

On behalf of all authors, I would like to extend my gratitude to the reviewers for the efforts and time they have spent reviewing our submission. The Reviewers made excellent and valuable suggestions to improve the manuscript. Please find our responses under each of the comments made by the reviewers below.

All changes or modifications made in the revised text are marked in red.

Because I did not find a possibility to send you the revised version, in which changes are marked in red, I send you a combined version. It includes

1. The revised version, changes in red
2. The original versions with the comments of reviewer 1, including our answers
3. The answers to the comments of reviewer 2

Reviewer 1

The authors need to describe the current available literature thoroughly. Also the lacunae in current literature need to be emphasized. The authors need to mention about the future directions in detail. The detailed comments are added in the manuscript file.

Answer:

We modified the paragraphs in the text as suggested by the Reviewer and answered the queries of Reviewer 1 in detail at the end of the revised version.

Reviewer 2

The article "Review: Esophageal Lichen Planus: Current Knowledge, Challenges and Future Perspectives" is interesting. I have some suggestions that could improve its quality.

Answer:

Thank you for these positive remarks.

In general terms, authors must reconsider the use of references, adapting them to the text and eliminating all those that are not necessary for ELP.

Answer:

We eliminated several unnecessary references, particularly in the "Background" paragraph.

Summary: - When you indicate that include your cohort of patients, which cohort are you referring to? What number of patients is included in this study from your cohort? Do the patients belong to previous studies? This point should be clarified –

Answer:

In the whole text we refer to the patients described in Ref. 20 (Schauer et al. 2019). This is indicated in Table 2 and in the modified text

From the review you provide, can it be subtracted that topical corticosteroids improve in 2/3 of the patients? Do you consider corticosteroids drugs immunosuppressive? “However, treatment with topical steroids induces symptomatic and histologic improvement in 2/3 of the patients. More severe cases may need immunosuppressive therapy.”

Answer:

In Table 2, we included details about therapeutic response in the cited studies. Because the numbers of patients in the studies are small, 2/3 might be an appropriate estimator. See Podboy, Ravi, Schauer. We prefer the term “systemic immunosuppressors”

Main text: - How did you select the bibliographical references included in the study? what database come from? - You present many bibliographical references that are not necessary for the description of the ELP. –

Answer:

We mentioned how we selected the cited studies in the Abstract: “Methods: Studies on ELP were collected by PubMed/Medline research and relevant clinical and therapeutical characteristics from published patient cohorts including our own cohort were extracted and summarized.” And in the paragraph “Esophageal Lichen Planus”. In addition, we mentioned that we wrote a narrative review, not a systematic review. Unnecessary references in the paragraph “Background” were eliminated. For every described entity of esophagitis we cited one representative study.

Bibliographical references must be adapted to the content of the sentence. For example “Good therapeutic response was reported with topical corticosteroids such as fluticasone or budesonide leading to clinical and/or endoscopic response rate of 62% up to 74% in ELP [24–28]”. Do references 24 and 25 provide data on the treatment of ELP?

Answer:

The comment of the reviewer is correct: Ref 24 was eliminated. However: The references were renumbered because we included few new refs.

However, when referring to Macroscopy and Histopathologic Features you do not indicate any reference. - When you make the following recommendation, what bibliographical reference do you base it on? “To evaluate microscopic changes in patients with known LP, we recommend to take at least two biopsies (in the lower and upper third of the esophagus) regardless if the above-mentioned endoscopic signs are not present.” –

Answer:

This was clarified in the paragraph “Diagnosis” as follows:

Diagnosis

Throughout literature, similar diagnostic macroscopic and histologic features for ELP have been repeatedly described (see Table 2). Alongside some findings which can be considered typical of ELP, some similarities with other esophageal disorders such as eosinophilic esophagitis, lymphocytic esophagitis, sloughing esophagitis can be

found, [3,9–11,13,81–86] hence making the diagnosis challenging. Based on published data and experience from our own patients' cohort, a diagnostic score combining endoscopic and histopathologic findings, as well as direct immunofluorescence (DIF), and a severity grading (no ELP, mild ELP, and severe ELP) has been previously proposed by our group [20]. These criteria are not completely new, but existing criteria and own findings are combined into a comprehensive and reproducible scoring system. Examples for endoscopic, histopathologic, and DIF findings are shown in Figures 1 - 4.

Table 2: the number of patients with ELP, the treatment received and their response, should be properly differentiated. –

Answer:

We modified Table 2. Data about type of therapy and of response were included.

Figure 5: The algorithm of Figure 5 is very ambiguous. You should specify sections such as, a) Therapy with topical steroids 2-3x/d, what type of steroid, how long, application method? b) Systemic immunosuppressants, what type and how long? –

Answer:

We modified Figure 5 accordingly. Because we can present only a suggestion, it is difficult to give more detailed proposals. We hope that the reader will accept our comments in the text that further studies are necessary about ELP.

Do the figures 1-4 belong to your cohort of cases? Should be clarified.

Answer:

We included short remarks in the legends.

-Limitations of the study should be noted.

Answer:

Because the present manuscript is not an original study, the limitation lies in the scarcity of relevant studies. Our manuscript should stimulate research about ELP as an important clinical entity.

References: Adapt the references to the guide of the journal

Answer:

We will do it in collaboration with the editorial office.

Revised version of the manuscript

Review: Esophageal Lichen Planus: Current Knowledge, Challenges and Future Perspectives

Annegrit Decker ¹, Franziska Schauer ², Adhara Lazaro ³, Carmen Monasterio ¹, Arthur Robert Schmidt ¹, Annette Schmitt-Gräff ⁴, Wolfgang Kreisel ¹

¹ Department of Medicine II, Gastroenterology, Hepatology, Endocrinology and Infectious Diseases, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

² Department of Dermatology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

³ Department of Medicine, Institute of Exercise and Occupational Medicine, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

⁴ Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany and
Institute for Dermatohistology, Pathology, and Molecular Pathology, Dr. Helmut Laaff, Freiburg

Corresponding author:

Prof. Dr. Wolfgang Kreisel

Department of Medicine II, Gastroenterology, Hepatology, Endocrinology and Infectious Diseases, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

+49 761 270 34010

wolfgang.kreisel@uniklinik-freiburg.de

Key words: Lichen planus; Esophagitis; T-Lymphocytes, Budesonide; Dysphagia; Precancerosis

Abstract

Background: Lichen planus (LP) is a frequent, chronic inflammatory disease involving the skin, mucous membranes and / or skin appendages. Esophageal involvement in lichen planus (ELP) is a clinically important albeit underdiagnosed inflammatory condition.

Aims: This narrative review aims to give an overview of the current knowledge on ELP, its prevalence, pathogenesis, clinical manifestation, diagnostic criteria, and therapeutic options in order to provide support in clinical management.

Methods: Studies on ELP were collected using PubMed/Medline. Relevant clinical and therapeutical characteristics from published patient cohorts including our own cohort were extracted and summarized.

Results: ELP mainly affects middle-aged women. The principal symptom is dysphagia. However, asymptomatic cases despite progressed macroscopic esophageal lesions may occur. The pathogenesis is unknown, however an immune-mediated mechanism is probable. Endoscopically, ELP is characterized by mucosal denudation and tearing, trachealization, and hyperkeratosis. Scarring esophageal stenosis may occur in chronic courses. Histologic findings include mucosal detachment, T-lymphocytic infiltrations, epithelial apoptosis (Civatte bodies), dyskeratosis, and hyperkeratosis. Direct immuno-fluorescence shows fibrinogen deposits along the basement membrane zone. To date, there is no established therapy. However, treatment with topical steroids induces symptomatic and histologic improvement in two thirds of ELP patients. More severe cases may require therapy with immunosuppressors. In symptomatic esophageal stenosis, endoscopic dilation may be necessary. ELP may be regarded as a precancerous condition as transition to squamous cell carcinoma has been documented in literature.

Conclusion: ELP is an underdiagnosed yet clinically important differential diagnosis for patients with unclear dysphagia or esophagitis. Timely diagnosis and therapy might prevent potential sequelae such as esophageal stenosis or development of invasive squamous cell carcinoma. Further studies are needed to gain more knowledge about the pathogenesis and treatment options.

INTRODUCTION

Inflammatory esophageal diseases comprise a broad spectrum of differential diagnoses ^[1–3] out of which reflux esophagitis is the most frequent condition ^[4]. Infectious etiologies include Candida or viral esophagitis which are mainly linked to compromised immune function ^[5]. Esophageal disorders based on immunological background include Crohn's disease ^[6], Behçet's disease ^[7], graft-versus-host disease after allogeneic stem cell transplantation ^[8], and eosinophilic esophagitis (EoE) ^[9–12]. The spectrum of differential diagnoses ranges to less defined subtypes such as lymphocytic ^[13] or sloughing esophagitis^[14]. **These differential diagnoses as summed up in Table 1 encompass additional manifestation of autoimmune bullous diseases such as mucous membrane pemphigoid or pemphigus vulgaris ^[2,3,15] as well as lichen planus.** Esophageal lichen planus (ELP), a mucocutaneous manifestation of lichen planus, should be considered in patients with signs and symptoms corresponding to esophageal inflammation. Since many aspects of this disease are still poorly understood, ELP tends to be underreported and often misdiagnosed. However, in the last decade, gastroenterologists and researchers provided more emphasis to this condition. Likewise, proposals for macroscopic and histopathologic diagnostic criteria were made and data on therapy has been increasingly available ^[16–20].

This narrative review aims to summarize current knowledge on ELP in order to increase awareness about this clinically important esophageal inflammatory disease and make it more accessible in clinical practice.

