DOI: 10.5281/zenodo.8212760
UDC: 616.72-002.951+612.017

LYMPHOCYTIC IMMUNO-INFLAMMATORY STATUS IN PATIENTS WITH PARASITIC ARTHRITIS DEPENDING ON THE ETIOLOGICAL AGENT

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Summary
Objectives. Most authors attest that parasitic arthritis manifests itself immunologically in a non-specific way and, until now, the most important reactions remain unclear. The objective of our study was to evaluate the indices of cellular immunity specifically in patients with parasitic arthritis in the case of various infestation agents.
Material and methods. In the study were included 161 patients, that were divided into 3 groups: first group (97 patients) with parasitic arthritis with echinococcosis infestation, the 2nd group (31 patients) – with parasitic arthritis with *Toxocara cannis* and the 3rd group (33 patients) – with parasitic arthritis with *Giardia lamblia* infestation.
Results. Within the framework of the development of parasitic arthritis, the most significant changes occur in the immune status of the patients, with *Giardia lamblia* parasitic arthritis, followed by those with echinococcosis infestation parasitic arthritis and *Toxocara cannis* parasitic arthritic, which were characterized by a marked increase in CD2 cytotoxic lymphocytes and a decrease in the number of CD4 and CD8 lymphocytes, against the background of the physiological constant number of CD3 lymphocytes.
Conclusions. Cellular immune status in parasitic arthritis is characterized by a deficit of control over the work of the system, expressed by a decrease in CD4 and CD8, against the background of the optimal concentration of CD3, but with increased cytotoxicity activity by increasing CD2.
Keywords: parasitic arthritis, echinococcosis, *Toxocara cannis, Giardia lamblia*, cellular immunity

Introduction

Most authors attest that parasitic arthritis is manifested by arthralgia, hyperemia, swelling of the joints and disturbance of their function, including morning redness. The clinical picture meets the characteristic signs of seronegative spondyloarthropathy, which includes more reactive arthritis and psoriatic arthritis. Among the distinctive features of parasitic arthritis, also found in spondyloarthropathies, we reveal enthesopathies (inflammation of the insertion areas of the tendon, ligament and joint capsule), dactylitis (swelling of the fingers) and asymmetric damage to the joints, sometimes oligoarticular damage and irritations [1-4]. Parasitic arthritis is more characteristic for men, it is binding seronegative, although some more recent studies have shown the possibility of the existence of an insignificantly increased diagnostic titer of rheumatoid factor in the case of coexistence of B-lymphocytic hyperactivity syndrome or long chronic helminthiasis [2-5].

Parasitic arthritis usually has a self-limiting course with the resolution of symptoms in 3-12 months, even in patients with acute forms [2, 3]. However, it has a tendency to recurrences, especially with gastrointestinal inflammatory processes.

In 15% of cases, patients with parasitic arthritis develop long-lasting destructive arthritis, enthesitis and spondylitis [3]. In some recent studies [2, 4, 6], 7 factors were analyzed as predictors of long-term forms in parasitic arthritis. The number of patients with parasitic arthritis in these studies was small, and the analysis of a truthful subgroup was not possible. Involvement of the coxo-femoral joint, erythrocyte sedimentation rate (ESR) over 30mm/h, as well as the lack of response to treatment with non-steroidal anti-inflammatory drugs (NSAIDs), probably indicate the presence of a serious form of psoriatic arthritis or the development of a chronic helminthic process [1-3].

There are some peculiarities by which parasitic arthritis differs from other arthropathies. Dactylitis occurs in more than 37% of cases, enthesitis and tendosynovitis are equally characteristic for arthritis, being present in most patients, although they are not always appreciated in clinical examination. According to the literature data, fibrosis and ankylosis of small joints are rarely determined. Early ankylosis of the proximal interphalangeal joints can manifest itself only within the framework of severe developments in the disease [3, 7].

However, despite knowing the clinical picture of parasitic arthritis, so far there are no reliable data on the specific cellular immune status, which makes it difficult to characterize the degree of development of the disease and the choice of treatment tactics.

The objective of the study was to evaluate the indices of cellular immunity, specifically in patients with parasitic arthritis in case of various infestation agents.

Material and methods

In the study were included 161 patients that were divided into 3 groups depending on the pathogen of infestation and the clinical variant of parasitic arthritis and was including into the study according to the WMA Declaration of Helsinki. The study was conducted at the Department of Rheumatology of "Nicolae Testemitanu" State Medical and Pharmaceutical University with approval of the Research Ethics Committee No. 88 from 19.06.2018. The first group (97 patients) consisted of patients with parasitic arthritis due to *Echinococcus* infestation, the 2nd group (31 patients) – patients with parasitic arthritis due to *Toxocara cannis* and the 3rd group (33 patients) included patients with parasitic arthritis due to *Giardia lamblia* infestation.

