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Radiation necrosis after definitive chemo-radiation of anal canal squamous cell carcinoma

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Introduction

Anal cancer comprises 2.5% of all newly diagnosed digestive system malignancies in the United States with 8600 new diagnoses projected in 2018 [1]. Squamous cell carcinoma is the most common histology with a strong association with HPV status. Historically, abdominoperineal resection was the standard treatment for anal cancer which resulted in a permanent colostomy, with a 5-year overall survival rate of 45-86% [2,3]. In 1974, an innovative study by Nigro et al. examining neoadjuvant chemo-radiation prior to surgery and found that there were complete responses and questioned whether surgery was needed at all in the upfront management for anal cancer [4,5]. After many other studies [6-9] confirmed these findings, concurrent chemo-radiation has revolutionized the care of anal cancer by allowing for organ preservation in over 75% of patients and achieving excellent local control [5]. While improved delivery of treatment through the use of IMRT has helped reduce short and long term side effects [9,10] we report on an interesting case of ischemic necrosis of the anal canal after definitive chemo-radiation.

Case Presentation

The patient is a forty-eight year old Caucasian female (ECOG Performance Status 0) who presented with several months of a tender peri-anal mass. Physical exam revealed a 2-cm condyloma in the right anterolateral aspect of the anal canal. Excision biopsy performed by a colorectal surgeon revealed invasive moderately differentiated squamous cell carcinoma with negative margins. HPV status was not tested. Systemic imaging showed no evidence of regional or distant metastasis and was staged cT2N0M0, stage II (AJCC 7th edition). Her past medical history was significant only for hypertension. She had a 15 pack year smoking history and quit smoking cigarettes a year prior to her anal cancer diagnosis. Her medications were potassium but she also took vitamin supplements. She used Tylenol EX 1000mg for pain and Ativan 0.5 mg for anxiety as needed. She did not have any known family members with malignancy. She had no history of previous radiation therapy, connective tissue disorder, inflammatory bowel disease, or autoimmune disease. A multidisciplinary tumor board recommended definitive chemo-radiation for her anal cancer. Her radiation field covered the pelvic lymph nodes at risk, which included the internal and external iliac, pre-sacral, peri-rectal, and superficial inguinal lymph nodes bilaterally; these lymph node regions were covered with 45 Gy in 25 fractions, at 1.8 Gy per fraction. The meso-rectum and the anal canal were treated with a sequential boost with an additional 3 fractions to 50.4 Gy in 28 fractions, at 1.8 Gy per fraction, using 6 MV photons in a 7-field step and shoot intensity modulated radiation technique (IMRT). Concurrent chemotherapy was continuous infusion 5-FU, 1000 mg/m^2, for 96 hours (day 1 – 4; day 29 – 32), and mitomycin C, 10 mg/m^2 (day 1 and 29). There were no unplanned treatment breaks and chemo-radiation was completed in 37 days. She developed loose bowel movements and moist desquamation in the bilateral groin regions and anus; Imodium, Aquaphor and Silvidene were recommended. During the last two weeks of her treatment, she was prescribed oxycodone and anusol to help with pain and swelling of the anal canal. She lost 4 lbs from her pre-treatment weight.

She was seen at one month post radiation for routine follow up. While her radiation dermatitis had resolved, she had persistent tenesmus, anal discomfort, and rectal spasms. Her 3-month post treatment PET/CT revealed an interval increase in intensity of the patient's rectal mass, SUV 12.7 compared to 10.7 prior to treatment. Anoscopy was performed and did not reveal any signs of residual disease. Unfortunately, her symptoms worsened and she developed rectal incontinence that affected her work schedule and her personal relationships. At 5 months post chemo-radiation, a formal exam under anesthesia was performed which revealed extensive circumferential tissue necrosis with exudative debris. These areas were debrided and biopsied. The pathology revealed extensive necrosis with ulcerated fibro-connective tissue and atypical mesenchymal spindle cells, compatible with radiation effect. There was acute inflammation seen in some areas with no evidence of malignancy. She had no signs of disease recurrence. She did, however, continue to have uncontrollable leakage with her bowel movements and the need to wear adult diapers going to work, which caused significant distress in her life.

A repeat exam under anesthesia was performed and a second debridement of the anal canal was performed. This again showed a significant amount of radiation necrosis with no evidence of tumor.

Within 1 month after her final debridement, she had a complete reversal of her symptoms and regained rectal continence. She became less anxious and returned to work without issues. She continues to be monitored without evidence of recurrence with a completely healed anal canal.

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Discussion

We report on the first published case of radiation necrosis of the anal canal after definitive treatment using standard radiation doses and chemotherapy.

In reviewing anal cancer studies including Nigro et al, ACT I, ACT II, ACCORD 03, RTOG 9811, and RTOG 0529, there is no mention of radiation necrosis [4,6,8,9]. In fact, the clinical trials that performed dose escalation did not report any radiation necrosis [11-13].

RTOG 0529 was a phase 2 multi-institutional randomized trial that compared IMRT dose painting radiation to 3D conformal radiation technique with concurrent mitomycin based chemotherapy [9]. The use of IMRT resulted in significant decrease in gastrointestinal, dermatologic, and hematologic toxicities but can increase radiation hotspots [10,14]. Review of the literature showed that some studies investigated the predictive factors of early and late local toxicities in anal cancer but none were related to radiation dosimetric parameters [15]. As radiation necrosis is seemingly a rare event for this dose and fractionation, there are no direct treatment correlates.

For our patient who developed radiation necrosis, IMRT was used with standard dosing and technique and the constraints for RTOG 0529 were all met. The maximum radiation hot spot was 55.54 Gy (110%). She also received standard chemotherapy dosing, and was not on any medications that could act as a radiosensitizer. We could not identify any risk factors that could contribute to the necrosis.

In conclusion, the treatment for localized anal cancer is concurrent chemo-radiation with good loco-regional control rate. Unfortunately, there can be a risk of radiation necrosis that can negatively impact the patient's quality of life. There are no clear risk factors for radiation necrosis in this case and perhaps the patient's genetic factors could predispose. Current practitioners should be aware of radiation necrosis as a possible cause of persistent symptoms in anal cancer patients.

Conflict of Interest

None

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