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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

IMPROVING THE DIAGNOSIS AND TREATMENT OF ORAL LİCHEN PLANUS

Speciality: 3226.01 – Dentistry
Field of science: Medicine

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GENERAL CHARACTERISTICS OF THE WORK

Relevance of the topic and degree of the research. Oral lichen planus (OLP) is characterized by its clinical polymorphism, its long-term, severe, relapsing course and its torpidity against existing treatment methods[1].

Despite the availability of excellent diagnostic methods and the application of modern treatment methods, the trend of increasing the number of patients with OLP continues [2].

According to the results of epidemiological studies, the prevalence of OLP is 0.5-2% of the population, and this disease is more common in women aged 40-65. Occurrences of OLP among children are not rare [3;4;5]. In 30-35% of cases, only the oral mucosa is damaged by OLP.

The "rejuvenation" of the disease has been noted in recent years. It is assumed that this is related to the anomalies occurring in the ecology, the increase in contacts with viral infections, radical changes in the body's reactivity, and the increase in cases of psycho-emotional stress.[6]

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The erosive-ulcerative and hyperkeratotic form of OLP is considered a facultative precancerous condition and the probability of turning into cancer is 7% [7;8].

In connection with the increase in the number of patients suffering from OLP, the long duration of the disease and its relapsing course, the low effectiveness of existing treatment methods, and the possibility of malignancy of the process, the search for new treatment schemes that have high efficiency and provide a stable therapeutic effect in a short time is considered relevant today [9].

Currently, as a rule, when the result of conservative treatment is not satisfactory, cases with a high probability of oncology result in the application of radical surgical treatment.

Significant changes in both humoral and cellular immunity are detected during OLP. For this reason, immune correction is considered one of the main aspects in the complex treatment of the disease [10].

The changes in the psychoemotional status of patients with OLP pathogenetically justify the addition of pharmacological agents with anxiolytic, antistress, antidepressant effects to the treatment complex of the disease [11;12].

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Despite the fact that OLP is a very common disease, the exact cause of its formation is still unknown.

The low effectiveness of local conservative treatment of OLP with traditional schemes is associated with a deficit in the amount of antioxidant potential of saliva, which is why it is necessary to include antioxidant effective drugs in the complex treatment of OLP.

Based on the listed facts, it can be concluded that the optimization of the complex treatment of OLP is relevant by influencing the pathogenetic mechanisms, i.e. by ensuring the normalization of the functional state of the nervous and immune system, as well as by applying antioxidants that inhibit the oxidation of lipids.

The object of study. The data included as scientific evidence in the research work were formed on the basis of examination and treatment of 141 (103 women, 38 men) patients suffering from OLP. Among them, 45 people with erosive-ulcer form were selected and involved in complex examination and treatment.

The aim of the study was to improve the diagnosis of oral lichen planus from oral mucosal keratoses and the complex therapy of its erosive-ulcerative form.

The study objectives:

1. Studying the frequency of occurrence of various forms of OLP among the diseases of the oral mucosa based on the retrospective analysis of archival materials (2016-2021) of the department of stomatology and maxillofacial surgery of the RCH;
2. Compilation of an individual examination card that fully reflects the anamnesis, clinical characteristics and the general condition of the hard and soft tissues of the oral cavity of the examined oral mucosa patient;
3. Studying the psychoemotional conditions of the examined patients based on the level of cortisol hormone and reactive anxiety (RA) and individual anxiety (IA) assessed on the basis of the Spielberg-Hanin scale;
4. Detection of cytogenetic disorders detected by the total number of nuclear aberrations in the buccal epithelium and

immunological changes (IL-1β, IL-2, IFN-γ and AAE) of patients with erosive-ulcerative form of OLP;

5. Evaluation of the effectiveness of the complex treatment (anxiolytic+antioxidant) according to the clinical indicators of the study, the state of anxiety disorders, immunological and cytogenetic changes.
6. As a result of the research, the heuristic diagnosis-treatment algorithm, designed by taking into account the individual course of various clinical variants of OLP was developed and presented as a practical tool in the form of an appropriate block-diagram.

Research methods.

- clinical
- immunological
- biochemical
- cytomorphological
- assessment of anxiety disorders
- examination method of Eastern Medicine
- statistical processing of the material

The main provisions for the defense:

- A generalized statistical result on the frequency of occurrence of various variants of OLP among diseases of the oral mucosa based on a retrospective analysis of archival materials of the Department of Dentistry and Maxillofacial Surgery named after A.Aliyeva ASATI and its databases;
- The result obtained from the analysis of anxiety-fear disorders accompanied by an increase in RA and İA based on the Spielberg-Hanin questionnaire and cortisol levels in patients with erosive-ulcerative OLP;
- Existence of a high correlation between changes in cytogenetic and immune indicators and disturbances in the homeostasis of the oral mucosa in patients;
- Discussion of the result of the effectiveness of the complex treatment (anxiolytic+antioxidant) during the treatment of patients with erosive-ulcer form of OLP, regarding the rapid

epithelization of erosions and the reduction of the inflammatory area in the mucous membrane;

- Positive dynamic effect of the complex treatment of patients with erosive-ulcerative OLP with the use of anxiolytic+antioxidant on disorders in cytogenetic indicators and immunity of the oral cavity mucosa (cytokines and AAE).
- Systematization of the diagnosis and treatment of OLP disease based on heuristic algorithm with reference to modern information processing and computer logical analysis methods and discussion of the block diagram presented as a result.

Scientific novelty of the study:

- The dynamics of indicators of psychoemotional disorders, which play a trigger role in the initial occurrence of OLP or in the exacerbation of the existing disease, were studied against the background of complex treatment (anxiolytic fabomotizole+ antioxidant vitamin A local and general);
- Clinical effectiveness of complex treatment (anxiolytic+ antioxidant) of patients with erosive-ulcerative form of OLP has been proven, having the ability to significantly accelerate erosion epithelization and reduce the inflammatory area of oral mucous membranes in the dynamics of treatment;
- It was determined that the proposed complex treatment resulted in the improvement of oral homeostasis based on local immune indicators;
- The effectiveness of the combined use of antimutagenic anxiolytic and local and general prescribed antioxidant drugs used in the complex treatment of patients with erosive-ulcerative form of OLP was determined according to the condition of anxiety-fear disorders (AFD) and cytogenetic disorders in the oral mucous membranes;
- The diagnostic-treatment strategy was algorithmized based on objective laboratory indicators, logical reasoning and heuristic approach, taking into account the individual course of various clinical variants of OLP, and was presented in the form of a block diagram as a practical tool.

