Glioblastoma multiforme – an overview

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Glioblastoma multiforme is a central nervous system tumor of grade IV histological malignancy according to the WHO classification. Over 90% of diagnosed glioblastomas multiforme cases are primary gliomas, arising from normal glial cells through multistep oncogenesis. The remaining 10% are secondary gliomas originating from tumors of lower grade. These tumors expand distinctly more slowly. Although genetic alterations and deregulations of molecular pathways leading to both primary and secondary glioblastomas formation differ, morphologically they do not reveal any significant differences. Glioblastoma is a neoplasm that occurs spontaneously, although familial gliomas have also been noted. Caucasians, especially those living in industrial areas, have a higher incidence of glioblastoma. Cases of glioblastoma in infants and children are also reported. The participation of sex hormones and viruses in its oncogenesis was also suggested. Progression of glioblastoma multiforme is associated with deregulation of checkpoint G1/S of a cell cycle and occurrence of multiple genetic abnormalities of tumor cells. Metastases of glioblastoma multiforme are rarely described. Treatment of glioblastoma multiforme includes tumor resection, as well as radiotherapy and chemotherapy. Drugs inhibiting integrin signaling pathways and immunotherapy are also employed. Treatment modalities and prognosis depend on the tumor localization, degree of its malignancy, genetic profile, proliferation activity, patient's age and the Karnofsky performance scale score. Although the biology of glioblastoma multiforme has recently been widely investigated, the studies summarizing the knowledge of its development and treatment are still not sufficient in terms of comprehensive brain tumor analysis.

Key words: glioblastoma multiforme, tumor, brain, etiology, risk factors, treatment.

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The term glioblastoma multiforme (GBM) was introduced by Cushing in the second half of the nineteenth century, while the first operation on a patient suffering from this type of tumor was conducted in Vienna in 1904 [1].

Glioblastoma multiforme is a primary brain neoplasm, consisting of a genetically and phenotypically heterogeneous group of tumors [2, 3]. Ninety percent of glioblastoma multiforme cases develop *de novo* (primary glioblastoma) from normal glial cells by multistep tumorigenesis. The remaining 10% of gliomas are cases of secondary neoplasm, developing through progression from low-grade tumors (diffuse or anaplastic astrocytomas) [4, 5], which takes about 4–5 years. Secondary glioma is diagnosed mostly in persons with the mean age 39 years, grows more slowly and has a better prognosis. Glioblastoma multiforme, which develops *de novo*, grows within 3 months [6]. Although the genetic basis, as well as the molecular pathways underlying development of primary and secondary gliomas are different [2], these two types show no morphological differences [7].

Epidemiology

Epidemiological data show that the number of recorded GBM cases in Europe and North America is 2–3 per 100 000 adults each year [8], and the incidence rate in men in comparison to women is at the level of 1.26 : 1 [9]. Cases of GBM in children and neonates are also reported. It is estimated that this tumor's incidence is 1.1 to 3.6 per 100 000 infants [10], with the proportion of 3.3 male children with glioblastoma to one female child. There is no morphological differences between GBM occurring in children and adults. Reported differences are related only to the proliferative activity of glioma cells – the proliferation index (Ki-67 index) is higher in children [9].

The incidence of GBM is higher among Caucasians, especially in those living in industrial areas [11]. In addition, a relationship between genotype and an increased susceptibility to development of this type of tumor was demonstrated – it includes people from the Han Chinese population with EGF +61 AA genotype [12].

Etiology

The etiology of GBM has not been fully elucidated. Glioblastoma is believed to be a spontaneous tumor, despite the fact that medical history describes development of glioma in related persons [13]. The familial form of this tumor is described for 1% of cases [12]. However, the genetic background for development of this type of glioblastoma is different from those arising spontaneously [14].

Glioblastoma multiforme may also occur in the course of genetic diseases: tuberous sclerosis [15], Turcot syndrome [16], multiple endocrine neoplasia type IIA [17] and neurofibromatosis type I, NF1 [18]. In addition, acquired head injuries, which occurred as a result of a brain contusion, may predispose to the onset of glioblastoma [19, 20].

Development of GBM is related to deregulation of the G1/S checkpoint in the cell cycle [21] and occurrence of many genetic disturbances in glioma cells (loss of genetic material within chromosome 10q, amplification of *EGFR*, *FGFR2*, *IRS2* and *AKT3* genes as well as mutations in *PTEN*, *TP16*, *TP53*, *PARK2*, *PTPRD* and *NF1* genes) [22, 23].

