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Literature Review

Radiographic, CT and MRI Features of the Cranium: A Review of The Patho- physiological Variations Associated with GBM and Astrocytoma

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Abstract

Brain Glioma is a common invasive brain tumor arising from glial cells, with various clinical presentations and risk factors like ionizing radiation and heterogeneity. Astrocytoma, named after astrocytes, is graded based on abnormality. Glioblastoma Multiforme (GBM) is the most malignant type, distinguished by histologic features and pathological diagnosis based on physical appearance, genetics, nuclear atypia, and cell mitotic activity. This paper explores variations in radiologic features and the correlation between GBM in CT and MRI modalities. The proposal of the GMB literature review was undertaken by searching the databases: Google Scholar, Cochrane Library, EBSCOHOST, Medline, Healthline Website, Medscape, PubMed, PsycINFO and CINAHL. 60 papers published till 2023 were reviewed. It was found that a GBM patient presents with various symptoms that vary with the tumor site. Moreover, GBM is characterized by rapid growth and invasion facilitated by cell migration and degradation of the extracellular matrix. Thus, despite technological advances in surgery and radio-chemotherapy, Glioblastoma remains largely incurable. Henceforth the great need for new approaches to study Glioblastoma and to design optimized therapies such as viral therapy [1]. However, to confirm the presence and the extent of tumor, various invasive and non-invasive imaging techniques require employment. Where an obvious variation between the normal brain anatomy and human brain damaged by the Glioblastoma is illustrated. Furthermore, understanding the molecular and genetic mechanisms underlying its aggressive behavior may lead to better management, appropriate therapies, and good outcomes [2].

INTRODUCTION

Brain Glioma is one of the most common invasive brain tumors that arise from the glial cells of the brain [3], that is accompanied with various clinical presentations and several risk factors such as ionizing radiation and heterogeneity. Though, one type of glioma called astrocytoma is named after astrocytes, the star-shaped cells from which they grow [4-6]. As stated in the American Brain Tumor Association (ABTA), astrocytomas are graded in accordance to their degree of abnormality using a scale of I to IV with early grades being benign tumors. Effectively treating GBM is still one of the most significant challenges in the therapy of brain cancer [7]. Yet, late grades represent "malignant glioma" [8]. However, gliomas are detected by MRI or CT scan where, obviously, a huge variation from normal brain anatomy is investigated [9]. Furthermore, Glioblastoma Multiforme (GBM) is the most malignant type of brain tumor, and it can be distinguished from other brain tumors by its histologic features. In addition, the pathological diagnosis is based on physical appearance, genetic features, nuclear atypia and the mitotic activity of the cell [10,11].

Prognoses as well as the treatment options that have been developed along the last decay (Figure 1), alter depending on the tumor type, size and the location and, however, despite, the advances in diagnostic and treatment modalities, GBM remains largely incurable [12]. The following report further explore the variations in radiologic features and the radiologic pathological correlation of GBM in CT and MRI modalities, which make up the core of this paper.

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NORMAL ANATOMY OF THE HUMAN BRAIN

The brain is a structure that regulates the functions of the body, which include the involuntary (controlling BP, HR and RR) and the voluntary acts like walking and talking, in addition to the other intellectual functions of the body [5]. Anatomically, the human brain consists of two hemispheres in the cerebellum, which is responsible for movement, sensation, thought, judgment, problem solving, and emotion [13]. The brain stem sits beneath the cerebrum and connects it to the spinal cord. There are four lobes in each hemisphere: frontal, parietal, temporal, and occipital. Brain cells consume glucose and O2 almost exclusively for their energy needs and unlike other organs in the body, the brain cannot store glucose for future use. In addition to these main structures other parts of the brain are labeled in figure 2.

Based on Benjamine's [14] study of the cerebral blood supply, the brain gets its blood supply through four major arteries, the right and left

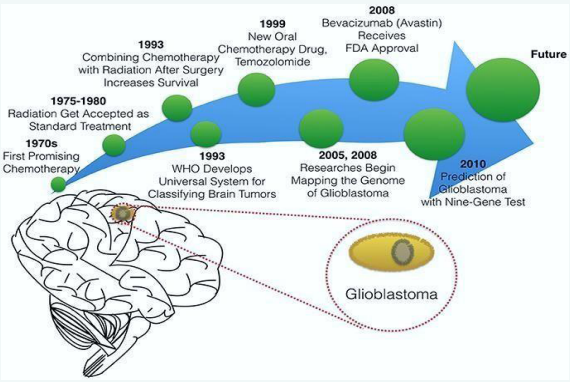


Figure 1: The timeline of glioblastoma therapy. Advances in glioblastoma multiforme treatment: new models for nanoparticle therapy, (2018).

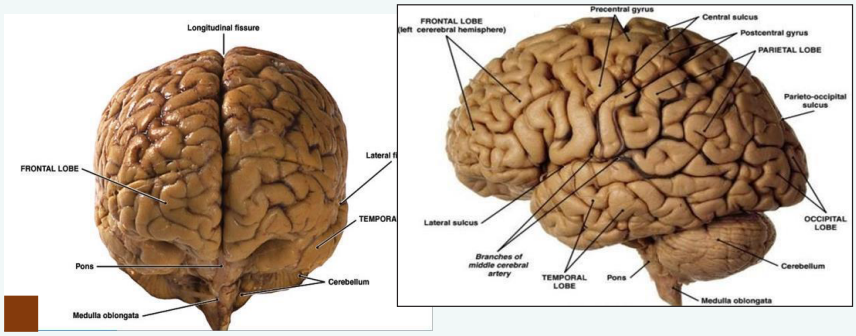


Figure 2: Anterior view of the demonstrating different structures including frontal and temporal lobe 1b.Lateral view of the brain illustrating various structures [13].

Table 1: Two main classifications of the brain cells.

Neurons	Glial cells
Cells that process and transmit information in the brain (TeachMePhysiology, 2018).	Metabolic support (TeachMePhysiology, 2018).
Have two connectors, the axon and dendrite [5].	Part of the immune system within brain tissue clears dead cells and other debris [5].
Special chemicals called neurotransmitters transfer the electrical impulse across the synapse so that one neuron can excite another [5].	Astrocytes are glial cells within the brain and spinal cord [5].

carotids and the right and left vertebral arteries. They join at the base of the brain at the Circle of Willis. Smaller blood vessels then branch out to provide oxygen and glucose rich blood to all regions of the brain.

Brain cells: Classifications structure and functions

The brain is composed of billions of cells that use chemicals and electricity to communicate between themselves and the rest of the body. As table 1 demonstrates, there are two major types of cells, neurons and glial cells. Glial cells and neurons are the two cell types that make up the nervous system. Neurons oversee detecting changes in their surroundings and sending electrochemical signals to other neurons [15]. In addition to eliminating waste products from metabolism, glial cells nurture, nourish, and insulate neurons. The purpose of neurons and glial cells will be covered in this article.