The practical significance of the study:

- The scientific-practical information obtained as a result of researches on the complex treatment of patients with erosive-ulcerative form of OLP was included in the curriculum of the department of dentistry and maxillofacial surgery of ASATID named after Aziz Aliyev;
- To be applied in clinical practice, an individual medical examination card has been prepared, which shows the objective state of hard and soft tissues in the oral cavity by means of symbols;
- The block diagram of the proposed and approved heuristic diagnostic-treatment algorithm can be used in practice to choose the optimal treatment of patients with OLP;
- The complex treatment scheme (fabomotizole+vitamin A) for patients with erosive-ulcerative form of OLP is of practical importance as an effective treatment method in terms of reducing the treatment time of the disease and prolonging the remission period. .

Approbation: Dissertation materials were presented at the conferences of ASATID named after A. Aliyev (2016-2020), at the scientific-practical conference dedicated to A. Aliyev's birthday (Baku-2022). The dissertation work was preliminarily discussed with the participation of the "Stomatology and Maxillofacial Surgery" and "Dermatovenerology" departments of A.Aliyev ASATI and the staff of the Central Scientific Research Laboratory (30.05.2023, protocol №1) and was discussed at the meeting of the scientific seminar of the ED 2.50 Dissertation Council at AMU (27.10.2023, protocol №2).

Implementation of research results into practice. The results of the research work were applied in the teaching program and practical activities of the Department of Dentistry and Maxillofacial Surgery named after A.Aliyeva ASATID.

The name of the organization where the dissertation work was performed. In order to deeply study the clinical aspects of the OLP, the research work was carried out at the Department of

Stomatology and maxillofacial surgery of the Azerbaijan State Medical Training Institute named after A. Aliyev and its base located at the Republican Clinical Hospital named after academician M. A. Mirgasimov.

Publications. 13 scientific articles (3 included in international summarizing and indexing systems), 13 theses (3 abroad), 1 methodical resource were published on the main content of the dissertation.

The volume and structure of the dissertation:The dissertation is composed of 188 pages (215,924 characters) of computer text. The dissertation consists of an introduction (19,579 characters), 6 chapters (chapter I (30,027 characters), chapter II (17,389 characters), chapter III (41,368 characters), chapter IV (17,966 characters), chapter V (59,635 characters), chapter VI (10,890 characters)), results, conclusions practical recommendations (19,069 characters) and 262 bibliographies (30 pages), of which 29 are local and 233 are from foreign sources. The research work is illustrated with 30 tables and 27 figures, 24 graphs.

MATERIALS AND METHODS

The data obtained from 141 examined patients were recorded in the outpatient examination card we prepared, which allows us to accurately assess the dental status and clinical condition in a visual way.

The age index of patients was as follows: 20-30 years old - 4 patients, 31-40 years old - 14 patients, 41-50 years old - 26 patients, 51-60 years old - 44 patients, 61-70 years old - 34 patients, 71 and more - 19 patients.

The condition of the OM was assessed by the presence of injury elements, their number, localization, severity of the inflammatory process, the condition of the edges of the ulcer elements and their size.

In all patients, before treatment and during the course of treatment, data on the area of erosive-ulcerative lesions and oral

mucosa membrane regeneration index (OMMRİ) were determined in percentages as follows:

$$\text{OMMRİ} = \frac{So - St}{So \; x \; t} \text{ x } 100,$$

where, So - area of erosive-ulcerative lesions before treatment; St - the area of erosive-ulcerative lesions on the day of determination; t-is the duration of treatment in days.

The area of inflammation and erosion is determined by the irregular circle formula: S=(πxd1xd2):4cm2, where - d1- the smallest diameter, d2 - the largest diameter, π =3.14.

The following laboratory studies were carried out in patients with OLP:

- *determination of cytokines in saliva:* IL-1β, IL-2, IFN-γ;
- *determination of steroid hormone in saliva:* cortisol;
-*cytomorphological studies in the oral cavity*: epitheliocyte adsorption activity (EAA), nuclear aberrations in buccal epithelial cells.

The level of anxiety-fear disorders of patients with OLP was assessed using the Spielberg-Khanin questionnaire test.

Methods of treatment: In order to evaluate the effectiveness of different therapy schemes, 45 patients with erosive-ulcerative forms of OLP were divided into three groups of 15 people each according to the simple randomization method. In group I, basic therapy under the name of traditional treatment, in group II traditional treatment + anxiolytic (fabomotizol-10 mg 3 times a day for 2 months), in group III traditional treatment + anxiolytic + antioxidant (10 drops of vitamin A at a dose of 100000 BV/ml 2 times a day in general and 3 times a day locally in the form of application for a period of 2 months) therapy was carried out. In addition, in order to analyze the laboratory indicators, a control group (n=10) without OLP was created. The age range of the control group corresponds to the age range of the clinical group. Complex laboratory examinations were performed on patients before treatment and on the 15th day of treatment, 1 month and 3 months later.

In all patients with OLP, generally accepted (Дмитриева, Л. А. Терапевтическая стоматология: национальное руководство,

2021.) basic therapy under the name of "traditional treatment" was carried out.

