Intramedullary Spinal Cord Tumors

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10.1 Introduction

Intramedullary spinal cord tumors (IMSCT) are rare lesions in the pediatric population, accounting for 4–8 % of central nervous system tumors in children (Bowers and Weprin 2003; DeSousa et al. 1979; Barker et al. 1976). They represent 55 % of intradural tumors in this age group (Yamamoto and Raffel 1999). They occur with an approximate incidence of 1 in 100,000, with 100–200 cases of pediatric IMSCTs diagnosed each year in the United States (Constantini and Epstein 1995; Constantini 1996). The majority of these lesions (nearly 60 %) are encountered in the cervical and thoracic regions and rarely involve the lumbar cord (Goh et al. 2000; Cooper 1989). They are distributed evenly between male and female patients (Goh et al. 1997). Primary glial tumors such as ependymomas and astrocytomas account for at least 80 % of IMSCTs (Cooper

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1989; Cristante and Herrmann 1994; Epstein et al. 1993; Hoshimaru et al. 1999; McCormick et al. 1990b; Sandler et al. 1992). Other less common but reported pediatric IMSCT tumor types include ganglioglioma (Lang et al. 1993; Hayashi et al. 2011), oligodendroglioma (Miller 2000), and hemangioblastoma (Lang et al. 1993; Roonprapunt et al. 2001; Weil et al. 2003). Rarer still have been case reports of primitive neuroectodermal tumors (Alexiou et al. 2013), subependymoma (Miller and McCutcheon 2000), pleomorphic xanthoastrocytoma (Das et al. 2014), neurocytoma (Singh et al. 2007), schwannoma (Kim et al. 2009), teratoma (Isik et al. 2008), germinoma (Madhukar et al. 2013), and non-Hodgkin's lymphoma (Bhushanam et al. 2014).

While presenting symptoms are usually minimal and parents typically report symptoms for months or years prior to diagnosis, tumor size, location, and pathologic type all factor into their presentation (Kothbauer 2007). The common clinical features are pain, weakness, paresthesias, spinal deformity, sphincter disturbance, and cervicomedullary symptoms (Goh et al. 1997). Larger tumors, rostral tumors, and those with higher grades or hemorrhaging will commonly present sooner (Ito et al. 2013). Pain centered over the tumor's location is also a common complaint. For the cervical spine, neck pain, torticollis, and/or upper extremity weakness can be expected. Thoracic lesions can present with some form of scoliosis. Lower extremity weakness can occur as well but may do so over a more prolonged course of many months. Lesions involving the conus can ultimately lead to sphincter dysfunction, but bowel and bladder dysfunction are not common presenting symptoms for IMSCT (Houten and Weiner 2000). Slow progressive deterioration of neurologic function can also occur (Constantini 1996; Kothbauer 2007). The surgical objective for primary IMSCTs is gross total resection, but in some cases, achieving this goal may leave a patient with severe neurologic deficits. The location of the tumor, age of the patient, pathology, and ability to achieve a gross total resection (GTR) usually determine whether radiation or chemotherapy will be used.

10.2 Astrocytoma

Astrocytomas are the most common type of IMSCT in children, constituting approximately 60 % of these lesions (Epstein and Epstein 1981; Reimer and Onofrio 1985; Rossitch et al. 1990; Epstein et al. 1992, 1993). These tumors are most likely to occur in the cervicothoracic region. Intratumoral and satellite cysts, as well as associated hydromyelia, can be seen in the pilocytic subtypes (Baleriaux 1999). The most common astrocytoma subtype in children is pilocytic astrocytoma. Although low-grade lesions represent the majority of astrocytomas, high-grade tumors occur in 10–15 % of cases (Allen et al. 1998; DeSousa et al. 1979).

10.2.1 Epidemiology

Pilocytic astrocytomas (PA) of the spinal cord often occur in the first two decades of life. In the adult population, they occur in young patients (mean age 29 years) with a slightly higher predilection for males (Baleriaux 1999). Intramedullary spinal cord astrocytomas can be clustered with inherited syndromes such as Li–Fraumeni syndrome, Turcot's syndrome, tuberous sclerosis complex (TSC), Maffucci/Ollier disease, and neurofibromatosis types 1 and 2 (NF1 and NF2) (Mellon et al. 1988; Frappaz et al. 1999; van Nielen and de Jong 1999; Lee et al. 1996).

10.2.2 Pathology

10.2.2.1 Grading

Spinal cord astrocytomas are graded according to the WHO grading system based on the region of the tumor with the highest degree of histologic anaplasia (Louis et al. 2007). Grade I astrocytomas are most common in the pediatric population. Pilocytic astrocytoma, the most common grade I tumor, typically have cysts and contrast enhancement on imaging (Lee et al. 1996; Allen et al. 1998; Baleriaux 1999). Grade II astrocytomas are diffusely infiltrative with cytologic atypia, while grade III astrocytomas additionally

show anaplasia and mitotic activity. MIB-1 labeling index can be used to differentiate grade II and III tumors (Neder et al. 2004). Microvascular proliferation and/or necrosis is required for a grade IV designation.

10.2.2.2 Histopathology

PAs are characterized by elongated, "hairlike" cells with cytoplasmic Rosenthal fibers and granular eosinophilic bodies. Although occasional cellular pleomorphism, mitoses, vascular proliferation, and invasion of meninges can be detected, these histopathologic findings have not been determined to be prognostic and are not considered to be malignant findings.

Grade II diffuse astrocytomas of the spinal cord are infiltrative and produce a fusiform, enlarging process of the tumor. Typically these lesions are characterized by hypercellularity, nuclear pleomorphism, and a diffuse infiltrative growth pattern in the spinal cord. Diffuse spinal cord astrocytomas are differentiated by a fibrillary or gemistocytic neoplastic astrocyte with a background of loosely structured microcystic matrix. Higher-grade intramedullary spinal cord astrocytomas have increased cellularity, anaplastic features, mitotic activity, vascular proliferation, and areas of necrosis.

10.2.2.3 Molecular Biology and Genetics

Spinal cord astrocytomas in general are thought to arise from glial cell predecessors. These tumors are usually sporadic and are rarely associated with other genetic syndromes (Mellon et al. 1988; Frappaz et al. 1999; van Nielen and de Jong 1999). Genetic analyses of PAs have found numerous genetic aberrations, but previously no specific tumor suppressor or oncogene was identified (Ransom et al. 1992). Platelet-derived growth factor receptor (PDGFR) expression has been implicated in the development of spinal cord gliomas of all types (Ellis et al. 2012a, b).

Although a novel gene fusion at the *BRAF* locus was recently identified in pilocytic astrocytoma in the brain (Jones et al. 2008), there is little genetic data available for spinal cord astrocytomas. Nevertheless, it is likely that some of the genetic alterations described in intracranial astrocytoma play a role in the progression of spinal cord astrocytoma. Three general pathways for glioma progression are proposed: (1) astrocyte to infiltrating astrocytoma, (2) astrocytoma to anaplastic astrocytoma, and (3) anaplastic astrocytoma to glioblastoma. In the first, initial mutations in *p53* and losses of chromosome 17p and 22q have been implicated. Rubio and colleagues have shown that the *NF2* gene was not mutated in 30 astrocytomas examined, making it an unlikely candidate for the 22q locus lost during this transition (Rubio et al. 1994). In the progression from astrocytoma to anaplastic astrocytoma, genetic defects include retinoblastoma (*Rb*) gene mutations, chromosome 13q loss, P16 gene deletions, chromosome 9p loss, and chromosome 19q loss (von Deimling et al. 1995). The transition from anaplastic astrocytoma to glioblastoma has been shown to involve chromosome 10 loss and epidermal growth factor receptor (*EGFR*) gene amplification (Liu et al. 1997).

