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ORIGINAL PAPERS

Describing some general aspects on the anatomoneuropathology, neuropsychological assessment and some genetics of Glioblastoma Multiforme

Alexandru Cristian POPOVICI[1], Mirela CIMPEANU[2], Ioannis MAVROUDIS[3]*, Cristian Sorin CIMPEANU[2], Alin CIOBICA[2,4,5], Alin IORDACHE [1,6]

[1] Emergency Hospital Professor Doctor Nicolae Oblu, Strada Ateneului 2, Iași 700309

[2] Department of Biology, Faculty of Biology, Alexandru Ioan Cuza University, Carol I Avenue, no 11, 700506 Iasi, Romania

[3] Leeds Teaching Hospitals, NHS Trust, Leeds University, United Kingdom

[4] Center of Biomedical Research, Romanian Academy, B dul Carol I, no 8, 700505 Iasi, Romania

[5] Academy of Romanian Scientists, Splaiul Independentei nr. 54, Sector 5, 050094 Bucuresti, Romania

[6] Grigore T.Popa" University of Medicine and Pharmacy, 16, Universitatii Street, 700115, Iasi, Romania

*Corresponding = Dr Ioannis Mavroudis Dip.Cr, CFM, MD, PhD, FRCP(London) Consultant Neurologist G Floor, Martin Wing, LGI LEEDS TEACHING HOSPITALS NHS TRUST Honorary Senior Lecturer, Faculty of Medicine Leeds University, i.mavroudis@nhs.net phone: 0113 3928118

Abstract. *Based on our previous experience, we are describing here some general aspects on the anatomoneuropathology, neuropsychological assessment and some aspect of molecular genetics in Glioblastoma Multiforme.*

Keywords: anatomoneuropathology, neuropsychological assessment , genetics, Glioblastoma Multiforme.

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Introduction

Glioblastoma Multiforme (GBM) is the most aggressive and most common cancer that originates in the central nervous system (CNS). The WHO classification of GBM is grade IV; it is the most prevalent and having the poorest prognosis (Lau et al., 2006). The term GBM is still used despite being dropped from the WHO classification. It has been the highest funded intracranial malignancy in the past 40 years by the NIH. Median survival is 15 months from

time of diagnosis (Llaguno et Parada, 2016). Compared to breast and lung cancer, survival rates have only marginally increased. It is most prevalent in white males over the age of 50. Nevertheless, research in understanding the mechanism by which GBM is able to achieve such a lethality will eventually lead to better treatments and eventually a cure. 15% of all intracranial neoplasms and 60-75% of astrocytic tumors are GBM. GBM derive from astrocytes that have undergone DNA damage to such an extent that their growth is unregulated.

Progression of symptoms is rapid and the cause is often unclear. GBM tumors present with histological features such as high mitosis, pleiomorphic cells, microvascular proliferation and resulting regions of necrosis. Risk factors for GBM are poorly understood but include genetic predisposition, environmental factors and exposure to radiation. The mechanism by which external factors induce GBM is through DNA damage causing gene mutations. Despite some risk factors being known, there is no deterministic way to prevent the disease. High grade gliomas (HGG) are characterized by rapid growth, unlike low grade gliomas (LGG), which are characterized by slow steady growth. De-novo growth of HGG occurs in 3-months (Lehman et al., 2017). Morphologically, they appear indistinguishable, but present genetic and epigenetic differences. LGG represent merely 10% of gliomas. Their occurrence is spontaneous, despite some rare hereditary incidences. Morphological differences are also absent when comparing pediatric and adult GBM; their distinction is again one of genetic and epigenetic nature.

GBM tumors are resistant to chemotherapy and radiation, and surgical intervention is preferred despite failing to remove the entire tumor. Resection (partial resection), is the most common surgical procedure associated with GBM. Maximal surgical resection has been shown to increase overall survival and quality of life (Young et al., 2015; Shahid et Hussain, 2017). Reoperation resection has also demonstrated to have merit in a select group of patients, despite tumor recurrence and eventual death. Radiation and chemotherapy are used in conjunction after surgery, or instead of, if surgery is not indicated. Radiation therapy destroys DNA in cancerous cells, leading to apoptosis. It is inevitable that a certain portion of healthy cells are killed as well, such as mucosa cells in the mouth and intestines or those of hair follicles. The merit of chemotherapy in postoperative patients is the destruction of residual GBM so as to prevent metastasizing.