MAIN BODY

Lichen planus

Lichen planus(LP) is a frequent mucocutaneous disease whose pathogenesis is only partly understood ^[21–24]. It affects 0.5%–2% of the general population and has female predominance (65%) ^[21,23,24]. Lesions of skin, oral, and genital mucosa are the most frequent manifestations, however involvement of nails, scalp, genitoanal mucosa, eyes, ears, urinary bladder, or nasal mucosa are also seen. Classic exanthematic, cutaneous LP manifests as flat, reddish, itching papules in the face, arms, wrists, with a tendency to develop postinflammatory hyperpigmentation. In two-thirds of patients, an oral manifestation is observed with reticular, erythematous, and erosive

subtypes. **Patients with oral LP** complain of oral discomfort or pain, exhibit characteristic fine white buccal lines (Wickham striae) and often have visible ulcerations on gingiva and palate, tongue and / or labial mucosa. **Genital LP may cause itching lesions on glans penis, prepuce or scrotum in men, and on vulva or vagina in women.** Involvement of genital mucosa may show all stages of inflammation, starting with erythema, progressing to erosions, plaque formation, and scarring. Lichen planus pemphigoides (LPP) is a rare, mostly IgG-mediated autoimmune variant of LP, exhibiting characteristics of bullous pemphigoid (reactivity against collagen XVII) [25]. As LP may involve multiple organ systems, this disease requires multidisciplinary approach involving dermatologists, dentists, gynaecologists, and gastroenterologists [26–29]. The European guidelines for therapy of LP have recently been published [30,31].

Pathogenesis

A T-cell mediated inflammatory reaction involving antigen-specific and antigen-unspecific mechanisms is regarded as the basic mechanism of pathogenesis [21,28,32]. A recent review about the immunogenetics of lichen planus reported that multiple imbalances of cytokines or interleukins are involved [33]. In addition, genetic influences and MHC associations were found. Micro-RNAs (mi-RNAs) might also be implicated in LP. Antigen-specific mechanisms include antigen presentation of an unknown trigger by basal keratinocytes, activation of CD4+ Th1-helper cells, cytokine production, and CD8-positive cytotoxic reaction against basal epidermal cells. On the other hand, antigen-unspecific mechanisms could involve upregulation of proinflammatory mediators such as **interferon- γ** , tumour necrosis factor-alpha, interleukins, and matrix metalloproteases, leading to T-cell infiltration in the epidermal cell layer.

The cytokine profile suggests a Th1/Th2-imbalance, whereas B-cells, plasma cells, or antibodies may play a minor role [33]. Similar to psoriasis or pemphigus [34–36], a disturbance in the IL17 / IL23 axis was observed [37,38]. Bacterial or viral antigens may trigger LP. An association with chronic hepatitis C was described, however data remains controversial [39,40]. An association with IgG4-related disease is possible [41]. LP may be triggered by several drugs, e.g. NSAIDs, beta-blockers, ACE-inhibitors,

and check-point inhibitors [42]. Amalgam or mercury are regarded as trigger for oral LP [43], while concomitant diabetes or smoking influence the clinical severity [44]. There are associations with systemic diseases and autoimmune disorders such as primary biliary cholangitis, autoimmune thyroiditis, myasthenia, alopecia areata, vitiligo, thymoma, and autoimmune polyendocrinopathy [28,45–47]. As in other immune-mediated diseases, psychological component may influence the disease progression [48–50].

Esophageal Lichen Planus (ELP)

Involvement of the esophagus in LP as another possible site of mucosal affection was first described in 1982, [51,52] followed by case reports and small case series presenting this new type of esophageal inflammatory disease with lichenoid features [53–64]. ELP was regarded then as a rarity, likely because its clinical, endoscopic, and histologic features were not yet clearly understood. In recent years, interest about this “new” disease was growing and consequently, larger case series and studies, [16–19,58,60,65–70] as well as two comprehensive reviews were published [71,72]. For this narrative review, studies were collected using PubMed/Medline and single case reports were excluded. Table 2 presents an overview of these studies and their key findings.

Epidemiology

The population-based prevalence of LP was estimated to reach an average of 1.3% [21,73]. Oral LP is considered the most predominant mucosal manifestation affecting two-thirds of patients with cutaneous LP [26–28]. A recent metaanalysis showed a varying global prevalence of oral LP (0.57% in Asia, 1.68% in Europe, and 1.39% in South America) [74,75]. Esophageal involvement was initially regarded as a rarity, however further studies showed an esophageal manifestation in up to 50% of patients presenting with cutaneous or oral LP [16,76]. Since the number of cases in these studies were limited and the patient groups non-randomized, the true prevalence of ELP might be overestimated. Surprisingly, ELP does not necessarily correlate with oral disease [65,77]. However, oral LP is found in most of the cases of severe ELP. Esophageal manifestation also correlates with the occurrence of other mucosal involvement such as genital LP. The median age at presentation is 60

years and 80% of patients are female [72,78]. Determining the true prevalence of ELP remains a challenge, as it would require endoscopic screening in a large group of patients with LP regardless of localization and symptoms. Focusing on patients with esophageal symptoms only, e.g. dysphagia, would underestimate the true prevalence of ELP. A previous study showed that more than 50% of patients with mild ELP did not report dysphagia [20]. Moreover, cases where the esophagus is the only affected site of LP could still be missed. Hence, the prevalence of ELP on a population-based level can only be roughly estimated thus far. Furthermore, assuming that about 10% of all LP patients would have an esophageal involvement, the prevalence could be as high as 0.1% in the general population, thus outnumbering the prevalence of eosinophilic esophagitis which has been reported to reach 0.04 – 0.05% in Western countries [79].

Diagnostic features of ELP

Clinical symptoms

Dysphagia is the leading symptom found in 80 – 100% of patients with ELP. Other symptoms include odynophagia, heart burn, regurgitation, weight loss, hoarseness, and chronic unproductive cough. In some studies, approximately 20% of patients with ELP did not manifest any esophageal symptoms [80]. Development of esophageal symptoms might be influenced by severity of disease. **In a previously published study, 94% of patients with endoscopically severe ELP presented with dysphagia. However, only 44.4% of patients with mild ELP complained about dysphagia [20]. On the other hand, up to 6% of LP patients had symptoms of dysphagia without esophageal involvement.** In clinical practice, ELP should be investigated in patients presenting with the above-mentioned symptoms, especially in patients with known LP. Moreover, ELP should be considered in all patients where other common causes of **esophagitis** (see Table 1) have been ruled out.

Diagnosis

Similar set of macroscopic and histologic features of ELP has been repeatedly described in literature (see Table 2). Alongside some findings which can be considered typical of ELP, some similarities with other esophageal disorders such as eosinophilic esophagitis, lymphocytic esophagitis, and sloughing esophagitis can be

found, [3,9–11,13,81–86] hence, making the diagnosis challenging. Based on published data and experience from our cohort of patients, a diagnostic score combining endoscopic and histopathologic findings, as well as direct immunofluorescence (DIF), and a severity grading (no ELP, mild ELP, and severe ELP) has been previously proposed by our group [20]. These criteria are not completely new, however existing criteria and our own findings were integrated into a comprehensive and reproducible scoring system. Examples for endoscopic, histopathologic, and DIF findings are shown in Figures 1 - 4.

Macroscopy

The endoscopic hallmark in nearly all studies analysed (see Table 2) is denudation or sloughing of the esophageal mucosa. It may occur spontaneously or during the endoscopic procedure. Less specific indicators of ELP are “trachealization” (an endoscopic sign well known in EoE) and presence of a rough and whitish surface of the mucosa which is the macroscopic correlate of hyperkeratosis as seen in histology. Stenoses or strictures may occur as sequelae of chronic inflammation in ELP as in other chronic inflammatory esophageal disorders. Endoscopic images of mucosal alterations are shown in Figure 1. Endoscopic changes may be observed in all parts of the esophagus, but mainly in the middle third. As reflux esophagitis often occurs simultaneously, macroscopic and histologic alterations directly above the gastroesophageal junction may be ambiguous. Thus, biopsies should be taken at least 5 cm above the gastroesophageal junction. To evaluate microscopic changes in patients with known LP, we recommend to perform at least two biopsies (in the lower and upper third of the esophagus) regardless if the above-mentioned endoscopic signs are not present.

Histopathologic Features

Esophageal biopsies provide a reliable assessment of mucosal lesions characteristic of ELP (Figure 2). Band-like inflammatory infiltrates are observed at the interface between the squamous epithelium and the lamina propria corresponding to a lichenoid esophagitis pattern. The predominant cell type in the inflammatory infiltrate of ELP are CD3+ T cells which spill over into the adjacent epithelium involving the lower third or lower half of the epithelial thickness. CD4+ cells are the main T-cell subset reported in cutaneous LP while ELP also frequently harbors abundant

intraepithelial CD8+ lymphocytes. Intraepithelial lymphocytosis is associated with scattered squamous cell apoptosis designated as Civatte bodies. The epithelium may become partially or completely detached from the tunica propria or show intraepithelial splitting reminiscent of sloughing esophagitis. However, superficial necrosis and neutrophilic aggregates seen in sloughing esophagitis are not a feature of ELP. The squamous epithelium may be hyperplastic and exhibit acanthosis similar to the saw-toothed rete ridges of cutaneous LP especially in long-standing esophageal involvement. In contrast to the normal esophageal epithelium, hypergranulosis is frequently observed in the superficial epithelium of ELP. Surface orthokeratosis, also termed esophageal epidermoid metaplasia (EEM), is the histologic correlate of the rough and whitish mucosal surface with leukoplakia. (Figure 3). This lesion is referred to as uncomplicated EEM as long as epithelial maturation is preserved and dysplasia/intraepithelial neoplasia (IEN) is absent. Chronic inflammation may lead to fibrosis and scarring of the tunica propria resulting in strictures and dysphagia.

