Esophageal Lichen Planus: Current Knowledge, Challenges and Future Perspectives

Esophageal Involvement in Lichen Planus


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 therapeutic 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.

**Key Words:** Lichen planus; Esophagitis; T-Lymphocytes; Budesonide; Dysphagia; Precancerosis


**Core Tip:** *Lichen planus is a frequent, chronic inflammatory disease involving the skin, mucous membranes and/or skin appendages. Esophageal involvement in lichen planus (ELP) is an underdiagnosed inflammatory condition. ELP mainly affects middle-aged women. The principal symptom is dysphagia. Asymptomatic cases may occur. An immune-mediated pathogenesis is probable. Endoscopy shows mucosal denudation and tearing, trachealization, and hyperkeratosis. Scarring esophageal stenosis occurs. Histology includes mucosal detachment, T-lymphocytic infiltrations, epithelial apoptosis, dyskeratosis, and hyperkeratosis. Direct immuno-fluorescence shows fibrinogen deposits along the basement membrane zone. Treatment with topical*
steroids or immunosuppression may induce symptomatic and histologic improvement. ELP can be regarded as a precancerous condition.

**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 [21,28,22]. 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 [20–28]. 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 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 [20,53,86,89]. 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. Intrallesional 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, azathioprin, cyclosporine, tacrolimus or rituximab have been used [24, 33, 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 [23] 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 immunosuppressants. 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 \cite{110-112} and should be evaluated in ELP.

New therapeutic approaches may be chosen vis-a-vis contemporary therapy of IBD \cite{113}. A favorable candidate could be ozanimod, an SP-1-modulator recently licensed for therapy of ulcerative colitis \cite{114,115}. Available data suggest a disturbance in the IL12/23 cytokines and/or IL-17 axis in ELP quite similar to psoriasis \cite{34-38}, promising possible targeting of these regulatory factors \cite{24}. A candidate influencing the interleukin 12 and 23 pathways would be tyrosine-kinase 2-inhibitor deucravacitinib\cite{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 \cite{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.