Chapter 10
Intramedullary Spinal Cord Tumors: Molecular insights and Surgical Innovation

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INTRODUCTION

The 1997 motion picture “Gattaca,” written and directed by Andrew Niccoll, is a futuristic film set in a time when society analyzes your DNA and determines where you belong in life. Ethan Hawke's character was born with a congenital heart condition, so, in turn, he assumes the identity of an athlete who has genes that would allow Hawke’s character to achieve his dream of space travel. Samples of blood and hair containing “good” deoxyribonucleic acid (DNA) serve as his disguise, as he negotiates his way through the rigorous testing necessary to attain his goal.

The application of the “futuristic” technology described in GATTACA now occurs on a daily basis, as clinicians and scientists around the world attempt to predict disease behavior based on specific genetic mutations. In this review, we describe the evolution of technical innovations that have improved the surgical treatment of intramedullary spinal tumors. Combining these technical innovations with recent molecular insights into tumor biology will likely optimize treatment in the decades to come.

SURGICAL ANATOMY RELEVANT TO INTRAMEDULLARY SPINAL TUMORS

The cross-sectional anatomy of the spinal cord consists of three funiculi, with one posterior and the other two anterolateral in location. The lateral attachments of the dentate ligaments to the cord define the anterior (ventral) and posterior (dorsal) halves of the spinal cord. Motor symptoms are caused by damage to the descending corticospinal or pyramidal tract in the posterior portion of the anterolateral funiculus. Chronic disruption along this anatomic course causes upper motor neuron (UMN) or long-tract findings that include a segmental level of paralysis or weakness, muscle atrophy, hyperactive deep-tendon reflexes, spasticity, a disturbance of fine movements, and a pathological extensor response of the toes to plantar stimulation. Acute disruptions may evoke a flaccid paralysis or weakness that ultimately progresses to spasticity. In both acute and chronic disruptions, motor symptoms are ipsilateral to the pathology. Bilateral symptoms herald more diffuse spinal cord involvement.

Lower motor neuron (LMN) deficits can originate from the anterior horn cell, nerve root, and any point along the peripheral nerve. LMN findings may occur jointly with a myelopathy and are otherwise associated with anterior horn-cell diseases, radiculopathies, and peripheral neuropathies. The clinical picture may overlap with pyramidal signs, but its distinguishing features include hypoactive or absent deep tendon reflexes, decreased tone or flaccidity, fasciculations, and the absence of a pathologic extensor response of the toes.

Within the descending motor tract, the cervical or arm axons are more centrally located, exiting through the ventral gray matter and ventral nerve roots first. This is the anatomic basis of a central cord syndrome, which leaves the arms weaker than the legs. The ascending sensory nerves traverse the dorsal root ganglia and dorsal nerve root to enter the dorsal-horn gray matter of the spinal cord. A portion of these sensory fibers carry position, tactile (deep

touch), and vibratory axons. They run directly to the ipsilateral half of the posterior funiculi or columns and ascend in the posterior portion of the cord. The remaining sensory fibers sub-serve pain (sharp, dull), temperature, and light touch. These fibers synapse over several spinal levels in the dorsal horns before crossing to the opposite anterolateral funiculus, where they begin an ascent as the lateral spinothalamic tract. The spinothalamic tracts are located anterior to the dentate ligaments. In acute central cord injuries, the more centrally located cervical axons of the spinothalamic tract are disrupted. The remaining lateral axons account for the sacral sparing of perianal sensation.

Because pain and temperature synapses occur in the dorsal horns over several spinal levels, localization of a spinal cord lesion can only be approximated to within three spinal segments. For localization, cord pathology is often dynamic and may ascend to include higher levels of motor, sensory, and autonomic dysfunction. The crossing of pain and temperature axons through the central cord to the opposite side is an anatomic correlate for two neurological findings. First, unilateral pain and temperature sensory levels or deficits are opposite the spinal cord lesion. Second, central cord disruption impairs the sensation for pain and temperature axons, with preservation of posterior column sensory modalities. Clinically, the second finding constitutes a dissociated sensory disorder.

