Teaching Case

Postprostatectomy Radiation Therapy in the Setting of a Rectal Vascular Malformation

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Introduction

External beam radiation therapy (EBRT) is a potentially curative management option for patients with prostate cancer that recurs after prostatectomy. Although generally well-tolerated, the risk of moderate-to-severe rectal bleeding is an important consideration in defining the therapeutic index for a potential course of pelvic radiation therapy (RT). Historically, rectal bleeding has been considered a well-documented side effect of EBRT for prostate cancer, both in the intact1 and postoperative2 settings. For example, in the SWOG 8794 study, the rate of rectal bleeding in the adjuvant, postoperative group was 3.3% versus 0% in the observation group.3 Risk factors, such as prior history of irritable bowel disease,4 prior abdominopelvic surgery,5 and higher radiation dose,6 have been associated with higher risks of rectal toxicity, including bleeding.

Contemporary techniques of EBRT, including intensity modulated RT, appear to mitigate a significant portion of the cumulative burden of rectal toxicity observed in prior eras.2,7 Although radiation is known to cause rectal injury, only a subset of symptoms typically attributed to radiation toxicity are, in fact, a result of endoscopically diagnosed radiation proctitis. In one prospective study, of 141 patients who were observed to have rectal bleeding after RT, approximately half were found to have other findings in addition to radiation proctitis, which may have been causally implicated in rectal bleeding.8

Whether pre-existing colorectal vascular abnormalities increase the risk of moderate-to-severe rectal bleeding after a definitive course of postprostatectomy RT is uncertain. Vascular malformations and anorectal varices are uncommon entities that present an independent risk of spontaneous bleeding, which can present as recurrent bleeding events or sudden onset, life-threatening bleeding. The rate of spontaneous bleeding in rectal varices is estimated to be between 0.45% and 3.6%.9-11 Thus, the safety of pelvic RT in the setting of anorectal vascular malformation or anorectal varices is uncertain. We present a case of biochemically recurrent prostate cancer in a patient with a rectal vascular malformation in whom postprostatectomy RT was indicated with a discussion of the resultant management considerations.

Case Report

A 70-year-old Caucasian man with a past medical history significant for internal hemorrhoids presented with unfavorable intermediate-risk prostate adenocarcinoma (cT1c N0 M0, Gleason score 3 + 4 = 7 [9 of 12 systemic

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cores, 10 of 10 targeted cores), prostate-specific antigen [PSA] level = 9.4 ng/mL). Multiparametric magnetic resonance imaging (MRI) with an endorectal coil was performed during staging evaluation, and revealed 5 suspicious intraprostatic lesions and no abnormalities of the rectum. The patient underwent an uncomplicated robotic assisted radical prostatectomy with obturator lymph node dissection, revealing a single focus of pT2 N0 (R0) Gleason score 3 + 4 = 7 adenocarcinoma involving 40% of the gland bilaterally. The lymphadenectomy specimen revealed 0 of 10 lymph nodes involved with metastatic disease. His postoperative PSA level was undetectable (< 0.02 ng/mL) at the 3-month postoperative follow-up timepoint.

At the 8-month postoperative timepoint, the patient was noted to have a detectable PSA level (0.1 ng/mL) that was confirmed on a second measurement. A restaging evaluation included a multiparametric MRI of the prostate bed with a phased array surface coil, computed tomography (CT) imaging of the chest, abdomen, and pelvis with contrast, and gallium 68 prostate-specific membrane antigen R2 positron emission tomography/CT imaging to investigate for evidence of gross locoregional recurrence. Although MRI did not reveal evidence of residual or recurrent disease, a vascular malformation was visualized in the right rectal wall, 4 cm from the anal verge (Fig. 1A).

In retrospect, this abnormality had likely been compressed and obscured by the endorectal coil during the presurgical staging MRI procedure and not noted at the time of surgical resection. The CT scans corroborated these findings, and additionally detected a component of this vascular malformation that extended to the anterior rectal wall (Fig. 1B). There was no evidence of locoregional recurrence on the positron emission tomography/CT scan. A lower endoscopy was performed to further characterize the lesion, and the results demonstrated the previously described internal hemorrhoids. In addition, a submucosal vascular malformation, which was compressible with insufflation, was visualized and deemed consistent with an arteriovenous malformation (AVM) or a rectal varix (Fig. 1C).

