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Case Report

Anaplastic Astrocytoma of the Spinal Cord. Case Report of Uncommon Tumor and Brief Review of the Literature

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Abstract

Anaplastic astrocytoma (AA) is a malignant, primary tumor of the central nervous system. AA often occurs due to transformation from lower-grade astrocytomas or less commonly arises as a de novo tumor. WHO classification of AA is characterized by increased cellularity, nuclear atypia, increased mitotic activity, presence of glial markers, and absence of neuronal markers. Astrocytomas are the most common intramedullary tumor within the spinal cord in pediatric patients, and have the second highest incidence in adult patients with intramedullary spinal cord tumors, behind ependymomas. However, primary tumors of the spinal cord are rare, accounting for 3-6% of tumors located in the central nervous system. In a patient with spinal cord AA, the median survival from surgery to death is 6 months to 1 year. We report a case of primary AA within the spinal cord along with a brief review of the literature.

Keywords: Anaplastic, Spinal cord, Histopathology, Molecular

ABBREVIATION

AA: Anaplastic astrocytoma, **GBM**: Glioblastoma multiforme, **IHC**: Immunohistochemistry, **TMZ**: Temozolomide, **IDH**: Isocitrate dehydrogenase enzymes

INTRODUCTION

Anaplastic astrocytoma (AA) is a diffusely infiltrating, malignant, primary central nervous system tumor. The World Health Organization (WHO) classifies AA as a grade III anaplastic glioma, characterized by increased cellularity, nuclear atypia, pleomorphism, increased mitotic activity, presence of glial markers, and absence of neuronal markers. AA affects males slightly more than females and represents 6–7% of all gliomas and 1.7% of all tumors [1]. AA constitutes 4% of all malignant CNS tumors [2]. 25% of AA arises as a *de novo* tumor and an estimated 75% occur from transformation of a lower-grade astrocytoma [3]. The survival of patients with AA varies depending upon molecular pathology. The WHO 2016 classification changed the diagnostic and prognostic approach to gliomas, which included consideration of molecular characteristics of the unique stages of the tumor [4]. AA is characterized as being without *1p/19q* codeletion, and can be separated into *IDH* wild-type and *IDH*-mutant variants. *IDH* wild-type has a poorer prognosis, while *IDH*-mutant type carries a younger median age of onset [5]. The median age of onset is 41 years old [6]. With conventional treatment of any central nervous system AA, median overall survival (mOS) and 5-year survival rates are 3 years and 28%, respectively [7].

Generally, primary tumors of the spinal cord are rare, accounting for 3-6% of tumors in the central nervous system [8]. A specific subset is spinal cord astrocytoma, an intramedullary glial cell tumor that accounts for 6%-8% of all primary spinal cord growths. In the spinal cord, astrocytomas have the second highest incidence, while ependymomas have the highest incident. However, within the pediatric population, astrocytoma is the most common intramedullary tumor within the spinal cord [9]. These lower-grade astrocytomas have the capacity to transform into higher-grade malignant tumors, such as AA. Well-established risk factors for developing AA are exposure to ionizing radiation and genetic syndromes such as Li-Fraumeni syndrome, neurofibromatosis type 1 and 2, Turcot syndrome and tuberous sclerosis [10]. While large case studies are limited in patient population, several studies have demonstrated a local recurrence of AA found in about 50% of patients [11]. In a patient with spinal cord AA, the median survival from surgery to death is generally 6 months to 1 year [12].

CASE PRESENTATION

A 46-year-old man with history of well managed neurofibromatosis type I presented with back pain, sensory abnormalities including tingling with burning sensations, weakness, numbness, bowel and bladder dysfunction and gait disturbances. Symptoms were observed few months prior, with recent increase in frequency.

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Imaging studies including MRI with gadolinium contrast showed a solitary hypotensive spinal cord mass on T1-weighted and a hyperintense mass on T2-weighted images located in the cervicothoracic region (C7-T2). Perfusion MRI sequences showed high blood volume within the mass. Infiltration into surrounding tissue suggested a malignant tumor.

