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A case of radiotherapy-induced bullous pemphigoid with unusually delayed onset: A case report

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Abstract

Bullous pemphigoid is an auto-immune blistering disease that generally affects older patients. Radiotherapy is one of the many triggering factors that have been described. Time to disease onset is variable; cases have been described during the course of radiotherapy while others have occurred up to 9 years later. We report a case of localized bullous pemphigoid on an irradiated site with unusual late presentation, 25 years after radiotherapy for left breast cancer. The pathophysiology of radiation-induced bullous pemphigoid is not clear, but the concept of an immunocompromised district seems to be a plausible explanation for the delayed onset of the disease.

Keywords

Bullous pemphigoid, radiotherapy, auto-immune bullous disease

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Introduction

Bullous pemphigoid is an auto-immune bullous disease that mainly affects older individuals.[1] It presents tense bullae and urticarial plaques on the trunk and extremities with significant pruritus.[1] Skin lesions may be localized or generalized, and mucosal involvement is reported in 10%–30% of cases.[1] The condition results from the degradation of the basement membrane zone as IgG and IgE auto-antibodies target hemidesmosomal proteins BP180 and BP230.[1] Association of bullous pemphigoid has been reported with multiple comorbidities, including neurologic conditions, auto-immune diseases, neoplasms, and cardiovascular diseases.[4] In addition, several trigger factors have been reported to induce or exacerbate bullous pemphigoid.[4] Among them is radiation therapy, for which an association with disease onset has been described by many authors since 1988.[5] The most recent review of radiation-induced bullous pemphigoid published in 2022 includes 13 articles published between 2014 and 2021.[2] In most cases, irradiated fields were the first site of the appearance of skin lesions, but the disease eventually extended to non-irradiated skin as well. The prognosis was generally favorable with adequate response to topical corticosteroids or systemic treatment with prednisolone or immunosuppressive agents.[2] The time interval between radiotherapy and disease onset was extremely variable: some patients developed skin lesions during radiotherapy while others developed lesions up to 9 years after its end.[2] A previous review published in 2014 analyzed 29 cases of radiotherapy-induced bullous pemphigoid.[6] However, inclusion criteria specified time to disease onset of up to 10 years, based on studies suggesting that immunosuppressive effects of radiation therapy may be present 10 years post-treatment.[7] The aim of this paper is to report a case of localized bullous pemphigoid on previously irradiated skin with unusual late presentation.

Case report

A 73-year-old female was referred to the dermatology clinic in February 2020 for suspicion of shingles on the left breast. She had no history of skin disease. Her past medical history

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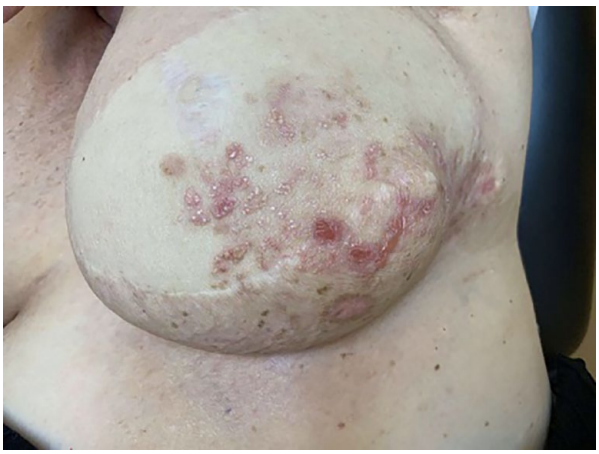

Figure 1. Erosions and milia on an erythematous base on the left breast.

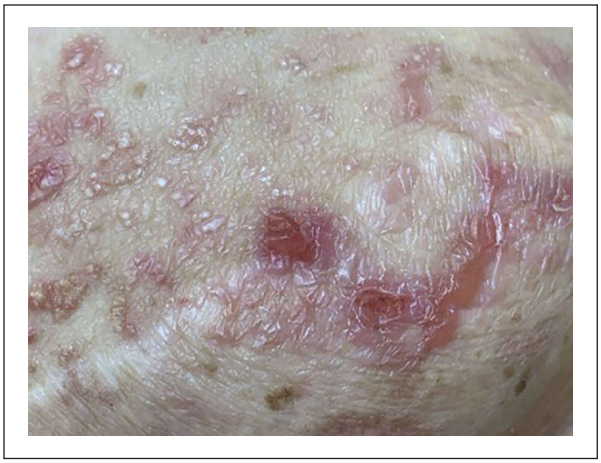

Figure 2. Close-up view of the left breast.

