Bullous pemphigoid masquerading as acute radiation dermatitis: Case report

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Summary

We report the first case of bullous pemphigoid complicating radiation therapy for vulvar cancer. Shortly after completion of post-operative radiation therapy for a T1N1 vulvar carcinoma, the patient presented with a rash that started within, but continued to extend, well beyond the radiation field. A biopsy of the lesions confirmed the diagnosis of bullous pemphigoid, and she had prompt clinical resolution with systemic tetracycline and steroids.

Key words: Vulvar cancer; Radiation dermatitis; Bullous pemphigoid.

Introduction

Radiation dermatitis is very common in patients undergoing radiotherapy for vulvar cancer. As a consequence, most skin reactions in these patients, especially those occurring within the radiation field, are generally attributed to the radiation therapy and treated empirically as such. We present the first reported case of post-radiation bullous pemphigoid of the vulva. Because of the close temporal relationship of the clinical presentation to the recent radiation therapy, the case masqueraded as radiation dermatitis and presented a diagnostic challenge.

Case Report

VV is a 78-year-old female who presented with a vulvar pruritus. Her medical history was unremarkable, except for allergies to penicillin, sulfa, vibramycin, biaxin, dust, mold and ragweed. A biopsy of the periclitoral area revealed an invasive poorly differentiated squamous cell carcinoma (SCC). A metastatic work-up was negative. She underwent a wide radical local excision of the vulvar lesion along with bilateral inguinal and femoral lymphadenectomy. The specimen showed a poorly differentiated SCC with a maximal depth of invasion of 4 mm. Margins were negative for tumor except for a focus of carcinoma-in-situ (CIS) at the 6 o'clock region. One out of 12 left inguinal nodes and one out of seven right inguinal nodes were positive for metastatic carcinoma - both right and left Cloquet's nodes were negative.

She was treated with postoperative adjuvant radiation therapy. She received 4500 cGy to an initial field, which included the vulva, and the inguinal and pelvic lymph nodes. Following this, both groins were boosted to a further dose of 1440 cGy employing 9 MeV electrons. She had the expected problems with moist desquamation during her radiation therapy. Despite these reactions, the patient completed the planned course of radiation therapy with only one short break, and by the end of the radiation therapy, on 5/26/99, most of these reactions had begun to subside. The moist desquamation had almost entirely healed, though she continued to have edema of the mons pubis along with some erythema and dry desquamation in the adjoining areas. At her first follow-up visit on 6/17/99, three weeks after completion of her radiation therapy, she continued to be "sore" in her perineal region. Examination revealed some residual pigmentary changes from her recent radiation therapy, but there was no erythema or desquamation. She had, however, developed a new 1.5 cm "blister" on her medial right thigh. This was located at the inferior edge of her radiation field, but it was also exactly at the level of the lower edge of her undergarment. Because of this, the blister was attributed to the friction from her undergarment, on the background of a post-radiation sensitive skin. She came back on 7/15/99 with extensive bullae in both groins and continued vulvar edema, with some new pruritus. She was treated empirically with topical steroid and antibiotic ointments for a presumed diagnosis of "radiation dermatitis". Unfortunately, she continued to progress over the next few weeks; by 8/3/99, the "blisters" extended over the medial aspect of both her thighs, and also extended to her groins and vulva (Figure 1). There was a pruritic rash, consisting of erythematous papules and patches, involving her left lower thigh and upper left leg. This rash extended to her trunk and left breast, with the breast lesion actually oozing a serous discharge. While this rash was not painful, it was extremely pruritic and a source of considerable distress to her. In view of her history of multiple drug allergies, it was confirmed that she had not started any new medications in the interim (which could have possibly accounted for this rash).

A dermatologic evaluation, including a perilesional and lesional biopsy of the thigh and breast lesions, was performed on 8/4/99. The biopsy revealed "subepidermal vesicle beneath which there is a mixed-cell infiltrate, including eosinophils" with the final diagnosis being bullous pemphigoid (BP) - Figure 2. She was placed on prednisone 60 mg daily along with tetracycline, with prompt resolution of all her lesions. When last seen in follow-up, in 10/2000, she had no residual stigmata of either her prior radiation therapy or the subsequent pemphigoid (Figure 3), and was on 5 mg of prednisone every other day, on a tapering schedule.

