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Review

Infiltrating spinal cord astrocytomas: Epidemiology, diagnosis, treatments and future directions

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ABSTRACT

Spinal cord gliomas, consisting mostly of ependymomas and astrocytomas, are rare entities. Of the gliomas, infiltrating astrocytomas are particularly challenging entities to treat due to their invasive nature. Surgical resection is oftentimes not possible without subjecting patients to permanent neurological deficits because of the difficulty in establishing clear tissue planes. As more is learned about the molecular genetics, genomics, and biology of these tumors, it is becoming more apparent that there are important differences between these tumors and their more common intracranial counterparts. There also appears to be important clinical differences between low-grade and high-grade astrocytomas. A multidisciplinary approach is needed to optimize the treatment of these difficult tumors.

1. Introduction

Spinal cord gliomas are rare entities, comprising 8–10% of all primary spinal cord tumors, which in turn account for 2–4% of all central nervous systems tumors [1,2]. The majority of spinal cord gliomas are located within the dura and parenchyma of the spinal cord, thus being classified as intramedullary spinal cord tumors (IMSCT). Spinal cord gliomas can be further subdivided based on cellular origin, with 60–70% classified as ependymomas and 30–40% classified as astrocytomas [3,4].

Infiltrating spinal cord astrocytomas are particularly challenging as they are more invasive than pilocytic astrocytomas or ependymomas and are more likely to recur after initial treatment [5,6]. In this review, we will focus on the epidemiology, diagnosis, and treatment of infiltrating spinal cord astrocytomas.

2. Epidemiology

Spinal cord astrocytomas are rare entities that account for a minority of spinal cord gliomas, which are already uncommon diagnoses. A recent review of the Surveillance, Epidemiology and End Results (SEER) database revealed that most patients with spinal cord astrocytomas presented between the ages of 40 and 59 years and most had low-grade lesions (Grade 1 or 2) at time of presentation [4]. A large retrospective review of all primary spinal cord astrocytomas seen at the Mayo Clinic over 40 years revealed an average age of 35 years at presentation with 60% of patients being male [2]. Pain is the predominant presenting symptom in most cases (70%) of spinal cord astrocytomas. This pain can be back pain, radicular pain or central pain [7]. The next most common presentation is sensory deficit (65%), followed by motor deficit (50%). The duration of symptoms before diagnosis is usually protracted due to their nonspecific nature, with one large series finding an average symptom duration of 3 years before diagnosis [7]. The site of these tumors is nearly evenly divided amongst cervical, thoracic and lumbar locations [7,8]. There is also a clear histological difference between intramedullary spinal cord tumors according to the age of diagnosis, with ependymoma being the most common IMSCT in adults, while astrocytomas are more prevalent in the pediatric population [1,4].

The World Health Organization (WHO) characterizes astrocytomas into four grades: pilocytic (Grade I), diffuse or low-grade (Grade II), anaplastic (Grade III) and glioblastoma (GBM) (Grade IV) [9]. Pilocytic astrocytomas are more common in children, while adults usually present with the diffuse type [10,11]. Although the most common intrinsic tumors in the brain are GBM, they are very rare in the spinal cord and are the most resistant to treatment. Infiltrating astrocytomas of the spinal cord likely comprise only 10–20% of all IMSCT [4].

3. Molecular biology of spinal cord astrocytomas

Studies limited to spinal cord astrocytomas are uncommon due to the rarity of the disease, the associated scarcity of tissue for exhaustive genetic and genomic studies, and the morbidity

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associated with surgical biopsy and/or resection. Large genomic studies have revealed the importance of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations in astrocytomas of both the brain and the spinal cord [12–14]. These mutations cause an abnormal production of 2-hydroxyglutarate, which normally inhibits histone demethylases and leads to abnormal DNA methylation [14]. Subtype analyses have revealed that GBM from the spinal cord have methylation clusters that are distinct from hemispheric GBM and could account for the particular resistance of spinal cord GBM to modern treatment, such as temozolomide [13]. Interestingly, the amino acid Lys27 was also found to be frequently mutated (Lys27Met) in pediatric GBM that harbor mutations in the replication-independent histone 3 variant H3.3 *(H3F3A)*, emphasizing the importance of DNA methylation in tumor pathogenesis [13].