The traditional treatment scheme refers to:

1. Motivation of the patient based on the importance of the treatment carried out by choosing individual oral hygiene methods and tools;
2. Professional hygiene of the oral cavity: manual and ultrasonic cleaning of tartar, rinsing with an antiseptic, polishing the teeth with "Detartrin" (Septodont) paste with a silicone head and a brush;
3. Smoothing the sharp edges of the teeth
4. Sanitation, electrosanitation of the oral cavity: elimination of local irritating factors and chronic infection centers;
5. Assessment of the condition of orthopedic constructions and, if necessary, replacing them with new ones;
6. Application with analgesic drugs ("Lidoxor" gel);
7. Rinsing the oral cavity with antiseptic solutions twice a day for 10-14 days (with 0.05% chlorhexidine solution);
8. Application with proteolytic enzymes (0.1% trypsin solution)
9. Application of the injured area with keratoplastic agents (sea buckthorn oil), applying a steroid dressing (Celestoderm-V and Solcoseryl in a ratio of 1:1).

The inclusion criteria are as follows:

- Diagnosis verification: erosive-ulcerative form of oral lichen planus, ICD-10 code - L-43.1.
- Those with informed consent.
- Those in the age range of 40-60.

The exclusion criteria are as follows:

- Patients without informed consent.
- Those with malignant tumors of local and general origin.
- Those with mental illness.
- Those during pregnancy and lactation.
- Those with cutaneous lichen planus
- Those in the decompensation phase of the main somatic disease.

RESEARCH RESULTS AND THEIR DISCUSSION

Clinical picture of oral lichen lanus: Patients who came to us for the first time and were under our control had complaints such as "burning", "needle prick "sensation, dryness and loss of sensation, "feeling of a foreign body in the mouth" and discomfort, bleeding gums and mobility of teeth.

Objectively, if the disease is classic forms, it is in the form of a "snowflake"-like picture (Wickham net) formed by the combination of hyperkeratotic papules with a diameter of 1-2 mm on the mucous membrane, if inflammation, dystrophy, and destruction variants are added to the injury area, complicated forms appear in the form of erythema, edema, erosion, and ulcers.

The papular form of OLP is more common - on the dorsal surface of the tongue, on the mucous membrane of the cheeks and lips, the annular form - on the dorsal surface of the tongue, the reticular form - on the retromolar area, on the mucous membrane of the cheeks and transitional membrane, exudative-hyperemic and erosive-ulcerative forms - on the mucous membrane of the cheeks and on the edges of tongue (closer to the root).

In our observations, we have witnessed permanent and wave-like variants of the disease (the phase of exacerbation is replaced by the phase of relief and such displacement is repeated many times).

The differential diagnosis of the disease was carried out with diseases similar to OLP according to its clinical symptoms (leukopenia, scarlet fever, syphilitic papules, vulgar cyst, multiform exudative erythema, allergic stomatitis and candidiasis).

Results of immunological studies: Taking into account the crucial role of IL-1β, IL-2 and IFN-γ, which are indicators of local and systemic immune reactions in the pathogenesis of various diseases of the body, we studied them before and during the treatment of serious oral pathology such as oral lichen planus

As a result of the research, it was found that the level of IL-1β, IL-2 and IFN-γ in the saliva of patients with OLP was increased. The average level of IL-1β in the saliva of patients with OLP was

58.0±1.5 pg/ml (respectively 45.2±4.8 pg/ml in the control group), the level of IL-2 in the saliva was 26.8 pg/ml (respectively 13.6±3.3 pg/ml in the control group). The level of IFN-γ was 8.8±0.8 pg/ml in practically healthy patients, while it was 14.6±0.6 pg/ml in chronic patients.

Assessment of psychoemotional disorders based on the cortisol hormone and Spielberg-Khanin questionnaire. Determination of the level of cortisol- a hormone of the adrenal cortex in saliva is the optimal method for assessing emotional stress. Before treatment, the level of cortisol in the saliva of patients with OLP is higher than normal indicators (25.6±0.8 nmol/l), and this indicator is 1.5 times higher than the indicators of the control group ($p<0.05$).

In order to characterize the psychoemotional states of the patients, the Spielberg-Hanin self-report questionnaire was used, which assesses reactive anxiety (RA) and individual anxiety (İA). The pre-treatment level of RA was 42.5±2.2 points, and the level of İA was 46±2.5 points in patients with OLP. Our results show that the disorder in the psychoemotional conditions of the examined patients is revealed by a large increase in RA and İA and statistically ($p<0.05$) exceeds the control group.

A positive correlation was found between the level of cortisol before the treatment and the level of RT ($r=0.8$) and İA ($r=0.7$).

Results of cytomorphological studies: Adsorption activity of epitheliocytes (AAE). A smear taken from the mucous membrane of the oral cavity was used for cytomorphological studies. Adsorption activity of epitheliocytes (AAE) was determined during microscopy. AAE is an indicator of the level of non-specific resistance of the organism. It is known that the weakening of immunity due to the influence of various somatic diseases and pathogenic factors reduces the adsorption activity of epitheliocytes.

According to the number of microorganisms adsorbed on the surface of epithelial cells during microscopy, they are classified into 4 categories. Epithelial cells belonging to categories I and II belong to the negative AAE cell group, and those belonging to categories III

and IV belong to the positive AAE cell group. During microscopy, the percentage of positive and negative AAE cells in each smear is determined. Based on the percentage of positive AAE, the level of non-specific resistance of the body is assessed: 70% positive AAE and above - the functional state of the body is good, 31-69% - sufficient, 30% and below - bad.

Adsorption activity of epitheliocytes of patients with OLP was on average 9.6±0.7% in category I, 18.7±0.6% in category II, 52.2±0.5% in category III, IV by category was 19.5±1.1%. Thus, the weakness of the adhesiveness of the epitheliocytes of patients with erosive-ulcerative form of OLP means low non-specific resistance.

Detection of cytogenetic aberrations in buccal epithelial cells: The state of the buccal epithelium (BE) is an important informative indicator used in the assessment of health, somatic pathologies, stress factors. Cytogenetic abnormalities occurring in the BE cells during the renewal process provide information about the homeostasis of the body. An increase in the share of micronuclear cells was observed in patients with OQYD compared to practically healthy ones (3.44±0.05 patients and 0.37±0.06 healthy). In addition, the total number of "broken egg", "tongue", "perinuclear vacuole", "karyopyknosis" type aberrations was 5.8 ± 0.1 before treatment (2.31 ± 0.1 in the control group).

