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EC MICROBIOLOGY
Review Article

Astrocytoma Classification, Presentation and Management

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Received: November 05, 2019; **Published:** November 13, 2019

Abstract

Introduction: Gliomas constitutes 80% of CNS malignant tumors and refer to any tumor that is histologically similar to glial cells. Glioma tumors are usually named according to histopathologic origin, these include Astrocytoma that arise from astrocytes.

Aim of Work: This is an overview of most recent advancement regarding astrocytoma including methods of classification, presentation and treatment.

Methodology: comprehensive and systematic search was conducted regarding astrocytic tumors, the updated method of classification, molecular varieties and advancement in their management.

Conclusion: The classification of astrocytic tumors is challenging and frequently updated. Recently, molecular parameters are essential in classifying astrocytoma in addition to histopathologic appearance. Isocitrate dehydrogenase (IDH) mutation play cardinal rule in classification of astrocytoma. Generally, their presence favors the outcomes. Astrocytoma could present in generalized or focal symptoms and signs. The MRI is the backbone of initial evaluation and surgical resection is the mainstay of initial management. Radiation and chemotherapy is usually needed post-resection.

Keywords: *Astrocytoma; Classification; Management*

Introduction

Brain and Central nervous system (CNS) tumors are the most common tumors in people under 20 years old [1]. Gliomas constitutes 80% of CNS malignant tumors and refer to any tumor that is histologically similar to glial cells. Glioma tumors are usually named according to histopathologic origin, these include Astrocytoma that arise from astrocytes, oligodendrogliomas that arise from oligodendrocytes

and mixed glioma that arise from previous cells in addition to ependymal cells. Each type of these tumors has a different spectrum that varies in aggressiveness. Many classification of gliomas have been suggested since the twenties of the last century [2-7]. Currently, the 2016 world health organization classification is the most commonly used classification [3]. Astrocytoma refers to Central nervous system tumor that arises from astrocytes and may affect any part of the CNS including the spinal cord. The term is basically based on histology rather than other elements essential for classification such as molecular finding. Thus, astrocytoma includes many types that may differ on molecular basis and severity. It is the most commonly encountered type of glioma in childhood. In this review, we will discuss most recent evidence about classification, presentation and management of astrocytoma.

Methodology

A comprehensive and systematic search was conducted regarding astrocytic tumors, the updated method of classification, molecular varieties and advancement in their management. PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com) were the mainly used database. All relevant available and accessible articles were reviewed and included. The terms used in search were: CNS neoplasm, astrocytoma, glioma, astrocytic tumors and neuroimaging of CNS malignancy.

Classification, molecular variation and prognosis

The World Health Organization (WHO) first attempt for classification of Central Nervous System Tumors was in 1979. Since then, the classification was updated and revised four times with the most classification being published in 2016 [3,5]. In this most updated version, molecular parameters were essential in classifying astrocytoma in addition to histopathologic appearance [3]. The well-known TNM staging and classification system of neoplasms has no rule in staging and classification of astrocytoma and all brain tumors as well. All previous attempts to develop a classification based on this system was impractical and was faced with poor compliance [1]. This is due to the facts that brain and spinal cord do not have a lymphatic system, the tumor size is less important than its histology and location, in addition that CNS tumors are known for their local spread and recurrence. Hence, features as growth pattern and isocitrate dehydrogenase (IDH) genetic status were crucial for classification and predicting the behavior of astrocytoma. Methylation profiling is a powerful that may be used in the future to further refining of astrocytoma classification [8]. Although the term low-grade astrocytoma is still used to dente grade I and II WHO classification, WHO updated guide advises against its use.

Isocitrate dehydrogenase (IDH) mutation include two types, type 1 (IDH1) and type 2 (IDH2). Type 1 IDH mutation is more common than type 2. These mutations play cardinal rule in classification of astrocytoma by World Health Organization (WHO) and tests should be done for full diagnosis and to distinguish IDH-mutant from IDH-wildtype astrocytoma. IDH mutations carry improved prognosis of grade II and III diffuse astrocytoma compared with IDH-wildtype tumors [9-11]. Testing for most common IDH mutation should be performed by Immunohistochemical staining. Immunohistochemical staining test can distinguish infiltrating astrocytoma cells from reactive gliosis [12,13]. On the other hand, less common mutations present 10 - 20 percent of total IDH mutations and can be detected using DNA sequencing approaches rather than antibody testing by staining [14,15]. If no test could be done, the tumor is given the term "not otherwise specified (NOS)". Table 1 summarizes the types of astrocytoma based on WHO most recent classification.

