

Teaching Case

Recurrent Radiation Recall Mucosal Toxicity of the Upper Aerodigestive Tract: A Case Report

Laura A. McGrath MSN, APRN, CNP, James A. Martenson MD*,
Randi R. Finley CMD, RTT

Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota

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Introduction

The dose, volume, and treatment field of radiation therapy can generally be used to predict the risks of immediate and late adverse events. However, radiation recall reactions can unexpectedly affect patients who receive systemic therapy after a course of radiation therapy. Radiation recall dermatitis is the most common recall reaction. Herein, we describe a case of radiation recall mucosal toxicity of the upper aerodigestive tract in a patient who received multiple chemotherapy regimens.

Case Presentation

A 54-year-old man presented with neck pain, left-arm weakness, and left-arm pain. Magnetic resonance imaging showed metastatic involvement of the C5 vertebra. Subsequent findings confirmed abdominal and retroperitoneal lymphadenopathy and bilateral pulmonary nodules. Cervical disectomy was performed. Pathology test results demonstrated metastatic well-differentiated adenocarcinoma, possibly from a primary gastrointestinal tract tumor. Staging with positron emission tomography/computed tomography showed metastatic disease in the abdomen and lungs but no obvious primary site. The

results of an upper endoscopy were negative. Ultimately, no primary tumor was identified.

We provide a timeline of the temporal relationship among the patient's radiation therapy courses, chemotherapy cycles, and episodes of mucosal toxicity (Fig 1). The patient began image guided radiation therapy at a dose of 20 Gy in 5 fractions to C4 through C6. The dose-volume histogram shows the amount of radiation administered to critical mucosal structures by course 1 of radiation therapy (Fig 2A). Immediately after radiation therapy, mild, self-limiting acute esophagitis developed. The patient's neck and arm pain improved within 2 weeks, and he began chemotherapy consisting of modified folinic acid (leucovorin), fluorouracil, and oxaliplatin (FOLFOX6) but without a bolus of fluorouracil.

Two weeks later, the patient returned for the next cycle of chemotherapy and reported a skin reaction in the radiation treatment field, dysphonia, and dysphagia that manifested as difficulty swallowing pills. His medical oncology provider diagnosed erythema and dry desquamation in the radiation field and weight loss (2 kg). Chemotherapy was continued. After cycle 3 of modified FOLFOX6, the patient continued to have dysphagia. An upper endoscopy showed diffuse candidiasis throughout the entire esophagus. Topical and systemic antifungal therapies were initiated; however, even after eradication of the infection, which was confirmed with an upper endoscopy, the patient continued to have dysphagia and odynophagia after each chemotherapy cycle. After cycle 6 of modified FOLFOX6, the patient was hospitalized for septic shock of an uncertain cause, and chemotherapy was suspended. The patient's neutrophil count was within the reference range on admission ($4.14 \times 10^9/L$). Two days

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* Corresponding author. Department of Radiation Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

E-mail address: jmartenson@mayo.edu (J.A. Martenson).

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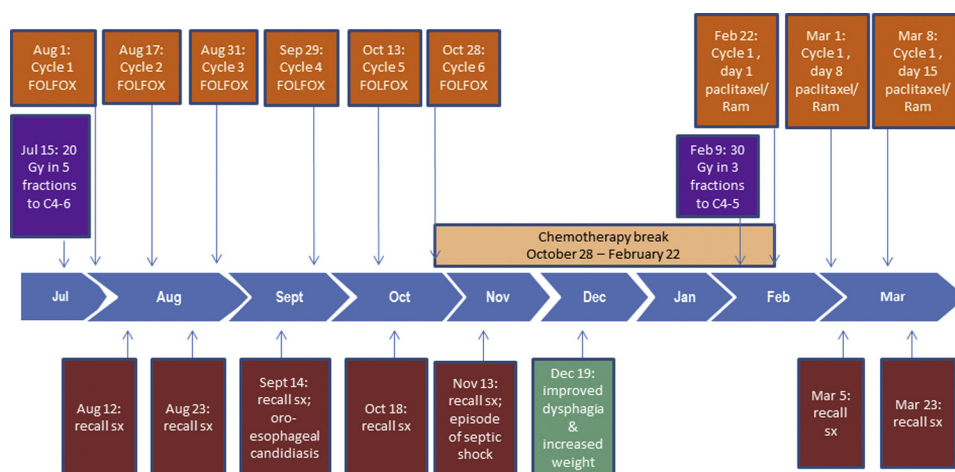


