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IMMUNOLOGICAL DIAGNOSTICS AND PREDICTION OF THE COURSE OF RENAL PARENCHYMA CANCER (LITERATURE REVIEW)

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Abstract. Despite the expansion of diagnostic capabilities to detect renal parenchymal tumors, one third of patients already have remote metastases at primary examination, which significantly limits the possibility of radical treatment. A close relationship was found between qualitative and quantitative changes of components of the immune system and histological structure of malignant neoplasm parenchyma of the kidney. In the cell link of immunity at early stages of development of renal parenchymal tumor, there is a pathological correlation between functional changes of regulatory T-lymphocytes, cytotoxic T-lymphocytes and natural killers. This dependence leads to immunological evasion of tumor cells and further proliferation of tumor tissue. In later stages, a key factor in the pathogenesis of anti-tumor immunological tolerance is the violation of immune humoral link factors (changes in serum concentration of immunoglobulins, activation of interleukins). The functional duality of interleukins under normal conditions balances proliferative and cytotoxic pathways of disease pathogenesis, leading to recovery. However, in the stroma of a tumor and its microenvironment, this duality not only promotes an increase in the tumor mass, but also leads to regional and distant metastasis. Clarification of the mechanisms of immunological changes leading to the development of anti-tumor immunological tolerance in patients with renal parenchymal cancer will allow early diagnosis of the oncological process, monitoring the effectiveness of personalized anti-tumor therapy. Definition of clear criteria for changing the composition of immune cells, identification of markers of the organism's immunological tolerance to tumor tissue is quite relevant and can serve as a basis for developing methods of predicting the course of the disease and monitoring the effectiveness of the treatment.

Keywords: immunological diagnostics, renal parenchyma tumor, immunological disorders, antitumor immunological tolerance, T-lymphocytes, tumor microenvironment, diagnostic early detection markers for renal cell carcinoma

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ИММУНОЛОГИЧЕСКАЯ ДИАГНОСТИКА И ПРОГНОЗИРОВАНИЕ ТЕЧЕНИЯ РАКА ПАРЕНХИМЫ ПОЧКИ (ЛИТЕРАТУРНЫЙ ОБЗОР)

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Резюме. Несмотря на расширение диагностических возможностей выявления опухолей паренхимы почки, у трети пациентов уже при первичном обследовании обнаруживаются отдаленные метастазы, что существенно ограничивает возможности радикального лечения заболевания. Выявлена тесная взаимосвязь между качественными и количественными изменениями компонентов иммунной системы и гистологической структурой раковой опухоли паренхимы почки. В клеточном звене иммунитета на ранних стадиях развития этой опухоли возникает патологическая взаимозависимость между функциональными изменениями регуляторных и цитотоксических Т-лимфоцитов и натуральных киллеров. Такая зависимость приводит к иммунологическому ускользанию опухолевых клеток и дальнейшей пролиферации опухолевой ткани. На более поздних этапах ключевым фактором в патогенезе противоопухолевой иммунологической толерантности становится нарушение гуморального звена иммунитета (изменение сывороточной концентрации иммуноглобулинов, активация интерлейкинов). Функциональный дуализм интерлейкинов в норме уравновешивает пролиферативные и цитотоксические пути патогенеза заболевания, приводя к выздоровлению. Однако в строме опухоли и в ее микроокружении такой дуализм способствует не только увеличению опухолевой массы, но и приводит к регионарному и отдаленному метастазированию. Уточнение механизмов иммунологических изменений, приводящих к развитию противоопухолевой иммунологической толерантности у пациентов с онкологическими заболеваниями паренхимы почек, позволит осуществлять раннюю диагностику онкологического процесса, контроль эффективности персонифицированной противоопухолевой терапии. Определение четких критериев изменения состава иммунных клеток, выявление маркеров иммунологической толерантности организма к опухолевой ткани весьма актуально и может послужить основанием для разработки методов прогнозирования течения заболевания и контроля эффективности проводимого лечения.

