Central Asian Journal of Medicine

CLINICAL FEATURES AND BLOOD CYTOKINE SPECTRUM IN PATIENTS WITH VARIOUS FORMS OF SKIN LEISHMANIASIS

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ABSTRACT

The purpose of the study: to study the features of the clinic and the cytokine spectrum of peripheral blood in patients with various forms of cutaneous leishmaniasis.

Materials and methods: clinical methods (clinic and course of cutaneous leishmaniasis in the endemic region of the Bukhara region, the Republic of Uzbekistan) were used; microbiological (detection of the pathogen - Borowski's bodies), immunological (IL-4, IL-6, IL-8, TNF-α, IFN - α and IFN -γ, relative and absolute number of B-lymphocytes (CD20+), markers of lymphocyte activation (CD25+, CD95+), statistical methods of investigation were used. The object of the study was 214 patients of both sexes with various clinical forms of cutaneous leishmaniasis aged from 1 to 68 years and 20 healthy individuals.

Results: according to the clinical forms of cutaneous leishmaniasis - tuberculous form was in 92 (43%), ulcerated leishmaniomas - in 68 (31.8%), ulcerated leishmaniomas with seeding tubercles with lymphangitis - in 53 (24.7%) and metaleishmaniasis - in 1 (0.5%) patient. Microbiological examination of lesions revealed in 190 (88.7%) of 214 patients Borovsky's body, in 161 (75.2%) cases zoonotic, in 53 (24.8%) cases - anthroponotic cutaneous leishmaniasis.

Conclusions: significant deviations of IL-6, IL-8 and TNF-α were found in all patients, while the most significant activation of pro-inflammatory cytokines was observed in patients at the stage of complications, lymphangitis, lymphadenitis and progression of the inflammatory process. In patients with ulcerated leishmaniomas with seeding tubercles and with lymphangitis, a deficiency of IL-4 and IFN-γ was recorded, as well as a decrease in the activity of markers of early activation of CD25+. The most pronounced expression of CD95+ receptors was recorded in patients with a protracted course and the development of complications, a less pronounced

form was noted in the tuberculous form of the disease. The results obtained made it possible to determine the main criteria for the progression of an immunodeficiency state in various clinical forms of cutaneous leishmaniasis.

Key words: leishmaniasis, clinic, cytokine spectrum.

INTRODUCTION

Cutaneous leishmaniasis (Leishmaniosi cutis), or Borovsky's disease (synonyms: Old World cutaneous leishmaniasis - Borovsky's disease; New World cutaneous leishmaniasis - American cutaneous leishmaniasis; visceral leishmaniasis - kala-azar) is a transmissible, protozoal disease with endemic distribution in countries with hot, tropical and subtropical climate [8,9,11]. The disease is accompanied by skin lesions, mainly ulcers, on exposed areas of the body, can leave permanent scars, cause severe disability and lead to stigmatization of people who have suffered from the disease. In the early 1990s, WHO estimates that leishmaniasis affects about 12 million people in 88 countries. About 95% of cases of cutaneous leishmaniasis occur in the Americas, the Mediterranean basin, the Middle East and Central Asia. The annual number of new cases of this form of the disease is estimated to range from 600,000 to 1 million, but only about 200,000 cases are reported to WHO. In Central Asia, the main endemic zones are located in Uzbekistan and Turkmenistan [5,6,13].

Cutaneous leishmaniasis (CL) in Uzbekistan is also a fairly common pathology among natural focal diseases. In the endemic regions of Uzbekistan (Bukhara, Surkhandarya, Kashkadarya, Jizzakh, Karakalpakstan), there is a rather high prevalence of zoonotic cutaneous leishmaniasis, where dozens of new cases of this disease are recorded annually. [6,7,12].

Leishmaniasis, depending on the region of distribution, causes damage to the skin, mucous membranes and internal organs. In the foci of this disease, large outbreaks often occur with the defeat of 60-90% of non-immunized people.

Affecting people of predominantly working age, CL deprives them of the ability to work, sometimes for a long time, which in turn brings great economic damage to the state. [5,7,11].

Currently, the existing methods of combating CL, including the extermination of reservoirs of the pathogen and carriers, are laborious and do not always give a significant result. Due to the increase in morbidity, registration of complications and atypical forms, insufficient preventive measures and pathogenetically substantiated methods of not only outpatient, but also inpatient treatment, make the problem of CL extremely relevant [1,2,4,10,13,14].

An important link in the immunopathogenesis of CL, which determines the outcome of the disease, is the state of immune reactivity. Moreover, the clinical

course of the disease largely depends not only on the form or stage of the disease, but also on the state of imbalance in the system of cytokines and their receptors with pro- and anti-inflammatory functions, which largely determines the mechanisms of dysregulation of cellular and humoral immunity and the development of the disease [3,9,12,15].