Figure 1 Time line of the temporal relationship between radiation therapy courses, chemotherapy cycles, and radiation recall mucosal toxicity. Chemotherapy cycles and radiation therapy courses are shown above the time line, and treatment responses are shown below. Dates for radiation therapy indicate the last day of treatment. *Abbreviations:* FOLFOX = folinic acid (leucovorin), fluorouracil, and oxaliplatin; Ram = ramucirumab; Sx = symptoms.

after admission, he had mild neutropenia (neutrophil count: $0.93 \times 10^9/L$). His neutrophil count was $1.27 \times 10^9/L$ on the day before discharge. Because the onset of sepsis predated neutropenia, the contribution of neutropenia to sepsis was not certain.

After a 4-month break from chemotherapy, the patient reported worsening neck and left-arm pain and near-complete loss of strength in the left deltoid and biceps muscles. Magnetic resonance imaging of the cervical spine showed evidence of progressive, residual malignancy

throughout the posterior elements of C4 through C5. Additional radiation therapy was considered superior to surgery, and a course of stereotactic body radiation therapy was delivered at a dose of 30 Gy in 3 fractions to C4 through C5. Dose-volume histograms show the amount of radiation administered to critical mucosal structures by course 2 of radiation therapy (Fig 2B) and the cumulative amount of radiation administered by courses 1 and 2 of radiation therapy (Fig 2C). The patient did not have any radiation therapy–related acute toxicity.

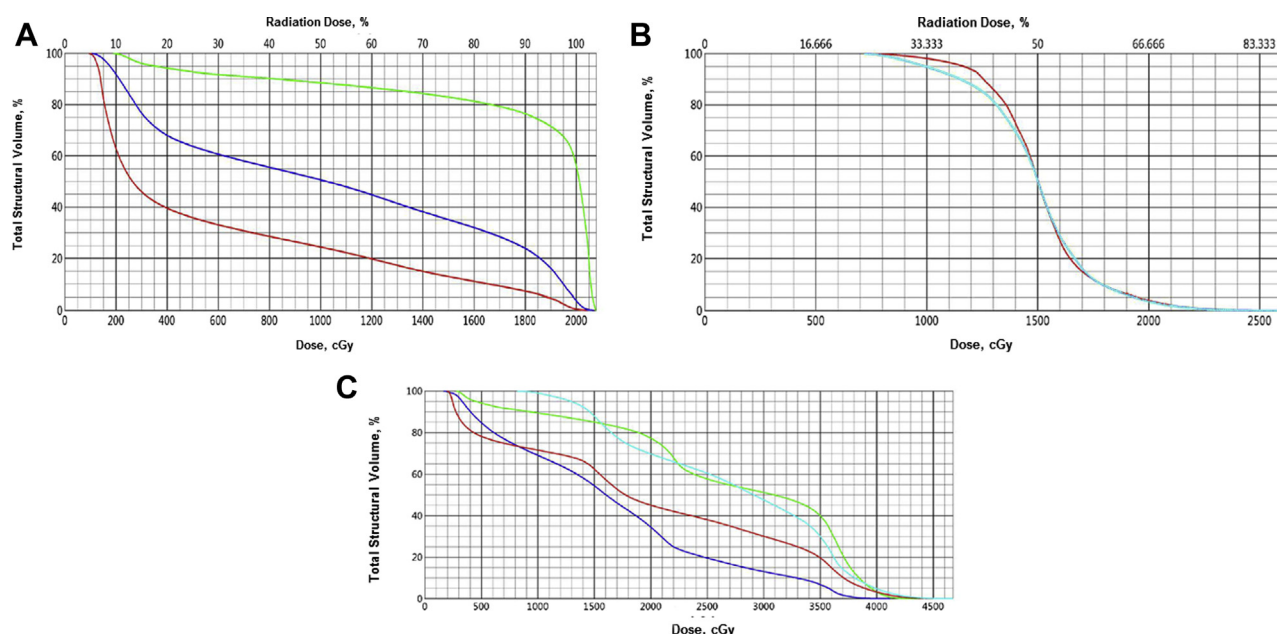


Figure 2 Dose-volume histograms showing radiation administered to mucosal structures. (A) Radiation administered by course 1 of radiation therapy; (B) radiation administered by course 2 of radiation therapy; and (C) cumulative radiation administered by both radiation therapy courses. Red indicates the larynx; green, esophagus; blue, hypopharynx; light blue, oropharynx.