Likewise, there are subtypes of these cells (Figure 3).

Table 2: Genetic mutations in GBM.

Mutations	Implication in GBM
Loss of heterozygosity on chromosome arm 10q	Associated with poor servival; apprears to be a likely contributor to development of GBM
p53 deletion	Allows for lack of tumor suppression
EGFR	Control cell proliferation; upregulated in GBM
VEGF	Controls angiogenesis; upregulated in GBM
MDM2 amplification	Upregulation allows for escape from p53 suppresion by binding to p53 and suppressing its normal activity
MGMT amplification	DNA repair enzyme that contributes to tumor resistance to chemotherapy

EGFR: Epidermal Growth Factor Receptor; GBM: Glioblastoma Multiforme; MDM2: Murine Double Minute; MGMT: Methylguanine Methyltransferase; VEGF: Vascular Endothelial Growth Factor

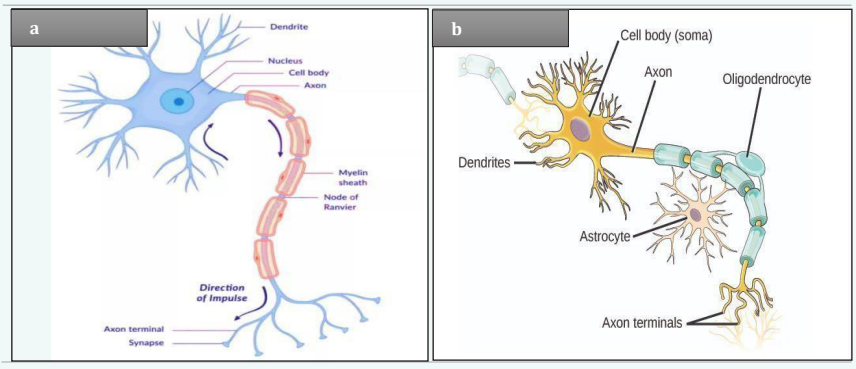


Figure 3: a). Illustrates the basic structure of a neuron. **b).** shows some of the glial cells in relation to a neuron [14].

Table 3: Primary Glioblastoma versus Secondary Glioblastoma.

Primary Glioblastoma	Secondary Glioblastoma
Develops de novo from glial cells.	Develops from low – grade diffuse astrocytoma of anaplastic astrocytoma.
Accounts for > 90% of biopsied or resected cases.	Comprises < 10% of GBM cases.
Clinical history of < 3 months.	Have a predilection for the frontal lobes.
Occurs in older patients (median age: 60 years).	Occurs in younger patients (median age: 45 years).
More aggressive.	Rare and less aggressive.

BRAIN PATHOPHYSIOLOGY: GENETIC AND CLINICAL CHARACTERISTICS GLIOBLASTOMA MULTIFORME (GBM)

When rating the brain tumors based on integrated phenotypic and genotypic parameters for their invasiveness, Glioblastoma Multiform is known to be the highest-grade glioma (grade IV) [16,17] form of astrocytoma with histological features demonstrating necrosis (dead cells) and abnormal growth of the blood vessels near the tumor [18], more details are shown in table 2 Consequently, it is a deadly disease with extremely poor prognosis and median survival rate of approximately 14 to 15 months from the diagnosis time [19]. GBM accounts for almost 80% of all malignant primary tumors of the brain. However, the tumors are rated on their growth perspective as low-grade (slow growth), mid-grade (moderate) and high-grade (rapid). Early grades tumors are considered as benign while surgical excision is curative option, yet they cause an excessive impairment. In traditional MRI methods, contrast enhancement is another metric that is associated with tumor grade. But according to reports, about 40% of cases of high-grade gliomas may not improve with gadolinium-based contrast media [20]. Moreover, advanced staged gliomas are encompassed in terms like malignant and anaplastic glioma due to their tendency to cause infiltration of the neoplasm with the demonstration of speculated shape cells. Besides, the growth rate (mitotic activity) and the appearance of cells (nuclear atypia) are utilized to determine the pathological diagnosis of the glioma [21]. As an example, tumors with methylated MGMT (inactive gene) have been found to predict a longer length of survival and respond better to chemotherapeutic agents in the treatment of Glioblastoma [22].

Table 4: Main proven risk factors that highly correlate with GBM.

1. Ionizing Radiation exposure, GBM occurrence was found linear to the radiation exposures during the radiotherapy, mostly these includes pediatric patients that undergo therapeutic intracranial radiation. The overall risk of developing GBM following radiotherapy is 2.5% [31].
1.1 People in/near the countries that had radiation accidents and atomic bomb
exposures have higher incidence of Glioblastoma such as, people in japan (Nagasaki and Hiroshima).
2. Chemotherapeutic drugs and the chemical agents used to treat the patient of Acute Lymphoid Leukemia (ALL) were more prone to be affected by the GBM.
2.1 Some pesticides and other agricultural chemicals have been suspected because they induce cancer in experiments with animals.
4. Usage of ovarian steroid hormones.
5. Rare genetic disorder including neurofibromatosis type 1 and type 2, tuberous sclerosis, are found to be associated with increased incidence.

Table 5: Signs and symptoms of GBM.

A. Direct Effect	1. Focal Neural Deficit (40-60%) and Cognitive Impairments
	2. The hearing and visual problems.
	3. A personality changes.
	4. Imbalance in gait and incontinence.
B. Secondary Effect	1. To a shift in intracranial contents.
	2. Headaches.
	3. Vomiting and papilledema.

How does primary GBM differ from secondary one?

Glioblastomas are commonly known as the most malignant lesions that are predominantly cerebral, accounting for 50% of all astrocytoma cases and approximately 15% of intracranial neoplasms [23]. As seen in table 3, GBMs have been traditionally classified as primary and secondary [24,25].

Primary glioblastoma

A more aggressive type of GBM that manifests de novo (without clinical history or histopathologic evidence of preexisting, less malignant precursor lesion) from glial cells. According to [26], 90% of primary GBM cases arise in patients older than 50 years after a short clinical history, usually less than 3 months [27].

Secondary glioblastoma

Secondary Glioblastoma Multiforme in contrast, develops in approximately 10% of younger adults who are in their 40s, progressing from low – grade diffuse astrocytoma (WHO grade II) or anaplastic astocytoma (WHO grade III) [28]. These tumors are relatively uncommon and tend to be less aggressive than Primary Glioblastomas [29], stated that interestingly, and of uncertain significance, secondary GBMs have a predilection for the frontal lobes.

What contributes to GBM?

The main causes evolving GBM has not been entirely explicated. It is believed to be a spontaneous tumor, even though medical history describes development of glioma in related persons [30]. However, table 4 lists main GBM's contributors according to the review done in 2017 [3].

