CASE REPORT

Docetaxel and cyclophosphamide chemotherapy induced radiation recall phenomenon in a postoperative breast cancer patient: a case report

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Abstract The radiation recall phenomenon (RRP) is an acute inflammatory reaction at a site previously treated with radiation, and is triggered by anti-cancer therapies such as chemotherapy or antibiotics. A 48-year-old Japanese woman with primary breast cancer underwent partial mastectomy and sentinel lymph node biopsy followed by postoperative radiotherapy. Subsequent to breast-conserving surgery, adjuvant chemotherapy, including docetaxel in combination with cyclophosphamide (TC), was administered after 16 days of radiotherapy involving the right breast. The patient experienced the RRP with erythema and burning pain at the site of the irradiation fields at 6 days after the administration of TC. The skin symptoms resolved after treatment with topical corticosteroid therapy over a few days. After the second course of TC, the patient had only mild symptoms relative to the first course. She successfully completed four cycles of TC without dose reduction and treatment delay. We report this case involving the RRP induced by TC together with a review of the literature.

Keywords Radiation recall phenomenon · Docetaxel and cyclophosphamide · Breast cancer

Introduction

The radiation recall phenomenon (RRP) is an acute inflammatory reaction at a site previously treated with radiation that is triggered by anti-cancer therapies, such as chemotherapy or antibiotics [1]. The RRP is an uncommon and unpredictable reaction. We reported a case of a patient who had experienced the RRP during adjuvant chemotherapy for early breast cancer.

Case report

A 48-year-old Japanese woman, who had allergic rhinitis and hypersensitivity to alcohol, was diagnosed with a cT1cN0M0 Stage I primary breast cancer. At first, the patient underwent a partial mastectomy and sentinel lymph node biopsy. Pathological diagnosis was as follows: invasive ductal carcinoma of no special type; invasive tumor size 16 mm; nuclear Grade 3; no sentinel lymph node metastasis; no lymphatic and vascular invasion; estrogen receptor-positive (50 %); progesterone receptor-positive (70 %); human epidermal growth factor receptor-2 (HER2)-negative (1+). On this basis the pathological stage was classified as pT1pN0M0 Stage I. The patient's breast tumor tissue was examined using the Oncotype Dx[®] breast cancer test to determine the indication for adjuvant chemotherapy.

The patient received breast-conserving radiotherapy at a total dose of 50 Gy delivered in 25 fractions before adjuvant systemic therapy, because it was estimated that ~1 month would be required to obtain the results of Oncotype Dx[®] test. During radiotherapy we obtained the result of the Oncotype DX[®] test (RS = 27). The patient decided to undergo adjuvant chemotherapy although the

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Oncotype Dx[®] test indicated an intermediate risk of relapse.

After 16 days from the completion of radiotherapy, the patient was started on docetaxel (75 mg/m²) and cyclophosphamide (600 mg/m²). She had taken premedication such as dexamethasone sodium phosphate (day 1, 16 mg/day; days 2–3, 8 mg/day; days 4–5, 4 mg/day), antihistamine (on day 1, 45 min before administration of TC; diphenhydramine 50 mg/body,) and H2-blocker (day 1: famotidine 20 mg/day) to prevent adverse events such as an allergic reaction, nausea, edema, and general fatigue. At 6 days after the administration of the first course of TC, erythema accompanied with a burning pain was evident on the skin of the conserved breast at a location that corresponded with the previously irradiated area (Fig. 1). Such a phenomenon was not observed in other areas of the patient's body. Blood biochemical findings at 8 days after TC were as follows: white blood cell count, 700/mm³ (neutrophils, 19.4 %; eosinophils, 4.2 %; basophils, 1.4 %; lymphocytes, 72.2 %; monocytes, 2.8 %); red blood cell count, $4.26 \times 10^6/\text{mm}^3$; platelet count, $12.4 \times 10^3/\text{mm}^3$; total serum bilirubin, 1.4 mg/dl; AST, 18 IU/l; ALT, 26 IU/l; γ -GTP, 93 IU/l; ALP, 230 IU/l; BUN, 18.3 mg/dl; creatinine, 0.58 mg/dl; and CRP, 0.98 mg/dl. No inflammation was found during hematological examination. The patient was diagnosed as having Grade 2 RRP from these findings. The skin symptoms resolved with the use of topical corticosteroid therapy over a few days. From the second course of TC, the patient also received an antihistamine drug (fexofenadine, 120 mg/day) as premedication for the prevention of the RRP. The addition of antihistamine therapy produced only mild symptoms such as slight erythema at the site of contact with the patient's bra (Fig. 2). She successfully completed the four cycles of TC

