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## Tuberculous periodontitis: clinical-laboratory and epidemiological aspects

*To the present day, tuberculous periodontitis is not diagnosed and not present in the classification of tuberculosis. Its microbiological diagnostics is the most complicated as it is performed by investigating small quantities of paucibacillary specimens. The purpose of work was defining the significance of mycobacterial population variability forms in the clinical picture and epidemiology of tuberculous periodontitis. Comparative analysis of clinical and epidemiological features of tuberculous periodontitis was performed in two groups of patients aged 20 to 70 years over different observation periods from 1980 till 2012. Group A was composed of 258 patients who were observed from 1980 till 1990, and Group B consisted of 250 patients who were examined from 2005 till 2012. Peridental focal points of infection in chronic forms of tuberculous periodontitis were used as the material for the advanced microbiological and pathohistological examination. It has been established that in Group A, peridental focal points of infection serve as a reservoir for persisting mycobacteria. The main form of such mycobacteria are unstable L-phase variants which were found in 50% of the investigated samples. We have noticed that the number of focal points of infection in which the changed mycobacteria forms vegetate tends to increase: L-forms (55,2%) and granular forms in Group B. L-form transformation of mycobacteria and emerging of granular forms is the reason of exacerbations coming up more frequently and persistent course of tuberculous periodontitis. The strains of mycobacteria in peridental focal points of infection susceptible to all antituberculous drugs that were detected 30 years ago has been supplanted by mycobacteria resistant to isoniazid and rifampicin in patients who had not taken antituberculous drugs before. At present, the fact that tuberculous periodontitis in HIV-positive patients can be a prognostic for clinical manifestations of AIDS is a point of interest. The clinical and epidemiological features of tuberculous periodontitis that have been revealed are similar to clinical pathomorphism of extrapulmonary tuberculosis, therefore tuberculous periodontitis can be included in the classification of tuberculosis as a separate nosological entity.*

### INTRODUCTION

This study has certainly become of current interest and taken on great significance in connection with tuberculosis pandemic. Despite the doctors' and scientists' efforts as well as numerous tuberculosis control programs, we cannot expect this dangerous disease will be defeated soon [4,10]. This is connected with aggravation of tuberculosis course concurrent with HIV/AIDS, Mycobacterium tuberculosis bacteria gaining multi-drug resistance to antituberculous drugs as well as the main diagnostics problem – detection of the pathogen in connection with mycobacterial population

diversity [8]. Microbiological diagnostics of extrapulmonary tuberculosis is the most complicated as it is performed by investigating small quantities of paucibacillary specimens. It is likely the reason that such a common form of extrapulmonary tuberculosis as tuberculous periodontitis remains undiagnosed in most observations and is not present in the classification by now.

Multiple peridental focal points of infection having tubercular origin in chronic forms of periodontitis represent one possible variation of extrapulmonary tuberculosis. Peridental focal points of infection develop when M. tuberculosis bacteria get in periodontal tissues through root

canals of destroyed teeth or by hematogenous transmission. A focal point of infection having tubercular genesis (or etiology, or origin) is formed around the tooth root apex in the form of granuloma, cystogranuloma or radiculodental cyst. Such focal points, on the one hand, have some features of tuberculosis of bones and joints and, on the other hand, some features of pulmonary tuberculosis. In apical periodontitis open root canals, like the trachea and bronchi, mediate between periodontal tissues and the ambient and improve aeration of these tissues. The infection enters periodontal tissues from oral cavity as well as vice versa, thus seeding the ambient. The first findings regarding involvement of mycobacteria in the development of specific inflammatory process in periapical tissues and their transformations from one form to another date back to the beginning of the 20<sup>th</sup> century [3].

Taking into account tuberculosis pandemic and common use of antibacterial drugs, we considered it reasonable to analyze the data about variability forms of *M. tuberculosis* bacteria and their susceptibility to antituberculous drugs in cases of tuberculous periodontitis over two periods: from 1980 till 1985 and from 2005 till 2012.