Thus, it is known from the indicators of laboratory studies that psychoemotional disorders play an important role in provoking the initial occurrence of OLP or in aggravating the existing disease. A complex treatment based on the correction of psichoemotional profiles of patients can give effective results.

Concept of heuristic diagnosis and effective treatment algorithm of OLP disease.

Heuristics is a way of thinking or a decision-making concept that refers to the development of a set of verification measures, the logical analysis of mutually exclusive and affirmative arguments.

Heuristic inference in medical diagnostics starts from practical observations and gives great importance to medical statistics.

Heuristics, being the art of making judgments based on factual material, making conclusions and making decisions, is a tool that paves the way for the involvement of computer algorithms in medical diagnostics as the ability to widely use the advantages that these factors can bring. In this regard, the development of the heuristic inference methodology seems to be very promising in the complex treatment of OLP keratoses.

Description of information related to clinical examination, laboratory research, disease development and doctor's appointment in a branched block diagram format

In the current period, the use of demonstrative tools, which include the diversity of the clinical picture of diseases, examination, diagnosis and decision-making algorithm is more and more justified as a trend. From this point of view, the search for a demonstrative method to comprehensively reflect the clinical picture of oral lichen planus which is the most problematic for both diagnosis and treatment among oral mucous membrane diseases diseases, reflects the natural tendency that we have set before ourselves as our goal.

In the fields of logical analysis and decision-making science, objective indicators and the effect that can be obtained from the composition of the logical judgment of the responsible decision-maker are given important advantages. Also, if empirical testing is also involved in this logical analysis (of course, within the framework accepted as an official recommendation), for example, if the examination phase is accompanied by means such as medication and emotional influence, this direction will contain important advantages.

It should be noted that the form of description in the block diagram format is also the most convenient form of analysis for drawing logical conclusions.

Block-schemes reflect, first of all, the recording of facts as primary information, the expression of the system of conditions subordinated to the purpose of the analysis, the branching that should take place in the block-scheme depending on whether the conditions are met or not.

If there is no branching in the representational form of the block-scheme, then such representational form will only have the essence of an information archive and will not have a decisive essence in logical analysis, that is, in decision-making for diagnosis.

Explanation of the diagnosis-treatment algorithm of oral lichen planus based on the concept of heuristic research

In the functional scheme that we have compiled, the types of logically exhausted activities or the results obtained for the corresponding stages are shown with rectangles. Conditional transitions marked with a rhombus indicate appointments aimed at a new stage - medical examination or testing, which are directly subject to logical results (Chart 1). Thus, in scheme 1, blocks 1, 2, and 3 each reflect block 4, i.e., the objective factors underlying the primary diagnostic result. 5 logical transition directly refers to short-term medical supervision and examination results. Determining a number of classic types that manifest themselves in the course of the disease is reflected in block 6, after which, naturally, remediation, hygiene and, if there are local traumas, measures are put forward to eliminate them (block 7). Of course, the application of examination and treatment methods in this direction can justify itself only in cases where there are no signs of complications.

The detection of signs of complications requires a cardinal change in the direction of examination and treatment, which is why the 5th block takes a superior position as the main block responsible for determining the direction of treatment.

In all cases where there is a complication, that is, in exudative-hyperemic forms (block 9-4), or in erosive ulcerative complications(block 9-2, 9-3), as well as in bullous and hyperkeratotic variants, the treatment involves resorting to a number of other identification procedures. The point is that different situations require different approaches regarding whether or not there is a suspicion of transformation.

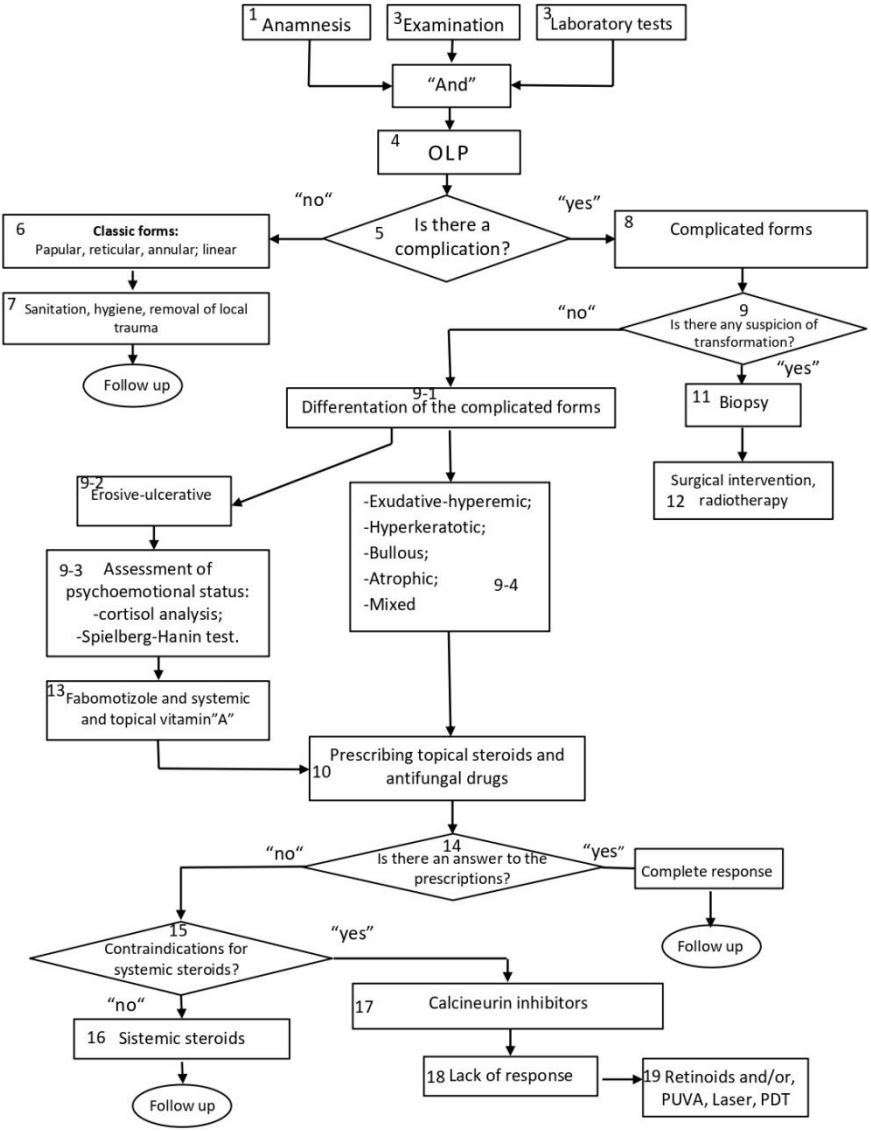

Chart 1. A heuristic diagnosis-treatment algorithm designed taking into account the individual course of various clinical variants of OLP