Several studies have identified the *PTEN* gene (also known as MMAC and TEP1) as one of the candidate chromosome 10 genes lost in glioblastoma (Liu et al. 1997; Parsons 2004). The gene encodes a tyrosine phosphatase, which is consistent with a tumor suppressor phenotype. When phosphatase activity is lost as a result of genetic mutation, signaling pathways can become activated constitutively, resulting in aberrant proliferation.

10.2.2.4 Association with Neurofibromatosis

There are two distinct types of neurofibromatosis, each affecting cells derived from the neural crest. NF1 is characterized by autosomal dominant inheritance with almost complete penetrance and variable expressivity (Ward and Gutmann 2005). NF1 is at least ten times more common than NF2. Spinal cord tumors in NF1 patients are usually astrocytomas, while ependymomas usually occur in patients with NF2 (Dow et al. 2005). In one small cohort of neurofibromatosis patients with IMSCTs, 3 had NF1, 5 had NF2, and 1 had an uncertain type (Lee et al. 1996). The reported incidence of IMSCTs in the

total neurofibromatosis population was approximately 19 % (9 out of 48). In 1997, Yagi and colleagues described a cohort of 44 adult patients with IMSCTs, 2 of whom had NF1 (Yagi et al. 1997). In both cases, the pathology of the lesion was astrocytoma (anaplastic astrocytoma and glioblastoma).

10.2.3 Clinical Features

The typical symptoms of an intramedullary spinal cord astrocytoma are shown in Table 10.1. They include gait disturbance, pain, reflex changes, motor or sensory symptoms, and bowel or bladder sphincter dysfunction (Steinbok et al. 1992; Constantini et al. 1996; Houten and Weiner 2000; Houten and Cooper 2000) Spinal deformity can be present in up to 30 % of patients (Epstein and Epstein 1981; Epstein et al. 1992; Steinbok et al. 1992). Intramedullary tumors involving the cervicomedullary junction can present with a myriad of symptoms, such as vomiting, choking, dysphagia, frequent respiratory infections due to chronic aspiration, dysarthria and dysphonic speech, sleep apnea, and failure to thrive (Abbott 1993; Robertson et al. 1994). A tumor in the cervical spinal cord can cause chronic neck pain, torticollis, progressive motor weakness, sensory changes, hyperreflexia, and, rarely, hydrocephalus (Abbott 1993; Robertson et al. 1994). Chronic pain at the level of the tumor can be present for months or years (Houten and Weiner 2000; Houten and Cooper 2000).

Table 10.1 Presenting symptoms of intramedullary spinal cord tumors in children

Pain
Motor regression
Weakness
Gait abnormality/deterioration
Torticollis
Progressive kyphoscoliosis
Hydrocephalus
Sphincter disturbance
Reflex changes
Sensory impairment

10.2.3.1 Diagnostic Imaging

MRI is the diagnostic tool of choice for all spinal tumors (Miyazawa et al. 2000; Sun et al. 2003). There is virtually no role for plain radiographs or computed tomography (CT) images because of the associated radiation exposure and limited anatomic detail seen. Astrocytomas are commonly located eccentrically within the spinal cord, and there is often heterogeneous contrast enhancement following injection of gadolinium (Baleriaux 1999; Osborn 1994) (Figs. 10.3 and 10.4). Diffusion tensor imaging (DTI) can be helpful in defining the relationship of the lesion to critical spinal pathway. In a series of ten patients, tractography was capable of demonstrating fiber splaying/displacement versus pathway infiltration. This information contributed to the decision between aggressive resection compared to debulking and biopsy (Choudhri et al. 2014). DTI and perfusion-weighted imaging (PWI) can be helpful in differentiating IMSCTs from other tumorlike lesions in the cervical cord (Liu et al. 2014). Approximately 75 % of astrocytomas occur in the cervicothoracic region, 20 % in the distal spinal cord, and 5 % in the filum terminale (Osborn 1994). Unlike ependymomas, which typically span three to four vertebral bodies, spinal cord astrocytomas are more extensive spanning several levels to holocord (Baleriaux 1999; Osborn 1994; Ebner et al. 2012).

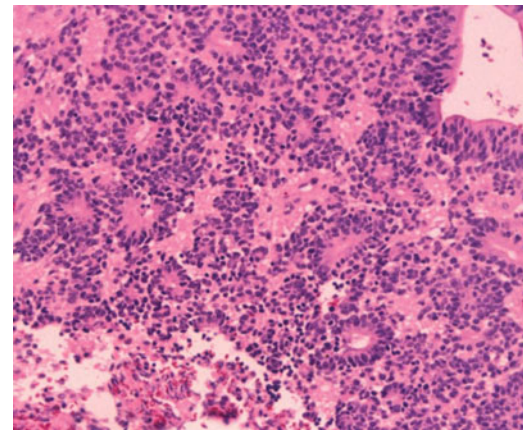

Fig. 10.1 Histological features of ependymoma. This image illustrates the ependymal rosettes which are formed from columnar cells arranged around a central lumen. Also in the top right hand corner, a pseudorosette, cells arranged radially around a blood vessels, can be appreciated

