



## GLIOBLASTOMA MULTIFORME: A REVIEW ARTICLE

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### ABSTRACT

Glioblastoma multiforme (GBM) is one of the most malignant types of central nervous system tumors. Despite advances in treatment modalities it remains largely incurable. Current treatment options at diagnosis are multimodal and include surgical resection, radiation, and chemotherapy. Significant advances in the understanding of the molecular pathology of GBM and associated cell signaling pathways have opened opportunities for new therapies for recurrent and newly diagnosed disease. The objective of our review is to provide a holistic picture of GBM epidemiology, pathogenesis, and imaging findings.

**Keywords:** Glioblastoma multiforme, surgical resection, radiation, chemotherapy.

## INTRODUCTION

Glioblastoma multiforme is the most aggressive of the gliomas, a collection of tumors arising from glia or their precursors within the central nervous system. Clinically, gliomas are divided into four grades; unfortunately, the most aggressive of these, grade 4 or glioblastoma multiforme (GBM), is also the most common in humans. Because most patients with GBMs die of their disease in less than a year and essentially none has long-term survival, these tumors have drawn significant attention; however, they have evaded increasingly clever and intricate attempts at therapy over the last half-century. These tumors also show intratumor genetic heterogeneity with subclones existing within the tumor cell population (1). It has been estimated that cultured neoplastic and p53-deficient cells may have mutations in any given gene at a rate as high as 1 in 1,000 cells (2). Although GBMs can be visualized on MRI scans as mass lesions that enhance with contrast, the neoplastic cells extend far beyond the area of enhancement. Even with repeat surgeries for tumor recurrences, the patients die from tumor spread into vital regions of the brain.

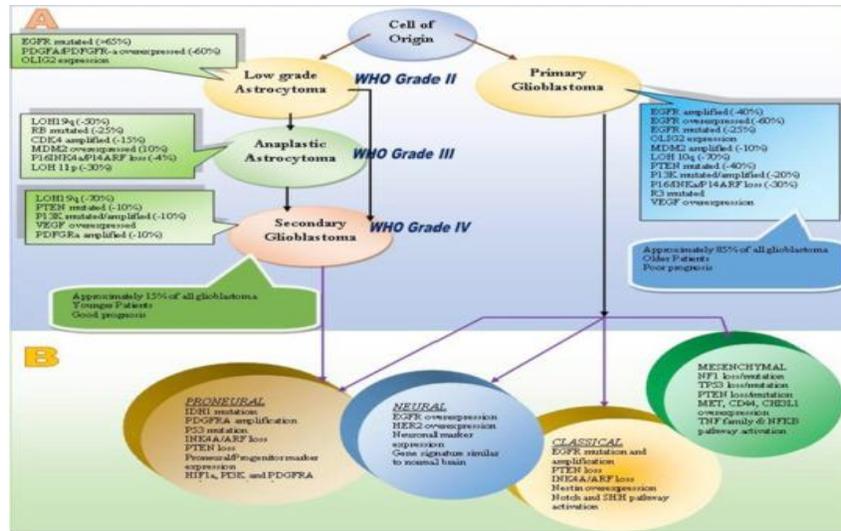
### **Epidemiology:**

Although GBM is rare tumor with global incidence of less than 10 per 100,000 people, its poor prognosis with survival rate of 14-15 months after diagnosis makes it a crucial public health issue (3). It can occur at any age but the peak incidence is between 55 to 60 years (4). Malignant gliomas are the reason of 2.5% of deaths due to cancers and are the third foremost cause of death from cancer in persons 15 to 34 years of age (Salcman, 1990). The ratio of GBM incidence is higher in men as compares to women (Ohgaki and Kleihues, 2005; Thakkar et al., 2014).

### **Pathogenesis:**

The cellular origin of glioblastoma is unknown. Because of the similarities in immunostaining of glial cells and glioblastoma, it has long been assumed that gliomas such as glioblastoma originate from glial type cells. However more recent studies suggest that astrocytes, oligodendrocyte progenitor cells and neural stem cells could also serve as the cell of origin (5). GBMs usually form in the cerebral white matter, grow quickly, and can become very large before producing symptoms. Fewer than 10% form more slowly following degeneration of low-grade astrocytoma or anaplastic astrocytoma. These are called secondary GBMs and are more common in younger patients (mean age 45 versus 62 years) (6). The tumor may extend into the meninges or ventricular wall, leading to high protein content in the cerebrospinal fluid (CSF) (> 100 mg/dL), as well as an occasional pleocytosis of 10 to 100 cells, mostly lymphocytes. Malignant cells carried in the CSF may spread (rarely) to the spinal cord or cause meningeal gliomatosis. However, metastasis of GBM beyond the central nervous system is extremely unusual. About 50% of GBMs occupy more than one lobe of a hemisphere or are bilateral. Tumors of this type usually arise from the cerebrum and may exhibit the classic

