

Radiation-induced lichen planus as a kind of isoradiotopic response: a narrative review

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Radiation therapy is frequently associated with a variety of adverse cutaneous effects. Some of these complications, such as radiodermatitis, are well known. However, some other skin reactions, such as radiation-induced lichen planus (LP) as a kind of isoradiotopic response, are rare, less known, and often under-recognized. An isoradiotopic response refers to the appearance of a secondary dermatosis in previously irradiated areas. In an isoradiotopic response, the new skin lesion presents with all the hallmarks of the primary dermatosis; however, the eruption is restricted to the field of radiation therapy. Radiation-induced LP as a kind of isoradiotopic response refers to the appearance of LP lesions in previously irradiated areas. This article presents a narrative review of the current literature about radiation-induced LP cases. The search was conducted on electronic databases, including PubMed, Web of Science, Cochrane, Scopus, Medline, Embase, and Google Scholar with the keywords, "isoradiotopic response," "isotopic response," "Koebner phenomenon," "lichen planus," "cancer treatment," "radiotherapy," and "radiation therapy." According to the results of this search, there were only nine case reports of radiation-induced LP in the literature. Due to the limited number of articles published in this field, there are important questions, the answers of which are not known yet. By reporting more patients with post-radiation LP, investigators will be able to gather more information about the pathogenesis of the disease and evaluate the significance of different factors in the development of post-radiation LP.

Keywords: lichen planus, isoradiotopic response, radiotherapy

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INTRODUCTION

Radiation therapy is frequently associated with a variety of adverse cutaneous effects. Some of these complications, such as radiodermatitis and recall phenomenon, are more common and familiar not only to dermatologists but also to radiotherapists and oncologists. However, some other skin reactions, such as an isoradiotopic response, are less known and often underestimated

or erroneously diagnosed ^{1,2}.

Wolf *et al.* suggested the new term 'isotopic response' be included in the glossary of dermatology in 1995 ³⁻⁵. They described an isotopic response as "the occurrence of a new dermatosis at the site of another, unrelated, and already healed skin disease" ^{3,4}. For example, the appearance of lichen planus (LP) in areas healed from herpes zoster can be considered as an isotopic response" ^{3,4,6}. Afterward, this term was changed to 'Wolf's isotopic

response' so it would not be mistaken with many references linked with radioactive isotopes³⁻⁶.

An isotopic response differs from an isomorphic response (also termed the Koebner phenomenon), which refers to the appearance of typical lesions of an existing dermatosis following an injury of any kind in skin areas that are not involved with the dermatosis⁶⁻¹⁰. In fact, the term 'isomorphic' means 'the same morphology' (as the existing disease), and an isomorphic response designates the development of a skin lesion that is morphologically similar to the existing skin disease in the site of injury. This is while 'isotopic' means 'at the same location,' and an isotopic response' refers to the occurrence of a new, unrelated disease that appears at the same location of a previously healed disease³⁻⁵.

An isoradiotopic response is a kind of isotopic response, representing a rare and less known complication of radiotherapy. This term refers to the appearance of a secondary dermatosis in previously irradiated areas. In an isoradiotopic response, the new skin lesion presents with all the hallmarks of the primary dermatosis; however, the eruption is restricted to the field of radiation therapy and is often responsive to treatment. Shurman *et al.* used this term for the first time in 2004¹¹. They used this term to describe the development of unrelated secondary dermatoses in previously irradiated fields. They reported a case of post-radiotherapy LP arising in the genital area two months after radiation therapy (RT) for squamous cell carcinoma of the penis. The LP lesions were completely restricted to the sites of radiation therapy¹¹.

There are very few cases of post-radiotherapy LP in the literature. This article presents a narrative review of the current literature about radiation-induced LP.

PARTICIPANTS AND METHODS

The search was conducted in electronic databases, including PubMed, Web of Science, Cochrane, Scopus, Medline, Embase, and Google Scholar with the keywords, "isoradiotopic response," "isotopic response," "Koebner phenomenon," "lichen planus," "cancer treatment," "radiotherapy," and "radiation therapy." The papers referring to this topic in English, ranging from 2000 to September 2021, were studied.

