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Glioblastoma multiforme - disease overview considering sports and neurorehabilitation

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Abstract:

The brain is the most important organ, coordinating the work of the entire body. However, even it sometimes makes mistakes. Mutations in its genetic material can lead to the development of one of the most aggressive cancers - glioblastoma multiforme.

Glioblastoma multiforme is the most common primary malignant tumor of the central nervous system (CNS). According to the WHO, it is classified as grade 4 in terms of malignancy. The 5-year survival rate is 7.2%. Occurs worldwide with a frequency of less than 10 cases per 100,000 inhabitants. It is more common in men than in women, with an average age at diagnosis of 65 years. The primary confirmed risk factor is exposure to ionizing radiation. Despite advances in medical research, the prognosis for individuals with glioblastoma multiforme remains unfavorable. The median survival time remains around 15 months.

This article provides an overview of glioblastoma multiforme, including its etiology, symptoms, diagnosis, and treatment. By elucidating the current state of knowledge on glioblastoma multiforme, this work aims to facilitate early detection, treatment, and raise awareness among both physicians and patients about the disease. [7,14,17]

Keywords: glioblastoma multiforme, glioblastoma, CNS tumor

Introduction:

Glioblastoma multiforme is the most common primary malignant tumor of the central nervous system (CNS). It arises from stem or progenitor cells of neuroglia and is characterized by significant molecular diversity. Glioma cells migrate along neural pathways, blood vessels, and meninges. Despite direct contact with blood vessels and the production of significant amounts of proteases, the spread of the tumor beyond the central nervous system is rare. The most common extracranial metastasis sites are the lungs and pleura. Some of the earliest cases of the tumor were identified in the late 19th century. The term "glioma" was first used by Rudolf Virchow in reference to a malignant brain tumor. The lack of a clear boundary with healthy tissue from the outset suggested its malignant nature. [3,32,16]

Etiology:

The etiology of glioblastoma is not fully understood, and its development is associated with multifactorial processes that involve genetic, environmental and demographic factors. Below are the main aspects related to the etiology of this tumor:

Genetic factors: Certain genetic syndromes such as Li-Fraumeni syndrome, neurofibromatosis type 1, and Turcot syndrome are associated with an increased risk of developing GBM.

Environmental factors: Ionizing radiation. Individuals who have been exposed to ionizing radiation (e.g., as a result of previous radiotherapy for cancer treatment) have a significantly increased risk of developing GBM.

Demographic factors: Race-more common in the white race than in other ethnic groups. Gender: More frequent in men. Age: The risk increases with age; the median age at diagnosis is 65 years

While some risk factors are known, most GBM cases develop sporadically, without a discernible cause. There is no evidence to suggest an increased risk of glioma associated with mobile phone use, exposure to extremely low-frequency magnetic fields. Interestingly, a history of atopic diseases and allergies reduces the risk of developing glioblastoma multiforme. [4,20,21]

Symptoms:

Patients with brain tumors typically visit their primary care physician an average of three or more times before receiving a diagnosis. Patients with focal neurological deficits are diagnosed more quickly, while those with more common symptoms, such as headaches, cognitive changes, or personality shifts, present greater diagnostic challenges.

Patients reported the following initial symptoms:

- Headache (23.5% of patients)**:** Typically more severe in the morning, often accompanied by nausea and vomiting, and may involve a change in pain pattern, frequently presenting as bilateral tension-type headaches.
- Generalized seizures (21.3%): Often focal in onset, most commonly occurring in the frontal and temporal regions.
- Unilateral weakness (7.1%)
- Instability (6.1%)
- Speech expression disorders (5.8%)
- Vision problems (3.2%)
- Disorientation (4.5%)
- Unilateral numbness (2.3%)
- Personality problems (1.6%)
- Double vision (0.3%)
- Other symptoms (24.2%) such as anosmia, apraxia, cognitive impairment (often misinterpreted as dementia), drowsiness, dysphagia, hallucinations, memory loss, nausea and vomiting, neck pain, and stiffness.