Clinical presentations

More than half of the patients with GBM frequently present with a short clinical history, which ranges between 3-6 months, however if the tumor is a low graded astrocytoma the clinical history will span over several years [3]. The symptoms of the GBM might develop rapidly and can be mistaken as a stroke. As table 5 Illustrates, there are three various mechanisms through which the signs and symptoms of GBM are distributed.

HISTOLOGY: MICROSCOPIC *VS.* MACROSCOPIC APPEARANCE

Benjamin KB, et al. [26], stated that the histopathology of the GBM is extremely variable and this is indicated by its name, "Glioblastoma Multiforme". He had proved that from two scientific views; clarify this precisely in the following page. Firstly, from a microscopic view, Glioblastoma Multiforme comprise a poorly differentiated, often pleomorphic astrocytic cells with marked nuclear atypia and brisk mitotic activity where the necrosis and prominent microvascular proliferation are an essential diagnostic features [32,33].

Macroscopically, Glioblastomas are poorly delineated with peripheral grayish tumor cells, central yellowish necrosis from myelin breakdown, and multiple areas of old and recent hemorrhages. Nevertheless, Glioblastomas of the cerebral hemispheres are clearly intraparenchymal with an epicenter in the white matter. Yet, some extend superficially and contact the leptomeninges and dura [26].

Clinically, GBM's symptoms last for short periods, despite this, GBMs present surprisingly large, occupying much of the cerebral lobe. Undoubtedly, Glial Fibrillary Acidic Protein (GFAP) remains the most valuable marker for neoplastic astrocytes. Although immunostaining is variable and tends to decrease with progressive dedifferentiation, many cells remain immune-positive for GFAP even in the most aggressive Glioblastomas. The regional heterogeneity of Glioblastomas is remarkable and makes histopathological diagnosis a serious challenge when it is based solely on stereotactic needle biopsies. Glioblastoma (GBM) is a highly aggressive form of cancer that begins in astrocytes, the cells responsible for supporting the function of nerve cells [34]. Tumor heterogeneity is also likely to play a significant role in explaining the meager success of all treatment modalities, including radiation, chemotherapy, and immunotherapy [35] (Figure 4).

RADIOGRAPHIC APPEARANCE OF NORMAL BRAIN & GLIOBLASTOMA MULTIFORME

Normal brain on CT & MRI

As illustrated in figure 5, it is important to consider the symmetry of the cranium by comparing the right and left sides, look for any midline shift, and review the cross – sectional anatomy of the brain when, systematically, interpreting a head CT and MRI. Moreover, looking for any blood collection adjacent to the skull and viewing the bone windows will ease the clarification of a present pathology if any. In a normal Computed Tomography (CT) scan of the brain, the ventricles are of normal size and the distinction between the grey and white matter is clear. The midline of the brain appears straight with the sulci being symmetrical on both sides. Having an intact skull with no scalp edema will also demonstrate the brain of a healthy individual. Using Magnetic Resonance Imaging (MRI) to scan the brain will show a higher-level detail in comparison to a CT scan [37]. In a typical MRI brain, a normal appearance and intensity of brain parenchyma will be visualized. Also, the ventricular system and cisternae spaces will appear normal and the visualized orbits, paranasal sinuses and calvarium will look unremarkable. To confirm the normality of an

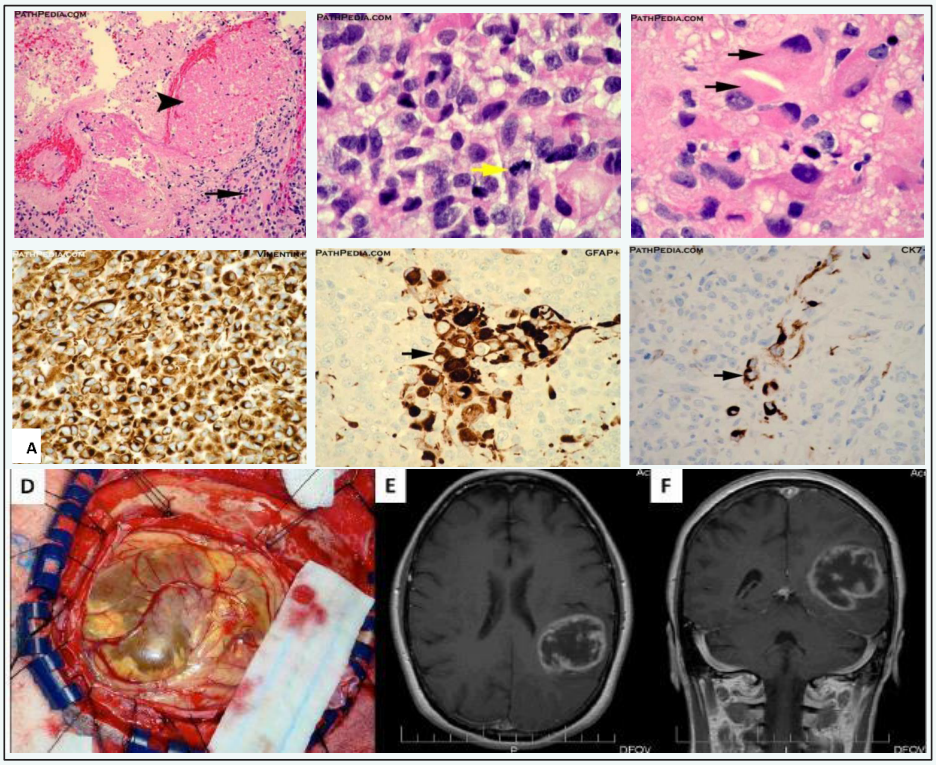


Figure 4: Microscopic view: GBM consist of neoplastic cells with elongated nuclei in association with variable amount of eosinophilic cytoplasm associated with an exaggerated degree of morphologic heterogeneity
characterized by an area of tissue necrosis (low oxygen) tension surrounded immediately by a rim of viable tumor cells [36].
The macroscopic appearance: Intraoperative picture of a GBM showing significant distortion of the gross morphology of the cerebral cortex resulting in expansion and discoloration of the gyri. Magnetic Resonance Imaging (MRI) of a GBM using T1 sequence in conjunction with intravenous administration of gadolinium (GAD) dye. The tumor is represented in the axial and coronal planes, which is essential for localization of the lesion and surgical planning.