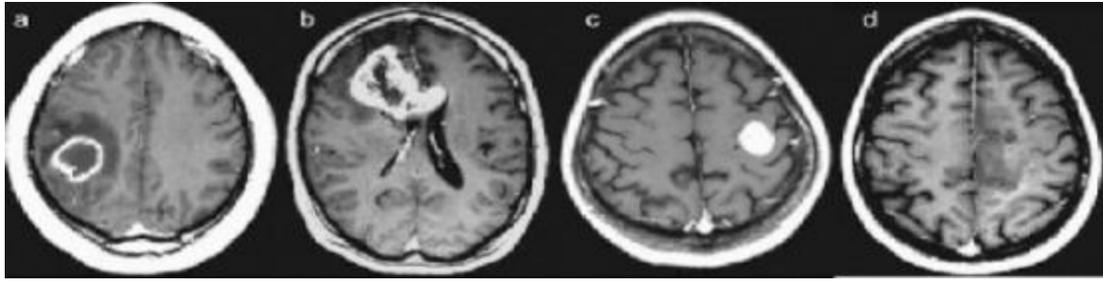
infiltration across the corpus callosum, producing a butterfly (bilateral) glioma. The most frequent location for GBM is cerebral hemispheres; with 95% of these tumors arise in supratentorial region, while only few percent of tumors occur in cerebellum, brainstem and spinal cord (Nakada et al., 2011).



**Figure 1:** Genetic and Molecular Pathogenesis of GBM. (A) Aberrations involved in primary and secondary GBMs (B) Subtypes of primary and secondary GBMs. (Adapted from Agnihotri et al., 2013)

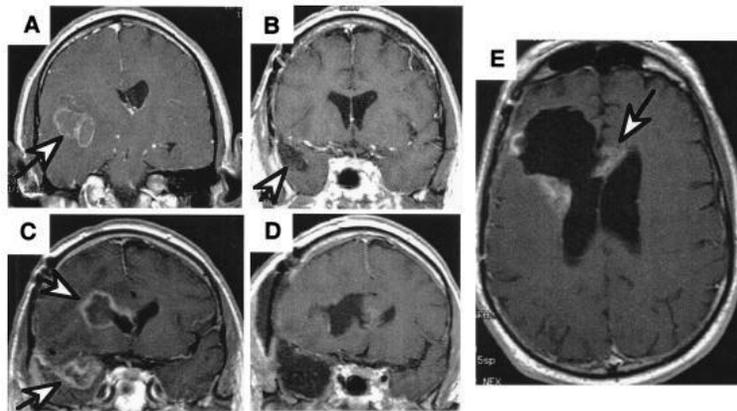
### Imaging:

Imaging techniques carried out on individuals suspected of having brain tumors include invasive procedures such as catheter angiography and non-invasive tests such as computed tomography (CT) and magnetic resonance imaging (MRI) scans which are more routinely used for the purpose of visualising the tumors (Nelson, 2003). CT scans are often advised when a patient cannot undergo MR scan due to some reasons, for example, patients with pacemakers (Omuro and DeAngelis, 2013). On a CT scan the lesions usually appears as hypointense areas in comparison to adjacent brain tissue and usually demonstrates a midline shift as a result of moderate to severe edema. However, the gold standard imaging technique used is MR scans due to their superior soft tissue contrast, which allows the complexity and the heterogeneity of the tumor lesion to be better visualized than a CT scan. Hypointense lesions are seen on T1-weighted MR scans, whereas hyperintense lesions are visualized on proton density weighted and T2-weighted images (Nelson, 2003). Usual findings on a MR scan enhanced with gadolinium of patients with malignant gliomas shows a central area of necrosis, surrounded by white matter edema (Figure 2). Tumors are usually unifocal but can be multifocal too (Omuro and DeAngelis, 2013).



**Figure 2:** Four Different Patients with GBM that Illustrate the Heterogeneity in the Anatomic Lesion. The contrast-enhanced axial T1-weighted (TR, 600 msec; TE, 14 msec) images demonstrate variegated appearance of GBM: (a) rim-enhancing mass with central necrosis in the right parietal lobe with surrounding edema; (b) irregularly enhancing mass that crosses the corpus callosum; (c) well-circumscribed homogeneously enhancing mass in the left frontal lobe with no associated edema; (d) ill-defined infiltrative mass in the left medial frontal lobe with no appreciable necrosis. (Adapted from: Nelson and Cha, 2003).

Recent advances in imaging techniques and especially in MR over the past few years have also helped in evaluating the changes in hemodynamics, tissue architecture and cellular metabolism of the gliomas. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) which are nuclear medicine techniques, are also being employed as problem solving tools to differentiate between active tumor and therapy-related changes in tumor (Nelson, 2003).



**Figure 3:** MRI scans of a patient with a right temporal GBM illustrating the spread of the disease. (A) Presurgical scan, GBM (arrow) is surrounded with edema. (B) Scan after surgery and radiation therapy showing “gross total resection” and clear resection cavity, and (C) six months later, showing recurrence not only at the resection margin (arrow) but a second focus of GBM across the Sylvian fissure in the frontal lobe (arrow). (D) Postresection scans of both recurrent tumors. (E) Scan 3 months later, showing the tumor recurring at the resection margin and crossing the corpus callosum to the other hemisphere (arrow).

Even under the best of circumstances, in which essentially all of the enhancing tumor seen on MRI scan can be surgically removed and the patients are fully treated with radiation and chemotherapy, the mean survival of this disease is only extended from 2 to 3 months (7) to 1 year.

## CONCLUSION

Glioblastoma multiforme (GBM) is one of the most malignant types of central nervous system tumors. Here we discussed about its epidemiology, pathogenesis and its imaging findings which are helpful for treatment of GBM.

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