The purpose of work: to define the significance of mycobacterial population variability forms in the clinical picture and epidemiology of tuberculous periodontitis.

## METHODS.

The study was performed using the capacities of dental clinics in the cities of Moscow, Dnepropetrovsk, Simferopol and Odessa. In the period from 1980 till 2010, comparative analysis of clinical and epidemiological features of tuberculous periodontitis was performed in two groups of patients aged 20 to 70 years. The analysis covered different observation periods. Group A was composed of 258 patients who were observed from 1980 till 1985, and Group B consisted of 250 patients who were

examined from 2005 till 2010. The diagnosis of tuberculous periodontitis was verified based on the medical history data and complex clinical-laboratory diagnostics.

Peridental focal points of infection (granulomas, cystogranulomas and radiculodental cysts in chronic forms of tuberculous periodontitis) were used as specimens for microbiological and pathohistological examination. To find *M. tuberculosis* bacteria, the following diagnostic techniques were used:

1) bacterioscopy for *M. tuberculosis* L-forms detection – direct microscopy of smears taken from the peridental focal points of infection specimens stained by Ziehl-Neelsen and with Auramine O as well as by Romanovsky-Giemsa;

2) culture methods with the use of different classical culture media and seeding techniques: Lowenstein-Jensen media and Finn-II, a series of semisolid media for L-form isolating;

3) seeding of the specimens using the method modified by us; it includes the following steps: the specimens – impression smears of peridental focal points of infection – are applied on a narrow microscope slide and treated sparingly with acid, and then the slide is placed in a test tube containing Finn-II medium. The test tube was filled with Shkolnikova medium by two thirds of the glass height, so that the smear would touch the inclined surface of solid medium, and was placed in a thermostat [1];

4) bioassay tests on guinea pigs;

5) immunoenzyme method; 6) biomolecular method using the TB-Biochip microarray system.

355 samples have been analyzed using microbiological (culture) methods – for *M. tuberculosis* and L-forms of *M. tuberculosis*, and 49 samples have been analyzed using biomolecular method. Microbiological and biomolecular studies were performed in the Division of Laboratory Diagnostics of Moscow Research and Clinical Center for Tuberculosis Control, Moscow Healthcare Department.

Because of complexity of mycobacteria identification, concurrent studies of isolated

cultures were performed in St. Petersburg Scientific Research Institute of Phthisiopulmonology. We used classical methods including bacteriological and biochemical identification as well as immunoenzyme biomolecular method allowing to define the species mycobacteria belong to with higher degree of reliability. Isolation of aerobic and non-sporulating anaerobic bacteria was also done. General structural changes were revealed in histologic specimens stained with hematoxylin and eosine, and distribution of *M. tuberculosis* bacteria in tissues was investigated under staining by Ziehl-Neelsen.

## RESULTS AND THEIR DISCUSSION

Microbiological study of 355 impression smears made from peridental granulomas, cystogranulomas and cysts in 258 apparently healthy persons allowed to detect mycobacteria in 53.7% of cases (when bacterioscopy was used) and did not show positive results when the specimens were seeded on solid egg media. Detection of mycobacteria by bacterioscopic method and their concurrent dormancy on culture media, by analogy with the data found in references, gives evidence of the fact that mycobacteria viability is being reduced [7]. Quantitative aspects of the results of different microbiological diagnostics methods use for detecting mycobacteria in peridental focal points of infection can be found the table below.

Most frequently, mycobacteria were found in the parietal part of the cystoid cavity contents (26.6%). In half of the investigated samples, mycobacteria in such parietal parts were detected in the form of plait-like congestions. Therefore, we can make a conclusion about cord-factor presence yet in the nidus and not in the culture, and, subsequently, about *M. tuberculosis* virulency. In sporadic cases (3.3%), mycobacteria were found in the envelope of cysts or cystogranulomas. In peridental granulomas, mycobacteria were detected in the foci of decay (19%) twice as frequent as in the «quiet» parts (9%).