Based on the concern for the possibility of future spontaneous, catastrophic bleeding or radiation-induced bleeding resultant from clinical or subclinical proctitis, an ablative procedure was performed. A fluoroscopy-guided arteriogram and venogram were conducted to map the vascular malformation, revealing that the arterial portion was fed by a branch of the right internal iliac artery, but the venous portion was found to map to a branch of the inferior mesenteric vein (Fig. 2). The portal venous pressure was noted to be elevated at 16 mm Hg. Vascular ablation was completed during the same procedure with a combination of sodium tetradecyl (Sotradecol) sclerosis, followed by embolization with an ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide (Onyx). Subsequently, MRI (Fig. 1E), CT (Fig. 1F), and a postembolization endoscopy verified a thrombosed rectal vascular malformation without signs of mucosal ischemia (Fig. 1G).

The patient was evaluated for possible causes of portal hypertension, including pre-, post-, and intrahepatic pathology testing. Laboratory tests included hepatitis serologies, human immunodeficiency virus testing, alkaline and aspartate aminotransferase, gamma glutamyl transferase, bilirubin, haptoglobin, ceruloplasmin, rheumatoid factor, antinuclear antibody, antimitochondrial antibodies, and a full hematology panel, all of which showed unremarkable results. There was no history of significant ethanol ingestion. Imaging did not show any evidence of splenomegaly or vascular occlusion. An esophagogastroduodenoscopy did not show esophageal varices or other vascular abnormalities in the upper gastrointestinal (GI) tract. In summary, there was no identifiable cause for this vascular abnormality.

After successful ablation of the vascular malformation, the patient underwent salvage RT to a dose of 70.2 Gy in 39 daily fractions. Treatment was delivered concurrently with a 6-month course of androgen deprivation therapy. Representative images of the plan from within the region of the vascular malformation are included in Figure 3. The patient did not require any treatment breaks and tolerated treatment as expected, experiencing a maximum of grade 1 GI and genitourinary adverse events that did not require management. The patient had 2 episodes of small volume (estimated < 2 mL) rectal bleeding between fractions 4 and 6, which resolved without management, and were consistent with episodes he had experienced before EBRT.

RT concluded in September 2019, and androgen deprivation therapy concluded in January 2020 with testosterone recovery by June 2020. At 32 months after EBRT, the patient remains in biochemical remission and free of rectal bleeding.

Discussion

The differential diagnosis for vascular malformations of the rectum includes vascular tumors (hemangioma, angiosarcoma, or Kaposi’s sarcoma), vascular malformations (with possible relation to Osler-Weber-Rendu, Bean’s, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, or Ehlers–Danlos syndrome), or sporadic vascular abnormalities (angiodyplasia or AVM, radiation-induced vascular ectasias, Dieulafoy lesions, or rectal varices). In this case, due the clinical features and historical findings, the differential diagnosis was refined to the most likely diagnosis of an AVM or rectal varix, because the lesion shared characteristics of both of these entities.
The arteriogram of the malformation demonstrated a large caliper arterial supply draining directly into a large caliper vein without routing through an intervening capillary plexus, which is consistent with an AVM. In contrast, moderately elevated portal venous pressures were observed on portal vein manometry, suggesting a diagnosis of a rectal varix. In this case, the arterial supply originated from the internal iliac artery, which typically

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**Fig. 1** Multimodal representations of preablation, A-D, and postablation, E-H, appearance of rectal vascular malformation, showing, A, preablation T2-weighted magnetic resonance imaging (MRI) with arrow indicating vascular malformation; B, preablation dynamic contrast-enhanced MRI with arrow indicating vascular malformation; C, preablation computed tomography with contrast with arrow indicating vascular malformation; D, preablation endoscopic view with arrows indicating mucosal distortion overlying vascular malformation; E, postablation T2-weighted MRI; F, postablation dynamic contrast-enhanced MRI; G, postablation computed tomography with contrast with arrow indicating iodinated embolization agent used to ablate vascular malformation; and H, postablation endoscopic view with no evidence of residual vascular malformation and arrow indicating ablation zone without evidence of residual malformation. *Abbreviations: MRI = magnetic resonance imaging.*

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**Fig. 2** Representative views of angiogram showing, A, cannulation of a branch of the right internal iliac artery; B, visualization of rectal vascular malformation; and C, drainage into inferior mesenteric vein.
supplies the middle and inferior rectal arteries. Classically, this territory often drains via systemic venous drainage (iliac veins to inferior vena cava), but in this case, the drainage was through the portal venous system via the inferior mesenteric artery.

