неконтрольованою бронхіальною астмою (p<0,05). Одночасно у пацієнтів із неконтрольованою та частково контрольованою бронхіальною астмою реєструвалось вірогідне зниження регуляторного індекса, зумовленого зменшенням частки CD4+ та зростанням вмісту CD8+ (p<0,05). Встановлено наявність позитиваного кореляційного зв'язку високого ступеня (r=0,79, p<0,05) між вмістом в сироватці крові IL-6 із тяжкістю перебігу БА у дітей.

Ключові слова: бронхіальна астма, діти, імунітет.

Стаття надійшла 24.04.2019 р.

неконтролированной бронхиальной астмой (p<0,05). Одновременно у пациентов с неконтролированной и частично контролированной бронхиальной астмой регистрировалось достоверное снижение регуляторного индекса, выражавшегося уменьшением процента CD4+ и увеличением CD8+ (p<0,05). Установлено наличие положительной корреляционной связи высокой степени (r=0,79, p<0,05) между содержанием в сыворотке крови IL-6 и тяжестью течения бронхиальной астмы у детей.

Ключевые слова: бронхиальная астма, дети, иммунитет.

Рецензент Катеренчук І.П.

DOI 10.26724/2079-8334-2020-1-71-83-88
УДК 616.988.55:576.858.1]-078.73

M.P. Lomikovska, I.G. Hayduchok, H.O. Potomkina, S.O. Zubchenko, I.Y. Kril, K.Y. Ishcheykin, V.V. Chopyak
Danylo Halytskyi Lviv National Medical University

PECULIARITIES OF TLR9 EXPRESSION ON IMMUNE COMPETENT CELLS IN REACTIVE ARTHRITIS PATIENTS WITH CHRONIC EPSTEIN-BARR VIRUS INFECTION

e-mail: ydmarta79@gmail.com

The work presents the study findings on the TLR9 expression in immune competent cells in reactive arthritis patients with chronic Epstein-Barr virus infection, and considers the possibility of the reactive arthritis transformation into rheumatoid arthritis. It was established that expression of TLR9+CD123+ on monocytes was reliably higher in the blood of reactive arthritis patients as compared to healthy individuals, while in patients in active phase of EBV-infection the expression of this receptor was reliably higher as compared to similar indices of patients at the latent phase. At that, the number of TLR9+CD123+-monocytes in patients with reactive and rheumatoid arthritis was not reliably different. The number of TLR9+CD123+-lymphocytes as compared to indices of healthy individuals was reliably higher in patients with rheumatoid arthritis at both phases of chronic EBV-infection, while in patients with reactive arthritis it was only characteristic at the active phase of the infection. Expression of this receptor on lymphocytes turned out to be reliably higher in patients with rheumatoid arthritis as compared to patients with reactive arthritis, particularly at the active phase of chronic EBV infection.

Key words: reactive arthritis , rheumatoid arthritis, chronic Epstein-Barr Virus Infection, TLR9.

The work is a fragment of the research project "Prediction of development of allergic diseases virus-induced phenotypes with personification of their diagnosis and treatment", state registration No. 0118U000110.

Over the last years, there has been a wide spread of reactive arthritis cases (ReA), especially among young people. The relevance of the problem of ReA is attributed to its high incidence and difficult differential diagnostics [14]. It is very often the case when clinically similar joint problems could be initial signs of systemic diseases. Currently, ReA is treated as a multifactor joint disease which belongs to the group of seronegative spondilo-arthropathies HLA-B27-associated that develop due to immune disorders after having the urogenital, intestinal, respiratory, and tonsilogenic infections. Today, dependency of the incidence of contraction of the ReA on the type of the pathogen has been well studied, however, there is no clear answer to the question why different micro-organisms can cause ReA, or cause it with different incidence. Currently, special focus in the development of ReA is allocated to the role of viruses, including also the chronic Epstein-Barr virus (EBV) [4]. EBV infection is one of the most widespread infections in the world. In the recent years, during primary introduction of infection, the virus has often caused blurred atypical forms of disease with rapid chronization. EBV persists lifelong in the human body due to its ability to suppress effector mechanisms of immune competent cells [3]. One of the theories on complications in ReA development is about its transformation into rheumatoid arthritis (RA). RA is an autoimmune disease characterized with chronic inflammation of joints that will gradually result in damage of cartilages and bones; it is characterized with synovial hyperplasia with massive infiltration of inflamed cells. Immune cells play a key role in RA progression due to production of pro-inflammatory cytokines [1]. One of the causing factors for the transformation could be Herpesviruses.

