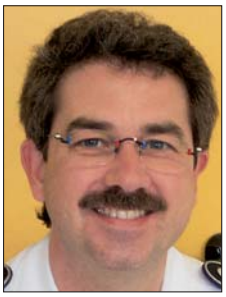
Thomas Eger

Mucocutaneous disorders from the dentist's point of view*



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According to current knowledge, some oral autoimmune diseases, such as oral lichen planus, should be assessed as precancerous conditions with a minor tendency for malignancy. Restitutio ad integrum from these diseases is not possible. Prognosis for degeneration is unpredictable, given the initial clinical and histological symptoms. It is important but difficult to motivate the patients to come in for follow-up exams at least once a year and to commit to more efficient oral hygiene.

■ Introduction

Mucocutaneous disorders may appear in the form of white and red lesions. Whereas, for the most part, patients rarely notice the white lesions, which are generally painless, this is not the case for red lesions as these often significantly restrict ingestion and oral hygiene.

Desquamative and blistering red lesions of the gingiva are often clinically termed as desquamative gingivitis. This is a common oral lesion, which is clinically characterised by diffuse erythematous desquamation, ulceration, erosion and possible blistering on the free and attached gingiva. The majority of these immune-mediated diseases, which are not caused by bacteria, occur in patients between 50 and 70 years of age. They are not always linked to skin diseases. Women are more frequently affected and hormonal factors are considered to be cofactors. Some of these mucocutaneous disorders are classified as precancerous (Table 1).

■ Occurrence of mucocutaneous disorders

In a number of epidemiological studies, white mucocutaneous disorders have been determined in up to 24.8% of the population[2]. The most frequent clinical and histological diagnoses were preleukoplakias (6.4%), smokers' leukoplakias (2.9%), idiopathic leukoplakias (0.7%) and oral lichen planus (OLP) (1.9 %). Of these diagnoses, 77% were reticular and 92% were on the cheek. In an ongoing clinical study

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Table 1 Group classification of mucocutaneous disorders (modified according to Reichart and Philipsen[1]).

Benign tumours and tumour-like hyperplasias	Fibroma, lipoma, fibrolipoma, haemangioma, osteoma, papilloma, adenoma, leiomyoma, neuroma, incisional neuroma, benign tumours of the salivary glands, fibro-hyperplasia, pyogenic granuloma, peripheral giant cell granuloma, gingiva hyperplasia
Malignant tumours and precancerous lesions	Cancers of the oral cavity mucosa and the salivary glands, oral lichen planus, oral leukoplakias
White and grey mucocutaneous disorders	Leukokeratosis nicotina palati and additional benign mucocutaneous disorders associated with tobacco, oral candidiasis, lichenoid lesion, verucca vulgaris
Brown/blue pigmented lesions	Nevus, amalgam tattoo
Bullous and erosive alterations of the mucous membrane (Autoimmune mucodermatoses)	Bullous pemphigoid, benign mucous membrane pemphigoid, linear IgA dermatosis, pemphigus vulgaris, bullö ser/erosive oral lichen planus
Cysts in the soft tissue	Salivary retention cysts, extravasation cysts, nasopalatine cysts
Mechanically irritative lesions	Chronic traumatic ulcerations, cicatrice, foreign body granuloma, hyperkeratosis

Table 2 Differential diagnosis of mucocutaneous disorders.

White mucocutaneous disorders	Red mucocutaneous disorders
• Oral lichen planus reticularis	• Reactions to drugs
• Premalignant dysplastic keratosis	• Lichenoid dysplasia
• Benign keratosis (trauma-related cheek biting)	• OLP atrophic/erosive
• Fordyce spots	• Lichen-type graft versus host disease
• White sponge nevus	• Erythema multiforme
• Lupus erythematosus syndrome	• Lupus erythematosus
• Candidiasis	• Benign scarring mucous membrane pemphigoid
	• Pemphigus vulgaris
	• Dermatitis herpetiformis
	• Adult linear immunoglobulin A disease
	• Reactions to pharmaceuticals
• Carcinoma in situ	• Carcinoma in situ
• Leukoplakia	• Erythroplakia

conducted by a university hospital in Switzerland, 2.6% of the mucocutaneous disorders have been classified as malignant tumours by clinical and histopathological study, and 15.9% as precancerous lesions (OLP and leukoplakias)[3]. The referral diagnosis matches the end diagnosis in 36.6% of patients and the working diagnosis matches the end diagnosis in 70% of patients.