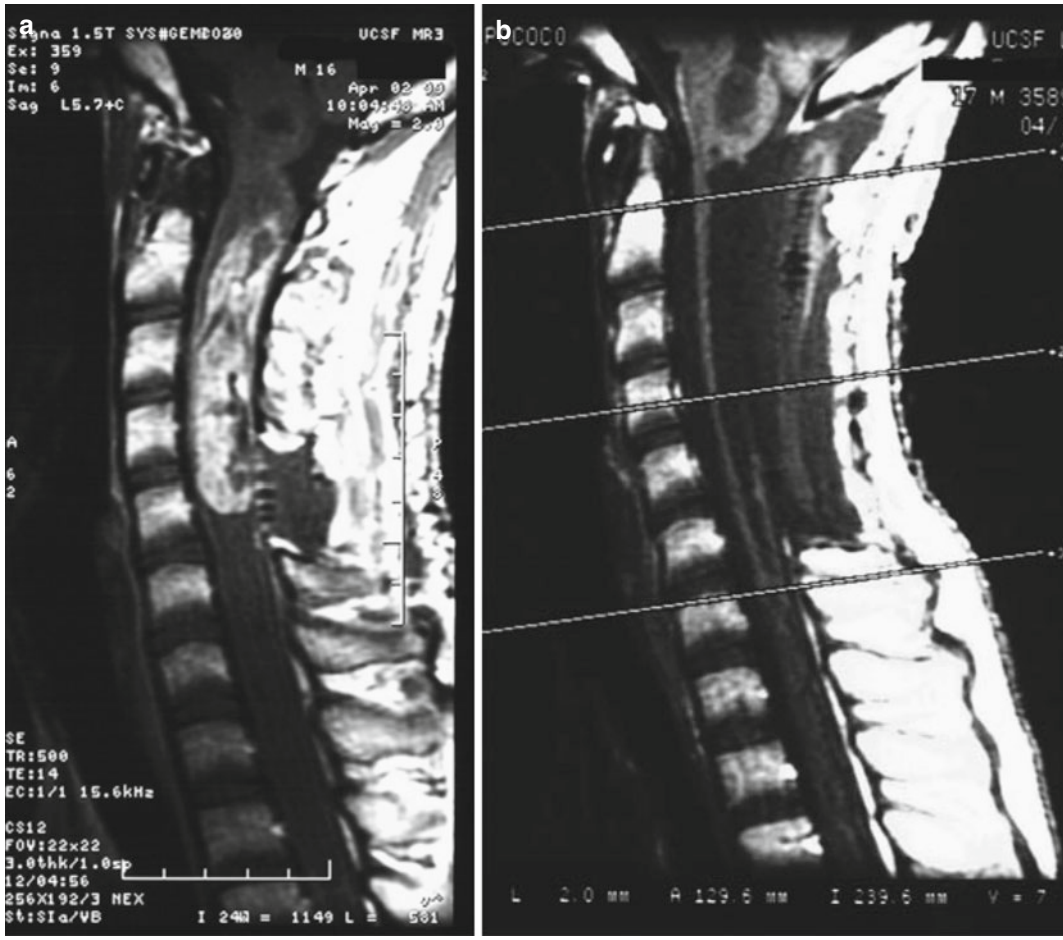

Fig. 10.2 A 17-year-old male presented with left-arm numbness and tingling. (**a**) The preoperative MRI scan reveals an intramedullary cervical cord mass in the sagittal T1-weighted image with contrast. Gross total resection was achieved, and pathology was consistent with a grade II ependymoma. (**b**) A postoperative MRI showed resection of the mass with no evidence of residual tumor as demonstrated in the sagittal T1-weighted image with contrast

Although MRI has improved our ability to identify the exact location of IMSCTs, a precise histopathologic diagnosis requires tissue biopsy (Kopelson and Linggood 1982; McCormick et al. 1990a; Hulshof et al. 1993; Minehan et al. 1995; Lee et al. 1996; Innocenzi et al. 1997; Jallo et al. 2001).

10.3 Ependymoma

10.3.1 Epidemiology

Ependymomas are thought to arise from the ependymal lining of the ventricles and central canal and can occur both in the brain and spinal cord. The majority of ependymomas are sporadic, but they can also be associated with NF2. In children, ependymomas usually arise in the cervical region and occur less frequently than astrocytomas (McCormick et al. 1990b; Brotchi et al. 1991; Fine et al. 1995; Goh et al. 1997; Miller 2000; Schwartz and McCormick 2000; Hanbali et al. 2002). Miller identified only 16 ependymomas out of 117 (14 %) cases of pediatric IMSCTs (Miller 2000). Although intramedullary ependymomas are the most common spinal cord tumor in adults (Mork and Loken 1977; Sonneland et al. 1985; Helseth and Mork 1989; Whitaker et al. 1991; Clover et al. 1993; Hulshof et al. 1993; Hoshimaru et al. 1999; Schwartz and McCormick 2000; Chang et al. 2002; Hanbali et al. 2002; Parsa et al. 2004),

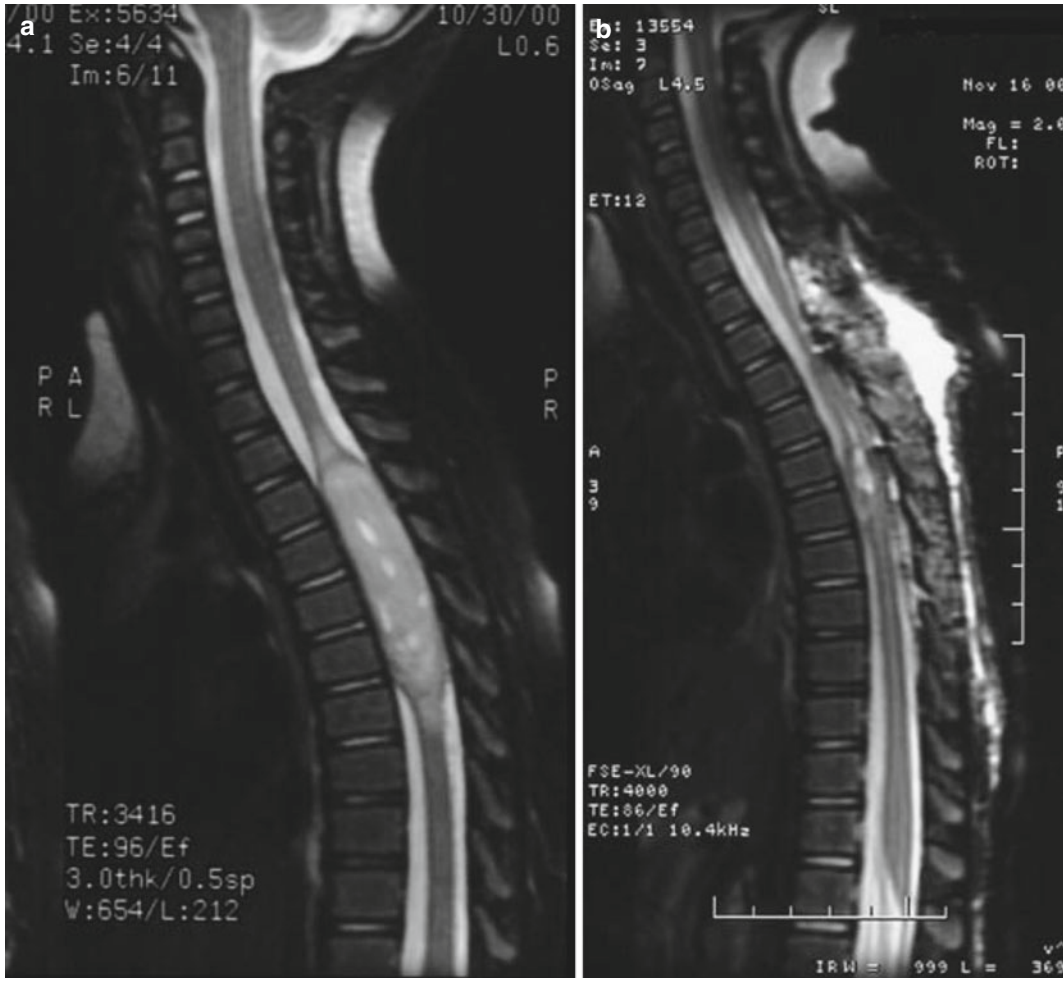

Fig. 10.3 A 3-year-old girl presented with 6 months of intermittent, worsening back pain. (**a**) The MRI scan revealed a large intramedullary mass extending from T3 to T7, shown here in a sagittal T2-weighted image. The histology was consistent with pilocytic astrocytoma. (**b**) The postoperative MRI scan demonstrates removal of the centrally located tumor. Nodular enhancement in the area of the surgery is seen in a sagittal T2-weighted image. Although nodular enhancement was present in the first imaging, subsequent MRIs showed complete resolution 6 months after resection

they are less common in the pediatric population (Constantini et al. 1996; Miller 2000; Constantini 1996) In their series of pediatric IMSCTs, Constantini and colleagues did not find any ependymomas in children less than 3 years of age (Constantini et al. 1996).

