A Case of Severe Rectal Hemorrhage Possibly Caused by Radiation Recall after Administration of Gemcitabine

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(Received for publication on November 1, 2014)
(Revised for publication on October 16, 2015)
(Accepted for publication on October 19, 2015)
(Published online on March 25, 2016)

Radiation recall is an acute inflammatory reaction that can be triggered when systemic agents are administered long time after radiotherapy. Because radiotherapy is now indicated for many types of cancer, care should be taken regarding possible toxic events relating to radiotherapy in combination with radio-sensitizing agents. Gemcitabine, one such anti-cancer agent, is widely used, especially for urologic cancers. We report an intriguing case of possible radiation recall in the rectum caused by gemcitabine administration 37 years after radiation therapy. From a review of the literature, it appears that there have been no reported cases of radiation recall in the rectum with such a long interval between radiation therapy and chemotherapy. Here, we describe the case and provide a literature review.

Keywords: gemcitabine, bladder cancer, radiation recall, rectal hemorrhage

Introduction

Radiation recall is an acute inflammatory reaction that is confined to previously irradiated areas and can be triggered by the administration of systemic agents, including gemcitabine.1-4 This rare phenomenon remains poorly understood, but increased awareness may aid its early diagnosis and appropriate management. According to the literature, in most cases, the interval between radiation therapy and chemotherapy is less than 1 year,1 although in a few cases the interval was more than 10 years.5,6

Gemcitabine was found to be effective for the treatment of squamous cell carcinoma (SCC) both experimentally7 and clinically.8 Primary bladder cancer, especially the histologic subtype that contains SCC, can also be treated by gemcitabine.9,10 In our case, because the surgical specimen indicated pure SCC, we applied systemic gemcitabine-cisplatin (GC) chemotherapy, which nowadays is a standard regimen for urothelial carcinoma.

Here, we report an intriguing case in which severe rectal hemorrhage was likely caused by radiation recall after gemcitabine administration. Surprisingly, the phenomenon occurred 37 years after the radiation therapy. In this report, we describe the course of the patient and discuss the relevant literature.

Case Presentation

An 86-year-old woman was referred to our hospital with gross hematuria. She had a history of radical hysterectomy and adjuvant extrabeam radiotherapy using cobalt (opposite two-dimensional irradiation, total of 50 Gy, Fig. 1A) for uterocervical carcinoma (at age 50 years) and bilateral mastectomy for breast cancer. At the first visit to our hospital, cytological examination of a urine sample showed atypical squamous cells (class 4). Com-
Computed tomography (CT) and magnetic resonance imaging showed a pelvic mass on the posterior wall of the urinary bladder with severe right hydronephrosis/hydroureter. In these images, no distant metastasis was detectable. Cystoscopic examination showed a mass involving the right ureterovesical junction.

A transurethral biopsy of the tumor revealed high-grade SCC. After providing informed consent, the patient underwent surgical treatment. Because the bladder was strongly adhered to the surrounding tissue as a result of the previous hysterectomy and radiotherapy, it was carefully dissected and its vasculature was appropriately handled. The right ureter was initially ligated at the upper portion because the right kidney was severely atrophic. The left ureter and the urethra were resected and the urinary bladder was removed together with the anterior vaginal wall. As a result, radical cystectomy, right distal partial ureterectomy, and ileal conduit diversion were performed. The pathological diagnosis was poorly differentiated bladder SCC invading the vagina with a negative surgical margin (pT4, N0, M0).

Systemic adjuvant chemotherapy was attempted on post-operative day 56. The regimen consisted of standard GC chemotherapy with 1200 mg of gemcitabine (days 1, 8, and 15) and 80 mg of cisplatin (day 2). On day 7, high-grade fever was reported (38.8°C), and the prophylactic wide-spectrum cephalosporin antibiotic cefozopran was administered for 4 days, although neutropenia was not observed. Because of this febrile event, the administrations of gemcitabine on days 8 and 15 were cancelled. On day 9, mild thrombocytopenia (6.2 × 10^4/µL, Grade 2 in the Common Terminology Criteria for Adverse Events version 4.0) was present, alongside a high white blood cell count (17.8 × 10^3/µL).

