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Review

Genetic and molecular distinctions in spinal ependymomas: A review

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ABSTRACT

While gross total resection of spinal ependymomas prevents recurrence, this surgical result is not always possible. Increasing evidence suggests that ependymomas occurring in the spine are genetically distinct from those originating in the brain. Herein we review the most recent developments detailing the molecular and genetic characteristics of spinal ependymomas, which may inform more effective and personalized adjuvant therapies for spinal ependymomas that are ineligible for gross total resection. We performed a key-word search for articles published on the molecular, genetic, chromosomal, and epigenetic transformations inherent in spinal ependymomas. We reviewed appropriate articles and their relevant citations. While resection can often achieve favorable outcomes in the treatment of spinal ependymoma, more research on the unique molecular, genetic, chromosomal and epigenetic traits must be conducted in order to tailor treatment and intervention for those patients for whom total resection is not possible.

Contents

1. Introduction

Spinal ependymomas are a subset of ependymomas, tumors of glial origin that arise from the ependymal lining of the ventricular system. Altogether ependymomas comprise 3–6% of all tumors of the central nervous system (CNS) and 15% of all spinal cord tumors [1]. The CNS location of ependymomas correlates with age, with intracranial tumors more common in pediatrics, and spinal ependymomas more common in adults (mean age of presentation, 40 years) [2,3]. Most spinal ependymomas are intramedullary, but intradural extramedullary and extradural ependymomas are known to rarely occur as well (Fig. 1A) [4]. Spinal ependymomas distribute throughout the spinal cord with half occurring in the cervical or thoracic region and half occurring in the lumbosacral region and filum terminale (Fig. 1B) [5]. Ependymomas appear on MRI as a local enlargement of the spinal cord and are hyperintense on T2-weighted images, and hypointense or isointense on T1-weighted images, with heterogeneous contrast enhancement (Fig. 1C).

According to the World Health Organization (WHO), there are four major groups of ependymomas: classic ependymoma, myxopapillary ependymoma, subependymoma, and anaplastic ependymoma [6]. These groups are further divided into cellular (most common), papillary, clear cell, and tanycytic subtypes [6]. Tumors in the classic ependymoma group typically occur in the cervical and sometimes thoracic region while those of the myxopapillary group tend to be in the conus medullaris and cauda equina [7,8]. Anaplastic ependymomas carry the worst prognosis and are extremely rare, occurring most often in the brain [9].

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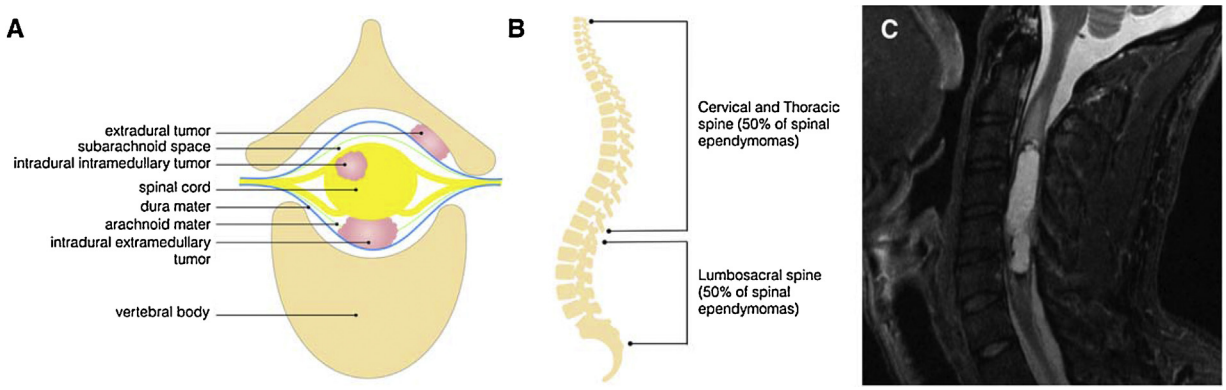

Fig. 1. Localization of ependymoma within the spinal cord. (A) Spinal ependymomas are generally intradural intramedullary tumors. (B) Half of all spinal ependymomas occur in the cervical/thoracic region, and the other half in the lumbosacral spine. (C) Sagittal T2 weighted STIR MRI showing a cervical intramedullary spinal ependymoma.