Criteria for inclusion in the study were: age of patients – 18-70 years; the presence of parasitic infection by *Echinococcus, Toxocara cannis* or *Giardia lamblia;* the appearance of symptoms of locomotor damage in the period of parasitic infestation; damage to the musculoskeletal system for the first time (unsolved causes); the patient's agreement to participate in the research. *Exclusion criteria were:* a history of rheumatic diseases (inflammatory, autoimmune); decompensated diseases (cardiovascular, hepatic, renal); neoplastic diseases; mental and cognitive disorders; age less than 18 years and older than 70 years.

We conducted a clinical and analytical study, selecting patients according to the inclusion and exclusion criteria. The studied groups of patients were comparable. The accumulation of the data was of the "witness case" type. Ethically, the study did not include elements of human experimentation, and the evaluation criteria did not change throughout the study. Analysis of the data obtained was carried out at the end of the study. Given the presence in the statistical examination of groups with several types of variants (nominal and scaling), they were processed separately. The data obtained were statistically processed by the variational, regressional, clusterian, multiple scanning, ANOVA (ANalysis Of VAriance) correlational analyses with the calculation of the arithmetic mean (*M*), the standard error (*ES*) and the standard mean deviation (*DS*), the parametric correlation coefficients (*r*) and the nonparametrics Spearman, Kendall Tau, gamma (*Rr*). The differences in the arithmetic averages (*P*) were compared using the Student criterion (*t*) StatSoft v.9.0. The methodological support was provided by using the methods exhibited in the works of well-known specialists in the field [2-5].

Results

An important marker for the work of the immune system is the lymphocyte. The research carried out by us has shown that the average percentage indices of the content of lymphocytes in the peripheral blood of patients with parasitic arthritis (21,5±0,4) were within the limits of the norm and did not undergo changes, having average values without statistical differences between the studied groups (Table 1).

Table 1

Relative (%) and absolute (109/l) lymphocyte indices of patients included in the study (%)

Lymphocyte content, %	***Echinococcus* parasitic arthritis n=97**	***Toxocara canis* parasitic arthritis n=31**	***Giardia lamblia* parasitic arthritis n=33**
Relative indices, % (M±m)	37.5±0.4	37.9±0.3	37.3±0.5
Absolute indices, 10^9/l (M±m)	2341±22.1	2344±21.6	2337±25.1

For the characteristic of the quantitative and functional indices of the T and B lymphocyte subclasses, we used the most effective method of identifying cells by determining the immuno-fermentative with the help of monoclonal antibodies. Thus, we conducted a series of researches on cell determinants (CD), the main purpose being to compare these results between the basic groups of patients. The investigated markers were: CD3 antigen (antigenic receptor marker on all T lymphocytes), antigens corresponding to suppressor lymphocytes – CD8, lymphocytes with cytotoxic function (killer) – CD2 and helper inducers – CD4, as well as CD22 antigen, specific to mature B lymphocytes secreting immunoglobulins.

The average percentage indices of the total concentration of CD3 lymphocytes did not differentiate between the studied groups ($p<0.05$) (Table 2), the content of CD2 lymphocytes assessed in patients with *Giardia lamblia* parasitic arthritis was significantly higher (19.1% in relative indices and 379x10^9/l in absolute indices, $p<0.05$) than in parasitic arthritis in *Echinococcus* or *Toxocara canis*. We anticipate, that *Giardia lamblia* parasitic arthritis is characterized by a more significant expression of cytotoxic reactions, which would also explain the more serious clinical condition (association of axial and peripheral musculoskeletal manifestations) in these patients compared to other groups of patients.

Human T lymphocytes, in addition to the previously analyzed CD3 and CD2 clones, are divided into two other subtypes, called CD8 suppressor and CD4 helper. It is assumed that these subpopulations interact with the effector cells, causing stimulation or suppression of the development of immune reactions [7-9]. In addition to the suppressor and helper cells, responsible for regulating the overall activity of immunocyocytes, the existence of antigen-specific regulating cells is assumed [1,3, 10-14].