A myelopathy may impair motor, sensory, or autonomic function and can vary in severity. A partial or incomplete myelopathy will present as one of several major spinal cord syndromes, each having a certain propensity for recovery, depending on the duration and extent of the spinal cord insult. Intramedullary spinal cord tumors can be associated with any of these syndromes depending upon the relative location of the tumor in the cord. Although clinical progression is typically slow, an acute decline can be caused by tumor hemorrhage.

The anterior cord syndrome results from damage to the anterior two thirds of the spinal cord, which includes the anterior horn cells of the ventral gray matter (LMN) and the axons or white-matter tracts of the anterolateral funiculi (UMN). The anterior cord syndrome occurs more commonly in the cervical region and is characterized by LMN paralysis of the arms and UMN paralysis of the legs. Below the level of injury, there is motor paralysis with complete deficits of pain (sharp/dull), temperature, and light-touch sensory modalities. The variable sparing of the posterior columns accounts for residual tactile, vibration, and position sense in the lower extremities.

The central cord syndrome is a common myelopathy in patients with intramedullary spinal cord tumors. Acute central-cord syndromes are distinguished from chronic syndromes by the sacral sparing of pain (sharp/dull) and temperature sensory modalities and by a more dense motor weakness in the arms as compared to the legs. A dissociated sensory disorder, LMN-type flaccid paralysis, and muscle atrophy of the upper extremities are typically associated with a chronic central-cord syndrome associated with intramedullary spinal cord tumors. A cord syrinx can present as an incomplete myelopathy and may extend rostrally to the medulla (syringobulbia) to impair various lower cranial nerve functions, such as phonation and swallowing.

The Brown-Sequard syndrome is less prevalent in patients with intramedullary spinal cord tumors than the previously mentioned incomplete myelopathies. The lesion impairs one-half of the spinal cord and spares the opposite half. Clinically, there is a UMN paralysis and a loss of position sense ipsilateral to the lesion. This is consistent with unilateral disruption of both the corticospinal tract and the posterior columns, neither of which cross during their course through the cord. Opposite the lesion, there is a level of sensory deficit for pain and temperature. Disruption of the spinothalamic tract impairs ascending pain and temperature axons, which have crossed from the side opposite

the lesion.

The isolated posterior-cord syndrome is a rare presentation of an incomplete myelopathy in patients with intramedullary spinal cord tumors. A level of sensory loss for posterior column modalities coincides with preservation of motor function. This syndrome of isolated posterior column damage occurs more commonly in non-surgical diseases such as multiple sclerosis, sub-acute combined degeneration (B12 deficiency), Freiderich's ataxia, tabes dorsalis, and pure sensory neuropathies. Pure sensory neuropathies may be observed in paraneoplastic syndromes and can be caused by the idiopathic synthesis of antibodies to the dorsal root ganglia. The posterior column axons, within the dorsal root ganglia, are the principle targets in pure sensory neuropathies.

EPIDEMIOLOGY AND PATHOLOGY OF INTRAMEDULLARY SPINAL CORD TUMORS

The location of a spinal tumor's cell of origin has an important anatomic correlate that serves to guide diagnosis and treatment. Spinal tumors are divided according to location into three major groups: intramedullary, intradural extramedullary, and extradural. Intramedullary tumors are typically derived from glial or ependymal cells that are found throughout the interstitium of the cord. Intradural extramedullary lesions include meningiomas derived from meningeal cells lining the surface of the cord. Extradural lesions are typically owing to metastatic disease or schwannomas derived from the cells covering the nerve roots. Occasionally, an extradural tumor extends through the intervertebral foramina, lying partially within and partially outside of the spinal canal (dumbbell or hourglass tumors).