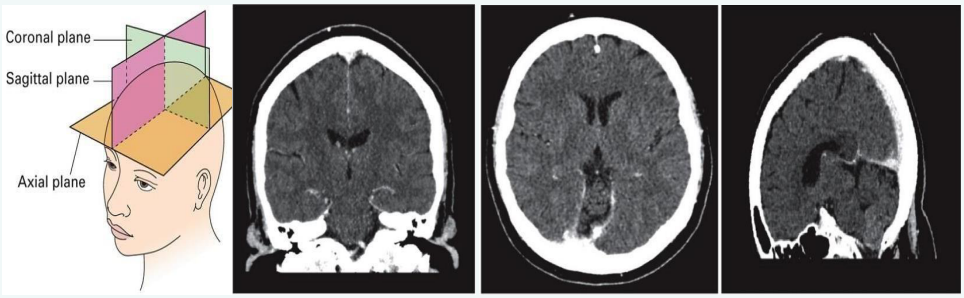


Figure 5: Diagram of the axial, coronal and sagittal planes. Corresponding CT images of a normal brain.

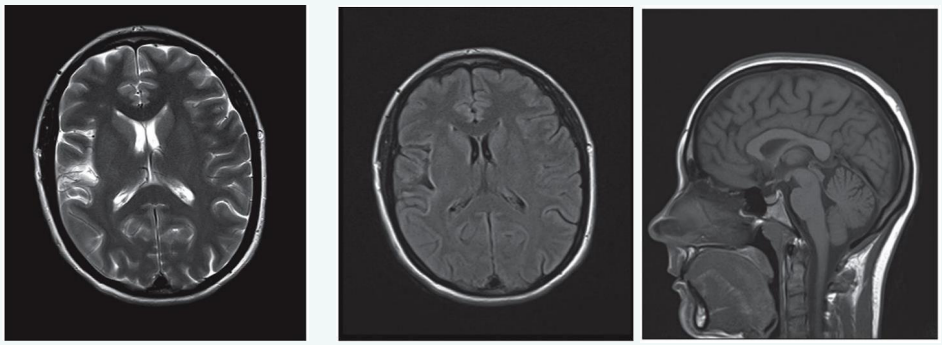


Figure 6: Normal brain MRI. The images are axial sections at the level of the lateral ventricles. a). T2- weighted image. b). FLAIR image. c). A midline sagittal section (T1-weighted) [26].

MRI brain, there should be no evidence of intracranial space occupying a lesion or no obvious vascular anomaly is detected [38-40] (Figures 5,6).

Glioblastoma on CT & MRI

The radiographic appearance of a brain image depends on the location and the size of the subsequent mass effect [41]. GBM are often large tumors at the time of diagnosis [42,43].

However, Figure 7 reveals Glioblastoma on a CT scan. The lesion appears as irregularly enhancing thick margins with a hypodense center representing a necrotic core, which also has a hemorrhagic component. The periphery of the lesion is a ring-like zone of contrast enhancement [44]. A penumbra of vasogenic-type edema, which in fact usually contains infiltration by neoplastic cells, is shown in both images. There is no evidence of calcifications as they are usually uncommon on a CT brain affected by GBM.

Another imaging choice is MRI, with and without contrast. An enhancing ring lesion is always apparent on T1-weighted images as seen in figure 8, while a broad surrounding zone of edema is present on T2-weighted images. The central heterogeneous signal represents a necrotic core with intratumoral bleeding, and the contrast-enhancing ring is composed of highly dense cells with abnormal vessels permeable to contrast agents [9]. The vasogenic edema evident within nonenhancing low attenuation peripheral zone contains varying number of invasive tumors. In his article, [26] stated that several pathological studies have clearly shown that the area of enhancement does not represent the outer tumor border because infiltrating glioma cells can be identified easily within, and occasionally beyond, a 2-cm margin [45,46] (Figure 9, Table 6).

What are the surgical procedures done to diagnose GBM?

Spinal cord procedures: Lumbar puncture

Generally speaking, lumbar puncture is contraindicated for patients with brain tumors because of the possibility of transtentorial herniation with increased intracranial pressure. However, if ruling out lymphoma, it may be necessary [15,25].

CSF studies

Studies conducted on the Cerebrospinal fluid collected by way of spinal punctures and biopsies are found to be not a significant in aiding the specific diagnosis of Glioblastoma Multiforme.

A stereotactic brain needle biopsy

This procedure gives a definitive diagnoses and prognosis to guide treatment decisions for a brain tumor. It is the choice for gliomas in hard-to-reach areas or very sensitive areas within the brain that might be damaged by a more extensive operation. As figure 10 illustrates, it is done by the neurosurgeon where he drills a small hole into the skull, followed by the insertion of a thin needle through this hole. Tissue include samples from the scalp, blood vessels or dura mater (the outermost membrane covering the brain), is removed through the needle, which is frequently guided by CT or MRI scanning. Further analytic studies are then done under a microscope on the biopsy sample to determine if it's cancerous or benign by examining the physical appearance and growth rate of the biopsy sample (molecular diagnosis).

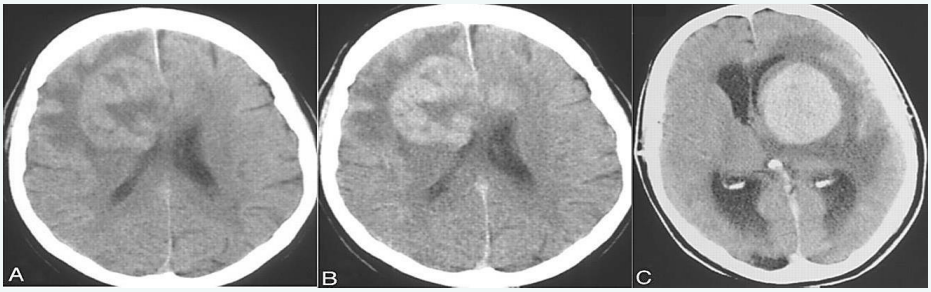


Figure 7: Solitary lesions on a non-contrast CT scan. Contrast-enhanced CT scans and an MR image (D) in 3 patients with non-AIDS PCNSL. Note a hyper-attenuated lesion in the frontal lobe on the non- contrast CT scan (A) with marked enhancement on the contrast series (B) and focal contrast-enhancing lesions in the left basal ganglia (C) [44].

