Pathological Classification of the Intramedullary Spinal Cord Tumors According to 2021 World Health Organization Classification of Central Nervous System Tumors, a Single-Institute Experience

Sung-Hye Park¹,², Jae Kyung Won¹, Chi Heon Kim³, Ji Hoon Phi⁴, Seung-Ki Kim³, Seung Hong Choi³, Chun Kee Chung²

¹Department of Pathology, Seoul National University College of Medicine, Seoul, Korea
²Institute of Neuroscience, Seoul National University College of Medicine Neuroradiology, Seoul, Korea
³Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea
⁴Department of Neuroradiology, Seoul National University College of Medicine, Seoul, Korea

According to the new 2021 World Health Organization (WHO) classification of tumors of the central nervous system (CNS) the classification of the primary intramedullary spinal cord tumors (IM-SCT) follows that of CNS tumors. However, since the genetics and methylation profile of ependymal tumors depend on the location of the tumor, the ‘spinal (SP)’ should be added for the ependymoma (EPN) and subependymoma (SubEPN). For an evidence-based review, the authors reviewed SCTs in the archives of the Seoul National University Hospital over the past decade. The frequent pathologies of primary IM-SCT were SP-EPN (45.1%), hemangioblastoma (20.0%), astrocytic tumors (17.4%, including pilocytic astrocytoma [4.6%] and diffuse midline glioma, H3 K27-altered [4.0%]), myxopapillary EPN (11.0%), and SP-subEPN (3.0%) in decreasing order. IDH-mutant astrocytomas, oligodendrogliomas, gliomegliomas, embryonal tumors, and germ cell tumors can occur but are extremely rare in the spinal cord. Genetic studies should support for the primary IM-SCT classification. In the 2021 WHO classifications, extramedullary SCT did not change significantly but contained several new genetically defined types of mesenchymal tumors. This article focused on primary IM-SCT for tumor frequency, age, sex difference, pathological features, and genetic abnormalities, based on a single-institute experience.

Keywords: Spinal cord, Intramedullary tumor, Ependymoma, Astrocytoma, Diffuse midline glioma

INTRODUCTION

The spinal cord belongs to the central nervous system (CNS) and is a tubular structure that leads to the medulla oblongata, from which any tumor arising from the brain can develop. All intradural extramedullary spinal tumors (EM-SPT) and intramedullary spinal cord tumors (IM-SCT) are rare and account for 2%–4% of CNS tumors.¹ The incidence of spinal cord tumors in Seoul National University Hospital (SNUH) is similar to that reported previously.² Reported IM-SCT accounts for approximately about 10% of spinal cord tumors.¹ For the classification of the IM-SCT according to the updated World Health Organization (WHO) classification in 2021, spinal tumors also required genetic studies with some tumors renamed by genetics and methylation profile.³ The tumor names were changed into spinal ependymoma (SP-EPN) and spinal subependymoma.
In order of increasing frequency, the types of IM-SCTs are:

1. SP-subEPN (9.4% of primary spinal tumors, 3.0% of IM-SCTs) are well-circumscribed tumors and have diffuse midline glioma (DMG) H3 K27M-altered (n = 13, 11.0% of IM-SCTs), diffuse leptomeningeal glioneuronal tumors (DLMGNT), and atypical teratoid/rhabdoid tumor (AT/RT) (0.1% of primary spinal tumors, 0.3% of IM-SCTs, each) were rare (Table 1).

2. SP-EPN (36.8% of spinal astrocytic tumors) and diffuse midline glioma (DMG) H3 K27M-altered (n = 13, 22.8% of spinal astrocytic tumors) were the most common. The latter high-grade astrocytic tumors included glioblastoma (GBM) IDH-wildtype CNS WHO grade 4 (n = 21, 36.8% of spinal astrocytic tumors) and diffuse midline glioma (DMG) H3 K27M-altered (n = 13, 22.8% of spinal astrocytic tumors). Spinal subEPN (0.6% of primary spinal tumors, 3.0% of the IM-SCTs), ganglioglioma (0.3% of primary spinal tumors, 1.5% of IM-SCT), diffuse leptomeningeal glioneuronal tumors (DLMGNT), and atypical teratoid/rhabdoid tumor (AT/RT) (0.1% of primary spinal tumors, 0.3% of IM-SCT, each) were rare (Table 1).