Direct immunofluorescence (DIF)

In ELP, direct immunofluorescence often highlights fibrinogen deposits along the basal membrane as another important criterion (Figure 4). This is based on the data on oral LP, where linear fibrinogen deposition (or granular IgG and IgM deposits) in DIF could discriminate the diagnosis from other lichenoid lesions^[87] and mucus membrane pemphigoid^[15,27]. Therefore, positive results in DIF support the diagnosis of ELP yielded by conventional histopathology and, in turn, differentiate the findings from diseases like mucous membrane pemphigoid or pemphigus vulgaris in erosive stages.

Therapy

In contrast to cutaneous and oral LP^[30,31], there are no generally accepted guidelines for therapy of ELP. Conventional management of cutaneous LP with retinoids does not seem to prevent the emergence of ELP, nor is it suitable for therapy of ELP^[20,53,88,89]. However, a few case reports described successful therapy using alitretinoin^[62]. Good therapeutic response was reported with topical corticosteroids such as fluticasone or budesonide leading to clinical and/or endoscopic response rate of 62%

up to 74% in ELP [17–20]. The type of budesonide preparation might play an important role for its efficacy. Viscous syrups or gels offer better adherence to the esophageal mucosa than swallowed sprays, and led to good response rates [20]. However, for a comparison of response rates based on specific preparation, case numbers in literature are too limited (see Table 2). Orodispersible tablets designed for eosinophilic esophagitis might play an interesting role but have not yet been studied in ELP. Intralesional injection of triamcinolone has also been described in literature [53,70,90]. Systemic corticosteroids have been proposed to induce rapid response in severe cases [66]. However, they are not suitable for maintenance therapy and tapering may lead to reoccurrence of symptoms. Therefore, more severe cases not responding to topical corticosteroids require therapy with systemic immunosuppressants. Different types of immunosuppressors such as adalimumab, hydroxychloroquine, mycophenolate, azathioprine, cyclosporine, tacrolimus or rituximab have been used [24,53,54,63,65,68,69,91,92]. In one of our patients, cyclophosphamide was the only drug which effectively induced at least a partial remission. Refractory cases also exist [64].

Since ELP mainly occurs as part of a systemic or multilocular LP, treatment should always be initiated in a multidisciplinary approach involving at least gastroenterologists and dermatologists, especially when topical therapy is not effective and systemic immunosuppressive therapy is necessary.

Complications

Esophageal stenosis/Food impaction

As with other inflammatory esophageal diseases, inflammatory or scarring stenosis can be a sequela of chronic untreated or refractory course leading to typical complications such as dysphagia, odynophagia, food impaction, and weight loss [17]. Therefore, ELP should be considered as one of the potential causes of food impaction [93], together with achalasia or eosinophilic esophagitis, or of unexplained esophageal stenosis [94–96]. This applies, not only, but especially to patients with known LP on other site or to patients presenting with signs of undiagnosed mucocutaneous disease.

Treatment of esophageal stenosis

In symptomatic esophageal stenosis, endoscopic dilation may be necessary and has been successfully performed in multiple cases [97,98]. The possibility of considerable

mucosal denudation, the main feature of florid ELP, prompted some authors to advice against endoscopic dilation in the past. However, this can be overcome by simultaneously treating the underlying inflammation as recommended in other esophageal inflammatory conditions. Anti-inflammatory treatment can reduce mucosal fragility, making it more resistant to physical stress, consequently preventing the reoccurrence of stenosis and inducing remission. The need for endoscopic dilation has been reported to decrease under anti-inflammatory therapy [72] and in a few cases, budesonide alone led to relief of symptomatic stenosis [20]. However, vis-a-vis therapy of stenosis in Crohn's disease, this may only apply for inflammatory and not for scarring stenosis.

Precancerous lesions and esophageal squamous cell carcinoma

Several factors may limit the life expectancy of patients with LP [99,100]. Oral squamous cell carcinoma is one of them, as oral lichen planus is widely regarded as a precancerous condition, even though the exact rate of malignant transformation is a matter of debate [55,101–104].

Accordingly, correlation between ELP and development of esophageal squamous cell carcinoma (ESCC) has been well documented. The number of case reports has been increasing in which esophageal inflammatory and hyperkeratotic lesions have progressed to squamous cell dysplasia/ intraepithelial neoplasia and even to invasive ESCC. In some studies, development of ESCC has been reported in up to 4.5% of ELP patients [105,106].

ELP-associated esophageal precancerous squamous lesions are generally detected in areas of esophageal epidermoid metaplasia (EEM) [107–109]. In low-grade dysplasia, cytologic and structural epithelial abnormalities are confined to the lower half of the esophageal epithelium, while high-grade dysplasia involves more than half of the epithelial cell layers with lack of surface maturation. Therefore, endoscopically detected areas of EEM/leukoplakia should be systematically sampled for histologic evaluation since these constitute a hallmark of orthokeratotic dysplasia (Figure 3). It should be noted that invasive ESCC may be detected underneath or adjacent to EEM. Our experience showed uncomplicated hyperkeratosis/EEM in a considerable number of patients with severe ELP (37.5 %), while predominantly low-grade orthokeratotic dysplasia was rare (6 %) and the transition to an early invasive ESCC

was diagnosed in only one patient ^[20]. Anti-inflammatory therapy did not lead to regression of hyperkeratotic areas in this cohort. New therapeutic strategies should aim to either slow down or arrest the development of EEM.

According to Singhi et al. ^[108], mutation in TP53 correlates with occurrence of or progression to ECC in ELP. p53 overexpression in immunohistochemistry has been frequently observed in our cohort. Additional molecular analyses have yet to be performed to gain more knowledge on risk stratification. Future advances in identifying the molecular landscape which drives the development of precancerous lesions and overt invasive carcinoma may help establish prognostic biomarkers for early detection of ELP cases at high risk of progression to overt ESCC.

Translating this knowledge to clinical practice, we recommend regular endoscopic surveillance of ELP patients for development of dysplasia. Detection of suspicious areas may be assisted by chromoendoscopy. Patients with known hyperkeratotic regions or florid inflammation should be assessed more often. In cases of low grade dysplasia, we recommend further endoscopy every six months; in cases of transition to high grade dysplasia, endoscopic mucosal ablation should be performed similar to patients developing dysplasia in Barrett's esophagus. Furthermore, other known risk factors for development of ESCC such as nicotine or alcohol intake should be discouraged.

Proposal for management of ELP

Figure 5 presents a proposal for clinical management of ELP. We recommend EGD in every patient with known LP (skin or mucosal manifestation) and with any associated esophageal symptoms as described above. Diagnosis can be established using the above-mentioned criteria (Table 3). We recommend to treat every newly diagnosed ELP initially with topical steroids and then to reevaluate therapeutic response after a certain time interval (e.g. three months). In our clinical experience, 0.5 mg budesonide in 5 ml viscous solution TID for the initial treatment period is used. Further therapy would depend on whether a clinical and/or histological remission has been established. Otherwise, systemic immunosuppressive therapy may be necessary as described above. At present, there is not enough data on recommended immunosuppressant. Every patient diagnosed with ELP with no known LP on other sites should also be assessed by a dermatologist.

To date, there is still no consensus on how to identify and treat asymptomatic ELP patients, specifically patients with asymptomatic hyperkeratosis, a potential precursor of esophageal squamous cell carcinoma. A wait-and-see strategy seems to be warranted [65,77]. However, in patients with EEM, we recommend EGD every six months to screen the emergence of dysplasia.

Future perspectives

Investigation of pathogenesis and search for targeted therapy

Current data on the pathogenesis of LP suggest an (auto)-immunological background with T-cells as key players. As in other diseases triggered by overactive immune system, environmental or lifestyle factors may play an important role, as well as psychological circumstances. Further investigation of mucosal lymphocyte populations in ELP might yield more insights on pathogenesis and establish new options for targeted therapies. Evaluation of environmental factors might lead to identification of triggers (e.g. dental fillings with gold or amalgam).

As no therapeutic option has been universally approved for ELP so far, there is a need for further investigation in larger cohort of patients. Although several studies had demonstrated beneficial effects of topical glucocorticoids, duration and maintenance of treatment still need to be defined. In terms of galenics, an orodispersible preparation of budesonide has recently been licensed for eosinophilic esophagitis [110–112] and should be evaluated in ELP.

New therapeutic approaches may be chosen vis-a-vis contemporary therapy of IBD [113]. A favorable candidate could be ozanimod, an SP-1-modulator recently licensed for therapy of ulcerative colitis [114,115]. Available data suggest a disturbance in the IL12/23 cytokines and/or IL-17 axis in ELP quite similar to psoriasis [34–38], promising possible targeting of these regulatory factors [24]. A candidate influencing the interleukin 12 and 23 pathways would be tyrosine-kinase 2-inhibitor deucravacitinib^[116] which has been already used in other diseases with an autoimmune background (e.g. Crohn's disease, ulcerative colitis) and localized or systemic lupus erythematosus [117–120]. In patients with precancerous lesions, new endoscopic mucosal resection techniques can prevent progression to invasive carcinoma.

CONCLUSION

ELP is an underdiagnosed yet clinically important inflammatory disease of the esophagus which should be considered in patients with unclear dysphagia or esophagitis, especially but not limited to those with history of mucocutaneous lichen planus. Its diagnosis may be based on endoscopic features and typical findings in histopathology and immunofluorescence. Management and treatment of ELP patients is a multidisciplinary challenge. Further understanding of the pathogenesis and new options for targeted therapies need to be established.