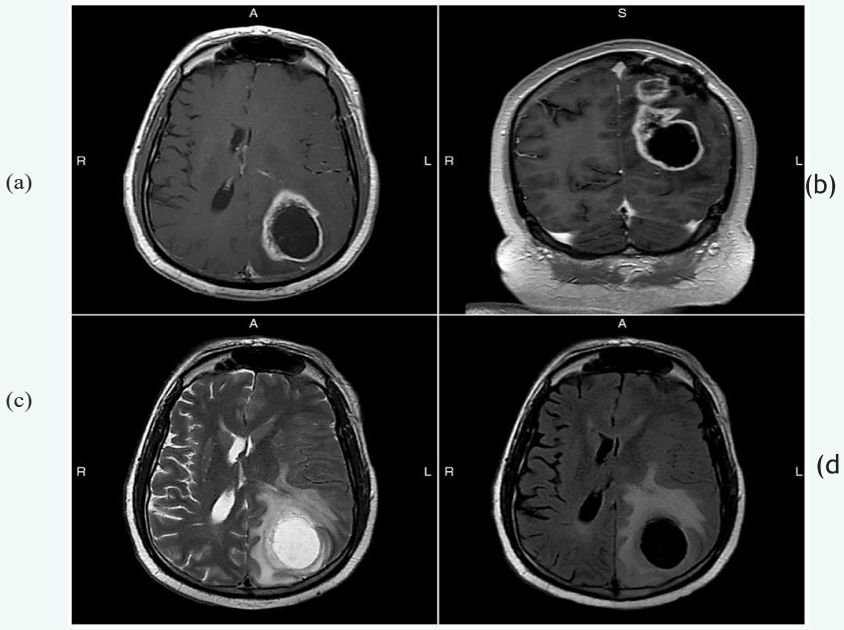
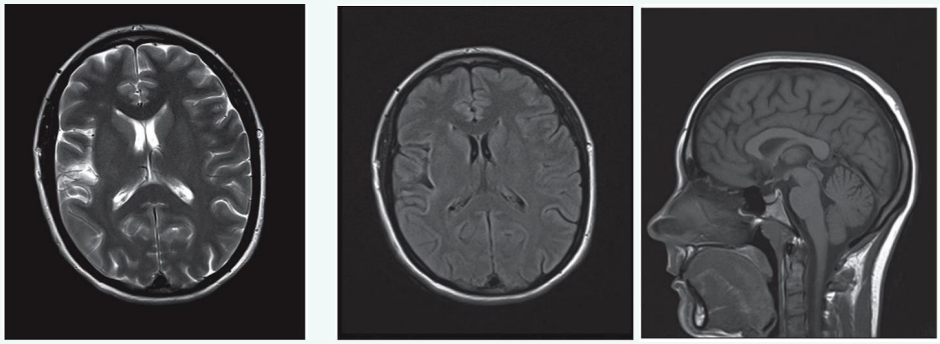


Figure 8: Glioblastoma Multiforme. The T1-weighted axial (A) and coronal (B) MR images after intravenous injection of contrast material demonstrate an irregular ring of contrast enhancement, representing solid vascularized tumor, surrounding a central low-density area of necrosis. C, the tumor and its surrounding edema demonstrate high signal intensity on a T2- weighted axial image. D, on a FLAIR axial image, the tumor demonstrates low signal intensity and the edema appears as high signal intensity, demonstrating the extent of involvement and a ventricular shift to the right. (Comprehensive Radiographic Pathology, 2012) [47].

Table 6: Summary of Radiographic Features of Glioblastoma Multiforme (53) [47].

Computed Tomography	Magnetic Resonance Imaging	
Irregular thick margins: iso to slightly hyperattenuating (high cellularity).	**T1**	**T2 / Flair**
Irregular hypodense center representing necrosis.	Hypo to isointense mass within white matter.	Hyperintense.
Marked mass effect.	Central heterogeneous signal (necrosis, intratumoral hemorrhage).	Surrounded by vasogenic edema.
Surrounding vasogenic edema.	Enhancement is variable but is almost always present.	Flow voids are occasionally seen.
Hemorrhage is occasionally seen.	Typically peripheral and irregular with nodular components.	
Calcification is uncommon.	Usually surrounds necrosis.	
Intense irregular, heterogeneous enhancement of the margins is almost always present.		



(a) (b) (c)

Figure 9: Axial CT scan without intravenous contrast. This image reveals a large right temporal intraaxial mass (Glioblastoma Multiforme (GBM). Extensive surrounding edema is present, as demonstrated by the peritumoral hypodensity, and a moderate right- to-left midline shift can be noted (eMedicine, 2009).

This radiologic appearance is typical of a multicentric Glioblastoma Multiforme. A T1-weighted axial MRI with intravenous contrast.

Heterogenous enhancement of the lesion is present within the right temporal lobe. The hypointensity circumscribed within the enhancement is suggestive of necrosis (GBM) (eMedicine, 2009).

A T2-weighted axial MRI. The tumor (Glioblastoma Multiforme [GBM]) and surrounding white matter within the right temporal lobe show increased signal intensity compared to a healthy brain, suggesting extensive tumorigenic edema (eMedicine, 2009).

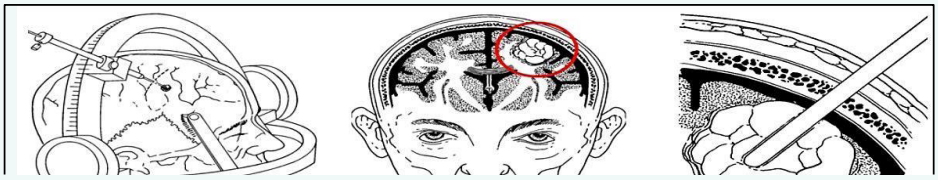


Figure 10: Neurosurgeon maps the brain in a three-dimensional coordinate system and select the appropriate target coordinates for guiding the biopsy needle.

VARIOUS THERAPEUTIC OPPORTUNITIES

In an oncology department, the treatment of GBM is usually the most challenging task, despite evidenced low competence, the following therapies might help in fighting the tumor without exposure to normal tissue as well as less toxicity to the patient [48-50].

Surgical involvement

Generally speaking, the initial phase in treating Glioblastomas is surgery, which is preferred with the majority of patients. However, GBM cannot be removed completely.

Radiation therapy

So, and to kill the remaining tumor cells, surgery is followed by radiotherapy course which shows the improvement on the life extending of GBM patient. However, limitation and risk factors are associated with radiation therapy including the radiation-induced permanent neuronal damage, invasive nature of GBM, radiation necrosis and radio-resistance of some tumors [26]. There are various kinds of radiation, which might be given using different dosages, and scandals and this include:

- Conformal photon radiation
- Image-Guided Radiation Therapy (IGRT)
- Proton beam therapy
- Interstitial radiation
- Stereotactic Radiosurgery (SRS) and Fractionated Stereotactic Radiosurgery (FSRS)

Chemotherapy

Several chemotherapeutic agents have been proven to improve the survival of the patients and effectiveness in the treatment of GBM. For the majority of GBM cases, they use alkylating agents like temozolomide or TMZ (methylating agent), BCNU (Bis-Chloroethyl Nitrosourea) and lomustine (CCNU). Furthermore, these drugs are harshly cytotoxic which will cause resistance and limiting the benefit as well as side effects. Temozolomide is commonly used and nowadays it used at the same time with radiotherapy and extends for 6 month more [51,52] (Table 7).