3. high-grade (n = 34, 14% of spinal astrocytic tumors) and low-grade (n = 8, 14% of spinal astrocytic tumors) astrocytic tumors were 2.6 times more common (n = 140, 42.7% of IM-SCT) than astrocytic tumors (n = 57, 17.4% of IM-SCT) at SNUH for 10 years from 2012. The incidence of SP-EPNs, myxopapillary EPN, and spinal subEPN comprised 42.7%, 11.0%, and 3.0% of IM-SCT, respectively, at SNUH. The CNS WHO grade 3 SP-EPN was found in 0.5% of primary spinal tumors, 2.4% of IM-SCT, and 5.4% of SP-EPN. The common age for SP-EPN was middle-aged (median, 44 years; range, 2–73 years) with a slight female predominance (male:female ratio 1:1.1) (Table 1). Among the SNUH cases, the most common sites for SP-EPN were at the level of the cervical, lumbar, and thoracic (8:3:1).

4. SP-EPNs are usually well-circumscribed tumors and have typical perivascular pseudorosettes consisting of a central blood vessel and a surrounding anuclear fibrillary zone (Fig. 1) or true ependymal rosettes with lumina. Tumor cells are monotonous with uniformly round to oval nuclei and salt-and-pepper chromatin. The nucleoli are usually inconspicuous. CNS WHO grade 2 SP-EPNs have a low rate of mitosis rates and a low proliferation index, but necrosis may be present. Rarely, papillary and tanyctic subtypes are observed in the spinal cord. Tanyctic EPNs favor the spinal cord over the intracranial, but intratumoral hemorrhage is common (Fig. 2). CNS WHO grade 3 SP-EPNs exhibit high cellularity and brisk mitosis (≥ 20/10 high-power field) with microvascular proliferation, but nuclear pleomorphism is not obvious (Fig. 2). Invasion to the spinal cord parenchyma can occur in CNS WHO grade 3 EPN.
Table 1. Epidemiology of the intramedullary spinal cord tumors of SNUH cases, which are listed by their frequency in the spinal cord

| Diagnosis                                      | n = 329 | % of primary spinal tumors (n = 1,765) | % of IM-spinal tumors (n = 329) | Age (yr), median (range) | Sex, male: female | Known genetics                                                                 |
|------------------------------------------------|---------|----------------------------------------|---------------------------------|-------------------------|-------------------|--------------------------------------------------------------------------------|
| **Ependymal tumors**                           |         |                                        |                                 |                         |                   |                                                                                   |
| SP-EPN, CNS WHO grade 2                        | 140     | 7.9                                    | 42.6                            | 47 (6–73)               | 1:1               | Chromosome 22 deletion (1 copy loss) NF2 mutation or deletion                     |
| SP-EPN, CNS WHO grade 3                        | 7       | 0.4                                    | 2.1                             | 44 (2–49)               | 1:2               | + multiple copy number aberration                                                 |
| SP-EPN-MYCN                                     | 1       | 0.1                                    | 0.3                             | 49                      | Female            |                                                                                  |
| Myxopapillary EPN                              | 36      | 2.0                                    | 11.0                            | 40 (15–80)              | 1:25:1            | Unknown                                                                        |
| Spinal subEPN                                  | 10      | 0.6                                    | 3.0                             | 38 (21–57)              | 1:1               |                                                                                  |
| **Diffuse adult-type astrocytic tumors**        |         |                                        |                                 |                         |                   |                                                                                   |
| Astrocytoma, IDH-mutant                         | 0       |                                        |                                 |                         |                   | IDH1/2 mutation, ATRX mutation, TP53 mutation, CDKN2A/2B homozygous deletion     |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeleted | 0     |                                        |                                 |                         |                   | IDH1/2 mutation, 1p/19q-codeletion, CIC and/or FUBP1 mutation                    |
| GBM, IDH-wildtype, CNS WHO grade 4              | 21      | 1.2                                    | 6.4*                            | 37 (4–59)               | 1:2               | EGF amplification, PTEN homozygous deletion 7p gain/10 homozygous deletion, TERT promoter mutation, TP53 mutation |
| **Diffuse pediatric-type glioma**               |         |                                        |                                 |                         |                   |                                                                                   |
| Diffuse low-grade glioma                        | 8       | 0.5                                    | 2.4*                            | 37 (1–65)               | 1.5:1             | Unknown                                                                        |
| DMG, H3 K27M-altered                           | 13      | 0.7                                    | 4.0*                            | 32.5 (19–75)            | 1:1:6             | H3F3A K27M mutation TP53 mutation, ACVR1 mutation, ATRX mutation                 |
| **Circumscribed astrocytic tumors**             |         |                                        |                                 |                         |                   |                                                                                   |
| Pilocytic astrocytoma, G1                       | 15      | 0.8                                    | 4.6*                            | 37 (1–65)               | 1:1:2             | FGFR1: TACC1 fusion, BRAF V600E, KIAA1549-BRAF                                   |
| **Ganglioglioma and neuronal tumors**           |         |                                        |                                 |                         |                   |                                                                                   |
| Ganglioglioma                                   | 5       | 0.3                                    | 1.5                             | 5 (2–10)                | 3:2               | KIAA1549-BRAF fusion, NF1 mutation, BRAF V600E mutation                         |
| Diffuse leptomeningeal ganglioglioma tumor       | 1       | 0.1                                    | 0.3                             | 5 Years                 | Male              | KIAA1549-BRAF fusion, 1p/19 codeletion or 1p deletion or 19q deletion            |
| **CNS Embryonal tumor**                        |         |                                        |                                 |                         |                   |                                                                                   |
| Atypical teratoid/rhabdoid tumor                | 2       | 0.1                                    | 0.6                             | 2 Years                 | 0:1               | SMARCB1 homozygous deletion or SMCB1 mutation                                    |
| **Germ cell tumor**                             |         |                                        |                                 |                         |                   |                                                                                   |
| Germinoma                                       | 2       | 0.1                                    | 0.6                             | 22 (the same ages)      | 0:2               | ALK mutation, KIT mutation                                                       |
| **Mesenchymal, nonmeningothelial tumors involving spinal cord** | | | | | | |
| Hemangioblastoma                                | 66      | 3.7                                    | 20.0                            | 43 (27–76)              | 2:1               | VHL gene mutation                                                               |

