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A MODERN VIEW ON THE ETIOLOGY AND PATHOGENESIS OF LICHEN PLANUS AND LICHENOID LESIONS OF THE ORAL MUCOSA (LITERATURE REVIEW)

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Annotation

Subject. The review which has been carried out allows us to consider the issues of etiopathogenesis of lichen planus and lichenoid lesions of the oral mucosa adapted to the modern classification. The analysis of clinical features must be carried out with an emphasis on differential diagnosis.

The aim is to conduct a systematic analysis of modern native and foreign literature sources to determine some features of the etiology and pathogenesis of lichen planus and lichenoid reactions of the oral mucosa, depending on risk factors.

Methodology. The search for research papers on the etiology and pathogenesis of this dermatosis was carried out using the following databases: PubMed, Web of Science, Medline, elibrary.ru, Scopus in the period from 2010 to 2021, and the review includes selected significant publications for the period from 2015 to 2021. The following keywords were used: lichen planus, oral lichenoid lesions, prevalence, clinical symptoms, clinical forms, risk factors. Special attention was paid to articles published in peer-reviewed scientific publications. Research methods used in the analysis process: content and descriptive-analytical analysis. As a result of an electronic search, 74 publications were found. The conducted research has a wide geography: Austria, Australia, Belarus, Great Britain, India, Spain, Italy, Iran, Yemen, China, Korea, Russia, Romania, USA, Saudi Arabia, New Zealand, Taiwan, Thailand, Tehran, Croatia, Scotland, Japan.

Results. Among all the pathological processes that were diagnosed on the oral mucosa, lichen planus occurs on average from 35 to 70% of cases, while only isolated or oral forms are diagnosed on average from 50 to 75% of cases of examinations, the frequency of simultaneous lesions of the mucous membranes and skin is 23-28.6%. The pathogenesis of the studied pathology has significant differences depending on the diagnosed form of lichen planus, or manifestations of lichenoid lesions.

Conclusions. In a comprehensive examination of these patients, it is very important to analyze not only the clinical features of oral forms of lichen planus, but also to evaluate the topographic location of morphological elements, their symmetry, and size. These data together allow for a differentiated approach in making an accurate diagnosis. The diagnostic process of oral forms of lichen planus and lichenoid lesions also includes the identification of general somatic diseases, the assessment of local risk factors, and the identification of the relative frequency and intensity of their clinical forms. The main diagnostic feature that allows you to distinguish lichenoid lesions from lichen planus is the fact that the elimination of the factor that provoked the symptoms leads to the disappearance of the damage.

Keywords: *lichen planus, lichenoid lesions, prevalence, clinical symptomatology, risk factors, aetiopathogenesis*

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СОВРЕМЕННЫЙ ВЗГЛЯД НА ЭТИОЛОГИЮ И ПАТОГЕНЕЗ ПЛОСКОГО ЛИШАЯ И ЛИХЕНОИДНЫХ ПОРАЖЕНИЙ СЛИЗИСТОЙ ОБОЛОЧКИ РТА (ОБЗОР ЛИТЕРАТУРЫ)

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Аннотация

Предмет. Проведенный обзор позволяет рассматривать вопросы этиопатогенеза плоского лишая и лихеноидных поражений слизистой оболочки рта, адаптированные к современной классификации.

Цель — провести системный анализ современных отечественных и зарубежных литературных источников для определения некоторых особенностей этиологии и патогенеза красного плоского лишая и лихеноидных реакций слизистой оболочки рта в зависимости от факторов риска.

Методология. Поиск исследовательских работ по этиологии и патогенезу данного дерматоза осуществлялся с помощью следующих баз данных: PubMed, Web of Science, Medline, elibrary.ru, Scopus в период с 2010 по 2021 год. Также в обзор включены отдельные значимые публикации за период с 2015 по 2021 год. Были использованы следующие ключевые слова: *красный лишай, лихеноидные поражения, распространенность, клиническая симптоматика, клинические формы, факторы риска*. Особое внимание уделялось статьям, опубликованным в рецензируемых научных изданиях. Методы исследования, использованные в процессе анализа: контент-анализ и описательно-аналитический. В результате электронного поиска было найдено 74 публикации. Проведенные исследования имеют широкую географию: Австрия, Австралия, Белоруссия, Великобритания, Индия, Испания, Италия, Иран, Йемен, Китай, Корея, Россия, Румыния, США, Саудовская Аравия, Новая Зеландия, Тайвань, Таиланд, Тегеран, Хорватия, Шотландия, Япония.