RESULTS

According to our search results, there were only nine case reports of radiation-induced LP in the literature (Table 1). Kim and Krivda were the first to report a case of radiation-induced LP in 2002 (the cutaneous reaction which was termed as an isoradiotopic response afterward by Shurman *et al.*). The LP lesions were completely restricted to the sites of irradiation. The nails, scalp, and oral mucosa were clear. The LP lesions developed one month after completion of radiotherapy of poorly differentiated carcinoma involving the thyroid gland and superior mediastinum. The clinical diagnosis of LP was histologically confirmed. The lesions responded to potent topical corticosteroids gradually within five months. In the next six months, less severe episodic recurrences of LP lesions occurred within the irradiated sites¹².

Shurman *et al.* reported a case of post-radiotherapy LP arising in the genital area two months after radiation therapy for squamous cell carcinoma of the penis. The LP lesions were completely restricted to the sites of radiation therapy. They proposed the term 'isoradiotopic response' for this phenomenon. They described it as the development of unrelated secondary dermatoses within the radiation therapy fields¹¹.

Pretel and España reported a case of post-radiation LP who had a prior history of LP lesions before radiotherapy. The female patient was a known case of LP whose primary LP lesions had spread over her trunk and extremities without any mucosal involvement. Her LP lesions had disappeared after five months of treatment with sulfasalazine. After a lesion-free period of two months, the patient was diagnosed with infiltrating ductal carcinoma of the breast. One month after terminating RT, LP lesions reappeared confined to the irradiated sites. The lesions responded to topical treatment with clobetasol propionate well and disappeared¹³.

In another case report, Vergilis-Kalner *et al.* presented the case of a 59-year-old woman with metastatic breast cancer who developed progressive post-radiation LP restricted to the RT sites. The LP lesions followed the Blaschko lines. She was treated with topical corticosteroids with some improvement¹⁴.

To the best of our knowledge, Eichbaum *et al.*

Table 1. Literature overview of cases with radiation-induced lichen planus

Authors; year	Age; gender; type of cancer	Time interval between completion of RT and onset of LP lesions; distribution of LP lesions	History of prior LP	Response to topical treatment	Recurrence after the 1st episode of LP
Kim JH, Krivda SJ; 2002	58 yrs.; M; poorly differentiated carcinoma of the thyroid gland	One month; confined to the site of RT	-	Gradual resolution within 5 months of treatment with potent topical CCS	Episodic recurrences in the next 6 months; less severe than initial lesions; always confined to the RT site
Shurman D, Reich HL, James WD; 2004	68-yrs.; M; penile SCC	2 months; confined to the site of RT	-	Good response to topical CCS; death due to his primary cancer	-
Sciallis GF, Loprinzi CL, Davis MD; 2005	68 yrs.; M; metastatic breast cancer	Time interval? Progressive linear LP RT of mediastinum and supraclavicular areas→ linear LP (left side of his chest, left shoulder, upper left part of his back, linear extension to the left arm and hand	-	Favorable response to topical tacrolimus	After palliative RT of the head, the LP lesions progressed to cross the midline
Eichbaum M, <i>et al</i> ; 2006	56 yrs.; F; high-grade ductal carcinoma in situ of the breast	Onset of LP concurrent with RT; generalized LP with cutaneous and oral involvement	-	Skin lesions: nearly complete resolution after 5 months of topical ichthyol and then potent topical CCS (betamethasone propionate) Oral lesions: topical tretinoin – some of the buccal lesions persisted	Buccal lesions: persistent
Pretel & España; 2007	44 yrs.; F; infiltrating ductal carcinoma of breast	Reappearance of LP lesions one month after RT; confined to the site of RT	+ ; Trunk + Extremities+ Mucosal lesions -	Disappearance of LP lesions 1 month after potent topical CCS (clobetasol propionate 0.05%)	-
Irene Josephine Vergilis-Kalner; Vishakha Sharma, Aisha Seth; 2008	59 yrs.; F; metastatic breast cancer	Confined to the sites of RT The lesions followed the Blaschko lines	-	Some improvement with topical CCS	-
Morar N, Francis ND; 2009	67 yrs.; M; extramedullary plasmacytoma	3 months; initially over the site of RT. Over the next 3 months→ progressed to the trunk, lip (severe ulceration), and glans penis	-	Response to systemic (taper: 6 mo.) & topical CCS	-
Wang YN, Chen HC, Wang B, Fang H; 2011	46 yrs.; M; early-stage nasopharyngeal carcinoma	2 months; lips, esophagus	-	Response to topical & systemic corticosteroids	-
Hopkins AM, White KP, Simpson EL; 2017	64 yrs.; F; invasive lobular carcinoma of right breast	3 months; confined to the site of RT	-	Good response to topical CCS (triamcinolone ointment)	After 10 months: new limited lesions (2 new papules) on her upper right posterior shoulder

