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**MODERN ASPECTS OF ETIOPATHOGENESIS OF CUTANEOUS
LEISHMANIOSIS**

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Resume

The article presents literature data over the past 30 years on the modern aspects of the etiology and pathogenesis of cutaneous leishmaniasis. The authors analyzed data from modern literary sources about the described natural foci, reservoirs and carriers of the disease. The geographical features of the etiology of cutaneous leishmaniasis in Central Asia, in particular in Uzbekistan, have been deeply studied in recent years.

Keywords: cutaneous leishmaniasis, etiology, pathogenesis, reservoir, carrier, mosquitoes, leishmanioma, ulcers, scars.

**СОВРЕМЕННЫЕ АСПЕКТЫ ЭТИОПАТОГЕНЕЗА КОЖНОГО
ЛЕЙШМАНИОЗА**

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Резюме

В статье представлены литературные данные за последние 30 лет о современных аспектах этиологии и патогенеза кожного лейшманиоза. Авторами были анализированы данные из современных литературных источников об описанных природных очагах, резервуарах и переносчиках заболевания. Были глубоко изучены географические особенности этиологии

кожного лейшманиоза в Центральной Азии, в частности в Узбекистане, за последние годы.

Ключевые слова: кожный лейшманиоз, этиология, патогенез, резервуар, переносчик, москиты, лейшманиома, язвы, рубцы.

ТЕРИ ЛЕЙШМАНИОЗИ ЭТИОПАТОГЕНЕЗИНИНГ ЗАМОНАВИЙ ТАМОЙИЛЛАРИ

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Резюме

Ушбу мақолада сўнги 30 йилдаги тери лейшманиози касаллигининг этиологияси ва патогенези ҳақида замонавий маълумотлар адабиётлардан келтирилган. Муаллифлар замонавий адабиётларда тасвирланган касалликнинг табиий ўчоқлари, резервуарлари ва ташувчилари тўғрисидаги маълумотларни таҳлил қилдилар. Сўнги йилларда Ўрта Осиёда, хусусан, Ўзбекистонда тери лейшманиози этиологиясининг географик хусусиятлари чуқур ўрганилди.

Калит сўзлар: тери лейшманиози, этиология, патогенез, резервуар, ташувчи, паиша, лейшманиома, яралар, чандиқлар.

Relevance

Skin leishmaniasis (Pendinskaya ulcer, cutaneous leishmaniasis of the Old World - Borovsky's disease, cutaneous leishmaniasis of the New World, Ashgabat ulcer) is an endemic vector-borne disease characteristic of countries with a hot and warm semi-desert climate, manifested mainly by skin lesions [10]. The disease develops after a person is bitten by mosquitoes infected with *Leishmania tropica*, and is characterized by skin lesions with the formation of tubercles, nodes, their ulceration and scarring. Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis and causes

skin damage, mainly ulcers, on exposed areas of the body, leaving scars and severe disability for life. Cutaneous leishmaniasis is a favorable form and accounts for 50-75% of all cases of the disease [22]. About 95% of cases of cutaneous leishmaniasis occurs in the countries of the Middle East, Brazil, Peru, in the Mediterranean countries, India, Central Asia, in sub-Saharan Africa, in the central - southern regions of Texas (USA) [26]. Leishmaniasis is endemic in 98 countries around the world, and an estimated 350 million people are at risk of infection. According to WHO estimates, more than 14 million people are infected worldwide, and about 2 million new cases of the disease occur annually [5].

The first reliable description of cutaneous leishmaniasis was made in 1745 by the English physician Pocock, who discovered it among the inhabitants of Syria. In the middle of the 19th century, during the period of colonization of the countries of Asia, Africa, the Middle East, among the military Europeans, the incidence of cutaneous leishmaniasis became widespread, which caused increased attention to its study.