Among women, a higher risk of its occurrence is noted in postmenopausal women, so a hypothesis on the involvement of sex hormones in glioblastoma development was created [4]. Incidence of this tumor is also related to height and BMI – high values of these two features increase the risk of glioblastoma incidence [24].

Viruses, such as human cytomegalovirus (HCMV), are also believed to be among the etiologic agents for glioma development. HCMV induces congenital encephalitis and multi-organ changes in immunocompromised adults. Human cytomegalovirus shows tropism for glial cells. The virus encodes proteins (such as IE1, US28, GB), which activate intracellular signaling pathways involved in mitogenesis, mutagenesis, apoptosis, inflammation and angiogenesis. Products of these genes cause dysregulation of the key signaling pathways (including PDGFR, Akt, STAT3), but also cause disturbances in monocyte and glial cell functions [25, 26]. It is believed that granulocyte-colony stimulating factor (G-CSF) is involved in the development of glioblastomas – a high level of expression of this glycoprotein and its receptor (G-CSFR) was found in glioblastomas of different grades of malignancy. Granulocyte-colony stimulating factor stimulates proliferation and migration of a commercially available glioblastoma cell line. Blocking of G-CSFR by antibody results in inhibition of the cell growth and mobility *in vitro* [27].

Ionizing radiation is one of the physical factors that increase the likelihood of developing this type of tumor. The following chemicals are considered as potentially dangerous: pesticides, polycyclic aromatic compounds and solvents. Electromagnetic fields and certain metals are also considered to be involved in glioma development [28]. It is believed that the use of a mobile phone does not increase the risk of developing glioblastoma, but the effect of long-term use of mobile phones is still undetermined. Glioblastoma multiforme can be considered as an occupational disease – persons employed in the rubber and petrochemical industry are considered to be at a higher risk of glioma incidence [29].

Biologic behavior

Glioblastoma multiforme develops mainly in the brain. This neoplasm is located in hemispheres [30] or subtentorially in the brain stem [31] and cerebellum [32]. It is characterized by infiltrating growth; therefore the tumor mass is not clearly distinguishable from the normal tissue [2, 19], a growing tumor causes an increase of intracranial pressure [33], and sometimes it leads to hydrocephaly [34].

Metastases of this neoplasm by cerebrospinal fluid [35] or blood [36] are rare and target the spleen, pleura, lungs, lymph nodes, liver, bones, pancreas and small intestine [37–42]. It has been hypothesized that the low metastatic potential of GBM results from the barrier created by cerebral meninges, but also from the rapid tumor growth and short course of this disease [43]. The brain is devoid of lymphatic vessels, so metastases through this pathway are impossible [37]. The available literature describes 8 cases of glioblastoma multiforme metastases to the skin – tumors usually developed around post-operative sutures. This suggests implantation of glioblastoma multiforme cells around post-operative wounds during the removal of a primary tumor [44].

Morphological features

Morphologically, GBM consists of small cells, characterized by polymorphism, anaplasia and significant anisokaryosis. Glioblastoma multiforme cells are polygonal to spindle-shaped with acidophilic cytoplasm and indistinct cellular borders. Their nuclei are oval or elongated and have coarsely clumped hyperchromatic chromatin with multiply distinct nucleoli located centrally or peri-centrally. Glioblastoma multiforme cells have increased nuclear to cytoplasmic ratio and show nuclear pleomorphism. Some cells contain intranuclear inclusions. Binuclear and multinucleated cells, as well as lymphocytes, neutrophils, macrophages and necrotic cells, can be also present [45]. Some cells resemble adipocytes due to the presence of large lipomatous vacuoles and they may constitute 5–10% of all the tumor cells and even 80% in single cases. Despite differences in the morphology, such glioblastoma shows several molecular features similar to a primary glioma, and is described as a "fat-rich" glioma [46].

Vascularization of GBM is very high [47]. The newly developed vessels are morphologically similar to renal glomeruli and their endothelial cells are phenotypically different from normal endothelial cells – they are overlapped focally, hyperplastic and heterogeneous in size and shape. Multiple Weibel-Palade bodies, normally absent in the brain endothelial cells, can be found in the cells of the newly formed vessels. The surface of these vessels is covered with a discontinuous layer of pericytes, without any contact with astrocyte processes [48]. Glioblastoma multiforme shows vascular thrombi leading to endothelial cell damage and proliferation. The resultant vascular damage causes red blood cells extravasation [49].

Necrotic foci are one of the most characteristic features of GBM. Histologically, two types of necrosis are typically encountered, depending on localization and size of the necrotic area. The first one consists of large areas of necrosis within the central area of the tumor, resulting from insufficient blood supply in all primary glioblastomas. The other type contains small, irregularly shaped necrotic foci surrounded by pseudopalisading areas created by radially oriented glial cells observed in both primary and secondary glioblastomas [50].

