APPLIED RADIATION ONCOLOGY

RADIATION ONCOLOGY CASE

Examining risk factors for rectal toxicity following radiation therapy for localized prostate cancer

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Radiation-induced bowel toxicity, such as radiation proctitis, is a relatively common side effect following radiation therapy (RT) for prostate cancer. Risk factors for late radiation bowel toxicity include patient-related factors such as smoking, hypertension, diabetes and atherosclerosis.[1] Treatment-related factors include the presence of seminal vesicle and/or pelvic irradiation, RT technique and total dose, as well as specific rectal dose-volume parameters such as the V30 and V60.[2-4]

These toxicities are generally graded on a scale based on symptom severity. The RTOG (Radiation Therapy Oncology Group) classification describes the severity of acute gastrointestinal toxicity, whereas the RTOG/EORTC (European Organization for Research and Treatment of Cancer) scoring system categorizes severity of chronic gastrointestinal toxicity.[5] The vast majority of bowel toxicity (> 90%) is grade 1 or 2.[6]

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However, approximately 5% of patients will experience higher grade toxicities, which are often refractory to initial treatment strategies and require more aggressive management.[7]

The aim of this case report is to examine potential, and possibly novel, risk factors that may have contributed to the development of severe rectal toxicity in a patient treated with external-beam RT for localized prostate cancer.

CASE SUMMARY

We present the case of a 70-year-old Haitian man whose past medical history is remarkable for type II diabetes mellitus, essential hypertension, hypercholesterolemia, hemorrhoids, an ischemic stroke with no lasting sequelae, and a coronary angioplasty in 2006. The patient was investigated for prostate cancer following a rise in his prostate specific antigen (PSA) over several years. An ultrasound-guided biopsy was performed in 2014 and confirmed the presence of Gleason score 7 (3 + 4) prostate adenocarcinoma on all 12 biopsies as well as a small periprostatic foci of Gleason score 8 (4 + 4) indicating extra-prostatic invasion. The clinical stage was T2c and the PSA was 15. His International Prostate Symptom Score (IPSS) was 2 at the initial consultation. Given the patient's high-intermediate risk disease, the diagnostic workup was expanded to include a bone scan and pelvic CT, all of which were negative for metastases.

The patient was started on monthly degarelix acetate subcutaneous injections and then received external-beam volumetric modulated arc therapy (VMAT) within 2 weeks. He was treated to a total dose of 78 Gy in 39 fractions that included pelvic nodal irradiation (44 Gy). Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) dose constraints were respected.[4]

After 10 fractions of RT, the patient developed a region of moist desquamation in the intergluteal cleft. He was prescribed silver sulfadiazine cream, offering little improvement. He was referred to a dermatologist who performed a punch biopsy of the lesion. Biopsy confirmed a herpetic lesion and the patient was given oral valacyclovir. The rest of the RT course was unremarkable. Serial PSA measurements at 2, 4, 6 and 8 months after the end of RT were 2.76, 1.39, 0.71, 0.47,

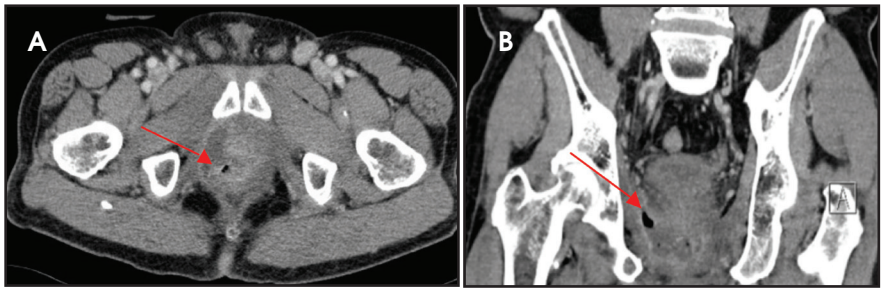

***FIGURE 1**. Axial (A) and coronal (B) CT imaging showing the perirectal abscess (arrows) at 3 months following diverting colostomy.*

respectively. After 6 months of degarelix acetate, the patient refused to pursue treatment due to the sexual toxicity.

The patient did not experience any late genitourinary side effects; however, his hemorrhoidal disease worsened, requiring a hemorrhoidectomy approximately 2 months after completing RT. Following surgery, the patient's lower digestive symptoms resolved temporarily. Unfortunately, he developed recurrent anorectal pain 6 months after completing RT (4 months after hemorrhoidectomy). A subsequent colonoscopy was performed and showed a rectal lesion suspicious of a primary rectal neoplasm. A biopsy of the lesion was performed and demonstrated a radiation-induced rectal ulcer. Initial medical therapy, including sulcralfate enemas, was ineffective.

The patient was referred and received 40 sessions of hyperbaric oxygen therapy with little to no symptomatic improvement. The patient was hospitalized to optimize his pain medication and perform a radiologic workup. CT imaging of the abdomen and pelvis revealed a perirectal abscess that required a diverting colostomy and intravenous antibiotics, as well as a recto-urethral fistula. Follow-up CT imaging at 1, 2 and 3 months after surgery and antibiotics showed no improvement in the abscess with fistulization in the levator ani muscle (Figure 1). Further surgical management of the abscess and fistula was assessed. Due to the extensive surgery that would be required and the high risk of complications, the consensus was to follow the patient with serial imaging and optimize his pain control. Currently, 8 months after the treatment with hyperbaric oxygen, the patient is followed by pain medicine specialists and requires opioids including methadone for pain management. His PSA at last follow up in May 2016 was 0.5 ng/ml.