Absence of suspicion of transformation means starting the treatment process immediately, which prioritizes the doctor's appointments indicated in block 10, including the strategy of applying local steroids and antifungal drugs. The other direction will require a biopsy and, if necessary, surgical intervention and radiotherapy.

Another block, which plays the role of the main stage in the course and treatment of the disease, is related to the results of repeated examinations after the appointment of anxiolytic drugs. Thus, the presence of a positive response to the mentioned appointments means keeping the disease under control, which is the basis for contentment with general control therapy due to the absence of more complicated complications.

Otherwise, the treatment strategy provided in blocks 15, 16 and 17 is waiting for its corresponding measures to be taken.

Among these measures, as is known, the administration of systemic steroids and subsequent monitoring in the absence of contraindications to the administration of systemic steroids, and in other cases the administration of topical tacrolimus and retinoids and PUVA in the absence of response are suggested.

Thus, the implementation of the diagnostic-treatment strategy according to the indicated algorithm leaves no room for doubt that it is important for information in terms of both the effectiveness arising from the systematic approach to treatment and the registration of the dynamics of the disease.

Peculiarities of using the heuristic diagnosis-treatment algorithm in the form of a block diagram andsome recommendations

The concept of heuristic diagnosis and treatment that we have proposed in connection with a specific disease, that is, OLP, is clearly of a methodological nature for medical practice in general. In other words, the embodiment of the system in the form of block diagrams, which combines the manifestation, symptomatology and development dynamics of the disease, treatment strategy options with logic and objective indicators, is not only related to a narrow diagnosis, but it is evident that it

should cover a wider group of diseases. It is in this respect that the block diagram related to OLP is not limited to a specific diagnostic boundary as an open system.

It should be noted that our initial proposal in this field was to develop a system based on a heuristic algorithm, so that it could primarily serve as a memory-methodical tool for the doctor.Personally, the specific results of our research constitute a specific branch of that block-scheme, which does not limit other directions in any way.

On the other hand, another aspect that specifically emphasizes the openness of the system is manifested in the regular expansion of medical information about the disease. Extensions that serve to improve theoretical and practical knowledge and treatment methods in this field, of course, should be reflected in the block diagram, and in this regard, the effectiveness of system technical tools at the level of a computerized information system cannot be doubted.

It is known that the statistical analysis of medical information is always relevant as a necessary issue, and it will always be loyal to such generalizations, which are carried out in the form of block diagrams at higher levels, from the medical institution to the medical-biological scientific institutions. In this regard, the consideration of these arguments during the design of block diagrams can directly affect the quality of the produced material.

Currently, computerized decision-making systems are widespread in the study of biological systems, as well as in many areas of science.

The more advanced systems in this field refer to computer logic algebra and information theory. Undoubtedly, as the development in this field increases, such information technologies as a computerized cybernetic system help to make optimal decisions. Of course, this applies to both diagnosis and treatment.

The modern cybernetic system that supports the doctor's decision-making suggests the optimal treatment decision, but the "last word" still rests with the decision-maker - the doctor. Of course, this factor should always be taken into account when designing and using the diagnostic-treatment heuristic block-scheme.

It should be noted that treatment decision-making based on a heuristic algorithm does not go beyond the scope of what we are looking at: that is, testing appointments, analysis of facts, logical judgment, etc. it does not mean the cybernetic system, but only the intellectual activity of the treating doctor. The doctor only improves the conditions of individual thinking by using the possibilities of computer information collection. However, in addition to this, we should also note that the systematization of the information collected in the direction of examination and diagnosis in the form of a block diagram will undoubtedly show its effectiveness as a positive factor in many directions of the doctor's activity, including treatment decision-making.

Statistical analysis reflecting treatment implementation and outcomes

Clinical indicators of OMM condition before treatment and during treatment dynamics are shown in chart 2. In the dynamics of treatment, it is possible to make judgments about the positive dynamics in terms of the presence of objective signs such as improvement of mood, weakening of pain during food intake, reduction of the sensation of "tightening" in the mouth, reduction of swelling and hyperemia, and removal of fibrinous plaque on erosive-ulcers.

However, if we look at the dynamics of complex treatment, on the 15th day of treatment, the inflammation area was on average 83.5±5.5 mm², and the erosion area was -57.3±0.5mm², which significantly differed from the analogous indicators in other groups ($p<0.05$).

After 1 month of complex treatment, positive dynamics were observed in 8 (53.3%) patients, the erosive-ulcerative form transformed into a typical form. On average, in the patient group, the inflammation area was 65.5±5.2mm2, the erosion area was 25.6±0.8mm2, ABSQRI was 2.7%.

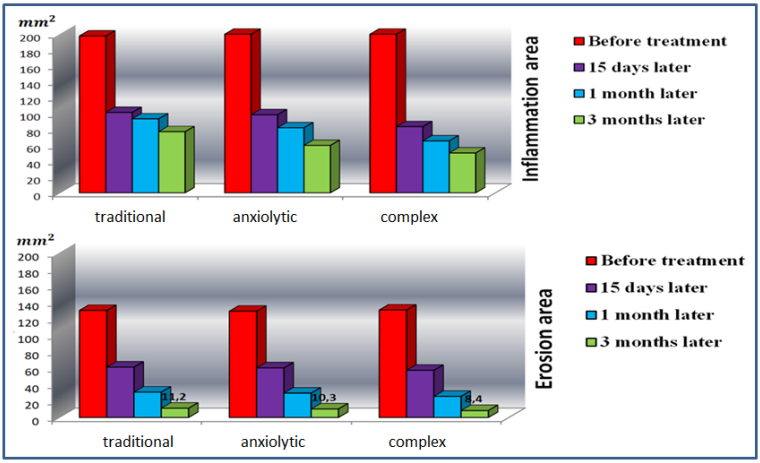

Chart 2. Dynamics of the clinical picture against the background of traditional, anxiolytic and complex therapy

During the 3-month treatment and follow-up period, no recurrences of erosion were noted in this group.