Therefore, the study of various issues regarding the clinical course, immunopathogenetic aspects and the development of effective methods of CL therapy on this basis has particular relevance.

Purpose of the study

To study the features of the clinical course and the cytokine spectrum of peripheral blood in patients with various course of cutaneous leishmaniasis.

Material and methods

Clinical methods (clinic and course of cutaneous leishmaniasis in the endemic region of the Bukhara region, the Republic of Uzbekistan) were used; microbiological (detection of the pathogen - Borowski's bodies), immunological (IL-4, IL-6, IL-8, TNF-α, IFN - α and IFN -γ, relative and absolute number of B-lymphocytes (CD20+), markers of lymphocyte activation (CD25+, CD95+), statistical methods of investigation were used. The object of the study was 214 patients of both sexes with various clinical forms of cutaneous leishmaniasis aged from 1 to 68 years and 20 healthy individuals.

Results and discussion

The 214 patients with CL under observation were aged from 1 to 68 years. There were 98 (45.8%) men and 116 (54.2%) women. There were 53 (24.8%) urban residents and 161 (75.2%) rural residents.

There were 115 (53.7%) patients under the age of 14 years, 32 (14.9%) at the age of 15-30 years, 12 (5.6%) at the age of 31-40 years and over 40 years of age. - 55 (25.8%) patients. The vast majority were rural residents (78.6%), and among the patients, children under the age of 14 years (53.7%) predominated among those surveyed.

The duration of the disease ranged from 15 days to 3 years, including up to 2 months in 117 (54.6%), from 3 to 4 months in 75 (35.1%), from 5 to 6 months in 20 (9.3%), from 7 months - up to 1 year in 1 (0.5%) patient, and over 1 year - in 1 (0.5%) patient.

According to the clinical forms of CL - tuberculous form was diagnosed in 92 (43%), ulcerated leishmaniomas - in 68 (31.8%), ulcerated leishmaniomas with tubercles of seeding with lymphangitis - in 53 (24.7%) and metaleishmaniasis - in 1 (0.5%) of the patient. Microbiological examination of lesions revealed in 190 (88.7%) of 214 patients with Borovsky's body positive.

As can be seen from the observations, zoonotic CL was detected in 161 (75.2%) cases, anthroponotic CL in 53 (24.8%) cases. Infection occurred at the place of residence of patients, and in most cases through blood-sucking insects - mosquitoes. The largest number of cases lived in the Romitan, Jondor, Peshku and Olot regions of the Bukhara.

Clinical observations showed that among patients with anthroponotic form of cutaneous leishmaniasis (53 patients), 27 had a tuberculous stage of the disease, the remaining 26 patients had a tuberculous-ulcerative stage of leishmaniasis. It should be noted that only 12 out of 53 patients with anthroponotic form of cutaneous leishmaniasis had specific lymphangitis or lymphadenitis. The number of foci varied from 1 to a maximum of 3, which is typical for anthroponotic leishmaniasis. In all patients with rural type of cutaneous leishmaniasis, rashes were represented by ulcerative and complicated forms of the disease. In one case, a complicated form of CL was found - metaleishmaniasis (tuberculoid type, the patient has been suffering from leishmaniasis for 9 years) with manifestations of new tubercle elements around the old scar.

An analysis of the clinical course showed that, lesions were more often localized in open areas of the body, mainly on the skin of the face, in the area of the nose, cheeks, and were presented in the form of tuberculous elements with an inflammatory infiltrate around in children. The skin was distinguished by a bright red color, and in the center of the tubercles there was a serous-bloody crust in the affected area.

In addition to tuberculous elements, there were also ulcerative rashes in adult patients, mainly located on the upper (shoulders, forearms, elbows, hands) and lower extremities (thighs, shins, feet) and on the trunk.

Zoonotic and anthroponotic types of CL had a typical clinical picture. In the anthroponotic form of CL, tubercular leishmanioma was manifested by a barely noticeable papule-tubercle with a diameter of up to 2-3 mm, the color of normal skin, which slightly rose above the level of the surrounding healthy skin, without visible inflammatory changes. The skin above it was tense, shiny and had a reddish-brown color. In the center of some tubercles there was a small crater-like depression with horny scales on the bottom or a rounded ulcer with a smooth or wrinkled bottom, covered with a purulent coating. At the same time, the edges of the ulcer were uneven, steep, the bottom was slightly granular with scanty serous-purulent discharge, as well as areas of necrotization. A roller-like infiltrate was formed around the ulcerative elements. As a rule, the number of ulcers did not exceed 1-3 and they were localized mainly on open areas of the skin accessible to mosquitoes (face, hands).