Patients often only present for medical attention with bleeding; thus, the incidence of asymptomatic AVMs within the population remains unknown. In patients undergoing a colonoscopy to evaluate GI bleeding, 1.4% to 3% will be found to have an AVM. Although most AVMs of the intestine are located in the cecum or ascending colon, AVMs of the rectum are not uncommon (14%). Asymptomatic AVMs are often observed, because the risk of subsequent bleeding is thought to be low, but symptomatic AVMs are often managed with resection or sclerotherapy. Fractionated RT has been used for ablation of cerebral and pancreatic AVMs, however, RT is not a standard management strategy for other GI vascular malformations.

Varices are another cause of symptomatic GI bleeding, however, most available literature describes the management of esophageal varices resulting from portal hypertension in patients with cirrhosis. Rectal varices are less commonly described as a source of catastrophic bleeding with an estimated incidence of 38% to 94% in patients with portal hypertension. In one report of 425 patients with portal hypertension, 40 patients with rectal varices were identified, and 15 of these patients were noted to have associated bleeding. Other series have suggested that the rates of bleeding from rectal varices is lower (3%-5%). Although most events are low grade, rectal variceal bleeding can be treatment refractory, high volume, and subsequently fatal. Thus, this diagnosis merits close attention by clinicians, especially for individuals undergoing other treatments or procedures that are independently associated with GI bleeding.

In the present case, the vascular malformation had features of both an AVM and rectal varix. Based on the size and location of the lesion, there was significant concern for clinically significant bleeding if proctitis or subclinical mucosal disruption resulted from RT. The development of rectal mucosal disruption might expose a submucosal AVM to the lumen, resulting in bleeding from elevated pressures during periods of straining or trauma caused by stool passage. In one prospective study, SPCG-7, which randomized patients to androgen deprivation therapy with or without EBRT, no difference was observed between the 2 groups in the histologic appearance of the rectal mucosa at long-term follow up, leading to the possible conclusion that any radiation-induced, late rectal

Fig. 3  Representative axial, sagittal, and coronal views of delivered plan with 70.2 Gy, 65 Gy, 45 Gy, and 30 Gy isodose lines overlaid.
bleeding may be a result of changes to the submucosa.\textsuperscript{39} Based on this possibility, late submucosal remodelling may also have led to an increased risk of delayed bleeding because the vascular malformation was located in the submucosal compartment.

The optimal management for biochemical recurrence after prostatectomy in the context of a rectal vascular malformation is unknown. Possible options include an expansion of the standard radiation volume to intentionally cover the vascular malformation with the intent of ablation, limitation of the standard radiation volume to avoid delivering high doses to the rectal mucosa and underlying connective tissue adjacent to the vascular malformation, close observation of the lesion after a standard course of postprostatectomy EBRT, or procedural ablation preceding a standard course of EBRT. In this case, the concurrent treatment of the vascular malformation was preferred less because of the variceal features of the lesion.

Moreover, extrapolated from the treatment of cerebral AVMs, the expected time course of complete nidus involution with the concurrent photon-based ablation strategy was judged to be longer than the time course for radiation-induced regional mucosal disruption, which was thought to increase the risk of rectal bleeding. The location of the lesion in the anterior rectal wall prevented exclusion from the RT treatment volume, because the lesion was located largely within the anatomic region at the highest risk of harboring occult, recurrent prostate cancer.\textsuperscript{40,41} Observation of the vascular lesion was also not favored due to the concern that regional RT may limit the effectiveness of future procedural ablation of the malformation in the event of a catastrophic bleed. As such, pre-RT procedural ablation was chosen, which led to the desired clinical outcome producing durable oncologic control without serious or persistent rectal bleeding. However, because of the follow-up duration of this report, the risk of late rectal bleeding (>2.7 years) in this patient cannot be excluded.

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