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Radiation-associated lichen planus: a case report and literature review

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Abstract

Percutaneous radiotherapy (RT) may cause a range of acute and chronic cutaneous side-effects on irradiated areas. Localized or generalized lichen planus (LP) has occasionally been reported after RT. The mechanisms of LP are unclear. A case report and a systematic review of the literature were performed. Including the present case, 12 cases of LP have been reviewed in association with oncologic radiotherapy since 2002. Of these, 83% of patients developed LP after RT. LP occurred with a median delay of 30.7 days after RT completion and a median dose of 50 Gy. LP is a rare complication during RT that mainly occurs at the site of radiation and can sometimes spread and become generalized. Its physiopathogeny remains unclear. In some cases, patients may have preexisting but asymptomatic LP before RT. RT would therefore act as an indicator of the disease. The treatment of RT-associated LP is similar to that for any LP.

Keywords: lichen planus, Koebner phenomenon, radiotherapy

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Introduction

A large number of acute and late cutaneous side-effects can occur after radiotherapy (RT). These include acute and chronic radiation dermatitis, radiation recall dermatitis, development of skin cancers, and elective localization of cutaneous disorders in situ (1).

Lichen planus (LP) is a benign inflammatory disorder characterized by itchy violaceous papules of the skin (2). It can affect the skin, the mucosae (mouth, genitalia, and anus), the folds, the scalp, and the nails. It is also a polymorphic condition with a wide range of clinical types (2). LP is usually self-limited, but it may also display recurrences and exacerbations with a protracted evolution over the years (2). In addition, the Koebner isomorphic phenomenon (KP) is inseparable from the pathogenesis of LP (3). The risk of localization of LP lesions on traumatized areas is higher when the disease is active or poorly controlled (2).

At the beginning of the twentieth century, RT was a popular treatment for cutaneous LP, especially in France (4, 5). At the time, the occurrence of LP lesions on RT areas as well as flare-ups of the disease had been well documented (6–8).

Interestingly, the first report of LP after percutaneous RT for cancer was only published in 2002, for a patient with thyroid cancer (9).

We report a typical case of LP that appeared after RT and we performed a systematic literature-based review of publications reporting LP after percutaneous RT.

Case report

In March 2017, a 66-year-old Finnish woman was referred for an itchy cutaneous eruption on the back and limbs after RT for lung cancer. During spring 2016, the patient was diagnosed with adenocarcinoma of the left lung in an advanced stage with involvement of hilar and mediastinum lymph nodes and lung metastasis (stage T3N3M1a). Because of the progression of the disease despite chemotherapy, palliative radiotherapy was initiated in January 2017 at a dose of 30 Gy, 3 Gy per session, 5 days a week. According to the patient, the rash developed quickly, most likely within the first 2 weeks after RT completion on the irradiated field of the back. The patient was initially diagnosed with herpes zoster in private practice. Despite antiviral treatment, the rash did not subside and other lesions appeared elsewhere, mainly on both lower limbs and hands.

At presentation, physical examination revealed a 15 × 10 cm erythematous and slightly scaly patch that was lateralized on the upper left side of the back, near the scapula. Wickham striae were clinically notable within the plaque. In addition, she also had scattered itchy erythematous papules on the lower limbs and hands (Fig. 1). Dermoscopy examination of the lesions on the back and limbs showed the typical aspect of LP (Fig. 2). Examination of the mouth revealed a whitish lichenoid network on the inner side of the cheeks facing the wisdom teeth. The patient denied any oral symptoms and had no knowledge in the past of such lesions. She did not have any lesions on the scalp, the folds, or the nails. We did not examine the vulvar or anal mucosae. A punch biopsy of the lesion on the back was performed and the pathologic analysis confirmed the diagnosis of LP (Fig. 3). She had not undergone any treatment that was identified as being a possible inducer of a lichenoid drug reaction. Highly potent corticosteroid ointment (betamethasone valerate) was applied once a day on the skin lesions. Six weeks later, at follow-up, the patch on the back subsided, leaving a post-inflammatory pigmentation. However, hypertrophic lichenoid papules were still noted on the lower limbs, the dorsum of the feet, and the right hand. The patient also reported that the oral lesions had become painful when eating acidic food and gave the food a metallic taste. Mouth rinses of 0.1% acetonide triamcinolone two to three times daily were initiated. The patient did not want to start any oral prednisolone. Three months later, in August 2017, the skin lesions had totally disappeared, leaving only post-inflammatory pigmentation. The oral symptoms had greatly improved with the mouth rinses. However, meanwhile she had been given oral prednisolone and then dexamethasone because of radiation pneumonitis and brain metastasis, which may explain the favorable response of her LP. In mid-August she again received external brain RT (30 Gy, 3 Gy per session, 5 days a week). Two months after brain RT completion, the patient did not have any flare-up of LP.