Astrocytic tumor	WHO 2016 grading
Pilocytic astrocytoma	I
Diffuse astrocytoma, IDH-mutant	II
Diffuse astrocytoma, IDH-wildtype	II
Anaplastic astrocytoma, IDH-mutant	III
Anaplastic astrocytoma, IDH-wildtype	III
Glioblastoma, IDH-mutant	IV
Glioblastoma, IDH-wildtype	IV
IDH: isocitrate dehydrogenase	

Table 1: *2016 world health organization (WHO) classification of astrocytic tumors [3].*

Pilocytic astrocytoma is considered grade I neoplastic astrocytoma. The majority of astrocytoma in cerebellum are of grade I and they are rarely malignant [3,5]. These tumors are often of slow-growing, well-demarcated and cystic in nature. The other known locations for pilocytic astrocytoma include the optic nerve, optic chiasm, brain stem and rarely spinal cord. It carries a very good prognosis and is considered as curable [16-21]. The overall survival rates ranges between 87 and 82 percent in 10 and 20 years respectively.

The majority of diffuse astrocytoma (Grade II and III) are associated with IDH mutations, whereas Grade IV glioblastomas are usually IDH-wildtype. Diffuse astrocytoma could be furtherly divided by the presence of alpha-thalassemia/mental retardation syndrome X-linked expression (ATRX). Grade II and III astrocytoma tumors with loss of ATRIX (presence of ATRX mutation) have worse prognosis than IDHmutant astrocytoma without ATRX loss. Again, IDH-mutant tumors have a better prognosis than IDH-wildtype astrocytoma [10,11,22-24]. Grade II Diffuse astrocytoma with IDH mutation are commonly diagnosed in cerebral hemispheres. This type most commonly affects young adult with peak incidence in the thirties. Although they show diffuse infiltration, usually there is no mitoses, endothelial proliferation, or necrosis. The median survival of patients with grade II diffuse astrocytoma with IDH mutation is approximately 11 years (Table 2) [9]. Diffuse astrocytoma (WHO grade II) with IDH-wildtype is rare tumor that may be reclassified in the future. These tumors have a histopathologic appearance resembling diffuse astrocytoma with no IDH mutation. However, these tumors may follow a clinical course similar to the more aggressive glioblastoma [25,26].

Astrocytic tumor	Estimated median survival (years)
Diffuse (grade II) astrocytoma, IDH-mutant	10 - 12
Diffuse (grade II) astrocytoma, IDH-wildtype	Variable; 1.5 - 3 with glioblastoma similar features
Anaplastic (grade III) astrocytoma, IDH-mutant	8 - 10
Anaplastic (grade III) astrocytoma, IDH-wildtype	1.5 - 3
IDH: isocitrate dehydrogenase	

Table 2: *Estimated median survival of some types of astrocytoma [3,9,27].*

Histological appearance of anaplastic astrocytoma (WHO grade III) with IDH mutation shows higher cellularity, mitoses and atypia. However, there is no endothelial proliferation nor necrosis. Studies include both IDH-mutant and IDH-wildtype anaplastic astrocytoma have estimated the survival to range from three to five years. Generally, IDH-mutant tumors carry better prognosis with a median survival closer to 10 years [9]. IDH-wildtype subset of anaplastic astrocytoma accounts for approximately 20 percent with a similar histopathological appearance. However, similar to grade II IDH-wildtype, anaplastic astrocytoma (Grade III) with IDH-wildtype share features of IDH-wildtype glioblastoma with the possibility of similar aggressive clinical course. Table 2 summarizes the estimated survival of diffuse and anaplastic astrocytoma.

Clinical presentation CNS tumors

Astrocytoma, among other CNS neoplasm, could present in generalized symptoms and signs as headache, nausea and vomiting and seizures (could also be focal); or focal symptoms as visual field defect, loss of hearing and aphasia. The condition may be asymptomatic [3]. High grade astrocytoma (WHO grade II and IV) frequently present by rapid progression of symptoms over weeks. By contrast, less aggressive grade may present over a period of months to years.

In spite of the fact that headache is rarely caused by brain tumors, about 50% of patients with CNS neoplasm may present with headache. Headaches due to CNS neoplasm are usually bifrontal, constant and dull in nature. However, throbbing headache may occur. The majority of headache is of a tension-type quality, migraine-like headache accounts for 10% percent of headaches due to CNS tumors

[28,29]. It may be worse at night and could disrupt sleep and awake the patient. This nocturnal pattern could be partially explained by transient increases in the partial pressure of carbon dioxide during sleep. Other possible physiologic explanations include decreased cerebral venous return in recumbent position.

CNS tumors could cause both focal and generalized seizures. Focal seizures are considered one of the most common presenting symptoms that occurs in 50 to 80 percent of patients with primary brain tumors. Interestingly, seizures are more common in low-grade tumors than high-grade tumors and usually seen in smaller neoplasm than a larger one. Focal seizures manifests clinically according to tumor location, this could range form of tonic-clonic movement to sudden behavioral changes and aura of sensational changes. Tumorrelated seizures are typically repetitive in nature. Status epilepticus may occur with astrocytoma and other CNS tumors at the time of diagnosis or later on [30]. Tumor location is directly related to focal signs, this could be in form of focal muscle weakness when the tumor is located in motor cortex, or a sensory loss if it is near a sensory cortex.

Increased intra cranial pressure (ICP) could manifest in patient with astrocytoma. This is more prominent in case of large mass. Obstruction of cerebrospinal fluid could also occurs. The symptoms could be indolent or could present in the classic triad of nausea, headache and papilledema. Loss of conscious may occur with significant increase in intracranial pressure.