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Chemical or physical damages
Reflux esophagitis
Chemical esophagitis (acids, leach)
Radiation induced esophagitis
Drug-induced esophagitis e.g. NSAR, bisphosphonates, tetracyclines, KCl, ferric sulfate, ascorbinic acid
Infectious esophagitis
Candida spp.
Viruses, e.g. Cytomegalovirus, Herpes simplex, HIV
Immune-mediated esophagitis
Eosinophilic esophagitis (EoE)
Crohn's disease
Graft-versus-host disease (GVHD)
Behçet's disease
Systemic sclerosis
Lymphocytic esophagitis
Lichen planus
Mucus membrane pemphigoid
Pemphigus
Congenital skin disease
Esophageal involvement in epidermolysis bullosa
Others
Esophageal intramural pseudodiverticulosis (EIPD)
Sloughing esophagitis

Table 1. Inflammatory diseases of the esophagus

Authors	Study design	Number of ELP cases	Further manifestation sites of LP	Macroscopic findings as described in the manuscript	Histologic findings as described in the manuscript	Signs and symptoms	Therapy
Keate et al. ^[53]	case series	3 (all ♀)	cutaneous oral genital	mucosal sloughing stenosis	band-like infiltrate hyperkeratosis acanthosis	dysphagia	Tacrolimus intralesional Pred. Response 3/3 Etreinate (no effect)
Donnellan et al. ^[121]	case series	5 (all ♀)	oral (all) genital (2) cutaneous (1)	ulcerations strictures	band-like lymphocytic infiltrate Civatte bodies	dysphagia (all)	dilation (4) Fluticasone Response 3/5
Franco et al. ^[70]	case series	6 (♀ 83%)	cutaneous and oral (4)	ulcerations strictures (5)	band-like lymph. infiltrate, Civatte bodies fibrinogen + in DIF	dysphagia (all) food impaction (2)	dilation (3) Flut/Pred/Triam Response 5/5
Dickens et al. ^[76]	19 LP patients	5	cutaneous (19) oral (4)	papular lesions mucosal detachment on biopsy erosions	submucosal lymphocytic infiltrate	dysphagia (1)	
Harewood et al. ^[66]	retrospective search in patient register	6 (♀ 100%)	oral (5) genital (3) cutaneous (2) ELP as initial manifestation (5)	proximal strictures (4)	lymphocytic infiltration (4)	dysphagia (6) odynophagia (2)	dilation of strictures (6) Prednisone (40- 60mg) Response 3/4
Quispel et al. ^[16]	24 LP patients	12	oral and/or cutaneous (all)	whitish papules (10) hyperemic lesions (3) mucosal detachment (2) submucosal plaques (3)	lymphohistiocytic infiltrations para-/hyperkeratosis hyperplasia Civatte bodies glycogen akantosis	dysphagia (4) odynophagia (3) heart burn (3) regurgitation (2)	
Katzka et al. ^[97]	retrospective review (10 years) of data base/ esophageal biopsies from	27 (♀ 92%)	oral (19) genital (13) cutaneous (3) ELP as initial	strictures (18) proximal (11), distal (3), both (4) mucosal detachment (11) erythema, plaques,	lichenoid lymphocytic infiltration damage of epithelial basal layer Civatte bodies	dysphagia (27) odynophagia (2)	dilation of strictures (17) dilation + Fluticasone Response 10/11

	patients with dysphagia		manifestation (13)	whitish mucosa, superficial ulcerations Koeber effect after dilat.	squamous cell carcinoma (1)		no dilation plus intralesional corticosteroids (2) or swallowed Fucicason/ Budesonide (2) <i>Response 6/6</i>
Fox et al. ^[80]	review of published ELP cases until 2009 (including 4 own cases)	72 (♀ 87%)	oral (89%) genital (42%) cutaneous (38%) scalp (7%) nails (3%) eyes (1%) ELP as initial manifestation (14)	pseudomembranes, bleeding, fragility, inflammation - proximal (64%) - distal (11%) - both (26%) stenosis (47%)	Lichenoid lymphocytic infiltrates dysplasia/ squamous cell carcinoma (6%)	dysphagia (81%) odynophagia (24%) weight loss (14%) heart burn (8%) regurgitation (3%) hoarseness (1%) asymptomatic (17%)	
Linton et al. ^[67]	retrospective analysis of esophageal biopsies from 273 patients out of a large cohort	1 typical ELP 6 possible ELP	no data	inflammation (7) stricture (5) trachealization (4) mucosal fragility (1) ulcerations (3) nodules (3)	lymphocytic infiltration (7) Civatte bodies (1) parakeratosis (6) mixed infiltration (6) elongation of lamina propria papillae (7) hyperplasia of basal cells (4) widened intercellular space (3) neutrophilic inflamm. (1)	dysphagia (7) odynophagia (4)	dilation of stenosis (3) topical Fluticasone (2) <i>Response 2/2</i> proton pump inhibitors (7) Sucralfate (2) 5-HT4-RA (1)
Podboy et al. ^[19]	retrospective analysis of a cohort of ELP-patients	40 (♀ 80%)	cutaneous (4) oral (19) genital (15) ELP as only manifestation (13)	strictures (29) ring formation (29) ulcerations (8) mucosal detachment (6) other mucosal lesions (14) squamous cell carcinoma (2)	<i>common findings (>5):</i> esophagitis (20) focal ulcerations (13) mucosal hyperplasia (10) intraepithelial lymphocytic infiltrate (13) eosinophilia <5 (13) dyskeratosis (11) <i>DIF in 20 cases:</i> positive, lichenoid (2) equivocal (5) not evaluable because of mucosal detachment (13)	dysphagia for solid food (32) even for fluids (8) odynophagia (6) reflux (1)	topical corticosteroids - Budesonide in honey 2x3mg (32) Fluticasone spray 880µg 2x/d (8) <i>Response rate:</i> endoscopic (72,5%) clinical (62%)
Ravi et al. ^[106]	retrospective analysis of ELP	132 (♀ 80%)		„Clinical diagnosis“ (77)	„Specific histology“ (55)		<i>Response to topical steroids 84/132</i>

	patients				esophageal carcinoma (8)		63.6% immunosuppressive therapy necessary 38/132 Response: no data
Kern et al. ^[18] Schauer et al. ^[20]	52 patients with proven LP on other site (♀ 75%)	34 - mild (18) - severe (16) <i>Diagnosis according to criteria in Table 3</i>	oral - 78-100% (vs. 78% in non-ELP) genital - 44-61% (vs. 6% non-ELP) cutaneous - 25-44% (vs. 28% non-ELP)	mucosal detachment - iatrogenic (12) - spontaneous (16) hyperkeratosis (7) trachealization (10) stenosis/strictures (7)	epithelial detachment lymphocytic infiltration Civatte bodies dyskeratosis <i>DIF:</i> fibrinogen deposits (17) (85% in severe ELP)	dysphagia - severe ELP: 15 - mild ELP: 8	topical corticosteroids (12) - Budesonide gel 3x0,5mg - Fluticasone <i>Response 11/12</i> <i>stenosis:</i> - topical corticosteroids - dilation

Table 2. Studies on ELP (numbers in braces indicate number/percentage of patients from the cohort to which the criterion applies).
Flut = topical Fluticasone; Bud = topical Budesonide ; Pred = systemic Prednisolone; Triam = intralesional Triamcinolone.
Response rates to respective therapies are italicized.

Macroscopic-endoscopic criteria	
Specific signs	
D	Denudation/sloughing of the mucosa
D1	Iatrogenic denudation (caused by biopsies)
D2	Spontaneous localized denudation < 1 cm ²
D3	Spontaneous spacious denudation > 1 cm ²
Possible signs	
S	Stenosis/stricture
S1	Passable with standard endoscope
S2	Not passable with standard endoscope
H	Hyperkeratosis (whitish, rough mucosa)
T	Trachealization
N	None of the criteria fulfilled
Microscopic criteria- histopathology (HP) and direct immunofluorescence (F)	
HP	Sloughing of the epithelia (subepithelial, intraepithelial) Lymphocytic infiltrate, mainly T-lymphocytes subepithelial, intraepithelial, junctional (region of the basal membrane) Intraepithelial apoptosis of keratinocytes (Civatte bodies) Dyskeratosis
HP0	Negative
HP1	Weakly positive
HP2	Positive
HP3	Strong positive
F	Fibrinogen deposition along the basal membrane
F0	No visible reaction
F1	Weak positive, discrete depositions visible
F2	Marked fibrinogen depositions along the basal membrane
Severity grading	
Severe ELP	≥ D2 and HP ≥1 and/or F ≥1
Mild ELP	D1 and HP ≥1 and/or F ≥1 S, H,T, N and HP ≥1 and F ≥1
No ELP	Criteria not fulfilled in a patient with LP on other localization

Table 3. Diagnostic criteria to establish diagnosis and assess disease severity (modified from Schauer et al.^[20])