On day 13, sudden melena (containing more than 300 g of blood) and subsequent hypotension were reported. A
blood test showed severe anemia (hemoglobin concentration: 6.3 g/dL), necessitating blood transfusion. An emergent colonoscopy showed diffuse multiple ulcerations in the rectum (Fig. 1B). Although we did not collect samples for culture, bacterial colitis including Clostridium infection (pseudomembranous colitis) was unlikely based on these macroscopic (endoscopic) findings. Biopsy specimens underwent polymerase chain reaction assays to detect tuberculosis; the results were negative. Although the fiberscope was not inserted as far as the rectosigmoid portion of the colon, active bleeding from the oral portion to the rectosigmoid portion was not observed. In contrast-enhanced CT images, multiple regions of discontinuity in the mucosa suggested ulceration (Fig. 1C). The CT images also showed rectal wall thickening, suggesting inflammation of all layers from the mucosa to the serosa. Interestingly, the locations of these lesions corresponded to the previously irradiated regions (Fig. 1A). In the same CT images, the colonic portion not previously irradiated was intact (data not shown). The microscopic findings of biopsied specimens indicated ulcerous rather than ischemic or pseudomembranous colitis, which was consistent with the endoscopic findings (data not shown). Inferior mesenteric angiography did not demonstrate active extravasation of contrast material (data not shown). The patient was therefore treated conservatively, and the rectal bleeding disappeared within 2 days. The patient did not complain of cutaneous symptoms in the irradiated area. However, the CT images taken on the day of the hemorrhage showed that the irradiated subcutaneous fat tissue was obliterated (Fig. 1F) compared to the findings before (Fig. 1E) and 4-years after (Fig. 1G) the hemorrhage. Based on the clinical course and findings, we retrospectively concluded that the rectal ulceration likely occurred because of radiation recall caused by the administration of gemcitabine, one of the major agents known to cause the recall phenomenon.

One year after GC chemotherapy was attempted, the tumor recurred in the left inguinal lymph nodes, and lymphadenectomy was carried out. Follow-up CT showed no evidence of rectal wall thickening or ulcerative lesions (Fig. 1D). After the surgery, the patient was transiently free from cancer. However, she subsequently died of systemic metastases 4 years after GC therapy.

**Discussion**

We describe a possible case of radiation recall that occurred 37 years after radiation therapy. If this is indeed a case of radiation recall, the interval is the longest reported to date, according to our search of the literature on radiation recall. Moreover, this would be the first case of rectal ulceration and bleeding caused by radiation recall. Therefore, care should be taken when gemcitabine is used in patients who have previously been irradiated, even if the radiation therapy was performed more than 30 years earlier.

To obtain an overview of the characteristics of radiation recall caused by gemcitabine administration, we reviewed articles found by conducting a search using the terms “gemcitabine” and “radiation recall.” From 1994 to 2014, 29 articles were published describing 37 cases, including 17 in men and 16 in women (in 4 cases, the sex was not given). The ages of the patients ranged from 14 to 79 years, with a mean (±standard deviation) of 52.5 years (±13.8). The reported numbers of patients with intervals from radiation therapy to chemotherapy of less than 1 month, 1–12 months, and more than 1 year were 8 (25.0%), 22 (68.8%), and 2 (6.3%), respectively. The most common symptoms of radiation recall were myositis (n = 12, 32.4%) and dermatitis (n = 12, 32.4%). In our patient, no skin or subcutaneous abnormality was reported at the time of melena. Therefore, we retrospectively compared subcutaneous inflammation in archival CT images as shown in Fig. 1E-G. In our case, radiation recall occurred prominently in the rectum, where the previous radiation effect might have been enhanced by the preceding surgery. Interestingly, our case had the longest reported interval between radiation therapy and chemotherapy. Furthermore, this is the only reported case of possible radiation recall involving proctitis resulting in severe rectal ulcers and hemorrhage.

The mechanism of radiation recall remains unclear, and this phenomenon has been described only in case reports. However, it is hypothesized that DNA damage, vascular damage, or epithelial stem cell inadequacy resulting from irradiation may cause hypersensitivity to gemcitabine. Administration of corticosteroids or non-steroidal anti-inflammatory agents is an effective treatment for radiation recall because of their anti-inflammatory action. The severity of radiation recall seems to be correlated with the dose of radiation. Case 32 in Table 1 was previously irradiated at two sites with different doses (20 Gy and 8 Gy), and subsequently, the reaction at the 20-Gy-irradiated site was more severe than that at the 8-Gy-irradiated site. The accumulation of more case reports is needed to explore the actual pathophysiology of radiation recall and to establish a better treatment protocol.

In conclusion, we reported a rare case of suspected radiation recall in the rectum as a result of gemcitabine administration. When gemcitabine is used in previously irradiated patients, radiation recall should be considered if physicians encounter atypical symptoms, including rectal hemorrhage. Appropriate treatment can then be provided, and patients may thereby avoid serious complications and recover successfully.
# Table 1 Literature review of radiation recall caused by gemcitabine