Anatomopathology

Treatment and prognosis options are strongly dependent on anatomic topographic location (Larjavaara et al., 2007; Peter et al., 2004]. Anatomical differences in tissue distribution may predict the role of risk factors generating

GBM. One widely accepted theory is that the volume of glial tissue affects the frequency at which gliomas develop in different lobes. The physiological stimuli of adjacent structures on glial tissue may determine susceptibility to developing GBM. Understanding the molecular basis of these interactions is likely to produce novel therapeutic strategies but understanding the anatomic basis is most integral in the surgical management of GBM.

Gliomas arise mainly from the anterior subcortical structures (Larjavaara et al., 2007]. In this study, a disproportionate number of tumors in the frontal and temporal lobes were observed even after accounting for tissue volume. There was a higher predisposition and tissue density in the right hemisphere compared to the left (Mu et al., 2017]. The incidence rate was comparable to previous studies in the country of Finland and higher than other countries, as expected. This is typical of other Nordic countries (Lonn et al., 2004]. Brain tumors do not show substantial variation at the international level compared to other forms of cancer (Preston-Martin et Mack, 1996]. Bilateral gliomas predominantly occur toward the frontal lobes because most gliomas involving both hemispheres are bifrontal (Inskip et al., 2003].

A study of the anatomic distribution of low-grade gliomas found the highest tumor frequency to be in the secondary functional areas (Duffau et Capelle, 2004]. Subcortical areas contain more glial cells compared to cortical gray material, explaining the prevalence of glioma in subcortical sites. This also explains the involvement of developmental, neurochemical, or functional factors in the pathogenesis of gliomas. Consistent with a previous study, allelic loss was most common in the frontal lobe where the highest tumor frequency was reported (Laigle-Donadey et al., 2004]. Differences in tissue distribution between the lobes of brain have been attributed to different precursor cells and extracellular matrix (ECM) interactions within these cell populations. 89% of tumors were shown to involve cortical regions, compared to only 12% of glioblastomas having contact with a ventricle wall (Chaichana et al., 2008]. Despite a slight overestimation in tumor frequency in superficial and frontal sites, there was no explanation for the skewed topographic distribution. This can be an attributed to a limitation in the used classification scheme. For example, the sphenoidal wing can be considered a part of the cerebrum or a part of the frontal lobe under the International Statistical Classification of Disease 10 (ICD-10) model. The results of this study apply only to adults because patterns of distribution of gliomas by anatomic site differ between adults and children. (28] In children, pilocytic astrocytoma occur predominantly in the cerebellum and brainstem (Burkhard et al., 2003].

Glial cells (GC), also known as neuroglia, are non-neuronal cells in the CNS, comprising the brain and spinal cord. Over 90% of newly diagnosed GBM are

primary glioma that arise from normal glial cells (Irena et al., 2016]. The transformation is a multistep process and understanding the anatomy is necessary to map out the proteome for the development of targeted therapies (Kaja et al., 2014]. GBM often form from astrocytes that have undergone irreversible DNA damage resulting in unregulated growth. Glial cells can be oligodendrocytes, astrocytes, ependymal cells or microglia. They maintain homeostasis and support and protect neurons in their vicinity. GCs hold neurons in place and insulate them from one another. They supply nutrients to neurons and dysregulation of metabolism can be used as a marker for GBM. Pathogens and dead neurons are removed by GCs. Adult neural stem cells of the subventricular zone and of the lateral ventricle (LV) walls generate young neurons and oligodendrocytes under normal conditions. These neural stem cells have been shown to be particularly susceptible to malignant transformation and are associated with decreased survival (Jayamanne et al., 2018]. A median survival of 8 months for LV tumors has been reported compared to 11 months for non-LV tumors (Gonzalez-Perez et Quinones-Hinojosa, 2010].

Astrocytes are the most abundant type of GC in the CNS. They form the blood brain barrier (BBB) by linking between themselves and with neurons. The BBB is restrictive and poses the challenge of delivering cytotoxic drugs to the tumors (fig 1.1) (Kaja et al., 2014]. The blood brain barrier makes treatment more difficult and tumor cells found in areas of hypoxia are resistant to radiotherapy (Nestler et al., 2015]. The internal environment is regulated by normalizing excess potassium and calcium ions, and recycling neurotransmitters released during synaptic transmission. Vasoactive metabolites such as arachidonic acid are produced by astrocytes to regulate vasoconstriction and vasodilation. The two main types of astrocytes are the protoplasmic and fibrous, which behave similarly but have distinct morphology and distribution. In white matter, the fibrous type is most common. Fibrous astrocytes present long, thin, and sparsely branched processes. Malignant astrocytoma present infiltration and invasion of functional structures (Chang et al., 2007].