Clinical symptoms primarily depend on the size and location of the tumor mass.
[1,5,9,24,26,28,33]

Diagnosis:

Typically, the first examination performed on patients is a brain CT scan, chosen for its accessibility. After identifying a mass and ruling out hemorrhage, MRI is recommended. MRI provides better soft tissue contrast. In MRI images, gliomas appear as heterogeneous lesions with irregular borders. They show enhancement after gadolinium contrast administration, usually featuring central necrosis and peritumoral edema. There may also be distortions or displacements of brain ventricles. However, the final diagnosis is based on histopathological examination of the entire tumor or a fragment of it. If tumor resection is not possible, a fine-needle aspiration biopsy is performed. The tissue sample provides us with a lot of information about the tumor—they check for mutations in genes such as IDH1 and MGMT, as well as the methylation status of the MGMT gene promoter, which has prognostic significance and may influence treatment options.[7,8,19.29,31]

Causal Treatment:

Treatment of glioblastoma multiforme (GBM) is multi-stage and involves several standard and modern methods aimed at maximizing patient survival. The main therapeutic approaches include:

Surgical Treatment:
The first step after diagnosing glioblastoma multiforme is maximum surgical resection. Modern techniques, such as surgical navigation with fMRI, fluorescence using 5-aminolevulinic acid (5-ALA), and fluorescein, aid in the precise removal of the tumor. Fluorescence allows for better detection and visualization of the tumor during surgery. Although complete resection is beneficial, the priority remains minimizing neurological deficits that could affect further treatment. Unfortunately, surgery rarely removes all tumor cells, necessitating postoperative treatment to prevent disease recurrence. [11,25,27]

Chemotherapy:

Temozolomide – a chemotherapeutic drug introduced in 1999, is the first-line treatment. The recommended standard after neurosurgery is radiotherapy combined with temozolomide, known as concomitant therapy. In this therapy, the initial dose of the drug is 75 mg/m² of body surface area daily for 42 days, with the possibility of extending to 49 days alongside targeted radiotherapy. If there are no complications from this treatment, temozolomide monotherapy should be continued for up to 6 cycles of 28 days each. Chemotherapy damages rapidly proliferating cells, which is beneficial, but by damaging healthy cells, it leads to complications. Side effects indicative of drug toxicity include myelosuppression, thrombocytopenia, and neutropenia, as well as nausea. These effects gradually diminish after chemotherapy ends. [23]

Radiotherapy:

Typically starts 3-5 weeks post-surgery. Standard radiotherapy involves administering 60 Gy in 2 Gy daily doses over 30 days. No significant benefit has been shown from delivering more than 60 Gy. It is important to be aware of possibility of radiation necrosis a serious adverse effect. If we want to irradiate a large tumor volume or the brainstem a slightly lower dose of 54 to 55.8 Gy in fractions of 1.8 Gy or 57 Gy in fractions of 1.9 Gy should be considered.[25,30]

Targeted Therapy:

Bevacizumab is a humanized antibody against VEGF (vascular endothelial growth factor). It prolongs progression-free survival but does not improve overall survival. Although the drug is FDA-approved for treating recurrent glioblastoma, its impact on patients' quality of life remains debatable. Patients often report worsened cognitive function and quality of life. The drug can be considered for managing symptomatic brain edema to reduce steroid use. [18,25]

Tumor Treating Fields:

A new treatment method approved by the FDA in 2015 as an adjunct therapy for recurrent gliomas. It involves applying a transducer array directly to the patient's scalp to create an electromagnetic field. This induces toxicity in rapidly dividing cells by disrupting microtubule formation. [25]

Despite multi-stage therapy, about 70% of patients with glioblastoma will experience a recurrence of the disease within a year of diagnosis. Reoperation is an option for a certain group of patients to alleviate symptoms such as seizures, aphasia, and motor disturbances, which are often encountered in recurrent disease. However, evidence for improved survival is inconclusive. Additional radiation is possible in some cases, but due to the risk of radiation necrosis, the tolerance of healthy brain tissue is limited. Various radiotherapy techniques are used, such as brachytherapy, gamma knife, and stereotactic radiosurgery. Chemotherapy and corticosteroids can alleviate symptoms, but the effects are usually short-lived.[8]

Supportive Care:

Seizures:
80% of patients will experience seizures at some stage of the disease. The most extensively studied drug among glioma patients is Levetiracetam. Research indicates it is safe and has relatively few interactions with other medications. Prophylactic use of anticonvulsants without a history of seizures in the patient is not recommended.

In the last month before death, up to 30-37% of patients experience seizures. One study shows an increase in the number of seizures as death approaches. However, managing seizures in the end-of-life stage is challenging due to swallowing difficulties and impaired consciousness, which make oral medication administration impossible. Alternative methods of administration, such as subcutaneous midazolam, subcutaneous levetiracetam, and subcutaneous phenobarbital, are good alternatives for oral treatment. For patients with drug-resistant epilepsy and a short expected lifespan, palliative sedation with subcutaneous midazolam may be considered.