Abbreviations: RT, radiotherapy; M, Male; F, Female; yrs, years; CCS, corticosteroids; SCC, squamous cell carcinoma

were the first to report the secondary generalization of post-radiation LP. They reported the case of a 56-year-old female who underwent breast cancer

surgery and standard local radiotherapy. In this patient, the LP lesions were initially localized to the radiation field. However, the LP lesions

progressed to generalized LP and spread out over the trunk, limbs, and oral mucosa. This case report was important from another point of view too. In other reports, there was a latency period between completing radiotherapy and the onset of LP lesions, but the first papules of LP occurred during radiation therapy in Eichbaum's report¹⁵.

Morar and Francis reported a case of post-radiotherapy LP arising in a patient's scalp three months after RT for extramedullary plasmacytoma. The LP lesions were initially localized to the radiation field. However, the lesions spread over his trunk, lips, and glans penis over the next three months. His lip ulceration was severe. His lesions responded to systemic (prednisolone 30 mg/day, tapered over six weeks) and topical corticosteroids¹⁶.

In another case report, Sciallis *et al.* reported a case of linear LP that was initially restricted to the field of radiotherapy of the mediastinum and supraclavicular areas for metastatic breast cancer, involving the left side of his chest, left shoulder, and upper left part of the back, extending distally following the lines of Blaschko in a linear form to the left arm and hand. However, after palliative radiotherapy of the head for management of brain metastases, the LP lesions progressed to cross the midline. The patient had no mucosal lesions. The course of the LP lesions did not parallel the disease response to radiotherapy or chemotherapy¹⁷.

Wang *et al.* were the first to declare the development of esophageal LP following radiotherapy of nasopharyngeal carcinoma. They reported a case of early-stage nasopharyngeal carcinoma in a 46-year-old man treated with radiotherapy alone due to the early diagnosis of the disease and the sensitivity of nasopharyngeal carcinoma to radiation. Two months after completion of radiotherapy, white plaques developed on the patient's lips. A biopsy was performed on the lower lip lesion. The histopathological findings and the typical clinical features of the lip lesions led to the diagnosis of oral LP. No sign of LP was observed on other sites of the oral mucosa, genital mucosa, conjunctivae, skin, scalp, or nails. Because of significant weight loss, dysphagia, and odynophagia, an endoscopic examination was carried out, which revealed ulcerative esophagitis and stricture. Biopsies were taken from the esophageal stricture. A diagnosis of lichenoid

esophagitis was finally considered. Due to the esophageal involvement, in addition to the topical corticosteroid (mometasone furoate) for the lips, systemic corticosteroids were also prescribed. The symptoms of dysphagia and odynophagia, which did not improve after taking proton pump inhibitors, alleviated remarkably within three weeks after taking prednisone (30 mg/day). The oral lesions disappeared five weeks later. Although post-radiotherapy lichenoid esophagitis was proposed for this case, paraneoplastic syndromes and esophageal mucositis should also be considered in the differential diagnosis¹⁸.

Hopkins *et al.* reported the case of a 64-year-old woman with invasive lobular carcinoma of the right breast and axilla, where localized postradiotherapy LP developed three months after completion of radiation treatment. Her symptoms were controlled with the application of topical corticosteroids. However, after ten months, two new pruritic papules of LP recurred on her upper right posterior shoulder¹⁹.