There was a red, acutely inflammatory, cone-shaped tubercle up to 2-4 mm in diameter in patients with zoonotic CL. The tubercles reached up to 15-20 mm in diameter in some patients. There was an inflammatory edema of the skin around the tubercles. Ulcerative elements with abrupt edges and necrotic bottom reached from 2-4 mm to 4-5 cm in diameter. A wide infiltrate and inflammatory edema with seeding tubercles around could be seen along the periphery of the ulcers. The ulcers were uneven with undermined edges, the bottom of which was filled with necrotic masses or copious serous-purulent discharge. In part of the ulcers, the edges were even, undermined, and an infiltrate rose up around it in the form of a roller.

Along with tuberculous and ulcerative elements, some patients had foci with growing granulations in the form of papillae, resembling a "fish caviar symptom". In some patients, the pathological process proceeded with complications in the form of lymphangitis, lymphadenitis and successive leishmania. There were swelling of the legs and feet due to lymphostasis on the lower extremities with complications of lymphadenitis. In 1 (0.5%) patient, metalishmaniasis was diagnosed, where the pathological process was represented by yellowish-brown small tubercles up to 2-3 mm in diameter. In place of the former tubercles and ulcerations, there were ulcerated old tubercles and the formation of scars was clearly visible, and new, fresh tubercles continued to appear along the edges of the infiltrate.

In some cases, an abortive course of CL, accompanied by a long-term preservation of small tubercular elements without the formation of an open ulcer was observed.

Elements of rashes in 121 (56.5%) patients were localized in the face (eyebrows, nose, cheeks, bridge of the nose, corner of the mouth, chin), in 26 (12.1%) - on the upper limbs (shoulders, forearms, elbows, hands).), in 20 (9.4%) - on the lower extremities (thighs, shins, feet), in 16 (7.5%) - on the trunk, upper and lower extremities, in 15 (7.0%) - on the face and upper limbs, in 9 (4.2%) patients in the upper and lower limbs, and in 5 (3.3%) patients in the chest and trunk.

In patients, the number of existing ulcers in the lesions varied from 1 to more than 10 pieces. Thus, 113 (52.8) patients had 1 ulcer, 73 (34.1%) - 2-3, 19 (8.9%) - 4-5, 5 (2.3%) - 6-7, in 4 (1.9%) - 8-9 ulcerative elements.

Subjective sensations against the background of inflammation in the form of itching were accompanied in 78 patients, pain in 54, 82 patients did not complain. Moreover, 18 patients had pain and itching at the same time.

The cytokine network is the most important regulatory mechanism of intercellular interactions. An imbalance in the production of cytokines is important in the immunopathogenesis of chronicity and disease progression. We have studied the content of anti- and pro-inflammatory cytokines in patients depending on the clinical forms of CL (IL-4, IL-6, IL-8, TNF-α and IFN-γ).

It was necessary to establish the features of cytokine-mediated mechanisms of dysregulation of the immune system and to characterize changes in the subpopulation composition of lymphocytes in patients with CL.

Blood sera of 96 patients with various clinical manifestations of CL were selected for the study. The control group consisted of data from 20 practically healthy individuals comparable by sex and age.

Studies have shown the highest values of pro-inflammatory cytokines IL-6, IL-8, TNF-α in patients with ulcerated leishmaniomas with seeding tubercles with lymphangitis ($p<0.001$). (Fig. 1) A less pronounced reaction from IL-8 was found in patients with ulcerated leishmaniomas, although within reliable limits. All patients with CL had significantly high levels of TNF-α, the highest values were obtained in the group with complicated forms. A different picture was observed in the level of IL-4. Relatively low values were determined only in patients with ulcerated leishmaniomas and ulcerated leishmaniomas with tubercles of seeding and with lymphangitis. The same dynamics was observed in relation to immune IFN-γ, the concentration of which in low limits was also characteristic of patients with complicated forms of CL.