Vasogenic edema:
This is very common in patients with glioblastoma multiforme. Swelling due to increased intracranial pressure generates severe headaches. The preferred drug is Dexamethasone. Its main advantage is the lack of mineralocorticoid activity. However, it should be noted that it has a wide range of side effects, such as Cushing's effect, steroid-induced diabetes, and muscle weakness. The lowest possible dose for the shortest time is recommended. The starting dose is 4 mg/day, with a maximum of 16 mg/day.

Venous thromboembolism:

20% of patients develop venous thromboembolism within the first year of the disease, influenced by increased activation of clotting factors and thrombin by the tumor, a high percentage of patients with limb mobility disorders, and neurosurgical procedures. Treatment is usually lifelong and involves continuous administration of low-molecular-weight heparin. They are safe for patients with glioblastomas. However, they should be avoided in cases of recent tumor bleeding, thrombocytopenia below 50,000 platelets/mm^3, and typical contraindications. There is a lack of data regarding modern anticoagulants and their potential interactions with chemotherapy or antiepileptic drugs. [10,22,33]

Depression:

Studies show that approximately 90% of patients with malignant brain tumors experience clinically significant depression, which is a much higher percentage compared to patients with other types of cancer (15-29%). Depression is an independent risk factor for shorter survival. It also negatively impacts pain perception, increases the risk of cardiac events, and lowers the quality of life in cancer patients. Unfortunately, there are no randomized clinical trials on the pharmacological treatment of patients with primary brain tumors. However, there are some reports of benefits from using methylphenidate, oxcarbazepine, bupropion SR, ginkgo biloba, and donepezil.

Cancer-Related Fatigue:

The biological mechanisms leading to this type of fatigue are complex and not yet fully understood. Researchers attribute the cause to elevated levels of inflammatory cytokines in the blood and reduced levels of glutamine and tryptophan in the brain. Treatment can be non-pharmacological (physical exercise, cognitive-behavioral therapy) or pharmacological (with modafinil, armodafinil, methylphenidate, or donepezil). However, there is no evidence of significant benefits from any of these methods in patients with brain tumors.

Neurorehabilitation:

Brain tumor patients often have multiple deficits in these areas. Although no randomized controlled trials have evaluated the effectiveness of specialist post-operative rehabilitation in patients with primary brain tumors, retrospective studies suggest significant benefits. These studies indicate that rehabilitation can lead to a 36% improvement in functional independence,

with an average inpatient stay of 1.5 months. Limited evidence also suggests that early physical training, massage therapy, and ambulatory rehabilitation may improve outcomes and quality of life in glioma patients. Rehabilitation during and after radiotherapy has shown functional gains, though it does not improve survival. However, regular strenuous exercise has been identified as an independent factor for longer survival in patients with malignant glioma. [10,22,30]

Palliative Care:

Palliative care in glioblastoma multiforme (GBM) plays a key role in managing symptoms and improving the quality of life for patients with advanced disease. Glioblastoma multiforme is an aggressive brain tumor, and standard treatment is often unable to cure it, making palliative care an essential component of therapy.

According to the WHO, "Palliative care is an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through early identification, correct assessment, and treatment of pain and other problems, whether physical, psychosocial, or spiritual." The most common symptoms in patients at the end of life are fatigue, followed by reduced consciousness and aphasia. It has been shown that many patients with glioblastoma multiforme received less support from palliative medicine than the average cancer patient. However, those who received it early had significantly better quality of life, fewer mood disorders, and generated lower treatment costs. [2,6,13,15]

Future Directions:

Glioblastoma (GBM) is the most common and aggressive primary central nervous system tumor in adults. Standard treatment for GBM includes surgical resection, radiotherapy, and chemotherapy; however, the prognosis remains poor, with a median survival of 15 months. Immunotherapy, which mobilizes the immune system to fight cancer, is of great interest, though it faces challenges related to GBM-induced immunosuppression and the blood-brain barrier. Nevertheless, various immunotherapeutic approaches are being developed, including

peptide vaccines, cellular vaccines, chimeric antigen receptor T-cells, checkpoint inhibitors, and oncolytic virotherapy. [12]

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