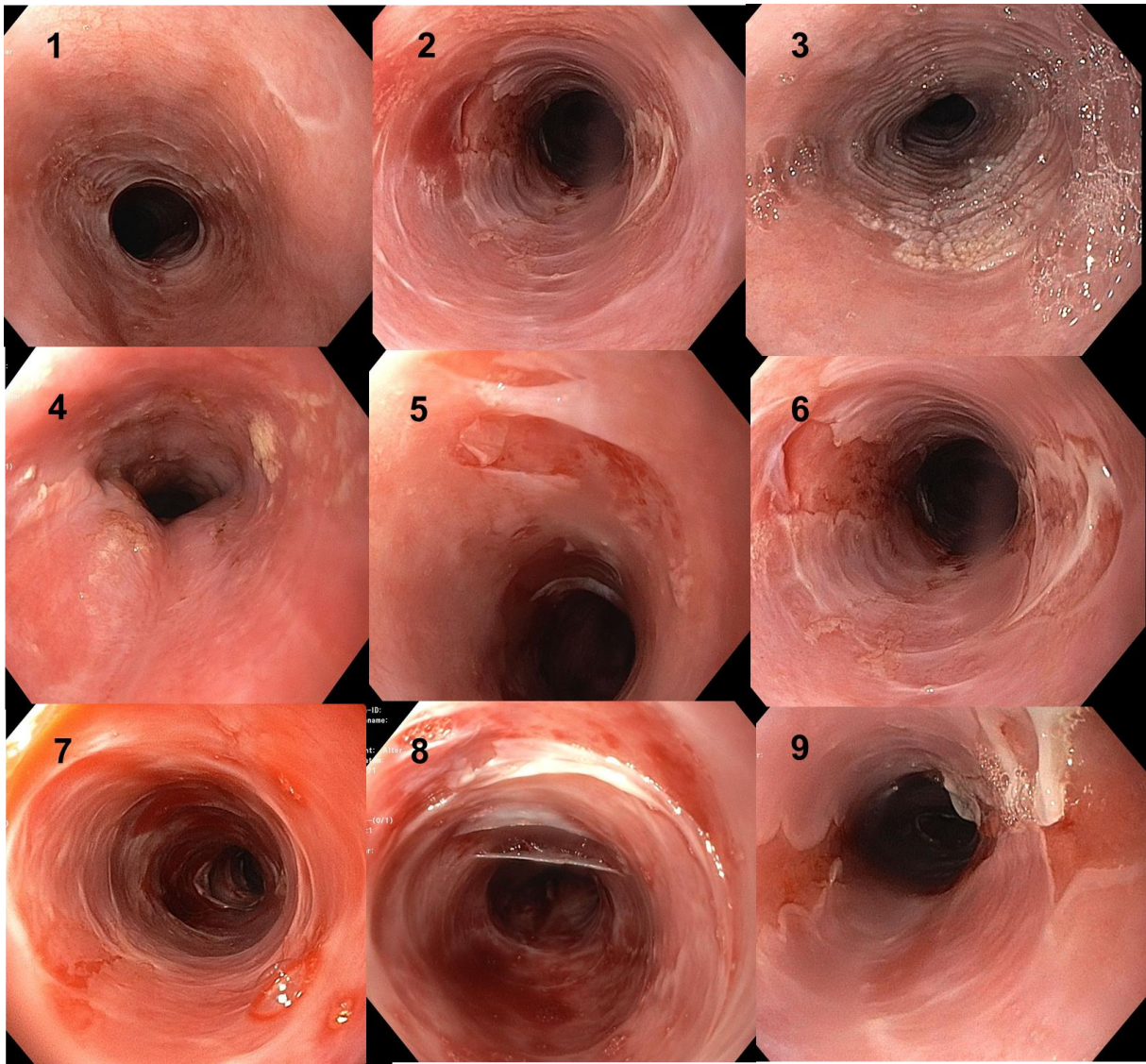


Figure 1. Endoscopic findings in ELP

1. Trachealization. 2. Trachealization and fragile mucosa. 3. Hyperkeratosis. 4. Hyperkeratosis and stenosis. 5 – 6. Tearing and localized denudation of the mucosa. 7 – 9. Tearing and spacious denudation of the mucosa. Endoscopic images were taken from our cohort of patients.

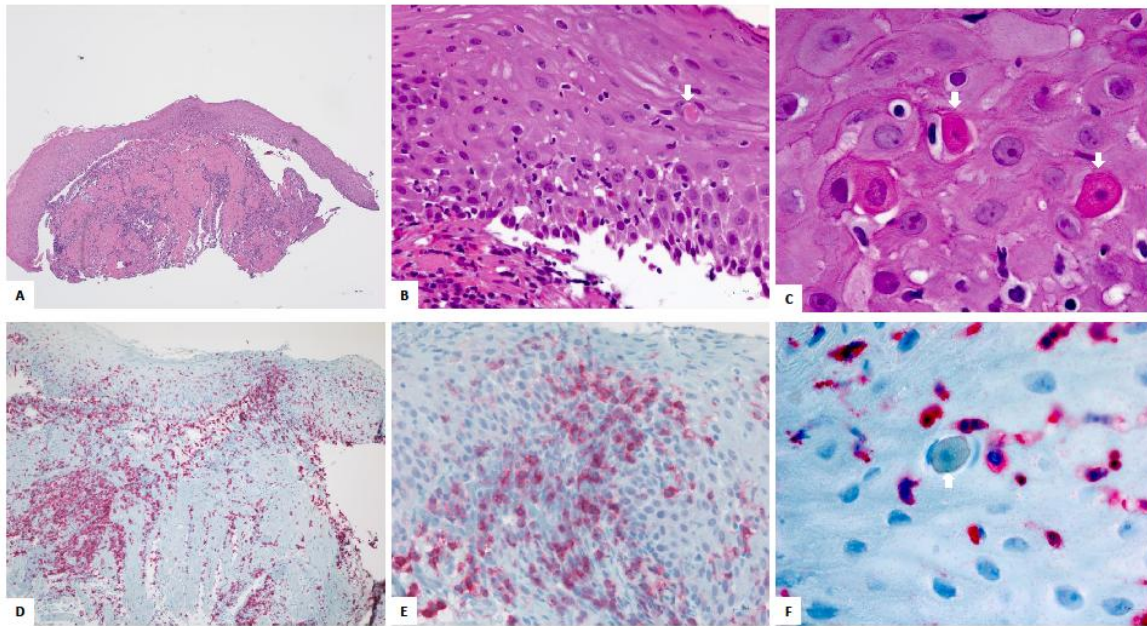


Figure 2. Histologic findings in ELP

A., B. Lichenoid lymphocytic infiltrate of the lamina propria spilling over to the partially detached squamous epithelium. B, C. Intraepithelial lymphocytosis associated with apoptotic squamous cells (Civatte bodies, arrows). D. Dense CD3+ T-cell rich inflammation of the lamina propria involving 2/3 of surface epithelium and muscularis. E. Presence of a CD4+T-cell subset in the infiltrate. F. Civatte body rimmed by CD3+ T-cells. A-C: H&E stain; D-F: Expression of CD3 (D, F) and CD4 (E) visualized by immunohistochemistry. **Histologic images were taken from our cohort of patients.**

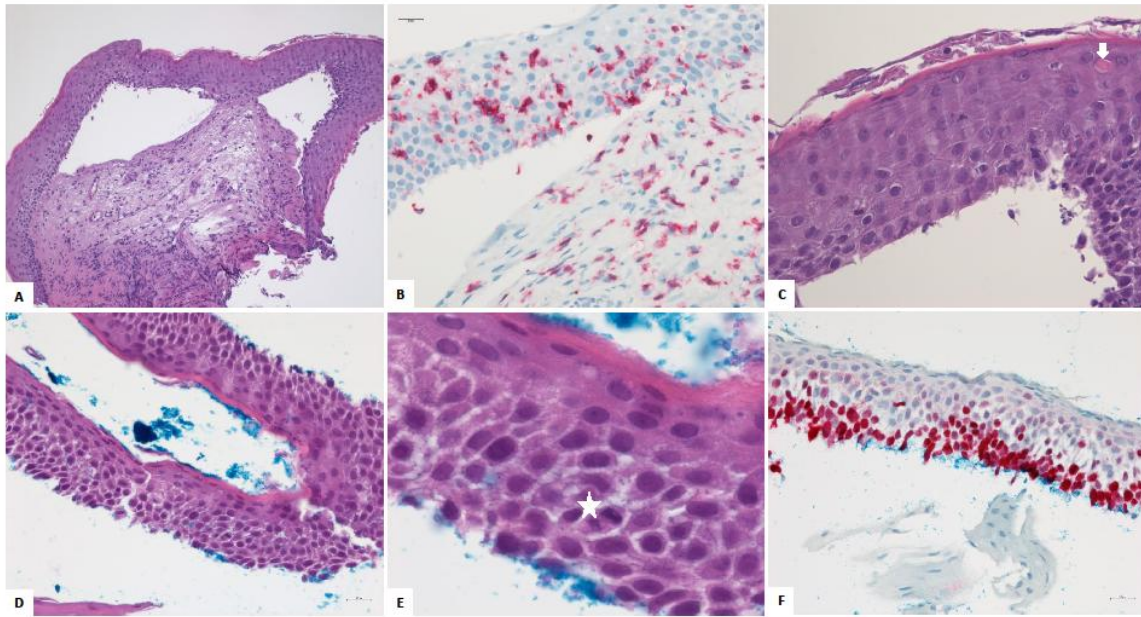


Figure 3. Esophageal epidermoid metaplasia (EEM) in ELP

A-C. Atrophic squamous epithelium showing extensive detachment from the lamina propria, subtle hyperkeratosis (A, C) and mild intraepithelial CD3+ T-lymphocytosis (B) associated with scattered Civatte bodies (C, arrow). D-E. Low-grade squamous orthokeratotic dysplasia in detached epithelium of ELP. Presence of basal-type cells in the lower half of the flat epithelium. Note presence of scattered mitosis (E, star) and an increased Ki67+ proliferation index (F). A, C, D, E: H&E stain; E, F: Immunostains for CD3 (B), and for the Ki 67 antigen (E). **Histologic images were taken from our cohort of patients.**

