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Localized Lichen Planus Induced by Radiotherapy of the Breast; the "Isoradiotopic Response"

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Introduction: Radiation therapy (RT) is frequently associated with acute and chronic cutaneous adverse effects. Due to the proximity of breast tissue (as the target of radiation therapy) to the skin, breast cancer patients are at risk of these complications. Some of these adverse effects such as radiodermatitis are much more common and familiar to both the dermatologists and radiotherapists. Conversely, some of the other cutaneous reactions such as radiation-induced lichen planus (LP) as a kind of "isoradiotopic response" are less known, much rarer, and usually misdiagnosed. "Isoradiotopic response" refers to the development of a secondary, unrelated dermatosis in previously irradiated sites. For the first time, this term was used by Shurman et al., (2004) to describe a case of post- radiotherapy LP arising in the genital area two months after RT for penile carcinoma. The LP lesions were completely restricted to the field of RT.

Case presentation: We report the development of localized lichen planus in a 34-year-old female patient who received radiotherapy for invasive ductal carcinoma of the breast. She had no history of prior LP. Her LP lesions developed nine months after the termination of RT and were confined to the radiation field. Her LP lesions responded well to topical corticosteroids. However, after six months, her LP lesions recurred, involving the same area that showed a positive response to the treatment with topical corticosteroids. Over the next few years, she underwent some cosmetic and non-cosmetic surgical procedures, including delayed breast reconstruction with an implant, without Koebner phenomenon induction at surgical incision lines.

Conclusion: Although radiation-induced LP is a rare complication of RT, it is necessary for clinicians, especially dermatologists and radiotherapists, to be acquainted with it. As more patients with post-radiation LP are reported, investigators will be able to provide more information about the pathogenesis of the disease and evaluate the significance of different factors in its development.

INTRODUCTION

Radiation therapy (RT) constitutes an important component of cancer treatment. Despite the increasing accuracy of radiotherapy technologies, radiation therapy is frequently associated with cutaneous complications. Up to 85%–95% of cancer patients receiving RT will develop some form of cutaneous complications [1]. Some of these adverse effects such as acute and chronic radiodermatitis are much more common and familiar to both dermatologists and radiotherapists. However, some other cutaneous complications such as radiation-induced lichen planus (LP) as a kind of "isoradiotopic response" are less known, much rarer and often underdiagnosed. Lichen planus (LP) is a chronic inflammatory and immune-mediated disease that most commonly occurs in middle-aged adults. It can involve the skin, mucous membranes (mouth, genitalia, and anus), nails, and hair. Cutaneous LP typically presents as itchy violaceous papules. The traditional 6 "P's" of cutaneous lichen planus constitute "Pruritic, Purple, Polygonal, Planar, Papules, and Plaques". The most common sites of involvement are the flexor surfaces of the extremities. The lesions are characteristically bilateral and almost symmetric [2, 3]. Although the exact etiology and pathogenesis of LP are not completely known yet, LP is considered as a T lymphocyte-mediated inflammatory disorder. The inflammatory cells, which participate in the pathogenesis of LP, consist of T helper and T cytotoxic lymphocytes, natural killer cells, and dendritic cells. The suggested predisposing and associated factors include genetics, trauma, stress, certain medications, internal malignancies, autoimmune diseases, and viral infections such as hepatitis C virus infection [2, 3].

Wolf et al., proposed the new term "isotopic response" to describe "the occurrence of a new dermatosis at the site of another, unrelated, and already healed skin disease". For example, the development of LP lesions in areas healed from herpes zoster can be considered as an "isotopic response" [4, 5]. An "isotopic response" differs from the traditional isomorphic response (Koebner phenomenon). The term isomorphic response is used to define the development of typical skin lesions of an existing dermatosis following an injury of any kind in skin areas not involved with the dermatosis [6, 7]. For example, in a patient with lichen planus, trauma to an unaffected area of skin can produce new, similar LP lesions at sites of trauma. Indeed, the term 'isomorphic' means "the same morphology" (as the existing disease), while 'isotopic' means "at the same location" of injury [8]. The term "isoradiotopic response" as a kind of isotopic response, represents a rare and less known adverse effect of RT. This term refers to the development of a new, secondary and unrelated dermatosis arising in previously irradiated areas [9]. This secondary skin disease presents with all of the hallmarks of the primary dermatosis; however, the eruption is usually confined to the sites of RT and often responsive to treatment. This term was used for the first time by Shurman et al., to define a case of post radiotherapy LP arising in the genital area two months after completion of RT for penile carcinoma. The LP lesions were completely confined to the radiation fields [9].