The maximum quantity of strains – six (12.8%) has been isolated from peridental granulomas tissue homogenate; two strains (2.9%) have been isolated from the exudate leaking out from peridental focal points of infection through the root canal, and one strain (4.5%) has been isolated from the fistulous drainage. It should be particularly noted that *M. tuberculosis* bacteria presence in the exudate leaking out from root canals and fistulous passages is epidemiologically essential as one of the ways of mycobacteria escaping into the ambient and possibly as a source of infection for the people around.

Bacterioscopy of smears in Group B indicated the presence of finely granular acid-fast forms of mycobacteria surrounded by pellucid area in 76% of peridental focal points of infection. Such forms were found 1.5 times more frequently compared to Group A. According to references data, *M. tuberculosis* granular forms are an aggravating factor in lung tuberculosis course [5].

Isolation of mycobacteria with reduced viability made it necessary to use improved bacteriological diagnostic techniques that also include isolation of the changed mycobacteria forms – L-forms.

To investigate small quantities of paucibacillary specimens from peridental focal points of infection, we have developed and introduced a modified seeding method. Under this method, the specimens in the form of smears or impression smears taken from the most infected parts of focal point of infection, i. e. cyst and cystoid cavity content as well as exudate from root canals and fistulas, was applied on narrow microscope slides. As a result of the study performed, 28 mycobacteria cultures have been isolated; in 57.8% of cases mycobacteria microcolony growth on narrow microscope slides has been noticed that allows to ascertain the presence of viable mycobacteria population in peridental focal points of infection.

Mycobacterial populations were mostly composed of L-forms found by bacterioscopy in more than 90% of investigated samples.

To identify mycobacteria, classical methods including bacteriological and biochemical identification as well as immunoenzyme method were used, and in Group B, the test system for *M. tuberculosis* detection by hybridization method with fluorescence imaging on the biological microarray system («TB-BIOCHIP») was employed [9]. These methods allowed to define what species mycobacteria belong to with higher degree of reliability. When 49 specimens taken from the peridental focal points of infection were investigated by biomolecular method, in nine cases (18.4%) *M. tuberculosis* bacteria have been identified and their drug susceptibility has been defined [6].

18 out of 28 isolated strains were analyzed in the microbiological and immunoenzyme studies from different points of view in order to identify them. The remaining 10 strains showed poor growth and died out in attempting to subculture them.

The remaining 14 out of 18 investigated strains had primarily orange pigment with different gradations; based on this characteristic, they were assigned to scotochromogenous bacteria under Runyon classification. Further identification also did not allow to assign any of the investigated strains to one or other classification group.

The results we have obtained while studying biochemical properties of the isolated mycobacteria together with the available data

provided by other researchers [2,7] suggest that these mycobacteria are revertants of *M. tuberculosis* bacteria.

The fact that the isolated mycobacteria are revertants of *M. tuberculosis* L-forms is indirectly proven by the results of defining mycobacteria drug susceptibility to 10 antituberculous drugs: all the strains of *M. tuberculosis* isolated by us show significant susceptibility to the first-line and second-line drugs, while the most nontuberculous mycobacteria are resistant to all the antituberculous drugs.

Identification of the obtained mycobacteria by immunoenzyme method allowed to find *M. tuberculosis* antigens of human type in 7 out of 18 cultures (38.9%), *M. fortuitum* antigens in 5 cultures (27.8%), and antigens of other atypical mycobacteria in 6 cultures (33.3%).

*M. tuberculosis* bacteria search using immunoenzyme method in 80 tissue samples from peridental granulomas and biomolecular method in 20 samples taken from peridental focal points of infection have not yielded positive results.

Productive tubercular process of the limited extent was noted in liver, spleen, kidneys and lungs of the guinea pigs and mice infected with typical acid-fast *M. tuberculosis* bacteria of human type isolated from peridental focal points of infection. The data obtained give evidence of reduced mycobacteria virulency more apparent in the changed mycobacteria.