IM, intramedullary; SP-EPN, spinal ependymoma; CNS, central nervous system; WHO, World Health Organization; IDH, isocitrate dehydrogenase; GBM, glioblastoma; DMG, diffuse midline glioma.

*Total astrocytic tumors including adult-type and pediatric-type diffuse gliomas and pilocytic astrocytoma was 17.4%.
All types of EPNs are positive for glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), S100 protein, and vimentin. GFAPs are usually more accentuated in the perivascular anucleated fibrillary zone but diffuse positivity is not uncommon. EMA positivity is represented by a dot-like or tiny ring-like appearance, which is an ultrastructural intracytoplasmic microrosette with microvilli and cilia. They are generally negative for oligodendrocyte transcription factor 2 (Olig2) and synaptophysin, and these markers are helpful for the differential diagnosis of astrocytic or neuronal tumors. Since SP-EPN does not show EZHIP overexpression or $H3K27me3$ loss in the immunohistochemical study, the presence of these 2 findings should first rule out the drop-down metastasis of posterior fossa group A-EPN. However, ZFTA-RELA fusion-positive primary SP-EPN has been reported.

Although SP-EPNs are morphologically similar to supratentorial and posterior fossa EPNs, the molecular genetics and methylation profiles of these SP-EPNs are different from those of intracranial EPNs. The most common genetic abnormalities of SP-EPNs are one copy loss of NF2 or NF2 mutations. CNS WHO grade 3 EPNs commonly have multiple chromosomal copy number aberrations, in addition to one copy loss of NF2 or NF2 mutations. According to Lee et al. the frequency of NF2 mutations in spinal and intracranial EPN was 32.1 and 4.4%, respectively.

$MYCN$ gene amplified SP-EPN ($SP-EPN-MYCN$) has been recognized as a rare subtype of SP-EPN characterized by multiple tumors and aggressive behavior. This SP-EPN-$MYCN$ has histopathological features of high-grade ependymoma, such as high cellularity, microvascular proliferation, brisk mitosis, tumor necrosis, and high MIB-1 proliferation index. Robust nuclear $MYCN$ expression or in situ hybridization with the $MYCN$ locus probe may be useful for detecting MYCN amplification, as well as NGS studies (Fig. 1D).

**MYXOPAPILLARY EPENDYMOMAS**

Myxopapillary EPNs, CNS WHO grade 2, are not uncommon, constituting approximately 11% of IM-SCTs in SNUH. These tumors commonly occur at the distal thoracic to lumbar region (T12 to L2, 3), including the sacrum and filum terminale, but rarely at the upper thoracic or cervical levels of the spinal cord. The median age of SNUH patients with myxopapillary EPNs was 40 years (range, 15–80 years). Grossly, these tumors are well-encapsulated and often dumbbell-shaped solid masses composed of hyalinized blood vessels and a myxoid or mucinous intercellular matrix. The tumor cells show a monotonous polygonal appearance but sometimes long bipolar fibrillary cytoplasmic processes. The nuclei are usually round to oval and
bland-looking, but sometimes enlarged nuclei is present due to degenerating atypia (Fig. 3). These tumors have a favorable prognosis with 10-year overall survival rates > 90%. Myxopapillary EPNs rarely metastasize to extraneural sites.