A conducting system providing for recognition of infections, and viruses in particular, is a system of Toll-like receptors (TLRs), and more specifically TLR9 [12]**.** The TLR9 is an important intracellular receptor expressed on immune competent cells; it mostly binds the DNA that is present in viruses; it launches signal cascades that lead to pro-inflammatory response of cytokines [4]. It has been found a different interaction of EBV with TLRs expressed on different cells [9].

The research proved that TLRs are actively engaged in the development of autoimmune diseases via direct and indirect activation of T-cells, activation of autoreactive B-cells [15]. Activation of TLRs has several functions in aggravation and progression of joint damage related to the increase of the polymorphism number in TLRs [6]. Some studies indicate the contrary, the lack of expression of TLR9 that contributes to aggravation and progression of autoimmune diseases [2].

For this reason, we set an objective to explore the immunepathogenetic mechanisms of ReA development engaging TLR9, and its possible impact on the transformation of ReA into RA.

The purpose of the work was to assess the extent of TLR9 expression on mononuclear cells of peripheral blood in reactive arthritis patients with chronic EBV infection, and values of TLR9 at the risk of transformation of reactive arthritis into rheumatoid arthritis.

Materials and methods. We had 64 patients under observation (33 ReA patients and 31 RA patients) who were staying on in-patient care in the rheumatology unit of Lviv Regional Clinical Hospital, and in out-patient care at the Regional Center for Clinical Immunology and Allergology. Among the 33 ReA patients, 19 were men (57.6%), and 14 women (42.4%), aged 18-35 (average age 26.5±7.4). The patients were divided into two sub-groups: 1) 21 active ReA patients of chronic EBV-infection – ReA EBV (+); 2) 12 patients with signs of ReA in latent phase of chronic EBV-infection – RA EBV (-).

Among the 31 RA patients, there were 12 men (38.7%) and 19 women (61.3%), aged 18-54 (average age 38.2±6.9). The group of patients was also divided into two sub-groups: 1) 10 RA patients with active chronic EBV-infection – RA EBV (+); 2) 21 RA patients with latent chronic EBV-infection – RA EBV (-).

Verification of ReA and RA was conducted on the basis of clinical data on joint damage, laboratory and instrumental tests. ReA patients met the diagnostics criteria pursuant to the protocol of the Ministry of Health Care of Ukraine dated 12.10.2016. RA patients complied with the diagnostic criteria of American and European collegium of rheumatologists ACR/EULAR (2010).

The phase of chronic EBV-infection (active or latent) was verified on the basis of the clinical laboratory tests, serologic (identification of specific IgM, IgG to different EBV antigens), and molecular-genetic (detecting the virus DNA) tests. Detection of specific antibodies was done with the method of immunoferment test using the Euroimmun test-systems (Germany). EBV DNA in blood serum, saliva, and mucous scraping of posterior pharyngeal wall was identified with the method of polymerase chain reaction (PCR) with the use of Ampli Sens diagnosticum (Russia) on Rotor Geen 6000 (Corbett Recearch, Australia). All patients with identified antibodies of class IgG EBNA of IgG VCA on the background of absent EBV DNA in three media were referred to the group of patients in latent phase of chronic EBV-infection. Patients with identified antibodies of class IgG (EBNA) and/or capsid antibodies of class IgM/IgG (VCA) and DNA virus were classified as patients in active phase of chronic EBV-infection. All patients underwent bacteriological testing to identify a possible infection with bacterial agents. In addition, they were also tested for markers of Chlamydia infection. Tests of TLR9 were made on the basis of the identified $CD123^+$ on mononuclear cells of peripheral blood with the method of ductal cytofluorometry with the use of flow cytofluorometer and Bekton Dickenson test system (USA).