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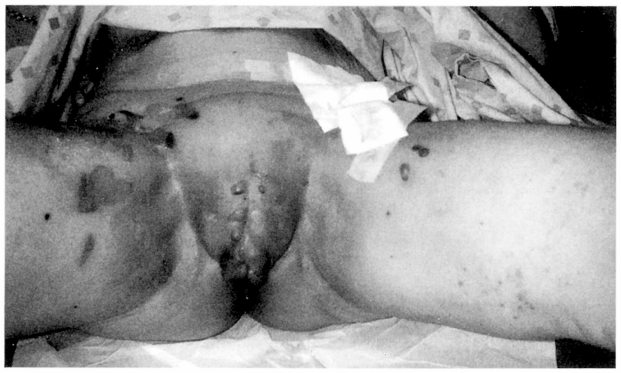

Figure 1. — Vesicular rash over both thighs and vulva.

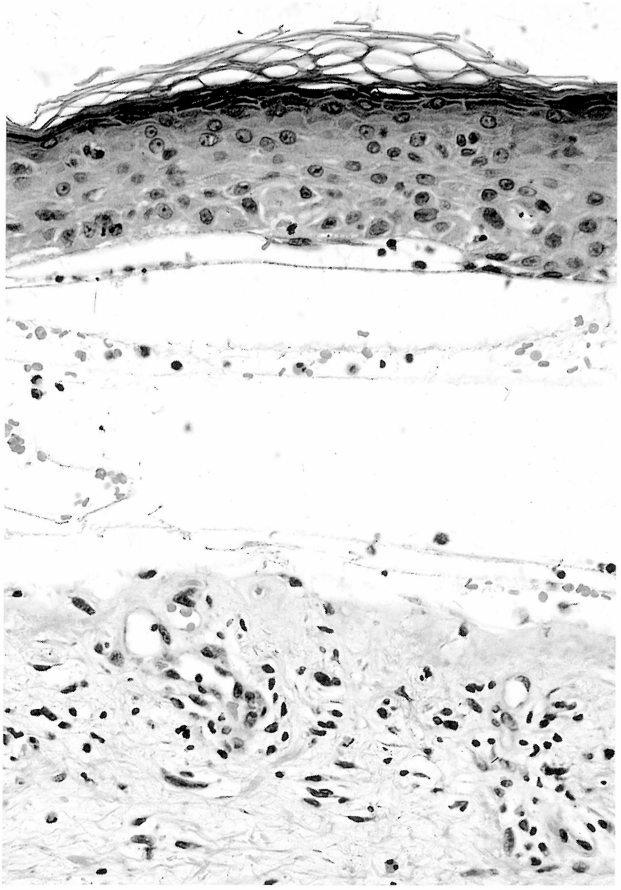

Figure 2. — Subepidermal vesicle beneath which there is a mixed-cell infiltrate, including eosinophils.

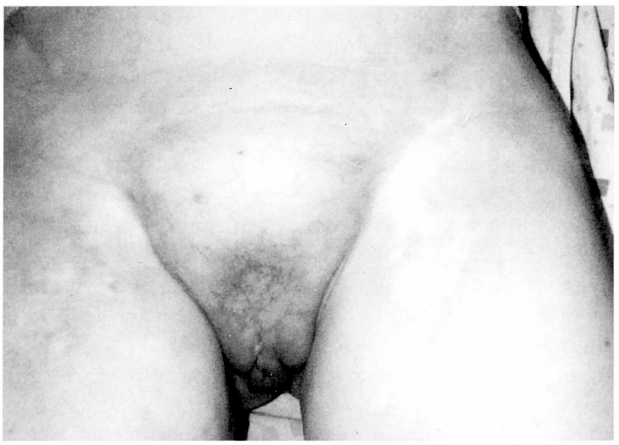

Figure 3. — Followup, showing completely healed rash with minor, residual, pigmentary changes.

