A Case of Bullous Pemphigoid Exacerbated by Irradiation After Breast Conservative Radiotherapy

Fumiaki Isohashi1,*, Koji Konishi1, Noriko Umegaki2, Tomonori Tanei3, Masahiko Koizumi1 and Yasuo Yoshioka1

1Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2Department of Dermatology, Osaka University Graduate School of Medicine, and 3Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

*For reprints and all correspondence: Fumiaki Isohashi, Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: isohashi@radonc.med.osaka-u.ac.jp

Received December 27, 2010; accepted March 13, 2011

We present a case, considered to be a form of the Koebner phenomenon, of bullous pemphigoid that was exacerbated mainly within the irradiated field after breast conservative radiotherapy. In May 2009, a 60-year-old woman was diagnosed with bullous pemphigoid, which was treated with steroid therapy. The following month, she was diagnosed with breast cancer (invasive ductal carcinoma, pT1cN0M0). After breast conservative surgery in December 2009, conservative radiotherapy to the right breast was performed (50 Gy in 25 fractions). Portal skin showed no serious change (up to grade 1 skin erythema) and no bullous neogenesis during conservative radiotherapy. However, 2 months after conservative radiotherapy, new blisters became exacerbated mainly within the irradiated field but also in the area outside the irradiated field. Increasing the dosage of oral steroid and minocycline resulted in relief of bullous pemphigoid, although patchy skin pigmentation remained especially in the irradiated skin.

Key words: bullous pemphigoid – radiotherapy – breast cancer

INTRODUCTION

Bullous pemphigoid (BP) is one of the most common autoimmune blistering disorders induced by the effect of autoantibodies on the cutaneous basement membrane zone. Tense blisters, erosions and crusts with itchy urticarial plaques, along with erythema, develop all over the body. Histological examination of subepidermal blisters shows inflammatory infiltration of eosinophils and lymphocytes into the dermis. Direct immunofluorescence of the regional skin shows linear in vivo deposition of immunoglobulin G (IgG) and complement 3 (C3) at the dermal–epidermal junction (DEJ) (1). BP is most prevalent in the elderly and Ogawa et al. (2) reported that the incidence of malignancies in Japanese BP patients was significantly higher than in controls. In view of the rapid aging of the Japanese population, it can therefore be expected that the administration of radiotherapy (RT) in the setting of malignancy accompanied by BP will increase. The Koebner phenomenon, also known as the isomorphic response, was first described by Prof. Heinlich Koebner in 1876 and involves the development of an isomorphic lesion of an underlying skin disease on normal appearing skin following mechanical stimulation, such as trauma, drug administration or ultraviolet or radiation exposure (3).

Here, we report a rare case, considered to be a form of the Koebner phenomenon, of BP that was exacerbated mainly within the irradiated field after breast conservative RT.

CASE REPORT

A 60-year-old post-menopausal woman was diagnosed with BP in May 2009, as confirmed by skin biopsy which showed formation of subepidermal blisters with dermal inflammatory cell infiltration mainly of eosinophils and lymphocytes. Direct immunofluorescence analysis of regional skin showed linear deposition of IgG and C3 at the DEJ. The serum anti-BP180 antibody level was elevated to 88 (normal range: <9). The patient was started on 20 mg daily of oral prednisone, which was gradually increased to 30 mg and minocycline at 200 mg. Nevertheless, bullous neogenesis spread...
over the entire body, so that a high-dose pulse intravenous steroid (methylprednisolone, 500 mg) was administered for 3 days. Because neogenesis of the skin eruption was controlled relatively successfully after 1 month of steroid therapy, the dosage was tapered. In June 2009, computed tomography screening revealed a nodule in the right breast, and stereotactic vacuum-assisted biopsy confirmed an invasive ductal carcinoma. The patient underwent breast conservative surgery with a sentinel lymph node biopsy in October 2009 and pathologic examination confirmed the presence of the invasive ductal carcinoma (pT1cN0M0). Nodal or distant metastasis was not evident. The tumor size was 18 mm, the nuclear grade was 1, and it was positive for estrogen receptor.

