On the Issue of Pathogenetic Factors of Myeloma Development

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ABSTRACT

The paper presents current views on the etiology and pathogenesis of multiple myeloma. The article reviews the literature on epidemiology, mechanism of development, and risk factors for the development of the disease. Multiple myeloma is a malignant tumor of B-cell origin, the morphological substrate of which is plasma cells that produce its monoclonal immunoglobulin. Literature data show that multiple myeloma has an ambiguous distribution pattern, and there is a tendency for its annual growth. Although the etiology of multiple myeloma is not fully understood, according to most researchers, the risk factors leading to a progressive increase in the incidence of the population include old and senile age, male gender, and exposure to negative environmental factors. Long-term antigenic stimulation plays a certain role, which is confirmed by the increased frequency of multiple myeloma in patients with chronic and inflammatory diseases. It was revealed that cytokines and genetic aspects play an important role in the development of the disease. Характерными для Multiple myeloma is characterized by non-specific symptoms and similarity of its clinical manifestations with other diseases, which is one of the reasons for late diagnosis. Injuries to internal organs, in particular the heart and kidneys, arene of the most frequent complications of multiple myeloma, the combined occurrence of which leads not only to mutual aggravation, but also is one of the factors of early adverse outcomes. Despite the research conducted to date, much of the pathogenesis of multiple myeloma has not been disclosed, which dictates the need for a more in-depth and comprehensive study of the problem.

Keywords: multiple myeloma, pathogenesis, bone marrow, malignant tumor

The study of myeloma is one of the most urgent tasks in medicine. Multiple myeloma, being one of the most common malignant tumors of the hematopoietic system, according to the classification of the World Health Organization (WHO) refers to tumors with a predominantlesion of B cells. In the first place in the structure of mortality among hematological diseases are acute leukemias, the share of multiple myeloma accounts for 11%. The incidence of multiple myeloma in recent decades, along with non-Hodgkin 's lymphomas and acute myeloblastic leukemias, has increased markedly. According to the National Cancer Institute, about 20,000 new cases of multiple myeloma are detected annually, which is the second most common type of hematopoietic cancer after non-Hodgkin's lymphoma [1].

Multiple myeloma is a disease of the blood system caused by malignant proliferation of plasma cells, followed by their infiltration of the bone marrow, the presence of monoclonal immunoglobulin (M-protein), osteolytic bone lesions and the development of renal failure [2, 3]. According to the classification, there are 5 immunochemical variants of multiple myeloma, depending on the produced immunoglobulin: G, A, D, E, as well as non-secreting myeloma, in

which immunoglobulins are not released. The frequency of distribution of normal immunochemical types of multiple myeloma corresponds to the concentration of normal immunoglobulins in the blood serum: G-myeloma is detected in 50% of cases, A-myeloma-in 25%, D-myeloma-in 1%, M-myeloma and the unclassifying form are very rare [4, 5]. The most prognostically favorable option is considered to be multiple myeloma of the G-immunochemical variant.

Among all malignancies in different ethnic groups, multiple myeloma accounts for 1%, and in the structure of hemoblastoses up to 20% 1%, and in the structure of hemoblastoses up to 20%. Four new cases per 100,000 populations are registered annually in European countries [6]. Mostly мmural myeloma is observed in patients aged after 40 years and the average age at diagnosis of the disease is 62 years. It describes only a single number of cases of patients over 30 years of age, the proportion of which is 2-3%, and there is no information about the incidence in children. Men suffer from this hematopoiesis somewhat more often than women [7, 8].

The effectiveness of any scientific research in medicine depends on the benefit to the patient directly or on the possibility of a clearer diagnosis, more effective treatment. At present, when traditional pathology has common borders with fundamental medical and biological disciplines, it is possible to determine the prognosis of many diseases, primarily tumor diseases. Therefore, research on multidimensional myeloma remains relevant, and as it was 50 years ago, it can be useful for solving a number of generalй medical-and biological problems.

This disease was first described in Russia by G. A. Alekseev and was called "myeloma disease". The term "multiple myeloma", proposed by Rustitsky, is widely used abroad. Other names of this disease - "Rustitsko-Kaleradisease", "generalized plasmocytomas" - are used infrequently at the moment.