The control group included 24 apparently healthy individuals of the corresponding age and gender.

Statistical processing of findings was carried out with the help of the Statistika software for Windows 6.0, using the Student criterion.

Results of the study and their discussion. Clinically, all 33 ReA patients showed arthritic syndrome. The pathological process affected shoulder, knee, ankle, and small joints of the feet. Among the 21 ReA EBV (+) patients, arthritis of one joint was recorded in one person (4.8%), two joints – in 8 individuals (38.1%), three and more – in 12 patients (57%). Among 12 ReA EBV (-) patients, arthritis of one joint was recorded in three (25%), two joints – in seven (58.3%), three and more – in two (16.7%) patients. Moreover, 11 (53.4 %) patients with ReA EBV (+) showed prolonged subfebrile condition, 17 (80.9%) patients showed a chronic fatigue syndrome, seven patients (33.3%) – had respiratory immunodeficit disorder, six persons (28.6%) had lymphadenopathy of mostly cervical and mandibular lymph nodes.

All RA patients showed signs of arthritic syndrome, while mostly small joints of hands and feet were affected. Activity of RA was identified with the help of visual analogue scale and activity index DAS28, when patients with EBV (+) had it with 5.94±1.31 and it was probably different from DAS28 in patients with EBV (-) - 4.11±1.09 ($P<0.05$). In addition, eight (25.8%) patients complained about temperature rise up to 38.5.

RA patients with EBV (+) had the average number of leukocytes of 6.80±2.14 g/l, ESR – 23.01±4.15 mm/h, CRP – 18.92±2.18 nmol/L. In 10 (47.6%) patients an absolute or relative lymphocytosis

was identified; in 7 (33.3%) - absolute lymphopenia, mild cases. In ReA patients with EBV (-), the number of leukocytes was 8.83±2.14 g/L, ESR average value - 19±3.15 mm/h, CRP – 9.92±2.18 nmol/L. All patients had a negative RF and antibodies to cyclic citrulline peptide; high levels of IgG EBNA and increased level of VCA-EBV (6 times higher and above norm). Of them, 4 patients from this group (19.1%) had a raised level of IgM-VCA EBV. With 3 (14.3%) persons, it was identified DNA of EBV (+) simultaneously in blood, saliva, and in mucous scraping of posterior pharyngeal wall, 6 (28.6%) patients had it at the same time in saliva and mucous scraping of posterior pharyngeal wall, 10 (47.6%) patients had in mucous scraping of posterior pharyngeal wall, and two persons (9.5%) –in saliva only.

Laboratory tests of RA patients with EBV (+) revealed the following: mean values of leukocytes – 7.14±1.10 g/L, ESR – 28.91±6.80 mm/h, CRP – 225.24±84.52 nmol/L. RA patients with EBV (-) had the mean values of leukocytes of 8.27±2.33 g/L, ESR – 23.60±4.46 mm/h, CRP – 169.24±65.25 nmol/L. Positive RF was identified in 26 (83.9%) patients; autoantibodies to cyclic citrulline peptide found in 27 (87.1%) patients. Mollecular genetic test of RA patients with EBV (+) showed DNA of EBV at the same time in blood, saliva, and mucous scraping of posterior pharyngeal wall – in one (10.0%) patient, in saliva and in the mucous scraping of posterior pharyngeal wall – in three (30.0%) persons, in mucous scraping of posterior pharyngeal wall – in four (40.0%), in saliva only – in two (20.0%) patients. In addition, three patients (30.0%) from this group showed a raised level of IgM-VCA EBV. 21 RA patient with EBV (-) showed only nuclear antibodies of class IgG (EBNA) and IgG (VCA), which levels were 6 times above norm on the background of no DNA of EBV in three media. The patients were referred to the sub-group of rheumatoid arthritis with EBV (-).