Discussion

Despite the frequently reported occurrence of BP in patients with malignant tumors [1], there are very few reports of BP occurring in conjunction with, or developing after radiation therapy for malignancies [2-8]. The majority of these cases have been reported in association with radiotherapy for breast cancer. Since irradiation of breast cancer is not commonly associated with brisk moist desquamation (with vesicle formation), the appearance of any vesicular rash usually results in a dermatologic evaluation with prompt establishment of the correct diagnosis (i.e. BP). Our case is the first report of BP occurring following irradiation for vulvar cancer. The actual pathogenesis of post-radiation BP is a matter of debate. The BP antigens are hemidesmosome protein components that are extractable from normal human skin. They consist of BP-Ag 1, a 230 kilodalton protein, and BP-Ag-2, a 180 kilodalton protein moiety [9], and can be detected all over the skin surface, with the highest density in the flexure areas of the extremities [10]. Binding of the antibodies to the BP antigen is followed by complement activation of both the classic and alternate pathways [11]. Through the involvement of the chemotactic factors, it induces the attraction of leucocytes, which may cause cleavage at the lamina lucida level by release of proteases [12]. On rare occasions, post-radiation BP is strictly limited to the radiation field [5, 13]. However, most cases are "generalized"; even in these, the BP lesions usually begin within the radiation field before becoming widespread [2-4, 6, 7]. This occurrence of the initial BP lesions within the radiation field, and the usually short interval between the completion of the radiotherapy and the appearance of BP suggests that radiotherapy is a genuine trigger mechanism. Radiation may cause an alteration in the permeability of the blood vessels leading to increased deposition of specific circulating antibodies on the basement membrane zone (BMZ) where the BP antigens are located [3]. However, given the rarity of BP developing after radiation therapy, it is proposed that these cases may have a preexisting, extremely low titer of circulating pemphigoid antibody, which is made clinically evident by the increased binding induced by radiation therapy. Subsequent generalized pemphigoid may represent either natural progression of the disease or acceleration of the antibody production once the antigen is locally "unmasked" [4]. As an alternative, radiation could either alter normal BMZ constituents, thereby changing their antigenic properties or unmasking structures previously inaccessible to the immune system and inducing autoantibody formation [2, 5]. Another propo-

sed mechanism involves an alteration of the immune system induced by radiotherapy [14]. Radiation may inhibit T-suppressor cell activity, with consequent unopposed T-helper cell activity resulting in the increase in B-lymphocyte antibody production, with some of these antibodies being directed against intercellular antigens [15].

Our patient presented with an initial "blister" at the edge of the radiation field on her thigh; the disease subsequently progressed within the radiation field, before becoming generalized. This pattern can often lead to a diagnostic conundrum. Radiotherapy for vulvar carcinoma is usually associated with a variable degree of radiation dermatitis (which can include areas of skin breakdown) and the initial reaction of physicians caring for these patients is to attribute skin reactions in the radiation field to radiation dermatitis. However, it is important to remember that radiation dermatitis, in the form of vesicles and skin breakdown, is an acute radiation reaction that is generally seen during the course of radiation therapy - it never manifests during the follow-up period, especially if the initial radiation reaction has actually subsided. The other differential diagnoses of such a "rash" include cellulitis, bullous drug reaction and erythema multiforme. Other skin changes after irradiation include the development of chronic graft-versus-host disease [16] and lichen sclerosus et atrophicus [17]. A biopsy is a must to sort these out. BP reveals a typical histological pattern consisting of subepidermal blisters, with preservation of the dermal papillae and the epidermis. This histological appearance allows differentiation from lesions of pemphigus in which intraepithelial damage predominates with marked acantholysis and intraepidermal bullae formation [2]. Similarly, a distinction can be made from the more common erythema multiforme, which is characterized by intercellular and intracellular epidermal edema, and vacuolar alteration along the dermoepidermal interface [18]. Immunofluorescence (IF) can aid in borderline cases; direct IF shows IgG and C3 along the BMZ, while indirect IF on a blood sample can be positive for circulating anti-BMZ IgG antibodies. However, IgG deposits are not found in every case of BP [19], and indirect IF can be negative in almost 30% of cases [3].

Conventional treatment of BP consists mainly of administration of systemic corticosteroids and/or immunosuppressive drugs (azathioprine and sulphones). Successful treatment with niacinamide and tetracycline has also been proposed [20]. Mycophenolate mofetil at 1000 mg twice a day has also been reported to be efficacious in the treatment of BP [6]. This is a non-competitive, selective inhibitor of synthesis of guanosin nucleotides, which are an important substrate of cell proliferation in lymphocytes. The drug also interferes with T cell-B cell collaboration, and therefore inhibits the production of autoantibodies. In our patient, institution of therapy with prednisone and tetracycline resulted in prompt resolution of her lesions.

Conclusion

The development of histologically proven BP "arising" from a site of recent radiotherapy indicates that radiotherapy should be considered a trigger mechanism for BP. It is also a rare, but important, differential diagnosis to be considered in the management of a patient presenting with atypical cutaneous manifestations following radiation therapy.

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