**SUBEPENDYMOMA**

SubEPNs are rare primary benign IM-SCTs classified as CNS WHO grade 1 tumors. In SNUH, they account for 0.6% of SPT and 3.0% of IM-SCT and usually occurred between 20 and 60 years (median, 38 years; range, 21–57 years). They commonly occur at cervical and thoracic levels. SP-subEPNs are well-circumscribed or well-encapsulated tumors that show typical microscopic features, including alternative cellular and acellular areas with microrosette-like multiple cell aggregates (Fig. 4). Metastases are extremely rare, and neither necrosis nor spinal cord invasion are observed. Degenerative nuclear atypia is rarely found, but is not a high-grade feature. Occasionally, in otherwise typical cases, fibrillar astroglial or gemistocytic cells may appear (Fig. 4). Immunohistochemical findings are similar to those of EPN; thus, GFAP is diffusely positive and might exhibit focal dot-like positivity for EMA, but negative for synapto-

Diffuse astrocytic tumors, including adult-type diffuse gliomas and pediatric-type diffuse gliomas

Astrocytomas constituted 17.4% of IM-SCT, including diffuse astrocytoma (n = 29, including 8 low- and 21 high-grade astrocytomas), DMG H3K27-altered (n = 13), and pilocytic astrocytoma (n = 15). Pilocytic astrocytoma, CNS WHO grade 1 was found in 4.6% of IM-SCT, diffuse low-grade gliomas (2.4% of IM-SCT), and diffuse high-grade glioma (DHGG, 10.4% of IM-SCT). In SNUH cases, GBM IDH-wildtype (6.4% of IM-SCT) and DMG H3 K27M-altered (4.0% of IM-SCT) were the most common malignant astrocytic tumors (DHGG).

According to Hamilton et al. only 13% of spinal gliomas,
including pediatric gliomas, was malignant. As the histopathology of spinal astrocytic tumors is similar to that of intracranial astrocytic tumors (Fig. 5), low grade gliomas (LGGs) have scant mitoses, no microvascular proliferation, no necrosis and low Ki-67 labeling index (Fig. 5B). GBM usually had pleomorphic nuclei of tumor cells, microvascular proliferation, and/or necrosis (Fig. 5A, C).

The genetics of spinal LGG is not well known because they are rare, but BRAF gene alterations have been reported. Most spinal GBMs were IDH-wildtype de novo tumors with EGFR amplification and/or PTEN or CDKN2A homozygous deletion, and TERT promoter and/or TP53 mutations have been found in the SNUH series, which is similar to the cases of Nagaishi et al. Although several cases of spinal IDH-mutant astrocytomas and spinal oligodendrogliomas have been reported, they are extremely rare. Hemispheric gliomas, such as diffuse hemispheric glioma, H3 G34-mutant, and infant-type hemispheric glioma, are also extremely rare.

DMG, H3 K27-altered in the spinal cord, is a relatively recently recognized aggressive glioma classified as CNS WHO grade 4. Since the median age of DMG H3 K27-altered was 32.5 years old (range, 19–75 years old) in SNUH cases, spinal DMG can occur at any age and is more common in adults. These tumors carry somatic mutations of H3F3A or HIST1H3B/C. Morphologically, DMG can have various grades of astrocytic tumors (Fig. 5D); therefore, it can appear as low-grade astrocytoma or typical GBM, or have a primitive neuroectodermal tumor-like appearance. The tumor cells were positive for GFAP, and the tumor cell nuclei were positive for the H3K27M-mutant specific antibody, K27M (Fig. 5D). However, spinal cord DMG H3 K27-altered has a slightly better prognosis than spinal GBM, CNS WHO grade 4, TP53, ATRX, and ACVR1 mutations commonly accompany these tumors. However, EGFR-mutant DMG, known as bithalamic glioma, and EZHIP-overexpressing spinal DMG have never been reported in the spinal cord.

**CIRCUMSCRIBED ASTROCYTIC GLIOMAS**

Pilocytic astrocytoma is a relatively well-circumscribed and indolent CNS WHO grade 1 astrocytoma. Although pilocytic astrocytoma commonly occurs in the posterior fossa and optic pathway in children and adolescents, spinal pilocytic astrocytoma accounted for 4.3% of all IM-spinal tumors at SNUH (Table 1). The age of onset of spinal pilocytic astrocytomas was slightly higher (median, 37 years; range, 1–65 years) than that of supratentorial tumors.