Bacterial swab test from the throat of all patients showed an opportunistic pathogenic microflora in physiological and slightly raised amount, which did not exclude engagement of bacteria in the development of ReA. All patients had negative markers of Chlamydia infection.

Table 1 shows data on expression of TLR9 on lymphocytes and monocytes of peripheral blood in reactive arthritis patients and rheumatoid arthritis patients with active and latent phase of EBV-infection.

Table 1

Activity of expression of TLR9$^+$ CD123$^+$ on monocytes and lymphocytes in patients with reactive arthritis and rheumatoid arthritis at the background of active and latent phases of chronic EBV-infection (M±m)

	Healthy individuals	ReA EBV(-)	ReA EBV(+)	RA EBV(-)	RA EBV(+)
TLR 9$^+$ CD 123$^+$ monoc., %	0.03±0.01	0.06±0.01*	0.09±0.01*^{o}	0.09±0.02*	0.12±0.03*
TLR 9$^+$ CD123$^+$ limphoc., %	0.80±0.12	1.22±0.34	1.62±0.15 *	1.50±0.12*	2.11±0.11*^{o}^

Notes:*P <0,05 – validity of difference between the indicators of healthy individuals and ReA and RA patients with EBV (+) and EBV (-); ^{o}P <0.05 – validity of difference between the indicators of ReA patients with EBV (+) and EBV (-) and RA EBV (+) and EBV (-); ^P<0.05 – validity of difference between the indicators of ReA patients with EBV (-) and RA EBV (-) and ReA patients (+) and RA EBV (+)

As the data from Table 1 shows, expression of TLR 9$^+$CD123$^+$ on monocytes in both ReA and RA patients, both in active, and latent phases of chronic EBV infection was validly higher as compared with indicators of healthy individuals (P <0.05). Compared to indicators of healthy individuals, expression of TLR 9$^+$CD123$^+$ on lymphocytes was also validly higher in RA patients in latent and active phases of chronic EBV-infection, while in ReA patients – it was only in active phase of the infection.

ReA patients in latent phase of infectious process had expression of TLR9 on monocytes (0.06±0.01%) validly 33.3% lower than in active patients of EBV-infection (0.09±0.01%, P<0.05). Expression of TLR9 on lymphocytes of these patients was validly not different in the active phase (1.62±0.15%) as compared to patients in latent phase with EBV-infection (1.22±0.34, P>0.05).

Patients with rheumatoid arthritis had expression of TLR9$^+$CD123$^+$ on monocytes validly not different in active phase (0.12±0.03%), as compared to patients in latent phase of EBV-infection (0.09±0.02%, P>0.05). Expression of TLR9 on lymphocytes in RA patients in latent phase of the infection (1.50±0.12%) showed as probably 28.9% lower as compared to patients in active phase of EBV-infection (2.11±0.11%, P<0.05).

Patients with rheumatoid arthritis had expression of TLR9 on monocytes which actually did not differ as compared to ReA patients both in active (0.09±0.01% and 0.12±0.03%, P>0.05, respectively), and in latent phase (0.06±0.01% and 0.09±0.02%, P>0.05, respectively) of chronic EBV-infection. The number of TLR9$^+$CD123$^+$-lymphocytes turned out higher by 23.2 % in RA patients (2.11±0.11%), as compared to ReA patients (1.62±0.15, P<0.05). However, it was only shown in active phase of the infection.

