GLIOBLASTOMA: EPIDEMIOLOGY, MOLECULAR BIOLOGY, CLINICAL FEATURES AND DIAGNOSTIC APPROACHES

Khakimov M.N.
Andijan State Medical Institute

Abstract: Glioblastoma (GBM) is the most aggressive primary malignant brain tumor in adults, characterized by rapid proliferation, extensive infiltration, and resistance to conventional therapies. Despite ongoing therapeutic advancements, the prognosis remains poor, highlighting the need for improved understanding of tumor biology. This review summarizes the epidemiology, molecular pathogenesis, clinical manifestations, and diagnostic strategies of glioblastoma, emphasizing the importance of integrated molecular diagnostics in the modern classification of diffuse gliomas.

Keywords: glioblastoma, epidemiology, clinical features, diagnostic approaches

Introduction. Glioblastoma, previously designated as glioblastoma multiforme (GBM), is classified by the World Health Organization (WHO) as a grade 4 diffuse astrocytic tumor. It represents the terminal stage of astrocytoma progression or may arise de novo from glial progenitor cells. The hallmarks of GBM include aggressive growth, diffuse parenchymal infiltration, necrosis, and microvascular proliferation, resulting in a devastating clinical course.

Major advances in molecular neuro-oncology have fundamentally changed the classification of gliomas, with emphasis on IDH mutation status, MGMT promoter methylation, and other key biomarkers. These factors are essential for diagnostic accuracy, treatment selection, and prognostic assessment.

Epidemiology

Incidence and Demographics

GBM accounts for approximately 45–50% of all malignant primary brain tumors and has an annual incidence of 3–4 cases per 100,000 individuals. The disease typically presents between ages 55 and 75, with a slight male predominance.

Risk Factors

Glioblastoma has few clearly established risk factors:

- Ionizing radiation is the only confirmed environmental risk.
- Genetic predisposition in rare syndromes (e.g., Li-Fraumeni, Turcot, NF1).
- Ethnic variation: Higher incidence in individuals of European descent.
- No strong evidence supports associations with smoking, mobile phones, or trauma.

Molecular Pathogenesis

Primary vs. Secondary Glioblastoma

▪Primary GBM (≈90%) arises de novo and is usually IDH-wildtype.

▪Secondary GBM evolves from lower-grade gliomas and is typically IDH-mutant, with better prognosis.

Key Genetic Drivers

Several recurrent alterations characterize GBM biology:

EGFR Amplification and EGFRvIII

Over 40% of GBMs exhibit epidermal growth factor receptor (EGFR) amplification. EGFRvIII, a deletion mutant, produces constitutive signaling essential for tumor growth.

TERT Promoter Mutations

Common in IDH-wildtype GBM, these mutations enhance telomerase activity and promote immortalization.

PTEN Loss and PI3K Pathway Activation

Loss of PTEN drives uncontrolled growth and metabolic adaptation.

TP53 Pathway Alterations

Frequently seen in secondary GBM.

Epigenetic Modifications

MGMT promoter methylation is a crucial predictive marker for response to alkylating chemotherapy (temozolomide).
DNA methylation profiling has emerged as a gold standard for classifying diffuse gliomas.

Tumor Microenvironment

▪GBM is characterized by:

▪Hypoxia-induced angiogenesis

▪Immunosuppressive milieu (T-reg enrichment, PD-L1 expression)

▪Tumor-associated macrophages and microglia, supporting invasion and resistance

These features significantly contribute to treatment resistance.

Clinical Presentation

General Symptoms

▪Persistent headache

▪Nausea, vomiting due to increased intracranial pressure

▪Progressive neurological deficits

▪Seizures (more common in secondary GBM)

▪Cognitive decline, personality changes

Localization-Dependent Features

▪Frontal lobe: apathy, executive dysfunction

▪Temporal lobe: memory impairment, seizures

▪Parietal lobe: sensory deficits, neglect

▪Occipital lobe: visual field loss

- Brainstem or thalamus: severe deficits, poor prognosis

GBM progression is typically rapid, with symptoms worsening over weeks to months.

Diagnostic Evaluation

Neuroimaging

MRI with contrast enhancement is the diagnostic modality of choice. Characteristic findings include:

- Ring-enhancing lesion with central necrosis
- Surrounding vasogenic edema
- Infiltrative growth along white matter tracts
- Restricted diffusion in hypercellular regions

Advanced imaging (perfusion MRI, spectroscopy, DWI, PET) aids in differentiating GBM from abscess, metastasis, or treatment effects.

Tissue Diagnosis and Molecular Testing

Stereotactic biopsy or resection is required. WHO classification mandates integrated diagnosis based on:

- IDH mutation status
- ATRX status
- TP53, TERT, EGFR, PTEN, CDKN2A deletion
- MGMT promoter methylation

Liquid Biopsy

Emerging biomarkers in plasma and CSF (ctDNA, exosomes) offer potential for non-invasive monitoring.

Discussion. Glioblastoma remains one of the most challenging tumors in modern oncology. Its highly heterogeneous molecular landscape and infiltrative growth complicate complete resection and limit therapeutic options. The integration of molecular biomarkers into diagnostic workflows represents a major advancement enabling more precise classification and individualized treatment planning.

Conclusion. Glioblastoma is an aggressive and devastating disease with limited therapeutic response. Accurate diagnosis requires combining radiological evaluation with detailed molecular profiling. Continued research in tumor genetics, immunobiology, and microenvironmental dynamics is critical for developing future therapies aimed at improving survival and quality of life.

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