The histological characteristics of different types of primary and secondary spinal tumors are similar to those of intra-cranial tumors. Intramedullary tumors are rare, accounting for only 5 to 10% of all spinal tumors. In contrast, the benign encapsulated tumors such as meningiomas and neurofibromas constitute between 55 and 65% of all primary spinal tumors. As a rule, intramedullary tumors are more common in children, and extramedullary tumors are more common in adults. The leading primary sites of metastatic tumors to the spine in order of frequency are lung, breast, and prostate. However, several other systemic sites of spinal metastasis have been reported including gastrointestinal tract, lymphoma, melanoma, kidney, sarcoma, and thyroid (21).

Tumors of the spinal cord are much less frequent than intracranial tumors, with the overall prevalence approximating one spinal tumor for every four intracranial lesions. When stratified for tumor type this ratio of prevalence varies. For example, the intracranial:spinal ratio of astrocytomas is approximately 10:1, whereas the intracranial:spinal ratio of ependymomas can range from 3:1 to 20:1, depending upon the specific histological variant. Gender prevalence is equal except in the case of meningiomas, which are more common in women, and ependymomas, which are more common in men. Spinal tumors occur predominantly in young or middle-aged adults and are less common in childhood and old age. Although spinal tumors are more common in the thoracic region, when the actual length of the various portions of the spinal cord is taken into consideration, the distribution is relatively equal. Ependymomas may be either intramedullary or extramedullary. Ependymomas that originate at the conus (i.e., myxopapillary ependymomas) can be wholly or partially extramedullary at this site.

PHILOSOPHY OF MANAGEMENT AND GENERAL SURGICAL TECHNIQUE

As with any neurosurgical procedure, the first step in approaching a surgical patient with an intramedullary spinal cord tumor is to define the surgical objective and subsequently identify options. The clinical status of the patient, radiographic characteristics, and location of the tumor should be considered specifically in each case. However, in general, it is advisable to assume that the majority of tumors are benign and resectable. A wide laminectomy over the rostral/caudal extent of the lesion should be planned to facilitate resection and to achieve the anatomic objective of spinal cord decompression. The goal of treatment is long-term control or cure with preservation of function. Accordingly, determination of the spinal cord tumor interface is the most important principle governing the extent of tumor resection. If no plane is apparent between the tumor and surrounding spinal cord, then it is likely that an infiltrative tumor is present. Biopsy is obtained to establish a histological diagnosis. If an infiltrating or malignant astrocytoma is identified and is consistent with the intraoperative findings, further tumor removal is not warranted. In most cases, however, a reasonably well-defined benign glial tumor will be identified. Ependymomas appear with a

smooth reddish-gray glistening tumor surface, which is sharply demarcated from the surrounding spinal cord. Large tumors may require internal decompression with an ultrasonic aspirator or laser. In contrast to the ependymoma, most benign astrocytomas will present varying degrees of circumscription. About one-third of these patients have benign, infiltrative tumors without an identifiable tumor mass. Biopsy for diagnosis becomes the only viable surgical objective. Occasionally, an astrocytoma may be so well developed as to mimic an ependymoma. Nevertheless, there is rarely as defined of a plane with astrocytomas as is typically seen with ependymomas. The surgeon must rely on judgment and experience in this regard. Obviously, if gross tumor is easily identified, then continued removal is reasonable. Changes in motor sensory evoked potentials or uncertainty of spinal cord/tumor interface should signal an end to tumor resection. Although neurophysiological monitoring can predict extent of post-operative deficit (27), it remains to be proven that conventional monitoring techniques can prevent postoperative deficits. This is an important point that warrants discussion with a prospective patient during the preoperative consultation. In the following sections we review three of the most common intramedullary spinal cord tumors as well as specific surgical and pathological features attendant to each.

