Oral, esophageal and cutaneous lichen ruber planus controlled with alitretinoin: case report and review of the literature

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Abstract: BACKGROUND: Therapy-resistant lichen planus (LP) can be a challenging condition for dermatologists. There are some case reports about successful treatments with alitretinoin of cutaneous and oral, but not of esophageal LP. OBJECTIVE: We present the unique case of a patient with cutaneous, oral and esophageal LP which was refractory to classical treatment options (topical clobetasol propionate and pimecrolimus, intramuscular triamcinolone acetonide); because of systemic side effects the patient did not tolerate systemic acitretin dosed up to 25 mg daily. Methods: Oral alitretinoin was used at a dose of 30 mg daily. RESULTS: Both oral and skin changes as well as dysphagia completely resolved within 4 weeks without any severe side effects and the drug was used for 6 months. No papules, intraoral striae or dysphagia recurred during the 6 months of treatment. After 4 months the patient relapsed with mucosal patches so that a second cycle was initiated for 6 months where oral LP lesions resolved after 4 weeks also (with sporadic mild headache). CONCLUSION: Further studies are needed to better understand the impact of alitretinoin in LP. Our observation suggests alitretinoin as a new, well-tolerated treatment option for esophageal LP after failed response to conventional treatments.

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Oral, Esophageal and Cutaneous Lichen Ruber Planus Controlled with Alitretinoin: Case Report and Review of the Literature

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Key Words
Oral lichen planus · Esophageal lichen planus · Cutaneous lichen planus · Lichen ruber planus · Alitretinoin

Abstract
Background: Therapy-resistant lichen planus (LP) can be a challenging condition for dermatologists. There are some case reports about successful treatments with alitretinoin of cutaneous and oral, but not of esophageal LP. ***Objective:*** We present the unique case of a patient with cutaneous, oral and esophageal LP which was refractory to classical treatment options (topical clobetasol propionate and pimecrolimus, intramuscular triamcinolone acetonide); because of systemic side effects the patient did not tolerate systemic acitretin dosed up to 25 mg daily. ***Methods:*** Oral alitretinoin was used at a dose of 30 mg daily. ***Results:*** Both oral and skin changes as well as dysphagia completely resolved within 4 weeks without any severe side effects and the drug was used for 6 months. No papules, intraoral striae or dysphagia recurred during the 6 months of treatment. After 4 months the patient relapsed with mucosal patches so that a second cycle was initiated for 6 months where oral LP lesions resolved after 4 weeks also (with sporadic mild headache). ***Conclusion:*** Further studies are needed to better understand the impact of alitretinoin in LP. Our observation suggests alitretinoin as a new, well-tolerated treatment option for esophageal LP after failed response to conventional treatments.

Case

We present the case of a 54-year-old woman suffering from purple, polygonal papules in a longitudinal configuration on the right medial thigh and whitish lacy patches of the oral buccal mucosa (fig. 1a). She complained about gradually increasing pruritus and burning sensation of the skin and mucosal lesions. The vulvovaginal area was uninvolved. Histology of the buccal mucosa revealed lichenoid skin inflammation (fig. 2). HIV, hepatitis B/C serologies, bacterial and fungal smears as well as laboratory investigations such as transaminases, creatinine and differential blood counts were inconspicuous. The diagnosis of oral and cutaneous lichen ruber planus was made.

After intramuscular injection of 40 mg triamcinolone acetonide, the skin changes resolved but the oral lesions expanded to the tongue and the patient developed dysphagia. Upon gastroscopy, discrete whitish patches were found on the whole esophagus (fig. 3a), but the larynx, stomach and duodenum were uninvolved. Acitretin was then started with 10 mg daily over 2 weeks and subsequently increased up to 25 mg daily and combined with topical oral clobetasol 0.05% gel. The oral lesions decreased in size and dysphagia resolved but the patient developed fatigue and weight loss, so acitretin was reduced to 10 mg daily for 4 weeks and subsequently stopped due to persistence of these side effects. Oral and skin changes relapsed after 8 weeks with additional involvement of the foot nails, hair loss and oral erosions. On the patient's wish, the therapy was continued only topically with corticosteroids and pimecrolimus and led to a stable state. Six months later, the patient developed new lesions on the right thigh, oral mucosa, dysphagia and nail dystrophy on digits IV and V on the left hand and on digit I of the right foot. Gastroscopy again showed whitish lacy patches in the whole esophagus.