| Reference | Age (years) | Sex | Radiation dose (Gy) | Interval between RT and chemotherapy (months) | Time until recall reaction (months) | Type of reaction |
|-----------|-------------|-----|---------------------|---------------------------------------------|-----------------------------------|-----------------|
| 1 J Clin Oncol 1994;12:1535–1540 | 35 | M | 56 | 4.4 | 0.93 | Dermatitis |
| 2 Ann Oncol 1999;10:1105–1108 | 60 | M | 45 | 0.93 | 4 | Myositis |
| 3 Ann Oncol 2000;11:1615–1616 | 58 | F | 33 | 1 | 3 | Myositis |
| 4 J Clin Oncol 2000;18:695–696 | 61 | M | 24 | 0.93 | 0.3 | Dermatitis |
| 5 J Clin Oncol 2000;18:693–694 | 41 | F | 30 | 5.5 | 0.47 | Dermatitis |
| 6 Lung Cancer 2001;33:299–302 | 65 | F | 36 | 3 | 1.4 | Myositis |
| 7 Tumori 2001;87:428–430 | 65 | M | 45 | 2 | 1.4 | Dermatitis |
| 8 Int J Radiat Oncol Biol Phys 2002;53:394–400 | 54 | M | 35 | 0.23 | 7.75 | Brainstem radionecrosis |
| 9 Same | 63 | F | 35 | 3.4 | 0.1 | Lower extremity lymphangitis |
| 10 Same | 79 | M | 30 | 0.37 | 0.33 | Dermatitis, typhilitis, and colitis |
| 11 Same | 59 | M | 40 | 3 | 3 | Optic neuritis |
| 12 Same | 52 | F | 50.4 | 0.7 | 2.1 | Myositis in rectus muscle, sq fat stranding |
| 13 Ann Oncol 2003;14:783–787 | ND | ND | ND | ND | ND | Dermatitis and pneumonitis |
| 14 Gynecol Oncol 2003;91:421–422 | 67 | F | 45 | 3 | 0.5 | Dermatitis |
| 15 Cancer 2004;100:1793–1799 | 62 | M | 50.4 | 1.3 | 2 | Myositis |
| 16 Leuk Lymphoma 2005:46:1313–1320 | 26 | F | 38+45b | 7 | 0.03 | Pericardial effusion |
| 17 Same | 37 | M | 45 | 15 | 0.13 | Pericardial effusion |
| 18 Same | 53 | M | 45+45b | 7 | 2.87 | Pericardial effusion |
| 19 Same | 31 | F | 25+45b | 14 | 3.27 | Pericardial effusion |
| 20 Am J Hematol 2005;80:91 | 32 | F | 60 | ND | 0.07 | Dermatitis |
| 21 JOP 2006;7:306–310 | 52 | M | 50.4 | 5 | 4 | Dermatitis, myositis |
| 22 Am J Clin Oncol 2006;29:636 | 54 | F | 30 | 1 | 2 | Myositis |
| 23 Anticancer Drugs 2006;17:107–111 | 57 | M | 50.4 | 3.03 | 0.5 | Pancreatitis, duodenitis |
| 24 Clin Lymphoma Myeloma 2006;7:51–58 | ND | ND | ND | ND | ND | Skin ulceration |
| 25 Clin Oncol 2006;18:85 | 58 | M | 24 | 2 | 0.82 | Myositis |
| 26 Strahlenther Onkol 2007;183:215–217 | 64 | F | 50.4 | 8 | 0.83 | Pneumonitis |
| 27 Clin Infect Dis 2007;45:e72–e76 | 53 | F | 25 | 6 | 0.03 | Dermatitis |
| 28 Same | 67 | M | 54 | 0.37 | 0.07 | Dermatitis (erysipeloid reaction) |
| 29 Curr Oncol 2008;15:53–62 | 55 | F | 20+20b | 0.33 | 0.07 | Dermatitis |
| 30 J Clin Oncol 2009;27:1456–1461 | ND | ND | ND | ND | ND | Pericardial effusion and pleural effusion |
| 31 J Ultrasound Med 2010;29:1499–1502 | ND | ND | 39.6 | 2 | 0.58 | Myositis |
| 32 Acta Oncol 2010;49:615–262 | 44 | F | 20+8b | 2 | ND | Erythema |
| 33 Oncol Lett 2011;2:85–90 | 50 | F | 44.1 | 1.87 | 1.87 | Myositis |
| 34 J Cancer Res Ther 2012;8:439–441 | 53 | M | 45 | ND | 3.07 | Dermatitis |
| 35 J Pediatr Hematol Oncol 2013;35:156–161 | 14 | F | 28+20b | 0.17 | 1.17 | Myositis + compartment syndrome |
| 36 Int J Rheum 2013;41971:Epub | 44 | M | ND | 2 | 2 | Myositis |
| 37 J Community Support Oncol 2014;12:188–190 | 66 | M | 56+56b | 1.4 | 3.23 | Myositis + pseudo-cellulitis |
| 38 Present case | 87 | F | unknown | 444 | 0.43 | Proctitis |

RT, radiation therapy; M, male; F, female; ND, not described.

*aTime between day of chemotherapy agent administration and day of radiation recall.

bTwo series or two sites of irradiation.
Acknowledgments

We thank Drs. Kentaro Ogata and Eri Konno at Tachikawa Hospital for excellent pathological examination and lymphadenectomy, respectively. We have nothing to disclose.

Conflict of Interest

The authors have no conflicts of interest to report.

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