Ключевые слова: иммунологическая диагностика, опухоль паренхимы почки, иммунологические нарушения, противоопухолевая иммунологическая толерантность, Т-лимфоциты, микроокружение опухоли, ранние диагностические маркеры почечно-клеточного рака

Currently renal parenchymal cancer is the most common malignant neoplasm of the kidney. It ranks 14th in the structure of cancer incidence worldwide [1, 2]. At the same time, the share of renal cell carcinoma (RCC) in the overall structure of cancer incidence in Russia is about 4.0%. Despite the improvement of modern methods of RCC diagnosis, which allow detecting up to 50–60% of cases of localized tumor process (stage T1-2N0M0), 25–30% of patients already have distant metastases at the time of initial consultation [1, 2]. According to the International Agency for Research on Cancer, more than 400,000 new cases and more than 170,000 deaths from RCC are registered worldwide each year. At the same time, the incidence among the working-age population worldwide is increasing by 3–5% annually, while mortality is gradually decreasing [3]. Nevertheless, early diagnosis, prognosis, and monitoring of the effectiveness of complex treatment of RCC remain relevant issues in oncological urology, requiring the development of new approaches and criteria for evaluating the process. Leading scientific centers are searching for specific tumor markers that characterize both the presence of the tumor process itself and its individual characteristics. Immunological markers of the disease are of particular interest. Recent research data indicate that the tumor and its microenvironment function as a "system within a system" during carcinogenesis and have their own separate complex of immunological defense against the immune response of the human body [1–3].

At present, convincing data has been obtained on the influence of the tumor microenvironment on the development, course, and progression of malignant processes of any localization. Under the influence of tumor cells, T-lymphocytes (which mainly infiltrate tumor tissue) acquire new properties, exhibiting both anti-tumor and protumor activity. A special environment is formed in the tumor microenvironment, which allows the recruitment of immune cells of the human body, changing their functions, thereby providing an opportunity for the favorable growth of tumor invasion and its spread throughout the body [4, 5].

Immunological surveillance plays a leading role in the body's antitumor defense system. The immune response, as a specific reaction of the immune system, is mediated by cellular immunity involving NK cells and cytotoxic T lymphocytes (CTL) [6, 7]. A number of studies have revealed the ability of neutrophils to exert a pronounced cytotoxic effect on tumor cells through the production of active oxygen species as a result of a process called "respiratory burst" [8, 9]. The diversity of receptors makes the cells of the immune system highly sensitive to any changes in homeostasis so that they can provide full protection for the body. The normal activation of the immune system in response to the formation of tumor cells in the body's tissues leads to a quantitative change in the composition of immune cells at the site of tumor invasion, the production of a wide range of cytokines and other active substances involved in the regulation of intercellular interactions and the activation of signaling pathways. As a result, processes of proliferation inhibition and activation of tumor cell apoptosis are triggered [8, 9]. However, in some cases, the development and growth of malignant neoplasms in various locations can cause malfunctions in the immune system. A decrease in its functional activity in response to the specific morphofunctional characteristics of tumor cells allows the latter not only to overcome the immunological barrier, but also to exert a local and general immunosuppressive effect. Tumor cells and immune cells in the tumor microenvironment are able to use immune system mediators for their own progression [10, 11].

The adaptive immune system within the structure of immunological surveillance is an important component of the human body's antitumor immune response. The main effector cells of adaptive antitumor immunity are cytotoxic T lymphocytes with the CD3+CD8+ phenotype. Clinical studies confirm a positive correlation between tumor infiltration by CD3+CD8+ T cells and patient survival [12–14]. Current understanding of the pathogenesis of antitumor immunological tolerance suggests that the reduction in immune response upon the emergence of a primary tumor of various locations is associated with infiltration by specific regulatory T lymphocytes (RTL; with the CD3+, CD4+, CD25+, CD45R0+, CD95+) into both the tumor itself and its microenvironment [11, 15].