Fig. 1 Painful erythema occurred on the skin of the *right* conserved breast after 6 days from the administration of the first course of docetaxel in combination with cyclophosphamide; the site corresponded with the previous irradiation site

Fig. 2 At the end of the course of docetaxel in combination with cyclophosphamide, the patient had only mild symptoms such as slight erythema at the site where the skin was in contact with the patient's bra

that were preplanned without a dose reduction or treatment delay.

Discussion

The RRP was first described in 1959 [2], and was a poorly understood phenomenon at that time. This phenomenon presents as the development of an inflammatory reaction localized to previously irradiated areas that is triggered by the administration of certain drugs. In contrast to radiosensitization, the RRP usually occurs on first exposure to a triggering drug; inflammation rapidly develops within minutes to days in the previously irradiated area.

The time interval between the end of radiotherapy and the administration of drug treatment is >7 days [3]. A previous trial reported that 9 of 50 (18 %) patients with breast cancer who had received chemotherapy at ≤ 3 weeks after radiotherapy developed the RRP, as compared with 6 of 81 (7.4 %) patients who had received chemotherapy alone at >3 weeks ($P = 0.09$) [4]. In our case, the time interval was 16 days; this fitted the definition of the RRP and might have a higher risk.

Most of the reactions are commonly developed on the skin, as was the case in our study. However, there have been some studies that have reported the RRP in the oral or laryngeal mucosa, gastrointestinal tract, lung, muscles, and brain. The drugs that have been most commonly reported to be associated with the RRP are doxorubicin [5–9], plant alkaloids, taxanes including docetaxel [10–15] and paclitaxel [16–18], and the antimetabolites capecitabine [19, 20] and gemcitabine [21–26]. A Japanese clinical study has reported that the frequency of docetaxel-induced RRP was

1.8 % during a 3 year period at a single institute [10]. A few case reports have found that docetaxel [11–15] or cyclophosphamide [27] induced the RRP. To our knowledge, there have been no previous studies that have reported on the RRP induced by the combination of docetaxel and cyclophosphamide. The development of the RRP in our case was considered to be related to treatment with docetaxel and/or cyclophosphamide, although it was difficult to demonstrate which agent was the most influential.

The management of the RRP depended on the symptoms. The symptoms associated with the RRP are classified into five grades using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [28]. As symptomatic treatment for dermatitis, topical or systemic corticosteroids or nonsteroidal anti-inflammatory drugs are sometimes used to reduce inflammation. Burris and Hurtig reported that antihistamines were helpful for symptomatic relief or prevention of the RRP after a second course of drug administration [1]. In our case, the patient had Grade 2 dermatitis; the TC regimen in our institute consisted of dexamethasone sodium phosphate and antihistamine as premedication in the original schedule. The use of a premedication was the possible reason that the patient's symptoms were relatively mild after the first exposure to chemotherapy. Subsequently, TC could be continued without a dose reduction or treatment delay. If the skin inflammatory reaction becomes severe and conservative supportive care for the RRP is ineffective, dose reduction, discontinuation of administration, or the use of another regimen need to be considered.

The mechanism of pathogenesis remains unclear. There are some hypotheses that were reviewed by Camidge et al. involving vascular damage, epithelial stem cell inadequacy and sensitivity, and a drug hypersensitivity reaction [3]. More recently, there have been several case reports on the RRP, which has come to be recognized by clinicians, although the main mechanism involved has not been demonstrated. Further studies in more patients are needed.