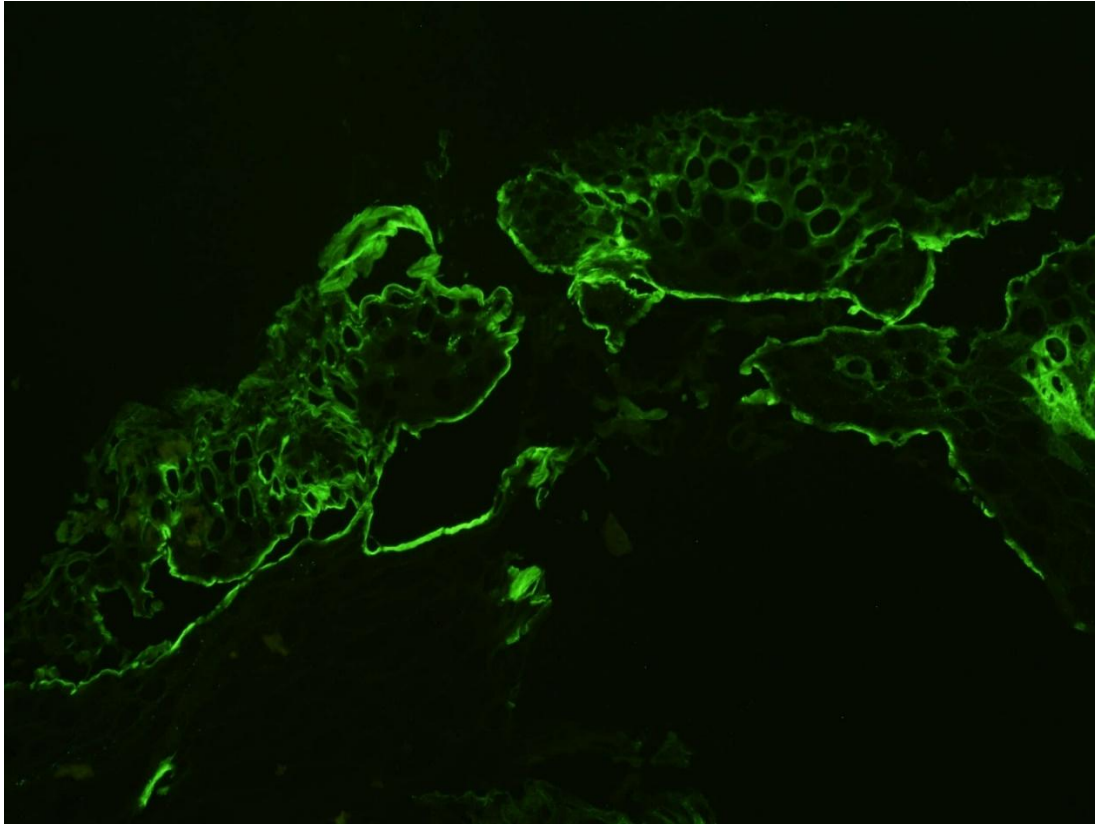


Figure 4. Direct immunofluorescence. Fibrinogen deposits in the basal membrane as a characteristic feature of Lichen planus. **DIF image was taken from one of our patients.**

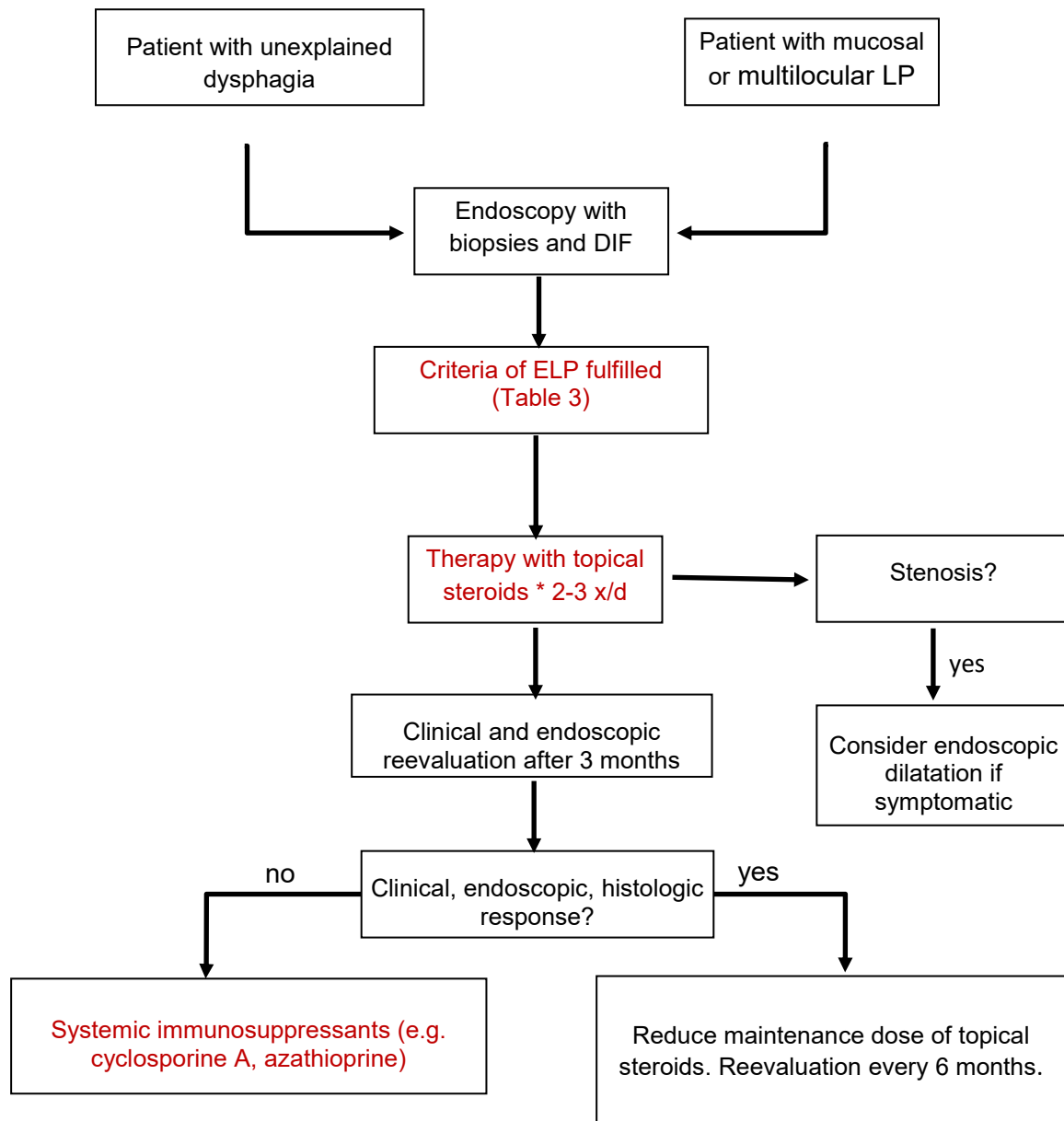


Figure 5. Proposal for management of ELP. * As topical steroids (i.e.budesonide or fluticasone), swallowed spray, viscous solution, or orodispersable tablets might be administered.

End of revised manuscript

Answer to Reviewer 1. Remarks

Review: Esophageal Lichen Planus: Current Knowledge, Challenges and Future Perspectives

Annegrit Decker ¹, Franziska Schauer ², Adhara Lazaro ³, Carmen Monasterio ¹,
Arthur Robert Schmidt ¹, Annette Schmitt-Gräff ⁴, Wolfgang Kreisel ¹

¹ Department of Medicine II, Gastroenterology, Hepatology, Endocrinology and Infectious Diseases, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

² Department of Dermatology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

³ Department of Medicine, Institute of Exercise and Occupational Medicine, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

⁴ Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany and
Institute for Dermatohistology, Pathology, and Molecular Pathology, Dr. Helmut Laaff, Freiburg

Corresponding author:

Prof. Dr. Wolfgang Kreisel

Department of Medicine II, Gastroenterology, Hepatology, Endocrinology and Infectious Diseases, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

+49 761 270 34010

wolfgang.kreisel@uniklinik-freiburg.de

Key words: Lichen planus; Esophagitis; T-Lymphocytes, Budesonide; Dysphagia; Precancerosis

Abstract

Background: Lichen planus (LP) is a frequent, chronic inflammatory disease involving the skin, mucous membranes and / or skin appendages. Esophageal involvement in lichen planus (ELP) is a clinically important although underdiagnosed inflammatory condition.

Aims: This review summarizes the contemporary knowledge on ELP. It describes the pathogenesis of LP, symptoms, and diagnostic criteria of ELP. Therapeutic measures are reviewed and preliminary data about its prevalence are presented.

Methods: Relevant studies on ELP were reviewed. Data from our patient cohort were included, as well as those obtained from literature.

Results: ELP mainly affects middle-aged women. The principal symptom is dysphagia. However, asymptomatic cases despite progressed macroscopic esophageal lesions may occur. The pathogenesis is unknown, however an immune-mediated mechanism is probable. Endoscopically, ELP is characterized by mucosal denudation and tearing, trachealization, and hyperkeratosis. Scarring esophageal stenosis may occur in long-lasting courses. Histologic findings include mucosal detachment, T-lymphocytic infiltrations, epithelial apoptosis (Civatte bodies), dyskeratosis, and hyperkeratosis. Direct immuno-fluorescence shows fibrinogen deposits along the basement membrane zone. To date, there is no established therapy. However, treatment with topical steroids induces symptomatic and histologic improvement in 2/3 of the patients. More severe cases may need immunosuppressive therapy. In symptomatic esophageal stenosis, endoscopic dilation may be necessary. ELP can be regarded as a precancerous condition as transition to squamous cell carcinoma has been observed.

Conclusion: ELP may potentially present as an emergency in clinical settings. This review should arouse alertness for timely diagnosis and provide an impetus for further studies.

