Updates in Molecular Pathology of Central Nervous System Gliomas in Adults

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ABSTRACT
Central nervous system (CNS) tumors are a heterogeneous group of neoplasms divided into two broad categories, glial and non-glial. Non-glial tumors are derived from such diverse structures as the pineal gland, meninges, germ cells, and hematopoietic cells, as well as metastases. Primary glial neoplasms, or those which originate from astrocytes, oligodendrocytes, or ependymal cells, include astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas. Each entity has a unique morphology and pattern of biologic behavior which portends a distinct prognosis and outcome. Individual outcomes show some variability based on tumor location and age of symptom onset; however, the underlying aggressiveness of the tumor often dictates the time course of the disease. With the advent and widespread use of fluorescent in-situ hybridization and polymerase chain reaction (PCR) techniques, molecular phenotyping of brain tumors has become mainstream and is now an integral part of patient care. The molecular genetics of CNS tumors is a rapidly growing field, and the volume of discoveries is growing at an ever increasing rate, compelling the need for updates in this exciting area of science.

KEYWORDS: Glioma, astrocytoma, oligodendroglioma, glioblastoma, 1p19q, MGMT, IDH1

INTRODUCTION
Within the broad spectrum of central nervous system (CNS) tumors, a number of common neoplasms carry a high rate of morbidity and mortality. In 2014, an estimated 22,850 adults in the United States were diagnosed with primary tumors of the brain and spinal cord. It was estimated that 15,320 of those affected would die of their disease that same year [1]. Furthermore, currently there are nearly 700,000 people in the U.S. living with a brain tumor [2]. While primary brain tumors are a diverse group of entities, with over 120 types of neoplasms, among the commonest, and one of the most studied, are the gliomas. Each neoplasm has a unique morphology and pattern of biologic behavior that shapes the clinical outcome of the individual. New discoveries in the molecular biology of these diverse brain tumors may offer advanced targeted therapies leading to decreased complication rates and improved quality of life.

Epidemiology
The incidence of CNS malignancies has been increasing. Most commonly, CNS tumors arise from glial cells, particularly astrocytes and oligodendrocytes. Gliomas account for approximately 77% of primary malignant brain tumors [3]. Most patients present between the fifth and seventh decade of life. High-grade tumors are more common than low-grade and present a high risk of morbidity and mortality. The World Health Organization (WHO) in 2000 formulated a classification system based on histologic findings that is used to stratify brain tumors into prognostic grades. High-grade gliomas (WHO grade III and IV) are most commonly seen in middle-aged to older adults, while grade II astrocytomas mainly affect younger adults. Management for low-grade neoplasms involves either observation or surgical excision, while high-grade tumors often require aggressive regimens involving chemotherapy and radiation after surgical debulking.

Pathology
CNS tumors are classified according to their predominant cell type. Therefore, most gliomas can be classified as astrocytic, oligodendroglial, or mixed oligo-astrocytic tumors. Furthermore, criteria such as atypia, mitoses, endothelial proliferation, and/or necrosis allow for application of the WHO grading scheme, which gives prognostic information based on tumor grade.

Diffuse gliomas are devastating cancers due to their locally aggressive behavior, insidious infiltration into the adjacent brain tissue, and resistance to current treatment options. In addition, low-grade gliomas have a tendency to progress to anaplastic (grade III) gliomas, with anaplastic astrocytomas ultimately progressing to glioblastomas (WHO grade IV).

Molecular alterations, such as changes in chromosomal copy number, deletions, and duplications, are common events in gliomas. In recent years, molecular analysis of tumors has sharply increased in terms of available molecular studies and their impact on diagnosis and prognostication. Currently, it is believed that changes in gene expression and other genetic abnormalities may underlie transformation and progression of gliomas. Some of the most common molecular changes that are tested in gliomas are co-deletion of 1p19q, O6-methylguanine-DNA methyltransferase [MGMT] methylation, and Isocitrate dehydrogenase 1 (IDH1) mutation.
1p/19q
The combined loss of chromosomal arms 1p and 19q are commonly seen in oligodendrogliomas and are thought to be a marker of good prognosis. Oligodendrogliomas derive their name from their non-neoplastic counterpart, the oligodendroglial cell, a native support cell of the central nervous system. These tumors are diffusely infiltrating, well-differentiated (WHO grade II) gliomas, often occurring in adults. They tend to arise in the cortex and white matter of the cerebral hemisphere, with the majority of cases in the frontal lobes. Oligodendrogliomas are slow-growing tumors that are well-demarcated, non-enhancing mass lesions on radiologic scans. Grossly, the tumors may show mucoid changes, with areas of cystic degeneration, hemorrhage, and calcification. Microscopically, they are diffusely infiltrating glial tumors composed of monomorphic cells with uniform round vesicular nuclei, distinct small nucleoli, and a classic perinuclear halo which is an artifact of fixation [giving rise to the name “fried egg” cells]. This is often accompanied by a delicate capillary (“chicken wire”) vasculature. These neoplasms infiltrate the adjacent cortex, specifically via perineurial, perivascular, and subpial spread. Grade II tumors may progress to grade III tumors, which are known to have increased cellularity, nuclear atypia, and mitotic figures. A common molecular alteration in oligodendrogliomas is co-deletion of the 1p and 19q chromosomal arms. This combined loss is rare in astrocytomas and glioblastomas (GBM); however, it is seen in approximately 40–70% of classical forms of oligodendroglioma. The incidence of 1p/19q loss is much lower in cases of mixed oligoastrocytoma (20–30%) [5]. Patients with anaplastic (grade 3) oligodendrogliomas whose tumors harbor the 1p/19q co-deletion have a more favorable prognosis if treated with chemotherapy and radiation therapy with an overall survival approaching 15 years compared to similarly treated patients whose tumors do not demonstrate the co-deletion in a large randomized clinical trial [overall survival of 7.5 years] [6]. While histopathology is the gold standard for diagnosis, molecular testing for the combined loss of 1p/19q is used as an adjunct for prognostication and treatment selection.