After 9 months, complications occurred in 3(%) patients. Fine erosions were noted in the mucous membrane of the oral cavity. The remission period was 8.7±0.1 months on average.

The addition of an anxiolytic drug and local vitamin A with regenerating, anti-inflammatory and antioxidant effects to the treatment scheme proves the appropriateness of the complex treatment method in the treatment of the erosive-ulcerative form of OLP.

In the dynamics of treatment of patients with OLP, in the indicators of RA and IA, despite the inclusion of sedative therapy (infusion of Valeriana , motherwort) in the traditional treatment, a high level of anxiety was maintained in the third month of treatment (RA-39.2±2.3 and IA-42.5±2.4). From this, it can be concluded that traditional treatment does not lead to intensive overcoming of psychoemotional disorders of patients with OLP.

Our results show that there is a significant improvement in the indicators of RA and IA in patients who received anxiolytic drugs compared to patients who received sedative treatment. So, if we look at

the 3rd month of treatment, the level of RA decreased from 42.6±2.4 to 34.8±2.3. This indicator decreased from 46.7 ± 2.8 to 35.4 ± 2.1 at the IA level.

Thus, as a result of the effect of anxiolytic drugs, it is clear that the psychoemotional conditions of patients with OLP have improved, and the results obtained for RA and IA prove the adequacy of the treatment.

We have studied IL-1β, IL-2 and γ-IFN in saliva in order to study the effectiveness of our treatment (Table 1).

Table 1

The state of the level of cytokines and cortisol hormone in the saliva of patients with OLP during treatment dynamics (M±m)

Indicatos	Practicly healthy individuals (n=10)	1st group (n=15)		2 nd group (n=15)		3 rd group (n=15)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
İL-1β, pq/ml	45,2±4,8	57,8±1,5^	55,8±1,4^	57,8±1,5^	55,7±1,3	58,4±1,4^	51,6±1,1*
İL-2, pq/ml	13,6±3,3	26,2±0,6	23,9±0,5*^	27,1±0,6^	23,2±0,4*^	27,1±0,6^	19,8±0,3*
İFN-γ pq/ml	8,8±0,8	14,3±0,6^	13,2±0,5^	14,5±0,6^	13,1±0,5^	15,0±0,7^	10,7±0,4*^
Cortisol nmol/l	17,1±0,6	25,2±0,8^	22,2±0,8^*	25.7±0,8^	20,3±0,7^*	26,3±0,8^	19,2±0,5^

*- Statistically significant differences compared to pre-treatment values

^- Statistically significant differences compared to the practically healthy

As a result of the treatments, the increased level of IL-1β in the saliva of all 3 groups of patients during the active phase of the disease decreased by 3.4% in the 1st group of patients, 5.4% in the 2nd group of patients, and 11.7% in the 3rd group of patients has been observed.

After the treatment, the level of IL-2 decreased in all 3 groups of patients (table 1). 1st group patients - 8.8%, 2nd group patients - 14.4%, 3rd group patients - 27.8%.

Positive dynamics also occurred in the level of γ-interferon in saliva. After treatment, there was a significant decrease in the level of γ-IFN, which was more pronounced in group 3 (10.7±0.4 pg/ml). However, this indicator was 1.2 times higher than the control value ($p<0.05$).

After treatment, against the background of clinical remission, laboratory indicators demonstrated an inflammatory reaction.

Thus, the complex treatment allows to obtain a positive result in the dynamics of the cytokines we are investigating, but when the treatment ends, a high level of mediators is maintained.

The changes we discovered allow us to recommend local immunocorrection in the treatment of OLP along with pathogenetic treatment in those patients.

Positive dynamics occurred in the level of cortisol hormone in patients' saliva.

After the treatment, there was a significant decrease in the level of cortisol, which was more evident in group 3 (19.2±0.5 nmol/l) (Chart 3).

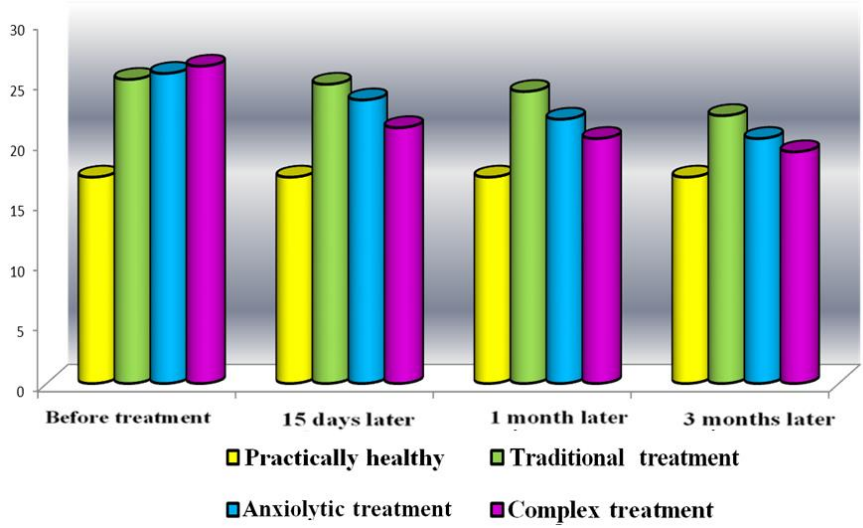

Chart 3. Dynamics of cortisol indicators in patients with OLP against the background of different treatments

Thus, the level of stress-hormone cortisol in the saliva of patients with OLP before treatment is high. Traditional treatment reduces cortisol levels. After the application of the complex treatment scheme that we have proposed, the level of corizol in the saliva of patients with OLP is significantly reduced.