Vascularization of GBM is very high, distinguishing it from lower grade glial tumors (Das et Marsden, 2013]. Interactions between tumor cells and blood vessels determine prognosis of GBM. Hypoxia-inducible factor is activated in GBM, resulting in greater transcription of vascular endothelial growth factor (VEGF), leading to endothelial proliferation and angiogenesis. Additionally, angiogenic factors released from the tumor cell recruit cells involved in neovascularization. These cells include bone marrow-derived endothelial progenitor cells, mesenchymal cells or hematopoietic stem cells. Another proposed mechanism, vascular mimicry, suggests that glioma stem cell lines are not limited to neuroepithelial lineage due to their ability to give rise to endothelial

cells and pericytes (Soda et al., 2011]. This mechanistic data is supported by the established fact that bevacizumab (BCZ) increases progression-free survival in both newly diagnosed and recurrent GBM through angiogenesis inhibition (Hardee et Zagzag, 2012]. fMRI

gain/chromosome 10 loss exhibit a clinical course comparable maps astrocyte activity indirectly through its correlation with blood flow to the brain.

Recurrences often demonstrate a predictable pattern within a local or regional site (Jayamanne et al., 2018]. In this study, 100 of 335 GBM patients receiving radiotherapy between 03/2007 and 07/2014 had GBM in the temporal lobe. 74% of the tumors were confined to one temporal lobe site and 94% were confined to both temporal lobes. Five local sites and five distant failure sites were chosen for the study. Temporal sites chosen were the anterior, the lateral, the medial, the posterior and the superior (fig 1.2). Adjacent region sites chosen were the occipital lobe, the inferior frontal lobe, the caudate, the thalamus the internal capsule, the external capsule, the fornix and the ventricular trigone. Extension sites at first presentation were the anterior, the superior, the medial and the posterior pathways. Subtotal resection (STR) greatly improved overall survival (OS) in patients with temporal lobe GBM compared to gross total resection (GTR) (Glenn et al., 2018].

Glioblastoma very rarely metastasizes presenting indistinguishable features from normal tissues (Talita et al., 2017; Mentrikoski et al., 2008; Lewis et al., 2017]. The low metastatic potential of GBM is attributed to the protective property of cerebral meninges considering the short course of the disease; death often ensues before metastasizing occurs (Davis, 2016]. Extracranial metastasis occurs with a reported frequency of only 0.44% (Robert et Wastie, 2008]. Metastasis can occur in a variety of locations, spleen, lungs, liver, bones, skin, etc. It is impossible for spread to happen through the lymphatic pathway because the brain does not have lymphatic vessels, though secondary spread may be found in the lymphatic vessels of the body. Rather, reimplantation occurs through the blood, as evidenced by tumors that form around post-operative sutures.

GBM presents a population of small polygonal cells that are spindle shaped. Cells can be multinuclear. The cells are polymorphic and anaplastic in aspect. There is excess increase in size of nuclei beyond the normal range. The cytoplasm is acidophilic. The cellular borders are indistinct. Infiltration of lymphocytes, neutrophils, macrophages, and necrotic cells may be present (Lehman et al., 2017]. The presence of large lipomatous vacuoles gives the tumor a fatty-like appearance. Red blood cell extravasation presents due to endothelial cell damage and proliferation caused by vascular thrombi. There are two types of necrotic foci;

central large necrotic foci (caused by avascular necrosis) and irregular shaped foci (caused by radially oriented glial cells) (Kaja et al., 2014].

Neuropsychological Assessment

Neuropsychological evaluation is the standardized testing of visuospatial function, memory, attention, executive function, language, praxis, and neuropsychiatric/behavioral features (Zucchella et al., 2018]. It differs from cognitive screening tests in that they can only offer general information about the state of the patient. Neurological examination applied to higher order cortical function can give information about the health of the brain because each cognitive domain has an anatomical basis. It is used in conjunction with imaging data to establish a baseline for the treatment outcome by quantifying the degree of impairment from tumoral mass effect and invasion. In awake craniotomy, it offers a functional assessment. Postsurgical residual deficits serve to guide recovery strategies for the patient and family.