Background

Inflammatory esophageal diseases comprise a broad spectrum of differential diagnoses ^[1–3] (**Table 1**) out of which reflux esophagitis is the most frequent condition ^[4]. Infectious etiologies include Candida or viral esophagitis which are mainly linked to compromised immune function ^[5–8]. Esophageal disorders based on immunological background include Crohn's disease ^[9,10], Behçet's disease ^[11,12], graft-versus-host disease after allogeneic stem cell transplantation ^[13], and eosinophilic esophagitis (EoE) ^[14–18]. The spectrum of differential diagnoses ranges to less defined subtypes such as lymphocytic ^[19,20] or sloughing esophagitis ^[21,22]. Other differential diagnosis encompasses additional manifestation of autoimmune bullous diseases such as mucous membrane pemphigoid or pemphigus vulgaris ^[2,3,23]. Esophageal lichen planus (ELP), a mucocutaneous manifestation of lichen planus, should be considered in patients with signs and symptoms corresponding to esophageal inflammation. Since many aspects of this disease are still poorly understood, ELP tends to be underreported and often misdiagnosed. However, in the last decade, gastroenterologists and researchers provided more emphasis to this condition. Likewise, proposals for macroscopic and histopathologic diagnostic criteria were made and data on therapy has been increasingly available ^[24–28]. This review aims to summarize current knowledge on ELP as a clinically important esophageal inflammatory disease and make it more accessible in clinical practice.

Lichen planus

Lichen planus(LP) is a frequent mucocutaneous disease whose pathogenesis is only partly understood ^[29–32]. It affects 0.5%–2% of the general population and has female predominance (65%) ^[29,31,32]. Lesions of skin, oral, and genital mucosa are the most frequent manifestations, however involvement of nails, scalp, genitoanal mucosa, eyes, ears, urinary bladder, or nasal mucosa are also seen. Classic exanthematic, cutaneous LP manifests as flat, reddish, itching papules in the face, arms, wrists, with a tendency to develop postinflammatory hyperpigmentation. In two-thirds of patients, an oral manifestation is observed with reticular, erythematous, and erosive subtypes. They complain of oral discomfort or pain, exhibit characteristic fine white buccal lines (Wickham striae) and often have visible ulcerations on gingiva and

palate, tongue and / or labial mucosa. In men, genital LP causes lesions on glans penis, prepuce or scrotum, in women on vulva or vagina. Itching is the most frequent symptom of genital LP. Involvement of genital mucosa may show all stages of inflammation, starting with erythema, progressing to erosions, plaque formation, and scarring. Lichen planus pemphigoides (LPP) is a rare, mostly IgG-mediated autoimmune variant of LP, exhibiting characteristics of bullous pemphigoid (reactivity against collagen XVII) [33]. As LP may involve multiple organ systems, this disease requires multidisciplinary approach involving dermatologists, dentists, gynaecologists and gastroenterologists [34–37]. The European guidelines for therapy of LP have recently been published [38,39].

Pathogenesis

A T-cell mediated inflammatory reaction involving antigen-specific and antigen-unspecific mechanisms is regarded as the basic mechanism of pathogenesis [29,36,40]. A recent review about the immunogenetics of lichen planus [41] reported that multiple imbalances of cytokines or interleukins are involved. In addition, genetic influences and MHC associations were found. Micro-RNAs (mi-RNAs) might also be implicated in LP. Antigen-specific mechanisms include antigen presentation of an unknown trigger by basal keratinocytes, activation of CD4+ Th1-helper cells, cytokine production, and CD8-positive cytotoxic reaction against basal epidermal cells. On the other hand, antigen-unspecific mechanisms could involve upregulation of proinflammatory mediators such as interferon- γ , tumour necrosis factor- α , interleukins, and matrix metalloproteases, leading to T-cell infiltration in the epidermal cell layer.

The cytokine profile suggests a Th1-reaction, whereas B-cells, plasma cells, or antibodies may play a minor role. Similar to psoriasis or pemphigus [42–44], a disturbance in the IL17 / IL23 axis was observed. Metal ions, drugs, bacterial, or viral antigens may trigger LP. An association with chronic hepatitis C was described, however data remains controversial [45,46]. An association with IgG4-related disease is possible [47]. LP may be triggered by several drugs, e.g. NSAIDs, beta-blockers, ACE-inhibitors, and check-point inhibitors [48]. Amalgam or mercury are regarded as trigger for oral LP [49], while concomitant diabetes or smoking influence the clinical

severity [50]. There are associations with systemic diseases [51,52] and/or autoimmune disorders such as primary biliary cholangitis, autoimmune thyroiditis, myasthenia, alopecia areata, vitiligo, thymoma, and autoimmune polyendocrinopathy [36]. As in other immune-mediated diseases, psychological component may influence the disease progression [53–55].

Studies on Esophageal Lichen Planus (ELP)

Involvement of the esophagus in LP as another possible site of mucosal involvement was first described in 1982, [56,57] after which case reports and small case series were described presenting this new type of esophageal inflammatory disease with lichenoid features [58–69]. ELP was regarded then as a rarity, likely because its clinical, endoscopic, and histologic features were not yet clearly understood. In recent years, interest about this “new” disease was growing and consequently, larger case series and studies, [24–28,63,65,70–74] as well as two comprehensive reviews were published [75,76]. **Table 2** presents an overview of these studies (excluding single case reports) and their key findings.

Epidemiology

The population-based prevalence of LP was estimated to reach an average of 1.3% [29,77]. Oral LP is considered the most predominant mucosal manifestation affecting two-thirds of patients with cutaneous LP [34–36]. A recent metaanalysis showed a varying global prevalence of oral LP (0.57% in Asia, 1.68% in Europe, and 1.39% in South America) [78,79]. Esophageal involvement was initially regarded as a rarity, however further studies showed an esophageal manifestation in up to 50% of patients presenting with cutaneous or oral LP [24,80]. Since the number of cases in these studies were limited and the patient groups non-randomized, the true prevalence of ELP might be overestimated. Surprisingly, ELP does not necessarily correlate with oral disease [28,75]. However, oral LP is found in most of the cases of severe ELP. Esophageal manifestation also correlates with the occurrence of other mucosal involvement such as genital LP. The median age at presentation is 60 years and 80% of patients are female [76,81]. Determining the true prevalence of ELP

remains a challenge as it would require endoscopic screening in a large group of patients with LP regardless of localization and symptoms. Focusing on patients with esophageal symptoms only, e.g. dysphagia, would underestimate the true prevalence of ELP. A previous study showed that more than 50% of patients with mild ELP did not report dysphagia [28]. Moreover, cases where the esophagus is the only affected site of LP could still be missed. Hence, the prevalence of ELP on a population-based level can only be roughly estimated thus far. Furthermore, assuming that about 10% of all LP patients would have an esophageal involvement, the prevalence could be as high as 0,1% in the general population, thus outnumbering the prevalence of eosinophilic esophagitis which has been reported to reach 0.04 – 0.05% in Western countries [82].

Diagnostic features of ELP

Clinical symptoms

Dysphagia is the leading symptom found in 80 – 100% of patients with ELP. Other symptoms include odynophagia, heart burn, regurgitation, weight loss, hoarseness, and chronic unproductive cough. In some studies, approximately 20% of patients with ELP did not manifest any esophageal symptoms [83]. Development of esophageal symptoms might be influenced by severity of disease. In a previously published study by Schauer et al. [28], 94% of patients with endoscopically severe ELP but only 44,4% of patients with mild ELP presented with dysphagia. On the other hand, up to 6% of LP patients had symptoms of dysphagia, although the esophagus was not involved. In clinical practice, ELP should be evaluated in patients presenting with the mentioned symptoms, especially in patients with known LP. Moreover, it should be considered in all patients where other common causes of esophageal symptoms (see Table 1) have been ruled out.

Diagnosis

The criteria for diagnosis of ELP were more or less comparable in recent studies using macroscopic and histopathologic parameters. Alongside some findings which can be considered typical of ELP, some similarities with other esophageal disorders such as eosinophilic esophagitis, lymphocytic esophagitis, sloughing esophagitis can be found, [3,14–16,20,22,84–88] hence making the diagnosis challenging. A diagnostic score

combining endoscopic and histopathologic findings, as well as direct immunofluorescence (DIF) and a severity grading (no ELP, mild ELP, and severe ELP) had been previously proposed by our group ^[28] based on data from current literature and our patient cohort (**Table 3**). Examples for endoscopic, histopathologic, and DIF findings are shown in **Figures 1 - 4**.

Macroscopy

The endoscopic hallmark is denudation or sloughing of the esophageal mucosa. It may occur spontaneously or during the endoscopic procedure due to contact with the endoscope. Less specific indicators of ELP are “trachealization” (an endoscopic sign well known from EoE) and presence of a rough and whitish surface of the mucosa which is the macroscopic correlate of hyperkeratosis as seen in histology. Stenoses or strictures may occur as sequelae of chronic inflammation in ELP as in any other chronic inflammatory esophageal disorder. Endoscopic images of mucosal alterations are shown in **Figure 1**. Endoscopic changes may be observed in all parts of the esophagus, but mainly in the middle third. As reflux esophagitis often occurs simultaneously, macroscopic and histologic alterations directly above the gastroesophageal junction may be ambiguous. Thus, biopsies should be taken at least 5 cm above the gastroesophageal junction. To evaluate microscopic changes in patients with known LP, we recommend to take at least two biopsies (in the lower and upper third of the esophagus) regardless if the above-mentioned endoscopic signs are not present.