ReA patients has expression of TLR9$^+$CD123$^+$ on mononuclear cells (both in active and in latent phases of chronic EBV infection) validly higher compared to healthy individuals (P<0.05). The obtained

results can be explained by the fact that EBV infection activates a signal pathway of TLR9, which leads to production of Tumor necrosis factor alpha (TNF-α), Interleukin 6 (IL-6), and to the development of inflammatory response. TLR9 on monocytes recognizes motives of CpG EBV DNA and enhances immune response caused by EBV infection [13]. After stimulation, EBV cells can release chemokine MCP-1 that has strong anti-inflammatory properties [8]. Number of TLR9+CD123+-monocytes in ReA and RA patients was validly not different in active and in latent phases of chronic EBV-infection. As we know, monocytes/macrophages cause inflammation in tissues where they are concentrated. The cells can recognize different ligands through TLR. In the process, production of anti-inflammatory cytokines is taking place. Thereupon, it has been described that synovia of RA patients might show enhanced expression of TLR2 and TLR9 [2]. Activation of TLR9 by EBV genome can facilitate inflammation in joints inducing production of a wide spectre of chemokynes and cytokines [2]. High level of expression of TLR9 on monocytes indicates to the possible contribution of this receptor into the development of autoimmune process [11]. Thus, increased number of TLR9+CD123+-monocytes in ReA patients with chronic EBV-infection and lack of valid difference from RA patients may indicate further progression of inflammatory process with transition into autoimmune process, through exhaustion of monocyte macrophage link of immune system.

However, the study of TLR9 in experimental models showed its anti-inflammatory effect [8]. Therefore, the function of TLR9 on monocytes can be interpreted twofold: as such that can activate or suppress inflammation, including also autoimmune one [7]. With EBV-infection, additional mechanisms may develop related to polymorphism of TLR9, which can cause in some patients transformations of reactive arthritis into rheumatoid arthritis.

As we know, RA patients have dominant autoimmune processes involving a humoral link into pathological process, with activation of autoreactive B-lymphocytes and T-cell link of immune system. Increased number of $TLR9^{+}CD123^{+}$-lymphocytes in RA patients in active phase of EBV-infection in our study can be explained by presence of direct and indirect activation of T-lymphocytes under the impact of TLR9, and activation of B-lymphocytes engaging them in the process of auto-aggression. The research conducted with RA patients points out the role of TLR9 in the phase of initiation of autoimmune processes engaging T-lymphocytes into pathological process [5]. B-lymphocytes can function as antigen-presenting cells, and enhanced expression of TLR9 on them, with active EBV-infection, can support switching of antibodies classes, expanded synthesis of auto-antibodies, intensification of inflammation and increase in activated $CD4^{+}$T-cells. One should mention the role of apoptosis in RA, and its relation to TLR9. It was demonstrated that DNA released due to cell damage can induce TLR9-dependent production of cytokines, thus intensifying the inflammatory process. As we know, during RA there is initiation of apoptosis with production of molecular patterns associated with tissue damage, with their further interaction with TLR, which is referred to key mechanisms of initiation of inflammation in the process of tissue damage with the development of auto aggression.

Chronic active EBV-infection facilitates broad infecting of immunocompetent cells (primarily, monocytes/macrophages, lymphocytes, neutrophils), which eventually leads to auto-aggression. No difference in expression of $TLR9^{+}CD123^{+}$ on monocytes in ReA and RA patients with chronic EBV-infection, and enhanced expression on lymphocytes in RA patients as compared to active ReA patients can be the precondition for transformation of reactive arthritis in rheumatoid arthritis. That is why the use of antiviral medications can fully prevent or slow down the development of auto immune process [8]. Instead, the use of steroid and disease modulatory medication will facilitate favorable conditions for the development of immune disorders and replication and generalization of viral infection. It has been confirmed by other researchers who claim that even in patients with periodic activation of viral infections, including EBV, who do have good disposition for disease modulatory medications, have serious interrupted fluctuations in clinical activity of the disease [12]. Application of antiviral medication that control active replication of the virus can restrain the enhancement of inflammatory process, including also the one of autoimmune origin.

Conclusions

Average age of reactive arthritis patients with chronic EBV-infection turned out to be lower, and was 26.5±7.4 years, with a higher share of men (56.6%), than the average age of rheumatoid arthritis patients – 38.2±6.9 years, with a higher share of women (76.2%).

The number of affected joints was higher in reactive arthritis patients in active phase of EBV infection than in latent phase; strength of inflammatory process of DAS28 was likely higher in rheumatoid arthritis patients with active EBV infection, rather than with latent.