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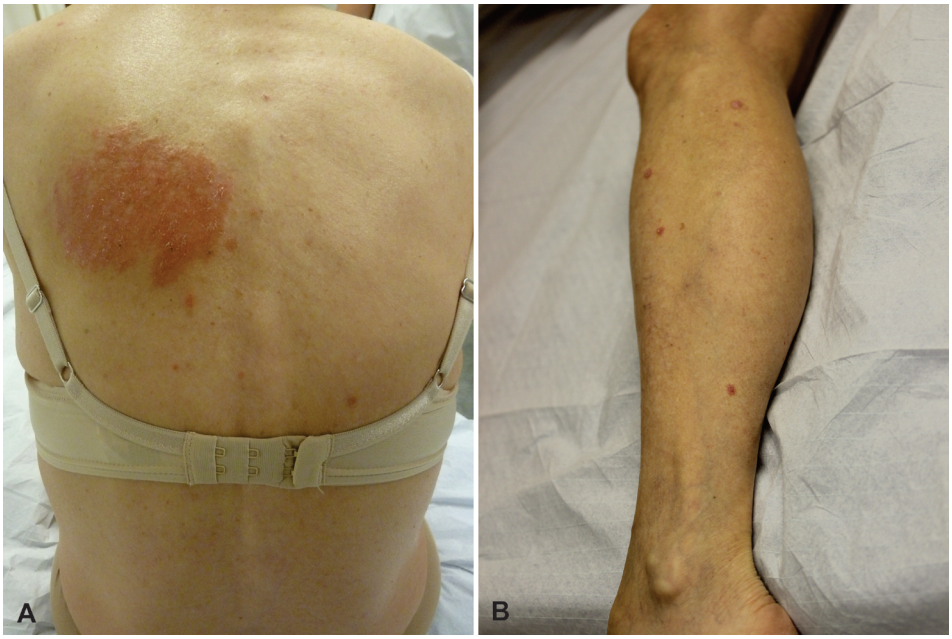

Figure 1 | A) Erythematous patch on the left side of the upper back. B) Itchy papules of the lower limb.

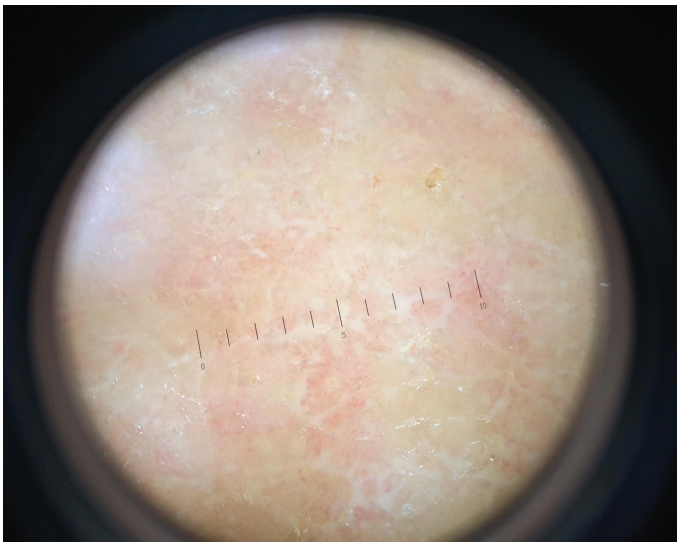

Figure 2 | Dermatoscopy of a papule: typical white Wickham striae within the lesion.