EPENDYOMA

Ependymomas are the most common intramedullary tumor in adults. They occur throughout life, but are most common in the middle adult years. Although the spinal cord and filum terminale account for only 3% of the central nervous system (CNS) by weight, nearly half of all CNS ependymomas originate within the spinal canal. The cervical region is the most common level of true intramedullary occurrence; however, 40% of intradural ependymomas arise from the filum (22). For anatomical and surgical reasons, these filum lesions are generally considered to be extramedullary tumors.

A variety of histological ependymoma subtypes may be encountered. The cellular ependymoma is the most common but epithelial, tanacytic (fibrillar), subependymoma, myxopapillary, or mixed examples also occur. Histological differentiation from astrocytoma may be difficult, but the presence of perivascular pseudorosettes or true rosettes establishes the diagnosis. Most spinal ependymomas are histologically benign, but necrosis and intratumoral hemorrhage are frequent. Although unencapsulated, these glial-derived tumors are usually well-circumscribed and do not infiltrate adjacent spinal cord tissue.

The role of surgery in the management of intramedullary ependymomas has evolved significantly in recent years. Once used for diagnosis alone, surgery now represents the most effective treatment for this benign well-circumscribed tumor. Because the majority of intramedullary spinal cord neoplasms are low-grade lesions, long-term tumor control or cure with preservation of neurological function can be achieved in most patients with microsurgical removal alone. The most important factor in determining the surgical objective is the plane between the tumor and the spinal cord. This interface can only be accurately assessed through an adequate myelotomy that extends over the entire rostral caudal extent of the tumor. Although presence of a syrinx may improve the chances of a gross-total resection, it cannot be used as an independent predictor of outcome.

Ependymomas, although unencapsulated, are noninfiltrative lesions and typically display a distinct plane. Gross-total removal is the treatment of choice in these cases for optimum disease control (Fig. 10.1). Intraoperative biopsy can be useful in certain circumstances, but should not be used as the sole criteria dictating the surgical objective. First, interpretation of tiny biopsy fragments often is inaccurate or non-diagnostic and may consist of only peritumoral gliosis, which may be erroneously interpreted as an infiltrating astrocytoma. Second, it is difficult if not impossible to accurately assess the nature of the tumor/spinal cord interface through a tiny myelotomy. Biopsy results, however, may be particularly helpful in some circumstances; for example, identification of a histologically malignant tumor independently signals an end to the procedure because surgery is of no benefit for malignant intramedullary neoplasms. In other cases in which the tumor/spinal cord interface may not be apparent, confident histological identification of an ependymoma reassures the surgeon that a plane must exist and that surgical removal should continue.

ASTROCYTOMA

About 3% of CNS astrocytomas arise within the spinal cord. These tumors occur at any age, but are most prevalent

in the first three decades of life. They are the most common pediatric intramedullary spinal cord tumor, comprising about 90% of intramedullary tumors in patients under 10 years of age and about 60% of adolescent intramedullary neoplasms. By about 30 years of age ependymomas become slightly more common than astrocytomas and increasingly predominate in the middle decades of life. After the sixth decade of life, astrocytomas and ependymomas are encountered with about equal frequency. Nearly 60% of spinal astrocytomas occur in the cervical and cervicothoracic segments. A thoracic, lumbosacral, or conus medullaris, location is less common. Filum terminale examples are rare.

Spinal cord astrocytomas represent a heterogeneous group with respect to histology, gross characteristics, and natural history. These tumors include the low-grade fibrillary and pilocytic astrocytoma, malignant astrocytoma and glioblastoma, ganglioglioma, and the rare oligodendroglioma. About 90% of pediatric astrocytic tumors are benign. Most of these are fibrillary astrocytomas. However, up to one-third represent juvenile pilocytic astrocytomas or gangliogliomas, which are both associated with a particularly indolent natural history. Malignant astrocytomas and glioblastomas account for about 10% of intramedullary astrocytomas. These lesions are characterized by rapidly progressing clinical course, high incidence of cerebrospinal fluid tumor dissemination, and poor survival. Fibrillary astrocytomas prevail in the adult, whereas juvenile pilocytic astrocytomas and gangliogliomas are rare and usually limited to early adulthood. The designation of a pilocytic astrocytoma in the adult usually reflects and abundance of pilocytic features which occur as secondary structures in an otherwise typical fibrillary astrocytoma. It is unclear whether these pilocytic features have an age independent prognostic significance.