There are few cases of post-radiotherapy LP in the literature. We report the development of localized lichen planus in a 34-year-old female patient who received radiotherapy for invasive ductal carcinoma of the breast. The LP lesions developed nine months after termination of RT and were restricted to the radiation fields.

CASE PRESENTATION

We report the case of a 34-year-old woman with invasive ductal carcinoma of the breast. Immunohistochemistry showed an estrogen (ER)- and progesterone receptor (PR)- and HER2 negative tumor. She underwent a right-sided radical mastectomy followed by chemotherapy and standard local radiotherapy. Nine months after completion of radiation therapy, the first signs of LP skin eruptions appeared on her upper right anterior chest and upper right posterior shoulder (Figures 1 and 2).

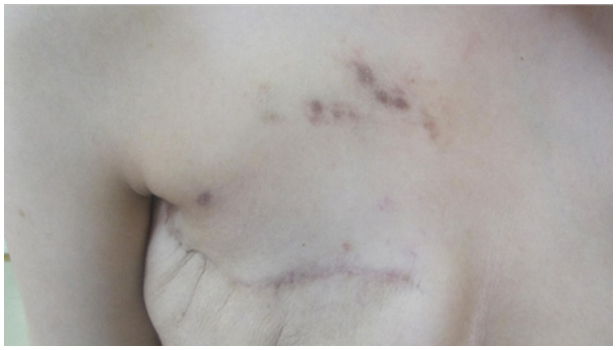

Figure 1: Post-Radiotherapy Lichen Planus (right breast, confined to RT field)

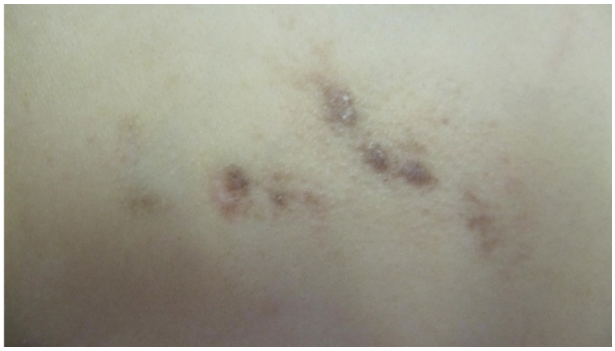

Figure 2: Post-Radiotherapy Lichen Planus (right breast of the same patient)

The skin lesions were confined to the radiation treatment field. Her nails, oral mucosa, and scalp were clear. She was referred to our department for dermatologic consultation eight months after the onset of the skin lesions. A skin biopsy was performed on her right shoulder lesion. Results of the biopsy showed hyperkeratosis, hypergranulosis, the sawtooth pattern of the rete ridges, basal cell degeneration of the epidermis, a bandlike predominantly lymphocytic infiltrate at the dermoepidermal interface, and a few scattered pigmented macrophages (Figure 3A and 3B). These histopathological findings were consistent with lichen planus. Necessary laboratory tests were carried out to detect any type of associated diseases, such as chronic viral hepatitis. The serological tests for hepatitis B and C virus infection were negative. No other precipitating factors for the development of LP were detected, leading to the diagnosis of radiation-induced LP. She had no personal or familial history of LP or any other special dermatosis. Her LP lesions responded well to topical treatment with potent corticosteroids, including clobetasol propionate 0.05% and fluocinonide 0.05% within three weeks. However, after six months, her LP lesions recurred, involving the same area that showed a positive response to the treatment with topical corticosteroids. Over the next few years, she underwent some cosmetic and non-cosmetic surgical procedures, including delayed breast reconstruction with an implant, without Koebner phenomenon induction at surgical incision lines.