Challenge

Cutaneous, oral and esophageal lichen planus (LP) was refractory to topical clobetasol propionate and pimecrolimus, in-

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Table 1. Overview of all reported LP patients treated with alitretinoin, including our case

Study	Gender	Age	Localization	Complaints	Duration of LP	Previous treatment	Additional therapy	Dose	Time to complete response	Treatment duration	Side effects
Brehmer et al., 2011 [1]	f	78	cutaneous	erythematous, partly confluent, scratched papules to plaques, mainly affecting extremities, severe pruritus	15 years	phototherapy, topical calcineurin inhibitors, topical corticosteroids	topical calcineurin inhibitors, topical corticosteroids	30 mg/day for 4 weeks, then 30 mg/every 2nd day for 4 weeks	8 weeks	8 weeks	–
	f	77	mucocutaneous	mucosal inflammation with whitish gingival striae, gum bleeding, burning	2 years	topical calcineurin inhibitors and topical corticosteroids	topical calcineurin inhibitors and topical corticosteroids	10 mg/day	4 weeks	4 weeks	hypertriglyceridemia (478 mg/dl)
	f	58	cutaneous and mucocutaneous	itchy papules on the back and burning in mouth	–	topical calcineurin inhibitors and topical corticosteroids	topical calcineurin inhibitors and topical corticosteroids	10 mg/day	4 weeks	4 weeks	headache and dizziness
Molin and Ruzicka, 2010 [2]	m	54	cutaneous	itching papules on trunk, back, legs, forearms, hyperkeratosis and fissures plantar	20 years sporadically	topical corticosteroids	initially with silver nitrate for fissures, topical betamethasone extraplantar, combination of steroids and salicylic acid plantar	30 mg/day	16 weeks on trunk, 6 months plantar	–	–
	f	48	cutaneous	pruritic papules palmoplantar and on wrists	7 months	–	cream PUVA 3–4 times per week, initially with topical mometasone and salicylic acid	30 mg/day	5 months	–	–
Pinter et al., 2011 [3]	m	43	cutaneous and nails	20 nail dystrophy, itching papules on both shins	1 year	topical and systemic antimycotic treatments	–	30 mg/day	6 weeks skin, 24 weeks nails	24 weeks	–
Present report	f	54	cutaneous, mucocutaneous, esophageal and nails	pruritic papules on right medial femoral, intraoral whitish striae, dysphagia	3 months	topical corticosteroids, acitretin, pimecrolimus	topical corticosteroids	30 mg/day	4 weeks skin, 4 weeks nails	2 cycles of 6 months each, totally 12 months	mild headache sporadically

tramuscular triamcinolone acetonide and systemic acitretin dosed up to 25 mg daily which had to be discontinued because of systemic side effects. There are several reports on effective treatment of LP unresponsive to classical therapies resolving under alitretinoin in cutaneous and mucosal but not in esophageal lesions [1–3] (table 1).

Results

The retinoid alitretinoin was started at a dose of 30 mg daily. Within 4 weeks both oral and skin changes as well as dysphagia completely resolved (fig. 1b); nail changes resolved within 6 months. The patient did not report any side effects and used the drug for a total of 6 months. No papules, intraoral striae or dysphagia recurred over the time of treatment. Gastroscopy after treatment showed no whitish mucosal changes anymore, however two small reddish plaques in the proximal esophagus remained (fig. 3b), and microscopic persistence of scattered cytotoxic T cell infiltrates was detected (fig. 4). After 4 months without treatment, the patient developed two new intraoral erosions, but no skin lesions. She was treated with low-dose alitretinoin 10 mg daily and temporarily with 0.1% triamcinolone paste for 2 weeks, but due to her oral complaints alitretinoin was raised to 30 mg daily again. Within 4 weeks the intraoral erosions resolved completely. After this second cycle of alitretinoin 30 mg daily over 6 months the patient remained free of any lesions but complained about sporadic mild headache.

