



Radiation recall dermatitis with azithromycin

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ABSTRACT

Radiation recall is a well-known phenomenon that involves the “recall” of an acute inflammatory reaction in a previously irradiated region after administration of certain drugs. The most common type of radiation recall is radiation recall dermatitis, which involves the reoccurrence of an acute inflammatory skin reaction in previously irradiated skin. Most radiation recall reactions are attributable to chemotherapeutic agents. One previously reported case of radiation recall dermatitis occurred after administration of an antibiotic. The present case report is the second of radiation recall dermatitis involving an antibiotic: azithromycin.

KEY WORDS

Radiation recall dermatitis, azithromycin

1. INTRODUCTION

Radiation recall is a well-known phenomenon in the field of oncology; the term describes the reoccurrence of an acute inflammatory reaction in a previously irradiated body area after the administration of certain drugs. The first radiation recall reaction was described by D’Angio in 1959. It involved actinomycin D, which, in previously irradiated skin, produced a reaction that was identical to the reaction initially produced by the radiation¹. Although radiation recall dermatitis is the most common radiation recall reaction, other organs—including lung, brain, muscle, and gastrointestinal tract—can also be involved²⁻⁶.

Most reported radiation recall reactions have involved the use of chemotherapeutic agents. However, radiation recall has also been reported with the use of tamoxifen, simvastatin, and anti-tuberculosis medication⁷⁻⁹.

One case of radiation recall dermatitis after antimicrobial therapy (with gatifloxacin) has previously been reported¹⁰. The present case report also describes an occurrence of radiation recall dermatitis after the use of an antibiotic agent, azithromycin.

2. CASE DESCRIPTION

In May 2003, a 44-year-old premenopausal woman presented with a palpable lump in her left breast. A bilateral mammogram confirmed a 1.6-cm mass at the 12 o’clock position of the left breast. A left breast ultrasound and core biopsy confirmed a 2.8-cm hypoechoic mass at the 12 o’clock position, which was identified as an invasive ductal carcinoma¹¹. Staging investigations were negative for metastatic disease. The patient was otherwise well.

A left lumpectomy and axillary node dissection was performed in June 2003. Final pathology showed a 4.8-cm, grade 1 infiltrating mammary carcinoma. Of 26 axillary nodes, 1 was positive for metastasis. The tumour was strongly positive in 90% of cells for both the estrogen and the progesterone receptors. The resection margin was positive, and so the patient underwent a re-excision in July 2003, with removal of two residual foci of carcinoma measuring 8 mm and 3 mm, the resection margins being negative at that time. Her diagnosis was therefore T2N1M0 infiltrating carcinoma of the left breast¹².

The patient then underwent 6 cycles of cyclophosphamide, epirubicin, and fluorouracil (CEF) chemotherapy from September 2003 to February 2004. During her chemotherapy, she developed pain and swelling of the left arm and was diagnosed with a deep vein thrombosis. She was started on low molecular weight heparin.

Following chemotherapy, she underwent adjuvant radiation to the left breast, which consisted of whole-breast radiation using 10 MV photons and tangent fields to encompass the whole breast to a dose of 5000 cGy in 25 fractions over 5 weeks. She received the radiation from February to March 2004. She tolerated the course very well and developed only mild skin erythema at completion of the breast irradiation. During the radiation course, she was also started on adjuvant tamoxifen, which she tolerated well, except for hot flushes.

Despite having minimal reaction to the breast irradiation and no residual skin changes of the breast on follow-up, the patient complained of ongoing left

breast pain. She therefore elected to have a left simple mastectomy in April 2005, which she underwent without any complications.

At a follow-up visit in February 2008, 4 years after the radiation treatment, this patient reported having pneumonia in January 2008, for which she was treated with the antibiotic azithromycin. On day 5 of the antibiotic treatment, she developed generalized urticaria, and on the left chest wall, she developed marked erythema with sharply demarcated borders conforming to the original area of the breast that was irradiated in 2004. The erythema cleared in 10 days without any specific treatment. At the time of the follow-up visit in February 2008, the skin of the left chest wall was normal, with no evidence of residual radiation reaction.

3. DISCUSSION

Although the exact pathogenesis of radiation recall reactions is not known, the condition is believed to be best explained by the mechanism of idiosyncratic drug hypersensitivity reaction^{13,14}. Such reactions are likely not linked to the immune system; the suggestion is that certain drugs trigger non-immune inflammatory pathways in patients whose inflammatory response threshold has been lowered by radiation. Radiation may induce cells to secrete low levels of cytokines, such as tumour necrosis factor α , that are responsible for an inflammatory response, and when a triggering agent is introduced, these cytokines are upregulated, causing a recall reaction.

