THE STATE OF THE IMMUNE SYSTEM IN PATIENTS WITH CUTANEOUS LEISHMANIASIS

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ABSTRACT

In patients with all clinical forms of cutaneous leishmaniasis, there is a violation in the work of the immune system, expressed by an imbalance of both cellular and hum oral links of the immune system of the body.

KEYWORDS: *Immunity, Cutaneous Leishmaniasis, Histiophagocytic System.*

INTRODUCTION

Currently, visceral and cutaneous (urban type) leishmaniasis has been practically eliminated in Central Asian countries, but zoonotic cutaneous leishmaniasis (ZKL) continues to occupy a certain place in regional pathology and tens and hundreds of fresh cases of this disease are registered annually **[1,3,5,9,11,15].** The main endemic foci have long been located on the territory of Uzbekistan and Turkmenistan, as well as in certain regions of neighboring Kazakhstan **[1].** The degree of manifestations of episodes in these territories is different and the morbidity of the population in each of them has its own characteristic features due to the mutual location of settlements and natural foci, the degree of contact of the population with foci and the level of the immune layer **[2,4,8].**

In Uzbekistan, cutaneous leishmaniasis is one of the most common parasitic diseases that have a large share in the regional pathology. A fairly high prevalence of zoonotic cutaneous leishmaniasis is noted in Turkmenistan and Uzbekistan, where dozens and hundreds of new cases of this disease are registered annually in endemic zones **[6,7,10,12,16].**

Epidemiological studies have shown that certain seasonality is characteristic of cutaneous leishmaniasis. 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 and in winter, as a rule, there may be isolated cases of zoonotic cutaneous leishmaniasis, and this applies to patients who have sought medical help late.

It should be emphasized that cutaneous leishmaniasis is one of the few protozoal diseases, the transfer of which leads, as a rule, to the development of persistent, tense and long-term immunity. Leishmania are obligate, intracellular parasites that are able to penetrate, transform, multiply and survive in the cells of the host's histiophagocytic system, so the body's response has its own characteristics **[13].**

Most authors explain the presence of persistent immunity of cutaneous leishmaniasis by the fact that a cellular immune response develops in the human body as a result of the transferred disease **[1,5,8,14,17].** Along with the cellular link, the humoral link of immunity has certain significance, which is also able to influence the synthesis of specific antibodies [**2].** It was noted that peripheral blood B-lymphocytes lose their functions, which, apparently, is associated with possible violations of the cooperation of immunocompetent cells, as well as an increase in the suppressive activity of blood **[3].**

According to modern concepts, disorders of the immune system are closely associated with certain cytokines that determine the types of immune response (Th1- and Th2 types), and studies in this direction are isolated and very contradictory **[2].**

The search for new effective drugs for the treatment of patients with cutaneous leishmaniasis is a very topical issue **[3].** Previously successfully used drugs, in particular, monomycin, have been discontinued; antimony preparations are highly toxic, etc. It should be pointed out that for the treatment of cutaneous leishmaniasis, a variety of surgical, chemotherapeutic, immunobiological and many other methods are used today that can cause serious complications. Therefore, the development of new methods of therapeutic effects, pathogenetically justified, is an urgent task of modern dermatology.

It should be noted that despite a large number of scientific studies devoted to the study of pathogenetic mechanisms of development and treatment of cutaneous leishmaniasis, the clinical structure and comprehensive study of the pathogenesis of cutaneous leishmaniasis, taking into account immune, biochemical and genetic aspects, have not been studied in our region. The study of the above parameters allows us to better understand the pathogenesis and improve the methods of treatment of cutaneous leishmaniasis.

These data indicate the need for further pathogenesis studies to address the development of cutaneous leishmaniasis, as well as the possibility of the development of complicated forms of cutaneous leishmaniasis, in particular, metalleishmaniasis.

Despite the detailed coverage in the literature about the participation of cellular and humoral factors in the formation of cutaneous leishmaniasis, information about their condition in patients with cutaneous leishmaniasis in the available literature is very scarce.

In order to exclude the influence of various pathological conditions on the immune system indicators, when studying the state of immunity, we limited ourselves to the study of persons who did not have diseases of other organs and systems.

The purpose of the study. To develop a method of molecular genetic diagnosis and pathogenetic therapy of cutaneous leishmaniasis based on the study of immune-biochemical studies.

