CLINICAL AND MORPHOLOGICAL FEATURES OF GLIOBLASTOMAS

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This scientific article is dedicated to a very relevant medical problem, since, inspite of the fact that of modern medicine has great advances and achievements, glioblastomas of the central nervous system are still one of the most dangerous and common primary malignant tumors. Patients with cerebral glioblastomas are characterized by a poor prognosis and a high mortality rate, which also makes this topic relevant. The etiology, risk factors, mechanisms of carcinogenesis of this tumor still are not completely clear. The article considers brief historical data, modern information about the clinical and morphological characteristics of glioblastomas, data on morbidity and mortality, current WHO classifications, known facts about the etiology, pathological anatomy, methods of diagnosing this tumor, a modern molecular classification is given. In addition, the currently known data on the main biomarkers, tumor stem cells, and modern methods of glioblastoma treatment are considered. The article focuses on a detailed macroscopic and microscopic description of this malignant tumor, compares three histological types of glioblastomas: giant cell glioblastoma, epithelioid glioblastoma and gliosarcoma. The newest methods of radiation therapy, chemotherapy, and the possibility of surgical intervention are discussed.

Keywords: glioblastoma, gliosarcoma, epithelioid glioblastoma, classification, etiology, morphology, molecular genetics

Glioblastomas are the most aggressive and common malignant brain tumors and have the lowest survival rate compared to other malignant tumors of the central nervous system [1]. The tumor develops from glial cells of nervous tissue, mainly from astrocytes, is characterized by clinical, morphological, molecular genetic heterogeneity, and constitutes the majority of all primary brain tumors in adults. Glioblastomas can be found in the cerebral hemispheres, in the cerebellum, and in the brainstem. The most common symptoms are seizures, headaches, and neurological disorders associated with the glioblastoma location [2]. Despite the latest advances in medicine, risk factors, etiology and mechanisms of carcinogenesis of glioblastomas have not yet been completely under-stood. Actual predictive and prognostic markers of the malignancy are currently being investigated, and a search for potential effective biomarkers, new approaches to treatment, targeted drug therapy is very important. These factors, as well as the high mortality rate from this oncological disease, make glioblastomas relevant for research.

The history of glioblastoma

In 1856 – 1865, Rudolf Ludwig Karl Virchow described neuroglia, characterized and divided gliomas into highly differentiated and poorly differentiated tumors. In 1926, Persival Bailey and Harvey Cushing published «A classification of the tumors of the glioma group on a histogenetic basis with a correlated study of prognosis». The authors categorized all studied gliomas into 13 groups based on microscopy and patient survival rate, and for the first time identified spongioblastoma multiforme as a separate tumor due to its specific cellular structure. By the 1940s, it had become better known as glioblastoma multiforme [3].

In 1938, Hans-Joachim Scherer put forward hypothesis according to which glioblastomas were divided into primary and secondary tumors. In 1979, the World Health Organization published the first edition of the «WHO classification of tumors of the central nervous system». 26 centers consisting of 300 pathologists from all over the world took part in preparing this work. The last WHO edition including the modern knowledge about tumors of the central nervous system was published in 2016 [3].

Morbidity and mortality

In 2020 Central Brain Tumor Registry of the United States (CBTRUS) was prepared a report that contains statistical data on primary brain tumors, including glioblastomas.

According to these data, glioblastoma makes up 48.6% of all malignant tumors of the central nervous system and 1.59 times more common among men than women. The survival rate for glioblastoma was 8 months – the lowest rate among primary malignant tumors of the central nervous system [1].

Glioblastoma makes up 57.7% of all gliomas, while the incidence rate is 3.23 cases per 100,000 population. It is more common in older people and is diagnosed at the age of about 65. The tumor is more often detected in urban areas than in rural areas, and the incidence is about 2 times higher in whites than in afro-americans. According to predictions there will be 2,970 people suffering from glioblastoma in the USA by the 2021 year [1].

In addition to the USA, the incidence of glioblastoma is also high in Canada, Australia, Northern and Western Europe [4].

Unfortunately, annual statistics on the incidence of specific types of primary malignant brain tumors is not maintained in the Russian

Federation. According to the statistics of 2000-2011, which was kept in in the Arkhangelsk region, glioblastoma accounted for 26.6% of all primary tumors of the central nervous system in 2000-2011 [5].

It should be taken into account that malignant brain tumors are a significant source of morbidity. Regional differences in the incidence, risk factors and duration of glioblastoma may help to understand the etiology and pathogenesis of the disease.