Expression of TLR9+CD123+ on monocytes turned out to be validly (P<0.05) higher in the blood of ReA and RA patients, both in latent and in active phases of EBV infection, as compared to healthy individuals. In ReA patients in active phase of EBV-infection, expression of TLR9+CD123+ on monocytes was higher by 33.3% as compared with similar indicators of patients in latent phase of infection, while the number of TLR9+CD123+-monocytes in patients with ReA and RA in both phases of chronic EBV infection was validly not different.

The number of TLR9+CD123+-lymphocytes compared to the indicators of healthy individuals was validly higher in RA patients in both phases of chronic EBV-infection, while in ReA patients it was only in active phase of the infection. Expression of TLR9 on lymphocytes in RA patients in active phase was by 28.9% higher than in patients in active phase of EBV-infection. Expression of this receptor on lymphocytes turned out to be higher by 23.2% in RA patients as compared with ReA patients in active phase of chronic EBV infection.

References

1. Boyko YY, Chernyshov VP. Tsytokinovi markery ta prohnostychni faktory nespryyatlyvoho perebihu yuvenil′noho idiopatychnoho artrytu. Ukrayinskyy revmatolohichnyy zhurnal. 2012; 49(3):16-21. [in Ukrainian]
2. Volkov MY. Rol Toll-podobnykh retseptorov i ikh endogennykh ligandov v patogeneze revmatoidnogo artrita (obzor literatury). Nauchno-prakticheskaya revmatologiya. 2016; 1(54): 78-85. [in Russian]
3. Zubchenko SO Lymphogram's peculiarities of Patients with Chronic Epstein-Barr Virus Infection at the Stage of the Replicative of the Virus and Autoimmune Syndrome Symptoms. Nauka i Studia. 2014; 123(13): 62-69. [in Ukrainian]
4. Chopyak VV, Potemkina HA, Zubchenko SO. Monitoring effektivnosti ispolzovaniya groprinozina na osnovanii analiza ekspresii TLR9 na immunokompetnykh kletkakh pri lechenii khronicheskoy Epshteyna-Barr virusnoy infektsii v stadii replikativnoy aktivnosti. Nauchno-teoreticheskiy i prakticheskiy zhurnal «Oraldyn Gylym Zharshysy». 2014; 86(7): 69-77. [in Ukrainian]
5. Chen JQ, Szodoray P, Zeher M. Toll-like receptor pathways in autoimmune diseases. Clin Rev Allergy Immunol. 2016; 50(1): 1-17.
6. Davis ML, LeVan TD, Yu F, Sayles H, Sokolove J, et al. Associations of toll-like receptor (TLR)-4 single nucleotide polymorphisms and rheumatoid arthritis disease progression: An observational cohort study. Int Immunopharmacol. 2015; 24: 346–352.
7. Duffy L, O'Reilly SC. Toll-like receptors in the pathogenesis of autoimmune diseases: recent and emerging translational developments. Immunotargets Ther. 2016; 5: 1–7.
8. Fiola S, Gosselin D, Takada K, Gosselin J. TLR9 contributes to the recognition of EBV by primary monocytes and plasmacytoid dendritic cells. J. Immunol. 2010; 185: 3620–3631.
9. Goh FG, Midwood KS. Intrinsic danger: activation of Toll-like receptors in rheumatoid arthritis. Rheumatology (Oxford). 2012; 1(51): 7-23.
10. Ivashkiv LB. PTPN22 in autoimmunity: different cell and different way. Immunity. 2013; 39(1): 91–93.
11. Lacerte P, Brunet A, Egarnes B, Duchêne B, Brown JP, Gosselin J. Overexpression of TLR2 and TLR9 on monocyte subsets of active rheumatoid arthritis patients contributes to enhance responsiveness to TLR agonists. Arthritis Res Ther. 2016; 18: 10.
12. McGettrick, AF, O'Neill, LA. Localisation and trafficking of Toll-like receptors: an important mode of regulation. Curr. Opin. Immunol. 2010; 1(22): 20-27.
13. Ning S. Innate immune modulation in EBV infection. Herpesviridae. 2011; 2: 1. doi: 10.1186/2042-4280-2-1
14. Schmitt SK. Reactive Arthritis. Infectious Diseases Clinics. 2017; 31(2): 265-277.
15. Vogelpoel LT, Hansen IS, Rispens T, Muller FJ, van Capel TM, et al. Fc gamma receptor-TLR cross-talk elicits pro-inflammatory cytokine production by human M2 macrophages. Nat Commun. 2014; 5: 5444.