Multidisciplinary meeting recommended surgical removal with safe margins for definitive diagnosis. The mass was surgically removed with intraoperative neurophysiology monitoring (IOM). Surgical excision failed to remove the mass entirely and surgical margins were involved by tumor. The excised tumor measured 4.5 cm. Histopathological examination revealed heterogeneous histology with areas of both low and infiltrating high grade tumor. The high grade areas of the tumor showed highly atypical astrocytes with increased cellularity, nuclear atypia, and increased mitotic activity (**Figure 1A-B**). The histomorphology was compatible with a high grade astrocytoma and absence of pseudopalisading necrosis or microvascularization ruled out glioblastoma multiforme (GBM). IHC studies showed the tumor cells immunopositive for mesenchymal and glial markers (Vimentin, and glial fibrillary acidic protein "GFAP") (**Figure-1C-D**), and Immunonegative for neural markers (Synaptophysin, NeuN and neurofibrillary protein. Additional IHC studies included 10% nuclear immunostain labeling with proliferation factor Mib-1 (Ki-67), and immunonegative for HMB-45 and S-100. Molecular testing was not performed in this case due to insurance issues. The histomorphologic features, together with IHC studies were diagnostic of Anaplastic Astrocytoma of the Spinal Cord (WHO grade –III).

Postoperative treatment included chemotherapy with Temozolomide (TMZ). Because surgery did not completely remove the tumor, additional radiation therapy was utilized five days a week for 6 weeks.

Patient expired 9 months after surgery and treatment due to recurrent tumor and respiratory failure.

DISCUSSION

Most spinal cord astrocytomas are benign, low-grade tumors that are readily diagnosed with magnetic resonance imaging (MRI). It is important that AA be distinguished from a variety of other CNS tumors and other neurological conditions with similar symptoms, including meningitis and pseudotumor cerebri. Focal or diffuse neurological symptoms may vary by mass location and size. Brain tumors that must be distinguished from AA include oligodendrogliomas, ependymomas, and the various classifications of astrocytomas such as pilocytic astrocytoma and glioblastoma multiforme (GBM). As such, diagnosis of AA is reliant on the use of imaging modalities

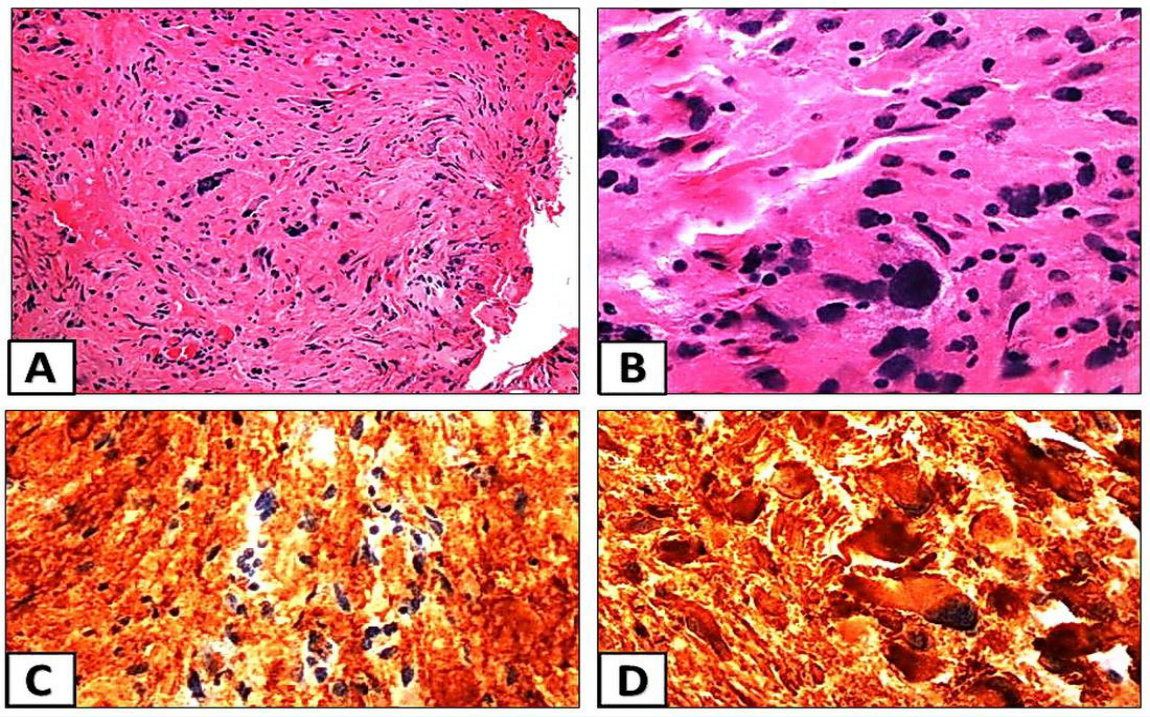

Figure 1 Pathological examination of the excised anaplastic astrocytoma
Figure 1A: Low power view showing infiltrating astrocytic tumor with heterogeneous histology displaying areas of both low and high grade malignant features (H&E stain X 20).
Figure 1B: High power view showing highly atypical astrocytes with increased cellularity, nuclear atypia and increased mitotic activity (H&E stain X 40).
Figure 1C: Tumor cells strongly positive for vimentin
Figure 1D: Tumor cells strongly positive for GFAP