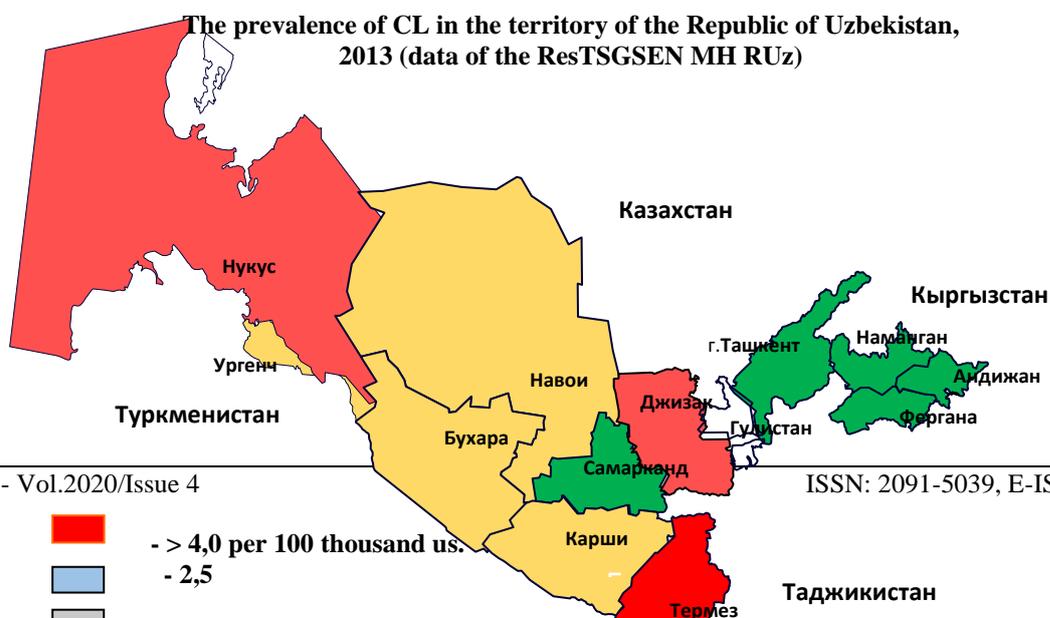
The acquaintance of Russian doctors with cutaneous leishmaniasis is associated with their assignment to work in Central Asia. In 1889, the resident of the Tashkent military hospital P.F. Borovsky was able to find and describe the causative agent of the disease, which the author attributed to the simplest. In 1899, an English doctor, Lieutenant General Sir William Boog Leishman, in smears from the spleen of a patient who died from the tropical disease kala-azar, discovered the causative agent of the disease, and in 1903, simultaneously with the Irish bacteriologist Charles Donovan, he described these parasites [24].

The widespread dissemination of cutaneous leishmaniasis (CL) in Central Asia and the Middle East was reflected in the works of the great scientist, thinker, physician Abu Ali ibn Sino "Canon of Medicine", which described the clinical course of Balkh ulcer, methods of its treatment and for the first time made exclusively an important assumption about the transmission of disease through the bite of a harmful mosquito. This idea of the great compatriot received its experimental confirmation only in the 20-30s of the XX century [27].

In the countries of the Central Asian region, leishmaniasis occurs in Uzbekistan and Turkmenistan, as well as in certain regions of Kazakhstan more often than in other regions [18]. Currently, in this region, visceral and anthroponous cutaneous (urban type) leishmaniasis is practically eliminated, however, zoonotic cutaneous leishmaniasis (ZCL) continues to occupy a certain place in the regional pathology [4]. In Uzbekistan, cutaneous leishmaniasis is one of the most common natural focal diseases and is more common in the form of zoonotic cutaneous leishmaniasis of the second, rural type [29]. Nevertheless, in the regions of the republic (Samarkand, Syrdarya, regions) considered for many decades to be free from cutaneous leishmaniasis in patients, for the first time by the PCR method, *L. tropica*, the causative agent of anthroponous cutaneous leishmaniasis, was identified, and in the Kashkadarya region (Mubarek city) where only PCL cases were reported annually, *L. tropica* was also identified. This indicates the intensification of the spread of anthroponous cutaneous leishmaniasis in the country [13]. In the endemic regions of Uzbekistan (Bukhara, Kashkadarya, Khorezm, Jizzak, Surkhandarya, Karakalpakstan), there is a fairly high prevalence of zoonotic cutaneous leishmaniasis, where dozens of new cases of this disease are registered every year [1]. Thus, according to the Republican Center for State Sanitary and Epidemiological Surveillance of the Ministry of Health of the Republic of Uzbekistan, the largest number of cases of cutaneous leishmaniasis in the republic is recorded in Surkhandarya, Jizzakh regions and the Republic of Karakalpakstan (Fig. 1). The degree of manifestation of epizootics in these territories is different and the morbidity of the population in each of them has its own characteristic features due to the interposition of settlements and natural foci, the degree of contact of the population with foci and the level of the immune layer [15].