The histopathology of spinal pilocytic astrocytoma is similar to that of intracranial pilocytic astrocytoma, showing low cellularity and bland-looking elongated nuclei with bipolar cytoplasmic processes. Vascular hyalinization and rosenthal fibers are common (Fig. 6). Occasionally, degenerative nuclear atypia is observed.

Ninety percent of posterior fossa-pilocytic astrocytomas and 60% of optic pathway-pilocytic astrocytomas are known to have KIAA1549:BRAF fusion, and the remaining cases have mitogen-activated protein kinase (MAPK) pathway gene alterations, including BRAF V600E, NFI, PTPN11, and FGFR1 mutations. Although 40% of spinal pilocytic astrocytomas have KIAA1549:BRAF fusion, BRAF V600E mutation has been found in 4% of spinal pilocytic astrocytomas. Furthermore, homozygous deletion of CDKN2A is slightly more common in spinal cord and brainstem pilocytic astrocytoma than in cerebellar ones (21.1% vs. 33.3%). FGFR1:TACC1 fusion has been reported in pilo-
cytic astrocytoma occurring in the brainstem and near full-length of the cervical spinal cord of a 22-year-old female. One of our spinal pilocytic astrocytomas in a 65-year-old male had an FGFR1: TACC1 fusion. Other circumscribed astrocytic gliomas, such as high-grade astrocytoma with piloid features, pleomorphic xanthoastrocytoma, and MN1-altered astroblastoma, rarely occur in the IM-spinal cord; however, subependymal giant cell astrocytoma and chordoid glioma have never been reported in the spinal cord.

GLIONEURONAL AND NEURONAL TUMORS

Ganglioglioma, CNS WHO grade 1 was the most common glioma, accounting for 1.5% of primary IM-SCT in SNUH. DLGNT rarely occurred in the spinal cord (0.3% of IM-SCT).

Ganglioglioma is a relatively well-demarcated, slow-growing neoplasm of childhood. The median age of patients with ganglioglioma was 5 years old (range, 2–10 years) in SNUH. Sometimes, they involve the long segments of the spinal cord. Gangliogliomas are composed of 2 cell components, neoplastic ganglion cells and glial cells (Fig. 7). These tumors are usually caused by alterations in the MAPK signaling pathway, usually with a KIAA1549:BRaf fusion; however, BRaf V600E and NF1 (sometimes biallelic) mutations or deletions have also been observed. Very rarely, spinal gangliogliomas contain only H3K27M mutations.

DLGNT is a low-grade glioneuronal neoplasm characterized by widespread diffuse involvement of the leptomeninges and superficial brain parenchyma by monotonous oligodendroglioma-like cells with bidirectional differentiation. These tumors are commonly found in the subpial region of the basal surface of the brain, brainstem, and spinal cord. Genetically, KIAA1549: BRaf fusion was found in 72% of the studied cases while 1p and/or 19q deletion was found in other cases. 1p/19q codeletion has been identified in 18%–33%. Based on the methylation profiles, these tumors are classified into methylation classes 1 and 2 (MC1 and MC2). Although MC1 is roughly similar to CNS WHO grade 2 gliomas in clinical course, MC2 has anaplastic features, 1q gain, and/or a worse prognosis than MC1.

CNS EMBRYONAL TUMORS

Among embryonal tumors, AT/RT, CNS WHO grade 4, rarely occur in the IM-spinal cord of infants (0.6% of IM-SCT), while other embryonal tumors are extremely rare. Approximately 7.6%
The pathological classification of intramedullary spinal cord tumors described in the text involves a detailed examination of various tumor types, including atypical teratoid rhabdoid tumor (AT/RT), germ cell tumors, and hemangioblastomas. Each type is characterized by specific histological and genetic features.

**AT/RT**
- **Pathology**: Monotonous small round cell tumor with an eccentric nucleus and a prominent eosinophilic rhabdoid appearance.
- **Genetics**: Characterized by SMARCB1 mutations or homozygous deletions.
- **Clinical Features**: Metastasis of extracranial malignant rhabdoid tumor should be ruled out first.

**Germ Cell Tumors**
- **Mature Cystic Teratomas**, **Immature Teratomas**, and **Pure Germinomas** can occur in the spinal cord. In the SNUH series, germinomas are rare, occurring in 0.1% of SPT and 0.6% of IM-SCT.
- **Histopathology**:
  - Germinomas consist of malignant germ cells and lymphoplasma cells.
  - Primitive neuroepithelial tubules are present.