New advancement: Viral therapy

Despite the moderate improvements, the efficacy of current managements limits the prognosis of GBM patients dismally. According to [53], the use of oncolytic viruses that are designed to selectively replicate in tumor cells, will therapeutically tackle the immunosuppressive GBM environment. However, utilizing these viruses as oncolytic agents is not particularly a new idea, on the other hand, using the engineered virus to kill the tumor cells via direct oncolysis and via stimulation of antitumor immune responses is a current promising working model to GBM treatment. The benefit of systemically delivering the virus over intratumoral injection is that the virus is able to break through the blood-brain barrier and reach the tumor cells and other sites not reachable by administrating the virus directly to the tumor. Strategies to improve

Table 7: Various pharmaceutical agents proven to affect the filtration of GBM [26].

Agent Brain Tumor	Dosage	Side Effects	Type
Carmustine (BCNU)	200 mg/m2 every 6-8 weeks	Nausea, myelosuppression, pulmonary fibrosis	Malignant Glioma
Lomustine (CCNU	60 mg/m2 days 8-21/56	Nausea, myelosuppression, pulmonary fibrosis	Malignant Glioma, Oligodendroglioma, Adult Low- l Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma), Glioblastoma,
Temozolomide	Concomitant with radiotherapy: 75 mg/m2 daily Adjuvant: 150- 200 mg/ m2 (5/28 days)	Nausea, fatigue, headache, constipation, myelosuppression	Malignant Glioma, Adult Low- Grade Infiltrative Supratentorial Astrocytoma /Oligodendroglioma Glioblastoma, Primary CNS Lymphoma.
Vincristine	1.4 mg/m2 days 8 and 29/56	Peripheral neuropathy, constipation	Oligodendroglioma, Glioblastoma, Primary CNS Lymphoma Adult Medulloblastoma.
Cisplatin	60 to 100 mg/m2 once every 3- 4 wks. Or: 60 to 100 mg/m2 once a day for 2 days every 3- 4wks	Nausea, renal Insufficiency, peripheral Neuropathy, myelosuppression	Malignant Glioma, Primitive neuroectodermal tumors, Adult Low-Grade Infiltrative Supratentorial Astrocytoma /Oligodendroglioma), Adult Medulloblastoma
Bevacizumab	10 mg/kg every 2 wk	Bleeding gums, body pain, burning, tingling, numbness, chest pain, chills, convulsions, cough, cracks in the skin, difficult breathing, dilated neck veins	Anaplastic Gliomas, Glioblastoma
Etoposide	50mg daily	Cough, difficulty in swallowing, dizziness, rapid heartbeat, headache, Itching, nervousness, numbness, puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue, sweating	Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Excluding Pilocytic Astrocytoma), Anaplastic Gliomas, Primitive neuroectodermal tumors, Adult Medulloblastoma
Procarbazine	110 mg/m2 day 1/56	Confusion, convulsions, tiredness, hallucinations, shortness of breath, thick bronchial secretions	Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma, Anaplastic Gliomas, Glioblastoma, Primary CNS Lymphoma.

Oncogenic Pathways	Intratumor heterogeneity
Most frequently altered pathway.	Presence of multiple different cell subpopulations.
Involves Receptor Tyrosine Kinases (RTKs), cell-surface receptors that bind Growth Factors (GFs).	Contributes to tumor aggressiveness, growth, and treatment failure.
Inducing conformational shift.	Related to astrocytic tumor invasion properties.
Prepare for downstream signaling cascades.	Linked to the migrating glioma stem cells.

viral toxicity and produce a synergistic therapy include the combination of intratumoral and intravenous doses of oncolytic viruses by inducing both local and systemic immune responses [53]. The potent stimulation of antitumor immune responses is considered as one the therapeutic benefits, where the viruses are used to warm / heat the naturally cold GBM immune microenvironment and this is demonstrated in figure 11.

SURVIVAL RATES

Despite all of the above various therapies of GBM, they are limited in efficacy due to several factors including high rates of recurrence, overall resistance to therapy, and devastating neurological deterioration [54]. According to [55] Glioblastoma Multiform is a lethal brain cancer, with an aggressive cancer hallmark including extensive infiltration and strong vascular proliferation into the surrounding brain parenchyma leading to median survival of 7–15 months from the time of diagnosis. We now know that benign masses have a higher Apparent Diffusion Coefficient (ADC) than hypercellular malignancies like glioblastoma and lymphoma, and that lymphomas have a lower ADC than gliomas [55]. A one new emerging and promising approach to brain nanotechnology-based drug delivery is greatly needed to address the overwhelmingly poor treatment results for patients currently diagnosed with Glioblastoma [56].

CASE STUDY 1: GLIOBLASTOMA MULTIFORME

A 3 weeks girl presented with macrocephaly, increase irritability and bulging fontanelle. A head Ultrasound revealed a large heterogeneous lesion in the right hemisphere. This lesion consisted of large solid component and large cyst. Also, a brain MRI was obtained where solid tumor measuring 10 × 11 × 8 cm was demonstrated, which was hyperintense signal on T1- and T2-weighted images, and showed restricted diffusion on the ADC map [57]. There was a heterogeneous enhancement in the solid component (Figure 12).

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Considering the cyst drainage, the right parietooccipital craniotomy was obtained. After the operation, patient was discharged. However, 1 week after, the patient came back with a poor feeding, bulging