Classification

All glioblastomas can be divided to groups due to 4 degrees of malignancy. Genetically, according to the mutations in the IDH1 and IDH2 genes, glioblastomas are divided into 3 types. The first type is IDH-wildtype glioblastoma, which occurs in 90% of cases and prevails in patients over 55 years of age. Clinically defined as a primary tumor that can occur de novo. The second type, IDH-mutant glioblastoma, occurs in 10% of cases and predominates in young people. Clinically, IDH-mutant is defined as a secondary tumor, which is usually preceded by a diffuse glioma of lower severity. The third type is NOS glioblastoma. This type is a reserve for those cases when, for certain reasons, studies on the IDH1 and IDH2 genes have not been carried out [6].

Glioblastoma IDH-wildtype is histologically subdivided into 3 subtypes: giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma. The latter is a relatively new subspecies of glioblastomas. All IDH-wildtype glioblastoma subtypes are characterized by the same approaches for treatment [7].

Etiology

The causes of glioblastomas are not completely studied. The most well-known factor is the effect of ionizing radiation on the central nervous system, and it should taken into account that the disease occurs after several years or decades. Also proven reasons that lead to an increased risk of developing glioblastomas are following: single nucleotide polymorphisms, high growth, high socioeconomic status, mutations in anti-oncogenes [8, 9].

Genetic diseases such as Recklinghausen's disease, Bourneville's disease, Li-Fraumeni syndrome, retinoblastoma and Turco's syndrome increase the risk of glioblastoma formation [8, 10].

There is no precise information, which can prove that smoking, alcohol or drug use, and the use of cell phones increase the risk of developing glioblastomas [8].

Pathomorphology: macroscopy and microscopy

During macroscopical examination we can observe the diffuse location of the glioblastomas in the brain parenchyma. Most of the tumors do not have clear boundaries with normal cerebral tissues. Glioblastomas of IDH-wildtype is characterized by a straw-colored necrotic center, yellowish patches that are connected with myelin breakdown, and hemorrhages. These changes, as a rule, are not typical for IDH-mutant glioblastoma. Sometimes the tumor can cross the corpus callosum, then it takes the shape of a butterfly (so named butterfly glioma). Gliosarcoma has a well-defined border due to the high content of connective tissue [11, 12].

The changeable appearance of glioblastomas is considered to be their peculiarity, since in some areas the tumor is soft and yellow, in other areas it is hard and white. Sometimes areas of cystic degeneration and hemorrhage are detected in the tumor tissue [13].

The main microscopic features of glioblastomas are following: necrosis, mitotic activity, poorly differentiated glial cells, and vascular proliferation. The pathomorphology of glioblastomas is very changeable, therefore, in the literature, one can find the term «glioblastoma multiforme» [11].

Giant cell glioblastoma is characterized by huge multinucleated (from 1 to 20 nuclei per a cell) tumor cells with size up to 400 μm and sometimes by an abundant network of reticular fibers is revealed. The nuclei, as a rule, are angular and contain prominent nucleoli and cytoplasmic inclusions. Perivascular glued lymphocytes are sometimes present. This type of glioblastoma is more limited and is most often localized subcortically in the temporal and parietal lobes. It is the reason why it is sometimes confused with metastases or meningioma, if the tumor is localized on the dura mater. The diagnostic problem is pleomorphic xanthoastrocytoma (RCA), which also contains giant cells and is located peripherally. But it should be remembered that RCA contains eosinophils and a lot of xanthomatous cells [14].

Gliosarcoma contains a «sarcomatous» component. If there is a lot of this component, then the tumor looks like a delimited dense mass with a homogenous contrast. Its distinctive feature is a two-phase structure, consisting of gliomatous and mesenchymal differentiations. The glial part looks like a typical glioblastoma, and the mesenchymal part resembles a fibrosarcoma patterns with densely packed

long bundles of spindle-shaped cells, looking like herringbone structures. The sarcomatous component often is characterized by nuclear atypia and consists of multiple mitoses and necrosis. It is formed by the reticular network, in which the glial elements are clearly delimited from the sarcomatous areas, and can be represented by such additional lines of mesenchymal differentiation as cartilage, bones and muscles. The diagnostic problem is the infiltration of a typical glioblastoma into the soft, arachnoid and dura mater, which can lead to a misconception about gliosarcoma, since the tissue is represented by a large number of collagen elements. Tumors with peripheral adhesion to the dura mater, it is similar to a meningioma, as well as giant cell glioblastoma [14, 15]. Gliosarcoma is more common in the temporal, parietal and frontal lobes of the brain [16].