Результаты. Среди всех патологических процессов, диагностируемых на слизистой оболочке полости рта, красный плоский лишай встречается в среднем от 35 до 70% случаев, при этом только изолированные или оральные формы диагностируются в среднем от 50 до 75% случаев обследований, частота одновременного поражения слизистых оболочек и кожи составляет 23–28,6%. Патогенез изучаемой патологии имеет значительные отличия в зависимости от диагностированной формы плоского лишая или проявлений лихеноидных поражений.

Выводы. При комплексном обследовании данных пациентов очень важно анализировать не только клинические особенности оральных форм плоского лишая, но и оценивать топографическое расположение морфологических элементов, их симметричность, размер. Эти данные в совокупности дают возможность дифференцированного подхода в постановке точного диагноза. Диагностический процесс оральных форм плоского лишая и лихеноидных поражений также включает выявление общесоматических заболеваний, оценку местных факторов риска, выявление относительной частоты и интенсивности их клинических форм. Основным диагностическим признаком, который позволяет отличить лихеноидные поражения от плоского лишая, служит тот факт, что ликвидация фактора, спровоцировавшего симптомы, ведет к исчезновению повреждений.

Ключевые слова: *плоский лишай, лихеноидные поражения, распространенность, клиническая симптоматика, факторы риска, этиопатогенез*

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Introduction

The problem of diagnosing oral forms of oral lichen planus (OLP), as well as lichenoid lesions of the oral mucosa, does not lose its relevance at the present time. This is due to the prevalence of lichen planus, the aggressiveness of its clinical manifestations and the appearance of a significant group of patients with a lichenoid reaction on the oral mucosa, as well as a malignant transformation of PL in 1.1-1.37% of cases [2, 29, 37, 39, 43].

According to WHO, the population frequency of oral lichen planus in different countries varies from 0.22% to 5.0%, while in the USA 1%, in India 0.8%, in Sweden 1.27%, in the Russian Federation 11.3-12.7% cases per 100,000 thousand population. On the oral mucosa, manifestations of oral lichen planus are diagnosed on average from 1 to 2.2% of cases, while this pathology can occur in both children and adults, most often women aged 30-66 years are susceptible to them [13, 26, 29, 31, 38, 43, 49, 59, 61].

Among all pathological processes diagnosed on the oral mucosa, OLP occurs on average from 35 to 70% of cases, while only isolated or oral forms are diagnosed on average from 50 to 75% of cases of examinations, the frequency of simultaneous lesions of the mucous membranes and skin is 23-28.6% [2, 28]. Injuries can be classified as “unilateral” or “bilateral”, as well as can be classified into clinical subtypes “white” or “red”, depending on the clinical type (the former include reticular and plaque lesions. The latter include erosive and ulcerative manifestations [40, 49].

In patients with dermatic forms of lichen planus, up to 60% of cases of examinations are detected on the oral mucosa, 15-30% of patients with oral manifestations may develop skin lesions. Isolated OLP lesions are diagnosed in 26.5% of cases, they are the most manifest in clinical manifestations, prone to relapse and resistant to treatment, especially often they occur as erosive-ulcerative, bullous, hyperkeratotic lesions. Skin lesions are self-limiting, oral lesions are not remission, alternate periods of exacerbation and rest. Atypical lichen planus diagnosed in 81 (23.96%) patients in 45 (55.6%) cases manifests itself on the oral mucosa [4, 7, 8, 12, 16, 21, 23, 27, 33, 60, 68].

In oral forms of LP, a continuously recurrent course and resistance to traditional therapy is observed. This is largely due to the anatomical and physiological features of the oral mucosa, the presence of local risk factors in the form of aggressive microbial biofilms on the teeth, gums, tongue, the presence of implants, prostheses, orthodontic structures in patients, the use of means with a lichenizing effect (toothpastes, rinses, chewing gum), medicines, restoration and construction materials [11, 17].

LP is characterized by progressive, stationary and regressing stages of the disease. The frequency of spontaneous regression of cutaneous forms of LP is significantly higher than that of oral forms. LP can occur acutely (up to 1 month), subacute (up to 6 months) and chronically (more than 6 months) [11, 17].

