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Features Of The Immunity T-System In Patients With Glomerulonephritis With Nephrotic Syndrome

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Keywords:*glomerulonephritis, nephrotic syndrome, T-lymphocytes, T-regulatory cells, subpopulation of T-lymphocytes.*

The study of issues related to glomerulonephritis with nephrotic syndrome is one of the pressing problems of medicine due to their prevalence throughout the world, mainly in the young age group. There are primary (idiopathic) nephrotic syndrome, which occurs in 80-90% of cases, and secondary nephrotic syndrome, associated primarily with systemic autoimmune diseases, diabetes mellitus and neoplasms. It is known that glomerulonephritis, manifested by nephrotic syndrome (membranous nephropathy, focal segmental glomerulosclerosis, minimal change nephropathy), are autoimmune diseases. To date, the immunological mechanisms of the pathogenesis of glomerulonephritis with nephrotic syndrome associated with the T-system of adaptive immunity remain unexplored.

Purpose of the study*– to study the role of the T-immune system in the pathogenesis of primary nephrotic syndrome based on the study of immunoregulatory, activated subpopulations of T-lymphocytes of patients with this pathology.*

Material and methods.*The study included 136 patients with chronic glomerulonephritis with nephrotic syndrome. Assessment of the T-system of immunity included determination of the phenotype of lymphocytes, immunoregulatory subpopulations of T-cells (T-helpers/inducers, cytotoxic T-lymphocytes), various subpopulations of activated T-cells (activated T-lymphocytes; activated T-lymphocytes, expressing CD25 - IL-2 receptor alpha chain; activated cytotoxic T lymphocytes expressing HLA-DR and CD38) and regulatory T cells (Treg cells).*

Research results*. In patients of the examined cohort, an increase in the number of T-lymphocytes and T-helper cells, as well as activated T-lymphocytes expressing HLA-DR antigens, was found. At the same time, the indicators of the content of cytotoxic T cells and the number of activated T cells expressing the IL-2 receptor – CD25 did not differ from similar indicators in healthy individuals. The content of Treg cells and activated cytotoxic T lymphocytes with the CD3+CD8brightCD38+ phenotype was reduced. The immunoregulatory index (T helper cells/cytotoxic T lymphocytes) was increased, which was due to an increase in the number of T helper cells against the background of a constant number of cytotoxic T lymphocytes.*

Conclusions.*The results of the study indicate that the main features of the T-system of the immune response in primary nephrotic syndrome are an imbalance in the*

ratio of the content of immunoregulatory cells due to the predominance of T-helper cells and a decrease in the number of Treg cells.

The study of issues related to glomerulonephritis (GN) with nephrotic syndrome (NS) is one of the acute problems of medicine due to their prevalence throughout the world, mainly in the young age group. Every year, an average of 3 new cases of NS are registered per 100,000 adults and 2-7 cases in children under 18 years of age [8].

There are primary (idiopathic) NS (pNS), which occurs in 80–90% of cases, and secondary NS, associated primarily with systemic autoimmune diseases, diabetes mellitus and neoplasms. The main features of NS are proteinuria above 3.5 g per day, hypoalbuminemia below 30 g/l, hyperlipidemia and severe edema [20]. Depending on response to therapy

Steroids are classified into steroid-sensitive NS (SSNS) and steroid-resistant NS (SRNS). SRNS leads to chronic kidney disease (CKD) and end-stage renal failure in approximately 50% of patients [23].

Although there is no doubt that the main link in the development of nephrotic proteinuria is an increase in the permeability of the glomerular filter due to damage to podocytes, the immunological mechanisms of the pathogenesis of GN with NS remain unexplored. It has been shown that the key link in the immunopathogenesis of PNS is the imbalance between the immunoregulatory subpopulations of T lymphocytes – CD4+ cells (T helper cells) and CD8+ cells (cytotoxic cells). It has been established that most children with pNS experience a decrease in the number of CD4+ T cells circulating in the blood and an increase in CD8+ T cells during the period of disease relapse [11, 16]. The opposite result was obtained by A. Kuroki et al. in a study of a group of patients with PNS who had an increased CD4+ T-cell/CD8+ T-cell index [16]. In recent years, data have been obtained indicating a key role in the development of autoimmune diseases, which include GN with NS, of T-regulatory cells (Treg cells) of the subpopulation of T-helper cells [14]. When analyzing immunological blood parameters, we focused on cellular differentiation markers – CD (from the English “Cluster of differentiation”).

At the same time, the indicators of the content of cytotoxic T cells and the number of activated T cells expressing the IL-2 receptor – CD25 did not differ from similar indicators in healthy individuals. The relative content of Treg cells and activated cytotoxic T lymphocytes with the CD3+CD8brightCD38+ phenotype was reduced. The immunoregulatory index (T-helper/cytotoxic T-lymphocytes) was increased, which was due to an increase in the number of T-helper cells against the background of a constant number of cytotoxic T-lymphocytes.

Notes: indicator values are presented as a fraction, the numerator of which is the median, the denominator is the interquartile range of values, NS - the difference is statistically insignificant (pm-w >0.05).