Neuropathology

Astrocytic tumors are characterized by cells that possess elongated or irregular hyperchromatic nuclei and eosinophilic cytoplasm that is GFAP-positive. On the other hand, oligodendrogliomas exhibit nuclei with a rounded shape, along with perinuclear halos, calcification, and delicate, branching blood vessels. As the tumors increase in histologic grade, they exhibit additional features of malignancy. Generally, grade 3 (anaplastic) tumors are characterized by nuclear atypia and increased mitotic activity, while grade 4 tumors (glioblastoma) exhibit microvascular proliferation and necrosis (Reuss et al., 2015].

IDH-wildtype glioblastoma, the most prevalent malignant primary brain tumor in adults, is characterized by diffuse infiltration, high cellularity, and pleomorphism, with both mitotic activity and microvascular proliferation or necrosis, or both. These tumors lack mutations in IDH1/2, H3 K27M, and H3 G34. In diffuse gliomas that are wildtype for IDH and H3, the presence of microvascular proliferation or necrosis is adequate for the diagnosis of glioblastoma (grade 4). For IDH-wildtype diffuse astrocytomas that do not exhibit anaplastic features, further molecular testing is required for an integrated diagnosis. Tumors with EGFR amplification, TERT promoter mutation, or concurrent chromosome 7 to that of glioblastoma (Velázquez et al., 2020; Mansouri et al., 2016] and are classified as IDH-wildtype glioblastoma in the 2021 WHO revision (Reuss et al., 2015].

Since the release of the WHO classification in 2016, gliomas have been classified based not only on their histopathologic appearance but also on well-

established molecular parameters (Reuss et al., 2015]. The integration of molecular features had a significant impact on the classification of astrocytic and oligodendroglial tumors, which are categorized together as diffuse gliomas, based on their growth pattern, behavior, and shared IDH genetic status. In addition, the 2021 (5th) edition of the classification includes additional molecular approaches, such as those outlined in the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) updates one through seven (Louis et al., 2018; Brat et al., 2018; Louis et al., 2018; Ellison et al., 2020; Ellison et al., 2019; Brat et al., 2020; Louis et al., 2020].

Histologic variants include giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma. The epithelioid variant is often characterized by a BRAF V600E mutation, superficial location, and younger age at diagnosis. It is recommended to test the promoter methylation status of O6-methylguanine-DNA methyltransferase (MGMT) in glioblastoma specimens that are of adequate size.

Key molecular tests

The identification of mutations in isocitrate dehydrogenase type 1 (IDH1) and type 2 (IDH2) is a critical molecular diagnostic test for most of the World Health Organization (WHO) grade 2 and 3 diffuse astrocytic and oligodendroglial tumors. These mutations are associated with a significantly improved prognosis compared to IDH-wildtype tumors (Brat et al., 2015; Eckel-Passow et al., 2015; Reuss et al., 2015].

Immunohistochemical staining for the most common mutant form of IDH1 (R132H) should be performed on all diffuse glioma specimens for diagnostic purposes, as it can help distinguish infiltrating astrocytoma cells from reactive gliosis in biopsy specimens (Camelo-Piragua et al., 2010; Horbinski et al., 2009].

Sequencing of IDH1 (codon 132) and IDH2 (codon 172) should be performed in patients with grade 2 and grade 3 diffuse gliomas and in younger patients (<55 years) with grade 4 tumors if immunohistochemistry for mutant IDH1 R132H is negative. The detection of noncanonical IDH mutations requires DNA sequencing approaches. Further molecular testing is required to reach an integrated diagnosis when no IDH mutations are detected by sequencing in such tumors. This includes evaluating IDH-wildtype astrocytomas located in midline structures for H3 K27M mutations to exclude diffuse midline glioma, H3 K27-altered, and evaluating IDH-wildtype hemispheric astrocytomas, particularly in younger patients, for H3 G34 mutations to exclude diffuse hemispheric glioma, H3 G34-mutant. IDH-wildtype, H3-wildtype grade 2 and 3 astrocytomas in children should be tested for the presence of molecular alterations found in pediatric-type diffuse gliomas, and IDH-wildtype, H3-wildtype grade 2 and 3 astrocytomas in adults should be tested

for high-risk molecular features that establish a grade 4 glioblastoma diagnosis independent of histologic features. Mutations in IDH result in the accumulation of R (-)-2-hydroxyglutarate (2HG), which can be detected by magnetic resonance spectroscopy (MRS) and may play a critical role in glioma formation, epigenetic dysregulation, and seizure risk (Reuss et al., 2015].