It has been proven that RTL contribute to the formation of antitumor immunological tolerance, which plays a key role in the development and progression of malignant neoplasms of the renal parenchyma. The formation of antitumor immunological tolerance is also associated with several factors:

- impaired MHC-I expression (decreased or complete absence of expression of major histocompatibility complex type I molecules hinders the recognition of tumor cells by the immune system);
- secretion of immunosuppressive cytokines (RTL infiltrating the tumor secrete interleukin-10 and transforming growth factor beta-1, which leads to the activation of the transcription factor FOXP3 (scuprin) and enhancement of the suppressive activity of CD4+ regulatory T cells);
- decreased functional activity of effector T cells, dendritic cells, and antigen-presenting cells, suppression of TCL co-stimulation [14–16, 30].

Thus, RTL actively participate in creating an immunosuppressive environment in the tumor, promoting its growth and progression.

Analysis of immunograms of patients with RCC revealed the greatest changes in the populations of immune system cells directly involved in the pathogenesis of this disease. The data obtained indicate a violation of T-lymphocyte (CD3+) activation in the peripheral blood of patients with RCC and a redistribution of the T-cell link of the adaptive immune system. This manifests itself in an increase in the number of CD3+, CD4+, CD25+, CD127+ T-lymphocytes and a more "mature" stage of their development. At the same time, these cell populations perform their main functions in the body's tissues. Consequently, the changes in the lymphocyte link detected in peripheral blood cannot sufficiently characterize the depth of pathological immunological disorders in the tumor microenvironment [17].

In a study devoted to the investigation of immunological blood parameters in patients with RCC depending on the histological structure of the tumor, it was established that in patients with clear cell histological type of RCC (ccRCC), the absolute number of mature T-lymphocytes (phenotype CD3+), B-lymphocytes (CD19+), and the percentage and absolute content of CD4+ cells in the preoperative period was also reduced. At the same time, despite an increase in the percentage of RTL expressing the "late" activation marker HLA-DR+ (sublocus DR of the human major histocompatibility complex class II), their absolute number was reduced. In the case of mixed-type RCC (mtRCC), only a decrease in the absolute number of CD19+ cells in venous blood was noted before surgery. After surgical treatment, a statistically significant decrease in the absolute content of RTL (phenotype CD3+, CD4+, CD8+) in peripheral blood was detected in this group of patients [18]. This fact can be used as one of the criteria indicating the sufficient radicalism of the surgical intervention performed. A number of other studies have shown that RCC is accompanied by an increase in the quantitative level of RTL (with the CD3+CD4+CD25highCD127low phenotype) while maintaining the total number of T-regulators (compared to control values) [17, 19].

To gain a comprehensive understanding of changes in the immune system in the event of malignant neoplasms of the renal parenchyma, canonical relationships between RTL, CTL, and NK cells were studied. In healthy individuals, a weak correlation with effector T-cell subpopulations was observed. It was found that RTL and T effectors demonstrate bidirectional activity during tumor growth, which is confirmed by a positive correlation with NK cells (expressing CD28 and CD57). At the same time, a negative correlation was found with mature and regulatory NK cell populations. The authors concluded that the interdependence of RTL, CTL, and NK cells, which provides the immune and pathogenetic mechanisms of malignant neoplasms of the kidney, can be used in the development of targeted immunotherapy aimed at activating antitumor immunity [20, 21].

The study of serum immunoglobulin concentrations (IgA, IgM, and IgG) is of great practical interest. Analysis of the laboratory data obtained showed that in the group of patients with ccRCC, an increase in IgG levels was recorded both in the preoperative and postoperative periods relative to the indicators in the group of patients with mtRCC. It is noteworthy that patients with mtRCC showed a significant decrease (1.8 times, $p < 0.05$) in serum IgA concentration after surgical treatment compared to patients with ccRCC [18, 22].

In the stroma of high-grade malignant renal parenchymal tumors (compared to low-grade tumors) according to Fuhrman, a higher content of positive actin-smooth muscle cells was found, which correlated with the level of tumor progression and survival in this group of patients. Although the stromal tissue of RCC contained a significant number of T lymphocytes (CD4+), which are the main source of IL-6, data on the significance of inflammatory infiltrate density in the progression of this disease are scarce and contradictory [23, 24].