such as MRI or CT along with tissue biopsy in most cases [13]. Histopathological characteristics, immunohistochemistry studies (IHC) and molecular testing is essential to determine different types of CNS tumors. Oligodendrogliomas on histology commonly demonstrate perinuclear halos that give it a "fried-egg" appearance on light microscopy [41]. Ependymomas will demonstrate histological features akin to the ependymal cells lining the ventricular system. They are more commonly found in the spinal cord and therefore a key differential in cases of spinal AA. Pilocytic astrocytomas predominately arise in children and young adults and are often identified via Rosenthal fibers and a cystic structure. Difficulty arises in distinguishing GBM and AA due to the numerous histopathological features they share. A key distinguishing factor is the presence of pseudopalisading necrosis in GBM [14]. The WHO classification system is most widely used for grading glial tumors. AA, defined by WHO as a grade III anaplastic glioma, is characterized by increased cellularity, mitotic activity, the presence of glial makers such as GFAP, nuclear atypia, and absence of neuronal markers. Importantly, necrosis or microvascularization is absent. The absence of these two features differentiates AA from GBM. The presence of necrosis or microvascularization is suggestive of a diagnosis of GBM [15]. Studies have also shown a way to differentiate specifically between AA and GBM via a 16-gene signature determined using RT-qPCR [16]. While AA commonly presents as a single CNS mass, cases in which multiple CNS masses are present have also been seen. As such it is important to also consider causes of multiple CNS lesions when it comes to differentials for AA. These causes include toxoplasmosis, brain abscesses, tuberculoma, multiple sclerosis, neurocysticercosis, brain metastases, and primary CNS lymphoma [17].

AA often reveals heterogeneous histology with areas of both low and high grade tumor. This is often seen due to AAs propensity to transform from a lower grade astrocytoma. WHO classifies AA as a grade III anaplastic glioma. AA is characterized by increased cellularity (greater than grade II diffuse astrocytoma), nuclear atypia and pleomorphism, increased mitotic activity, presence of glial markers, and absence of neuronal markers. Histologic evidence of vascular proliferation and necrosis are pathognomonic of GBM, and therefore can help differentiate GBM from AA. Historically, histologic classification and grading of gliomas has poor reproducibility among pathologists and often poorly predicts clinical outcome [18]. Clinicians are increasingly utilizing the molecular classifications of gliomas to guide clinical decision making [19].

There is not a pathognomic molecular marker for AA. However, mutations in TP53 and ATRX occur in up to 70% of AA [20]. Identification of ATRX gene on immunohistology is mutually exclusive with 1p/19q codeletion and TERT proteins. Mutations of the ATRX gene result in a truncated protein and abrogated protein expression. ATRX is a multiprotein complex important in incorporating histones H3.3 into telomeric regions of chromosomes and is one mechanism of telomere maintenance [21]. Mutations of the isocitrate dehydrogenase enzymes (IDH1 and IDH2) play a critical role in the pathogenesis of most AA. The IDH enzymes catalyze the metabolic conversion of isocitrate to α-ketoglutarate, a key metabolite of the Krebs cycle [21]. The IDH enzymes utilize NAD+ as a cofactor in generating α-ketoglutarate and NADPH in a reversible reaction. The overwhelming majority (95%) of IDH mutations in gliomas affect IDH1 and in particular, the IDH1 R132H genotype [22]. The IDH1 mutations target specific arginine residues resulting in a novel gain-of-function phenotype whereby the mutant enzymes produce high levels of what is ordinarily a minor metabolic product R(-)-2-hydroxyglutarate and NADPH. It is unclear at present the role of 2-hydroxyglutarate in astrocytoma development [23]. Epigenetic silencing of the O6-methyl-guanyl-methyl-transferase (MGMT) DNA repair enzyme gene is associated with longer survival in AA and GBM patients, especially those being treated with alkylating chemotherapy [24]. A 2012 retrospective study by Juratli *et al.* of 64 cases of anaplastic glioma showed a trend of longer median survival times with MGMT methylation than without (9.7 vs 6.1 years). However, there was no statistical significance between the two groups [25]. A 2009 randomized Phase III trial study of 202 cases of anaplastic glioma by Wick *et al.* showed MGMT promoter methylation was associated with improved progression-free survival, regardless of treatment option (alkylating chemotherapy agents or radiation therapy). The authors also reported that those with the hypermethylated phenotype were more responsive to radiation therapy [26].