The pathogenesis is based on the interaction of bone marrow with neoplastic cells. As a result of a violation that can cause tumor adhesion, a violation of the balance between osteoblasts and osteoclasts, which leads to stimulation of the production of pro - and anti-inflammatory cytokines and tumor growth [3, 9, 10]. The causes that contribute to the development of multiple myeloma are still unknown today. So far, many theories have been proposed about the transformation of normal cells into cancer cells. Potential risks that contribute to the occurrence and progression include contact with carcinogens, radioactive substances, as well as deterioration of the general state of the surrounding ecological situation and neurological disorders in humans [11].

Overall, there has been an increase in the total number of cases of multiple myeloma in recent years. Rejuvenation of the disease is observed, and more often multiple myeloma occurs in people younger than 55 years, which may indicate the importance of environmental influence as an etiological factor. The more frequent development of multiple myeloma in close relatives and identical twins indicates the significance of genetic factors and hereditary predisposition [12, 13].

The path genetically decisive factor is prolonged, chronic antigenic stimulation after viral infections or other chronic diseases, prolonged exposure to toxic substances and radiation. As a result of a long series of genetic events, a pathological clone of B-cells of ok is formed, capable of differentiation, but producing non-functional immunoglobulin. Biological and clinical features of multiple myeloma are associated with genetic aberrations, such as rearrangement of immunoglobulin heavy chain gene loci, as well as chromosomal deletions, somatic gene mutations, and chromosomal hyperdiploidy involving an odd number of chromosomes. The presence of a significant number of different genetic disorders causes high variability in the course of the disease [14, 15, 16, 17].

Так же в качестве одной из причин развития множественной миеломы рассматривают Translocation of the 14q32 gene under the influence of infections or chronic inflammation is also considered as one of the reasons for the development of multiple myeloma. As a result of additional gene

mutations, cells change, cancer develops, and inflammation progresses [18]. In the pathogenesis of multiple myeloma, the biochemical marker IL-6 plays a special role, as it promotes the growth of hepatocytes and stimulates osteoclastic activity, suppressing osteoblasts. It also inhibits pro-inflammatory cytokines, and promotes the stimulation and proliferation of myeloma cells and their progenitors.

В патогенезе множественной миеломыCytokines are important in the pathogenesis of multiple myeloma. The most important is IL-6, which is the main factor in stimulating the synthesis of myeloma and its precursors. A high level of IL-6 concentration is observed in the aggressive course and progression of multiple myeloma. Plasma cell proliferation can also be stimulated by other cytokines (IL-1, IL-3, IL-5, GM-CSF). The development of generalized osteoporosis and foci of bone destruction and hepatitis is caused by the production of myeloma and bone cells of cytokines b (TNF-α, IL-1, IL-6, M-CSF), which stimulate stromal cells and osteocells and promote bone marrow tissue resorption. Cytokines IFN-γ and α, IL-4, IL-2, on the contrary, inhibit the proliferation of myeloma cells. Cytological studies of bone tissue cannot determine any specific differences between myeloma cells and normal plasma cells. The most important markers, according to experts.

The molecular pathogenesis of multiple myeloma is multi-stage. Initially, the development of a translocation of IgH complex chain genes IgHinvolving five oncogenes: 11q13 (cyclin D1), 6p21 (cyclin D3), 4p16 (fibroblast growth receptor), 6q23 (c-maf), and 20q11 (MafB). In particular, the development of karyotype instability, in particular делеции13q deletions and somatic mutations (ras). Secondary translocation of IgG genes and secondary mutation of IgG genes were detected at the stage of disease formation IgG [12, 19].

Despite a number of studies, the relationship between a malignant tumor and the characteristics of the immune system response has not been fully determined. There are no studies that comprehensively studied the features of innate and adaptive immunity, and no simultaneous study of non-specific, regulatory, cellular, or humoral links of the immune system, depending on the stages of the disease and the presence of complications [20, 21].