10.3.2 Pathology

10.3.2.1 Grading

The World Health Organization (WHO) classification of CNS tumors (Kleihues et al. 2002; Louis et al. 2007) divides ependymomas into four types: subependymoma (grade I), myxopapillary ependymoma (grade I), benign or "classic" ependymoma (grade II), and anaplastic ependymoma (grade III). Subependymomas are considered benign, slow-growing, and intraventricular tumors and have a good prognosis, although they are rarely encountered in the spinal cord. Myxopapillary ependymomas are unique tumors because they usually arise from the filum terminale or conus medullaris (Sonneland et al. 1985). Nearly all are histologically benign and are associated with a good long-term survival (Mork and

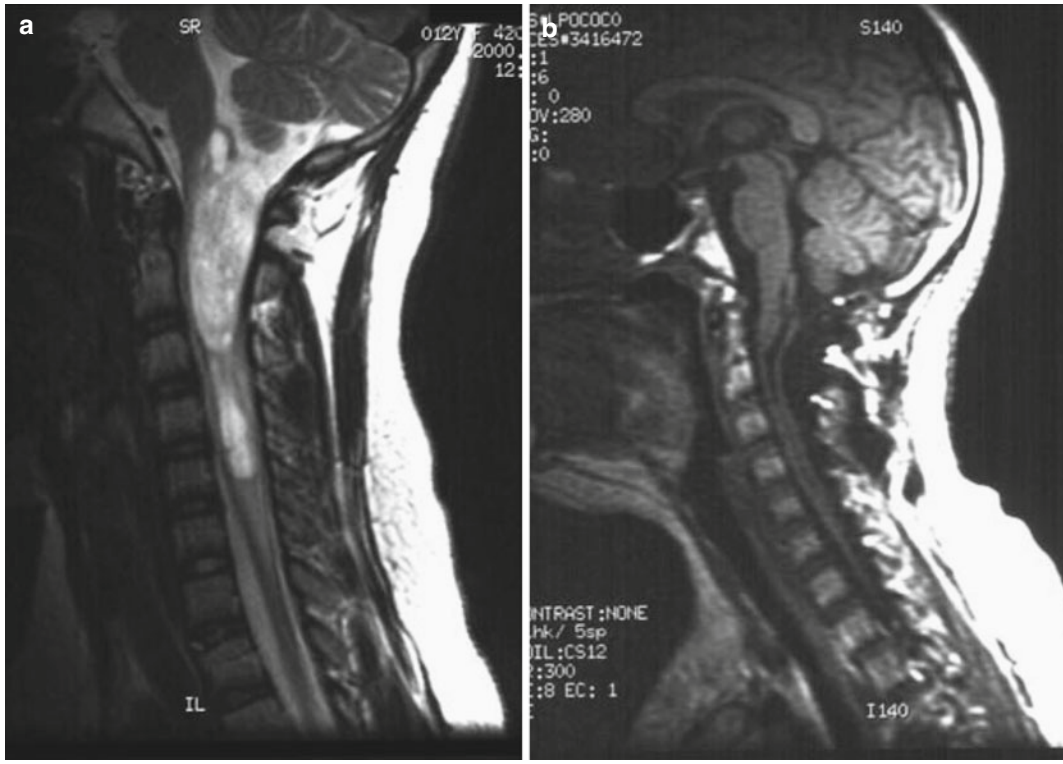

Fig. 10.4 A 12-year-old girl presented with a 3-month history of progressive right arm weakness and clumsiness. (**a**) The preoperative MRI scan revealed an intramedullary spinal cord tumor extending from the cervicomedullary junction to C4, as shown in sagittal T2-weighted image. Histology was consistent with a pilocytic astrocytoma. (**b**) The postoperative MRI demonstrates that the enhancing mass has been resected, as shown in the sagittal T1-weighted image

Loken 1977; Cooper 1989; McCormick et al. 1990b; Epstein et al. 1993; Chang et al. 2002; Hanbali et al. 2002; Russell 1989). Although most spinal cord ependymomas in children are grade II tumors, anaplastic ependymomas do occur infrequently and are believed to arise from the malignant transformation of lower-grade tumors (Kleihues et al. 2002).

10.3.2.2 Histopathology

Subependymomas are characterized by clusters of glial cells in a dense fibrillary matrix and are often associated with small cysts. Ependymomas are highly cellular tumors, irrespective of their grade. Myxopapillary ependymomas are characterized by cuboidal or elongated tumor cells arranged in a papillary and radial pattern around the vascular and stromal cores. Little mitotic activity is present, but a matrix of abundant mucin can accumulate between myxopapillary ependymoma cells and vessels.

The gross appearance of grade II spinal cord ependymomas is that of a soft, red or grayish-purple, somewhat friable mass (McCormick et al. 1990b; Schwartz and McCormick 2000; Sun et al. 2003). Cystic degeneration and hemorrhage are common in these vascular tumors (Sun et al. 2003). Although unencapsulated, these tumors are usually well circumscribed and do not infiltrate adjacent spinal cord tissue (Goh et al. 1997; Parsa et al. 2004; Parsa and McCormick 2005). Microscopic features include pseudorosettes and perivascular clustering and cuffing and immunoreactivity for glial fibrillary acidic protein (GFAP). Pseudorosettes are formed by clustering of cuboidal or columnar cells in a radial pattern around the blood vessels (Fig. 10.1). True rosettes, which appear as a ring of several nuclei from which interlacing neurofibrils converge in the center, can also be present (Schwartz and McCormick 2000). Mitotic figures are rare, but

an occasional nonpalisading focus of necrosis can be found in low-grade ependymomas. As measured by MIB-1 immunohistochemistry, the proliferative activity of spinal cord ependymoma is significantly lower than that of intracranial ependymoma. Proliferative indices greater than 2.0 % may be associated with an increased risk of recurrence (Iwasaki et al. 2000). The atypical variants clear cell ependymoma and tanycytic ependymoma can mimic oligodendroglioma and astrocytoma, respectively (Goh et al. 1997).

Anaplastic ependymomas differ from grade II ependymomas. While grade II ependymomas morphologically appear similar to nonneoplastic ependymal cells, anaplastic ependymomas demonstrate clear evidence of malignancy such as increased mitotic activity, increased cellularity with microvascular proliferation, and pseudopalisading necrosis. Anaplastic ependymomas can be extremely invasive and are poorly differentiated.

10.3.2.3 Molecular Biology and Genetics

Myxopapillary ependymomas have a much higher propensity for aneuploidy or polyploidy, especially of chromosome 7, when compared to other ependymomas (Gilhuis et al. 2004; Santi et al. 2005). Anaplastic ependymomas (WHO grade III) of the spinal cord are rare, and genetic alterations remain largely undefined (Ebert et al. 1999).

Molecular and genetic events associated with spinal ependymoma have been described. Ebert and colleagues analyzed 62 ependymal tumors, including myxopapillary ependymomas, subependymomas, classic ependymomas, and anaplastic ependymoma. They showed allelic loss of chromosomes 10q (5 out of 56) and 22q (12 out of 54) (Ebert et al. 1999). Somatic mutations of the *NF2* gene were detected in six of the tumors examined, and in each case the tumor was from a grade II spinal cord ependymoma. These results were confirmed by another group which also found mutations in the *NF2*. In addition, loss of heterozygosity (LOH) of 22q was present in all spinal intramedullary ependymomas ($n=6$) (Lamszus et al. 2001). Allelic loss on 22q was also frequently observed and was more common in intramedullary spinal ependymomas than in tumors in other locations (Lamszus et al. 2001).

In a report of 22 pediatric ependymomas, LOH at chromosome 22 was observed in two cases, deletions of chromosome 17 in another two cases, and the deletion or rearrangement of chromosome 6 in another five cases (Kramer et al. 1998). In addition, a low-penetrance ependymoma susceptibility locus has been mapped to chromosome 22q11 (Hulsebos et al. 1999; Ammerlaan et al. 2005), suggesting the role of alternative predisposing genes apart from *NF2*.