DISCUSSION

In examining this case, several factors likely to contributed to the patient's overall toxicity and clinical course. First, the patient's multiple comorbidities including type II diabetes, atherosclerotic heart disease and hypertension are all vascular risk factors that likely increased the probability of radiation toxicity. Also, as demonstrated by several published nomograms, the use of anticoagulants, presence of hemorrhoids and use of androgen deprivation can contribute to increased lower GI toxicity.[4]

Second, the multiple biopsies and hemorrhoidectomy may have increased the patient's risk of abscess formation or fistulization. A recent review concluded that rectal biopsies may initiate chronic wounds or infections, do not contribute to the diagnosis of chronic radiation proctitis and, thus, should be avoided unless deemed necessary to eliminate suspicion of a neoplastic lesion.[8] Other studies have described fistula formation following rectal biopsies.[9-11] Interestingly, in a study by Chrouser et al, 38% of patients who developed rectal fistulas after RT had undergone a prior rectal biopsy.[11] This supports the hypothesis that in an irradiated field, further tissue damage from interventions such as a biopsy, likely increase the risk of fistula and/or abscess formation. With regard to the hemorrhoidal surgery, due to the much more proximal localization of the rectal ulcer in relation to the site of surgery, it is unlikely this intervention contributed to the development of the rectal ulcer.

Another consideration is whether the use of a high-dose-rate brachytherapy (HDR) boost may have produced a different outcome in this patient. Given that this patient's dosimetry was well within acceptable limits, there was no formal indication to favor an HDR boost over VMAT alone for this patient. However, in our experience, the use of a single-fraction HDR boost can often limit the V75 (volume of rectum receiving 75% of the prescription dose) to 1 to 2 cc since no PTV is used. In contrast, this hypofractionated technique uses a larger dose per fraction (often 15 Gy in a single fraction) and may potentially have opposite repercussions on normal tissues. Using an alpha/beta = 3 Gy, the EQD2 for an HDR boost of 15 Gy in 1 fraction is 54 Gy. To our knowledge, it is unknown what impact achieving a lower volume of irradiated rectum, and using a high dose per fraction, would have on long-term rectal toxicity. As such, it is unclear what impact an HDR boost would have had in our patient.

One may question whether the use of hyperbaric oxygen therapy (HOT) was indicated for our patient or if it may have led to increased bacterial proliferation in a patient already at risk of infection following a rectal biopsy. HOT involves patients breathing pure oxygen in a pressurized room or tube at 3 times the normal air pressure.[12] These conditions lead to highly oxygenated blood, which may be beneficial because it inhibits bacterial growth and stimulates the release of growth factors and stem cells, promoting wound healing and possibly reversing progressive changes caused by RT.[13,14] HOT is generally recommended in cases of radiation

proctitis after initial medical pharmacotherapy has failed. A Cochrane review revealed a significantly increased chance of improvement or cure following HOT for radiation proctitis (RR 1.72; 95% CI 1.0 to 2.9, p = 0.04).[15] Therefore, it does not appear likely that our patient's HOT contributed to further GI toxicity. The ideal HOT regimen is not known; however, one randomized trial used 30 daily sessions with an option for additional sessions if a clinical improvement was noted.[16]

Also, we have considered whether our patient's oral antiviral therapy may have played a role in increasing his risk of GI toxicity. Published animal and human phase I-II clinical trials have investigated the potential therapeutic effect of adenovirus mediated gene therapy combined with RT for localized prostate cancer.[17-20] This treatment approach often involves intraprostatic insertion of either an adenovirus gene vector followed by subsequent administration of an antiviral prodrug such as valacyclovir. RT was initiated 48 hours after the start of antiviral therapy. Gene therapy was not associated with any grade 3 or higher toxicity and, at 5 years, no late side effects were reported.[21] Despite these results, it remains unclear whether antiviral therapy in patients with viral lesions in noncancerous tissues may act as a radiosensitizer and increase RT toxicity.

Finally, it is well-known that the toxicity profile patients experience for a given dose of RT varies considerably, depending on differences in underlying individual normal tissue radiosensitivity.[22] Several rare genetic syndromes such as ataxia telangiectasia and Nijmegen syndrome that are characterized by mutations in genes in the detection and repair of DNA damage are associated with accrued sensitivity to ionizing radiation.[23,24]

Currently, the investigation of potential genetic differences to explain variable radiation sensitivity is an area of intense research. Genome-wide association studies (GWAS) have revealed polymorphisms associated with radiation toxicity risk.[25,26] The possibility of a genetic predictive risk "signature" is, therefore, promising. As many patient and treatment-related factors affect the overall risk of toxicity for a given dose, new risk models need to be developed that combine patient, treatment and genetic data.

CONCLUSION

In summary, our patient's clinical course represents a rather exceptional case of the development of multiple late radiation toxicities. Although this patient's comorbidities placed him at higher risk of developing radiation-related toxicities, other factors were also likely to be involved. Rectal biopsies are rarely indicated and should be avoided in the setting of GI radiation injury as they may facilitate further complications, as was the case for our patient.

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