**Table. Detection rate for *M. tuberculosis* bacteria and their L-forms in the specimens taken from peridental focal points of infection in Group A using different techniques of microbiological diagnostics**

Diagnostic techniques	Sample number	Cultures isolated:			
		M. tuberculosis, abs. (%)			L-forms
		typical	changed	microcolonies	
Bacterioscopy	355	84 (23.6%)	107 (30.1%)	-	321 (90.4%)
Seeding on solid media	140	No growth	No growth	No growth	-
Seeding on semisolid media	258	-	-	-	185 (71.7%)
Seeding by a modified method	417	4 (0.9%)	24 (5.7%)	241 (57.8%)	298 (71.4%)
Bioassay tests on guinea pigs and mice of the CBA strain	65	30 (46.1%)	15 (23.1%)	-	20 (30.8%)
Immunoenzyme method	18	7 (38.9%)	11 (61.1%)	-	-



Seeding of 417 samples taken from periodontal focal points of infection helped to reveal mycobacteria L-forms in the most cases (71.4%) along with mycobacteria. L-form population was heterogenous in its biological properties and varied in balancing degree. In the most observations made by us (52.2%), L-forms that had reversed into *M. tuberculosis* bacterial forms on culture media were assigned to unstable forms.

While performing bioassay test by injecting L-forms to guinea pigs the animals show tubercular inflammation of the limited extent similar to the one when *M. tuberculosis* bacteria with reduced virulency were injected, as well as paraspecific and non-specific changes like immunoprotective reaction.

The data available in references together with the results of the studies performed by the authors extend traditional assumptions about periodontal focal points of infection microflora by the established fact about mycobacteria and their changed forms involvement in periodontal focal points of infection emerging and development.

Based on cumulative results of the microbiological study performed in 1980–1990, it has been established that in periodontal focal points of infection in people apparently healthy in terms of tuberculosis and having chronic periodontitis forms, *M. tuberculosis* bacteria persist in 20% of cases [1].

The results of the performed microbiological study formed the basis for studying clinical symptoms and signs as well as course of apical periodontitis depending on the mycobacterial population structure in periodontal focal points of infection.

Group 1A included 44 (17,1%) patients; in specimens taken from their periodontal focal points of infection, bacterial forms and L-forms of mycobacteria have been detected. Group 2A included 129 (50%) persons with unstable L-forms found in periodontal focal points of infection. Group 3A was composed of 85 (32,9%) patients; in specimens taken from their periodontal focal points of infection few

stable L-forms of mycobacteria have been found.

Aggravated course with severe symptoms has been noted in 18.2% of patients in Group 1A; 5,9 times less frequently in patients from Group 2A and was not noted at all in patients from Group 3A. In Group 1A, aggravated course of the process was associated with fistula presence more frequently (Fig.1). It is known that tuberculous fistula act as a drain channel for purulence in tuberculous lesions of spine, hipbones and in other forms of tuberculosis [11]. *M. tuberculosis* bacteria discharging from fistulous passage (Fig.2) escape into the ambient and play significant part in epidemiology of the pathogen. Most patients have fistula with one external opening.

However, complex fistula with branches may have several external openings (Fig. 5). Appearance and nature of purulent fistula discharge can often help to suspect the specific process in periodontal tissues while performing initial oral exam. Specific features of this process are: 1) fluid, almost colorless purulence or yellowish exudate leaking out in a quite considerable amount; 2) slender, dryish tyroid inclusions in exudate; 3) pale, thinning mucosa with cyanotic shade in the fistula opening area. In patients from Group 1, periodontal focal points of infection of medium (34.1%) and large sizes (65.9%) have been revealed, and large periodontal focal points of infection were encountered 1.9 times more frequently compared