The goals of intramedullary astrocytoma surgery are to obtain a tissue diagnosis while maintaining neurological function. Unlike ependymomas, these tumors do not typically demonstrate a clear plane of demarcation from the normal spinal cord (Fig. 10.2). Accordingly, the risk of attempted resection must be weighed against the risk of neurological impairment. The best surgical candidates are those for whom functional independence may be prolonged by forestalling the development of severe motor deficit. Some patients with significant deficit may still benefit from surgery if sphincter function or the ability to position in bed is preserved. A patient in good health with a minimal number of comorbidities will generally have better postoperative course with fewer complications than a neurologically compromised patient.

The preoperative consultation should stress the primary goal of surgical intervention being diagnosis, and emphasize the fact that restoration of function is not the treatment goal. Patients with complete neurological deficits and extensive tumor dissemination are not optimal candidates for attempted gross total resection. The decision to proceed to surgery in patients with very slowly progressive or minor motor or sensory deficit is difficult, particularly if imaging studies suggest the presence of an infiltrating astrocytoma, which may not be removed without significant risk of neurological deficits. However, in general, patients demonstrating a solitary intraspinal mass, good neurological function, and demonstration of tumor growth are considered appropriate candidates for early surgical intervention.

HEMANGIOBLASTOMA

Hemangioblastomas are benign tumors of vascular origin that are sharply circumscribed but not encapsulated (18, 19). Almost all have a pial attachment and are dorsal or dorsolaterally located. They are distributed evenly throughout the spinal cord, but show a cervical predominance when they occur in association with the von Hippel- Lindau (VHL) syndrome. Spinal hemangioblastomas account for 3 to 8% of intramedullary tumors and arise in any age group, but are rare in early childhood. Most patients present before the age of 40 years. Lesions are generally sporadic, but up to 25% of patients will have evidence of VHL. Patients with VHL tend to become symptomatic at an earlier age and occasionally have multiple tumors.

Microsurgical resection is the primary treatment for spinal cord hemangioblastomas (Fig. 10.3). The indications for surgical resection in the setting of sporadically occurring spinal cord hemangioblastomas differ from those occurring in VHL patients. Resection of the tumor in patients with sporadically occurring spinal cord hemangioblastomas is often necessary for diagnosis and facilitates removal before symptom formation. Because spinal cord hemangioblastomas have variable patterns of growth (including long quiescent periods) and VHL patients may require multiple surgeries over a lifetime, the indications for surgery in the VHL patient are based on the presence of

signs and symptoms attributable to the hemangioblastoma and/or its associated edema and/or syrinx. Accordingly, asymptomatic spinal cord hemangioblastomas may be followed clinically, but should be resected once they become symptomatic in VHL patients. Any delay in removal of a symptomatic hemangioblastoma can result in progressive neurological deficits that are not reversible.

Because the vast majority of spinal cord hemangioblastomas are located posterior to the dentate ligament, a direct posterior approach to remove these tumors is preferable. Hemangioblastomas located anterior to dentate ligament should be approached via a direct anterior or anterolateral approach to minimize the rotation and manipulation of the spinal cord during resection that are inherent to posterior or posterolateral approaches. Post-operatively many patients (66%) develop new and/or have exacerbation of preoperative signs and symptoms in the early postoperative period. These neurological changes are typically mild in nature (do not limit function), and transient (generally lasting 2–6 weeks). Transient signs and symptoms found in the immediate postoperative period may include sensory disturbances (dysesthesia, pain, and numbness), motor dysfunction (mild weakness, and spasticity), or bladder dysfunction (19).