Material and methods of research. Immunological parameters were studied in 119 patients with cutaneous leishmaniasis. Of these, 38 patients were diagnosed with a tubercular form of cutaneous leishmaniasis, 52 – ulcerated leishmaniomas, 22 – ulcerated leishmaniomas with tubercles with lymphangoitis and 7 – metalleishmaniasis. The control group consisted of data from 20 practically healthy individuals aged 25 to 40 years.

The state of the immune system was assessed by the expression of CD-differentiated and activation antigens. Markers of immunocompetent cells were determined by indirect rosette formation using an immunoreagent – human erythrocytes of group 0 (I) Rh – loaded with monoclonal antibodies through a 3% solution of chromium chloride (manufactured by Sorbent LLC, Moscow, Russia) specificity CD3 – for T-lymphocyte receptors, CD4 – for T-helper/inducers, CD8 – for T-suppressors/cytotoxic lymphocytes, CD19 – for B-lymphocytes.

The results of the study showed (Table. 1) that in patients with cutaneous leishmaniasis of the general group, a significant increase in the absolute number of leukocytes (5800 ± 75 cl / mcl) was observed before the start of treatment compared with the data of the control group (5380 ± 82 cl / mcl). The relative and absolute number of lymphocytes remained at the level of control values ($p>0.05$). The study of the state of the cellular link of the immune system showed that in patients of the general group there was a statistically significant decrease in both the relative number of CD3 cells ($p<0,001$) and the absolute number of CD3 cells ($p<0,05$) and on average they were 48,27 ± 0,40% and 881 ± 19 cells/μl, respectively, against 58,15 ± 0,74% and 1013 ± 31 cl/ml, respectively, in the control.

TABLE 1 INDICATORS OF THE IMMUNE SYSTEM IN PATIENTS WITH CUTANEOUS LEISHMANIASIS (M±m)

Immunity indicators	Control group n=20	Patients with cutaneous leishmaniasis n=119
Leukocytes, cl/mcl	5380 ± 82	5800± 75*
Lymphocytes, %	32,40 ± 0,76	31,62± 0,77
Lymphocytes, cl/mcl	1743 ± 50	1823± 35
CD3, %	58,15 ± 0,74	48,27± 0,40**
CD3, cl/mcl	1013 ± 31	881 ± 19*
CD19, %	16,80 ± 0,39	23,52± 0,53**
CD19, cl/mkl	288 ± 11	429 ±13*
CD4, %	38,30 ± 0,38	30,23± 0,36**
CD4, cl/mcl	652 ± 24	550± 12*
CD8, %	18,85 ± 0,43	19,76 ± 0,22
CD8, cl/mkl	320 ± 13	361± 8
IRI	2,04 ± 0,05	1,56± 0,03**
IgA, g/l	2,32 ± 0,05	2,73± 0,03**
IgM, g/l	1,42 ± 0,05	1,74± 0,02**

IgG, g/l	12,25 ± 0,31	19,49± 0,32**
CEC, cu.	13,95 ± 0,48	30,43± 0,62**

Note: p is the reliability of the data in relation to the control.

* - p<0,05; ** - p<0,001

The study of the content of the subpopulation composition of T-lymphocytes showed that in patients with cutaneous leishmaniasis before treatment, compared with the data of the control group, the relative and absolute number of CD4 cells was significantly reduced and averaged 30.23 ± 0.36% and 550 ± 12 cells/μl, respectively, versus 38.30 ± 0.38% and 652 ± 24 cells/mcl, respectively, in control. The content of another population of T-lymphocytes, CD8 cells, was inclined to increase (p>0.05) compared with the data of the control group.

In patients of this group, the immunoregulatory index (IRI), that is, the ratio of CD4/CD8 cells, was significantly reduced (p<0.001) and on average was equal to 1.56 ± 0.03 versus 2.04 ± 0.05 in the control.

When studying the state of the humoral link of the immune system, it was revealed that in patients with cutaneous leishmaniasis of the general group, there was a statistically significant increase in both relative (23.52 ± 0.53% at 16.80 ± 0.39% normal, p <0.001) and absolute (429 ±13 cl/μl versus 288 ± 11 cl/μl in the control, p<0.05) the number of CD19 cells. The study of the concentration of serum immunoglobulins showed that in patients of this group there was a significant increase in the level of three classes of immunoglobulins IgA, IgM and IgG relative to the control (p<0.001).