Discussion

Lichen ruber planus (Greek *leichen*, 'tree moss'; Latin *planus*, 'flat') is a chronic inflammatory disease affecting the skin, mucous membranes, nails and hair. The prevalence of LP is about 0.5–1% of the population and LP is characterized by polygonal, flat, pruritic, purple papules to

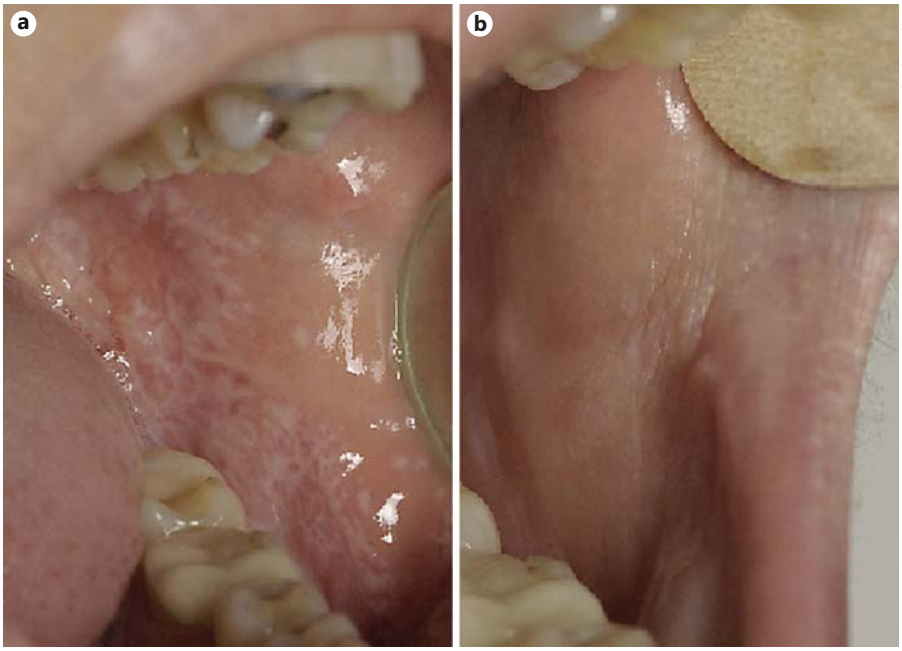

Fig. 1. Oral mucosa before (**a**) and after (**b**) treatment.

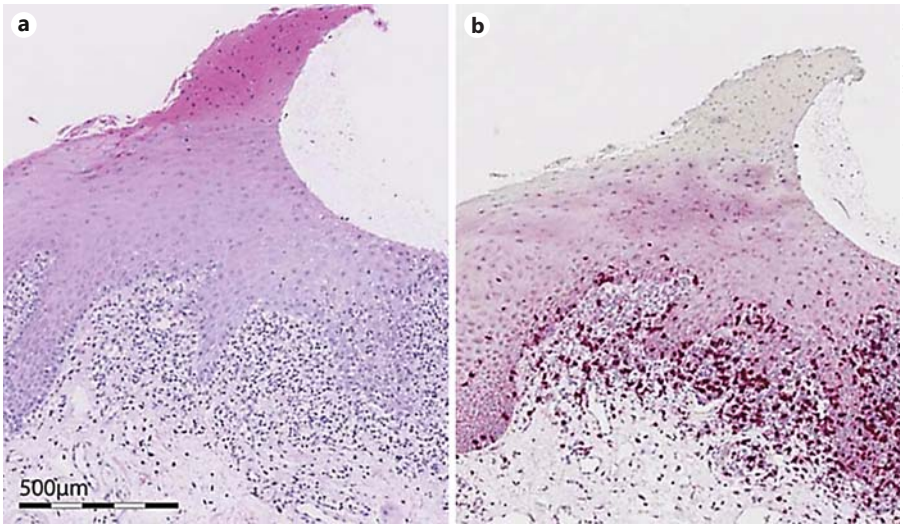

Fig. 2. Buccal histology, HE staining (**a**) and CD8 staining (**b**).