Реферати

ОСОБЛИВОСТІ ЕКСПРЕСІЇ TLR9 НА ІМУНОКОМПЕТЕНТНИХ КЛІТИНАХ У ХВОРИХ НА РЕАКТИВНИЙ АРТРИТ З ХРОНІЧНОЮ ЕПШТЕЙНА-БАРР ВІРУСНОЮ ІНФЕКЦІЄЮ

Ломіковська М.П., Гайдучок І.Г., Потьомкіна Г.О., Зубченко С.О., Кріль І.Й., Іщейкін К.Є., Чопяк В.В.

У даній статті авторами представлені результати дослідження експресії TLR9 на імунокомпетентних клітинах у хворих на реактивний артрит з хронічною Епштейна-Барр вірусною інфекцією та розглянуто можливість трансформації реактивного артриту в ревматоїдний артрит. Встановлено, що експресія TLR9+CD123+ на моноцитах виявилась достовірно вищою у крові хворих на реактивний артрит порівняно зі здоровими особами, при цьому в хворих в активній фазі ЕБВ-інфекції експресія цього рецептора була достовірно вищою порівняно з аналогічними показниками хворих в латентній фазі, а число TLR9+CD123+-моноцитів - у хворих на реактивний та ревматоїдний артрит достовірно не відрізнялось. Кількість TLR9+CD123+-лімфоцитів порівняно із

ОСОБЕННОСТИ ЭКСПРЕССИИ TLR9 НА ИММУНОКОМПЕТЕНТНЫХ КЛЕТКАХ У БОЛЬНЫХ РЕАКТИВНЫМ АРТРИТОМ С ХРОНИЧЕСКОЙ ЭПШТЕЙНА-БАРР ВИРУСНОЙ ИНФЕКЦИЕЙ

Ломиковская М.П., Гайдучок И.Г., Потемкина Г.О., Зубченко С.О., Криль И.Й., Ищейкин К.Е., Чопяк В.В.

В данной статье авторами представлены результаты исследования экспрессии TLR9 на иммунокомпетентных клетках у больных реактивным артритом с хронической Эпштейна-Барр вирусной инфекцией и рассмотрена возможность трансформации реактивного артрита в ревматоидный артрит. Установлено, что экспрессия TLR9+CD123+ на моноцитах оказалась достоверно выше в крови больных реактивным артритом по сравнению со здоровыми лицами, при этом у больных в активной фазе ЭБВ-инфекции экспрессия этого рецептора была достоверно выше по сравнению с аналогичными показателями больных в латентной фазе, а число TLR9+CD123+ моноцитив - у больных реактивным и ревматоидным артритом достоверно не отличалось. Количество TLR9+CD123+лимфоцитов по сравнению с

показниками здорових осіб була достовірно вищою у хворих на ревматоїдний артрит в обох фазах хронічної ЕБВ-інфекції, а в пацієнтів з реактивний артритом - тільки в активній фазі цієї інфекції. Експресія цього рецептору на лімфоцитах виявилась достовірно вищою у хворих на ревматоїдний артрит порівняно із хворими на реактивний артрит саме в активній фазі хронічної ЕБВ інфекції.

Ключові слова: реактивний артрит, ревматоїдний артрит, хронічна Епштейна-Барр вірусна інфекція, TLR9.

Стаття надійшла 24.05.2019 р.