It is known from the percentage indicators of MAR- a non-specific immunity indicator, during the microscopy of the buccal epithelium of patients with OLP, that in the 3rd month of the complex treatment with local and systemic use of vitamin "A" the number of epitheliocytes of categories I and II compared to the indicators before the treatment was 2, 8 and 1.8 times decrease, and a 1.2 and 1.3 times statistically significant increase in the number of category III and IV epitheliocytes (Table 2).

Table 2

Indicators of EAA in the buccal epithelium of patients with OLP in the course of treatment (%) (M±m)

Categories	1st group (n=15)		2nd group (n=15)		3rd group (n=15)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	
I	8,7±0,5	5,6±0,5*	9,7±0,9	7,1±0,7*	10,4±0,7	3,7±0,3*
II	18.3±0,5	14,8±0,6*	18,5±0,6	15,8±0,5*	19,3±0,6	10,5±0,7*
III	52,8±0,4	57,3±0,4*	53,1±0,4	56,1±0,5*	50,7±0,6	60,4±0,5*
IV	20,1±0,7	22,4±1,2	19,1±1,1	21±0,9	19,5±1,4	25,4±0,8*

*- Statistically significant differences compared to pre-treatment values

Thus, we have clarified that the oily solution of vitamin "A" used locally and systemically in the complex treatment of OQYD increases the adsorption activity of epitheliocytes. The treatment of OQYD should be carried out comprehensively, and the oil solution of vitamin "A" should be added systemically and locally

During the study of the frequency of occurrence of nuclear abnormalities such as "micronucleus", "broken egg", "tongue", "perinuclear vacuole", "karyopyknosis" in the buccal epithelium of patients with OLP, it was found that the frequency of occurrence of micronucleus-type cytogenetic disorder was high in all groups. , and after treatment, a decrease of these indicators was observed in all 3 groups (respectively - 1.7±0.1%, 1.6±0.09%, 1.1±0.08%).

In the dynamics of treatment, the positive dynamics of "broken egg"-type nuclear aberration in the buccal epithelium of all 3 groups

of patients towards the norm occurred (respectively, 0.26±0.02%, 0.2±0.02%, 0.57±0, 05%).

"Tongue" type anomaly was at a high level before treatment, but after treatment it was -0.1±0.02%, 0.08±0.01%, 0.3±0.03%, respectively (Table 3).

Table 3

The frequency of occurrence of cytogenetic disorders in the buccal epithelium of patients with OLP during treatment dynamics (M±m)

Indicators	Practicaly healthy individuas	1st group (n=15)		2nd group (n=15)		3rd group (n=15)	
		Before treatment	After treatment	Before treatment	After treatment		After treatment
Micronucleus	0,37±0,06	3,44±0,05^	1,7±0,1*^	3,5±0,06^	1,6±0,09*^	3,6±0,05^	1,1±0,08*^
Broken egg	0,32±0,07	0,91±0,08^	0,26±0,02*	0,95±0,08^	0,2±0,02*	1,1±0,09^	0,57±0,05*^
Egg	0,12±0,02	0,37±0,03^	0,1±0,02*	0,5±0,02^	0,08±0.01*	0,57±0,03^	0,3±0,03*^
Perinuclear vacuole	1,5±0,11	1±0,1^	1,19±0,07^	0,9±0,1^	1,4±0,03*	0,96±0,1^	1,47±0,04*
Karyopyknosis	-	0,04±0,01	0,24±0,03*	0,2±0,03	0,26±0,03	0,2±0,04	0,1±0,02
The total number of aberrations	2,31±0,1	5.8±0,1^	3,6±0,09*^	6,1±0,097^	3,6±0,1*^	6,4±0,1^	3,5±0,1*^

*- Statistically significant differences compared to pre-treatment values

^- Statistically significant differences compared to the indicators of practical healthy

During the study of "perinuclear vacuole" and "karyopyknosis"type of nuclear anomalies, we observed an increase in their frequency in groups 1 and 2. We observed 1.1 and 6 times in group 1, 1.5 and 1.3 times in group 2, respectively and 1.5 times increase in perinuclear vacuole type aberration and 2 times decrease in karyopyknosis type in group 3.

Thus, we investigated that after the complex treatment, the level of cell disorders indicative of apoptosis (karyopyknosis) and nuclear destruction (perinuclear vacuole) increased, and the level of cells with cytogenetic disorders (micronuclei and protrusion) decreased. This is explained by the fact that the activation of apoptosis leads to the elimination of cells with cytogenetic disorders.

Studies have shown that complex treatment of patients with OLP leads to a slight decrease in genetically disordered cells and an increase in cells with apoptotic activity, which results in the release of OMM from such aberrant cells.

We have analyzed the relationship between RA and İA indicators and cytogenetic changes in the cells of BE in order to fully and accurately assess the effect of psychoemotional conditions of patients with OLP on their genetic apparatus. Such relationships were found, moreover, they were more clearly expressed before the start of sedative treatment (Chart 4).

As can be seen, RA is positively correlated with the incidence of micronucleated cells (r=0.61 before treatment, r=0.46 after 1 month, r=0.3 after 3 months). Comparison of İA dynamics and nuclear abnormalities revealed that ST interacts with micronuclei of buccal cells (r=0.63 before treatment, r=0.51 after 1 month, r=0.4 after 3 months).

