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CUTANEOUS LEISHMANIASIS AND CONCOMITANT TISSUE HELMINTHIASIS

Salamova L.A.
Department of Dermatovenerology,
Samarkand State Medical Institute

Baratova M.R.
Department of Dermatovenerology,
Samarkand State Medical Institute

Oripov R.A.
Department of Dermatovenerology,
Samarkand State Medical Institute

Islamov N.X.
Department of Dermatovenerology,
Samarkand State Medical Institute

Abdullaev X.D.
Department of Dermatovenerology,
Samarkand State Medical Institute

Abdullaev D.M.
Department of Dermatovenerology,
Samarkand State Medical Institute

Suvonkulov U.T.
Research Institute of Medical Parasitology
named after L.M. Isaeva

Abstract:
We reviewed the literature on the prevalence of cutaneous leishmaniasis in the world and in the endemic zones of Uzbekistan and the relationship of this pathology with concomitant helminthiasis

Key words: Cutaneous leishmaniasis, leishmania, immune response, cytokines, tissue helminthiasis.

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Leishmaniasis is a group of diseases caused by various types of leishmanias - from visceral, which ends in death in the absence of treatment (Leishmania donovani), to cutaneous, spontaneously healed (L. major) [1]. Every year, from 0.7 million to 1.3 million new cases of cutaneous leishmaniasis (CL) are registered in the world [2]. Uzbekistan has long been an endemic area for cutaneous leishmaniasis. The population of a number of regions has cases of both anthroponous and zoonotic cutaneous leishmaniasis caused by Leishmania tropica and Leishmania major, respectively. The highest incidence rate is noted in the Surkhandarya, Bukhara regions, the Republic of Karakalpakstan. In recent years, there has been a tendency for an increase in morbidity in other regions of the republic - Navoi, Jizzakh and other regions. The incubation period of anthroponous CL ranges from 2–4 months. up to 1-2 years, occasionally up to 4-5 years, the pathological process from the moment of the appearance of the tubercle lasts an average of 1 year. The incubation period of zoonotic CL lasts from 1 to 4–6 months. The whole process from the moment a papule or tubercle appears until complete scarring lasts from 2 to 5-6 months. Both anthroponous and zoonotic CL can be complicated by the stratification of secondary flora, which increases painfulness, inflammation and complicates the process of epithelialization of leishmanias and, as a result, lengthens the duration of the disease. Usually, if the disease does not cause everyday inconvenience to the patient, etiotropic therapy for CL is not performed. When leishmaniasis is localized in the joints, face and in other cases, parenteral administration of drugs used to treat visceral leishmaniasis (preparations of 5-valent antimony, amphotericin B) is used [3]. Pentavalent antimony preparations have been used in the treatment of leishmaniasis for over 60 years, but nevertheless remain first-line drugs, although they are toxic, because during treatment, pentavalent antimony is partially transformed into trivalent, which is more toxic, causing anorexia, nausea, vomiting, headache, polyneuritis, hypersensitivity reactions: arthralgia, myalgia, rash, etc., pancreatitis, increased activity of liver enzymes, impaired renal function, arrhythmias. Resistance to them is growing rapidly, including in L. major and L. tropica, and the efficiency is low [4–6]. Amphotericin B, whose efficiency is higher, has nephro- and hepatotoxic properties, has a number of contraindications and side effects [7]. In addition, these drugs are expensive [6, 8], their effectiveness in CL of the Old World limited [9]. In Peru, in the treatment of ulcerative CL with sodium stibogluconate (intramuscular or intravenous administration for 20 days), no effect was observed in 21% of

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patients. Patients with involvement of mucous membranes with disseminated or diffuse lesions in the pathological process were excluded from the study. The risk factors for the failure of treatment with pentavalent antimony drugs include leishmaniomas that are spaced apart at a considerable distance, which may be associated either with defects in the immune status or with multiple bites of infected mosquitoes [10]. There are indications of leishmanicidal activity in the antibiotic claforan [11]. Due to the lack of new leishmanicidal drugs, various combinations of pentavalent antimony with other drugs are being developed: allopurinol, paromomycin [37]. It is promising to create topically applied drugs for the treatment of CL, which will largely avoid the side effects of drugs. It is assumed that not only drugs with leishmanicidal action, but also with reparative properties can have a positive effect [13]. The preparations are being tested, devoid of antiparasitic activity, but possessing wound healing and antioxidant properties, including the use of nanoparticles [14]. The prospects for the use of cryotherapy, thermotherapy and photodynamic therapy for the treatment of CL are discussed [6]. A special problem is the treatment of CL in HIV-infected patients [15], especially considering that Leishmania contribute to the progression of HIV infection [16]. It should be noted that, in general, there is a lack of evidence base in clinical trials of CL treatment with various drugs [17]. Despite numerous attempts and various approaches to the creation of protective immunity, an effective vaccine against CL has not yet been created, although various methods of isolation and processing of antigens, targeted effects on dendritic cells, etc. have been tested [18, 19]. The duration of the pathological process, the lack of vaccines and the above-mentioned features of etiotropic therapy raise the question of timely diagnosis and effective treatment of background and concomitant diseases that can negatively affect the course of CL. In this case, it is possible to reduce the duration of the pathological process and reduce the risk of complications. Here helminthiases come to the fore, especially since in regions endemic for CL, they are often recorded, including tissue. The human immune system provides protection against microparasites (viruses, bacteria) and macroparasites (unicellular Protozoa and multicellular Metazoa). In humans, acquired resistance to L. major is formed due to the implementation of the Th1 immune response [20]. The same is observed in the experimental CR model. When mice were infected with L. major, it was found that resistance / susceptibility to infection is due to Th1 and Th2 responses, respectively. The response of the L. major resistant