DISCUSSION

The isoradiotopic response is a rare and less known adverse effect of radiotherapy. This term refers to the developement of a new, secondary, unrelated dermatosis in previously irradiated fields [9]. We presented a new case of localized LP induced by radiotherapy. The first signs of LP skin eruptions occurred nine months after the completion of RT. Her LP lesions were confined to the radiation treatment sites. She had no personal or familial history of lichen planus. Her LP lesions responded well to topical corticosteroids. However, after six months, her LP lesions recurred, involving the same area that showed a positive response to the treatment with topical corticosteroids.

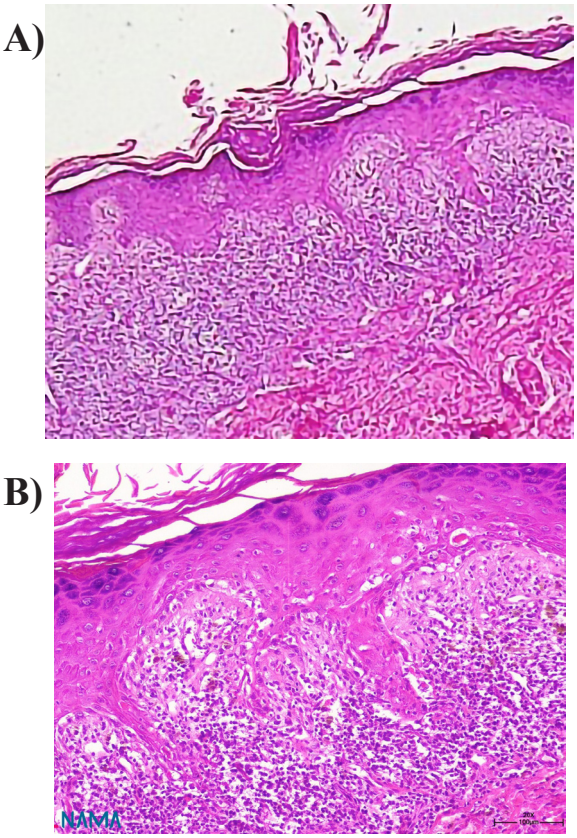

Figure 3: The Histopathological Feature of the Lesions
A) H&E×40 band like lymphocytic infiltration at the dermoepidermal junction; B) H&E×200 basal layer vacuolar degeneration with numerous cytoid bodies

There are some interesting points of view regarding our patient. In the reported cases of post-radiation LP, the latency period between completing RT and the appearance of LP lesions did not exceed five months, while the latency period in this study was about nine months. More importantly, over the next few years, she underwent some cosmetic and non-cosmetic surgical procedures, including delayed

breast reconstruction with no Koebner phenomenon induction at surgical incision lines. Kim and Krivda were the first to report a case of radiation-induced lichen planus in the literature in 2002 (the cutaneous reaction, which was termed "isoradiotopic response" by Shurman in 2004). The LP lesions, which were completely confined to the radiation field, developed one month after the completion of RT for thyroid carcinoma [10]. Shurman et al., reported a case of post-radiotherapy lichen planus arising in the genital area two months after RT for penile carcinoma. The LP lesions were completely restricted to the radiation field. They suggested the new term "isoradiotopic response" for this phenomenon. They described the term "isoradiotopic response" as the occurrence of new, unrelated secondary dermatoses within previously irradiated sites [9].

There are few cases of post-radiotherapy lichen planus in the literature. None of the previous studies reported a history of prior LP lesions, except Pretel's study, in which a history of lichen planus lesions was reported seven months before the diagnosis of breast cancer. Her LP lesions were completely resolved after five months of treatment and two months before the diagnosis of infiltrating ductal carcinoma of the breast [11]. The majority of cases of radiation-induced lichen planus have been reported in women with breast cancer after radiotherapy [11-15]. Moreover, Komori et al., reported a case of metastatic breast cancer whose LP lesions developed following combination therapy with nivolumab and RT. Nivolumab can also trigger drug-induced LP [16]. The primary cancer types of other patients with radiation-induced LP included: penile cancer, thyroid carcinoma, lung carcinoma, nasopharyngeal carcinoma, extramedullary plasmacytoma, dermatofibrosarcoma protuberans, B-cell lymphoma, and prostate carcinoma [9, 10, 12, 15, 17-23].

