Regorafenib-Induced Radiation Recall Presenting as Acute Blood Loss Anemia With Rectal Bleeding and Severe Proctitis

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Abstract

Radiation recall is a rare inflammatory reaction that occurs in an area that was subjected to prior irradiation that is usually triggered by certain drugs or chemotherapy agents. This reaction is drug-specific for each individual and occurs in about 6% to 9% of the patients receiving chemotherapy after radiation therapy. We report a case of radiation recall–induced severe proctitis which is thought to be triggered by administration of regorafenib for stage IV rectal adenocarcinoma with lung metastases. We present a 65-year-old female patient who was initially diagnosed with stage III T4N1M0 rectal adenocarcinoma that was treated with neoadjuvant concurrent chemoradiotherapy, followed by low anterior resection. The tumor was pathologically staged a ypT3 yN1 with a partial response to the treatment. After the surgery, the patient was found to have lung nodules consistent with metastatic disease, when she was treated initially with folinic acid, fluorouracil, and oxaliplatin, plus bevacizumab. The patient had further disease progression with metastases in her lungs despite treatment with several chemotherapy agents. She was started on regorafenib, an oral vascular endothelial growth factor inhibitor, as a fourth line of therapy. However, in a month after initiation of oral regorafenib, and 9 months after the prior radiation treatment, the patient presented to the emergency room with a complaint of bright red blood per rectum. She was diagnosed with severe radiation proctitis that was treated therapeutically with argon plasma coagulation. This particular case serves as a reminder that although infrequent and rare, radiation recall may result in an inflammatory reaction in an organ such as rectum. To the best of our knowledge, this regorafenib-induced severe proctitis secondary to radiation recall has not been reported in the literature before.

Hematology oncology, metastatic rectal adenocarcinoma, chemoradiotherapy, regorafenib, radiation recall proctitisIntroduction

Radiation recall is a unique, acute inflammatory reaction that develops in a previously irradiated area, triggered by the administration of certain drugs or chemotherapeutic agents.[1,2] This reaction is drug-specific for each individual and occurs in about 6% to 9% of patients receiving chemotherapy after radiation therapy.[1,2] Radiation recall may occur anywhere from weeks, months to years after radiation therapy. Regorafenib is an oral active multikinase inhibitor of vascular endothelial growth factor (VEGF), stromal and tyrosine kinases, that has demonstrated prolonged overall survival[3] in patients with metastatic colorectal cancer (mCRC) pretreated with chemotherapeutic agents. Regorafenib causes hypertension, proteinuria, hand-foot syndrome, stomatitis, diarrhea[4] as frequent adverse effects (AEs); however, gastrointestinal bleeding is a rare adverse event. The development of acute blood loss anemia with severe proctitis in the setting of prior chemoradiotherapy in our patient makes it an interesting presentation of radiation recall phenomenon.

Case Presentation

We report a 65-year-old woman with past medical history of hypertension and type 2 diabetes mellitus who initially presented to the emergency room after an elective ventral hernia repair with complaints of severe nausea, intractable vomiting, intermittent abdominal cramps, tenesmus, and diarrhea associated with a weight loss of about 42 pounds within 6 months of presentation. She subsequently had a colonoscopy that showed a rectal mass about 10 cm from the anal verge.

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She was then referred to our cancer center for further evaluation and managment.

Computed tomography (CT) of the chest showed an indeterminate noncalcified 5-mm nodule in the right upper lobe. There was no discrete mediastinal or hilar lymphadenopathy. Small axillary lymph nodes were present, all less than 1 cm. The CT scan of the abdomen and pelvis revealed a perirectal mass measuring about 3.1 cm × 2.8 cm without any evidence of enlarged lymph nodes. Also noted was a mild diffuse fatty infiltration of the liver without evidence of focal hepatic lesion. Subsequently, a positron emission tomography (PET) CT scan was also done that showed a hypermetabolic 5-mm right upper lobe lung nodule with an SUV (Standardized Uptake Value) of 1.4. There was abnormal activity within the rectum with an SUV of 23. Moderate diffuse activity was seen throughout the rectum and colon. There was an abnormal fat stranding and nodular soft tissue in the right perirectal space with an SUV of 10.5. There was a presacral lymph node which measured about 10 mm with an SUV of 4.0. Uterus showed diffuse thickening of the endometrium. Patient did have lower endoscopic ultrasound and was clinically staged as a T4N1 tumor. Thus, the patient was diagnosed with stage III T4N1M0, KRAS wild-type, rectal adenocarcinoma with a 10-mm presacral nodule and a 5-mm right upper lobe lung. The patient was initially started on treatment with concurrent chemoradiotherapy with capecitabine as the chemosensitizing agent during the days of radiation therapy. She received radiation treatment, 25 fractions, dose per fraction 180 cGy, total dose delivered 4500 cGy. She then underwent low anterior resection, primary anastomosis along with total abdominal hysterectomy with a bilateral salpingo-oophorectomy. The histopathological analysis of tumor specimen revealed a YpT3 yN1 stage with residual moderately differentiated adenocarcinoma invasive into the pericolic adipose tissue, presence of perineural invasion, surgical margins negative, and 2 of 15 lymph nodes positive for metastatic carcinoma.