Overall, 75 % of all ependymomas display chromosomal aberrations or rearrangements over several different chromosomes, the most frequent LOHs being found on the long arms of chromosomes 6 (30.3 %), 9 (27.3 %), and 17 (Huang et al. 2003). In 18 pediatric ependymomas, von Haken and colleagues reported a 50 % incidence of allelic mutations on the short arm of chromosome 17 (von Haken et al. 1996). LOH was also detected on 3p14 (13.3 %), 10q23 (10.3 %), and 11q (18.2 %). Monosomy of chromosome 22 is present in approximately 30 % of ependymomas (Scheil et al. 2001), with aberrations or alterations of 22q existing in up to 40 % of all ependymomas.

Another distinction between spinal and cranial ependymoma may lie in the methylation of particular tumor-related genes. A study examining the methylation of a putative tumor suppressor gene, *HIC-1* on chromosome 17p13.3, showed a significant correlation between hypermethylation of *HIC-1* and cranial localization ($p=0.019$, $n=52$) (Waha et al. 2004). Losses in chromosomes 1p and 16q, which occur in other CNS tumors, have not been found in ependymoma (Bijlsma et al. 1995). The apparent genetic differences between ependymomas in the brain and those in the spine suggest that different molecular mechanisms exist that lead to the pathogenesis of each. Because primary brain and spine tumors are rarely, if ever, associated with each other, these distinctions may indicate the need to reclassify spinal ependymoma separately from intracranial ependymoma.

10.3.2.4 Association with Neurofibromatosis Type 2

NF2 is a rare autosomal dominant genetic disorder associated with tumors of the CNS (see Chap. 12) (Mulvihill et al. 1990). Its prevalence is 1 in 40,000 individuals (Evans et al. 1992), and is caused by a mutation of the *NF2* tumor suppressor gene (also known as *merlin* or *schwannomin*) located on chromosome 22 (Rouleau et al. 1987, 1993; Trofatter et al. 1993). Patients with NF2 have a high incidence of several CNS tumors, including vestibular schwannomas and meningiomas (Martuza and Eldridge 1988). Several authors have also noted an association between NF2 and intramedullary spinal cord ependymomas (Martuza and Eldridge 1988; Rodriguez and Berthrong 1966; Mautner et al. 1993; Lee et al. 1996; Lamszus et al. 2001; Egelhoff et al. 1992). NF2 patients represent approximately 2.5 % of patients with IMSCTs, yet only 0.03 % of the population (Lee et al. 1996). In addition, in one small study, 71 % of patients with intramedullary spinal cord ependymomas and no other clinical features of NF2 were shown to possess mutations in the *NF2* gene (Birch et al. 1996). More recently, Garcia and Guttman investigated the mechanism by which the *NF2* protein Merlin regulates spinal neural differentiation and glial proliferation. They demonstrated that Merlin negative regulates these cell functions in a manner dependent on ErbB2, and they further observed increased Erb2 activation in NF2-associated ependymomas; they further hypothesize that ErbB2 may be a rational therapeutic target for medical therapy for NF2-associated spinal ependymoma (Garcia et al. 2014).

10.3.3 Clinical Features

Arising from ependymal cells lining the central canal, intramedullary ependymomas are well circumscribed, slow-growing tumors usually located in the center of the cervical spinal cord and cause symmetric expansion of the cord (McCormick et al. 1990a; Brotchi et al. 1991; Fine et al. 1995; Goh et al. 1997; Miller 2000; Schwartz and McCormick 2000; Hanbali et al. 2002). Patients typically complain of dysesthesia correlating to the level of the tumor for months to years prior to diagnosis. Other symptoms include paresthesia, radicular pain, bowel and bladder dysfunction, and other sensory disturbances (Rawlings et al. 1988; McCormick and Stein 1990; McCormick et al. 1990b; Clover et al. 1993; Epstein et al. 1993; Hulshof et al. 1993; Asazuma et al. 1999; Hoshimaru et al. 1999; Schwartz and McCormick 2000; Chang et al. 2002; Hanbali et al. 2002; Peker et al. 2004; Shrivastava et al. 2005). Children most often present with pain, weakness, gait abnormality, torticollis, or progressive kyphoscoliosis (Constantini et al. 1996, 2000). Hydrocephalus also is more common in pediatric patients with intramedullary spinal cord ependymomas than in adult patients and may require cerebrospinal fluid (CSF) shunting (Houten and Weiner 2000; Houten and Cooper 2000). A sudden decline in neurologic function may occur following intratumoral hemorrhage (McCormick et al. 1990b). Motor impairment usually occurs late in the disease progression as the expanding tumor thins the surrounding spinal cord to a few millimeters (Epstein et al. 1993) (Table 10.1). This differs from intramedullary astrocytomas, which tend to present with pain and progressive motor dysfunction over a shorter time (Epstein et al. 1993).

10.3.4 Diagnostic Imaging

The anatomic features of spinal cord tumors are best evaluated with magnetic resonance imaging (MRI) (Miyazawa et al. 2000; Sun et al. 2003). Intramedullary spinal cord ependymomas are typically centrally located lesions with sharply defined rostral and caudal margins, enhancing borders, and typically spanning three to four vertebral body segments (Baleriaux 1999; Miyazawa et al. 2000). Spinal cord ependymomas commonly demonstrate symmetric enlargement of the spinal cord, unlike astrocytomas, which exhibit a nodular or asymmetric pattern of growth (Kopelson and Linggood 1982; McCormick et al. 1990a; Hulshof et al. 1993; Minehan et al. 1995; Lee et al. 1996; Innocenzi et al. 1997; Iwasaki et al. 2000; Miyazawa et al. 2000; Jallo et al. 2001).

Table 10.2 Magnetic resonance imaging of intramedullary spinal cord tumors

	Ependymomas	Astrocytomas
Location	Centrally located; mostly in the cervical spine but in children also present in the conus	Eccentrically located, usually widens the spinal cord, 75 % of astrocytomas in the cervical and thoracic regions, 20 % in the distal cord, 5 % in the filum terminale
T1	Isointense/hypointense	Isointense/hypointense
T1 with contrast	Axial view – cord symmetrically expanded. Enhances with contrast but less than astrocytomas	Ill-defined borders axial view – cord asymmetrical, "lumpy"; heterogeneous, moderate, partial contrast enhancement

Spinal cord ependymomas are isointense on T1-weighted MR images and slightly hyperintense on T2-weighted MR images (Miyazawa et al. 2000; Sun et al. 2003) (Table 10.2). However, signal heterogeneity can occur with cyst formation, necrosis, or hemorrhage (Miyazawa et al. 2000). A "cap sign" is typically associated with spinal cord ependymomas and represents areas of low signal density on either border of the tumor mass itself. This "cap" hypointensity at the tumor margin is often due to hemosiderin deposits from secondary, chronic hemorrhage (Baleriaux 1999; Miyazawa et al. 2000; Chang et al. 2002). Almost all intramedullary ependymomas enhance with contrast, but to a lesser degree than intracranial ependymomas (Sun et al. 2003) (Fig. 10.2). Occasionally, these spinal cord ependymomas can present with subarachnoid hemorrhage.