Pseudopalisades range from 30 to 1500 μm in the greatest internal width and from 50 to 3500 μm in the greatest internal length. Pseudopalisades, especially those < 100 μm wide, have hypercellular zones surrounding internal fibrillarity but usually lack central necrosis. Medium-sized pseudopalisades (200–400 μm) are characterized by central necrosis, central vacuolization, and individual dying cells but

typically have a peripheral zone of fibrillarity immediately inside the pseudopalisade. The largest pseudopalisades (those > 500 µm) have extensive necrotic zones and nearly always have central vessels. Pseudopalisades can have evidence of a central vascular lumen, either viable, degenerating or thrombosed. The pseudopalisading cell population could represent rapidly proliferating neoplastic cells that have "outgrown their blood supply" and undergone central necrosis; a population resistant to apoptosis, which has accumulated because of increased cell survival; a mixed population of tumor and inflammatory cells adjacent to necrosis; or a population of cells migrating to or from a central focus. Cell density of pseudopalisades is almost twice as high, but proliferation activity is from 5 to 50% lower than in other tumor zones [51].

The pseudopalisading areas show the presence of multiple apoptotic cells as well [52].

The increased malignancy of these tumors is accompanied by an increase of degree of atypia, nuclear hyperchromatosis, increased mitotic index, presence of necrotic areas and atypical blood vessels [53].

Clinical signs

Depending on the localization and the increasing intracranial pressure, as the result of the clinical stage of the disease, the most common signs of GBM include headaches, ataxia, dizziness, vision disturbances (blurred vision, diplopia), and frequent syncope [31, 54]. Due to these unspecific symptoms, glioma is often misdiagnosed as infections, inflammatory processes and circulatory and immunological diseases [31]. The occurrence of back and leg pain and sciatica may also suggest a herniated lumbar [55]. The occurrence of seizures in people who have not been previously diagnosed with epilepsy can also be an indication for neuroimaging because of glioblastoma suspicion [56].

Diagnosis

Magnetic resonance imaging is the primary diagnostic tool for GBM. The tumor diameter at the time of diagnosis is usually approx. 4 cm [57], although data collected by Simpson *et al.* (1993) showed that in 38% of 645 patients, the tumor diameter at the diagnosis was < 5 cm, in 56% of cases was within 5–10 cm, while in 6% of patients the tumor was > 10 cm [58]. The tumor involving the corpus callosum and growing bilaterally into occipital and temporal lobes results in a butterfly pattern on MR imaging ("butterfly glioma") [59].

Definitive diagnosis is based on histopathological examination of the intraoperatively removed tumor or its parts, using traditional histological, cytologic and histochemical methods [60]. When neurosurgical tumor resection is not possible, fine needle aspiration biopsy is performed [45].

Morphological diagnosis is based on criteria defined by the WHO. Staging of the tumors in the central nervous system includes assessment of their morphology, grade of malignancy (grade I–IV), proliferative index, response to treatment and survival time. Grade I includes non-malignant tumors, grade II is used for relatively non-malignant tumors, grade III includes tumors of low-grade malignancy, while grade IV denotes the most malignant tumors, with median survival of 6–12 months. Glioblastoma multiforme is classified as grade IV [61].

Verification of a primary diagnosis is performed on the basis of immunohistochemistry for the presence in the glioma cells of glial fibrillary acidic protein (GFAP), which is a major intermediate filament protein of mature astrocytes [52, 62] with the mass of 50 kD [63]. This protein is the most specific marker of astrocytes, both in normal and pathological conditions. It is believed that this protein plays a role in maturation of astrocytes. Increasing malignancy of tumors of astrocytic origin is associated with the loss of GFAP expression [64]. Similar effects are observed for GBM – glioma cells negative for GFAP proliferate faster in comparison to positive cells. Loss of GFAP expression indicates significantly undifferentiated tumor cells, but does not decide about tumor progression and development [52]. Sometimes, astrocytes with GFAP and characteristic lipomatous cytoplasm can occur [46]. The acid protein S100 present in glial cells is another specific marker for tumors of the central nervous system, but its expression cannot constitute a basic criterion in differential diagnosis [65].