Discussion

We report a new case of LP associated with RT with extension to non-irradiated cutaneous areas as well as the oral mucosa. We performed a MEDLINE search using the keywords lichen planus and radiotherapy until April 2017 without restrictions on publication year, language, or study design. After identifying the search results, only articles published in English or French were selected. From the 16 search hits, we excluded one article in Dutch. Five articles prior to 2002 were related to LP associated with RT for LP. Including the present case, 12 cases of LP have been reviewed in association with oncologic radiotherapy since 2002 (9–19). The characteristics of the patients are summarized in Table 1. Briefly, seven women and five men (median age 57 years, range 26–68) were reported. RT preceded LP in most of the cases (83%; 10/12). Only two patients had a past history of LP. Patients were treated for various cancers: breast carcinoma, lung carcinoma, thyroid carcinoma, penile carcinoma, lymphoma, and others. Patients

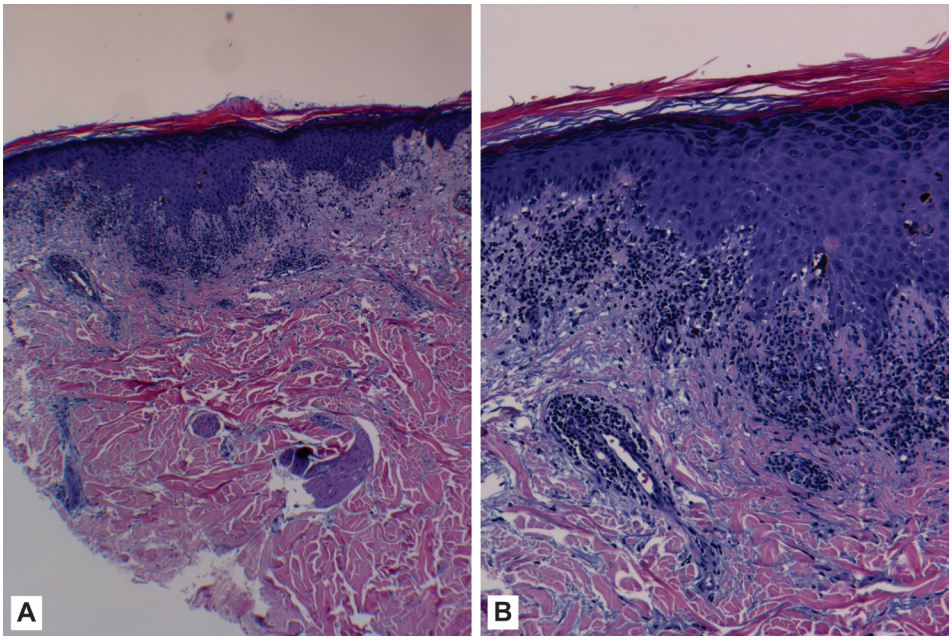

Figure 3 | A) Epidermal hyperkeratosis and well delimitated lymphocytic infiltrate of the upper dermis and the dermalepidermal interface (H&E × 4). B) Close-up view of the dermalepidermal junction with basal cell vacuolization (H&E × 20).

were irradiated with a median dose of 50 Gy (total dose ranges: 18 to 66.8 Gy). The articles were rarely specific regarding the type of irradiation that was performed. The patients most likely received X-rays or gamma ray irradiation. One patient was treated with cobalt therapy (16) and another with a 10 Mv beam (15). Electron therapy seems unlikely because it is useful only for superficial lesions. The median delay of onset after RT was estimated to be 30.7 days. Nine cases (82%) occurred within the first 3 months following RT. Two patients presented with LP very rapidly: one during RT (11) and the second within the next 2 weeks after RT completion (our case). In one case, a delay of 9 years was reported: the patient developed lichen plano-pilaris after brain radiotherapy. This case is strikingly different from the others. In the lack of other similar cases, the possibility of a fortuitous association should be considered (18). All of the patients developed LP on the irradiation field. Four patients (33%) also developed additional lesions elsewhere at some distance from the RT areas. In one case, lichenoid esophagitis was diagnosed (15).