After breast conservative surgery in December 2009, conservative irradiation of the right breast was performed (50 Gy in 25 fractions) in tangential fields using a 4-MV photon linear accelerator. At the beginning of RT, the use of 15 mg daily of oral prednisone resulted in controlling the activity of BP. Portal skin within the skin mark appeared normal, whereas that outside the portal skin showed patchy pigmentation, suggesting a bullous vestige (Fig. 1A). During RT (December 2009–February 2010) the portal skin showed no major changes (it reached grade 1 skin erythema) and no bullous neogenesis was observed. The oral steroid dosage was therefore reduced to 10 mg during RT and was decreased to 5 mg after RT. Aromatase inhibitor (AI) was started for hormonal therapy 7 weeks after RT. After reduction of the prednisone dosage, anti-BP180 antibody level decreased gradually to within normal range. Two months after RT, however, the patient developed tense blisters, erosions and crust on skin. Skin changes developed mainly in the irradiated field, however, the involved area was not always equal to the field, and distribution of skin changes are different from that of common skin reaction induced by RT (Fig. 1B). The serum concentration of anti-BP180 antibody increased to 139. Biopsy of the irradiated skin confirmed exacerbation of BP. In addition, bullous neogenesis was detected outside of the irradiated field, especially on both wrists and the axillae 1 week after the development of BP on the portal skin (Fig. 1C). Oral prednisone was increased to 25 mg daily and minocycline at 200 mg daily was started. Along with controlling the activity of BP, oral steroid was gradually tapered. After 3 months of this regimen, relief of BP was achieved with almost a normal level of anti-BP180, although patchy skin pigmentation remained, especially in the irradiated skin. At her last follow-up in October 2010, no manifestations of tumor activity were seen, though patchy skin pigmentation still remained (Fig. 1D). Clinical course of this patient showing changes in the serum anti-BP180 and daily oral prednisone dose summarized in Fig. 2.

**DISCUSSION**

This report deals with a case of BP with recurrence of blisters mainly in the irradiated field after breast conservative RT, although only mild radiation dermatitis was observed during RT. Exacerbation of BP outside the irradiated field was relatively mild just after recurrence. The development of isomorphic lesions after RT of normal appearing skin of a patient with BP is a clinical condition referred to as the Koebner phenomenon.
BP is a very common pruritic bullous skin disease in older patients, but is rarely seen in combination with RT. According to the main review paper (4), association of BP with RT was found in 27 patients (median age: 75 years), the majority of whom experienced blistering confined to the irradiated area (24/27, 89%); and had breast carcinoma (21/27, 78%). In most cases, onset of BP occurred more than 1 year after RT. Only five patients developed BP within weeks and six patients after 1–6 months post-radiation. The median dose for these patients was 50 Gy (range: 29–66.4 Gy). Four patients developed BP during RT at a dose of 20 Gy (three patients) or 32 Gy (one patient). Five cases reportedly used hormonal therapy. Interestingly, while BP occurred initially after RT in all 27 cases in this review, only three cases, including the present one, reported that BP was exacerbated by RT during the course of BP. Mul et al. (5) reported a case in which exacerbation of BP in pre-existing locations occurred outside of the irradiated field. However, this case does not accord with the definition of the Koebner phenomenon because BP recurred in pre-existing locations outside of the irradiated field. Another case report in Japanese that accord with the definition of the Koebner phenomenon concerned a case of uterine cervical cancer with exacerbation of BP within the irradiated field during the course of BP (6). To the best of our knowledge, this is therefore the second report of occurrence of the Koebner phenomenon induced by RT during the course of BP.

Several studies have reported that RT may induce the Koebner phenomenon in some diseases including psoriasis (7). In BP cases, the Koebner phenomenon can be induced by stimulation such as *Sarcoptes scabiei* (8) or drug administration (9).

The mechanism of irradiation that triggers BP may be related to RT itself. That is, RT changes antigenic properties and induces autoantibody formation through alteration of the basal membrane by unmasking the antigen. Alternatively, patients who develop BP may already possess circulating anti-basement membrane antibodies, and tissue damage through RT may enhance the deposition of antibodies, i.e. through a change in blood vessel permeability (4). The mechanism that caused the Koebner phenomenon in the case reported here is thought to be related to RT which triggered the initial BP, although the precise nature of the mechanism remains largely unclear.

Because BP became exacerbated just after the start of AI administration, we cannot rule out that AI may have caused the Koebner phenomenon or that RT and AI may have a synergistic effect. However, because the exacerbation of BP began within the irradiated field, it is very likely that RT made a major contribution to the occurrence of the Koebner phenomenon. As far as we know, no reported study has established a correlation between AI and the Koebner phenomenon.

We conclude that it is very important for dermatologists and radiation oncologists to be aware that BP may be exacerbated by RT. It seems that reduction of prednisone dosage was one of the major causes of recurrence in this case. Therefore, during RT for patients with BP, even if the symptoms are controlled relatively successfully, careful observation of the skin and watchful tapering of the steroid are therefore essential. Because in our case BP became exacerbated after RT even though there was only relatively mild radiation dermatitis during RT, periodical and continuous follow-up after RT is also very important.

**Conflict of interest statement**

None declared.

**References**