Fig. 1. Fistula on the gum with several external apertures

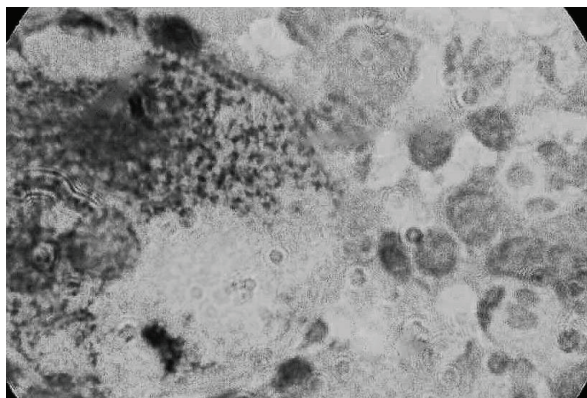


Fig .2. Microcolony of mycobacteria tuberculosis in the liquid content of fistula passage

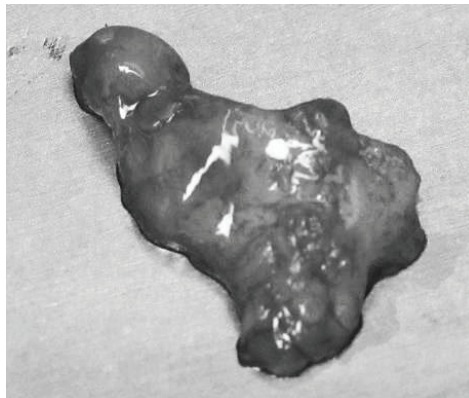


Fig .3. Multifocal periodontal focus of infection – cystic granuloma, received in resection of apex of dental root

to medium ones. X-ray images in persons having asymptomatic course of periodontal focal points of infection showed blurred focal point contours (27.3%) that speak for latent progressing of the inflammatory process in periodontal tissues. In 15.9% of cases, osteosclerosis of bone tissue surrounding periodontal focal points of infection is caused by purulent exudate and microabscesses, as further morphologic studies have shown. In 10 out 109 (9.2%) large periodontal focal points of infection (more than 0.5 cm in diameter) multifocal points of infection were observed (Fig.3). The central focal point of infection and «growth zone» differed not only in their form, shade intensity and contour sharpness on X-ray images, but also in their histological structure: the central focal point of infection is a cystoid cavity, and the growth zone is similar to a simple granuloma in its structure (Fig.4) . In 5% of the investigated samples the central focal point of infection was similar to cavitary lesion, and histobacterioscopy helped to reveal acid-fast *M. tuberculosis* bacteria in it.

Mixed mycobacteria population vegetation has been established primarily in young persons (20–29 years old) and patients older than 50 years. According to our findings, periodontal focal points of infection with mycobacteria and L-forms in young people have been found in 17.1% of cases, and in 60-year-old and older patients – in 24.3% of cases.

Some authors who had studied mycobacterial populations in different tuberculosis forms in older age groups note a potential hazard of tuberculosis reactivation in connection with mycobacteria presence concurrent with

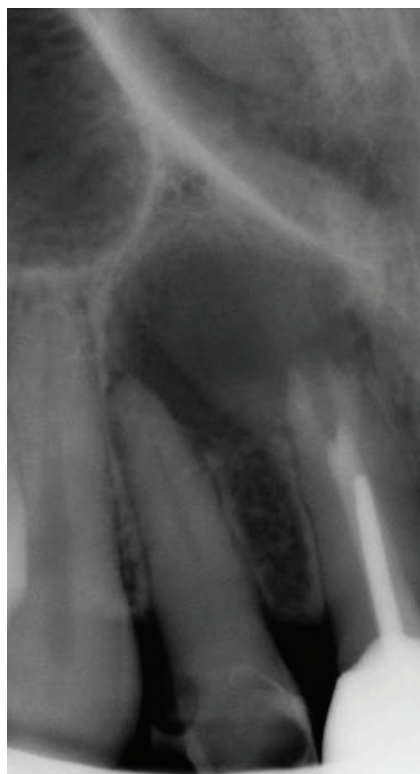


Fig . 4. X-ray picture of radicular cyst in tuberculosis periodontitis

lowered resistance of the macroorganism [2]. It should be marked that in periodontitis exacerbations anaerobic microorganisms were isolated from peridental focal points of infection alongside with mycobacteria. The findings of the researchers having studied associated microflora in tuberculosis show that mycobacteria in association with anaerobe bacteria cause peracute progressing of inflammatory process with extensive necrotic patches forming [12]. The results comparison of the peridental focal points of infection integrated study allowed us to make a similar conclusion.