In the periodontal consultation, white and red mucocutaneous disorders are distinguished from inflamed, plaque-related chronic and acute periodontal diseases as well as fungal and viral infections of the oral mucosa by means of differential diagnosis (Table 2).

■ Medical history and clinical diagnostics, documentation and severity codes

For all patients with mucocutaneous disorders, particular value is placed on taking a medical history which specifically relates to the mucocutaneous disorder, taking into account exacerbations and prior treatment as well as the medication-based medical history (psychotropics, soporifics) and primary diseases, i.e. skin diseases, chronic hepatic diseases or Hepatitis C. Stress factors[4,5] are likewise of importance aetiologically.

According to Roed-Petersen and Renstrup[6],it is advisable to produce detailed documentation about

the findings of a mucositis inspection (keratotic striae, plaque, erythemas, ulcerations) in line with the graphical documentation schematic recommended by the WHO (World Health Organization).

For progressive documentation in clinics and practices, this, combined with photographic documentation, is a valuable criterion when it comes to making subsequent decisions regarding treatment. The severity coding and improved progressive documentation of these disorders, which are mainly chronic with many periods of remission and exacerbation, are specified in the following oral mucositis index for 'red' mucocutaneous disorders in Ronbeck et al[7]:

0 = normal gingiva,
1 = slight erythema of the gingiva propria,
2 = clear erythema of the gingiva propria/alveolaris,
3 = blisters,
4 = desquamations.

For everyday mucocutaneous disorders which appear harmless, such as pre- and early stages of oral cavity cancer (so-called broken-down cancer), so-called brush biopsies can be recommended for exploratory histological investigation without local anaesthetic.

In general, an inspection should always be carried out by a dermatologist and if necessary gynaecologist and an internist before surgical sampling is conducted at the precise location. Disposable punches with a diameter of 5 to 8 mm can be used for executing biopsies. Biopsies should cover the border area of the mucocutaneous disorder (Fig 1) in order to assess the histological difference between the healthy and the mutated sections of tissue. Surgical wound closure using absorbable stitching material is recommended in order to prevent further irritation. If a large punch is used, the biopsates may be divided and part may be used for differential diagnosis of immune mediated diseases by means of immunofluorescence microscopic analysis.

■ Therapy concepts with regard to white mucocutaneous disorders

After diagnosis, the most important step is to provide the patient with detailed information with regard to the changeable nature of the clinical lesions and the risk of deterioration associated with them. The removal of sharp edges, the replacement of the amalgam filling material that is in direct contact with the mucocutaneous disorders, and medicinal candidiasis treatment may be necessary. White striae usually persist and do not require treatment. Oral mucosa inspections are recommended at least annually.

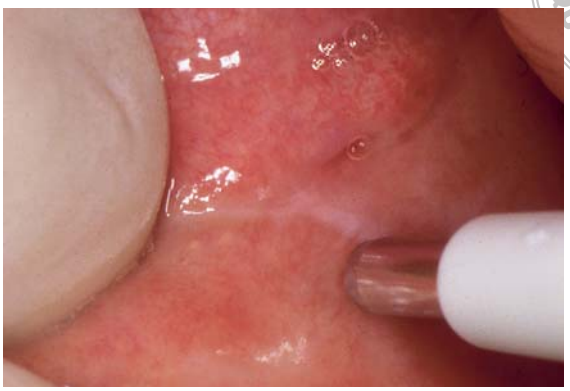


Fig 1 Sampling using a mucosal punch.

■ Oral fungal infections

Oral fungal infections mainly present as a white wipeable covering or diffuse erythematous area. They can be distinguished from leukoplakia (not wipeable) and erosive autoimmune mucocutaneous disorders during differential diagnosis. These are suitable for direct swabbing on Nickerson's medium (analysis after 24 hours and 48 hours at room temperature). Evidence of mycelia and if necessary of hyphae is provided by cytology and, in chronic candidiasis, by biopsy and serology.

Candida species (*Candida albicans*) are the most frequent cause of oropharyngeal fungal infections (Fig 2). Predisposing factors include long-term use of antibiotics, immuno-suppressive medication, endocrine dysfunction, malignant disorders, radiotherapy, inadequate nutrition, insufficient prostheses, xerostomia and old age.

Aspergillus species are the second most frequent cause of fungal infections. Patients with blood disorders are predisposed to such infections. They evolve very quickly. The lesions are similar to noma (Fig 3).