MOLECULAR BIOLOGY OF INTRAMEDULLARY SPINAL CORD TUMORS

Charles Elsberg's 1925 description of spinal cord tumors is among the first extensive series on surgery of the spine (2, 5) In 1926, a year after Elsberg's treatise was published, Hermann Muller and Lewis Stadler independently confirmed that x-rays could induce mutations in living cells (23, 30). Several years later, in 1953, James Watson and Francis Crick put forth the complementary, double stranded helical model of DNA (38). Currently, it is known that genetic mutations in DNA can result in uncontrolled cell growth. Investigators in laboratories around the world have identified mutations in DNA from intramedullary spinal cord tumors. Despite these exciting discoveries, several important goals remain. One objective is to correlate these mutations with specific patterns of disease or recurrence after surgical resection. Another goal is to apply novel therapeutic modalities such as administration of small molecule inhibitors or gene therapy based on specific genetic mutations detected in an individual's tumor.

A PRIMER IN MOLECULAR BIOLOGY

The appearance and behavior of a cell, whether normal or malignant, is owing in large part to cellular proteins. The synthesis of a protein and subsequent biological action of that protein is the endpoint of a series of events (i.e., DNA is transcribed into ribonucleic acid (RNA), which is translated into protein) (32). Genetic mutations occur at the level of genomic DNA and include base-pair changes, deletions, insertions, and inactivation through methylation. Genomic DNA is organized into two sets of chromosomes each containing specific genes. However, the overwhelming majority of DNA found in the genome does not code for proteins (26). Instead, this noncoding DNA has important regulatory and structural functions. Each gene has a discrete organization that includes genetic sequences designated for transcription into RNA and elements that regulate transcription. Downstream of the transcriptional start site, the DNA sequence is divided into exons and Introns (17). The final messenger RNA (mRNA) molecule is made up of exons joined together, while introns contain intervening sequences that are spliced out during processing (40). Protein synthesis occurs after mRNA moves from the nucleus into the cytoplasm.

Translation refers to the process that converts the information encoded by nucleic acid sequence into the amino acid sequence constituting a protein (13). In the flow of genetic information from DNA to protein, RNA is the least stable molecule with a half-life that can last from seconds to minutes (15). The relative instability of RNA can make it the rate-limiting molecule in the events that lead up to the synthesis of most proteins (28).

Mutations at the level of DNA are thus carried forward in the form of proteins that are mutated, overexpressed after genetic amplification, or underexpressed after genetic deletion. The process of identifying genetic mutations in a specific tumor starts with the operative specimen. Over the past three decades, several techniques have been developed to study DNA, RNA, and protein from freshly obtained or archived tumor specimens. More recent technical innovations, such as differential display polymerase chain reaction methodology (20), representational difference analysis (8), and gene chips (37) are expediting the detection of genetic lesions in cancer.

GENETIC MUTATIONS ASSOCIATED WITH SPORADIC INTRAMEDULLARY EPENDYOMA

Much of the work characterizing genetic lesions in sporadic intramedullary ependymoma has focused on the NF2 gene. In a study from Columbia University, five out of seven patients had mutations of the NF2 gene in their tumor (1). All of these mutations resulted in a truncated protein product and occurred in the region of the transcript that is functionally homologous to cytoskeletal proteins. Other groups have also shown NF2 mutations and loss of chromosome 22 in sporadic intramedullary spinal ependymoma, as well as loss of 17p (34).

A molecular distinction may exist between the events that lead up to a spinal ependymoma versus those that contribute to intracerebral tumor progression. In a recent study, Ebert et al. analyzed 62 ependymal tumors, including myxopapillary ependymomas, subependymomas, ependymomas, and anaplastic ependymoma (4). They showed informative allelic loss of 10q (5 out of 56) and 22q (12 out of 54). Somatic mutations of NF2 were detected in six of the tumors examined and in each case the tumor was from a Grade II intramedullary ependymoma.