Spinal cord ependymoma-related cysts are common and are classified into three types: cystic tumors from tumor necrosis and hemorrhage, syrinx formation from disturbances of CSF formation, and rostral and caudal cysts from reactive products of IMSCTs (Sun et al. 2003). Ependymoma-associated cysts appear hypointense on T1-weighted MR images and hyperintense on T2-weighted images (Sun et al. 2003). These cysts are also centrally located and cause symmetric expansion of the spinal cord (Sun et al. 2003). A tumor-associated syrinx has similar MR characteristics to CSF and is present in over 50 % of spinal cord ependymomas (Chang et al. 2002). Multivariate analysis has determined that the presence of syringohydromyelia strongly favors a diagnosis of ependymoma over astrocytoma (Kim et al. 2014). The majority of rostral and caudal cysts are also hypointense on T1-weighted MR images and hyperintense on T2-weighted MR images (Sun et al. 2003).

10.4 Von Hippel–Lindau Disease and Spinal Hemangioblastoma

Hemangioblastomas are benign (WHO grade I) vascular tumors predominantly found in the cerebellum and spinal cord (see Chap. 12). First described by Arvid Lindau as cystic lesions in the cerebellum, CNS hemangioblastomas are usually sporadic, but 20–30 % of cases occur in association with von Hippel–Lindau (VHL) disease (Glasker 2005). VHL is an autosomal dominant disorder with 90 % penetrance attributable to loss of a tumor suppressor gene on chromosome 3p25–26 (Kley et al. 1995). The *VHL* gene encodes for a protein required for oxygen-dependent degradation of hypoxia-inducible factor-1 alpha (HIF-1a). Dysfunction or absence of the *VHL* gene product leads to constitutive overexpression of HIF-1a, which then leads to increased levels of vascular endothelial growth factor (VEGF) and other pro-angiogenic signals (Kim and Kaelin 2004). Additional information is provided in Chap. 12.6.

Lesions associated with VHL include CNS hemangioblastoma, retinal angioma, renal cysts, renal cell carcinoma, pancreatic cysts, pheochromocytoma, and epididymal cystadenoma (Glavac et al. 1996). VHL families can be grouped according to the presence or absence of pheochromocytomas (Neumann et al. 1995). Nearly all families with pheochromocytomas have missense mutations of the VHL gene. Using tissue

microdissection, Vortmeyer and colleagues have demonstrated consistent LOH at the VHL gene locus in the stromal cells, implicating these cells in the pathogenesis of hemangioblastoma (Vortmeyer et al. 1997).

CNS hemangioblastoma occurs in both type I (without pheochromocytoma) and type II (with pheochromocytoma) VHL disease. Common sites include the posterior fossa (80 %) and the spinal cord (20 %). VHL-related hemangioblastomas have been reported to harbor germline mutations (94 %) and LOH (62 %) at the *VHL* gene (Glasker et al. 1999, 2001; Glasker 2005). Over 150 different germline mutations have been identified and include deletion and missense and nonsense frameshift mutations. The resultant biallelic inactivation of the *VHL* gene suggests a "2-hit" model of tumorigenesis in VHL patients. VHL patients are usually heterozygous for the germline VHL mutant, and a "second hit" at the remaining wild-type *VHL* gene then causes neoplastic progression. In contrast, sporadic hemangioblastomas contain only 50 % LOH and 23 % germline mutations at the *VHL* gene, suggesting alternate pathways to biallelic inactivation and tumorigenesis in sporadic cases (Glasker 2005).

Other mutations and sites of LOH have been implicated in the development of sporadic hemangioblastomas. LOH of chromosome 22q13 was found in 5 of 8 patients with non-VHL-related hemangioblastoma, with only 3 of 8 patients harboring LOH at chromosome 3p21–23 (Beckner et al. 2004). Differences in the molecular and genetic origins of hemangioblastoma may indicate differences between patients with VHL disease and CNS hemangioblastomas and those with sporadic CNS hemangioblastomas.

10.5 Other Intramedullary Spinal Cord Tumors and Lesions

Inclusion tumors and cysts, metastases, nerve sheath tumors, neurocytoma, and melanocytoma account for much of the remainder of intramedullary mass lesions. Approximately 4 % of apparent IMSCTs are nonneoplastic lesions (Lee et al. 1998). Lipomas are the most common developmental lesion and account for about 1 % of all intramedullary spinal cord masses (Lee et al. 1998).

10.6 Treatment

Surgery is the treatment of choice for IMSCTs, and excellent results are associated with gross total resection (Houten and Weiner 2000; Iwasaki et al. 2000). Although the outcome for low-grade spinal cord astrocytomas is better in children than in adults, the prognosis for spinal cord astrocytomas is not as favorable as that of ependymoma (Goh et al. 1997; Houten and Weiner 2000; Iwasaki et al. 2000; Hanbali et al. 2002; Houten and Cooper 2000). Radical resection has been shown to prolong survival for non-disseminated WHO grades II and III astrocytomas, but must be weighed against the risk of causing neurologic deficits. GTR currently has no role in treatment of WHO grade IV tumors. Adjuvant radiotherapy is commonly used in cases of malignant astrocytomas or subtotally resected tumors. Little is known about the utility of chemotherapy for spinal cord astrocytoma or ependymoma.

10.6.1 Surgery

10.6.1.1 Surgical Principles

Surgery is effective for diffusely infiltrating spinal cord astrocytomas, and often a tissue diagnosis is all that can be safely accomplished (Houten and Weiner 2000; Houten and Cooper 2000). Pilocytic spinal cord astrocytomas, however, can be completely resected. The goal of surgery for intramedullary ependymoma is gross total resection (GTR) and preservation of neurologic function (Cooper 1989; McCormick et al. 1990a, b; McCormick and Stein 1990; Epstein et al. 1993; Cristante and Herrmann 1994; Chang et al. 2002; Peker et al. 2004). Ependymomas are typically non-infiltrative lesions that cause compression of the adjacent cord parenchyma, and the presence of a well-defined interface between the spinal cord and the tumor facilitates surgical resection (Sandalcioglu et al. 2005). An adequate myelotomy is necessary

to fully expose the tumor and allow an accurate tissue diagnosis (Hanbali et al. 2002). An intraoperative frozen section diagnosis consistent with ependymoma should prompt an attempt at GTR. Conversely, identification of a malignant tumor requires that the surgeon carefully weigh the risks versus benefits of further resection, factoring in the WHO grade, intraoperative appearance, quality of tumor margins, and stability of neuromonitoring signals. The presence of a syrinx may improve the chances of a GTR, but it cannot be used as an independent predictor of outcome (Samii and Klekamp 1994; Chang et al. 2002; Peker et al. 2004).

10.6.1.2 Surgical Approach

Pediatric IMSCTs are approached by performing a laminectomy or, more commonly, an osteoplastic laminotomy. The osteoplastic technique has been associated with decreased rates of progressive kyphotic deformity requiring fusion (McGirt et al. 2008b). It involves removal of the bony lamina to expose the dura and spinal cord at the relevant levels as indicated by the preoperative MRI, followed by replacement of the posterior bony elements after the tumor resection is completed. To expose the dura, parallel cuts are made in the lamina of the involved spinal segments with either a high-speed side-cutting drill or rongeurs. The supraspinous and intraspinous ligaments are then sharply dissected at the caudal end of the laminoplasty flap prior to its elevation. Following tumor resection, the flap is resecured with sutures or plates (metal or absorbable). Preservation of the posterior tension band in this manner restores the normal anatomy after tumor resection, may promote bony fusion, and minimizes the potential for spinal deformity (Houten and Weiner 2000; Houten and Cooper 2000; Raimondi et al. 1976); (Constantini et al. 1996, 2000).