Oral lichenoid lesionsof the oral mucosa resemble lichen planus by clinical signs and are often an allergic reaction to certain medications, metals, materials for dental treatment and food residues. The drugs that currently most often lead to lichenoid lesions are – angiotensive, enzyme inhibitors, thiazides, diuretics, immunosuppressants (penicillamine), immunomodulatory agents (levamizole), beta-blockers, antimalarial agents (quinine, pyrimethamine), antiarrhythmic agents (quinidine), antituberculous (para-aminosalicylic acid, streptomycin, isoniazid), neuroleptics (derivatives phenothiazine, levomepromazine), anticonvulsants (carbamazepine), anti-gout (allopurinol), tranquilizers (lorazepam), antifungal (ketoconazole), as well as drugs for the treatment of arterial hypertension and regulation of heart rhythm disorders (beta-blocking agents), calcium channel blockers with a predominant effect on brain vessels (cinnarizine) and many others [11, 37, 40, 42, 43].

In oral lichenoid lesions, there is no successive change in the serum level of immunoglobulins. Different levels of IgA, IgG, IgM, IgE and IgD were observed in LP, a minority of patients with lichenoid lesions react to certain products [11, 20, 55].

The main diagnostic feature that allows you to distinguish lichenoid lesions from other skin and mucosal diseases is the fact that the elimination of the causal factor that provoked the symptoms leads to the disappearance of damage. However, in most cases, it is still necessary to conduct a course of treatment. The term lichenoid reaction is a purely histological description that is used to encapsulate the pathological characteristics of skin diseases resembling LP [60, 63].

Various areas of the oral cavity are affected, and the most common place is the cheek mucosa, followed by the tongue and gum-the cheek mucosa along the line of the molars (75%), less often on the tongue (32%), on the palate (21%), on the gums (11%), on the lips (7%), at the bottom of the oral cavity (3.9%), in the pharynx (2%). Rashes on the lower lip are observed more often than on the upper lip [11, 29, 46].

Oral lichen planus of the oral mucosa is most often a nodular chronic disease, which in more than 65% of cases affects various parts of the oral mucosa-the cheeks (in 78.5-90.0% of cases), the tongue (30.0-51.3%), as well as the area of the alveolar process, gums and lips (13.0-27.5%), the retromolar region, the mucous membrane of the palate and the bottom of the oral cavity is less often affected (1.9-9.3% of cases) [11, 15, 17, 18, 19, 24, 29, 49, 63].

The purpose of this study is to conduct a systematic analysis of modern national and foreign literary sources to determine some features of the etiopathogenesis of lichen planus and lichenoid lesions of the oral mucosa.

Material and methods

The search for research papers on the etiology and pathogenesis of this dermatosis was carried out using the following databases: PubMed, Web of Science, Medline, elibrary.ru, Scopus in the period from 2010 to 2021, as well as some significant publications of Russian and foreign researchers for the period from 2015 to 2021 are included in the review. The following keywords were used: lichen planus, lichenoid lesions, clinical symptoms, risk factors. Special attention was paid to articles published in peer-reviewed scientific publications.

Conclusions and discussion

Currently, an active study of the etiology and pathogenesis of lichen planus and lichenoid lesions of the oral mucosa is continuing. All factors can be conditionally divided into groups: neurogenic, microbial, viral, allergic, toxic [12, 66].

It is quite difficult to determine the exact causes of the development of this disease. But it is possible to track a number of events and changes in a person's life that have contributed to the beginning of the development of this pathology and the deterioration of their general condition [3, 17, 59]

Oral forms of PL are characterized by histological features that consist of hyperkeratosis (hyperorthokeratosis or hyperparakeratosis) of the epithelium, hydropic or diluting degeneration of basal epithelial cells, atrophy or acanthosis of spinous epithelial cells, sawtooth epithelial ridges, homogeneous eosinophilic deposits at the epithelium-connective tissue junction and banded lymphocytic infiltrate in the surface plate propria. Degenerating keratinocytes can be seen in the area of the border of the epithelium and connective tissue, which is why they were called colloidal, cytoid, hyaline or cyatt bodies. Compared with skin lesions of the LP, lesions on the oral mucosa less often show sawtoothed epithelial ridges and more often show atrophy of the epithelium with non-obvious epithelial ridges. Moreover, epithelial dysplasia should not be detected in oral forms of PL [9, 12, 49].