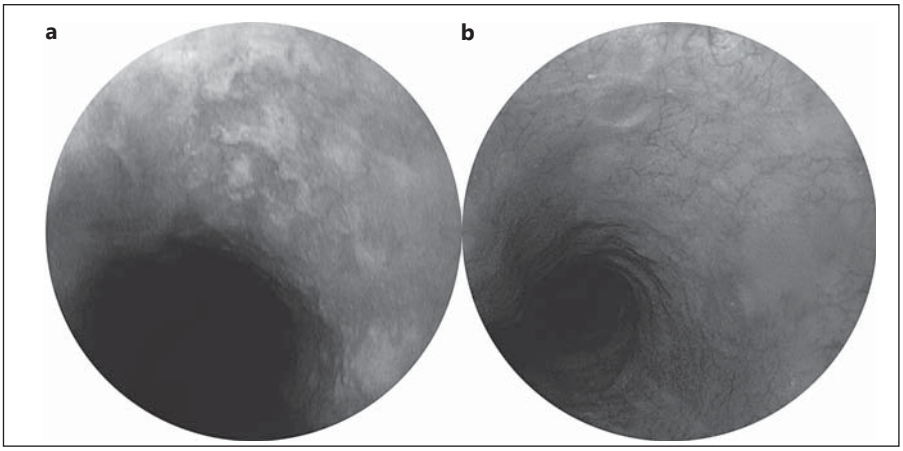

Fig. 3. Endoscopy of the esophagus before (**a**) and after (**b**) treatment.

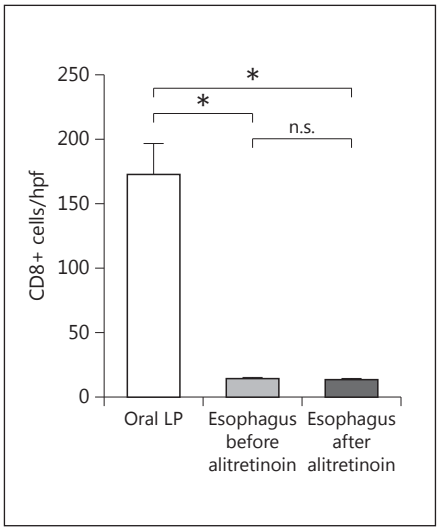

Fig. 4. CD8+ T cell infiltrates in biopsies of oral and esophageal lichenoid patches before and after 6 months of alitretinoin (3 high-power fields counted by two independent observers). * Significant, $p < 0.001$. n.s. = Not significant.

plaques commonly afflicting the wrists, ankles or the mucous membranes like the oral cavity, vulvovaginal or penile area [3–5]. Nail changes and scarring alopecia can also appear. Overlaid, reticulated, white streaks called 'Wickham striae' can be seen on the skin, and mucosal changes enhanced by applying water or oil or using dermatoscopy can be observed.