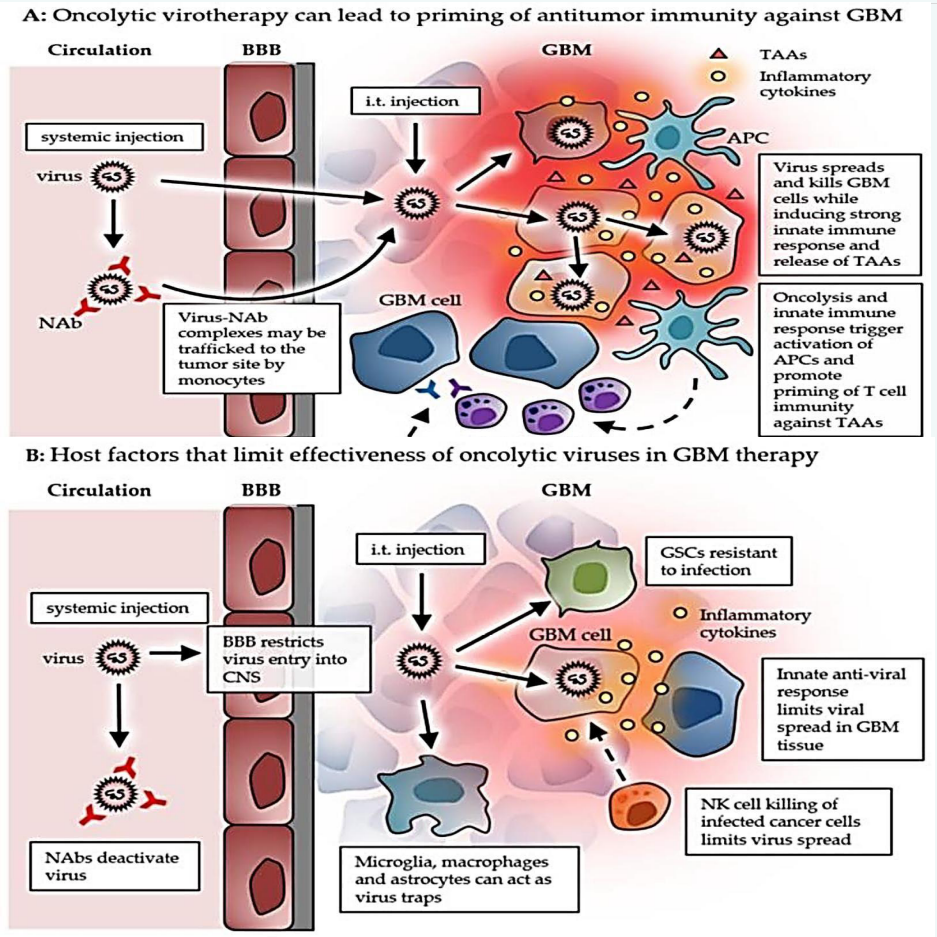

Figure 11: Schematic picture summarizing the events and factors related to successful oncolytic immunotherapy (A), and to limited effectiveness of oncolytic viruses (B) in GBM. Abbreviations: BBB: blood–brain barrier, GBM: Glioblastoma, TAA: tumor-associated antigen, NAb: neutralizing antibody, APC: antigen-presenting cell, CNS: central nervous system, GSC: glioma stem cell, NK: natural killer cell. (Magnus, 2019) (50) (Agosti, 2023) (4).

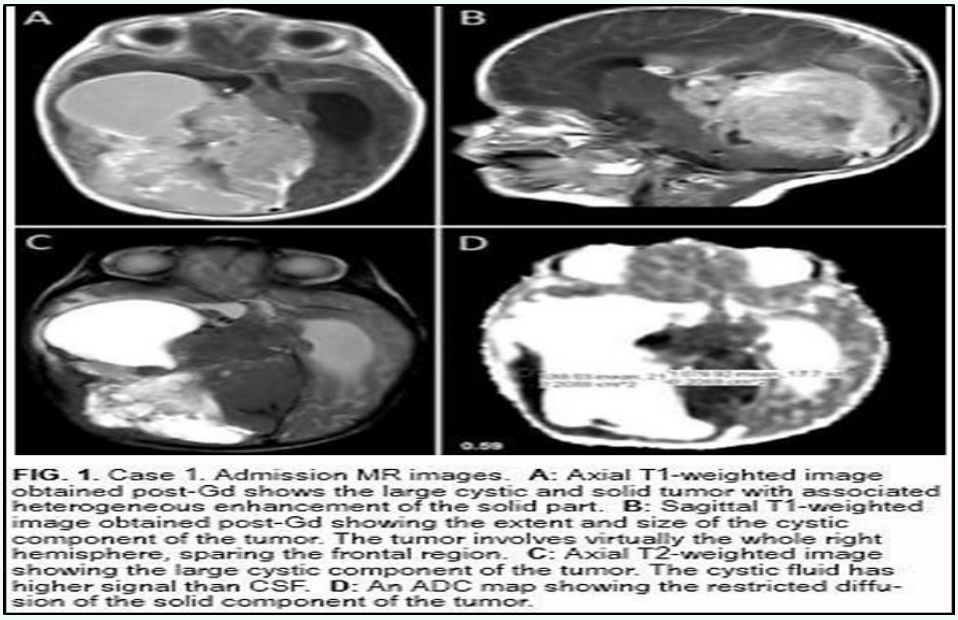

FIG. 1. Case 1. Admission MR images. A: Axial T1-weighted image obtained post-Gd shows the large cystic and solid tumor with associated heterogeneous enhancement of the solid part. B: Sagittal T1-weighted image obtained post-Gd showing the extent and size of the cystic component of the tumor. The tumor involves virtually the whole right hemisphere, sparing the frontal region. C: Axial T2-weighted image showing the large cystic component of the tumor. The cystic fluid has higher signal than CSF. D: An ADC map showing the restricted diffusion of the solid component of the tumor.

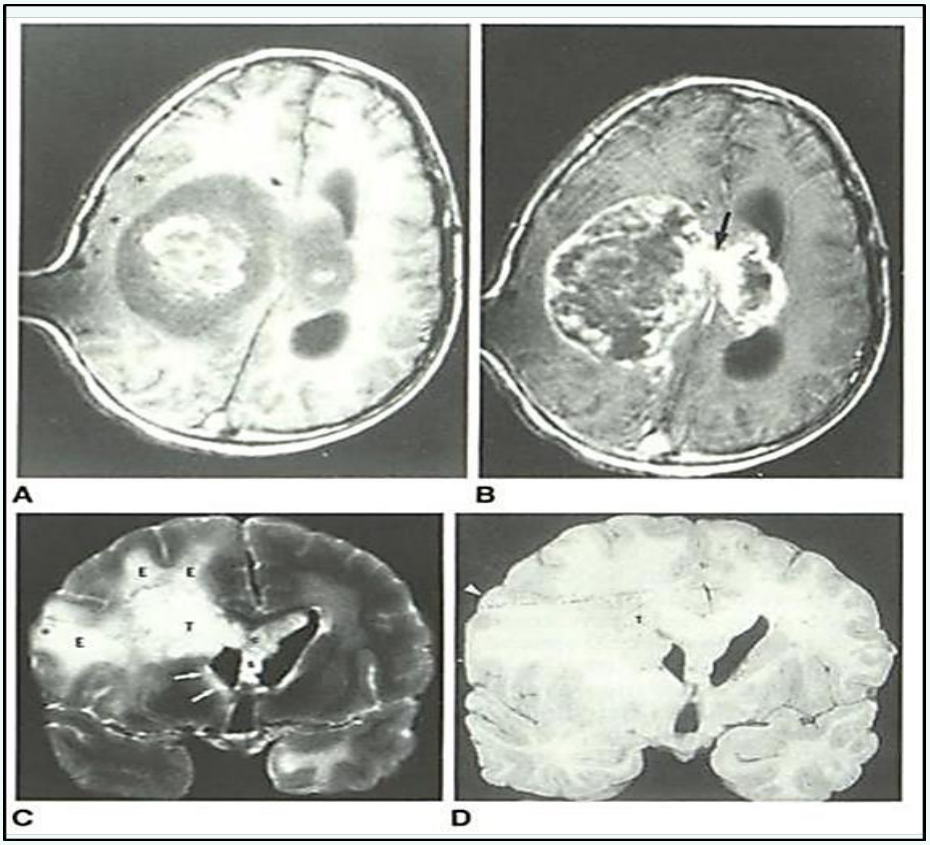

Figure 12: Axial non contrast MR T1 - weighted image shows a large mass in the right hemisphere (also present on T2-weighted images) is presumed to represent haemorrhage (methemoglobin). NOTE: The right- sided artifact is secondary to a cerebrospinal fluid shunt. B, Axial T1-weighted image after gadolinium administration at the same level as A. Enhancing tumor is noted crossing the midline compatible with transcallosal extension (arrow). C, Postmortem coronal T2-weighted image of the fixed brain in the same patient obtained 1 month after the studies shown in A and B. D, Coronal section of the fixed brain at the same level as C [58].