Modern research identifies some factors that contribute to the development of the disease: occupational hazards, the impact of certain medicines and filling materials that are used in dentistry. However, fillings should not be the only factor involved in the cause of these lesions [63].

The development of the disease can occur against the background of other dermatoses, or against the background of reduced immunity, viral, fungal and bacterial etiology, hereditary factors, endocrine pathology, neurogenic causes and stress, deficiency of hemoglobin, iron, vitamin D, B12 and folic acid, abnormally high levels of homocysteine, serum autoantibodies, zinc, serum hematocrit, the presence of diabetes, diseases of the gastrointestinal tract, hepatitis C, B, cardiovascular system, thyroid gland. In addition, there may be lichenoid lesions of the mucous membrane of the mouth, esophagus, stomach, intestines, bladder, endometrium, which allows us to speak about the multi-system nature of the pathological process in LP [3, 11, 22, 30, 34, 43, 45, 48, 50, 56, 57, 60, 65, 70].

The influence of neurogenic factors is due to the fact that in many patients the disease is observed after nervous overstrain, frequent stressful situations, as well as against the background of neuralgia due to other diseases.

Viral factors are due to the fact that frequent damage to the oral mucosa and the development of oral lichen planus can occur both independently due to diseases of the oral cavity, or against the background of reduced immunity, and after poor-quality dental services [12, 50].

The T-cell-mediated nature of the histopathology of LP with localization on the oral mucosa suggests that a viral infection may be involved in its pathogenesis [12, 29, 74].

Some viruses, including human papilloma virus (HPV) and hepatitis C virus (HCV), were detected with a higher frequency in patients with manifestations of PL on the oral mucosa. However, the relationship between infection with these viruses and OLP is contradictory [12, 57, 64].

According to a number of authors, there is a relationship between the lesion of the mucous membrane in oral lichen planus and the persistence of infection in the tissues of the oral cavity [1].

In 1936, Brain confirmed the presence of a microbial factor in the development of lichen planus – β-hemolytic streptococci, Streptococcus pyogenes, Staphylococcus aureus, Pyogenic cocci, Fungiform rods, Pseudomonas aeruginosa, Capnocytophaga sputigena, Eikenella corrodens, Lactobacillus crispatus, Mobiluncus curtisii, Neisseria mucosa, Prevotella bivia, P. intermedia, Bacteroidesureolyticus, Dialister spp., Staphylococcus haemolyticus, и Streptococcus agalactiae. Additional studies have confirmed the correlation between the disease and microbial dysbiosis of the oral cavity [44, 52, 57, 69, 71, 72, 73].

In 98.7% of patients with the presence of LP in the oral cavity, proteobacteria 31,32%, bacteroids in 15.19%, Fusobacteria в 11.27% and Actinobacteria in 7.80% of cases were detected. The abundance of Fusobacterium, Leptotrichia and Lautropia and a lower abundance of streptococcus for the microbiota (average relative abundance > 5%). The Shannon diversity index showed a significant increase ($P = 0.004$) in oral forms of LP bacterial diversity. In addition, higher levels of infection with several periodontal pathogens, including Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, Treponema denticola have been reported in patients with oral mucosal LP [51, 57]

Several pathogenic periodontal bacteria were found at higher levels in patients with oral forms of LP, but the

correlation between these bacteria and the development of dermatosis is also not clear. M. salivarium is the most common species isolated from the oral cavity – dental plaques and gingival grooves similar to pathogenic periodontal bacteria. Although the role of M. salivarium in the development of clinical manifestations of LP is unclear, it is assumed that there is a close relationship between the localization of M. salivarium in epithelial cells and hyperkeratosis of the epithelium of the oral mucosa. Hyperkeratosis is considered as a histopathological sign of oral forms of LP. Wickham striae appear in reticular types corresponding to focal areas of hyperkeratosis or parakeratosis. Thus, it was postulated that M. salivarium cells are present in the epithelium of tissues with LP, especially in tissues with a reticular shape [57].