CD4 and CD8 lymphocytes can be identified with the help of monoclonal antibodies, but because they are also equipped

Table 2

Total content of CD2, CD3, CD4, CD8 and CD22 lymphocytes in peripheral blood of patients included in the study (ind. rel., % and abs., 10^9/l)

	***Echinococcus* parasitic arthritis n=97**	***Toxocara canis* parasitic arthritis n=31**	***Giardia lamblia* parasitic arthritis n=33**
Content of CD3 lymphocytes			
Relative indices, %	54.7±1.6	56.2±1.1	57.1±1.0
Absolute indices, 10^9/l	916,2±47.3	950.2±31.2	941.8±27.12
Content of CD2 lymphocytes			
Relative indices, %	14.2±0.28	13.9±0.31	19.1±0.19[*1]
Absolute indices, 10^9/l	321±12.7	308±14.6	379±11.9[*1]
Content of CD4 lymphocytes			
Relative indices, %	32.2±0.22	34.7±0.12	27.9±0.19[*2]
Absolute indices, 10^9/l	549.1±21.2	552.2±23.2	443.0±22.3[*2]
Content of CD8 lymphocytes			
Relative indices, %	17.7±0.3	18.3±0.3	13.9±0.4[*3]
Absolute indices, 10^9/l	341.2±4.1	349.7±2.9	219.0±5.4[*3]
Content of CD22 lymphocytes			
Relative indices, %	20.1±0.31	16.0±0.18[*4]	19.51±0.22
Absolute indices, 10^9/l	443±3.2	391.1±3.9[*4]	431±4.4

Note: *[*1]$p<0.05$ – parasitic arthritis by giardiasis vs echinococcosis and toxocariasis; [*2]$p<0.01$ – parasitic arthritis by giardiasis vs toxocariasis; [*3]$p<0.01$ – parasitic arthritis by giardiasis vs echinococosis; [*4]$p<0.01$ – parasitic arthritis by toxocariasis vs echinococcosis and giardiasis*

with a number of properties, they can be determined by other methods, especially CD8 lymphocytes (suppressors).

According to the accumulated data (Table 2), the population of CD8 lymphocytes (mean indices) in patients with parasitic arthritis *Giardia lamblia* was lower compared to the values revealed in patients in the group with parasitic arthritis *Echinococcus* or *Toxocara canis*, both as absolute values and as relative values ($p<0.01$). This result was conditioned by the fact that 74% of patients with parasitic arthritis *Echinococcus* and *Toxocara canis* had in their blood over 18% CD8 lymphocytes, compared to patients with parasitic arthritis *Giardia lamblia*, who had such a proportion in only 31% of cases ($p<0.01$). This phenomenon could be generated by the massive migration of CD8 lymphocytes to synovial fluid and joint structures [2, 5, 7, 11]. The absolute mean indices of CD8 lymphocyte content were also, statistically, significantly altered in the group of *Giardia lamblia* parasitic arthritis patients, compared to the groups of patients with parasitic arthritis *Echinococcus* and *Toxocara canis* ($p<0.01$; Table 2). The marked suppressor and cytolytic impact of CD8 lymphocytes could explain the more serious course of *Giardia lamblia* parasitic arthritis.

Another subpopulation of T-lymphocytes, responsible for regulating the immune response and performing effector functions are T-helper (Th) lymphocytes. These lymphocytes are distinguished from other subclasses of T lymphocytes by the clonal determinant CD4. The determination of the percentage content of CD4 helper lymphocytes in patients with parasitic arthritis (Table 2) demonstrated their decline in the group of *Giardia lamblia* parasitic arthritis patients, compared to those with *Echinococcus* and *Toxocara canis,* the estimated difference being also statistically significant (parasitic arthritis *Giardia lamblia* 27.9±0.19 *vs Echinococcus* parasitic arthritis – 32.2±0.22 and *Toxocara canis* parasitic arthritis – 34.7±0.12; $p<0.01$). Determination of absolute indices of CD4 T lymphocytes (Table 2), also demonstrated a decrease in their average values in *Giardia lamblia* parasitic arthritis (parasitic arthritis *Giardia lamblia* 443.0±22.3 *vs Echinococcus* parasitic arthritis – 549.1±21.2 and parasitic arthritis *Toxocara canis* – 552.2±23.2; $p<0.01$). The decrease in the average indices of CD4 lymphocytes is probably determined by the fact that in *Giardia lamblia* parasitic arthritis there is a more pronounced immunodepression than in parasitic arthritis *Echinococcus* and *Toxocara canis.* This immune deficiency inherent in *Giardia lamblia* parasitic arthritis can be explained by the involvement of two factors [3, 5, 15]: the first factor would be the excessive consumption of effector cells and their massive migration to the inflammatory joint focus, the second can be defined by the excess of supraactive helminthic antigens generated by endogenous toxic-infectious syndrome and, as a result, their massive migration from peripheral blood to tissues with the numerical decline of CD4 lymphocytes.