Different subtypes have been defined by configuration or morphology [5, 6]. Hypertrophic LP (also called lichen planus verrucosus) shows hyperkeratotic, flat-topped, reddish-brown, very pruritic plaques which typically affect the anterior distal lower extremities with a chronic course and normally resolve with scarring, associated with hypo- or hyperpigmentation [6]. Bullous LP (also called lichen vesiculobullosus) presents with vesicles or bullae within existing lesions of LP. This diagnosis requires prior exclusion of immunobullous disorders. Actinic LP appears as atrophic, hyperpigmented, annular, melasma-like, dyschromic or violaceous plaques with rolled edge in sun-exposed areas, seems to be UV-induced and tends to appear in patients with pigmented skin [7–11]. Linear LP can follow a 'blaschkoid' distribution in adults but is also described in a case report of a child [12–15]. Zosteriform LP follows dermatomal lines and is thought to be an isotopic response to herpes zoster or at least showing antigens against varicella zoster virus in lesional skin [16–18]. Lichen planus pigmentosus-inversus is suggested to be a rare variant of LP limited to intertriginous regions and seems to have a short inflammatory phase with fast transformation into a long noninflammatory regressive phase with brown, nonpruritic, small inflammatory macules; scaling is limited [19–25]. Only one case of coexistence of classic LP and lichen planus pigmentosus-inversus has been described [26]. Annular atrophic LP is a rare variant of LP and characterized by annular, violaceous plaques with central atrophy. Up to date 10 cases have been described [27–35]. Erosive LP is a painful variant of LP with eroded or ulcerated lesions mainly in mucocutaneous sites which is often difficult to treat and may lead to scarring [36–38]. Lichen planus pemphigoides refers to a cross-over syndrome of LP and bullous pemphigoid [5] and associations with drug intake have been described (PUVA [39], UVB, paracetamol or ibuprofen [40], simvastatin [41] and ramipril [42, 43]). Several reports show antibodies against 180, 130 and 200 kDa epidermal antigens [40, 44–51]. Some reports also describe an overlap between LP and lupus erythematosus [52–57].

LP shows oral involvement in 30–70% [58, 59]. Oral LP is located commonly in the posterior buccal mucosa (about 90%), in 30% of cases on the tongue and the alveolar mucosa. Oral LP presents with asymptomatic or tender, white, reticulated patches to plaques (reticulated oral LP) or as painful erosions and ulcers (erosive oral LP) [5, 60]. Bullous LP can involve the mucosal lower lip [61]. In analogy to adults, oral LP in pediatric patients also manifests as erosive LP in the buccal mucosa [62].

Genital LP commonly affects the vulva, the vagina as well as the glans penis and presents as erosive LP [63, 64]. Without treatment it can lead to scarring and disfigurement. Lichen sclerosus is the most important differential diagnosis. Vulvovaginal gingival syndrome is an uncommon and severe variant of LP and characterized by erosions or desquamation of vulval, vaginal and oral mucosa with a predilection for scarring and stricture formation, and 80% of patients bear the allele DQB1*0201 (vs. 41.8% in the control group) [65].

Esophageal LP was first described in 1982 [66] and presents with dysphagia, odynophagia, heartburn or regurgitation; its prevalence ranges from 1 to 50% [67–70], and nearly all patients are women (only few male cases [67, 71]) older than 40 years. Esophageal LP is strongly associated with oral LP, but genital or skin involvement has been described as well. Esophageal involvement is characterized by lesions in the form of peeling of the friable mucosa, hyperemic lesions, white plaques, ulcers, erosions and stricture formation [67, 72] and typically affects the upper and mid esophagus, sparing the gastroesophageal junction, in contrary to reflux esophagitis [73].

In an endoscopic study of 24 patients, high-magnification chromoendoscopy was used and biopsy samples were taken from all levels of the esophagus. In 75% of esophageal LP patients the diagnosis was made by histology of the proximal esophagus, in 25% of normal-appearing mucosa, in 50% of normal-appearing mucosa and focal abnormalities, and in 17% on focal abnormalities alone. Endoscopic abnormalities ranged from subtle papular lesions, superficial layers of esophageal mucosa peeling off, hyperemic lesions, submucosal plaques/papules, whitish papules, segments of cylindrical epithelium above the squamocolumnar junction to erosive changes in both proximal and distal esophagus [67, 74]. Reflux esophagitis is seen in 15–50% of esophageal LP patients, but it is controversial whether it is a separate condition or secondary to esophageal LP. A decreased resistance of the esophageal mucosa in esophageal LP has been suggested [67, 75].