Another important marker in glioma behavior and malignant transformation is the BRAF gene [15,16]. BRAF is a member of the mitogen-activated protein kinase (MAPK) pathway which is important for cellular division, cell cycle progression and malignant transformation [17]. Importantly, it has recently been shown that in a majority of pilocytic astrocytomas, a previously uncharacterized gene, *KIAA1549*, and the *BRAF* gene form a fusion oncogene that causes constitutive BRAF kinase activation [18]. Additional mutational analysis of the BRAF gene revealed a valine to glutamate substitution at position 600 (*BRAF V600E*), causing constitutive activation of the MAPK pathway [19]. The combination of the V600E mutation and a homozygous deletion of *CDKN2A*, which encodes P14ARF and P16INK4A, in human neural progenitor cells has been demonstrated to cause tumor cell expression with histology most similar to malignant astrocytomas [20]. These mutations also have important prognostic and therapeutic meaning, with fusion-negative patients having better overall survival (OS) and progression-free survival (PFS) compared to fusion-positive patients [17,21]. Interestingly, numerous studies have shown that supratentorial pilocytic astrocytomas are more likely to harbor the *BRAF V600E* mutation, while posterior fossa and spinal cord pilocytic astrocytomas are more likely to harbor fusion oncogenes [21]. Currently, there are a number of BRAF inhibitors being studied in both preclinical and Phase I, II and III studies [17]. Preliminary results suggest that treatment responses are complicated and drug regimens that target multiple pathways may be more successful than those targeting only one of the known molecular pathways [20].

Patients with neurofibromatosis type 1 (NF-1) have been known to have a high incidence of high-grade intramedullary astrocytomas [22]. This is thought to be caused by abnormal replication of non-myelinating Schwann cells in the peripheral nervous system [11]. Another important player in spinal cord GBM appears to be the tumor suppressor protein 53 (TP53) [23]. As more information is accumulated regarding the similarities and differences in the molecular biology between intracranial and spinal cord astrocytomas, the hope is that more specific therapies may be developed for the treatment of spinal cord astrocytomas.

4. Diagnosis

MRI is the modality of choice for diagnosing infiltrating spinal cord astrocytomas. Upon visualization on MRI, these tumors often cover multiple vertebral segments, with up to five vertebral segments involved on average [2]. Infiltrating astrocytomas often appear expansile, hypo- to iso-intense on T1-weighted images, hyperintense on T2-weighted and fluid attenuated inversion recovery images, and have variable contrast enhancement [24]. Although CT imaging is not typically not needed for making the diagnosis, it may be useful in presurgical planning [25].

Importantly, there is emerging evidence that as tumors transform to higher grades, there is an important vascular "switch" that occurs as tumors begin to recruit new and pathologic blood vessels. This angiogenesis is thought to be an important mediator for both tumor infiltration and transformation [26,27]. Contrast enhancement is considered a marker of this transformation, although there is evidence that other modalities such as susceptibility-weighted imaging and perfusion imaging may be better markers for these molecular changes [28].

Due to the fact the spinal cord astrocytomas can involve many segments, may be associated with drop metastases, and can even have intracranial involvement, it is strongly recommended to image the entire neuro-axis [27]. There has been some interest in using other techniques such as MR spectroscopy and diffusion weighted imaging to help with diagnosis and surgical planning, but the utility of these imaging modalities in routine tumor imaging workup has yet to be determined [29,30].

To illustrate our approach to infiltrative gliomas of the spinal cord, we next present two cases illustrating how treatment strategies can vary based on clinical circumstances.

4.1. Patient 1: Low-grade infiltrating spinal cord glioma

A 44-year-old woman had low back pain and her MRI demonstrated a left-sided dorsal spinal cord mass at T10–T11 with an exophytic and expansile component. The lesion did not enhance with contrast administration (Fig. 1A–D) and the symptoms of back pain subsided without intervention. The patient was subsequently followed with serial imaging and the lesion remained stable over the following 2 years (Fig. 1E–H). The patient remained asymptomatic. Although a tissue diagnosis was not obtained, both the lack of growth over 2 years and the lack of contrast enhancement favored the fact that the glioma was of a low grade [31].

4.2. Patient 2: High-grade infiltrating spinal cord glioma

A 56-year-old woman originally presented with complaints of bilateral lower extremity weakness and imbalance over 12 months. A thoracic spine MRI demonstrated an intramedullary expansile mass extending from T7 to T10, with homogenous T2 prolongation but no noted contrast enhancement (Fig. 2, Column A). The initial differential diagnosis included demyelination and spinal vascular fistula, but all tests for these pathologies were negative. Biopsy was recommended but deferred by the patient due to high perceived procedural risks. Twelve months subsequently elapsed, during which time she developed worsening myelopathy, progressive growth of the lesion, and a new area of enhancement on serial surveillance imaging (Fig. 2, Column B). Thereafter, she was taken for an open biopsy with a T6–T11 laminectomy and T7–T10 expansile duraplasty. Surgical pathology was consistent with anaplastic astrocytoma (Grade 3). Other notable pathology results included moderate cellularity, severe atypia, vascular proliferation, and negative IDH1 staining (MIB > 20%), but no necrosis or active mitotic figures. She was subsequently treated with 3 months of focused radiation therapy followed by temozolomide. At 1 year follow-up following biopsy, there was no evidence of tumor progression, but her symptoms had progressed to the point where she was wheelchair-bound due to severe lower extremity myelopathy (Fig. 2, Column C, D).

5. Treatments

There is no current consensus on the best treatment for infiltrating spinal cord astrocytomas. Oftentimes, there is a need for a tissue diagnosis as imaging itself cannot differentiate between