Clinical picture of periodontitis when unstable L-forms (Group 2) were isolated from peridental focal points of infection was marked by unstable course just like the population itself. The early period of the disease was mostly hidden with undulating course and remission and exacerbation periods. Persistent progressing of peridental focal points of infection with local manifestations of different degree can be associated not only with unstable mycobacteria L-forms presence, but also with anaerobes most frequently isolated along with L-forms.

Intoxication symptoms at the time of exacerbation, especially in case of multiple peridental focal points of infection, are characterized by faintness, temperature rise, transient joint pain and headache. Face skin is pale with yellowish and grayish tints. Weight loss is observed in some patients.

In teenagers with conversion of tubercular tests, tuberculous periodontitis often progresses in intact teeth and soon exacerbates with periostitis or an abscess. A large volume of *M. tuberculosis* bacteria is found in the necrotizing pulp of such teeth.

On examination: the tooth is more often destroyed; a crown of the tooth has a changed color ranging from light grey to dark grey. On probing: the cavity of decay is opened into the dental cavity. Vertical percussion of the tooth is painful; the mucosa around the causative tooth is edematous and reddened. Vasoparesis symptom is positive.

During histological examination of peridental focal points of infection in patients of this group areas of subtle tubercular inflammation were revealed. In case of such subtle inflammation architectonics of the tubercle is preserved, but the composition of cells specific for tuberculosis is lost, i. e. signs of chronic productive nonspecific inflammation emerge.

Therefore, peridental focal points of infection serve as a reservoir for persisting mycobacteria with predominant persistence form – unstable L-phase variants of *M. tuberculosis* bacteria. Studying *M. tuberculosis* bacteria variability in tuberculous periodontitis over the period from 1980 till 2012 shows tendency to increasing the number of peridental focal points of infection in which changed mycobacteria forms persist, i. e. L-forms and granular forms.

It has been revealed that L-form transformation of *M. tuberculosis* bacteria and emerging of granular forms is the reason of exacerbations coming up more frequently and persistent course of tuberculous periodontitis. Presence of fistulas is important both from diagnostic and epidemiological points of view. Massive and diversified *M. tuberculosis* bacteria population in tooth root canals and fistula content can become a source of tuberculous infection dissemination and its propagation in the ambient.

It has been found out that the strains of mycobacteria in peridental focal points of infection susceptible to all antituberculous drugs that were detected 30 years ago has been supplanted by multi-drug resistant mycobacteria.

At present, the fact that tuberculous periodontal disease in HIV-positive patients can be a prognostic for clinical manifestations of AIDS is also a point of interest.

The clinical and epidemiological features of tuberculous periodontitis that have been revealed are similar to clinical pathomorphism of extrapulmonary tuberculosis, therefore tuberculous periodontitis should be included in the classification of tuberculosis as a separate nosological entity.



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### **ТУБЕРКУЛЬОЗНИЙ ПЕРІОДОНТИТ: КЛІНІКО-ЛАБОРАТОРНІ ТА ЕПІДЕМІОЛО- ГІЧНІ АСПЕКТИ**