Studies done by The Cancer Genome Atlas (TCGA) [27], Suzuki *et al.* [28], and Eckel-Passow *et al.* [29] have provided evidence that utilizing molecular subgroups of AA more accurately predicts prognosis than histology alone. In these studies, subgroups of AA were constructed generally by using 1p/19q codeletion, IDH, TP53, and TERT mutations. However, in contrast to the WHO classifications, there is currently not a well-agreed upon and clear-cut categorization of AA molecular subgroups. These studies were not performed in our case due to insurance issues.

MRI with gadolinium contrast is the gold standard for AA diagnosis and management. AA usually appears as a hypointense mass on T1-weighted and as a hyperintense mass on T2-weighted MRI. AA often has homogeneous signal intensity and has a well-defined margin. Calcifications on imaging are often absent, in contrast to usual oligodendroglioma histology. As well, there is often surrounding vasogenic edema and nodular areas of enhancement in AA. However, around one third of all AA display no contrast enhancement [30]. Perfusion MRI sequences have high sensitivity to distinguish low-grade from high-grade astrocytoma, with high-grade having higher blood volumes [31]. As well, perfusion MRI is superior to MR spectroscopy for grading astrocytoma [32]. Positron emission tomography using the amino acid transport tracers 11C-MET, 18 F-FET, and 18 F-FDOPA reported higher accuracy in primary diagnosis, differential diagnosis and glial tumor grading [33].

Treatments of anaplastic astrocytoma are multidisciplinary with the first step being surgical resection of the tumor. During the procedure, tumors, particularly those of higher grade, have the characteristic to avidly absorb certain dyes that are given intravenously just before surgery. In this way, the tumor tissue becomes colored by the specific dye, while the normal nervous tissue does not. This allows a much more precise definition

of what should be resected. Among the most reliable dyes are 5-ALA, which colors the tumor violet, and Fluorescein, which colors the tumor yellow. Conjugate therapies include chemotherapy and radiation. Temozolomide (TMZ) is a well established first line treatment for grade 3 or 4 astrocytoma. It is taken for five days consecutively followed by a rest period of 3 weeks. TMZ is a type of chemotherapy drug called an alkylating agent [34]. Alkylating agents add alkyl groups to DNA, disrupting its structure enough to cause damage and eventually killing the cell. It is possible to predict the tumor's sensitivity to TMZ by assessing the activity of the MGMT, which is capable of repairing the genetic damage induced by the therapeutic. As discussed earlier, epigenetic silencing of the MGMT DNA repair enzyme gene by promoter methylation is associated with longer survival for AA patients and particularly those treated with alkylating chemotherapy [35]. In addition, Bevacizumab (Avastin), is a drug approved by the FDA for its use in recurrent astrocytomas and glioblastomas. Bevacizumab targets vascular endothelial growth factor (VEGF). Bevacizumab blocks this protein and stops the cancer from growing blood vessels and prevents angiogenesis [36]. The drug is effective in limiting swelling to the nervous tissue and helps improve symptoms. However, unlike TMZ, bevacizumab does not increase long-term survival. Radiation has been a part of astrocytoma treatment for the past 50 years and is extremely effective. Standard protocols consist of small doses of radiation to the lesion of the tumor, five days a week for 6 weeks [37]. In addition to chemotherapeutic drugs, since 2011 the use of tumor treating electrical fields has been used as a supportive therapy [38]. The device produces low current electric fields which have been clinically supported to delay tumor growth. Antiseizure drugs, most commonly levetiracetam (Keppra), is most widely used as seizure prophylaxis and is usually reserved for patients with a previous history of seizure.

A review of the recent literature has documented a few cases of spinal cord AA. In one case report, a patient was found to have a primary spinal cord AA that metastasized to the subarachnoid space and later disseminated intracranially [39]. A separate 2020 case report found spinal cord AA in a 17 year old girl in the conus medullaris at the T11-T12 level. Genetic analysis revealed a BRAF V600E mutation, the first report of this mutation in spinal cord AA [40].

Our current understanding of spinal astrocytoma is limited as the literature revealed small institutional case reports and series. There are currently no universally accepted treatment guidelines for patients with either type of spinal astrocytoma. Thus, the best management strategy remains controversial. Preservation of neurological status is an important treatment goal. The rarity of these tumors resulted in a lack of a standardized management protocol. Multimodal treatments, including surgery and adjuvant therapy, are recommended. It is our hope that this report raises awareness of what remains an unmet need in diagnosis and management of spinal anaplastic astrocytoma and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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