Cryptococcal infections, histoplasmosis and blastomycosis rarely present in immunocompetent patients. Additional oral fungi, such as *Rhodotorula*

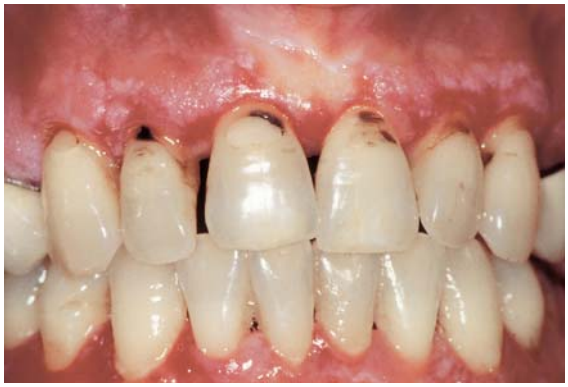


Fig 2 *Candida albicans*: superinfection with erosive oral lichen planus.

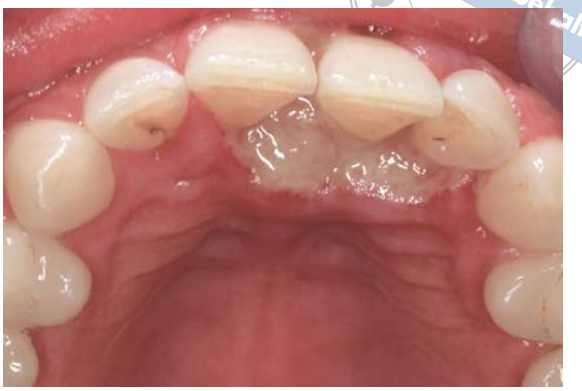


Fig 3 *Aspergillus* infection with lymphoma.

glutinis and *Saccharomyces cerevisiae* are found in the oral cavity. However, these are not linked with an infectious disease.

Oral fungal infections are initially treated by informing the patient and improving oral and prosthesis hygiene through the use of chlorhexidine preparations. Local antimycotic treatment is carried out using amphotericin B, nystatin or miconazole, which is applied for at least two weeks in the form of lozenges, mouthwash, chewing gum, gel, ointment or denture lacquer. If patients do not respond to local anti-fungal treatment within two weeks, their immunocompetence should be tested.

In immunosuppressed patients, an antimycotic prophylaxis with chlorhexidine or systemic polyenes can likewise be used for a period of at least two weeks. Note that systemic treatment of an infection of the intestinal tract using amphotericin B may also be necessary.

■ Oral herpes virus infections

Concentration-related, undesirable side effects of local and systemic antibiotic treatment include the overgrowth of the oral mucous membranes by non-sensitive bacteria, resistances and fungal infections as well as viral infections (Fig 4).

Gingivostomatitis herpetica constitutes primary infection with the *herpes simplex virus* (HSV-1). This is also referred to as 'aphthous oral infection' and presents in 2–4-year-old children. There are at least eight different strains of the herpes virus.

With viral infections, necrotising ulcerative gingivitis and erythema exsudativum multiforme are eliminated during differential diagnosis. Herpes viruses can remain latent in the nerve tissue and may cause recurring infections when they are reactivated.

Treatment of oral viral infections is primarily palliative with the aim of providing local pain relief by means of anaesthetising gels and mouthwashes. Antiviral topical treatment is conducted using aciclovir. Aciclovir is used in the effective treatment of HSV-1, HSV-2, the *Varicella zoster* virus, the Epstein-Barr virus and the *Cytomegalovirus*. The active ingredient penciclovir is used as an ointment in the treatment of recurrent herpes labialis.

Systemic use of aciclovir (200 to 400 mg/day) is recommended for the treatment of severe herpetic gingivostomatitis when combined with general symptoms and with recurrent herpes labialis. When the *Varicella zoster* viral infection is detected during swabbing, alternative treatment with aciclovir (800 mg five times a day) or valaciclovir (1000 mg three times a day for seven days) may be prescribed after consultation with the treating internist or paediatrician.