DISCUSSION

This narrative review demonstrated that there were only nine case reports of radiation-induced LP in the literature. In all of these case reports, the diagnosis was confirmed by histopathological findings.

The majority of the reported cases of radiation-induced LP have been reported in women after local radiation therapy for breast cancer (5/9 cases)^{13-15,17,19}. The underlying malignancy of the other four patients with radiation-induced LP included penile SCC, poorly differentiated thyroid gland carcinoma, extramedullary plasmacytoma, and early-stage nasopharyngeal carcinoma^{11,12,16,18}. All of these patients underwent surgery except for Wang *et al.*'s case, whose early-stage nasopharyngeal carcinoma was treated with RT alone due to the early diagnosis of the disease and the sensitivity of nasopharyngeal carcinoma to radiation¹⁸.

In these case reports, the latency period from the end of RT to the onset of LP did not exceed four months. None of these patients reported a history of prior LP lesions, except for Pretel *et al.*'s case, who reported a history of primary LP lesions on her trunk and extremities without any mucosal involvement seven months before the diagnosis of breast cancer.

Her LP lesions had resolved after five months of treatment with sulfasalazine. After a lesion-free period of two months, the patient was diagnosed with breast cancer. One month after the end of RT, LP lesions reappeared confined to the irradiated sites¹³. The case reported by Eichbaum *et al.* was the only one whose LP papules occurred for the first time during radiation therapy¹⁵.

An isoradiotoxic response is not restricted to post-radiation LP. Some other dermatoses may also be induced by megavoltage radiotherapy. Localized bullous pemphigoid following RT is a well-known phenomenon²⁰⁻²⁵. Most of these cases have been reported in women after local RT for breast cancer. Other bullous eruptions induced by radiation therapy include pemphigus vulgaris, pemphigus foliaceus, Brunsting-Perry cicatricial pemphigoid, and paraneoplastic pemphigus²⁶⁻³⁰. In some patients with paraneoplastic pemphigus, the initial signs of the disease develop within the radiation field²⁹. However, the full-blown clinical features of paraneoplastic pemphigus with mucous membrane involvement follow subsequently²⁹. Some of the other dermatoses that have been reported to be induced by megavoltage radiotherapy include radiation-induced morphea³¹⁻³⁵, DLE³⁶, postirradiation pseudosclerodermatous panniculitis^{37,38}, prurigo nodularis³⁹, radiation-induced hidradenitis suppurativa^{40,41}, erythema multiforme⁴², lichen sclerosus et atrophicus^{43,44}, and comedonal acne^{45,46}.

The precise mechanisms by which RT induces localized dermatoses such as LP are not known yet. However, some hypotheses have been proposed in this field. Pretel *et al.* suggest that ionizing radiation increases the expression of proinflammatory molecules such as major histocompatibility complex, cytokines, and adhesion molecules (E-selectin and ICAM-1 in the endothelium) through unclear mechanisms. They propose that an increase in the expression of adhesion molecules may facilitate the transendothelial migration of leucocytes and subsequently activate an inflammatory reaction, leading to LP¹³. Another hypothesis suggests that RT promotes antigen expression, which provokes autoimmunity localized to the RT field in susceptible patients with loss of self-tolerance. Loss of self-tolerance combined with antigen exposure might be a valuable hypothesis in this field.

Some important questions persist, the answers

of which are not known yet. Why does radiation therapy stimulate the development of LP (or other isoradiotoxic responses) just in certain individuals? Do other factors such as genetics, the dose of radiation, the duration of exposure, the number of RT sessions, drug reactions, etc., participate in the susceptibility of certain patients to post-radiation LP? Why does post-radiation LP remain confined to the radiation field and, in some cases, generalize secondarily? Is there a direct relationship between the generalization of the dermatosis with metastasis or paraneoplastic syndromes? As more and more patients with this condition are reported, investigators will be able to evaluate the significance of different factors in post-radiation LP development and answer these questions.

CONCLUSIONS

This narrative review demonstrated that there were only nine case reports of radiation-induced LP in the literature. Due to the limited number of studies published in this field, some critical questions are yet to be answered. 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.

ETHICAL CONSIDERATIONS

Not applicable.

Conflict of interest: None declared.

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