Epithelioid glioblastoma is characterized by the presence of epithelioid cells, an intermediate neuropil, a clear cell membrane, eosinophilia, Rosenthal fibers, and a laterally located nucleus. Microscopy also shows necrosis, but not of the palisade, but of the zonal type [11].

Morphologically, glioblastomas of the IDH-wildtype and IDH-mutant types are similar. However, in IDH-mutant glioblastoma, areas of ischemic, palisade necrosis are observed much less frequently, and oligodendroglioma-like components are much more frequent, they are mainly located in the frontal lobes of the brain, and glioblastomas with no mutations in the IDH-1 genes are characterized by necrosis without pseudopalisades, vascular in the form of garland-like growths and a large number of necrosis [11, 17].

Neurodiagnostics

On CT and MRI, glioblastomas tend to have large and irregular shape. Central necrosis is well defined. The distinguishing feature of giant cell glioblastoma is its annular appearance. It is easy to confuse it with metastasis. Gliosarcoma is well demarcated and has a dense texture. Epithelioid glioblastoma is characterized by a dense texture and sometimes the presence of cysts, hemorrhages. Central necrosis is not typical for IDH-mutant glioblastoma [11, 18].

Molecular classification

Since glioblastoma is a very aggressive and complex disease, its molecular classification is very important for understanding of carcinogenesis, the search of new approaches for treatment, target therapy possibilities. Histological classification cannot distinguish all characteristics of glioblastomas. Classification based on gene expression profiling can explain the clinic and help with treatment. Thus, some glioblastomas are sensitive to radiochemotherapy, while others, on the contrary, are resistant [19].

Using a molecular genetic methods for brain tumor examination in 2006, three molecular subtypes of glioblastoma were identified. They were named according to the genes that characterize each group: proneural, proliferative, and mesenchymal. The proliferative subtype exhibited overexpression of proliferation markers, mesenchymal tumors – overexpression of angiogenesis markers, proneural tumors expressed genes associated with the process of neurogenesis. The latter had a higher survival rate compared to other subclasses.

In 2010, a classification was created using unsupervised hierarchical cluster analysis, resulting in four clinically significant subtypes of glioblastomas characterized by abnormalities in the PDGFRA, IDH1, EGFR and NF1 genes. These are proneural, neural, classical and mesenchymal subtypes, respectively. The proneural class consists mainly of oligodendroglial cells and has a better prognosis. Neural glioblastomas show connection with oligodendrocytes and astrocytes. They also contain genes connected with neurons. The classical group demonstrates a connection with the astrocytic line. The mesenchymal class exhibits a mesenchymal phenotype and expresses Schwann cell markers and microglial markers [20].

Major biomarkers for glioblastomas

In modern oncology the different biomarkers are described. They are certain genes, DNA and RNA molecules, proteins, enzymes, antigens, and other cellular and biological products that can be detected at various stages of carcinogenesis, with therapeutic effects. In accordance with the type of biomolecules and methods of their detection, genomic, transcriptomic, and metabolic factors (immunohistochemical, biochemical and others) are distinguished. Biomarkers can be divided into diagnostic and clinical which includes prognostic and predictive. There are factors that can simultaneously have both prognostic and predictive properties. At present the following biomarkers for glioblastomas are known:

1. O6-methylguanine-DNA methyltransferase (MGMT) – encodes proteins that are consumed during DNA repair. It is responsible for the sensitivity of the tumor to temozolomide; therefore, its high activity is the reason for ineffective chemoradiation therapy [21].

2. Epidermal growth factor receptor (EGFR) – controls high tumor proliferation,

converts extracellular signals into cellular responses. It very often undergoes amplification, which leads to its increased expression. It is a hallmark of glioblastomas. Its activation leads to excessive proliferation of tumor cells [22, 23].

3. Platelet-derived growth factor receptor alpha (PDGFRα) – overexpression of this marker leads to abnormal and uncontrolled cell growth [22].

4. Isocitrate dehydrogenase (IDH) is an enzyme whose main function is to catalyze the process of oxidative decarboxylation in the Krebs cycle. Mutations in the IDH1 and IDH2 genes are one of the main prognostic factors in the diagnosis of glioblastomas. They lead to inactivation of some protooncogenes and destabilization of the cell genome [22, 23].