**Hemangioblastomas**
- **CNS WHO Grade 1**, accounting for 3.7% of IM-SCT.

These tumors are characterized by specific histological features and genetic mutations, aiding in their differential diagnosis.

---

**Fig. 8.** Atypical teratoid rhabdoid tumor. (A) Magnetic resonance imaging shows a 2.8-cm elongated epidural enhancing mass between C5 and T1. (B) Light microscopically the tumor shows small round cells with eccentrically located nuclei and eosinophilic cytoplasm (arrows), which is a rhabdoid feature. (C) The tumor cell nuclei are negative for INI-1, but include internal control, such as endothelial cells and some inflammatory cells are positive for INI-1 (INI-1 immunohistochemistry; scale, 50 μm). (D) The tumor cells are at least focal positive for epithelial membrane antigen (EMA; scale, 50 μm).

**Fig. 9.** Germinoma. (A) Magnetic resonance imaging shows T2 heterogeneous intensity mass at T12–L1 spinal cord, involving conus medullaris. (B) The tumor is composed of biphasic, malignant germ cells and lymphplasma cells (H&E; scale, 20 μm). The malignant germ cells show large round nuclei and prominent nucleoli. There are frequent mitoses. (C) The tumor cell membrane is positive for c-kit (scale, 50 μm), and (D) placental alkaline phosphatase (PLAP; scale, 50 μm).
Hemangioblastomas do not undergo malignant transformations. However, both IM and EM hemangioblastomas have been reported. In SNUH cases, hemangioblastoma was 1.5 times more common than astrocytic tumors and 1/3 less common than SP-EPN. Hemangioblastomas are adult tumors that occur in a wide range of patients (mean age, 43 years; range, 16–81 years). The male to female ratio was 2:1. Hemangioblastomas occur at any level from the cervical spine to the lumbar spinal cord. The tumors are well-circumscribed, pseudoencapsulated, and capillary-rich solid tumors. The tumor cells are stromal cells with foamy cytoplasm, and the capillaries are nonneoplastic components (Fig. 10). Ultrastructurally, tumor cells have many cytoplasmic fat vacuoles and intermediate filaments, which produce foamy cytoplasm on H&E staining. Tumor cells express NSE, S100, alpha-inhibin, D2-40, and brachyury (cytoplasmic expression), which can help in the differential diagnosis. The pathogenesis and cells of origin remain unknown. In rare cases, hyaline globules are present. This tumor may be sporadic or be associated with von Hippel-Lindau disease. However, the tumor usually has various kinds of VHL gene mutations, such as missense, slicing, insertion, or deletion mutations.

When the tumor is completely removed, the prognosis is good.

CONCLUSION

Theoretically, any type of primary CNS tumor can occur in the intramedullary spinal cord; however, the most common IM-SCT is EPN, followed by hemangioblastoma and astrocytoma. SP-EPN and SP.subEPN are morphologically identical to those of the supratentorial or posterior fossa, but their molecular genetic and methylation profiles differ from those of intracranial EPN. Therefore, these tumors should have ‘spinal’ in the tumor name. DLGNT can arise in the spinal cord and are characterized by a KIAA1549:BRAF fusion, 1p and/or 19q deletion, or 19q gain. In addition, some spinal pilocytic astrocytomas are characterized by FGFR1:TACC1 fusion, in addition to alterations in the MAPK pathway. Myxopapillary ependymomas characteristically occur in the lumbosacral area and are regarded as CNS WHO grade 2. Although spinal DMG H3 K27M-altered is a high-grade glioma, the biological behavior of spinal DMG is better than that of spinal GBM IDH-wildtype, CNS WHO grade 4. Rarely, pilocytic astrocytoma, ganglioglioma, diffuse leptomeningeal glioma, and atypical teratoid rhabdoid tumors occur in IM-SCT; they may share a KIAA1549:BRAF fusion. However, although several cases of spinal IDH-mutant astrocytomas have been reported, hemispheric gliomas (such as diffuse hemispheric glioma, H3 G34-mutant, and infant-type hemispheric glioma) or IDH-mutant gliomas (including IDH-mutant astrocytoma and oligodendroglioma) are extremely rare.

NOTES

Ethics Statement: The institutional review board of our hospital approved this study (IRB No: 2202-097-1301) and has therefore been performed under the ethical standards set out in the 1964 Declaration of Helsinki and its subsequent amendments. As this study is a retrospective review of anonymized electronic medical records, pathology, and results of NGS data utilizing a brain tumor-specific somatic gene panel, informed consent was waived from our IRB under the Korean Bioethics and Safety Act. All materials had been obtained for the electronic medical record of the patients, which were anonymized and retrospectively reviewed. No extra-human materials were obtained from the patients for this study. Under the Korean Bioethics and Safety Act, additional consent to publish was waived.