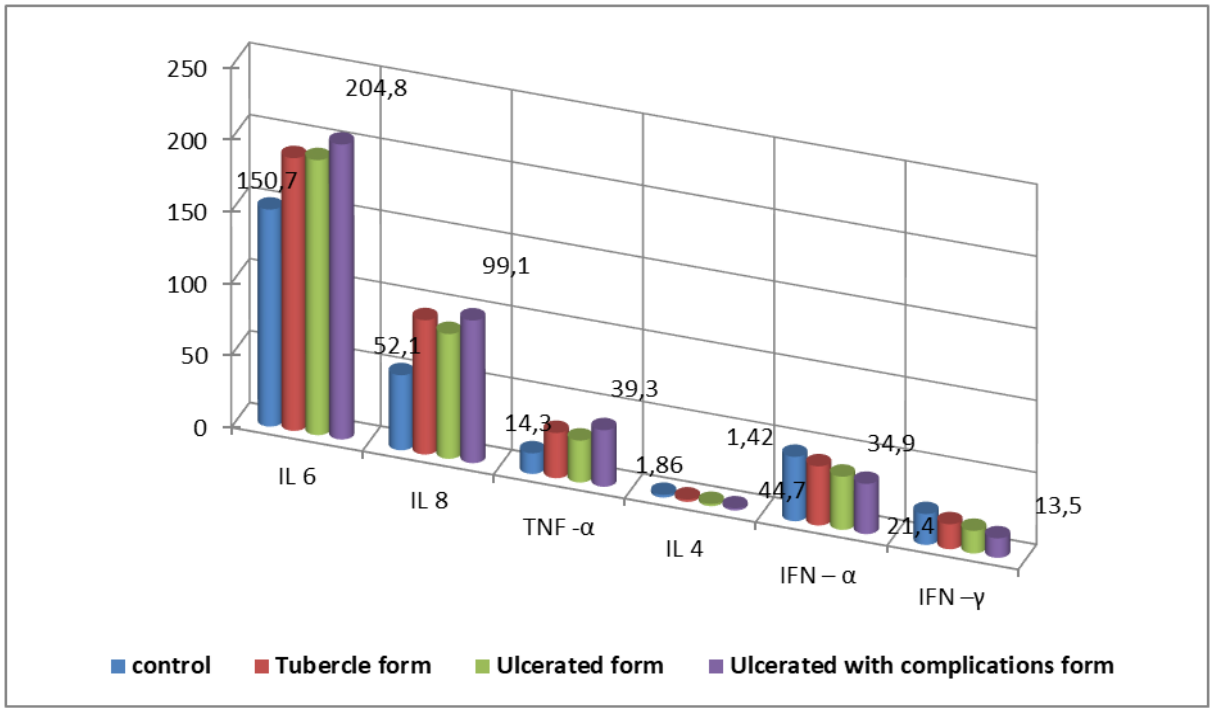

Fig. 1. Indicators of blood cytokines in patients with various clinical forms of cutaneous leishmaniasis.

Thus, the analysis of the obtained data shows that changes in the content of cytokines are detected in CL, which is expressed by a deficiency in the blood serum of the concentration of the anti-inflammatory cytokine IL-4, as well as IFN-γ, and an increase in the content of pro-inflammatory cytokines IL-6, IL-8 and TNF-α, which are directly dependent on the clinical form of the disease.

The analysis of the content of lymphocytes in the blood of patients expressing activation antigens showed a significant increase in the relative and absolute number of CD20+ cells in all patients with CL compared with the control, which suggests activation of the B-cell component of the immune system as a whole. A significant decrease in the absolute number of cells with the CD25+ marker was noted in patients with all clinical forms of CL, however, the absolute value was reduced in patients with ulcerated leishmaniomas with seeding tubercles and with lymphangitis. Increased expression of CD95+ receptors indicates an imbalance in activation signals, which leads to the development of an immune response through apoptosis. At the same time, in the tubercular stage, increased expression of CD95+ was less pronounced than in other clinical forms.

Conclusions

Thus, clinical and epidemiological studies have shown that CL mainly affects children under 14 years of age (53.7%), women (54.2%), with the duration of the process in most cases from 2 to 6 months. The tuberculous form was diagnosed in 92 (43%), ulcerated leishmaniomas - in 68 (31.8%), ulcerated leishmaniomas with tubercles of seeding and with lymphangitis - in 53 (24.7%) and metaleishmaniasis - in 1 (0.5%) of the patient. In 161 (75.2%) cases, zoonotic CL was detected, in 53 (24.8%) cases - anthroponotic CL. In children, ulcers were more often localized in open areas of the body, mainly on the skin of the face, in the area of the nose, cheeks, and in adults - on the skin of the lower and upper extremities. The number of lesions in the form of ulcers ranged from 1 to more than 10. Clinical observations made it possible to identify the features of the course and characterize the skin-pathological process of CL in the conditions of the Bukhara region and the city of Bukhara.

A comparative analysis of the studied immunological parameters in patients with CL made it possible to establish their pronounced changes. Significant deviations of IL-6, IL-8 and TNF-α were noted in all patients with CL, the most significant activation of pro-inflammatory cytokines was observed in patients at the stage of development of complications, lymphangitis, lymphadenitis and progression of the inflammatory processAt the same time, against the background of IL-4 and IFN-γ deficiency, a pronounced activation of B-lymphocytes with the

CD20+ phenotype was observed, which was inherent in all patients with various forms of CL. In addition, a decrease in the activity of markers of early activation of CD25+ was recorded in patients with ulcerated leishmaniomas with seeding tubercles and with lymphangitis. The most pronounced expression of CD95+ receptors was recorded in patients with a protracted course and the development of complications, less pronounced in patients with tuberculous form of CL.

The obtained results made it possible to determine the main criteria for the progression of an immunodeficiency state in various clinical forms of CL, and, on this basis, to develop approaches to therapy.

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