More recently, Yu et al. (2020) returned to the topic of saliva microbiome dysbiosis in patients suffering from oral forms of LP. The authors described that the beta-diversity of the microbiome varied in different clinical forms of the disease, and their results showed that microbiomes can be unique and different in two manifestations of the disease, erosive and non-erosive. It should be noted here that dysbiosis is caused by the presence of Pseudomonas aeruginosa in the oral cavity, which causes an increase in the concentration of nitric oxide (NO), it is considered one of the leading causes of squamous cell carcinoma of the oral cavity [5, 72].

The cause of various lesions of the oral mucosa, ranging from idiopathic oral lichen planus to "contact" lesions, has not been studied, but all lesions are histologically characterized by a typical "lichenoid tissue reaction", characterized by a striated lymphohistiocytic infiltrate filling the propria of the plate; and diluting degeneration of basal keratinocytes [56].

These reactions can be the result of several different possible triggers, but they all end with a common pathological process-directed by T-lymphocytes, mediated by immunity, damage to the basal epithelial cells of the oral cavity [35].

The autoimmune nature of lichen planus of the oral mucosa is evidenced by the chronic and prolonged course of the disease, its later age of onset, higher prevalence in women compared to men, its association with other autoimmune diseases, proven autoreactivity of T cells and increased autocytoxicity against basal keratinocytes, in connection with which two theories have been put forward to explain the autoimmune nature, in particular, the loss of self-tolerance of basal keratinocytes: violation of immune suppression due to the absence of T-transforming growth factor-β1 (TGF-β1); and loss of "immune resistance", polymorphism of the genes of tumor necrosis factor (TNF)-α, TNF-β and interleukin (IL)-10, IFN-γ (874A/T), micro RNA, expression of proangiogenic factors CD 34 are associated with susceptibility to the development of oral forms of PL [34, 41, 43, 47, 58, 67].

There is a high prevalence of thyroid diseases among patients with lichen planus of the oral mucosa, while contradictory results were obtained when analyzing the relationship between dermatosis and diabetes mellitus. Other diseases of altered immunity, in particular alopecia, ulcerative colitis, vitiligo, morphea, sclerosing lichen and myasthenia gravis, are more common in patients with lichen planus. Patients with lichen planus present a higher risk of developing dyslipidemia, which can be explained by cytokines involved in the pathogenesis of the disease, such as s TNF-a, IL-6, IL-10, IL-4, therefore, screening of lipid levels in patients with lichen planus is recommended to identify people at risk of developing cardiovascular diseases [29, 34, 53, 54, 67].

In the works of foreign and domestic researchers aimed at studying the transformation of lichen planus of the oral cavity and the clinical features of lichenoid lesions, it can be concluded that the modern classification of LP remains unchanged, as previously determined, and the following types are distinguished: reticular or typical, exudative-hyperemic, erosive-ulcerative, bullous, hyperkeratotic and atypical forms [6, 18, 19, 32].

Let's consider and analyze each of the above forms. A typical, reticular or non-erosive form of oral red lichen planus of the oral mucosa is characterized by features of intertwining white lines, the so-called Wickham striae in the distal parts of the oral mucosa, most often bilaterally or bilaterally. However, the lateral and dorsal surfaces of the tongue, the gum and the gingival papilla are also involved. The reticular form most often does not manifest itself at the initial stage.

In the typical form of lichen planus, excessive thickening of the stratum corneum of the epithelium is determined as a result of excessive keratinin formation (a narrow band of hyperkeratosis). Damage to the basal layer of the multilayer flat epithelium is associated with a violation of the keratinization process, which is expressed by incomplete keratinization of the surface cells of the spiny layer and the preservation of flattened, elongated nuclei in them – the process of parakeratosis, proliferation of cells of the spiny layer, the appearance of cells with granular cytoplasm, round-cell infiltration, the presence of linear infiltrates of lymphoid cells along the border of the epithelium and subepithelial layer, with a large number of T-lymphocytes, many activated macrophages, B-lymphocytes, plasma cells, a significant number of Langerhans cells, leukocytes [1, 2, 11, 28, 34].

The hyperkeratotic form of lichen planus of the oral mucosa is most often localized on the dorsal surface of the tongue and it is difficult to distinguish it from leukoplakia. Objectively, with this form, patients may be diagnosed with reticular or erosive forms with localization on the distal parts of the cheek mucosa. This form is presented in the form of large foci of mucosal lesions with a high degree of keratinization. In addition, these patients usually do not have risk factors – chewing

of betel, smoking cigarettes and drinking alcohol [1, 2, 11, 28].