Thus, following the analysis of CD4 lymphocyte values, depending on the clinical variant of parasitic arthritis, we established the same regularity as in the case of CD8 lymphocytes. The lowest values were recorded in *Giardia lamblia* parasitic arthritis compared to *Echinococcus* and *Toxocara canis* parasitic arthritis ($p<0.01$), the respective decline causing the more serious course of this clinical form. CD4 lymphocyte values were generally similar in patients with parasitic arthritis *Echinococcus* and *Toxocara canis.*

Significant changes occur in the immune status in case of *Giardia lamblia* parasitic arthritis – immune deficiency are probably due to the aggressiveness of the helminthic pathogens. The number of CD22 lymphocytes appears in the blood of people with parasitic arthritis (Table 2), especially in patients with *Giardia lamblia* and *Echinococcus* parasitic arthritis ($p<0.05$), compared to patients with parasitic arthritis *Toxocara canis* ($p<0.01$). Thus, we can conclude in favor of the existence, in patients with parasitic arthritis, of a disturbed state of the immune system, which is characterized by deterioration of the effective control function on the part of CD4 and CD8 lymphocytes against the background of an increased expression of cells with cytotoxic effect CD2 and CD22 (immune-humoral). The CD3 value persists within physiological limits.

Discussions

Currently, more and more data are accumulating on the similarity of some parasitic antigens and antigens of human tissues, primarily the myocardium, synovia and nervous tissue, such as glyco-sphingolipids, ribosomal proteins, etc [1-3, 6-8, 15]. This adaptation mechanism is considered molecular mimicry, in which the surface antigens of the parasite coincide with the host antigens, and the molecular structure of parasitic proteins reproduces the structure of a number of immuno-regulatory proteins of the host [6, 9, 16].

Residual products of helminths, such as proteins and host cells modified in the pathogenic process (dystrophy, inflammation, necrosis), become a powerful immune stimulus, being pathogens and including the mechanisms of general and local immunity. At the same time, both humoral and cellular mechanisms of nonspecific (complement, phagocytosis, etc.) and specific (B and T systems), aimed at eliminating parasites, are activated [11-13, 17].

Thus, following the analysis of CD4 lymphocyte values, depending on the clinical variant of parasitic arthritis, we established the same regularity as in the case of CD8 lymphocytes. The lowest values were recorded in *Giardia lamblia* parasitic arthritis compared to parasitic arthritis with *Echinococcus* and *Toxocara canis* ($p<0.01$). The respective decline causes the more serious course of this clinical form. CD4 lymphocyte values were generally similar in patients with parasitic arthritis *Echinococcus* and *Toxocara canis.*

In addition, "parasitic metabolites have a cytotoxic effect on somatic, generative and possibly immune host cells, causing the growth of apoptotic cells among them" [1-4, 18]. It has been shown to "increase the level of apoptosis of lymphocytes in *schistosomiasis*, the cells of the host spleen in the acute stage of Manson's schistosomy, as well as an increase in the level of apoptosis of CD4+ T lymphocytes in the peripheral blood of mice infected with *microfilariae Brugia pahangi*" [8-11].

The mechanisms of induction of apoptosis of host cells in helminthiasis are not fully understood. Of the four main molecules, whose production causes cell death, authors considered that the helminths themselves actively stimulate the production of tumor necrosis factor in the host body, although it is believed that the synthesis of this cytokine is used by the host as a protective immune response in most helminthiases, aimed at inducing apoptosis in the tissues of the parasite [1, 3, 7, 14].

Conclusions

Parasitic arthritis is characterized by the diversity of clinical joint manifestations, which fall into 3 clinical variants: induced by infestation with *Echinococcus*, *Toxocara canis* and *Giardia lamblia*, among which giardiasis correlates with a more severe clinical course, followed by echinococcosis and toxocarosis. Cellular immune status in parasitic arthritis is characterized by a deficit of control over the work of the system, expressed by a decrease in CD4 and CD8, against the background of the optimal concentration of CD3, but with increased cytotoxicity activity by increasing CD2.