Testing for 1p/19q-codeletion status, ATRX mutation, TP53 mutation, and CDKN2A/B deletion are critical molecular diagnostic tests for diffuse gliomas. Whole-arm loss of 1p and 19q due to an unbalanced translocation between chromosomes 1 and 19 is a defining feature of oligodendroglial tumors and a powerful predictor of favorable therapeutic response and survival among patients with diffuse gliomas. Testing for 1p/19q-codeletion status should be performed on all tumors with oligodendroglial differentiation. ATRX mutations are commonly found in diffuse astrocytic gliomas, and immunohistochemical staining for ATRX expression has diagnostic utility for confirming a diffuse astrocytic tumor. Missense somatic mutations in the TP53 gene are present in the vast majority of IDH-mutant astrocytomas, and strong nuclear staining for mutant p53 is frequently observed in these tumors. Homozygous deletion of CDKN2A/B is a negative prognostic marker in IDH-mutant diffuse gliomas, and its presence helps to establish an integrated diagnosis. H3 K27M mutations in either H3F3A or HIST1H3B/C are present in most diffuse gliomas in the pons and other midline locations, most commonly in children. The H3F3A K27M mutation can be detected by immunohistochemistry using a mutation-specific antibody, which should be used in the workup of diffuse gliomas in the spinal cord, brainstem, and thalamus, both in children and adults. Evaluating H3 K27me3 by immunohistochemistry may also be useful in diagnosing these tumors.

Genetics and pediatric glioblastoma

In the genetical context, we can mention the pediatric form of GBM (pGBM) is a distinct from the adult form because it is characterized by a different genetic profile (Vaishali et al., 2009]. Genetic and epigenetic profiling has impacted the treatment of pGBM by allowed for classification into subgroups of heterogeneous tumors, sometimes to the point of renaming tumor types (Dang et Phillips, 2017]. The new 2016 WHO classification scheme has updated the subgrouping of primitive neuroectodermal tumors with subgroups defined by their specific chromosomal abnormalities. This classification system does not include the more recent epigenetic-based subgrouping of atypical teratoid/rhabdoid tumors, though it is expected to impact the treatment strategies of future clinical and preclinical trials. A molecular diagnosis can be made even as soon as intraoperatively. The methylation of the O6-methylguanine DNA methyltransferase (MGMT) promoter has been shown to be a strong prognostic factor for outcome of resection with

adjuvant TMZ and is also a marker for TMZ sensitivity (Supriya et al., 2015; Donson et al., 2007; Haj et al., 2017; Emmanuel et al., 2018]. Intraoperative flow cytometry may be used to sample DNA ploidy, an indicator for the extent of EOR required to achieve better outcome (Suzuki et al., 2018]. Maximizing EOR has been shown advantageous in IDH mutated LGG but not in wtlDH LGGs (Patel et al., 2018].

A study conducted on 15 patients between 2000 and 2013 had a median survival time was 13.5 months (Nikitovic et al., 2016; Mahvash et al., 2011]. As in adult GBM, GTR produced a longer survival compared to STR; 73.5 months compared to 13 months. A 2016 study confirmed that GTR is independently correlated with survival for pGBM (Adams et al., 2016]. There was no significant correlation between outcome and type of radiotherapy. Clinical and histopathological data from 13 children having undergone craniotomy was analyzed (Mahvash et al., 2011]. Regarding localization, 6 of the cases were infratentorial and 7 were supratentorial. Of the infratentorial cases, 4 were in the brainstem and 2 in the cerebellum. Of the supratentorial cases, 2 were in the frontal, 3 were parietal and 2 were temporal. Interestingly, all infratentorial occurrences belong to the 0-10 years age group and supratentorial occurrences belonged to the 11-20 age group. The authors reported no significant differences in histologic morphology between children and adults.

As with adult cases, intraoperative neuronavigation, intraoperative ultrasound, intraoperative MRI, intraoperative cortical mapping, and others have significant impact on the quality of resection and long-term survival. As in adults, EOR can be significantly improved iMRI, at least regarding low-grade gliomas (LGG) (Roder et al., 2016; Sharma et al., 2018]. In this cohort study, RV on 3-month postoperative MRI were significantly smaller in the iMRI cohort. Only 50% of cases in which the surgeon was convinced they had achieved complete resection turned out to be true. The rate of complete resection increased from 30% at the time of iMRI to 85% at the 3-month postoperative MRI.

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