Although such complications have been reported only recently, or 15 years ago (9), the occurrence of LP with RT has long been known. From the early 1920s to end of the 1970s, various RT protocols have been tried for LP treatment. They utilized either direct irradiation methods on skin lesions (4, 7) or indirect methods aiming at the spine. In those days the concept of the involvement of the sympathetic nervous system in the physiopathogeny of LP was actually in vogue in France (5). Flare-ups of LP on RT-irradiated areas as well as LP generalization were then observed (6, 8).

The physiopathogeny of LP remains unclear, as does this subtype "induced" by RT. Oral LP is currently considered the result of an immune reaction triggered by an antigen that alters the basal keratinocytes of the oral mucosa, making them susceptible to cell immune response. It induces the activation of CD4+ T and CD8+ T lymphocyte and cytokine production, such as interleukin-2 (IL-2), interferon gamma (IFN-γ), and tumor necrosis factor (TNF), which determine keratinocyte apoptosis. The antigen is unknown and could have either an intrinsic origin (heat shock protein or stress) or an extrinsic origin (drug or viral infection such as HPV or HCV) (20). It is hypothesized that RT would impair cutaneous integrity, causing the release of autoantigens or antigenic peptides. The subsequent ongoing cytokine release would result in unmasking peptide epitopes on keratinocytes to which CD8+ cytotoxic T cells are directed. In addition, RT may cause nonspecific mechanisms of keratinocyte and basement membrane damage such as the release of mast-cell mediators and matrix metalloproteases. The question of whether RT is the cause of LP or simply reveals the disease should be emphasized. One cannot rule out with certainty that some patients may have asymptomatic lesions of LP, such as oral lesions, before RT. The question of additional co-factors is likely. Komori et al. recently reported a case of RT-induced LP associated with nivolumab, a monoclonal antibody against programmed cell death protein 1 (PD-1) (19). Drug-induced lichenoid reactions are also possible. A wide range of different cancers have been reported (Table 1), making it unlikely that a specific type is associated thus far. Moreover, LP is not considered a paraneoplastic syndrome.

The management of RT-induced or RT-associated LP is similar to any LP. Local corticosteroid ointments and short-term oral corticotherapy at a low dose or phototherapy is the treatment of choice.

Table 1 | **Literature overview of cases of lichen planus in combination with radiotherapy.**

Sex	Age	Past history of LP	RT indication	Total dose RT (Gy)	Delay of onset of LP	Oral LP	Genital LP	Hair LP	Nail LP	Evolution (L: stayed localized, G: became generalized)	Miscellaneous	Ref
M	58	No	Thyroid carcinoma	59	1 mo	No	No	No	No	L		9
M	68	No	Penile carcinoma	NA	2 mo	No	No	No	No	L		10
F	56	No	Breast carcinoma	50.4	During	Yes	No	No	No	G, rapidly		11
F	44	Yes, G	Breast carcinoma	60	1 mo	No	No	No	No	Reappearance		12
F	59	No	Breast carcinoma	NA	NA	No	No	No	No	L		13
M	67	No	Plasmatocytoma	45	3 mo	Yes, lip	Yes	Scalp	No	G, 3 mo later		14
M	46	No	Nasopharyngeal carcinoma	66.8	2 mo	Yes, lip	No	No	No	L	Lichenoid esophagitis	15
M	40	Yes, LP of the left leg	Non-Hodgkin lymphoma of the knee	45	1 mo	No	No	No	No	L		16
F	48	No	Dermatofibrosarcoma protuberans	50	5 mo	NA	NA	NA	NA	L		17
F	26	No	Acute lymphoblastic leukemia	18	9 y	NA	NA	LPP	NA	L	Fortuitous association?	18
F	67	No	Hepatic lymph node (Breast carcinoma)	30	1.3 mo	NA	NA	NA	NA	L	Nivolumab	19
F	66	No	Lung carcinoma	30	1–2 wks after	Yes	NA	No	No	G		Present case

LP = lichen planus, RT = radiotherapy, F = female, M = male, mo = month, NA = not available, Ref = reference, wks = weeks, LPP = lichen plano-pilaris.

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