Histology resembles that of oral LP and shows a band-like or lichenoid lymphocytic infiltrate involving the superficial lamina propria and basal epithelium. In the infiltrate mature T cells are predominantly present and are associated with degeneration of basal keratinocytes, often including characteristic Civatte bodies (necrotic keratinocytes with anucleate remnants). Other histological findings include dilated intercellular spaces, hyper- or parakeratosis, hyperplasia and glycogenic acanthosis [67]. However lymphocytic infiltration is not pathognomonic for esophageal LP, and other conditions such as infections, reflux disease or medications (gold, thiazides, antimalarials) can induce LP-like lesions. Esophageal LP typically involves the upper or mid esophagus which alone would be unusual for gastroesophageal reflux disease [76]. Esophageal LP has a chronic course and can lead to complications such as dysphagia, strictures (40% in the proximal esophagus [68]) and stenosis which may

require dilatation. Different systemic therapies are described. Systemic corticosteroids are supposed to be most effective as well as retinoids, cyclosporine, azathioprine, tacrolimus, rituximab and griseofulvin or intralesional corticosteroids [71, 72, 76–86].

In esophageal LP patients other upper gastrointestinal illnesses such as esophagitis, gastritis (up to 91%), bulbitis, duodenal ulcer or esophageal sphincter dysfunction are described as well and should be investigated [74, 87]. One case of esophageal LP also showed laryngeal and conjunctival involvement, but also a facial and abducens nerve paralysis which could be coincidental; an immunological explanation via mast cell activation was suggested [88, 89]. Esophageal LP may also lead to malignant transformation and cause squamous cell carcinoma ([76, 90, 91] and unpublished data).

As previous described, due to the different findings in endoscopy and histology complementing each other or not, esophageal LP is a challenging diagnosis and might currently be underestimated.

Nail changes appear in about 10% of LP patients and present as specifically as dorsal pterygium (wedge-shaped, raised deformity of the nail bed) and nonspecifically with onychorrhexis (longitudinal ridging, distal splitting and thinning of the nail plate) and trachyonychia. The differential diagnosis includes psoriasis, alopecia areata, idiopathic onychorrhexis, nail-patella syndrome or onychomycosis [5].

Women are commonly affected much more than men by lichen planopilaris, which involves the hair follicles and presents with painful or pruritic, irregularly shaped patches of scarring alopecia on the frontal, parietal or occipital scalp [1, 82]. 28–50% of lichen planopilaris patients show LP lesions elsewhere [92, 93]. Frontal fibrosing alopecia and Graham-Little syndrome are rare lichen planopilaris variants and its differential diagnosis includes discoid lupus erythematosus, cicatricial pemphigoid and alopecia areata. Lichen planopilaris may result in cicatrizing alopecia [92, 93].

Since 1903 over 90 cases of malignant transformation of cutaneous LP into squamous cell carcinoma have been described, with a higher incidence in hypertrophic LP and the possibility to metastasize [94, 95]. In oral LP a higher risk has been proven and the WHO defines oral LP as a 'premalignant condition' [96, 97]. Malignant transformation in oral LP is about 0.8–10% [59, 89] respectively 1–3% [98–101]. It has been discussed that the chronic inflammation plays a role in the malignant transformation of LP by analogy to ulcerative colitis and colorectal carcinoma [102]. Malignant transformation to squamous cell carcinoma is also described in penile, anal and vulvovaginal LP as well as in esophageal LP [90, 91, 103–108], as it was observed in another case at our hospital that developed an esophageal carcinoma within a chronic LP of the esophagus. With the chronic course of LP, especially in its hypertrophic variant, and an incidence of 9–26% in pediatric LP, it is very important to keep the risk of malignant transformation in mind, particularly in those patients [109, 110]. Cyclooxygenase-2 (COX-2) plays a role in inflammation as well as in cancer development. It could be shown that in LP lesions COX-2 is increased and microRNA-26b (an inhibitor of COX-2) is decreased, together possibly leading to COX-2 increase with a stronger activation of inflammation and carcinogenesis [111].