Approximately 2 weeks after completion of radiation therapy, treatment with paclitaxel and ramucirumab was initiated. Two weeks after this chemotherapy regimen was started, the patient reported throat pain and dysphagia. Empirical antifungal therapy was administered; however, despite completing this course, the patient continued to have debilitating symptoms. Computed tomography of the neck did not show clinically significant changes, and the results of a video-fluoroscopic swallowing examination were negative for esophageal stricture.

The patient was referred to the Department of Otorhinolaryngology to undergo flexible nasopharyngoscopy, which showed mild hypopharyngeal edema without any concerning lesions, ulcerations, necrosis, or signs of infection. Edema was believed to be consistent with postradiation changes. In the 10 months since cancer was diagnosed, the patient's weight had decreased by 24%, from 110.2 kg to 83.8 kg. Because of the severity of the patient's swallowing symptoms and associated weight loss, a percutaneous endoscopic gastrostomy tube was placed to administer nutrition and hydration.

Six weeks after his first infusion of paclitaxel and ramucirumab, the patient reported improved dysphagia and odynophagia. The patient was informed that his symptoms were consistent with radiation recall and that a similar reaction should be expected if he continued chemotherapy. After he received this information, the patient made the informed decision to receive additional paclitaxel and ramucirumab. At successive follow-up visits, the patient reported postchemotherapy dysphagia and odynophagia with limited ability to eat.

Discussion

With the exception of mild, self-limiting esophagitis after the first course of radiation therapy, the patient's episodes of mucosal toxicity, including the worst episodes, were temporally related to the administration of chemotherapy (Fig 1). According to published tables,¹ the doses of radiation administered with course 1 (20 Gy in 5 fractions) and course 2 (30 Gy in 3 fractions) would be equivalent to total doses of 23 Gy and 50 Gy, respectively, if administered with 2-Gy fractions and assuming an α/β ratio of 10. The results of these calculations must be interpreted with caution, particularly for large fractions administered with stereotactic radiation therapy.² Taken together, the temporal profile of symptoms in relation to the chemotherapy cycles that the patient received supports the diagnosis of radiation recall mucosal toxicity.

Radiation recall is a poorly understood and unpredictable phenomenon that is characterized by acute inflammation confined to an area that previously received radiation therapy; generally it is caused by antineoplastic therapy.³ Various chemotherapeutic drugs have been

associated with radiation recall, and the most common causative agents are cytotoxic antibiotic medications (daunorubicin, doxorubicin, daunorubicin, and bleomycin) and taxanes (paclitaxel and docetaxel).⁴ The pathophysiologic mechanisms of radiation recall are unknown, but increased sensitivity of radiated stem cells and drug hypersensitivity have been suggested.⁵ In a retrospective study of 171 patients who received docetaxel after radiation therapy, the incidence of radiation recall was 1.8%.⁶

A diagnosis of a radiation recall reaction is usually made by reviewing prior oncologic treatments, taking a thorough medical history, and performing a physical examination. A recall reaction usually occurs within a few days or weeks after exposure to the precipitating drug.³ Cutaneous manifestations are the most common; however, one-third of cases involve sites other than the skin.³

Treatment of radiation recall consists of supportive care but depends on the affected organ system and the severity of the reaction.³ Systemic corticosteroid and nonsteroidal anti-inflammatory drugs have not been proven to affect the time to symptom resolution.³ Double-blind, placebo-controlled, phase 3 clinical trials have shown that liquid doxepin and "magic mouthwash" effectively mitigate mucosal toxicity related to radiation therapy and chemotherapy.^{7,8} Although these agents have not been evaluated for the treatment of radiation recall toxicity, a therapeutic trial of these agents could be considered for appropriately selected patients. Withholding the causative agent is recommended because symptom resolution rarely occurs when the precipitating treatment is continued.³ Rechallenge with the reaction-eliciting drug does not always provoke another reaction; however, care should be taken because the reaction may recur.⁹ In the present case, radiation recall symptoms may have worsened after the second course of radiation therapy because the patient received a prior course of radiation therapy and multiple cycles of chemotherapy. An evaluation of dosimetric parameters (Fig 2), including an assessment of hot spots, can assist in the diagnosis of radiation recall toxicity. Our patient chose to continue palliative chemotherapy after radiation recall toxicity was diagnosed and after discussion with health care providers.

Although dermatitis is the most common manifestation of radiation recall, our case shows that mucosal manifestations of radiation recall can occur and that recurrence may be observed even if the systemic regimen is changed. This case shows the importance of recognizing mucosal toxicity as a manifestation of radiation recall.

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