Surgery was complicated with development of wound abscess and multiple infections. She underwent incision and drainage of abdominal wall abscess. The wound eventually resolved with vacuum-assisted closure of wound. Restaging PET CT scan revealed a 2.2-cm right upper lobe nodule, 13-mm left upper lobe nodule, multiple bilateral pulmonary nodules, and multiple hypermetabolic pulmonary nodules, suggesting progression of pulmonary metastatic disease. Low-grade fluorine-18 fluorodeoxyglucose uptake in the rectum was also confirmed. Subsequently, right upper lobe lung nodule biopsy was done that was consistent with metastatic adenocarcinoma, with tumor cells staining positive for CDX2 and CK20, and negative for CK7 and TTF1.

She was then switched to an oral active inhibitor of VEGF, stromal and tyrosine kinases, regorafenib 160 mg orally once daily for 3 weeks and then 1 week off for 28-day cycle as fourth-line therapy due to continuous disease progression. Within a month after initiation of regorafenib and 9 months after she completed her concurrent chemoradiotherapy, the patient presented to the emergency room with complaints of rectal pain, tenesmus, and rectal bleeding with passing of blood clots. Her laboratory workup was remarkable for acute anemia with hemoglobin (Hgb) of 8.9 g/dL. Her prior laboratory workup performed a week prior did not show any anemia with her baseline Hgb being 14 g/dL. She was transfused 1 unit of pooled red blood cells (PRBCs) and a colonoscopy was performed subsequently that revealed severe proctitis (Figures 1 and 2) which was attributed to previous radiation. Thereafter, bleeding ceased after being treated with argon plasma coagulation (APC) (Figure 3).

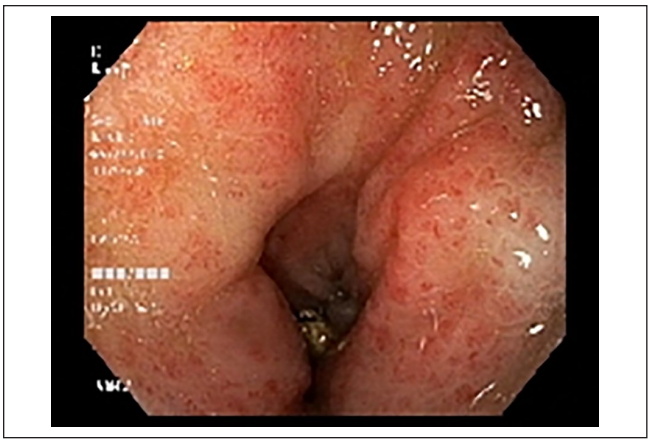

Figure 1. Image from the colonoscopy showing inflammation in the rectum.

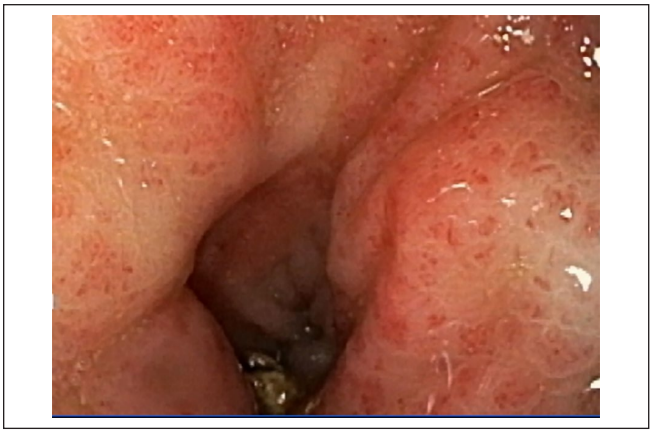

Figure 2. Another image from the colonoscopy showing proctitis.

Discussion

Our case demonstrates that a radiation recall is a rare and infrequent inflammatory reaction of a previously irradiated area precipitated by drug administration,[1,2] regorafenib in our patient. A pivotal phase III clinical trial, the Colorectal Cancer Treated with Regorafenib or Placebo after Failure of Standard Therapy (CORRECT) study,[3] demonstrated that

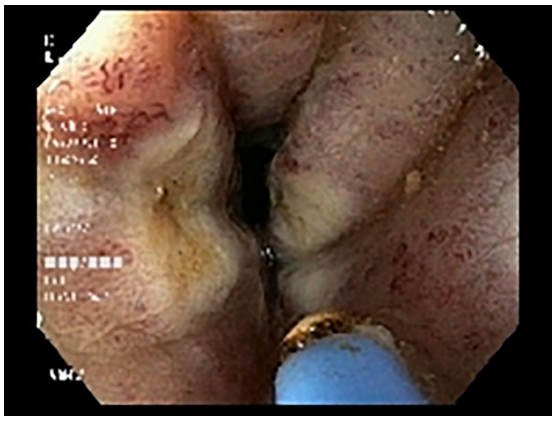

Figure 3. Treatment with argon plasma coagulation (APC).

regorafenib reduces disease progression and prolongs overall survival for up to 1.4 to 2.5 months when compared with placebo in the patients with mCRC who were pretreated with chemotherapy agents. Regorafenib causes frequent AEs such as hypertension, hand-foot syndrome, diarrhea, fatigue, stomatitis, hoarseness, and proteinuria.[4] One case study reported retinal hemorrhage and mild hematochezia in a patient with underlying liver dysfunction.[5] However, profuse gastrointestinal/rectal bleeding complication from regorafenib-induced radiation recall with endoscopic evidence of proctitis in a patient pretreated with radiotherapy has not been reported in the literature before, to the best of our knowledge.