Conflict of Interest: The authors have nothing to disclose.

Funding/Support: This study was supported by a grant from
the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: H14C1277).

**Author Contribution:** Conceptualization: SP; Data curation: JKW, CHK, JHP, SK, SC, CKC; Writing - original draft: SP; Writing - review & editing: SP

**ORCID**

Sung-Hye Park: 0000-0002-8681-1597  
Jae Kyung Won: 0000-0003-1459-8093  
Chi Heon Kim: 0000-0003-0497-1130  
Ji Hoon Phi: 0000-0002-9603-5843  
Seung-Ki Kim: 0000-0002-0039-0083  
Seung-Hong Choi: 0000-0002-0412-2270  
Chun Kee Chung: 0000-0003-3485-2327

**REFERENCES**

1. Abd-El-Barr MM, Huang KT, Moses ZB, et al. Recent advances in intradural spinal tumors. Neuro Oncol 2018;20:729-42.
2. Chamberlain MC, Tredway TL. Adult primary intradural spinal cord tumors: a review. Curr Neurol Neurosci Rep 2011;11:320-8.
3. Witt H, Gramatzki D, Hentschel B, et al. DNA methylation-based classification of ependymomas in adulthood: implications for diagnosis and treatment. Neuro Oncol 2018;20:1616-24.
4. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 2021;23:1231-51.
5. Sloan EA, Chiang J, Villanueva-Meyer JE, et al. Intracranial mesenchymal tumor with FET-CREB fusion-A unifying diagnosis for the spectrum of intracranial myxoid mesenchymal tumors and angiomatoid fibrous histiocytoma-like neoplasms. Brain Pathol 2021;31:e12918.
6. Alexandrescu S, Meredith DM, Lidov HG, et al. Loss of histone H3 trimethylation on lysine 27 and nuclear expression of transducin-like enhancer 1 in primary intracranial sarcoma, DICER1-mutant. Histopathology 2021;78:265-75.
7. Sakaguchi M, Nakano Y, Honda-Kitahara M, et al. Two cases of primary supratentorial intracranial rhabdomyosarcoma with DICER1 mutation which may belong to a “spindle cell sarcoma with rhabdomyosarcoma-like feature, DICER1 mutant”. Brain Tumor Pathol 2019;36:174-82.
8. Yang S, Liu L, Yan Y, et al. CIC-NUTM1 sarcomas affecting the spine. Arch Pathol Lab Med 2022;146:735-41.
9. Koeller KK, Shih RY. Intradural extramedullary spinal neoplasms: radiologic-pathologic correlation. Radiographics 2019;39:468-90.
10. Lamszus K, Lachenmayer L, Heinemann U, et al. Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. Int J Cancer 2001;91:803-8.
11. Leeper H, Felicella MM, Walbert T. Recent advances in the classification and treatment of ependymomas. Curr Treat Options Oncol 2017;18:55.
12. Lim KY, Lee KH, Phi JH, et al. ZFTA-YAP1 fusion-positive ependymoma can occur in the spinal cord: Letter to the editor. Brain Pathol 2022;32:e13020.
13. Cho HJ, Park HY, Kim K, et al. Methylation and molecular profiles of ependymoma: influence of patient age and tumor anatomic location. Mol Clin Oncol 2021;14:88.
14. Ahmad O, Chapman R, Storer LC, et al. Integrative molecular characterization of pediatric spinal ependymoma: the UK Children’s Cancer and Leukaemia Group study. Neurooncol Adv 2021;3:vdab043.
15. Zemmoura I, Vourc’h P, Paubel A, et al. A deletion causing NF2 exon 9 skipping is associated with familial autosomal dominant intramedullary ependymoma. Neuro Oncol 2014;16:250-5.
16. Lim KY, Lee K, Shim Y, et al. Molecular subtyping of ependymoma and prognostic impact of Ki-67. Brain Tumor Pathol 2022;39:1-13.
17. Lee CH, Chung CK, Kim CH. Genetic differences on intracranial versus spinal cord ependymal tumors: a meta-analysis of genetic researches. Eur Spine J 2016;25:3942-51.
18. Ghasemi DR, Sill M, Okonechnikov K, et al. MYCN amplification drives an aggressive form of spinal ependymoma. Acta Neuropathol 2019;138:1075-89.
19. Acri F, Vetrano IG, Sattin T, et al. The role of indocyanine green videoangiography with FLOW 800 analysis for the surgical management of central nervous system tumors: an update. Neurosurg Focus 2018;44:E6.
20. Abdallah A, Emel E, Gunduz HB, et al. Long-term surgical resection outcomes of pediatric myxopapillary ependymoma: experience of two centers and brief literature review. World Neurosurg 2020;136:e245-61.
21. Fujimori T, Iwasaki M, Nagamoto Y, et al. Extraneural metastasis of ependymoma in the cauda equina. Global Spine J 2013;3:33-40.
22. Fischer SB, Attenhofer M, Gultekin SH, et al. TRPS1 gene
alterations in human subependymoma. J Neurooncol 2017; 134:133-8.