показателями здоровых лиц была достоверно выше у больных ревматоидным артритом в обеих фазах хронической ЭБВ-инфекции, а у пациентов с реактивным артритом - только в активной фазе этой инфекции. Экспрессия этого рецептора на лимфоцитах оказалась достоверно выше у больных ревматоидным артритом по сравнению с больными реактивным артритом именно в активной фазе хронической ЭБВ инфекции.

Ключевые слова: реактивный артрит, ревматоидный артрит, хроническая Эпштейна-Барр вирусная инфекция, TLR9.

Рецензент Катеренчук І.П.

DOI 10.26724/2079-8334-2020-1-71-88-93
UDC 616.915/.24-002-053

I.I. Nezhoda, A.O. Havryliuk, A.A. Asaulenko, L.P. Kholod, Ye.S. Onofriychuk
Vinnytsya Pyrohov Memorial National Medical University, Vinnytsya

MEASLES PNEUMONIA IN CHILDREN: CLINICAL AND MORPHOLOGICAL FEATURES OF THE COURSE

e-mail: asaulenko.alla@gmail.com

The article presents the results of a retrospective analysis of 96 patients' histories with measles established, with a detailed course study and the anamnestic data analysis. The measles infection course was accompanied with signs of the intoxication syndrome, the classic catarrhal triad manifestation (coughing, rhinorrhea and conjunctivitis), and the exanthema syndrome. Most of the diseased children are not vaccinated against measles. The patients had a complicated disease course with manifested symptoms of measles pneumonia, as the most common complication in this pathology. Morphological and histological changes of the lungs in children with severe mesles course were characterized by abundant infiltration of both the interalveolar septa and alveolar lumens by polymorphocellular infiltrate, consisting of neutrophilic leukocytes, eosinophils, lympho-histiocytes with numerous parietal hyaline masses (hyaline membranes). There was a giant-cell metaplasia of the alveolar epithelium.

Key words: measles in children, pneumonia, pathomorphological changes, histological examination.

The work is a fragment of the research project "Early diagnosis of dysplastic, metaplastic and neoplastic changes in the pathology of the gastrointestinal tract, respiratory, urogenital and neuroendocrine system", state registration No. 0117U000001.

At the present stage, measles remains an extremely important problem of today. Both in the world and in Ukraine, every five to six years an increase in the measles incidence is observed. According to the European Regional Bureau of the World Health Organization (WHO), since 2017, over 22,300 measles cases have been reported in different countries of Europe. In 8 countries of the European Region, 57 people died from measles during the first half of 2018 [2].

At the same time, Ukraine occupies a leading position among the countries of the said region. In the period from 1 January to 31 August 2018, 29 465 measles cases were reported in Ukraine, with fatal cases (13 deaths) [2].

Measles is a very threatening and contagious infection. It is known that the risk of this infection lies in the development of serious complications, such as pneumonia, otitis, encephalitis, renal toxicity, polyneuritis, etc. [4, 5]. They are caused directly by the action of the virus itself [6]. Since the measles virus causes cells dystrophy in all mucous membranes, particularly in the respiratory tract, and due to its effect on monocytes, there is an increased production of interleukins, tumor necrosis factor, histocompatibility molecules, and the presentation of antigens to T-lymphocytes is inhibited, these factors cause immunosupression, reduce cellular immunity [7]. T-cell immunodeficiency is particularly pronounced, persisting for 25-30 days after the disease (post-measles anergy) [4]. Against this background, all conditions are created for the development of secondary bacterial complications [7].

In the Vinnytsya region, for the period from January 2018 to February 2019, 4805 persons were diagnosed with measles, including 2210 children. It should be noted that children with the most severe measles course were treated at the Vinnytsya Regional Children's Clinical Infectious Diseases Hospital (VOCDIL).

Within the period from January 2018 to April 2019, 781 patients with measles were treated in hospital. Among all cases of the complicated measles course, measles pneumonia was most commonly reported. In one of the complicated measles cases, the disease had fatal outcome. The death was due to the development of pneumonia against the background of congenital lung pathology.

The purpose of the study was to find out clinical and morphological features of the pneumonia course in children with measles.