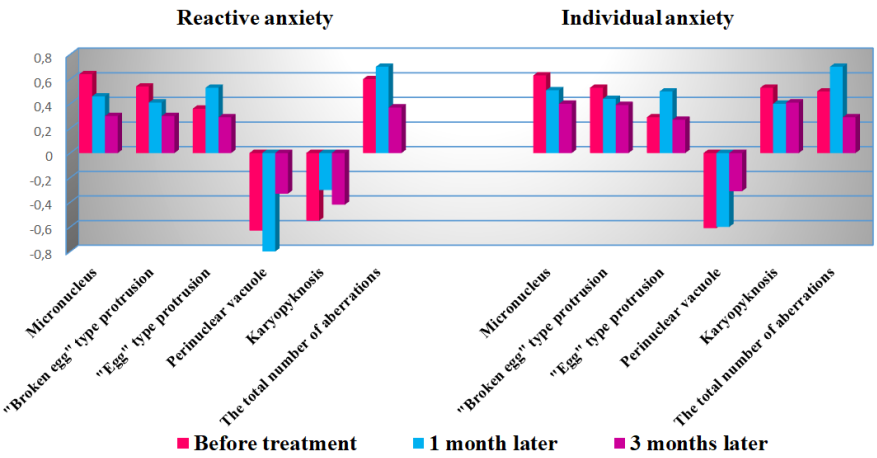

Chart 4. Matrix of correlation coefficients between reactive and personal anxiety and cytogenetic disorders in buccal epithelial cells in the dynamics of treatment of patients with OLP

Before treatment, the "broken egg" type protrusion in the cells of the BE showed a positive correlation with RA and İA (r=0.54; r=0.53, respectively). The occurrence frequency of "tongue"-type nuclear

protrusion is also positively correlated with RA and İA (r=0.36; r=0.29, respectively).

To assess nuclear aberrations associated with nuclear destruction, cells with perinuclear vacuoles and karyopyknosis are considered. The frequency of BE cells with perinuclear vacuoles was negatively correlated with RA and İA (r=-0.63; r=-51, respectively). In addition, nuclear aberrations in BE cells with karyopyknosis are also correlated with RA and İA (r=0.55; r=0.53, respectively).

Thus, a comprehensive examination of patients with OLP and receiving anxiolytics with antimutagenic effect, with the addition of analysis of the level of anxiety and abnormal cells of BE, showed that this drug is able to have a statistically significant effect on the frequency of abnormal nuclei of BE. The results of the study indicate the prospective use of this drug for the purpose of antistress and antimutagenic treatment of patients with OLP.

CONCLUSIONS

1. According to the results of the retrospective analysis of archival materials, OLP was observed in 26% of cases of diseases of the oral mucous membrane. The frequency of occurrence of aggravated forms was 1.3 times higher than other forms. During 2016-2021, the erosive-ulcer form of the disease was 22.7% among other forms [1, 2, 4, 5, 6, 12].
2. Comparison of anxiety-fear disorders of patients examined on the basis of the medical card prepared by us with healthy individuals, in them reactive anxiety is 1.4 times ($p<0.05$) and personal anxiety is 1.7 times ($p<0.05$), cortisol level is 1, 3 times ($p<0.05$) superior, and this reflects the essence of the mechanism of development of the pathological process in oral mucous during OLP and is an objective indicator for the selection of the treatment to be carried out [3, 10, 24].When comparing the cytogenetic abnormalities in the buccal epithelium of patients with OLP with healthy individuals, the nuclear anomaly of "micronucleus" type - 9 times more, "broken

egg" type - 2.8 times more, "tongue" type - 3 times more, "perinuclear vacuole" type - detected 1.5 times less [3, 8, 10,15,24].

3. The proposed complex treatment (fabomotizole + vitamin A) was determined to increase the regeneration index of the oral mucosa by 3.5 times ($p<0.05$), leading to faster epithelization of erosions and reduction of the inflammation area and prolongation of remission period by 5.8±0.1 months compared to the group that received the conventional treatment scheme [7, 19, 24].
4. Complex therapy with the use of anxiolytics and antioxidants in the dynamics of treatment lead to a decrease anxiety disorders (reactive anxiety-1.4 times, personal anxiety-1.5 times) and cortisol level ((1.3 times) ($p<0.05$)) [7, 14, 20].
5. Anxiolytic with antimutagenic properties and antioxidant reduced the overall level of aberration in the nuclei of buccal epithelial cells by 2.5 times compared to traditional treatment.The level of inflammatory cytokines - IL-1β and IL-2 - 1.1 times ($p<0.05$), IFN-γ -1.4 times ($p<0, 05$) decreased, and AAE increased by 1.2 and 1.3 times ($p<0.05$), respectively, for III and IV categories, in the dynamics of complex treatment of patients with ulserative-erozive form of OLP, which manifested itself with the reduction of inflammation and the increase of the activity of local immunity [14, 17, 18, 25, 26].
6. A block diagram of the diagnostic-treatment algorithm, which allows for differential diagnosis and individual therapy of various forms of OLP, has been developed [27].

PRACTICAL RECOMMENDATIONS

1. It is important to prescribe an anxiolytic to erosive-ulcerative form of the OLP patient with increased anxiety-phobic disorders according to the Spielberg-Hanin scale and elevated levels of cortisol
2. Complicated therapy is recommended for patients with OLP: Cytoprotective, antimutagenic, antiteratogenic Afobazol anxiolytic 10 mg 3 times a day for 2 months and antioxidant

vitamin "A" (3.4% retinol acetate) 10 drops 2 times a day at a dose of 100000 IU/ml systemically and and 3 times a day in the form of an application to the injured area locally for a period of 2 months is recommended.

3. The methodical resours called "complex treatment algorithm based on the correction of the psychological profile of patients with oral lichen planus" can be safely applied in the complex rehabilitation of such patients.
4. The individual examination card prepared for dental patients provides an opportunity to visually assess the dental status and clinical condition in the dynamics of treatment during an outpatient examination.
5. The block diagram of the heuristic diagnosis-treatment algorithm developed by us can be successfully applied because it allows the doctor to make logical judgments by taking into account all possible situations in the diagnosis and treatment of OLP, and thus achieves high results in the treatment.

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LIST OF ABBREVATIONS

ICD - the International Classification of Diseases;
LP – lichen planus;
OLP – oral lichen planus;
OM - oral mucosa;
IA – individual anxiety;
RA – reactive anxieth;
IL-1β – interleukin-1β;
IL-2 – interleukin-2;
IFN - interferon;
Th – T helper cells;
AAE - adsorption activity of epitheliocytes;
AFD - anxiety-phobic disorders;
RIOM - regeneration index of the oral mucosa;
PUVA - P-psoralen; UVA- ultraviolet A;
BE - buccal epithelium.

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