GENETIC MUTATIONS ASSOCIATED WITH APORADIC INTRAMEDULLARY ASTROCYTOMAS

There are few published studies specifically examining the genetic mutations in sporadic intramedullary astrocytomas. However, extensive work has been done on the pathogenic events causing intracerebral glioma. It is likely that some, if not all, of the genetic alterations described in intracerebral astrocytoma play a role in the progression of spinal astrocytoma. Three general transitions have been studied as a paradigm for glioma progression: 1) astrocyte to astrocytoma, 2) astrocytoma to anaplastic astrocytoma, and 3) anaplastic astrocytoma to glioblastoma (10, 11). In the first transition p53 mutations, chromosome 17 p loss and chromosome 22 q loss have been implicated. Recently, Rubio et al. have shown that the NF2 gene was not mutated in 30 astrocytomas examined, making it an unlikely candidate for the 22 q locus lost during this transition (29). In the progression from astrocytoma to anaplastic astrocytoma genetic defects include retinoblastoma gene mutations, chromosome 13q loss, P16 gene deletions, chromosome 9p loss, and chromosome 19q loss(33). The transition from anaplastic astrocytoma to glioblastoma has been shown to involve chromosome 10 loss and EGF receptor gene amplification (16).

Several studies have identified the PTEN gene (also known as MMAC and TEP1) as one of the candidate chromosome 10 genes lost in glioblastoma (25). The gene encodes a tyrosine phosphatase located at 10q23.3. The function of PTEN as a cellular phosphatase is consistent with the tumor suppressor label. Phosphatases act by turning off signaling pathways dependent upon phosphorylation. When phosphatase activity is lost as a result of genetic mutation, signaling pathways can become activated constitutively, resulting in aberrant proliferation.

More specific description of genetic lesions in intramedullary spinal astrocytomas will require analysis of large cohorts of patients. This may prove difficult owing to the rarity of this disease process and the paucity of tumor that is resected once the diagnosis of astrocytoma is suspected. Unlike patients with intramedullary ependymoma, aggressive surgical resection of tumor from patients with intramedullary astrocytoma is currently of questionable long-term benefit.

GENETIC MUTATIONS ASSOCIATED WITH INTRAMEDULLARY HEMAGIOBLASTOMA AND VHL

VHL disease is an autosomal dominant disorder with 90% penetrance attributable to loss of a tumor suppressor gene on chromosome 3p25–26 (12). Lesions associated with VHL include CNS hemangioblastoma, retinal angioma, renal cysts, renal cell carcinoma, pancreatic cysts, pheochromocytoma, and epididymal cystadenoma (6). VHL families can be grouped according to the presence or absence of pheochromocytomas (24). Nearly all families with pheochromocytomas have missense mutations of the VHL gene. Hemangioblastomas are predominantly made up of endothelial cells and pericytes in a dense network of vascular channels, intermixed with lipid laden stromal cells. Using tissue microdissection, Vortmeyer et al. have demonstrated consistent loss of heterozygosity at the VHL gene locus in the stromal cells, implicating these cells in the pathogenesis of hemangioblastoma (35).

CNS hemangioblastoma occurs in both Type I (without pheochromocytoma) and Type II (with pheochromocytoma) VHL families. Sites of predilection are the posterior fossa (80%) and the cervical or lumbar regions of the spinal cord (20%). Specific point mutations and deletions in the VHL gene have been characterized in both sporadic and VHL

related spinal hemangioblastoma. Hypermethylation of the VHL gene has also been implicated as a modality of inactivation. Several models of how VHL inactivation results in tumor formation have been proposed. The VHL tumor suppressor protein is known to inhibit transcription elongation through interaction with the elongin protein (31). The VHL protein also suppresses vascular endothelial growth factor (VEGF) production (7). Loss of VHL protein function could cause VEGF upregulation followed by angiogenesis.