23. Yuh WT, Chung CK, Park SH, et al. Spinal cord subependymoma surgery: a multi-institutional experience. J Korean Neurosurg Soc 2018;61:233-42.

24. Hamilton KR, Lee SS, Urquhart JC, et al. A systematic review of outcome in intramedullary ependymomas and astrocytoma. J Clin Neurosci 2019;63:147-50.

25. Shankar GM, Lelic N, Gill CM, et al. BRAF alteration status and the histone H3F3A gene K27M mutation segregate spinal cord astrocytoma histology. Acta Neuropathol 2016;131: 1014-35.

26. Nagaishi M, Nobusawa S, Yokoo H, et al. Genetic mutations in grade IV gliomas of the adult spinal cord. Brain Tumor Pathol 2016;33:267-9.

27. Konovalov NA, Asyutin DS, Shayhaev EG, et al. Rare cases of IDH1 mutations in spinal cord astrocytomas. Acta Neurochir 2021;163:1201-7.

28. Solomon DA, Wood MD, Tihan T, et al. Diffuse midline gliomas with histone H3-K27M mutation: a series of 47 cases assessing the spectrum of morphologic variation and associated genetic alterations. Brain Pathol 2016;26:569-80.

29. Balasubramanian A, Gunjur A, Gan HK, et al. Response to combined RAF/MEK inhibition in adult RAF V600E mutant spinal pilocytic astrocytoma. J Clin Oncol 2019;37:1-9.

30. Rossini S, Rodriguez FJ, Mota RA, et al. Primary leptomeningeal oligodendroglioma with documented progression to anaplasia and t(1;19)(q10;p10) in a child. Acta Neuropathol 2009;118:575-7.

31. Deng MY, Sill M, Chiang J, et al. Molecularly defined diffuse leptomeningeal gliounuclear tumor (DLGNT) comprises two subgroups with distinct clinical and genetic features. Acta Neuropathol 2018;136:239-53.

32. Sali AP, Epari S, Nagaraj TS, et al. Atypical teratoid/rhabdoid tumor: revisiting histomorphology and immunohistochemistry with analysis of cyclin D1 overexpression and MYC amplification. Int J Surg Pathol 2021;29:155-64.

33. Hasselblatt M, Thomas C, Hovestadt V, et al. Poorly differentiated chordoma with SMARC1/INI1 loss: a distinct molecular entity with dismal prognosis. Acta Neuropathol 2016;132:149-51.

34. Phi JH. Sacrococcygeal teratoma: a tumor at the center of embryogenesis. J Korean Neurosurg Soc 2021;64:406-13.
toms and high cell proliferative activity in intra- and extra-medullary spinal hemangioblastoma: a need for earlier surgery. Global Spine J 2017;7:6-13.

49. Arumalla K, Deora H, Rao S, et al. Spinal extradural hemangioblastoma: A systematic review of characteristics and outcomes. J Craniovertebr Junction Spine 2020;11:254-61.

50. Roy S, Chu A, Trojanowski JQ, et al. D2-40, a novel monoclonal antibody against the M2A antigen as a marker to distinguish hemangioblastomas from renal cell carcinomas. Acta Neuropathol 2005;109:497-502.

51. Li J, Jiang XH, Chen AQ, et al. Surgical management of a cervical intramedullary hemangioblastoma presenting with intracystic hemorrhage by hemi-semi-laminectomy via a posterior approach. J Int Med Res 2019;47:3458-64.

52. Shankar GM, Taylor-Weiner A, Lelic N, et al. Sporadic hemangioblastomas are characterized by cryptic VHL inactivation. Acta Neuropathol Commun 2014;2:167.

53. Sadashivam S, Abraham M, Kesavapisharady K, et al. Long-term outcome and prognostic factors of intramedullary spinal hemangioblastomas. Neurosurg Rev 2020;43:169-75.