Cardiovascular pathology, chronic kidney disease (CKD), and respiratory, endocrine, and cerebral disorders are the most frequently detected comorbidities [22, 23]. At the same time, as noted in the above studies, the frequency of detection of concomitant diseases, as well as comorbid background, directly depends on the increase in the age of patients.

One of the key mechanisms of heart muscle damage, which leads to a decrease not only in its contractile capacity, but also in organic changes, is free light chains of immunoglobulins, which are produced by neoplasms of plasma cells and lead to their amyloidosis [24, 25]. This phenomenon is not observed in all patients: according to studies by some authors, amyloidosis is registered in 15-50% of patients, mostly with a rapid course of the disease that does not respond to chemotherapy.

Myeloma nephropathy is the most important unfavorable prognostic factor and equally reduces the survival rate of patients at different stages of the disease. Renal failure is one of the leading causes of death in patients with multiple myeloma. Kidney damage is manifested in the form of paraproteinemic nephrosis, which occurs with pronounced proteinuria, the presence of hyaline, less often granular and epithelial cylinders. Often, Bence-Jones protein (BJ) is found in the urine, which precipitates when the urine is heated to 50-60 °C and dissolves with further boiling. Multiple myeloma is characterized by rapid development of kidney failure [26].

Damage to the heart, lungs, and kidneys is one of the most frequent manifestations and complications of multiple myeloma, the combined occurrence of which leads not only to mutual aggravation, but also is one of the factors of early adverse outcomes. In this regard, there is a need to carry out scientific research on the early diagnosis and prevention of the development of visceral complications of multiple myeloma.

Clinical manifestations of multiple myeloma are extremely diverse, but are largely determined by bone marrow infiltration and organ damage. Clinical signs of multiple myeloma are manifested by symptoms caused by bone damage (bone pain, skeletal fractures, spinal cord compression, radicular pain), hypercalcemia (polyuria, polydipsia, nausea, vomiting), renal failure (nausea, vomiting, malaise, weakness), amyloidosis (peripheral neuropathy, edema, organomegaly), infiltration of bone marrow myeloma cells (anemia, hemorrhagic syndrome), decreased levels of normal immunoglobulins (frequent infections, pneumonia), cryoglobulinemia (Raynaud's syndrome, acrocyanosis), hyper viscosity syndrome (shortness of breath, transient ischemic attacks, deep vein thrombosis, retinal hemorrhage, central retinal vein thrombosis or its branches, nosebleeds).

Clinical symptoms of multiple myeloma appear with a tumor mass of about 10^{12} white blood cells, with a positive response to chemical therapy, the number of myeloma cells decreases by 1-2 orders of magnitude, and the "plateau" phase stabilizes at this level. In most cases, the nature of the course of the disease is determined by the cytokinetic features of the tumor. KClones: the lower the activity of proliferating plasma cells, the lower the activity of proliferating cells over the duration of the "plateau" phase and the patient's life span. In the case of multiple myeloma progression, which is unavoidable in the case of standard chemotherapy, new tumor clones appear, as well as new tumor clones [1, 2, 7].

Conclusion. Thus, the analysis of literature data shows that the prevalence of multiple myeloma is uneven, in addition, there is a tendency to increase the incidence among the population of most regions of the world, mainly among men, the elderly and senile. Multiple myeloma is the second most common hematological malignancy in high-income countries. Although the etiology of MM is still not fully understood, according to most researchers, the risk factors leading to a progressive increase in the incidence of the population include the elderly and senile age, male gender, exposure to negative environmental factors (ionizing radiation, chemical agents), family predisposition, an increase in the number of chronic autoimmune processes and obesity. It was revealed that cytokines and genetic aspects play an important role in the development of the disease. Multiple myeloma is characterized by non-specific symptoms and similarity of its clinical manifestations with other diseases, which is one of the reasons for late diagnosis. Injuries to internal organs, in particular the heart and kidneys, are one of the most common complications of multiple myeloma, the combined occurrence of which leads not only to mutual aggravation, but also is one of the factors of early adverse outcomes. Ignorance of pathogenesis aspects will lead to a fatal outcome of patients from the disease and some of them complicate treatment. Current research strategies point to increasing knowledge of the etiopathogenesis and detection of diseases in the early stages of multiple myeloma.

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