The following treatment patterns are common to viral mucocutaneous disorders:

- Prevention of a superinfection with pathogenic bacteria by means of SRP
- Use of chlorhexidine preparations and anaesthetising gels or mouthwashes
- Possible prescription of a local virustatic agent (aciclovir)
- If necessary, referral to/consultation with internist/paediatrician

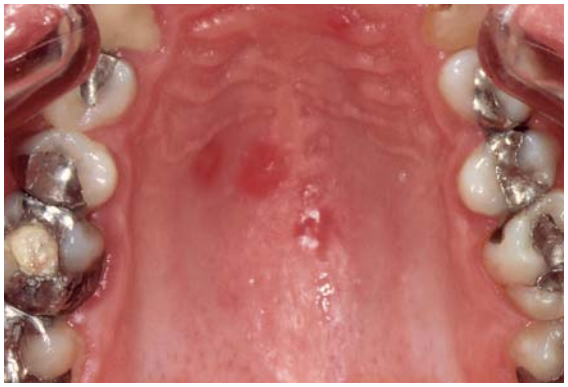


Fig 4 Herpes virus infection of the palatal mucous membrane.

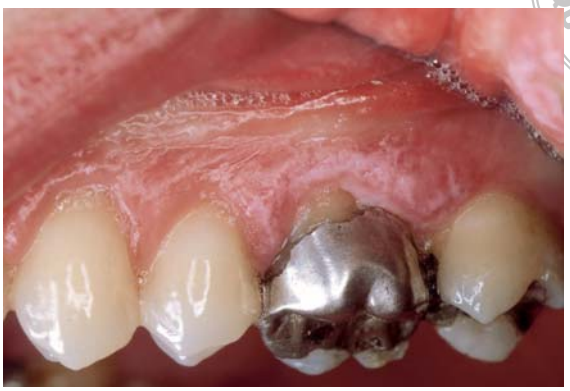


Fig 5 Reticular oral lichen planus.

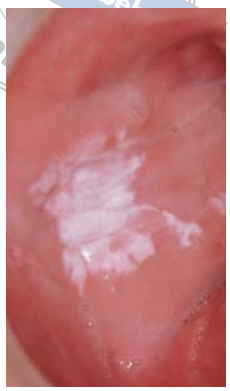


Fig 6 Papular oraler lichen planus.

- If necessary, an HIV test
- Possible prescription of a systemic virustatic agent.

■ Oral lichen planus mucosae

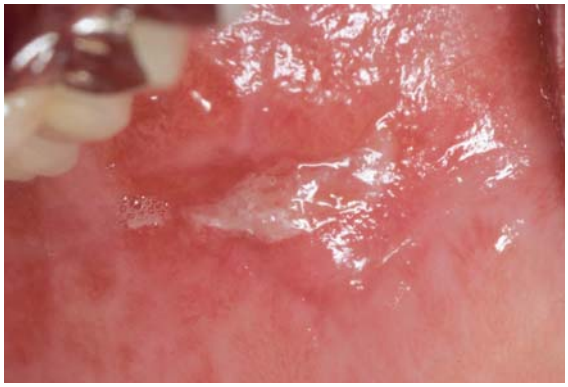
In his 'lecture on lichen planus' (1869), Wilson[8] described, for the first time, the white papule on the buccal mucosa and the tongue as well as reticular and plaque-like lesions. This refers to a non-infectious inflammatory disorder, which is triggered by cellular components of the immune system. This disorder, which presents on the skin, is also referred to as lichen rubra planus.

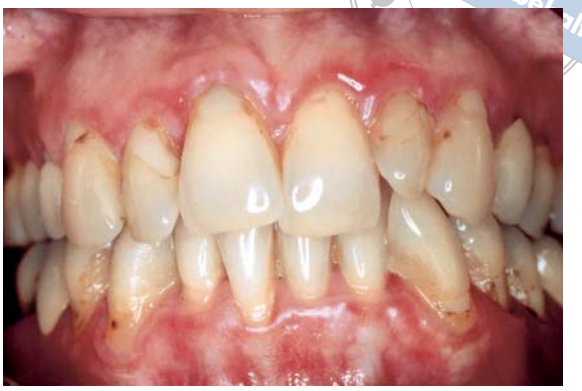
Theoretically, the lymphocytes react to antibodies (foreign or their own) in the basal cell layer. If the reaction is mild, this leads to the stimulation of epithelial activity, i.e. to the development of additional white film and plaque. If the reaction is more severe, this leads to epitheliotrophy and ulcerations[9].