Nausea and vomiting are not specific and less common, however, abrupt episode of emesis that occur with changing position could be indicative of CNS neoplasm. They are usually associated with other neurological symptoms such as headache, seizure, or neurological deficit.

Diagnosis and evaluation

Patient with suspected CNS astrocytoma should undergo full neurologic examination and brain magnetic resonance imaging (MRI) with contrast. Further testing is usually not necessary prior to biopsy or resection. The visual fields, retina and particularly the optic discs should be performed. This is especially important with associated ICP or suspicion of tumor arising from or near the optic pathway.

Magnetic resonance imaging (MRI) with contrast is the optimal investigation to detect the presence of astrocytoma and other CNS neoplasm. The finding is not specific to types of tumors, hence, after suspecting the diagnosis of neoplasm, histopathologic sampling is usually required to determine the type and grade of primary tumors. Computed tomography (CT) is of less important due to its much lower resolution. It may be used in the setting of emergencies and in patients with a contraindication to MRI.

Pilocytic astrocytoma is almost always circumscribed on imaging studies. It shows enhancement on CT and MRI neuroimaging. The enhancement is thought to be due blood vessels degenerative changes rather than microvascular proliferation that explains the enhancement in high-grade gliomas [31-33].

Low-grade astrocytoma generally appear as hypertense lesions in T2/FLAIR neuro images. In adults, it usually involves the cerebral cortex and underlying white matter. Most of grade II astrocytoma show no enhancement. However, the presence or absence of enhancement is not a reliable indicator of tumor grade. Vasogenic edema is usually absent.

High-grade gliomas (grade III and IV) are typically seen as hypotense lesion on T1-weighted images with heterogeneous enhancement with contrast. A surrounding edema is present as hypotense signal on T1-weighted that is distinguished from the lesion after enhancement by contras. Vasogenic edema appears as hyperintense signal on T2/FLAIR-weighted imaging. On perfusion imaging, these tumors often show evidence of increased blood flow and volume.

Overview of astrocytoma management

Optimal management of CNS astrocytoma is often guided by multidisciplinary professionals of cancer management and neuro surgeon.

In low grade astrocytoma, observation could be considered as an option in children with asymptomatic, incidentally discovered masses [34-37]. The rationale behind this option is that spontaneous regression has been repeatedly reported [38-40]. Regardless, maximal safe surgical resection constitute the initial treatment of low grade astrocytoma even if discovered accidentally [34,35,41,42]. However, the choice to operate relies largely on tumor site and size. Pilocytic astrocytoma (grade I) in the cerebellum could be completely or near completely removed [41]. On the other hand, extensive resection may not be feasible in deeply located astrocytoma and may result in permanent neurologic sequelae [43]. In addition, there is a debate about the role of surgery versus observation in small non enhancing tumors associated with minimal symptoms [44,45]. Recently, the tendency is moving toward favoring maximal safe resection without delay [45-50].

Surgery should be performed at the time of presentation. This applies for patients with large, symptomatic, or features suggesting a high-grade astrocytoma (edema, necrosis, enhancement). Surgery has diagnostic role as it aids with tumor grading and its histologic and molecular features. Such information is essential for treatment selection, urgency and prognosis. Evidence based on observational studies encourages more extensive resection rather than partial resection or biopsy as long as it is possible [49,51-53]. Such resection positively impacts progression-free survival and overall survival [52,54]. Extensive resection is advised for all molecular variants of astrocytoma, this is especially relevant for IDH-mutant astrocytoma [54].

Although surgery is essential in most types of astrocytic tumors, it is not curative in patients with diffuse astrocytoma, even for low grade (grade II). Hence, additional therapy by either radiation and/or chemotherapy is ultimately required. Experts consensually agree that anaplastic astrocytoma (WHO grade III) should be treated at the time of diagnosis with radiation and chemotherapy regardless of their IDH status. However, they are still debating about the strategies for diffuse grade II astrocytoma, immediate post-operative initiation versus delayed therapy should be individualized. The National Comprehensive Cancer Network (NCCN) and the European Association for Neuro-Oncology (EANO) have published a guidelines for additional treatment of astrocytic tumor variant [55,56].

Conclusion

Brain and Central nervous system (CNS) tumors are the most common tumors in people under 20 years old [1]. Gliomas constitutes 80% of CNS malignant tumors and refer to any tumor that is histologically similar to glial cells. The classification of astrocytic tumors is challenging and frequently updated. Recently, molecular parameters are essential in classifying astrocytoma in addition to histopathologic appearance. Isocitrate dehydrogenase (IDH) mutation play cardinal rule in classification of astrocytoma. Generally, their presence favors the outcomes. Astrocytoma could present in generalized or focal symptoms and signs. The MRI is the backbone of initial evaluation and surgical resection is the mainstay of initial management. Radiation and chemotherapy is usually needed post-resection.

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Volume 15 Issue 12 December 2019