The most pronounced changes were found when determining the amount of CEC in the blood serum. In the examined group of patients, there was a more than 2-fold increase in the CEC level compared to the control group and on average it was 30.43 ± 0.62 cu versus 13.95 ± 0.48 cu in the control.

The data obtained by us show that, in general, patients with cutaneous leishmaniasis have a violation in the immune system, which is expressed by a decrease in cellular activity and an increase in the humoral link of the body's immunity.

In further studies, we studied the state of the immune status of patients with cutaneous leishmaniasis, depending on the clinical form of the disease.

The revealed patterns in the dynamics of immunological indicators, when determining the immune status in patients with cutaneous leishmaniasis without differentiating them by clinical forms, are preserved even when they are separated into separate groups.

TABLE 2 INDICATORS OF THE IMMUNE SYSTEM IN PATIENTS WITH TUBERCULAR FORM OF CUTANEOUS LEISHMANIASIS (M±m)

Immunity indicators	Control group n=20	Patients with tubercular form of cutaneous leishmaniasis n=38
Leukocytes, cl/mcl	5380 ± 82	5739± 120*
Lymphocytes, %	32,40 ± 0,76	31,13± 1,00
Lymphocytes, cl/mcl	1743 ± 50	1796± 77
CD3, %	58,15 ± 0,74	51,95± 0,41*
CD3, cl/mcl	1013 ± 31	935± 42
CD19, %	16,80 ± 0,39	19,55± 0,53**
CD19, cl/mkl	288 ± 11	352±18*
CD4, %	38,30 ± 0,38	33,95± 0,55*
CD4, cl/mcl	652 ± 24	606± 25
CD8, %	18,85 ± 0,43	19,13± 0,43
CD8, cl/mkl	320 ± 13	345± 18
IRI	2,04 ± 0,05	1,80± 0,04*
IgA, g/l	2,32 ± 0,05	2,71± 0,04*
IgM, g/l	1,42 ± 0,05	1,66± 0,02*
IgG, g/l	12,25 ± 0,31	18,12± 0,42***
CEC, cu.	13,95 ± 0,48	25,97± 0,82***

Note: p is the reliability of the data in relation to the control.

* - p<0,05; ** - p<0,01; *** - p<0,001

The results of the study showed (Table. 2) that patients with the tubercular form of cutaneous leishmaniasis had a significant decrease in the relative number of CD3 cells ($p<0.05$). At the same time, the absolute content of CD3 cells in patients of this group did not change much in comparison with the control ($p>0.05$).

Analysis of the content of the subpopulation composition of T-lymphocytes showed that in patients of this group before the start of treatment, the relative number of CD4 cells ($p<0.05$) was statistically significantly reduced compared to the control group and averaged 33.95 ± 0.55% versus 38.30 ± 0.38% in the control group. The absolute number of CD4 cells remained at the level of the control group data ($p>0.05$). The content of another population of T-lymphocytes – CD8 cells had no statistically significant differences with the control group ($p>0.05$). Along with this, there was a decrease in the IRI index by 1.1 times in relation to the indicator of the control group.

A study of the state of the humoral link of immunity showed that in patients of this group there was a significant increase in both relative and absolute ($p<0.01$ and $p<0.05$, respectively) CD19-cell content.

The study of the level of immunoglobulins revealed that in patients with the tubercular form of cutaneous leishmaniasis, a statistically significant increase in the concentration of IgA ($p<0.05$), IgM ($p<0.05$) and IgG ($p<0.001$) was observed in the blood serum.

In patients of this group, compared with the control, there is a 1.9-fold increase in the content of CEC in the blood serum.

A study of the state of the immune system in patients with ulcerated leishmaniomas showed (Table. 3) that in patients of this group, a significant decrease in the relative number of CD3 cells ($p<0.01$) was detected before the start of treatment, and on average it was 48.33 ± 0.36% versus 58.15 ± 0.74% in the control, and the absolute content of CD3 cells tended to decrease compared to the control group ($p>0.05$).