This form of cutaneous leishmaniasis with a characteristic localization of the elements of the rash on open skin areas can lead to pronounced cosmetic defects [19]. This, in turn, leads to psycho-emotional discomfort, a decrease in the quality of life and can cause problems associated with the disability of patients for a long time and causing economic damage to the state [35].

Leishmaniasis is caused by protozoan intracellular parasites, which are represented by more than 20 species of Leishmanias. The pathogen is transmitted by female mosquitoes, in whose body the parasites are in flagellated form (promastigotes). Old World leishmaniasis is transmitted by Phlebotomus mosquitoes, while New World leishmaniasis is transmitted by Lutzomyia mosquitoes. Mosquitoes are small in size, allowing them to penetrate standard window screens and even through nets in military helmets. The life span of mosquitoes is 30 days, during the day they rest, they are active from dusk to dawn and fly poorly (no more than 2 m). Mosquito bites can be painless and therefore patients often do not report the insect bite. The situation is aggravated by the fact that mosquitoes do not buzz and therefore do not attract attention. After being bitten by a mosquito, the parasite invades the host's mononuclear phagocytes and transforms into amastigotes (flagellate form). It should not be ruled out that infection with cutaneous leishmaniasis is possible with a needle or syringe prick if these instruments contain infected material. The response to infection depends on the number of pathogens, leishmania strains (macrophage resistant strains have been described) and the person's immune response. It is known that a pronounced Th1 response with the production of IL-2 and IFN- γ leads to a rapid resolution of the infection, with a weak Th1 response or a Th2 response with the production of IL-4 and IL-10, the infection continues to develop, which is observed in diffuse cutaneous leishmaniasis. After a disease, a stable immunity develops to this particular type of Leishmania. Cases of lifelong immunity against all types of Leishmania have been described [18, 33, 34].



(fig. 1)

Thus, the disease is caused by the protozoa of the genus *Leishmania*. the pathogen is transported by mosquitoes of the *Psychodidae* family, the main route of infection is transmissible. According to the doctrine of the natural focus of diseases, developed by academician E.N. Pavlovsky, a natural reservoir of infection with cutaneous leishmaniasis in humans is the rodent gerbil.

It should be pointed out that the natural reservoirs of the GCL causative agent are the great and red-tailed gerbils, and the vectors are mosquitoes (*Phlebotomus papatasi*). The incidence rate of cutaneous leishmaniasis in great gerbils in different foci is in the range of 12.3-98.2%, and in red-tailed gerbils - 9.2-15.2% [15]. На территории Узбекистана выделяются лейшмании трех видов: *L.major*, *L.turanica*, *L.gerbilli* [9]. In humans, the typical course of zoonotic cutaneous leishmaniasis is caused only by *L. major*, but *L. turanica*, as shown by limited studies, can cause abortive dermatosis in humans and subsequently lead to their resistance to *L. major* [25, 31].

It should be emphasized that the nature and type of settlements of natural carriers of the pathogen are changing, and settlement populations of mosquitoes appear [7]. Analysis of the long-term incidence of PCL shows that rises are observed in about 5-7 years and can continue for 2-3 years in a row [29].

Epidemiological studies have shown that cutaneous leishmaniasis is characterized by a certain seasonality. The first patients appear at the end of May, then the incidence increases, reaching its maximum in September-October, and then there is a gradual decline in the incidence, when in December and January there are already isolated patients with cutaneous leishmaniasis, and in these cases, it is usually late who applied

to patients with cutaneous leishmaniasis. The incidence of leishmaniasis rises sharply in June - September. The season of infection is associated with the period of active life of mosquitoes [3].

Human infection occurs during his stay in endemic areas in the summer. The source of infection with urban-type cutaneous leishmaniasis is a sick person. For cutaneous leishmaniasis, an incubation period is characteristic, which ranges from several days to 3-4 weeks, and in rare cases can be even 1-2 months [11, 21].

According to Z.M. Abidova et al. (2016), the age composition of patients with cutaneous leishmaniasis is also gradually changing, if at the end of the last century pediatric patients prevailed, then in recent years, about 75-90% of cases, this is mainly the adult population [1].