Of the entire population, 0.1 to 2.2% exhibits, for the most part, asymptomatic OLP[10]. Initial symptoms predominately comprise unpleasant sensations when eating hot or tangy food. Women are more frequently affected by the mild form of the disorder with 60 to 65% of them experiencing this. The most common sites are the buccal mucosa, the tongue and the gingiva, generally on both sides[11]. In 30 to 50% of cases, the lichen planus is combined with skin lesions[12]. Twenty to 30% of patients also suffer from a *Candida* infection[13]. In 30% of cases, the lichen planus is combined with sensitivity toamalgam/nickel sulphate, and in 1 to 1.5% of cases, a malignant transformation must be anticipated in the long-term[14].

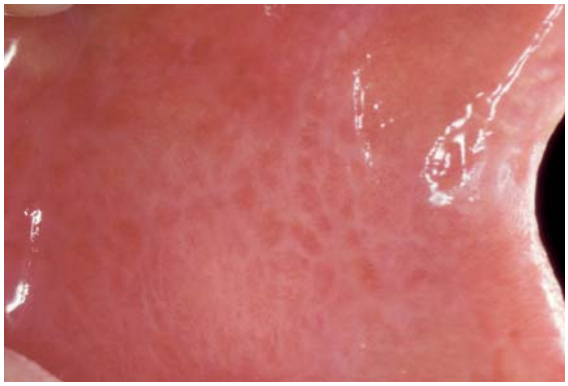
Andreasen[15] classified OLP as having six forms (reticular, papular, plaque-like, atrophic, erosive or bullous), which may present either individually or in combination (Figs 5 to 8). The first three forms are classified as hyperkeratotic, non-erosive forms and the last three forms are classified as inflammatory or erosive forms. According to Thorn et al[16], 92% of OLP patients were diagnosed with reticular forms, 44% atrophic forms, 36% plaque-like forms, 11% papular forms, 9% ulcerous forms and 1% bullous forms. A variety of factors and substances appeared to be highly significant in causing or exacerbating the OLP. However, it is accepted that they only bring latent disorders out into the open and do not induce new ones on their own (Table 3).

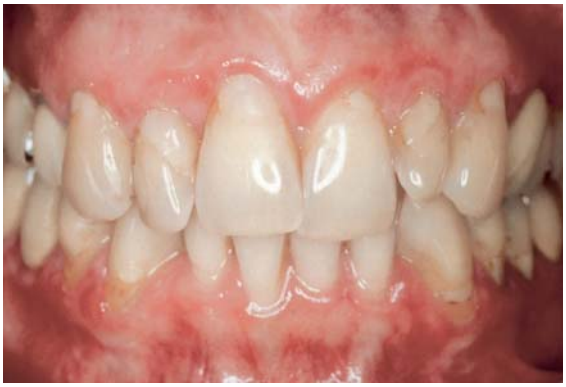
Due to the various aetiological factors, Krutschoff and Eisenberg[17] composed the histological description of a lichenoid lesion and OLP for the first time in 1985 (Table 4). Lichenoid dysplasia is characterised as being lichen with additional dysplastic characteristics in the epithelium, i.e. tear-drop shaped rete pegs. OLP can be differentiated from other autoimmune mucodermatoses (see Table 1) of the oral mucosa during differential diagnosis using direct immunofluorescence techniques.





Figs 7a and 7b Erosive oral lichen planus.





Figs 8a and 8b Erosive oral lichen planus after eight-day treatment with betamethasone valerate.

■ Management of symptomatic mucocutaneous disorders

It is primarily essential to have an extensive medical history and a saliva diagnosis. It is also recommended to have a record of medicines taken (psychotropics, soporifics), supplementary medicines taken (psychotropics, soporifics), additional skin diseases, gynaecological disorders, chronic hepatic diseases/ Hepatitis C and other stress factors.

Alongside the findings related to the oral mucosa, the collected findings should also contain the location of metallic restorations and photographic documentation. Surgical sampling is mandatory in the case of the suspected diagnosis of a symptomatic mucocutaneous disorder.

It is recommended that a direct and if necessary an indirect immunofluorescence analysis be carried out if immune mediated diseases are suspected, as this will enable precise diagnosis.

Detailed information about the patient is crucial to his treatment. References to the changing nature of the clinical lesions and the risk of deterioration associated with them are of particular importance. Gynaecological and dermatological examinations should be initiated, if required. Patients can prevent pain at home by avoiding mouthwashes containing iodine, chlorhexidine or alcohol as well as hot and tangy foods and those containing fruit acids.

Dental treatment includes eliminating mechanical irritant factors by removing sharp edges and correcting filling materials that are directly associated with the mucocutaneous disorders. The replacement of amalgam fillings is recommended by a number of authors[18,19]. Supragingival restorations make effective and largely painless plaque inspection easier. The patient should only carry out mechanical plaque inspection using supersoft toothbrushes in order to minimise damage to the gingiva.