In patients of this group, the relative ($p<0.001$) and absolute ($p<0.05$) number of CD4 cells was significantly reduced compared to the data of the control group, and the content of CD8 cells was at the level of control values ($p>0.05$). In patients of this group, a decrease in the IRI index was revealed by 1.4 times compared with the indicator of the control group.

TABLE 3 INDICATORS OF THE IMMUNE SYSTEM IN PATIENTS WITH ULCERATED LEISHMANIOMAS (M±m)

Immunity indicators	Control groups=20	Patients with ulcerated leishmaniomasn=52
Leukocytes, cl/mcl	5380 ± 82	5808± 116*
Lymphocytes, %	32,40 ± 0,76	32,35± 0,90
Lymphocytes, cl/mcl	1743 ± 50	1861± 51
CD3, %	58,15 ± 0,74	48,33± 0,36**
CD3, cl/mcl	1013 ± 31	899± 26
CD19, %	16,80 ± 0,39	23,46± 0,67***
CD19, cl/mkl	288 ± 11	437±19**
CD4, %	38,30 ± 0,38	29,25± 0,25***
CD4, cl/mcl	652 ± 24	544± 15*
CD8, %	18,85 ± 0,43	19,86 ± 0,32
CD8, cl/mkl	320 ± 13	369± 11
IRI	2,04 ± 0,05	1,48± 0,03**
IgA, g/l	2,32 ± 0,05	2,75± 0,05**
IgM, g/l	1,42 ± 0,05	1,80± 0,02**
IgG, g/l	12,25 ± 0,31	18,97± 0,44***
CEC, cu.	13,95 ± 0,48	30,69± 0,85***

Note: p is the reliability of the data in relation to the control.

* - p<0, 05; ** - p<0,01; *** - p<0,001

In patients with ulcerated leishmaniomas, a significant increase in both the relative and absolute number of CD19 cells is detected in the blood ($p<0.001$ and $p<0.01$, respectively). Against this background, there is a significant increase in the concentration of IgA ($p<0.01$), IgM ($p<0.01$) and IgG ($p<0.001$) compared to the control.

In patients of this group, there is a 2.2-fold increase in the concentration of CEC in the blood serum.

TABLE 4 INDICATORS OF THE IMMUNE SYSTEM IN PATIENTS WITH ULCERATED LEISHMANIOMAS WITH TUBERCLES OF INFECTION WITH LYMPHANGOITIS (M±m)

Immunity indicators	Control group n=20	Patients with ulcerated leishmaniomas with tubercles of insemination with lymphangoitisn=22
Leukocytes, cl/mcl	5380 ± 82	5904± 185*
Lymphocytes, %	32,40 ± 0,76	31,23± 1,32
Lymphocytes, cl/mcl	1743 ± 50	1819± 66
CD3, %	58,15 ± 0,74	44,50± 0,80***
CD3, cl/mcl	1013 ± 31	809± 31*
CD19, %	16,80 ± 0,39	27,68± 1,24***
CD19, cl/mkl	288 ± 11	506±32**
CD4, %	38,30 ± 0,38	26,73± 0,74***
CD4, cl/mcl	652 ± 24	489± 26**
CD8, %	18,85 ± 0,43	20,23± 0,37*
CD8, cl/mkl	320 ± 13	369± 15
IRI	2,04 ± 0,05	1,41± 0,06**
IgA, g/l	2,32 ± 0,05	2,65± 0,06**
IgM, g/l	1,42 ± 0,05	1,74± 0,05**
IgG, g/l	12,25 ± 0,31	21,24 ± 0,76***
CEC, cu.	13,95 ± 0,48	35,36± 1,34***

Note: p is the reliability of the data in relation to the control.

* - p<0,05; ** - p<0,01; *** - p<0,001

The results of the study show (Table.4) that in patients with ulcerated leishmaniomas with tubercles of seeding with lymphangoitis, before the start of treatment, there was a significant decrease in both the relative ($p<0.001$) and absolute number of CD3 cells ($p<0.05$) and on average they were 44.50 ± 0.80% and 809 ± 31 cells /ml, respectively, at 58.15 ± 0.74% and 1013 ± 31 cl/µl, respectively, in the control.

