful consideration of the volume irradiated to the highest doses because long-term function, particularly of the anorectum, is important for continence.[18] This is significant because the majority of patients choosing such an approach may do so to avoid APR; by consensus contouring guidelines, inclusion of the anal canal would be indicated because the primary tumor would lie within 5 to 6 cm of the anal verge.[21] This would mean that the full circumference of the anal canal would receive 45 Gy so that the boost dose should be precisely targeted to minimize the volume of the anal sphincters receiving the highest doses to maximize an organ preservation approach.

Biomarkers to measure tumor radiation sensitivity have been reported[20,21] and are becoming closer to clinical practice integration, so they may soon have a role as well in personalization of RT. One such test, the Radiation Sensitivity Index, measures the expression profiles of multiple somatic genes from the tumor DNA such that the genomically adjusted radiation dose can be predicted.[22] Future tools such as this may have a role in prospectively identifying those patients with the highest likelihood of achieving a cCR, so that optimizing cure without increasing long-term morbidity may be possible.

Conclusions

Although radiation toxicity is common, acute treatment-limiting toxicity is less frequent and may prompt consideration of an underlying genetic predisposition in DNA damage response genes. This patient was a carrier for FA and developed severe early radiation toxicity necessitating cessation of CRT. As additional genes associated with radiation toxicity are discovered, genetic testing may become more commonplace to provide a germline etiology for radiation sensitivity.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi: https://doi.org/10.1016/j.adro.2021.100717.

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