Discussion of the research results. Frequency analysis

of various histomorphological forms in the patients with GN and NS included in the study demonstrates the predominance of BNP. FSGS is in second place in terms of

frequency of occurrence. According to the literature, BNP is one of the most common causes of NS in adults and one of the main causes of end-stage renal failure [4]. The incidence of MNP has increased dramatically in recent years. A retrospective study of medical records of 630 patients hospitalized in various medical institutions in China, who underwent histomorphological examination of nephrobiopsy samples from January 1, 2009 to December 31, 2018, confirmed that the incidence of BNP (24.96%) exceeded the incidence of IgA nephropathy (24). .09%), which was considered the most common type of primary GN in China in adults [9]. Our data correspond to the literature data on the predominance of BNP among all histomorphological variants of pNS in European countries and China. Information known from the literature that GN with NS affects young people, mainly males, is also confirmed by the demographic indicators of the cohort of patients we examined. 39.7% of hospitalized patients had frequent relapses of NS, which explains the rather high average number of relapses during the year.

Summarizing the results of the analysis of immunological parameters in patients with GN, it should be noted that the identified changes indicate the presence of an imbalance between the main immunoregulatory subpopulations of T-lymphocytes - T-helper cells and cytotoxic T-lymphocytes due to an increase in the number of the former. A. Kuroki et al. also reported an increase in the T-helper/cytotoxic T-lymphocyte ratio in patients with BNP against the background of preservation

the content of cells of these subpopulations at the levels of healthy individuals [15]. In accordance with our data, the content of immature T-lymphocytes was lower than in healthy individuals, which is apparently due to the activation of T-lymphocytes and the acquisition of an activation marker - HLA-DR. It is known that HLA-DR are antigens of the human histocompatibility complex class II; the degree of their expression on the surface of T cells increases in the later stages of activation [1]. The content of cells of the most active subpopulation of cytotoxic T lymphocytes carrying the CD38 antigen turned out to be reduced against the background of a high density of expression of the CD8 antigen. Lymphocytes of this subpopulation are activated, proliferating and cytotoxic transport cells [12]. A decrease in their number relative to healthy individuals indicates depression of T-cell cytotoxicity. Previous studies did not reveal significant changes in the T-system of immunity in adult patients with GN and NS [3, 5]. Changes have been described only in the content of Treg cells [19], which have the ability to suppress immune reactions to ensure an adequate balance of the immune system’s response to foreign antigens and self-antigens. The main functions of these cells are blocking the pathogenic immunological response mediated by autoreactive cells, establishing and maintaining immune homeostasis in tissues. So, the data obtained indicate an increase in the content of T-helper cells and a depression in the activation of cytotoxic T-lymphocytes - the main effector cells of the cellular link of adaptive immunity.

Mutual regulatory relationships between the cellular and humoral mechanisms of adaptive immunity suggest activation of the humoral mechanism in conditions of depression of the cellular component of the adaptive immune response. It seems that the

increase in the number of T helper cells in patients with pNS that we discovered is due to an increase and activation of type 2 T helper cells (Th2), associated with the activity of humoral immunity. Previously, it was reported about the predominance of Th2 cell activity in patients with NS under conditions of suppressed self-tolerance associated with a decrease in the content and activity of Treg cells. An increase in the number of Th2 cells is an important cause of abnormal secretion of IgG by B cells and deposition of immune complexes (Ig + antigen) in the kidneys [15]. Activation of the humoral component of adaptive immunity causes the formation of autoantibodies that bind to autoantigens of glomerular podocytes. The resulting immune complexes are localized subepithelially, activating the complement system, the effector components of which have a damaging effect on podocytes and cause an increase in the permeability of the glomerular filter. Evidence of the participation of autoimmune mechanisms of the humoral type in the development of GN with NS may be the detection in 70-90% of patients with BNP, the main histomorphological variant of PNS, of circulating autoantibodies against transmembrane phospholipase A2 receptor 1 (PLA2R1) or against thrombospondin containing domain type 1 7A (THSD7A) [18]. Another evidence of the importance of humoral mechanisms in the pathogenesis of GN with NS are the successful results of their treatment with rituximab, an mAb against CD20 B lymphocytes, the main cells of humoral immunity. These mCA are fixed on the surface of B-lymphocytes, activate the complement system and cause the destruction of these cells through the mechanism of complement-dependent cytotoxicity [12].

Conclusions. The results of the study indicate that the main features of the T-system of the immune response in GN with NS are an imbalance in the ratio of T-helper and cytotoxic cells and a decrease in the number of Treg cells. The content of the number of cytotoxic T-lymphocytes is comparable to that in healthy people, and the number of cells of their most active subpopulation – CD3+CD8brightCD38+ – is reduced, therefore, cytotoxic T-lymphocytes are not involved in the pathogenesis of GN with NS. Continued research is required to clarify the role of immunoregulatory subpopulations of T helper cells - Th1, Th2, Th17, Treg cells in the development of refractory NS. For this purpose, it is necessary to study the features of the cytokine profile in pNS with an emphasis on cytokines associated with the activity of cell subpopulations altered in pNS.

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