included infiltrative lobular carcinoma on the left breast for which she had a total left mastectomy with reconstruction in April 2016, and a cutaneous metastasis on the left breast operated in October 2019. She had a history of breast cancer on the same site treated with radiotherapy back in 1996. Her other medical conditions included diabetes, hypertension, dyslipidemia, and a thyroid nodule. She has been taking letrozole since September 2019, as well as indapamide, perindopril, and esomeprazole for many years. At the first visit in February 2020, the patient had a localized eczematous dermatitis on the left breast with a few erosions, that were treated with topical betamethasone valerate and fusidic acid ointment. The patient returned in July 2020 with two hemorrhagic bullae of 1.5×0.5 cm on the left breast, surrounded by multiple milia on an erythematous base (Figures 1 and 2). At this point, localized auto-immune bullous disease was suspected. A biopsy with direct immunofluorescence and

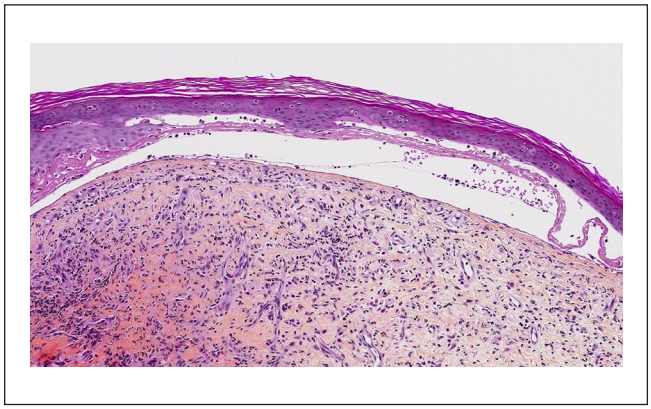

Figure 3. Sub-epidermal bulla and dermal infiltrate of eosinophils and lymphocytes. Hematoxylin and eosin stain, magnification power 10.

salt split was performed. A sub-epidermal bulla containing few inflammatory cells overlying a dermis containing granulation tissue with multiple eosinophils and lymphocytes was seen (Figure 3). Discontinuous linear IgG deposits (++) and granulo-linear C3 deposits (++) were seen at the roof of the basement membrane zone. Anti-basement membrane antibodies were detected at 1/1280. A diagnosis of localized bullous pemphigoid on a previous site of radiotherapy was made. The patient was treated with topical corticosteroids (betamethasone dipropionate then clobetasol propionate) with excellent response. She had a complete resolution of the bullae 2 months later, and a good clinical response was maintained at the last follow-up in April 2021.

Discussion

Although the association between radiotherapy and bullous pemphigoid has been well documented, the underlying pathophysiology remains uncertain.[6] Multiple hypotheses have been described and partially supported by isolated pieces of evidence.[6] One theory is that radiation-induced apoptosis of skin epithelial cells causes them to release BP 180 and BP 230 antigens.[6] These endogenous antigens are then recognized by Langerhans cells, which are thought to be resistant to radiation-induced apoptosis, and the production of autoantibodies ensues.[6] Another theory is that patients already have circulating low levels of anti-basement membrane antibodies.[6,8] Radiation therapy then enhances the binding of these antibodies to the basement membrane zone on the irradiated skin, in a context of enhanced vascular permeability.[6,8] However, the development of bullous pemphigoid many years after radiation therapy, such as in our case, seems to be better explained by the "immunocompromised district" concept. In fact, Ruocco described a unifying explanation for the occurrence of localized skin diseases secondary to local dysregulated immunity in the context of regional chronic lymphedema, herpes-infected sites, or otherwise

damaged areas, which include irradiated skin.[3] These conditions cause an alteration of lymph circulation, potentially impairing the trafficking of immune cells, as well as damage to peripheral nerves, which can alter the signaling of neuromediators.[3] An abnormal neuroimmune interaction results, leading to an altered immune response which can be either defective, leading to infections or neoplasms, or excessive, leading to auto-immune phenomena such as bullous pemphigoid.[3] The secondary disease in the immunocompromised district may occur after an extremely variable time period, ranging from a few days to decades.[3] It seems to be a plausible explanation for cases of localized bullous pemphigoid occurring many years after surgery[9] or, as in our case, 25 years after radiotherapy.

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Patient consent

Patient consent was obtained for the publication of this case.

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