Several risk factors for development of a progressive spinal deformity have been identified, including preoperative scoliotic deformity, an increasing number of resections, an age less than 13 years, tumor-associated syrinx, surgery involving more than four levels, surgery spanning the thoracolumbar junction, and adjuvant radiotherapy (Yao et al. 2007; Ahmed et al. 2014a; Knafo et al. 2014; McGirt et al. 2008c). For multilevel surgery, data suggests that in situ fusion can decrease the risk of postresection deformity by 30 % and as much as 42 % in skeletally mature children (Anakwenze et al. 2011). Intraoperative localizing x-rays are crucial to identify the correct level of surgery. Once the dura is exposed, intraoperative ultrasonography improves the accuracy of surgical exposure and identification of the intramedullary tumor, which in turn reduces the size of the dural opening and myelotomy (Epstein et al. 1993; Maiuri et al. 2000; Hanbali et al. 2002; Brunberg et al. 1991; Raghavendra et al. 1984).

During tumor resection, real-time neurophysiologic monitoring is critical adjunct. Common modalities of monitoring include motor evoked potentials (MEPs), somatosensory evoked potentials (SSEPs), and measurement of D-waves (Nash et al. 1977; Morota et al. 1997; Goh et al. 2000; Calancie et al. 1998; Jones et al. 1996; Pechstein et al. 1996; Costa et al. 2013). Intraoperative changes in these signals can predict postoperative deficits (Quinones-Hinojosa et al. 2005; Cheng et al. 2014b). Neurophysiology can also be useful in delineating an appropriate entry point by mapping the dorsal surface of the spinal cord (Auguste and Gupta 2006; Cheng et al. 2014b). A bipolar stimulator can be swept from a lateral to medial direction until no SSEPs are recorded. This is then delineated as "septum," and the process is confirmed from the contralateral side. This is especially helpful in cases where the tumor does not extend to the cord surface or if the anatomy is rotated or distorted.

The technique of tumor removal is determined by the surgical objective, tumor size, and gross and histological characteristics of the tumor. If no physical plane is present between the tumor and surrounding spinal cord, then it is likely that an infiltrative tumor is present. A biopsy is performed to establish a histological diagnosis. If an infiltrating or malignant astrocytoma is identified and is consistent with the intraoperative findings, further tumor removal may not be warranted. If tumor is easily identified, then continued removal is reasonable with close attention paid to motor

and sensory evoked potentials. A reduction in these signals can predict postoperative deficits (Asazuma et al. 1999; Quinones-Hinojosa et al. 2005; Cheng et al. 2014a). Uncertainty of spinal cord–tumor interface should signal an end to tumor resection (Asazuma et al. 1999). On the other hand, 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, and the surgical goal in these cases is gross total resection.

10.6.1.3 Postoperative Management

Postoperatively, early mobilization is encouraged to prevent complications of recumbency such as deep venous thrombosis and pneumonia (Smith et al. 2004). Patients with severe motor deficits are particularly vulnerable to thromboembolic complications. Compression stockings are routinely used, and subcutaneous heparin (Epstein 2005) is begun on the second postoperative day in these patients. Orthostatic hypotension may occasionally occur following removal of upper thoracic and cervical intramedullary neoplasms. This is usually a self-limited problem that can be managed with liberalization of fluids and more gradual mobilization. A posterior fossa syndrome occasionally occurs following removal of a high cervical intramedullary neoplasm. Neck pain and stiffness can be managed with steroids and anti-inflammatory medications, although a lumbar puncture may sometimes be required to exclude a diagnosis of meningitis (Cooper and Epstein 1985; McCormick and Stein 1990). Early and aggressive use of physical and occupational therapy results in a better functional recovery.

Despite evidence to support a GTR, there is a risk of recurrence (Whitaker et al. 1991; Chang et al. 2002). Long-term clinical and radiographic follow-up is warranted in these patients (Sandalcioglu et al. 2005). An early postoperative MRI establishes the completeness of resection and serves as a baseline against which further studies can be compared. GTR is defined as more than 90 % tumor removal, subtotal resection (STR) as 50–90 %, and partial as less than 50 %. Serial gadolinium-enhanced MRIs are obtained because radiographic tumor recurrence usually precedes clinical symptoms (Chang et al. 2002; Hanbali et al. 2002). Serial radiographs should be obtained in high-risk patients to monitor for development of a progressive kyphotic deformity.

10.6.2 Radiation

Radiation therapy plays an adjunctive role in the treatment of malignant tumors and incompletely resected low-grade astrocytomas (Isaacson 2000; Guss et al. 2013). Low-grade astrocytomas and ependymomas that undergo GTR can be followed with serial imaging only. Radiotherapy in young children is associated with significant adverse effects, and therefore it is preferable to avoid or delay radiation therapy as long as possible in low-grade tumors (Rousseau et al. 1994; Perilongo et al. 1997; Prados et al. 1997; Gornet et al. 1999; Zuccaro et al. 1999; Grill et al. 2001; Teo et al. 2003; Valera et al. 2003).

GTR of grade II intramedullary ependymomas provides better long-term tumor control compared to STR and radiation therapy (McCormick et al. 1990b; Epstein et al. 1993; Hulshof et al. 1993; Cristante and Herrmann 1994; Hoshimaru et al. 1999; Lee et al. 2013). Although some authors recommend that radiation therapy is unnecessary following gross total resection (Cooper and Epstein 1985; Cooper 1989; McCormick et al. 1990b; Epstein et al. 1993; Hulshof et al. 1993; Samii and Klekamp 1994; Isaacson 2000; Kothbauer 2007), some studies have reported a 5–10 % recurrence rate following surgery (Guidetti et al. 1981; Cooper 1989; Hulshof et al. 1993; Chang et al. 2002). Surgery followed by external beam radiotherapy has been shown to result in 84 % local control of tumor for IMSCT of multiple tumor types (O'Sullivan et al. 1994).

Subtotal resection, as expected, has a very high recurrence rate (Cooper 1989; Linstadt et al. 1989; Chang et al. 2002). The data supporting postoperative radiation after STR is largely based on studies with small patient populations, limited

follow-up, and inadequate controls treated without radiation therapy (Isaacson 2000; O'Sullivan et al. 1994). Despite these limitations, the overall results suggest that radiation may be beneficial after STR of spinal cord ependymomas (Kopelson and Linggood 1982; Garcia 1985; Shaw et al. 1986; Cooper 1989; Linstadt et al. 1989; Guss et al. 2013). The usual dose delivered is approximately 5,000 cGy in 180–200 cGy fractions using external beam radiation therapy. In some cases, reoperation and another attempt at GTR should be considered if a recurrent tumor is more accessible or better defined from the normal spinal cord (Cooper 1989; Chamberlain 2002b; Hanbali et al. 2002).

Patients who present with focal disease usually recur locally and do not manifest late dissemination (Chamberlain 2002a, b). Craniospinal radiation is only indicated for the rare patient who presents with multifocal disease (Garrett and Simpson 1983; Linstadt et al. 1989; Hulshof et al. 1993). Although the outcome is worse for this subgroup, good control rates have been reported (Garcia 1985; Linstadt et al. 1989).

10.6.3 Chemotherapy

Currently, chemotherapy is not routinely used in the initial treatment of IMSCTs, although some clinicians consider the use of chemotherapy for recurrence or in combination with radiation therapy for high-grade or incompletely resected tumors. Very little published data exists to provide insight into the impact of chemotherapy on outcomes, and chemotherapy regimens are typically based on those with some demonstrated activity in the setting of intracranial disease. Objective radiographic responses for supratentorial ependymoma have been observed with the use of combination platinum agent with etoposide, but the effect of chemotherapy on survival and functional outcome is still unclear (Massimino et al. 2002; Valera et al. 2003). The prospect of preoperative chemotherapy for second-look surgery has been explored in small trials with mixed results (Foreman et al. 1996; Schiffer and Giordana 1998; Chamberlain 2001; Valera et al. 2003). Also, because of the desire to avoid or delay radiation therapy in young children under 3 years of age, adjuvant chemotherapy may have a potential role (Prados et al. 1997). In a series of adult patients with recurrent spinal low-grade astrocytoma treated with temozolomide, there was a modest effect (Chamberlain 2008).