The hyperkeratotic form of LP is characterized by a powerful layer of hyperkeratosis, parakeratosis, acanthosis, round-cell striate infiltrate, and the absence of a basement membrane. The presence of Sivatt colloid bodies is described in 37% of cases, which indicates significant destructive changes in the region of the basal membrane of the SOR [1, 6, 11].

With an exudative-hyperemic form with an increase in an inflammatory reaction on the oral mucosa, patients most often complain of soreness when taking a meal, a burning sensation and dryness. An objective examination reveals hyperemia and puffiness on the oral mucosa, while a pattern of merged papules forming "fern leaves" is clearly observed. Complaints in patients in this case of dryness, peeling and burning, and other discomfort when taking a meal and drinking water. More often this form is noted on the mucous membrane of the cheeks and gums [1, 6, 10, 12, 14, 16, 25, 28, 62].

The exudative-hyperemic form of LP is characterized by hyperkeratosis, parakeratosis of the stratum corneum of the epithelium, as well as thickening of the epithelial layer of the mucous membrane with elongation of the interstitial processes due to increased proliferation of basal and spiny cells (acanthosis), rupture of the basement membrane, a powerful layer of diffuse round-cell infiltration. The infiltrate contains full-blooded vessels, parietal standing of leukocytes, their diapedesis, intraepithelial, intracellular edema [6, 12, 14].

The erosive-ulcerative form is a complication after the typical form, and is considered quite severe of all in terms of the well-being of patients and the treatment process itself. In this case, a person experiences pain when taking liquids, food, swallowing and talking, that is, the quality of life of a person is greatly reduced. The visually affected part of the mucosa is edematous and hyperemic, there are papules and erosions with uneven edges and combined with each other, as a result of which a large area is affected. If this type of lichen planus of the oral cavity is not treated for a long time, ulcers with keratinization lines are formed [6, 14, 36].

The bullous form of lichen planus of the oral mucosa is the rarest of all forms, and occurs in some patients in the form of not only papules, but also blisters, which can be both very small and increase to the size of a coin. Clinically, it is characterized by the formation of blisters with a dense cap, the size of a pinhead to a bean, with serous or hemorrhagic contents; there are blisters on the hyperemic mucous membrane, along the periphery of which there is a papular pattern. Subepithelial blisters exist from several hours to several days, then, opening up, they form extensive erosive surfaces. Nikolsky's symptom is negative. In this form of the disease, violations of the general condition are often observed [2, 11, 28].

Bullous and erosive-ulcerative forms of LP are represented in the center of the lesion by round-cell infiltration, necrotic masses; on the periphery, the picture corresponds to the typical form of lichen planus of the oral mucosa. Intraepithelial, intercellular edema is also observed. The cells of the spiny layer change their shape, become round, with a large nucleus. In the bullous form, slit-like formations are noted inside the epithelium – the formation of an intraepithelial bubble begins. There is an increased desquamation of keratinized epithelial cells (up to 75%) with non-nuclear and nucleated cells, a lot of white blood cells and neutrophils. The number of epithelial cells of intermediate maturity is relatively low [11, 12]. Malignancy of this process occurs in 1.1-6.3% of cases in patients with erosive-ulcerative and bullous forms [6, 11, 12].

The atypical form in most cases is localized on the mucous membrane of the lips and gums. Externally, two areas are defined on the lip, in which there is congestive hyperemia. The formations are covered with a whitish plaque, which in turn is not removed, or it is very difficult remove this plaque [6, 11].

Conclusion

Having analyzed the modern view on the etiology and pathogenesis of lichen planus and lichenoid lesions of the oral mucosa, it can be concluded that these manifestations of pathology of the oral mucosa are quite common, especially among young and middle-aged women, as well as among people using various types of prosthetic dentures, and among people with somatic diseases and allergies.

The high incidence of mucosal lesions in lichen planus and the possibility of detecting lichenoid reactions on the mucosa indicate the need for clear interdisciplinary interactions – a dentist, a dermatologist, a gastroenterologist, a therapist, a gynecologist, a psychotherapist in the final formulation of a detailed diagnosis of the disease, as well as timely routing of patients to appropriate medical institutions and coordination of dispensary observation.

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