MGMT
MGMT (O6-methylguanin-DNA-methyltransferase), a DNA repair enzyme located on chromosome 10q26, is involved in repairing damaged DNA from toxic effects of alkylating agents. In addition, this enzyme contributes to drug resistance of gliomas by protecting tumor cells from alkylating agents. MGMT promoter hypermethylation and epigenetic silencing lead to MGMT gene inactivity and loss of protein expression. In effect, methylation leads to susceptibility of tumor cells to the alkylating effects of agents such as temozolomide, thereby allowing for more effective treatment of high-grade gliomas that are methylated. A study by Heigi et al. showed a survival benefit among patients whose glioblastoma (grade IV) contained a methylated MGMT promoter.

In those treated with temozolomide and radiotherapy, the median survival was 21.7 months compared to 15.3 months among those who only receive radiotherapy [7].

MGMT inactivation is an important marker of therapeutic application, commonly tested in GBM. GBM is a malignant primary brain tumor (WHO grade IV) that is often supratentorial. It may occur de novo [primary] or progress from lower-grade gliomas, such as anaplastic astrocytoma (WHO grade III). GBM is an aggressive neoplasm that shows contrast enhancement on radiologic scans, often with large areas of peritumoral edema and mass effect on surrounding brain tissue. Grossly, the tumors are variegated with necrosis and hemorrhage. Microscopic features include hypercellularity with atypia, mitoses, endothelial proliferation, and either geographic or pseudopalisading necrosis. Due to their aggressive nature, early diagnosis with proper therapeutic management is essential.

In recent studies, MGMT was methylated in approximately 45-50% of glioblastomas and irrespective of treatment, MGMT promoter methylation was an independent favorable prognostic factor. Furthermore, a survival benefit was observed in that same group of patients following treatment with temozolomide and radiotherapy [7-8].

IDH1
IDH1 [isocitrate dehydrogenase-1], a metabolic enzyme, is known to undergo mutations that are associated with gliomas and are thought to give prognostic implications to the diagnosis. The most common mutation affects codon 132, which causes conversion of arginine to histamine [R132H]. Immunohistochemical analysis can detect mutant IDH1, which is found in neoplastic gliomas cells and not in reactive gliosis. IDH1 mutations are frequently found in low-grade gliomas and to a lesser extent high-grade gliomas, including secondary GBM, and are associated with a favorable prognosis when compared to IDH1 wild-type [9–11]. A study by Ichimura et al. showed that codon 132 mutations were seen in up to 65% of oligodendroglial tumors, 54% of astrocytomas and 6% of glioblastomas [3% of primary GBM and 50% of secondary GBM] [12]. Using current WHO grading schemes, anaplastic astrocytoma (WHO grade III) has a better prognosis than GBM (WHO grade IV). Some research supports combining histologic grading of tumors with molecular phenotype, thereby creating a combined classification that gives a clear diagnostic and prognostic picture of each entity. For example, Hartmann et al. [13] proposed a sequence of favorable (median survival of 18–24 months) to clearly less favorable (median survival of 6–9 months) outcomes based on histologic and molecular status that ranged from anaplastic astrocytoma with IDH1 mutation, GBM with IDH1 mutation, anaplastic astrocytoma without IDH1 mutation and finally GBM without IDH1 mutation. Future randomized trials are needed to further elucidate the interaction and prognostic implications of this molecular alteration.
CONCLUSION
CNS tumors are a heterogeneous group of neoplasms with a wide array of histologic subtypes and an increasingly complex group of molecular abnormalities. Current standards of practice dictate that diagnosis is based primarily on histopathology; however, it is becoming increasingly common to order molecular studies to further characterize, classify, and prognosticate tumors. The vast catalogue of molecular alterations is steadily increasing, and further studies will be necessary to determine their significance in terms of diagnosis and prognosis.

References
12. Ichimura et al. IDH1 mutations are present in the majority of common adult gliomas but rare in primary glioblastomas. Neuro Oncol. 2009; 11 (4): 341-47.