GENETIC MUTATIONS ASSOCIATED WITH NEUROFIBROMATOSIS AND INTRAMEDULLARY TUMORS

There are two distinct types of Neurofibromatosis (NF), each affecting cells embryologically derived from the neural crest. NF1 is a disease characterized by autosomal dominant inheritance with almost complete penetrance and variable expressivity (36). Approximately 50% of cases are new mutations with a 1 in 3000 prevalence. The NF1 gene is located on the long arm of chromosome 17 and codes for a neurofibromin guanosine triphosphatase activating protein that influences cell proliferation and differentiation. Tumors associated with the NF1 syndrome include neurofibromas, malignant nerve sheath tumors, optic nerve gliomas, rhabdomyosarcomas, pheochromocytomas, and carcinoid tumors.

NF2 also segregates by autosomal dominant inheritance, with high penetrance. The NF2 gene is located on chromosome 22q12 with about 50% of reported cases representing new mutations. It is much less prevalent than NF1 with a rate of 1 in 40,000. The NF2 gene product encodes the protein “Merlin,” which is a member of the ezrin-radixin-moesin protein family that links the cytoskeleton to the plasma membrane (9). Neoplasms associated with NF2 include bilateral acoustic schwannomas, neurofibromas, ependymomas, gliomas, and meningiomas. There are two subtypes of NF2. The severe or “Wishart” form is characterized by early onset, rapid clinical progression, and multiple tumors. The mild or “Garner” form has a later onset, slower clinical progression, and fewer tumors.

In 1996, Lee et al. published one of the largest series of intramedullary spinal cord tumors in patients with NF (14). Nine patients were described including three patients with NF1, five patients with NF2, and one with “type uncertain.” The predominant pathology associated with NF1 was astrocytoma (two low-grade and one anaplastic) while ependymoma was most closely associated with NF2 (four out of five patients). The reported incidence of intramedullary spinal cord tumors in the NF population was approximately 19% (nine out of 48). This incidence may reflect referral patterns associated with highly specialized neurosurgical services. In 1997 Yagi et al. described a series of 44 patients presenting with intramedullary spinal cord tumors, two of who had NF1 (39). In both cases, the pathology of the lesion was astrocytoma (i.e., anaplastic astrocytoma and glioblastoma). Taken together, along with selected case reports in the literature, these studies support the presumption that solitary intramedullary spinal cord tumors in NF1 patients will most likely be astrocytoma. Similarly, it is reasonable to assume that an NF2 patient presenting with an intramedullary tumor will most likely have an ependymoma (3).

CONCLUSION

How can molecular biology impact what we do in the operating room? The insights described regarding genetic mutations in intramedullary spinal cord tumors will likely translate into practical applications at some point in the future. Each of these mutations represents a possible target for adjuvant therapy. As we develop more specific inhibitors of pathways in a cancer progression, we may be able to reduce treatment morbidity associated with attempted gross total resections.

It is clear that extent of resection correlates with postoperative surgical morbidity; however, the true effect of resection on disease-free survival for some indolent lesions remains unknown. Molecular profiling of intramedullary spinal cord tumor may help us answer the most fundamental question for our patients: Does the benefit of more complete surgical resection justify the risk?

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Fig. 10.1 Operative view of ependymoma during resection (A), and after complete removal (B). The macroscopic plane between ependymoma and spinal cord tissue has a microscopic correlate where there is a clear delineation between spinal cord and tumor.

Fig. 10.2 Operative view of astrocytoma during surgical resection (A) and after subtotal resection (B). The lack of a clear tumor spinal cord interface is a direct result of the tumor infiltrating the spinal cord parenchyma at a microscopic level (C).

Fig.10.3 Operative view of hemangioblastoma during surgical resection (A) and after complete removal (B).