5. Tumor protein P53 – is a tumor suppressor of proteins that regulate apoptosis and participate in some mechanisms of the cell cycle. Performs various functions in suppressing tumor growth. Mutations in the P53 gene play an important role in carcinogenesis [21].

6. MicroRNA (miRNA) is a short non-coding RNA molecule that plays an important role in the development and progression of a tumor. It gives more than 90% specificity in the detection of glioblastomas [22].

Glioblastoma stem cells

Glioblastoma stem cells maintain its resistance, renewal, and invasion and have a specific set of markers. Research results have shown that CD133, CD95, Sox-2, Nanog, nestin are especially reliable markers. They all have predictive value. Glioblastoma has a heterogeneous structure, which can be divided into a zone of support for proliferation, invasion and hypoxia. It is described that there are 2 populations of glioblastoma stem cells, depending on the zones: supportive and invasive. The supportive population regulates the renewal and proliferation, the invasive one – the progressive growth of the tumor. Zones of population support and invasion can pass into each other, changing the phenotype of glioblastoma stem cells. Further research into glioblastoma stem cells may improve understanding of the mechanisms of tumor progression and develop new effective treatments [24].

Treatment

The standard treatment for patients with glioblastoma consists of surgical removal of the tumor, radiation therapy, and chemotherapy. The key ingredient in the treatment of globiastomas is surgery. Intraoperative MRI, neuronavigation, ultrasound and fluorescence surgery provide the safest and greatest surgical resection. Complete resection is possible with fluorescence imaging of the tumor using 5-aminolevulinic acid. Under blue light, the tumor tissue becomes red, but normal tissue does not change color. Also, thanks to ICG angiography, injuries associated with vascular damage can be avoided [25].

If the tumor is inoperable due to certain contraindications, then stereotaxic biopsy may be performed for histological diagnosis, but the risk of a false negative result stands at 25% [26].

Radiation therapy is one of the main treatments for glioblastomas and is usually given in conjunction with chemotherapy. Thanks to focal, fractional, and brachytherapy treatments have become safer and more effective. Focal radiation therapy consists of irradiation of 2-3 cm covering the tumor. During brachiotherapy, after resection of glioblastoma, a radioactive isotope is inserted into the tumor cavity, which provides minimal radiation to normal brain tissue. Focal radiation therapy consists of irradiation of 2-3 cm covering the tumor. During brachiotherapy, after resection of glioblastoma, a radioactive isotope is inserted into the tumor cavity, which provides minimal radiation to normal brain tissue [27].

The standard of chemotherapy is the use of temozolomide at a dose of 75 mg / m2 on an empty stomach 2 hours before radiation therapy and on an empty stomach in the morning without radiation therapy. It causes lymphopenia, increases the number of regulatory T cells, and improves dendritic cell function [28, 29].

In the near future, along with the standard treatment for glioblastomas, it will be possible to use vaccines. The DCVax-L vaccine has passed Phase 3 clinical trials. It is administered 6 times in the first year and 2 times in the second year and can be combined with other drugs. The median overall survival after surgery was 23.1 months, while the median overall survival without vaccine after surgery was 15-17 months. Of 331 patients, side effects were identified only in 7 patients [30].

Supportive care

Glioblastoma patients often have progressive neurologic symptoms due to the tumor itself and difficult treatment. This reduces the standard of living, complicates labor activity.

Seizures occur in up to 80% of patients during the course of the disease, which requires antiepileptic therapy, while the dosage of drugs must be minimized to avoid side effects. The

use of antiepileptic drugs is not recommended unless the patient has seizures.

Glioblastoma increases the risk of thromboembolism due to increased activation of blood clotting factors. Treatment is usually lifelong with heparin [7].

Conclusion

Thus, modern medicine does not stand still and offers more and more new methods of diagnosis and treatment of such an aggressive and widespread tumor disease as glioblastoma. Scientists have managed to improve the overall survival of patients with glioblastoma, but it still has an extremely low survival rate. The key to the treatment of glioblastomas is maximum tumor removal, made possible by discoveries such as fluorescence imaging of the tumor and ICG angiography. Newer types of radiation therapy such as focal radiation therapy, fractionated radiation therapy and brachiotherapy have increased the life expectancy of patients after surgery. An important role is played by palliative care, with the help of which it is possible to increase the duration and quality of life of patients.

Currently, great progress can be associated with understanding the molecular genetic mechanisms of carcinogenesis during the development of glioblastomas, with the search for effective biomarkers and targeted drugs for their treatment.

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