CL classification (Fitzpatrick T., 1999):

- cutaneous leishmaniasis of the Old World:
 - anthroponous cutaneous leishmaniasis (urban, dry, late ulcerating), variety - tuberculoid cutaneous leishmaniasis;
 - zoonotic cutaneous leishmaniasis (rural, wet, acutely necrotizing);
- cutaneous leishmaniasis of the New World:
 - cutaneous leishmaniasis of the new world;
 - mucocutaneous leishmaniasis;
 - diffuse cutaneous leishmaniasis;
- visceral leishmaniasis

Because of the geographic "attachment" of pathogens, cutaneous leishmaniasis of the Old World and cutaneous leishmaniasis of the New World are distinguished. Old World leishmaniasis is endemic in Asia, Africa, the Middle East and the Mediterranean. Cutaneous leishmaniasis of the Old World is caused by *L. major* or *L. tropica*, less often *L. infantum*, *L. aethiopica*; in the Mediterranean and Caspian seas, cutaneous leishmaniasis is caused by *L. infantum* and *L. Chagasi* [26].

The causative agents of CL of the New World are leishmania mexicana (Chiclero's ulcer), leishmania amazonensis (Amazonian leishmaniasis), leishmania venezuelensis, leishmania lainsoni, leishmania peruviana (uta), leishmania colombiensis, leishmania guyanensis (forest yaws); mucocutaneous leishmaniasis - leishmania species belonging to the subgenus Viannia: leishmania brasiliensis (espundia), leishmania panamensis, leishmania guyanensis; diffuse cutaneous leishmaniasis - leishmania pifanoi (Venezuela), leishmania amazonensis (Brazil, Haiti island), leishmani amexicana (Haiti island), leishmania aethiopica (Africa); visceral leishmaniasis - leishmania donovani, leishmania infantum, leishmania chagasi.

The clinical form of the disease is determined by the type of pathogen. Different types of Leishmania are characterized by their own reservoirs and geographical distribution (Table 1).

Table 1 - Reservoirs and distribution of Leishmania.

Group	View	Storage tank	Spread
<i>Leishmania donovani</i>	<i>L. donovani</i>	Human	Sudan, Kenya, Tanzania, India
	<i>L. infantum</i>	Dogs, foxes	Mediterranean region
	<i>L. chagasi</i>	Dogs, foxes, possums	Central and South Africa
<i>Leishmania tropica</i>	<i>L. major</i>	Rodents	Arid regions of Africa
	<i>L. tropica</i>	Man, dogs	(Sahara), Central Asia,
	<i>L. aethiopica</i>	Damans	Near East
<i>Leishmania mexicana</i>	<i>L. mexicana</i>	Forest rodents	Eastern Mediterranean,
	<i>L. amazonensis</i>	Forest rodents	Middle East, Central Asia
	<i>L. venezuelensis, pifanoi, garnhami</i>	Unknown	Ethiopia, Kenya, Yemen
	<i>L. braziliensis</i>	Forest rodents	Mexico, Central America

<i>Leishmania</i> (<i>Viannia</i>) <i>braziliensis</i>	<i>L. guyanensis</i>	Sloths, anteaters	South America
	<i>L. panamensis</i>	Sloths	Venezuela
	<i>L. peruviana</i>	Dogs	Central and South America

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In 1940 P.V. Kozhevnikov and N.I. Latyshev identified two forms of cutaneous leishmaniasis: late ulcerating and acutely necrotizing [10,13].

Anthroponous cutaneous leishmaniasis (urban, late ulcerating) is predominantly common in the Mediterranean, the Near and Middle East, in the western part of the Indian subcontinent. The incubation period is from 3 to 9 months. A pea-sized nodule appears at the site of the mosquito bite, after 3-5 months. a dense crust appears on it, covering the erosion, and after 2-8 months. erosion transforms into a superficial ulcer of an irregular shape with a pronounced infiltration at the base. The resolved infiltration leaves behind a pronounced scar - "the seal of Cain". The disease lasts for about a year ("one year old") [10].

Zoonotic cutaneous leishmaniasis (rural, acutely necrotizing) is common in rural oases of desert and semi-desert regions of the Middle East, Central Asia, India, Africa. Rashes are more often located on open areas of the skin: face, neck, arms, legs. In the area of a mosquito bite in 2-4 weeks. a furuncle-like infiltrate appears, ulcerating after 1-2 weeks. A deep painful ulcer is formed with purulent discharge. After 2-3 months. it begins to clear itself of necrotic masses. When resolving, a deep scar also forms. The disease is complicated by lymphangitis and lymphadenitis [10, 22].