The mainstay of treatment for spinal ependymomas is surgical resection. Although gross total resection (GTR) can achieve local control rates of 90–100%, GTR is not achieved in a large subset of patients (35–50%) [7]. For patients with subtotally resected spinal ependymomas who do not receive adjuvant radiotherapy, recurrence is seen in up to 50–70% of cases [7]. The extent of resection must be balanced with the potential neurologic deficits of aggressive surgical removal of the lesion. Damage to adjacent spinal tracts may occur during resection, and the use of neuromonitoring during these cases has become standard [10]. Neither adjuvant radiotherapy nor chemotherapy has shown a definitive benefit [7,11]. Given the ineffectiveness of chemotherapy, the 5-year survival rate for grade 3 spinal ependymomas is approximately 65% [12]. Ependymomas of the spinal cord carry a more favorable prognosis than those arising intracranially, as spinal cord ependymomas are less prone to relapse. The median progression-free survival and overall survival of spinal ependymomas is 82 months and 180 months, respectively [13]. Unfortunately, few prognostic factors other than extent of resection have proven to be clinically meaningful.

For those who are ineligible for gross total resection or with highly aggressive disease, alternative interventions tailored to the unique molecular, genetic, chromosomal, and epigenetic aspects of the tumor may be of benefit. Thus, we sought to perform a review of subcellular traits of spinal ependymomas – from chromosomes to molecules – in order to inform such treatment options.

2. Methods

We performed a PubMed search for all papers including the following terms: spinal ependymoma, ependymoma and spinal cord, ependymoma and spine, molecular and ependymoma, genetic and ependymoma, chromosome and ependymoma, ependymoma and pathway, ependymoma and sequencing, ependymoma and epigenetics, ependymoma and methylation. We reviewed appropriate articles and relevant citations.

3. Results

3.1. Genomic alterations

Much of the early work in characterizing spinal ependymomas focused on aberrations of the NF2 gene, which is mutated in the cancer predisposing syndrome, neurofibramatosis type 2. NF2 is a tumor suppressor gene located on 22q12.2 and encodes the cell protein, merlin. Merlin is thought to mediate contact inhibition of cell growth [14]. During conditions of high cell density, the protein is in a closed hypo-phosphorylated form that accumulates in the nucleus to inhibit cell growth [15]. Conversely, during periods of low cell density, an open phosphorylated form predominates which is permissive for cell growth [15]. When mutations disrupt the closed "active" form of the protein, merlin mediated contact inhibition of cell growth is abolished, thus promoting tumorigenesis [15].

To date, NF2 is the only known driver mutation for a spinal ependymoma. Early studies utilizing small cohorts of spinal ependymoma tumor samples revealed that the NF2 gene product was frequently mutated [16,17]. Birch et al. [16] and Ebert et al. [18] reported that this gene was mutated in 5 of 7 and 6 of 14 spinal intramedullary ependymoma samples. A recent study by Garcia and Gutmann [19] utilized an in vitro model system of neural progenitor cells isolated from NF2 deficient mice to investigate the pathogenesis of spinal ependymoma. The authors concluded that NF2 inhibits neural progenitor cell survival in an ERBB2 (also known as HER2) dependent manner by selectively suppressing this receptor tyrosine kinase. Thus, in NF2 deficient cells, ERBB2 activity was consequently high which raises the possibility of therapeutically targeting this protein.

Large chromosomal aberrations may result in the loss of tumor suppressor genes or may indirectly drive the expression of oncogenes. Like many cancers, they are commonly seen in spinal ependymomas. Pajtler et al. [20] described allelic loss on 22q in 19 of 21 spinal ependymomas of the classic subtype. Although alterations of chromosome 22q including NF2 mutations are often seen in spinal ependymoma, these aberrations are not exclusive to ependymoma nor is the NF2 mutation the only abnormality found in spinal ependymomas. Loss of chromosomes 13 and 14 and gains of 7 and 12 in spinal ependymomas of the classic subtype also occurred, though these occurred much less frequently [20]. For myxopapillary ependymoma, the authors reported mostly chromosomal gains with 9, 16, 17, and 18 occurring in approximately half of the 26 myxopapillary ependymoma tumors tested [20]. For spinal subependymomas, only loss of 6 and 13 were reported; however, only 7 samples of this subtype were present in the cohort [20]. These results are summarized in Table 1.

A number of comparative genomic hybridization studies have shown clear cytogenetic differences between intracranial and spinal ependymomas. In Hirose et al., spinal ependymomas were found to have more copy number aberrations (median 6, range

Table 1
Chromosome gains and losses in spinal ependymoma [20].

Spinal ependymoma subtype	Chromosomal gain/loss
Classic	Gain of 7 and 12 and loss of 13, 14, and 22
Myxopapillary	Gain of 9, 16, 17, and 18
Subependymoma	Loss of 6 and 13