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mouse strain, C57BL / 6, is characterized by the production of IFN-γ at high concentrations, which is a Th1 cytokine that controls infection, leading to death
leishmania by activating macrophages [21-23]. In BALB / c mice susceptible to L. major, a Th2 response with active production of IL-4 develops, which is accompanied by the progression of infection [24]. The role of IL-4 as a factor contributing to the preservation of leishmanias is confirmed experimentally: the introduction of monoclonal antibodies to IL-4 in BALB / c mice infected with L. brasiliensis led to a decrease in the volume of leishmaniasis lesions and parasitic load [25]. This is consistent with the data [26] on the ability of IL-4 to reduce the influx of lymphocytes into the inflamed / infected skin of mice infected with L. major and promote the preservation of parasites. In recent years, an experimental mouse model has shown the role of IL-10 in the control of L. major: IL-10 has an anti-inflammatory effect, inhibiting phagocytosis, the expression of the main histocompatibility complex (MHC - abbr. From the English Main Hystocompatibility Complex) of class II and the secretion of pro-inflammatory cytokines by macrophages and dendritic cells. IL-10 facilitates the spread of leishmanias in the skin and plays an important role in the progression of leishmaniasis, especially in the early stages of infection. The IFN-γ / IL-10 ratio is a reliable prognostic indicator of the effectiveness of vaccine preparations [27]. The role of the multifunctional proinflammatory cytokine, tumor necrosis factor-α (TNF-α), in the formation of immunity to CL turned out to be ambiguous. Increased susceptibility to L. major was observed in individuals receiving TNF-α inhibitors [28]. At the same time, the use of pentoxifylline (a TNF-α inhibitor) in a leishmaniasis-endemic region of Brazil led to faster healing of leishmaniasis [29]. The local use of granulocyte-macrophage colony-stimulating factor (polypeptide cytokine) in combination with a parenteral antimony preparation made it possible to obtain a positive effect in patients who had previously been repeatedly unsuccessfully treated with antimony preparations in the form of monotherapy [30], and its use in combination with local application of low doses of antimony preparations allowed to achieve 100% healing of ulcers within 60 days, while in the control group (only local use of antimony preparations), 50% were cured [31]. It is known that IL-4 (Th2 cytokine) inhibits the proliferation of Th1 lymphocytes and the production of IFN-γ, contributing to the evasion of parasites from protective immune responses and chronic disease [21, 32–34]. The value of IFN-γ in the formation of protective immunity in CL was shown in the work of

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G. Harms et al. [35], who presented data on faster healing of leishmaniasis after intradermal administration of recombinant IFN-γ to patients with Brazilian mucocutaneous leishmaniasis. A similar effect of IFN-γ therapy was observed in chronic CL induced by Leishmania donovani [36]. S. Ajdary et al., Incubating peripheral blood leukocytes of patients with zoonotic CL with L. major antigens, found a higher secretion of IFN-γ in patients with active CL and healing leishmaniomas compared with patients with chronic CL with non-healing leishmaniasis [37]. It is known that a distinctive feature of tissue helminthiases is a pronounced Th2 response [38–40]. The opposite nature of the protective immune response in leishmaniasis and helminthiases suggests a negative effect of parasites on the course of leishmaniasis. Experimental leishmaniasis caused by both L. major and L. mexicana in mice previously infected with the cestode Taenia crassiceps was characterized by a high level of parasitemia and a large size of leishmaniasis. There were no significant changes in the production of IFN-γ by lymphocytes in response to stimulation with Leishmania antigens, but a significantly higher synthesis of IL-4 was noted. In animals with coinfection, the level of IgG and total serum IgE was increased. The presence of cestodes markedly reduced the leishmanicidal activity of macrophages [41]. Similar results were obtained when mice were infected with Schistosoma mansoni. Helminthiasis slowed down the healing of ulcers caused by L. major, reducing the level of leishmania-induced IFN-γ, TNF-α and nitric oxide with a high production of IL-4 [42]. IFN-γ-stimulated macrophages isolated from S. mansoni-infected mice had a decreased leishmanicidal activity. Concomitant helminthiases (S. mansoni, A. lumbricoides, T. trichuris) prolonged the course of CL caused by L. brasiliensis in humans in an area endemic for mucocutaneous leishmaniasis, reduced the effectiveness of pentavalent antimony, stimulated the Th2 response, and increased the level of total serum IgE [43]. S. mansoni antigens changed in vitro the cytokine response of lymphocytes of CL patients to L. major antigens: in 37–50% of patients, the synthesis of IFN-γ and TNF-α decreased, the level of IL-10 and IL-5 did not change significantly. In CL patients in whom S. mansoni antigens did not reduce IFN-γ production, the size of leishmaniomas was smaller. Differences in the synthesis of TNF-α were not reflected in the clinical manifestation of CL [44]. At the same time, parasitizing with Strongyloides did not significantly affect the course of CL induced by L. major, despite the detectable moderate suppression of the Th1 response caused by nematodes [45, 46]. In patients with Brazilian CL, the elimination of intestinal

helminths had no effect on the CL course [47]. Thus, the number of works on the effect of helminthiases on the course of CL with the study of the cytokine profile of patients is not numerous, and the results obtained are somewhat contradictory. Reliable information on the effect of concomitant helminthiasis and the nature of their treatment on the course of CL can lead to a reduction in the duration of CL, a decrease in the intensity of its manifestation and a decrease in the number of complications of bacterial etiology due to timely diagnosis and adequate treatment of helminthiasis.

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