Radiation recall may occur anywhere from weeks, months to years after radiation therapy.

Various chemotherapy agents such as taxanes and anthracyclines have been found to be associated with triggering this phenomenon. The literature also revealed that several nonchemotherapeutic medications such as quinolones, levofloxacin, azithromycin, antitubercular drugs, tamoxifen, nitrofurantoin, and simvastatin[6] have an association with radiation recall.[7-10]

The usual presentation of radiation recall is dermatitis precipitated by a medication that is preceded by radiation exposure which was first described with dactinomycin.[1] Our patient represents, to our knowledge, the first case of this rare rectal tissue inflammation that was secondary to administration of regorafenib. Various hypotheses have been set forth to explain this radiation recall phenomenon. Radiation therapy lowers the threshold for an immunological response in an individual and distorts the morphological balance by accelerating fibrosis and lowering immunological competence primarily related to endothelial cell damage, resulting eventually in capillary proliferation and increased fibrosis.[11] One possible mechanism that has been widely hypothesized is that the radiation therapy induces cells to secrete low levels of cytokines, interleukin-1 and interleukin-6, platelet-derived epidermal growth factor β, transforming growth factor β, and tumor necrosis factor α that are responsible for an inflammatory response and continue to secrete low levels of cytokines until a precipitating drug is introduced resulting in the upregulation of the cytokines, causing a recall reaction.[12] Radiation recall reactions that were reportedly seen after the first administration of certain drugs in individuals previously exposed to radiation varied from one another as described in the literature, mostly by the time interval between the completion of radiation therapy, administration of precipitating drug, and the occurrence of recall. The time interval between radiation exposure and recall reaction ranged from 2 days to 15 years. The time interval between the first dose of administration of chemotherapy and development of recall reaction also varies anywhere from within 18 to 48 hours to 7 days to as long as 15 years.[13] Radiation recall reaction may involve almost any organ system including skin, mucous membranes of gastrointestinal tract, lung, and muscle; although only cutaneous manifestation, radiation recall dermatitis (RRD) has been widely reported in the literature.[10] Radiation recall differs from radiation enhancement that results from early initiation of precipitating or chemotherapy agent within 7 to 10 days of radiotherapy. Administration of chemotherapeutic agent at least 7 to 10 days after radiation therapy, followed by occurrence of adverse tissue or skin reaction, is usually required to make a diagnosis of radiation recall.[13] Standard treatment for radiation recall includes withdrawal of the precipitating agent and supportive care. As for RRD that has relatively more evidence of rechallenge in the literature, drug rechallenge tends to produce either only a mild recurrence or no recurrence of recall.[1] We held the patient's regorafenib and administered PRBCs for acute blood loss anemia. She had a colonoscopy that demonstrated multiple areas of friability and oozing in the rectum, consistent with radiation proctitis. She was treated therapeutically with APC.

Our case report is important in that it presents the first report of radiation recall proctitis associated with regorafenib. Our patient received much higher doses of radiation in treatment of her cancer, which may have put her at further risk for radiation recall. In addition, our patient had a longer interval of approximately 9 months between starting the radiation and starting regorafenib. Our patient also had the shortest interval of about a month between starting regorafenib and presenting with rectal bleeding. Late effects of radiation can also cause symptoms that are chronic such as severe rectal pain, tenesmus, fibrosis, fistula formation but rarely sudden onset rectal bleeding. Recent studies suggested that regorafenib is likely to enhance the tumor radiosensitivity by blocking the VEGF and thereby inhibiting the angiogenesis. We need more studies to investigate whether regorafenib induces radiation recall in an area subjected to prior irradiation. Our patient had a definitive diagnosis of radiation proctitis based on endoscopic findings and she developed acute rectal bleeding in the setting of recent initiation of regorafenib that is suggestive of radiation recall.

Radiation recall from regorafenib is rare but can potentially arise in any site that has been previously irradiated. Treating physicians are reminded of the potential toxicity from regorafenib followed by radiation. Our case particularly serves as an important reminder to the treating physicians that patients with cancer who were exposed to prior radiation could develop radiation recall involving any organ, in our case, rectum, frequently triggered by either chemotherapy or the targeted therapies. This case demonstrates the importance of looking beyond the common lower gastrointestinal pathologies such as hemorrhoids and cancer as potential culprits of bleeding per rectum.

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Declaration of Conflicting Interests

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Ethics Approval

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Informed Consent

Informed consent for patient information to be published in this article was not obtained because patient passed away by the time we began this manuscript.

Prior Presentation of Abstract Statement

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