Almost two thirds of radiation recall reactions occur in skin. They can range from mild erythema to marked desquamation¹⁵. Although radiation recall dermatitis is the most common type of radiation recall reaction, other organs can be involved as well, resulting in pneumonitis, esophagitis, colitis, mucositis, and myositis²⁻⁵. The heart has also been reported to be involved in radiation recall (resulting in pericardial effusion and tamponade), as has the central nervous system (causing optic neuritis and brainstem necrosis); a case of vaginal necrosis has also been reported^{6,16,17}.

The frequency of radiation recall dermatitis is not known, because most of the reports are case reports. Recently, Kodym *et al.* prospectively studied 91 patients who underwent palliative radiation followed by cytotoxic chemotherapy delivered within 6 months of the radiation. In total, 8 patients developed radiation recall dermatitis, for a frequency of 8.8%¹⁸.

The clinical signs of radiation recall dermatitis are varied. They include erythema, desquamation, edema, urticaria-like lesions, vesicles, necrosis, ulceration, and hemorrhage. A toxicity grading system for radiation recall dermatitis was developed in 2000 by the U.S. National Cancer Institute, currently documented in the revised Common Toxicity Criteria, version 2.0 (Table 1)^{13,19}.

TABLE 1 Common Toxicity Criteria, version 2.0, for radiation recall dermatitis

Grade 0	No event
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate-to-brisk erythema or patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
Grade 3	Confluent moist desquamation, ≥ 1.5 cm in diameter, not confined to skin folds; pitting edema
Grade 4	Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion

The time interval between completion of radiation therapy and the development of a recall reaction can range from days to years, with the longest interval reported being 15 years²⁰. The most severe recall reactions occur with short time periods between the end of radiation and the initiation of the triggering drug, and with intravenous as compared with oral administration. The “recall” usually occurs on first exposure to the precipitating drug, with subsequent or rechallenge use producing no recall reaction or only a mild reaction if a reaction does occur²¹. Often, the recall reaction is more severe than the original radiation reaction. In this case report, the patient developed the recall reaction 4 years after completion of radiation treatment, and she described the recall reaction as being more severe than the original reaction, with marked skin erythema as compared with the minimal erythema experienced during the radiation treatment.

Most of the drugs associated with recall reactions are chemotherapeutic agents. The first case described involved the antitumour antibiotic actinomycin D. However, recall reaction also occurs with other classes of chemotherapy agents, including anthracyclines (doxorubicin), alkylating agents (cyclophosphamide), antimetabolites (methotrexate), nucleoside analogs (gemcitabine), and taxanes^{13,14}. It has also occurred with other classes of drugs including tamoxifen, simvastatin, and the anti-tuberculosis drugs (isoniazid, rifampicin, pyrazinamide)^{7-9,22,23}. Although radiation recall is usually precipitated by drugs, it has also occurred with exposure to ultraviolet light²⁴.

Only one previously reported radiation recall reaction occurred with antibiotic therapy using gatifloxacin¹⁰. The case involved a woman treated with pelvic radiation and concurrent fluorouracil and mitomycin for anal carcinoma; 3 years later, she was prescribed gatifloxacin for an upper respiratory tract infection. The recall reaction occurred after 3 days of antibiotic therapy and involved moist desquamation in the perineal and gluteal area. Rectangular borders delineated the previous radiation field. With conservative management, the reaction cleared within 4 days of stopping gatifloxacin. Gatifloxacin is one of the fluoroquinolones, which can produce phototoxicity.

The present case report is the second involving a radiation recall reaction associated with antibiotic therapy. The antibiotic azithromycin, which provoked the reaction, does not belong to the class of fluoroquinolones. Azithromycin is frequently used to treat upper respiratory tract infections; it is popular because of its convenient oral use, once daily over 5 days. It is helpful to know that, in patients who have been treated with radiation, a recall reaction can occur with commonly prescribed antibiotics. Treatment consists of stopping the causative agent and, if indicated, initiating corticosteroids or nonsteroidal anti-inflammatory agents.

4. CONCLUSIONS

Radiation recall is a well-known phenomenon that most commonly involves the skin, resulting in the reoccurrence of radiation dermatitis in a previously irradiated region. Although most commonly associated with chemotherapeutic agents, recall reaction also can be precipitated by commonly prescribed antibiotic drugs, including fluoroquinolones and azithromycin.

5. REFERENCES

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