If there is evidence of a fungal infection, it is necessary to carry out candidiasis treatment for the elimination of superinfections. The teeth should also be

Drugs	Non-steroidal anti-rheumatics, gold salts, allopurinol, angiotensin converting enzyme inhibitors, quinidine, penicillamine, beta-blockers, antimicrobial agents, antiparasitic agents (sulphadoxine, pyrimethamine, chloroquine, quinacrine), antihypertensives (methyldopa), oral hypoglycemics (sulphonylurea derivative, chlorpropamide)
Contacting agents	Film developer, restorative materials (amalgam, metals, plastic, cyanoacrylate)
Stress, anxiety	
Viral infections	
Reasons for immunity	

Table 3 Aetiological factors of oral lichen planus.

Essential criteria	Secondary criteria	Exclusion criteria
1. Liquefied degeneration of the Basal cell region	1. Saw tooth-like rete pegs	1. Dysplasia characteristics
2. Band-shaped infiltrate of lymphocytes in the lamina propria, which is densely mixed with the basal cell region of the epithelium	2. Hyper-/parakeratosis	2. Heterogeneous round cell infiltrate in lamina propria
	3. Separation of the epithelium and connective tissue in uneven distribution	3. Submucous infiltrate
	4. Isolated individual cell keratinisation in the acanthocyte region	

Table 4 Characteristics of oral lichen planus.

Medium-term local treatment of erosive oral lichen planus	Hydrocortisone; triamcinolone[23,24]; betamethasone valerat (0.1%, 3x/d for 3 weeks)[25-27]; fluocinonide (0.05% 3–4x/d, 1.5 g/d for 3 weeks)[28,29]; clobetasol propionate (0.025%)[30,31]
Intra-lesional injection for erosive ulcerous oral lichen planus, when local and systemic application was not successful	Triamcinolone acetonide (10–20 mg in 2% lidocaine solution, if necessary with 2–3 repetitions[32,33]; 0.5 ml triamcinolone (40 mg/ml with a second injection after 2 weeks)[34]
For severe disease patterns with acute exacerbation	30–60 mg prednisolone initially for 2–3 weeks with gradual discontinuation of medication, followed by topical subsequent treatment[35]
In cases of treatment refractory, which do not react to topical corticosteroid therapy alone	Retinoids: acitretin, etretinate, fenretinide, temarotene (systemic for 2–3 weeks)[35]
In cases of treatment refractory, which do not react to corticosteroid therapy	Cyclosporin A (systemic[36]: 2.5 mg/kg body weight in two separate doses decreasing; local[37]: 25 mg/g adhesive pointment, 3x/d rub 1 cm pointment into skin for 10 min)

Table 5 Therapeutic procedures for symptomatic autoimmune mucodermatoses.

cleaned professionally, possibly under surface anaesthetic, in order to prevent unnecessary discomfort. It is very sensible to continue with a local corticosteroid therapy with few side effects for a few days after the discomfort has abated (Table 5).

Intralesional injections of triamcinolone for the treatment of erosive ulcerous OLP are restricted to cases where local and systemic application was not successful. At the same time, undesired systemic effects with adrenocortical suppression, atrophy of the tissue and secondary candidiasis[20] cannot be ruled out.

With severe disease patterns with acute exacerbation, it is wise to undergo systemic corticosteroid therapy after consultation with internists and dermatologists. It is necessary to pay attention to and critically examine undesirable side effects such as gastrointestinal discomfort, polyuria, insomnia, mood swings, hypertension and diabetic metabolism.

In cases of treatment refractory, which do not react to topical corticosteroid therapy alone, the supplementary systemic prescription of retinoids is like-

wise possible. However, cheilitis, pruritus, desquamations in the hands, paronychia and hair loss should also be considered as possible undesirable side effects. In cases of treatment refractory, which do not even react to corticosteroid therapy, cost-intensive treatment with cyclosporin A has been successfully used in particular cases.

Due to the malignancy rate, it is recommended that three to four oral mucosa inspections are carried out annually in combination with professional teeth cleaning in order to minimise local irritant factors. Surgical treatment methods using a CO_2 laser are currently preferred to cryosurgery or free mucous membrane transplantation[21,22]. They are to remain limited to aesthetically unproblematic regions and to the removal of dysplastic lesions.

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