There are four main clinical forms of the disease - cutaneous leishmaniasis, mucocutaneous leishmaniasis, diffuse cutaneous leishmaniasis, and visceral leishmaniasis [28].

Clinically, cutaneous leishmaniasis can present with localized, chronic recurrent, diffuse, and acute forms. A localized form of cutaneous leishmaniasis is manifested by papules or nodules that occur at the site of the bite, most often the face and open areas of the body. Over time, the papules / nodules develop into well-circumscribed, painless sores with a purple corolla. The color of the corolla is explained by the destruction of the epidermis and the translucence of the vessels of the dermis. Lymphadenopathy and the presence of satellite tubercles are possible. Ulcers heal with the formation of depressed scars. When localized, a cosmetic defect develops on the face, which leads to serious psychological problems for the patient and is a certain stigma of social disadvantage [2].

It should be noted that an important clinical sign of cutaneous leishmaniasis is leishmaniasis, the number of which is very variable. So, according to A.M. Mukhamedov, on average, there are 11.4 ulcers per patient, according to A.Sh. Vaisov, 4.2 ulcers are recorded in patients with cutaneous leishmaniasis, and according to M.K. Sharipova et al. in 80% of patients with cutaneous leishmaniasis, 1-3 ulcers were detected [6, 17, 29]. An important clinical point is the fact of the localization of leishmaniasis ulcers, depending on the ongoing anthropogenic transformation of the eco-carrier. So, for example, according to studies carried out by Kh. M. Mustafaev and others [16,17], the number of patients with localization of leishmaniasis ulcers on the extremities has significantly increased and localization on the skin of the face has decreased.

Chronic recurrent leishmaniasis is characterized by the appearance of new papules along the periphery of the scars formed after the transferred cutaneous leishmaniasis. This is due to the persistence of single parasites at the sites of infection or, possibly, in the nearest lymph nodes. Cases of chronic recurrent leishmaniasis have been reported in patients receiving immunosuppressive therapy with infliximab (tumor necrosis factor blocker). Chronic recurrent leishmaniasis is caused by *L. tropica* and *L. infantum*. The disease becomes chronic due to the predominance of the Th2 type in the immune response. The cause of diffuse (disseminated) cutaneous leishmaniasis in the

Old World is *L. aethiopica*, and the New World is *L. mexicana*. Diffuse cutaneous leishmaniasis is characterized by painless nodules that progress slowly and can spread to the entire skin, although the preferred sites are the face, ears, knees, and elbows. Some nodules may have a warty surface or resemble xanthomas, keloids. In some patients, the nasopharynx or oral cavity or nasal mucosa is affected without destruction of the nasal septum. Diffuse cutaneous leishmaniasis may present as large, hypopigmented patches, resembling tuberculoid leprosy. Of the rare forms of cutaneous leishmaniasis (up to 5% of cases), the following are described: lupoid, psoriasiform, zosteriform, verrucous, palmar-plantar, chancriform, resembling paronychia, erysipeloid, mycetoma [30,32]. Leishmaniasis should be suspected in every person living / visiting epidemically dangerous regions, since in the case of severe forms of leishmaniasis (visceral), a late diagnosis can be the cause of death of the patient.

The literature data indicate that, despite the obvious successes in the fight against cutaneous leishmaniasis, there is a high probability of local outbreaks of this disease. Despite its long history, the incidence of cutaneous leishmaniasis remains at a fairly high level. The disease leading to severe cosmetic defects (scars) has undoubtedly a social problem, for the solution of which effective anti-epidemic measures should be carried out and highly effective methods of etiological and pathogenetic therapy should be developed [21].

Despite the ongoing complex work, it is not always possible to provide early diagnosis and prevention of this disease, and therefore the problem of treating patients with cutaneous leishmaniasis remains one of the most urgent in dermatology today.

Thus, the problem of cutaneous leishmaniasis in the Republic of Uzbekistan is still of particular interest in view of the presence of endemic zones. Due to the high incidence and prevalence of the disease, the existing difficulties in diagnosing and conducting adequate therapy, we can say about the imperfection of diagnostic and therapeutic methods used in cutaneous leishmaniasis.

The above indicates the urgency of the problem and the need for research, which will further contribute to the timely diagnosis, optimization of therapy methods and the development of effective measures for the prevention of cutaneous leishmaniasis in Central Asia.

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