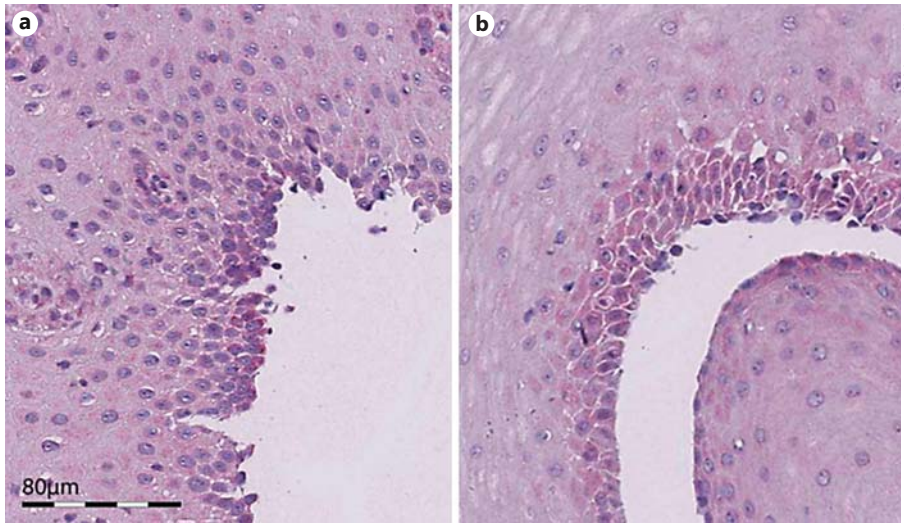

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Fig. 5. Esophageal immunohistology of IL-1β before (**a**) and after (**b**) treatment.

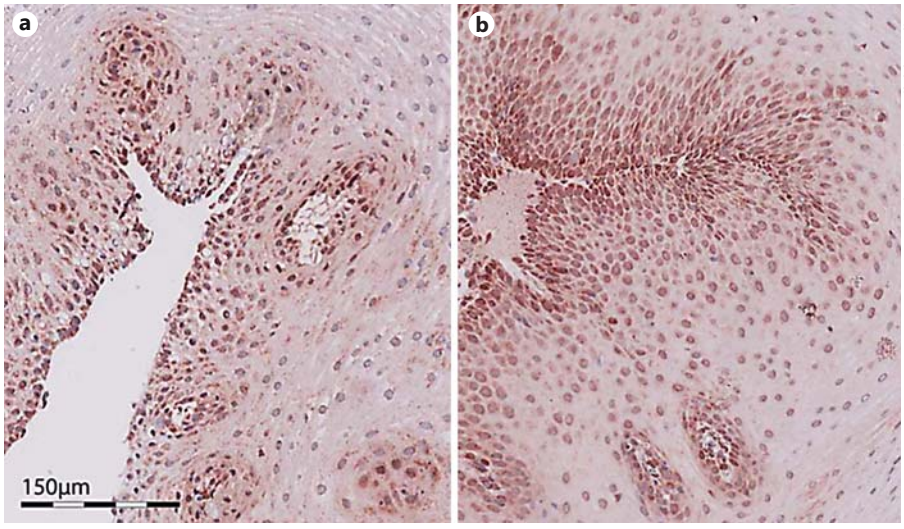

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Fig. 6. Esophageal immunohistology of IL-17 before (**a**) and after (**b**) treatment.

The pathogenesis is as yet unclear, but associations with hepatitis C, diabetes, genetic background, dental materials, drugs, infections, autoimmunity, immunodeficiency, stress and malignant neoplasms have been described [60].

The histopathology of LP is characteristic with hyperkeratosis, focal hypergranulosis, irregular sawtooth-like acanthosis, vacuolar degeneration of the dermo-epidermal junction zone and band-like lymphocytic infiltrates. Sometimes Civatte bodies, which are hyaline, amorphous apoptotic keratinocytes, and Caspary-Joseph spaces, which is a confluence of vacuolar degeneration, are found.