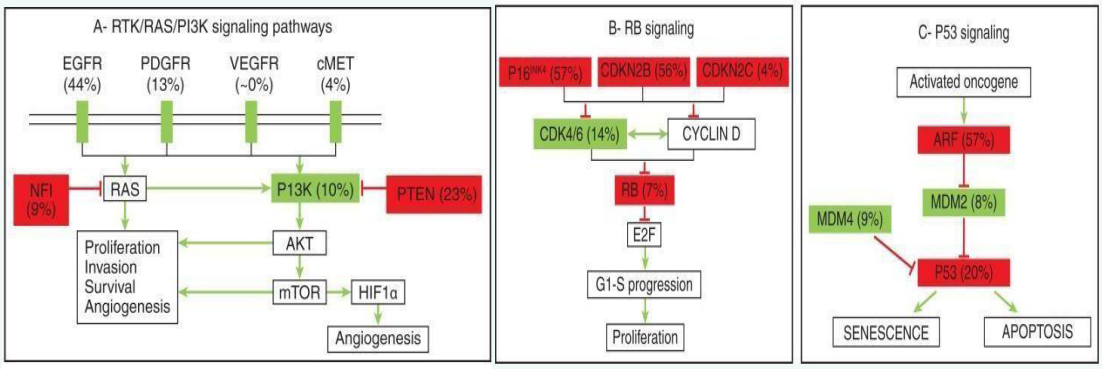

Figure 13: Genetic alterations in major key pathways altered in Glioblastoma. Mutations, deletions, and amplifications in (A) RTK/RAS/PI3K, (B) RB, and (C) p53 signaling pathways are shown. Green boxes indicate activating mutation and amplifications.

fontanelle, and increasing irritability. MRI was repeated and showed that the solid component is enlarged, recurrence of the cyst, blood clot in cyst and evidence of leptomeningeal dissemination along the lining of the ventricles and along the spinal cord. So, palliative measures were recommended, and the child died a week later.

CASE STUDY 2: INTRACRANIAL ASTROCYTOMA

Bouldin TW, et al. [58] presents a case of an 8-year-old boy with progressive left lower extremity weakness of 2-weeks duration. A mass in high right parietal convexity was confirmed via Contrast-enhanced Computed Tomography (CT) and consequently, an open biopsy revealed low-grade astrocytoma. Steroids and anticonvulsant medications were prescribed, and the patient was discharged. One month later, he was readmitted due to increasing left sided paresis.

Repeated contrast-enhanced CT showed interval development of low-attenuation regions in the center of the mass. Results of second open biopsy showed similar results. Radiation therapy was started but hydrocephalus developed requiring paleocurrent of a ventriculoperitoneal shunt.

Increasing lethargy, anorexia, and generalized weakness cause the patient to be readmitted 2 months later. At this stage, the tumor was metastasized into the left cerebral hemisphere via the corpus callosum (Figures 1A,B). Supportive treatments were continued but the patient unfortunately, died 2 weeks later. Postmortem examination revealed a right hemisphere GBM that had extended to the left hemisphere via the corpus callosum (Figures 1C,D)

Table 8: Major genomic, epigenomic, transcriptomic, and proteomic differences between primary and secondary GBM [14,59].

	Primary		Secondary
Genetic alterations	EGFR Amplification	constitutive activity	IDH1/2 mutation LOH of 22q, 13q, 19q TP53 mutation Platelet-derived growth factor receptor (PDGFR) gene amplification
		increased proliferation	
		survival of mutated cells	
	CDKN2A-p16INK4a deletion		
	LOHa of chromosome 10		
	PTEN mutation		
Gene/protein expression profiles	Centrosome-associated protein 350 Enolase 1 Fas IGFBP2b MMP-9c Survivin Tenascin-X-precursor VEGFd VEGF fms-related TK		ADAMTS-19e ASCL1f Cadherin-related tumor suppressor homolog precursor DUOX2g ERCC6h HNRPA3i Loss of TIMP-3j PDGFR TP53 WNT-11k protein precursor
Promoter methylation	CDKN2A-p14ARF CDKN2A-p16INK4a MGMTl RB / TIMP-3		

GLIOBLASTOMA GENOMICS: A COMPLICATED STORY

In their book [59], stated that Glioblastoma is a deadly disease due to its severe genetic instability and the fact that is progressing via somatic evolution, in which an accumulation of mutations causes the genome of a cancer cell to deviate from that of a healthy cell [59], also demonstrated how GBMs have a specific genetic alteration. Moreover, this heterogeneity in tumors results from the characterized genetic instability and increased mutation rates that accompany all neoplasms [60]. This necessitates a specific drug targets and pharmacological agents to inhibit cell migration, dispersal, and angiogenesis is indeed immense [19]. It is worth mentioning the two different pathways GBM pathogenesis in table 8, figure 13.

Classification of GBM based on genetic markers: genomic abnormalities of primary and secondary GBM

Primary and secondary GBMs are histologically similar, yet they evolve from different genetic precursors and show distinctive genetic alterations that can allow for differentiation (Table 8).

CONCLUSION

The most aggressive brain tumor, grade IV brain tumor, variably, arises from glial cells, hence the name Glioblastoma Multiforme. Its contributors include ionizing radiation and certain genetic syndromes. A GBM patient presents with various symptoms that vary with the tumor site. Moreover, GBM is characterized by rapid growth and invasion facilitated by cell migration and degradation of the extracellular matrix. Thus, despite technological advances in surgery and radio-chemotherapy, Glioblastoma remains largely incurable. Henceforth the great need for new approaches to study Glioblastoma and to design optimized therapies such as viral therapy.

However, to confirm the presence and the extent of tumor, various invasive and non-invasive imaging techniques require employment. Where an obvious variation between the normal brain anatomy and human brain damaged by the Glioblastoma is illustrated. Likewise, two case studies were investigated for pathogenesis. Furthermore, understanding the molecular and genetic mechanisms underlying its aggressive behavior may lead to better management, appropriate therapies, and good outcomes.

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