Cytokines are known to play an important role in regulating the main stages of the immune response. They can act as antagonists and synergists, complementing each other. The functional dualism of cytokines normally balances the proliferative and cytotoxic pathways of disease pathogenesis, leading to recovery [11, 14, 25]. However, in the tumor stroma and its microenvironment, such dualism not only contributes to an increase in tumor mass, but also leads to regional and distant metastasis [11, 26].

The transformation of the cytokine network in the tumor microenvironment is associated with the development of epithelial-mesenchymal transition (EMT), which accompanies tumor growth and activation of metastasis [27]. During a comparative analysis of the functional properties of various cytokines, their production in the tumor microenvironment and blood of patients with RCC was studied. It was found that in the tumor tissue of patients with RCC, the induced production of interleukin-10 (IL-10), interferon γ (IFγ), and tumor necrosis factor α (TNFα) was significantly reduced compared to this indicator in blood serum. At the same time, the induced production of IL-6 in the tumor microenvironment was significantly lower, and the production of vascular endothelial growth factor (VEGF) was significantly higher compared to the serum concentration. A high number and degree of RTL infiltration was noted, as well as a low content of TCL and activated NK cells in the organ

parenchyma. The tumor «microenvironment» in patients with RCC was characterized by low induced production of a number of cytokines (IL-6, IL-8, IL-10, IFγ, TNFα) and high induced production of VEGF, high spontaneous production of certain cytokines (IL-6, IL-10, IFγ, TNFα) [23, 27]. Some researchers suggest using TNFα, IL-6, IL-8, and IL-10 values as prognostic and predictive factors for evaluating the effectiveness of immunotherapy [28].

Thus, there is now sufficient evidence that studying the concentration of cytokines — mediators of immunoregulatory processes in blood serum and tissues that characterize the activity of immune cells infiltrating tumors — in patients with RCC is extremely important. Undoubtedly, the increase in the level of pro-inflammatory cytokines (IL-6, IFγ, TNFα) in the peripheral bloodstream due to their paracrine secretion is caused by the restructuring of the cytokine network of the tumor microenvironment associated with the development of EMT. This leads to a change in the activity of the antitumor immune response, which, in turn, contributes to invasion and metastasis of malignant cells.

A comprehensive analysis of immunological changes leading to the development of antitumor immunological tolerance depending on the severity of RCC has demonstrated the need for further study of the qualitative and quantitative composition of immune cells and the content of immunological markers in blood serum and tumor tissue in patients with malignant neoplasms of the renal parenchyma. The data obtained, as well as the validation of the degree of identified disorders at different degrees of severity of RCC, can be used to monitor the effectiveness of antitumor therapy, predict the course of the oncological process, and the development of complications [29, 30].

Further study of the coordinated activity of RCC, effector T cells, and NK cells is advisable for the development of new directions in targeted immunotherapy aimed at increasing antitumor immunological tolerance. Despite data obtained in numerous studies indicating changes in the components of the immune system in blood serum and tumor tissues in patients with malignant neoplasms of the renal parenchyma, there is no validation of changes in the qualitative and quantitative composition of immune cells that characterize the stage and predict the course of RCC. Further research and the development of clear diagnostic and prognostic criteria for the course of the tumor process are needed. Nevertheless, an increase in the number of RTL in peripheral blood and renal parenchymal tissues, as well as changes in mediator values (TNFα, IL-6, IL-8, IL-10), can be considered predictors of the aggressiveness and progression of the tumor process. It is obvious that blood immunological parameters (percentage of RTL, mature T-lymphocytes with CD3+, CD19+, CD4+, CD8+ cell phenotypes, serum immunoglobulin A concentrations) in patients with RCC depend on the histological structure of the tumor. A more in-depth study of the mechanisms of immunological disorders developing in patients with malignant lesions of the renal parenchyma at various stages of the oncological process of the organ, taking into account histological, pathological and morphological characteristics, will make it possible to predict the course of the oncological process, develop and monitor the effectiveness of personalized antitumor therapy, predict the development of complications, which will help reduce the risk of recurrence and metastasis, improve the quality of life of patients and its duration.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Competing interests. The authors declare that they have no competing interests.

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