In all cases, except Eichbaum's case, whose first papules of LP developed during radiation therapy, there is a latency period between completing RT and the appearance of LP lesions [12]. The average latency period has been reported to be about three months [17], not exceeding five months, while the latency period lasted about nine months in this case. The first reported cases of radiation-induced LP were typically restricted to the sites of radiation [9-11, 15, 20]. To the best of our knowledge, Eichbaum et al., were the first to report the secondary generalization of radiation-induced lichen planus [12]. Since then, some other cases of post-radiation LP have been reported to extend to non-irradiated areas and progress to generalized LP [12, 19, 21]. The isoradiotopic response is not limited to radiation-induced LP. Some other dermatoses may also be induced by radiotherapies such as localized bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, benign mucosal pemphigoid, paraneoplastic pemphigus, morphea, lichen sclerosus et atrophicus, postirradiation pseudosclerodermatous panniculitis, DLE, prurigo nodularis, suppurative hidradenitis, comedonal acne, and erythema multiformis [24-29].

The exact mechanisms by which radiation therapy can induce localized dermatoses, such as LP are not understood yet. However, investigators have proposed some hypotheses in this field [10, 11, 17, 19]. They suggest that local irradiation could damage the keratinocytes and promote the elaboration of cytokines by the damaged cells and severe injury of the skin barriers in susceptible patients. The disruption of the skin barriers permits the normally protected antigens to be presented to lymphocytes in the skin, which provokes loss of self-tolerance and autoimmunity. In addition, RT can increase the expression of proinflammatory molecules such as major histocompatibility complex, cytokines (IL-1, IL-6, IL-8, TNF-alpha and TGF beta), and adhesion molecules (ICAM-1 and E-selectin) through not completely clear mechanisms [11]. It has been proposed that an increase in the expression of adhesion molecules may induce the transendothelial migration of leucocytes and activation of the inflammatory reactions, which can lead to lichen planus 13. Another hypothesis suggests that radiation therapy can promote antigen expression, which provokes localized autoimmunity and loss of self-tolerance in susceptible patients [11]. Loss of self-tolerance combined with antigen exposure might be a helpful hypothesis in this field [10, 11, 17, 19]. For the time being, some important questions persist because the answers of which are not identified yet. Why does RT stimulate the development of LP just in certain patients? Do other factors such as genetics, cumulative radiation dose, fraction sizes, the number of RT sessions, drug reactions, and patient factors such as underlying diseases,

immune status, etc. take part in susceptibility of certain patients to radiation-induced LP? Why does radiation-induced LP remain restricted to the radiation field in some patients while extending to generalized LP in some other cases? May there be a relationship between generalization of radiation-induced LP with tumor relapse or metastasis? As more and more patients with radiation-induced LP are reported, the investigators will be able to answer these questions and achieve a better understanding about the nature of this phenomenon.

Although radiation-induced LP is a rare complication of RT, it is necessary for clinicians, especially dermatologists and radiotherapists, to be acquainted with it. Radiation-induced LP is clinically and histopathologically similar to idiopathic LP; however, the patients with radiation-induced LP have a history of radiation therapy to the affected sites. In the localized form of the disease, positive history of radiation therapy and correlating the distribution of the LP lesions with sites of RT may be helpful in the diagnosis of localized radiation-induced LP. In the generalized form of the disease, initiation of the lesions in the RT field and subsequent generalization of the lesions can be helpful in the diagnosis of the disease. A skin (or mucosal) biopsy and histopathologic examination confirm the diagnosis.

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CONFLICTS OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

The patient signed the written informed consent regarding the publication of her data and photographs as a case report.

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