Туберкульозний періодонтит дотепер залишається не діагностованим і відсутнім в класифікації туберкульозу. Мікробіологічна діагностика його є найбільш складною, тому що здійснюється шляхом дослідження незначної кількості олігобацилярного матеріалу. Мета роботи полягала у вивченні значення змінених форм мікобактеріальної популяції в клініці та епідеміології туберкульозного періодонтиту. Був проведений порівняльний аналіз клініко-епідеміологічних особливостей туберкульозного періодонтиту в двох групах пацієнтів у віці 20-70 років у різні періоди спостереження з 1980 по 2012 р. Групу А склали 258 пацієнтів, спостереження яких проходило з 1980 по 1990 рік, група В була представлена 250 пацієнтами, обстеження яких проходило з 2005 по 2012 рік. Матеріалом розширеного мікробіологічного та патогістологічного дослідження були навколорубні вогнища інфекції (НВІ) при хронічних формах туберкульозного періодонтиту. Встановлено, що в групі А навколорубні вогнища інфекції є резервуаром персистуючих мікобактерій, основна форма яких - нестабільні Л-варіанти, виявлені в 50% спостережень. Відзначено зберігання тенденції збільшення кількості НВІ, в яких вегетують змінені форми мікобактерій: Л-форми (55,2%) і зернисті форми в групі В. Л-трансформація мікобактерій і поява зернистих форм призводить до більш частих загострень і прогресуючого перебігу туберкульозного періодонтиту. На зміну медикаментозно-чутливим до всіх протитуберкульозних препаратів штамів мікобактерій в НВІ, що були виявлені 30 років тому, прийшли резистентні до ізоніазиду і рифампіцину мікобактерії у пацієнтів, які не приймали раніше протитуберкульозні препарати. Актуальним нині є той факт, що туберкульозний періодонтит у ВІЛ-інфікованих пацієнтів може бути передвісником клінічних проявів СНІДу. Виявлені клініко-епідеміологічні особливості туберкульозного періодонтиту відображають клінічний патоморфоз позалегеневого туберкульозу, тому туберкульозний періодонтит може бути внесений в класифікацію туберкульозу як окрема нозологічна форма.

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### **ТУБЕРКУЛЕЗНЫЙ ПЕРИОДОНТИТ: КЛИНИКО-ЛАБОРАТОРНЫЕ И ЭПИДЕМИО- ЛОГИЧЕСКИЕ АСПЕКТЫ**

Туберкулезный периодонтит до настоящего времени остается не диагностированным и отсутствует в класси-

фикации туберкулеза. Микробиологическая диагностика его является наиболее сложной, так как осуществляется путём исследования незначительного количества олигобацилярного материала. Цель работы заключалась в определении значения форм изменчивости микобактериальной популяции в клинике и эпидемиологии туберкулезного периодонтита. Был проведен сравнительный анализ клинико-эпидемиологических особенностей туберкулезного периодонтита в двух группах пациентов в возрасте 20-70 лет в различные периоды наблюдения с 1980 по 2012 г. Группу А составили 258 пациентов, наблюдение которых проходило с 1980 по 1990 год, группа В была представлена 250 пациентами, обследование которых проходило с 2005 по 2012 год. Материалом расширенного микробиологического и патогистологического исследования служили околозубные очаги инфекции (ООИ) при хронических формах туберкулезного периодонтита. Установлено, что в группе А околозубные очаги инфекции являются резервуаром персистирующих микобактерий, основная форма которых - нестабильные Л-варианты, обнаружены в 50% наблюдений. Отмечена сохраняющаяся тенденция увеличения количества ООИ, в которых вегетируют измененные формы микобактерий: Л-формы (55,2 %) и зернистые формы в группе В. Л-трансформация микобактерий и появление зернистых форм приводит к более частым обострениям и прогрессирующему течению туберкулезного периодонтита. На смену лекарственно-чувствительным ко всем противотуберкулезным препаратам штаммам микобактерий в ООИ, выявленным 30 лет тому, пришли резистентные к изониазиду и рифампицину микобактерии у пациентов, не принимавших ранее противотуберкулезные препараты. Актуальным в настоящее время является тот факт, что туберкулезный периодонтит у ВИЧ-инфицированных пациентов может являться предвестником клинических проявлений СПИДа. Выявленные клинико-эпидемиологические особенности туберкулезного периодонтита отражают клинический патоморфоз внелёгочного туберкулеза, поэтому туберкулезный периодонтит может быть внесен в классификацию туберкулеза как отдельная нозологическая форма.

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