Treatment

Glioblastoma multiforme is characterized by high proliferative activity [66]. Since GBM infiltrates surrounding tissues, its complete resection is impossible and radiotherapy not always efficient [2]. The blood-brain barrier makes treatment more difficult and tumor cells found in the areas of hypoxia are resistant to radiotherapy [67]. Anti-cancer treatment should lead to tumor regression and provide as long as possible disease-free survival [68]. Surgical resection to the extent feasible, followed by chemotherapy and radiotherapy, is the mainstay of GBM treatment [58]. Surgical treatment, chemotherapy and radiotherapy prolong the survival time in young people up to 202 weeks [9]. The best results are obtained when radiotherapy is performed after the surgery, with the doses of 5000–6000 cGy. Dose escalation over 6000 cGy has resulted in increased toxicity without a survival benefit [67].

The standard treatment scheme for glioma most frequently includes temozolomide. When comparing the results of chemotherapy, the highest median survival time is observed in patients treated with temozolomide, in comparison to other chemotherapeutics [69]. It is known that the survival advantage among patients treated with temozolomide and radiotherapy is longer compared with radiotherapy alone [70]. The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma is connected with minimal additional toxicity [71].

Furthermore, blockage of NHERF-1 synthesis in glioma cells increases their sensitivity to cytotoxic action of temozolomide and induction of apoptosis in tumor cells [69].

Glioblastoma multiforme is one of the most vascularized cancers. This inspired development of an anti-angiogenic gene therapy, aimed at blocking the VEGF-dependent pathway [72]. Another anticancer agent is bevacizumab. It

is a humanized IgG1 monoclonal antibody that selectively binds with high affinity to human VEGF and neutralizes its biologic activity [73]. Several mechanisms of bevacizumab action exist. They include direct inhibition of tumor-associated angiogenesis, a direct anti-GBM effect on VEGF receptor-expressing GBM cells, disruption of the glioma stem cell microvascular niche, and improved vascular function or its normalization. Bevacizumab has been shown to improve patient outcomes in combination with chemotherapy and was granted accelerated approval as a single agent in recurrent GBM [74].

It has also been shown that inhibition of the Mer receptor for tyrosine kinase in glioblastoma cells influences their survival in vitro, and increases their sensitivity to chemotherapeutics. It also changes the morphology and invasiveness of glioma cells in vivo. One possible method for inhibition of this receptor activity is the use of newly obtained monoclonal antibodies, which gives new therapeutic and research possibilities [75]. Monoclonal antibodies can also inhibit activity of integrins [69].

RNA interference (RNAi) is another treatment modality leading to a total or partial silencing of gene expression. RNAi therapy can be used in combination with other methods, improving patient outcomes [76]. The use of this treatment method led to decreased levels of GBP1 – a binding protein which participates in the regulation of metalloproteinases and decreases the capacity of glioma cells for invasion into normal brain tissue [77].

Immunotherapy, consisting of vaccines prepared from autologic dendritic cells, is also used for treatment of patients with GBM. Adjuvant therapy using the lysate prepared from whole dendritic cells improves the short-term survival in patients with GBM [78].

Hormone treatment is another therapeutic method for patients with GBM. It blocks, among others, the c-Jun N-terminal kinase (JNK)-dependent signaling pathway, which further blocks pro-apoptotic action of estradiol in glioblastoma cells. This method indicates a key role of the JNK pathway in growth inhibition of GBM and induction of the apoptotic pathway [79].

Prognostic factors

Selection of an appropriate made of treatment and prognosis in patients suffering from GBM depend on the tumor location, its histological grade, genetic profile, proliferative index, completeness of surgery resection and the patient's age and position on the Karnofsky performance status scale (KPS)[80] before radiotherapy [81]. The KPS allows one to define a patient's general condition and the quality of life in oncology and palliative medicine. The performance scale includes 11 positions with 0 to 100 points; 100 points means no evidence of disease and 0 is a patient's death [82, 83].

Recursive partitioning analysis (RPA) is one of the first, simplest and the most-used prognostic schemes available for estimating survival in patients with newly diagnosed brain tumors. It incorporates patient age, KPS score, status of the primary tumor, and extent of extracranial disease into a model for predicting prognosis in these patients. The classic pattern of RPA risk stratification is from highly favorable to highly unfavorable [84]. Recursive partitioning analysis can be employed to refine the stratification and design of malignant glioma trial and permits examination of the interaction between prognostic variables not possible with other forms of multivariate analysis [85]. A proper diet undoubtedly plays an important role in the patient's response to treatment, as well as in the recovery process [86].

Summary

Etiology of glioblastoma multiforme together with its metastatic mechanism are subjected to intensive studies. The progress in radiologic diagnostics significantly facilitates development of an appropriate treatment regimen and its monitoring, which further directly influences the quality of a patient's life. Due to the location of the tumor and its rapid spread, it is necessary to intensify research work devoted to the biology of this tumor.

The authors declare no conflict of interest.

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