Bibliography

1. Marquez J, Espinoza LR. Mycobacterial, brucellar, fungal and parasithic arthritis. In: Hochberg MC, editor. Rheumatology. 7th ed. Philadelphia: Elsevier; 2019:943–54.
2. Restrepo JP, Molina Mdel P. Perfuração do colo por colite amebiana invasiva durante terapia anti-TNF para espondiloartrite(§) [Colonic perforation due to invasive amebic colitis during anti-TNF therapy for spondyloarthritis]. Rev Bras Reumatol. 2014;54(6):483-485. doi:10.1016/j.rbr.2013.09.004
3. Bouzid M, Hunter PR, Chalmers RM, Tyler KM. Cryptosporidium pathogenicity and virulence. Clin Microbiol Rev. 2013;26(1):115-134. doi:10.1128/CMR.00076-12
4. Painter JE, Gargano JW, Collier SA, Yoder JS; Centers for Disease Control and Prevention. Giardiasis surveillance - United States, 2011-2012. MMWR Suppl. 2015;64(3):15-25.
5. Gibney KB, O'Toole J, Sinclair M, Leder K. Disease burden of selected gastrointestinal pathogens in Australia, 2010. Int J Infect Dis. 2014;28:176-185. doi:10.1016/j.ijid.2014.08.006
6. Painter JE, Collier SA, Gargano JW. Association between Giardia and arthritis or joint pain in a large health insurance cohort: could it be reactive arthritis?. Epidemiol Infect. 2017;145(3):471-477. doi:10.1017/S0950268816002120
7. Lewis JM, Clifford S, Nsutebu E. Toxoplasmosis in immunosuppressed patients. Rheumatology (Oxford). 2015;54(11):1939-1940. doi:10.1093/rheumatology/kev115
8. Hosseininejad Z, Sharif M, Sarvi S, et al. Toxoplasmosis seroprevalence in rheumatoid arthritis patients: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12(6):e0006545. Published 2018 Jun 5. doi:10.1371/journal.pntd.0006545
9. Masocha W, Kristensson K. Human African trypanosomiasis: How do the parasites enter and cause dysfunctions of the nervous system in murine models?.

Brain Res Bull. 2019;145:18-29. doi:10.1016/j.brainresbull.2018.05.022
10. McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ, Zhou XN. Schistosomiasis. Nat Rev Dis Primers. 2018;4(1):13. Published 2018 Aug 9. doi:10.1038/s41572-018-0013-8
11. Rakotomalala HN, Ranaivoarison MV, Andrianjafison F, Ralandison DS. Bilharzial arthropathy: Rare cause of chronic arthritis in tropical areas. Eur J Rheumatol. 2017;4(3):229-230. doi:10.5152/eurjrheum.2017.16084
12. Alım B, Çetinel S, Servi MA, Bostancı F, Bingöl MO. The Case of Reactive Arthritis Secondary to Echinococcus Infestation. Case Rep Rheumatol. 2017;2017:3293060. doi:10.1155/2017/3293060
13. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev. 2004;17(1):107-135. doi:10.1128/CMR.17.1.107-135.2004
14. Alishani M, Sherifi K, Rexhepi A, et al. The impact of socio-cultural factors on transmission of Taenia spp. and Echinococcus granulosus in Kosovo. Parasitology. 2017;144(13):1736-1742. doi:10.1017/S0031182017000750
15. Samorek-Pieróg M, Karamon J, Cencek T. Identification and Control of Sources of Taenia Solium Infection - the Attempts To Eradicate the Parasite. J Vet Res. 2018;62(1):27-34. Published 2018 Mar 30. doi:10.1515/jvetres-2018-0004
16. Symeonidou I, Arsenopoulos K, Tzilves D, Soba B, Gabriël S, Papadopoulos E. Human taeniasis/cysticercosis: a potentially emerging parasitic disease in Europe. Ann Gastroenterol. 2018;31(4):406-412. doi:10.20524/aog.2018.0260
17. Dsilva G, Kulkarni V, Aher S. An uncommon manifestation of a common disease. Ann Parasitol. 2017;63(4):357-360. doi:10.17420/ap6304.124
18. Segarra-Newnham M. Manifestations, diagnosis, and treatment of Strongyloides stercoralis infection. Ann Pharmacother. 2007;41(12):1992-2001. doi:10.1345/aph.1K302

Received – 10.02.2023, accepted for publication – 07.07.2023
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Conflict of interest Statement: The authors reports no conflicts of interest in this work.
Funding Statement: The authors reports no financial support.
Citation: Grosu M, Groppa L, Russu E. Lymphocytic immuno-inflammatory status in patients with parasitic arthritis depending on the etiological agent. Arta Medica. 2023;87(2):15-19.