Recently different immunological modifications have been reported, including modulation of Toll-like receptors 2 [112] and 4 that bind bacterial lipopeptides and lipopolysaccharide, suggesting chronic host-pathogen interactions in oral LP whereby the pathogen may be a microorganism present on the skin and/or in saliva [113]. The majority of epithelial lymphocytes are CD8+ whereas in dermal tissue more CD4+ lymphocytes are present [114, 115].

Also increased expression of microRNA-146a and microRNA-155 in oral LP, which are also found in other inflammatory and autoimmune diseases like lupus erythematosus, as well as a polymorphism of DNMT3B (DNA methyltransferase 3b) have been described [116–119]. These microRNAs appear to favor Th1 responses by IFN-γ signaling and may be involved in reduced T-reg activation [120, 121].

Increased levels of TNF-α, RANTES-dependent mast cell degranulation and matrix metalloproteinase facilitate T cell migration into connective tissue [122–124]. Additionally, increased levels of IL-1α, IL-6 and IL-8 in oral lesions may indicate a NF-κB-dependent immune activation pathway [125].

Interestingly, elevated serum levels of IL-17 have also been found in patients suffering from oral LP and hepatitis C, and IL-17 also causes a matrix metalloproteinase response [126]. We performed esophageal immunohistology with IL-1β (fig. 5) and IL-17 (fig. 6) stainings which were positive compared with controls but did not show a significant difference between before and after treatment.

A large choice of treatment options for LP is available, including topical corticosteroids, topical calcineurin inhibitors, phototherapy, systemic steroids, systemic cyclosporine, thalidomide [127] and mycophenolate mofetil [128]. TNF-α inhibitors like etanercept [129, 130] and adalimumab [4, 131] can ameliorate but paradoxically also elicit LP. Meta-analyses show very weak evidence of effectiveness of any treatment of oral and erosive LP [37, 132, 133].

The RXR/RAR ligand alitretinoin resulted in suppression of multifocal lichen ruber planus, including the potentially dangerous esophageal involvement that can predispose to spinocellular carcinoma ([134] and own unpublished observation).

In our case the patient was unresponsive to or suffered from side effects from previous therapies including topical corticosteroids, topical pimecrolimus and acitretin. We therefore chose a regimen of 30 mg alitretinoin daily over a period of 24 weeks, as it is used for chronic hand eczema with clearance up to 48% [135]. In the hope of stabilizing remission we extended the treatment with alitretinoin 30 mg daily.

Taken together, this case reports the successful use of alitretinoin for esophageal LP with dysphagia. All sites of lichen ruber planus improved under therapy with alitretinoin (table 1). We propose that alitretinoin may be effective in suppressing disease activity in LP, but may not definitively inactivate the immunologic process driving LP within a 6-month course of therapy. In our case, at the end of 24 weeks of treatment with alitretinoin, scattered mucosal CD8+ T cell infiltrates in the esophagus were still detectable, suggesting that therapy beyond 6 months may be of value (as in our patient a second course of treatment over 6 months was necessary).

Alitretinoin could be a future additional treatment option for LP, including LP with esophageal involvement, in case of nonresponse to previous treatments. A larger monocentric, prospective, open-label study (NCT01538732) is currently being performed at our department to further investigate this question.

Author Contributions

A. Navarini and A.G.A. Kolios had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: A.G.A. Kolios, A. Navarini. Acquisition of data: A.G.A. Kolios, E. Marques Maggio, C. Gubler. Analysis and interpretation of data: A. Navarini, A.G.A. Kolios, A. Cozzio, R. Dummer, L.E. French. Drafting of the manuscript: A. Navarini, A.G.A. Kolios, R. Dummer, L.E. French. Critical revision of the manuscript for important intellectual content: A. Navarini, E. Marques Maggio, C. Gubler, A. Cozzio, R. Dummer, L.E. French. Obtained funding: A. Navarini. Administrative, technical or material support: A. Navarini, E. Marques Maggio, A.G.A. Kolios. Study supervision: A. Navarini, R. Dummer, L.E. French.

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Disclosure Statement

None of the authors have any financial relationships relevant to this paper.

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