In conclusion, we encountered a comparatively rare case of the RRP which was triggered after the administration of TC. Clinicians need to record the incidence of the RRP in cases where anti-cancer agents are administered after irradiation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical

standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- Burris HA 3rd, Hurtig J (2010) Radiation recall with anticancer agents. *Oncologist* 15:1227–1237
- D'Angio G, Farber S, Maddock C (1959) Potentiation of X-ray effects by actinomycin D. *Radiology* 73:175–177
- Camidge R, Price A (2001) Characterizing the phenomenon of radiation recall dermatitis. *Radiother Oncol* 59:237–245
- Haffty BG, Vicini FA, Beitsch P et al (2008) Timing of chemotherapy after MammoSite radiation therapy system breast brachytherapy: analysis of the American Society of Breast Surgeons MammoSite breast brachytherapy registry trial. *Int J Radiat Oncol Biol Phys* 72:1441–1448
- Stein RS (1978) Radiation-recall enteritis after actinomycin-D and adriamycin therapy. *South Med J* 71:960–961
- Cassady JR, Richter MP, Piro AJ et al (1975) Radiation–adriamycin interactions: preliminary clinical observations. *Cancer* 36:946–949
- Hill AB, Tattersall SF (1983) Recall of radiation pneumonitis after intrapleural administration of doxorubicin. *Med J Aust* 1:39–40
- Ma LD, Taylor GA, Wharam MD et al (1993) “Recall” pneumonitis: adriamycin potentiation of radiation pneumonitis in two children. *Radiology* 187:465–467
- Jimeno A, Ciruelos EM, Castellano D et al (2003) Radiation recall dermatitis induced by pegylated liposomal doxorubicin. *Anticancer Drugs* 14:575–576
- Mizumoto M, Harada H, Asakura H et al (2006) Frequency and characteristics of docetaxel-induced radiation recall phenomenon. *Int J Radiat Oncol Biol Phys* 66:1187–1191
- Yeo W, Leung SF, Johnson PJ (1997) Radiation-recall dermatitis with docetaxel: establishment of a requisite radiation threshold. *Eur J Cancer* 33:698–699
- Borgia F, Guarneri C, Guarneri F et al (2005) Radiation recall dermatitis after docetaxel administration: absolute indication to replace the drug? *Br J Dermatol* 153:674–675
- Culp LR, Pou AM, Jones DV et al (2004) A case of radiation recall mucositis associated with docetaxel. *Head Neck* 26:197–200
- Kandemir EG, Karabudak O, Maydagli A (2005) Docetaxel-induced radiation recall dermatitis. *Swiss Med Wkly* 135:34–35
- Morkas M, Fleming D, Hahl M (2002) Challenges in oncology. Case 2. Radiation recall associated with docetaxel. *J Clin Oncol* 20:867–869
- Bokemeyer C, Lampe C, Heneka M et al (1996) Paclitaxel-induced radiation recall dermatitis. *Ann Oncol* 7:755–756
- Phillips KA, Urch M, Bishop JF (1995) Radiation-recall dermatitis in a patient treated with paclitaxel. *J Clin Oncol* 13:305
- Schweitzer VG, Juillard GJ, Bajada CL et al (1995) Radiation recall dermatitis and pneumonitis in a patient treated with paclitaxel. *Cancer* 76:1069–1072
- Saif MW, Black G, Johnson M et al (2006) Radiation recall phenomenon secondary to capecitabine: possible role of thymidine phosphorylase. *Cancer Chemother Pharmacol* 58:771–775
- Ortmann E, Hohenberg G (2002) Treatment side effects. Case 1. Radiation recall phenomenon after administration of capecitabine. *J Clin Oncol* 20:3029–3030

21. Friedlander PA, Bansal R, Schwartz L et al (2004) Gemcitabine-related radiation recall preferentially involves internal tissue and organs. *Cancer* 100:1793–1799
22. Castellano D, Hitt R, Cortes-Funes H et al (2000) Side effects of chemotherapy. Case 2. Radiation recall reaction induced by gemcitabine. *J Clin Oncol* 18:695–696
23. Fakih MG (2006) Gemcitabine-induced rectus abdominus radiation recall. *JOP* 7:306–310
24. Ganem G, Solal-Celigny P, Joffroy A et al (2000) Radiation myositis: the possible role of gemcitabine. *Ann Oncol* 11:1615–1616
25. Jeter MD, Janne PA, Brooks S et al (2002) Gemcitabine-induced radiation recall. *Int J Radiat Oncol Biol Phys* 53:394–400
26. Saif MW, Sellers S, Russo S (2006) Gemcitabine-related radiation recall in a patient with pancreatic cancer. *Anticancer Drugs* 17:107–111
27. Borroni D, Vassallo C, Brazzelli V et al (2004) Radiation recall dermatitis, panniculitis, and myositis following cyclophosphamide therapy. *Am J Dermatopathol* 26:213–216
28. National Institutes of Health (2010) National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03, published June 14. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed 13 Nov 2015