Analysis of the content of the subpopulation composition of T-lymphocytes showed that in patients of this group, both the relative ($p<0.001$) and absolute ($p<0.01$) number of CD4 cells was statistically significantly reduced compared to the control group and averaged 26.73 ± 0.74% and 489 ± 26 cells/ml, respectively, versus 38.30 ± 0.38% and 652 ± 24 cl /µl, respectively, in the control. The relative content of another population of T-lymphocytes, CD8 cells, was significantly higher than in the control ($p<0.05$), and their absolute number remained at the control level. Along with this, there was a decrease in the IRI index by 1.4 times in relation to the indicator of the control group.

The study of the state of the humoral link of immunity revealed that in patients with ulcerated leishmaniomas with tubercles of seeding with lymphangoites, there was a significant increase in both the relative (27.68 ± 1.24% at 16.80 ± 0.39% normal) and absolute (506 ±32 cl/µl versus 288 ± 11 cl/µl in the control) number of CD19 cells ($p<0.001$ and $p<0.01$, respectively).

The study of the concentration of serum immunoglobulins in patients of this group before the start of treatment revealed a significant increase in the level of IgA ($p<0.01$), IgM ($p<0.01$) and IgG ($p<0.001$) compared with the control values.

The most pronounced changes were found when determining the amount of CEC in the blood serum. In the examined group of patients, there was a more than 2.5-fold increase in the CEC level compared to the control group and on average it was 35.36 ± 1.34 cu versus 13.95 ± 0.48 cu in the control.

TABLE 5 INDICATORS OF THE IMMUNE SYSTEM IN PATIENTS WITH METALLEISHMANIASIS (M±m)

Immunity indicators	Control group n=20	Patients with metalleishmaniasis n=7
Leukocytes, cl/mcl	5380 ± 82	5743± 436
Lymphocytes, %	32,40 ± 0,76	30,14± 1,53
Lymphocytes, cl/mcl	1743 ± 50	1701± 78
CD3, %	58,15 ± 0,74	39,71± 1,44***
CD3, cl/mcl	1013 ± 31	674± 38**
CD19, %	16,80 ± 0,39	32,43± 1,02***
CD19, cl/mkl	288 ± 11	552± 31**
CD4, %	38,30 ± 0,38	28,43± 1,52***
CD4, cl/mcl	652 ± 24	483± 34*
CD8, %	18,85 ± 0,43	21,00± 1,40*
CD8, cl/mkl	320 ± 13	355± 22
IRI	2,04 ± 0,05	1,37± 0,10**
IgA, g/l	2,32 ± 0,05	2,87± 0,11**
IgM, g/l	1,42 ± 0,05	1,81± 0,06**
IgG, g/l	12,25 ± 0,31	25,26± 0,82***
CEC, cu.	13,95 ± 0,48	37,14± 1,71***

Note: p is the reliability of the data in relation to the control.

* - $p<0,05$; ** - $p<0,01$; *** - $p<0,001$

Studies have shown (Table. 5) that in patients with metalleishmaniasis, a significant decrease in both the percentage ($p<0.001$) and the absolute number of CD3 cells ($p<0.01$) was detected compared with the data of the control group.

The study of the T-lymphocyte subpopulation showed that in patients of this group, both the relative number and the absolute content of CD4 cells were also significantly reduced compared to the control group ($p<0.001$ and $p<0.05$, respectively), and the relative content of CD8 cells significantly increased, while the absolute number remained at the control level ($p>0.05$). Along with this, there was a decrease in the IRI indicator by 1.5 times in relation to the indicator of the control group.

A study of the state of the humoral link of immunity revealed that in the examined group there was a significant increase in both the relative and absolute number of CD19 cells ($p<0.001$ and $p<0.01$, respectively).

Along with this, there is a statistically significant increase in the level of IgA ($p<0.01$), IgM ($p<0.01$) and IgG ($p<0.001$).

In patients with metaleishmaniasis, compared with the control, there is a 2.7-fold increase in the content of CEC in the blood serum.

It should be noted that the revealed changes in the immune system in patients with leishmaniasis were more pronounced than in patients with other clinical forms of cutaneous leishmaniasis.

Thus, in patients with all clinical forms of cutaneous leishmaniasis, there is a violation in the work of the immune system, expressed by an imbalance of both cellular and humoral links of the immune system of the body.

The most pronounced changes in the immune system are observed in patients with severe forms of cutaneous leishmaniasis, in particular, ulcerated leishmaniomas with tubercles of infection with lymphangoitis and metalleishmaniasis.

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