Chemotherapy guidelines for pediatric IMSCTs have been mainly derived from the clinical experience with intracranial ependymomas and low-grade astrocytomas. No randomized clinical trials have been performed (Kothbauer 2007). Etoposide, a topoisomerase II inhibitor, has been used to treat recurrent intramedullary ependymomas. This drug appeared to be well tolerated with modest toxicity (Chamberlain 2002a, b). Further trials are needed to determine the efficacy of this potential therapy for recurrent and refractory intramedullary ependymomas. Fakhreddine and colleagues demonstrated an association between chemotherapy (primarily temozolomide) and improved progression-free survival, but not overall survival, in infiltrative astrocytomas (Fakhreddine et al. 2013). They saw no association between extent of resection or adjunctive radiotherapy and outcome in these patients (Fakhreddine et al. 2013).

10.6.4 Disease Control

The WHO grade of the tumor and neurologic status of the patient at the time of surgery are the primary determinants of oncologic prognosis in children with IMSCTs (Cristante and Herrmann 1994; Karikari et al. 2011). Over time, outcomes have improved in these patients. In 1992, Sandler reported a 5-year survival of 57 % in patients with grade I or II spinal cord astrocytomas (Sandler et al. 1992). With radical resection, Ahmed et al. reported long-term survival rates of 75 % and 64 % at 10 and 20 years, respectively, in a cohort of 55 IMSCT patients that included predominantly astrocytomas (Ahmed et al. 2014b). Another group also reported that children with non-disseminated anaplastic astrocytomas may have increased survival with radical resection

(McGirt et al. 2008d). Children with JPAs have better prognoses than those with diffuse spinal cord astrocytomas (Houten and Weiner 2000). Patients with WHO grade IV astrocytomas, unsurprisingly, do very poorly with no correlation between the extent of resection and survival (Fig. 10.5) (McGirt et al. 2008d).

The most important determinant in the treatment of ependymomas is the extent of resection (Nazar et al. 1990; Rousseau et al. 1994; Pollack et al. 1995; Perilongo et al. 1997; Schiffer and Giordana 1998; Souweidane et al. 1998; Chamberlain 2001; Grill et al. 2001; Teo et al. 2003; Valera et al. 2003; Lee et al. 2013). It should be noted that late recurrences can occur, even up to 12 years after surgery (Linstadt et al. 1989). As noted earlier, GTR results in cure or long-term control more frequently than STR and radiation. Regardless of whether radiation is used following surgery, long-term imaging surveillance is required.

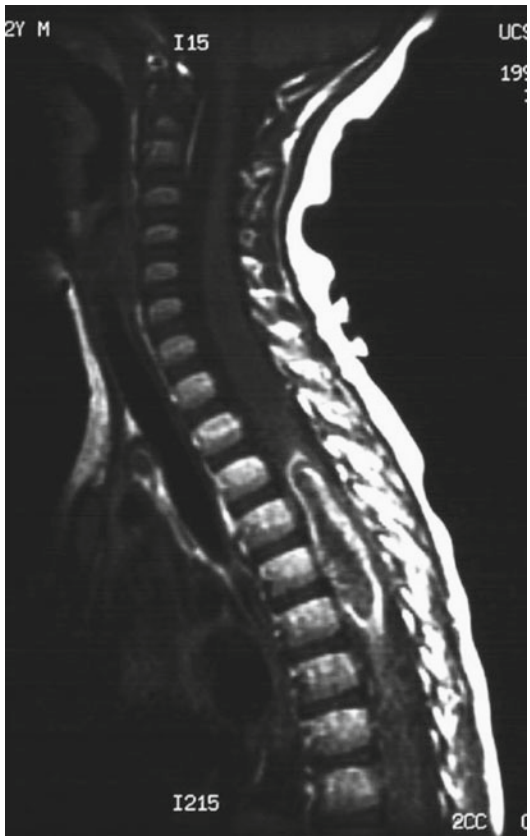

Fig. 10.5 A 2-year-old boy presented with several weeks of slowly progressive disuse of his lower extremities. The preoperative MRI demonstrated a 6 cm intramedullary thoracic cord mass from T3 to T7 with marked edema spanning the entire length of the spinal cord. Histopathology showed the tumor to be a grade III oligoastrocytoma. The patient's tumor progressed despite treatment

10.6.5 Functional Outcome

Children tolerate surgery for IMSCT very well, and their overall quality of life years after surgery is comparable to normal, healthy cohorts (Schneider et al. 2014). The strongest predictor of postoperative functional outcome is preoperative functional ability (Cooper 1989; McCormick and Stein 1990; McCormick et al. 1990b; Epstein et al. 1993; Cristante and Herrmann 1994; Hoshimaru et al. 1999; Chang et al. 2002; Sandalcioglu et al. 2005). While significant improvement of a severe or long-standing preoperative neurologic deficit rarely occurs (Chang et al. 2002), fortunately the incidence of permanent extremity paralysis after resection is also rare (Constantini et al. 2000; McGirt et al. 2008a). Surgical morbidity is greater in patients with more significant preoperative deficits (Hoshimaru et al. 1999; Chang et al. 2002; Hanbali et al. 2002; Peker et al. 2004). A shorter duration of preoperative symptoms may favor improvement even in patients with a significant preoperative deficit (Hoshimaru et al. 1999). In general, most patients note sensory loss in the early postoperative period, most likely as a result of the midline myelotomy, transient edema, or vascular compromise (McCormick and Stein 1990; Epstein et al. 1993). These deficits usually resolve within 3 months (Hoshimaru et al. 1999; Peker et al. 2004), although sensory ability may not return to preoperative baseline (McCormick and Stein 1990).

Additional surgical morbidity is directly related to the location of the tumor and the presence of spinal cord atrophy and arachnoid scarring (Cooper 1989; McCormick and Stein 1990; Cristante and Herrmann 1994; Samii and Klekamp 1994; Hoshimaru et al. 1999). A thoracic location has been correlated with a decline

in postoperative function (Cristante and Herrmann 1994; Hoshimaru et al. 1999; Hanbali et al. 2002; Sandalcioglu et al. 2005), perhaps due to a more tenuous blood supply in this region.

Conclusions

Early diagnosis of IMSCTs plays an important role in the management of these lesions and as a factor in long-term outcome. Because preoperative functional status is a significant prognostic factor, early diagnosis and surgical intervention are critical to the successful treatment of these tumors. Unexplained and chronic back pain in a child should be investigated immediately with a high-quality MRI with gadolinium. For intramedullary ependymomas, the extent of surgical resection is the strongest predictor of long-term survival. Adjuvant therapy should be reserved for malignant, disseminated, or progressive subtotally resected tumors.

A postoperative MRI scan and serial imaging are important for long-term follow-up of patients who have an IMSCT. New adjuvant therapeutic agents will likely play an increasing role in the treatment of spinal cord astrocytomas in children. Finally, improved knowledge of the genetic and molecular features of these tumors made possible through analysis of small tissue specimens will allow the identification of new therapeutic targets.

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