Histopathologic Features

Esophageal biopsies provide a reliable assessment of mucosal lesions characteristic of ELP (**Figure 2**). Band-like inflammatory infiltrates are observed at the interface between the squamous epithelium and the lamina propria corresponding to a lichenoid esophagitis pattern. The predominant cell type in the inflammatory infiltrate of ELP are CD3+ T cells which spill over into the adjacent epithelium involving the lower third or lower half of the epithelial thickness. CD4+ cells are the main T-cell subset reported in cutaneous LP while ELP also frequently harbors abundant intraepithelial CD8+ lymphocytes. Intraepithelial lymphocytosis is associated with scattered squamous cell apoptosis designated as Civatte bodies. The epithelium may become partially or completely detached from the tunica propria or show

intraepithelial splitting reminiscent of sloughing esophagitis. However, superficial necrosis and neutrophilic aggregates seen in sloughing esophagitis are not a feature of ELP. The squamous epithelium may be hyperplastic and exhibit acanthosis similar to the saw-toothed rete ridges of cutaneous LP or atrophic especially in long-standing esophageal involvement. In contrast to the normal esophageal epithelium, hypergranulosis is frequently observed in the superficial epithelium of ELP. Surface orthokeratosis, also termed esophageal epidermoid metaplasia (EEM), is the histologic correlate of the rough and whitish mucosal surface with leukoplakia. **(Figure 3)**. This lesion is referred to as uncomplicated EEM as long as epithelial maturation is preserved and dysplasia/intraepithelial neoplasia (IEN) is absent. Chronic inflammation may lead to fibrosis and scarring of the tunica propria resulting in strictures and dysphagia.

Direct immunofluorescence (DIF)

In ELP, direct immunofluorescence often highlights fibrinogen deposits along the basal membrane as another important criterion **(Figure 4)**. This is based on the data on oral LP, where linear fibrinogen deposition in DIF could discriminate the diagnosis from other lichenoid lesions^[89] and mucus membrane pemphigoid ^[23,35]. Granular IgG and IgM deposition can be possible. Therefore, positive results in DIF augment the diagnosis of ELP yielded by conventional histopathology and, in turn, differentiate the findings from diseases like mucous membrane pemphigoid or pemphigus vulgaris in erosive stages.

Therapy

In contrast to cutaneous and oral LP^[38,39], there are no generally accepted guidelines for therapy of ELP. Conventional management of cutaneous LP with retinoids does not seem to prevent the emergence of ELP, nor is it suitable for therapy of ELP ^[58,90–92]. However, a few case reports described successful therapy using alitretinoin^[67]. Good therapeutic response was reported with topical corticosteroids such as fluticasone or budesonide leading to clinical and/or endoscopic response rate of 62% up to 74% in ELP ^[24–28]. The type of budesonide preparation might play an important role for its efficacy: Viscous syrups or gels offer better adherence to the esophageal mucosa than swallowed sprays and thus led to good response rates in our hands ^[28].

Orodispersible tablets designed for other esophageal inflammatory disorders might play an interesting role in the future. Intralesional injection of triamcinolone has also been described in literature [58,74,93]. Systemic corticosteroids have been proposed to induce rapid response in severe cases. However, they are not suitable for maintenance therapy and tapering may lead to reoccurrence of symptoms. Therefore, more severe cases not responding to topical corticosteroids require therapy with immunosuppressants: Multiple different types such as adalimumab, hydroxychloroquine, mycophenolate, azathioprin, cyclosporine, tacrolimus or rituximab have been used [28,32,58,59,68,72,73,94,95]. In an own patient, cyclophosphamide was the only drug to induce an at least partial remission (unpublished). However, refractory cases may exist [69].

As ELP mainly occurs as part of a systemic or multilocular LP, treatment should always be managed in a multidisciplinary approach involving at least gastroenterologists and dermatologists especially when topic therapy is not efficient and systemic immunosuppressive therapy is needed.

Complications

Esophageal stenosis/Food impaction

Like other inflammatory esophageal diseases, inflammatory or scarring stenosis can be a sequela of chronic untreated or refractory course leading to typical complications such as dysphagia, odynophagia, food impaction, and weight loss [25]. Therefore, ELP should be considered among the potential causes of food impaction [96], like achalasia or eosinophilic esophagitis, or of unexplained esophageal stenosis [97–99]. This applies not only, but especially to patients with known LP on other site or to patients presenting with signs of a (not yet diagnosed) mucocutaneous disease.

Treatment of esophageal stenosis

In symptomatic esophageal stenosis, endoscopic dilation may be necessary and has been successfully performed in multiple cases [100,101]. The fear of strong mucosal denudation, the main feature of florid ELP, lead to advise some authors against dilation in the past. However, this can be overcome when causal treatment of the underlying inflammation is performed simultaneously as it is also advised in any other esophageal inflammatory condition. Anti-inflammatory treatment can reduce mucosal fragility, making it more resistant to physical stress, prevent reoccurrence of stenosis

and induce remission: Need of dilations has been reported to decrease under anti-inflammatory therapy ^[76] and in a few cases, budesonide alone led to relief of symptomatic stenosis ^[28]. However, in analogy to therapy of stenosis in Crohn's disease, this may only apply for inflammatory and not for scarring stenosis.

Precancerous squamous lesions and esophageal squamous cell carcinoma

Several factors may limit the life expectancy of patients with LP ^[102,103]. Oral squamous cell carcinoma is one amongst them, as oral lichen planus is widely regarded as a precancerous condition, even if the exact rate of malignant transformation is a matter of debate ^[60,104–107].

Accordingly, correlation between ELP and development of esophageal squamous cell carcinoma (ESCC) has been discussed. Data of case reports are increasing where esophageal inflammatory and hyperkeratotic lesions have progressed to squamous dysplasia/ intraepithelial neoplasia and even to invasive ESCC: In some studies, development of ESCC has even been reported in up to 4.5% of ELP patients ^[108,109].

ELP-associated esophageal precancerous squamous lesions are generally detected in areas of esophageal epidermoid metaplasia (EEM) ^[110–112]. In low-grade dysplasia, cytologic and structural epithelial abnormalities are confined to the lower half of the esophageal epithelium, while high-grade dysplasia involves more than half of the epithelial cell layers with lack of surface maturation. Therefore, endoscopically detected areas of EEM/leukoplakia should be systematically sampled for histologic evaluation since these constitute a hallmark of orthokeratotic dysplasia (**Figure 3**). It should be noted that invasive ESCC may be detected underneath or adjacent to EEM. Our experience showed uncomplicated hyperkeratosis/EEM in a considerable part of patients with severe ELP (37.5 %), while predominantly low-grade orthokeratotic dysplasia was rare (6 %) and the transition to an early invasive ESCC was diagnosed in only one patient ^[28]. Anti-inflammatory therapy did not lead to regression of hyperkeratotic areas in this cohort. New therapeutic strategies should aim to either slow down or arrest the development of EEM.

According to Singhi et al. ^[111], mutation in TP53 correlates with occurrence of or progression to ECC in ELP. p53 overexpression in immunohistochemistry has been frequently observed in our cohort. Additional molecular analyses have yet to be

performed to gain more knowledge on risk stratification. Future advances in identifying the molecular landscape which drives the development of precancerous lesions and overt invasive carcinoma may help to establish prognostic biomarkers contributing to early detection of ELP cases at high risk for progression to overt ESCC.

Translating this knowledge to clinical practice, we recommend regular endoscopic surveillance of ELP patients for development of dysplasia. Detection of suspicious areas may be assisted by chromoendoscopy. Patients with known hyperkeratotic regions or florid inflammation should be controlled more often. In case of low grade dysplasia, we would recommend further endoscopic controls every six month; in case of transition to high grade dysplasia, endoscopic ablation should be performed similar to patients developing dysplasia in Barrett's esophagus. Furthermore, other known risk factors for development of ESCC such as nicotine or alcohol intake should be discouraged.

Future advances in identifying the molecular landscape which drives the development of precancerous lesions and overt invasive carcinoma may help to establish prognostic biomarkers contributing to early detection of ELP cases at high risk for progression to overt ESCC.

Proposal for management of ELP

Figure 5 sums up our proposal for management of ELP in clinical practice. EGD should be performed in every patient with known LP (skin or mucosal manifestation) with any of esophageal symptoms as described above as probability of esophageal involvement is high. Diagnosis can be established using the proposed criteria (Table 3). We would recommend to treat every newly diagnosed ELP with topical steroids at first and reevaluate therapeutic response after a certain time interval, e.g. three months. Further therapy would depend on whether or not a clinical and/or histological remission has been achieved; immunosuppressive therapy may be necessary as described above. Every patient diagnosed with ELP without known LP on other site should be assessed and screened by a dermatologist.

To date, there is still no consensus on how to identify and treat asymptomatic ELP patients, specifically patients with asymptomatic hyperkeratosis, the potential

precursor of esophageal squamous cell carcinoma. A wait and see strategy seems to be warranted ^[28,75]. However, in patients with EEM, we recommend EGD every six months to screen the emergence of dysplasia.

Future perspectives

Investigation of pathogenesis and search for a targeted therapy

Current data on the pathogenesis of LP suggest an (auto)-immunological background with T-cells as key actors. As in other diseases triggered by an overactive immune system, environmental or lifestyle factors may play an important role, as well as psychological circumstances. Further clinical studies may elucidate associations with nutritional influences or dental fillings such as gold or amalgam.

Further investigation of mucosal lymphocyte populations in ELP might yield more insights regarding pathogenesis and establish new options for potential targeted therapies.

As no therapeutic option has been universally approved for ELP so far, there is need of further investigation. Even if several studies demonstrated beneficial effects for topical glucocorticoids, length and maintenance of treatment still need to be defined. In terms of galenics, an orodispersible preparation of budesonide has recently been licensed for eosinophilic esophagitis ^[113–115] and should be evaluated for its use in ELP.

Further therapeutic approaches may be chosen vis-a-vis modern therapy of IBD ^[116].

A favorable candidate could be ozanimod, a SP-1-modulator recently licensed for therapy of ulcerative colitis ^[117,118]. Available data suggest a disturbance in the IL12/23 cytokines and/or the IL-17 axis in ELP quite similar to psoriasis, promising possible successful targeting of these regulatory factors^[32]. A possible candidate affecting the interleukin 12 and 23 pathway would be tyrosine-kinase 2-inhibitor deucravacitinib^[119] which has been already used in other diseases with an autoimmune background such as Crohn's disease, ulcerative colitis, and localized or systemic lupus erythematosus ^[120–123].

