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Rare Primary CNS Tumors Encountered in Pediatrics

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Abstract

As part of the special issue on Pediatric Neuro-Oncology, this article will focus on four of the rarer tumors in this spectrum, including atypical teratoid rhabdoid tumors, embryonal tumors with multilayered rosettes, choroid plexus tumors, and pleomorphic xanthoastrocytoma. Incidence, and current understanding of the molecular pathogenesis of these tumors is discussed, and avenues of therapy both current and prospective are explored.

Keywords

Rare tumors; pediatric oncology; CNS malignancies

Introduction

The staggering number of histopathologic variants of childhood malignancies is most readily apparent in considering those affecting the central nervous system. A comprehensive list of the rare malignancies (accounting for less than 5% of all pediatric CNS tumors) is found on Table 1; this chapter will focus on four of the more frequently encountered tumors within the rare spectrum, including atypical teratoid rhabdoid tumors, embryonal tumors with multilayered rosettes, choroid plexus tumors, and pleomorphic xanthoastrocytoma.

1) Atypical teratoid rhabdoid tumors

As a distinct pathologic entity, atypical teratoid rhabdoid tumors are highly malignant primary central nervous system embryonal tumors, estimated to account for less than 5% of all pediatric CNS tumors.¹ Atypical teratoid rhabdoid tumors are encountered in infants and young children, predominantly under 5 years of age², and are exceedingly rare in adults. The median age at diagnosis is 17 months, with a male predominance.³ About 50% of atypical teratoid rhabdoid tumors arise in the posterior fossa, with up to 40% demonstrating leptomeningeal spread at the time of diagnosis.⁴

Pathology and Genetics—As a highly malignant tumor, atypical teratoid rhabdoid tumors are comprised of sheets of rhabdoid cells, admixed with both epithelial and

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mesenchymal elements, WHO grade IV. Mitoses are abundant (Figure 1). With a small cell component, these tumors can be erroneously classified as medulloblastomas or other embryonal tumors, and epithelial cells may mistakenly suggest teratoma. Immunohistochemistry is noted for expression of both epithelial membrane antigen and vimentin.⁵ As one of the first pediatric malignancies associated with a tumor suppressor gene, Rorke et al. first reported the link between atypical teratoid rhabdoid tumors and chromosome 22.³ Biegel and colleagues identified germ-line and acquired mutations of the INI-1 gene, which maps to chromosome 22q11.2⁶, accounting for the hallmark and invariable loss of INI-1 expression in the final analysis. Many names for this tumor suppressor gene have appeared in the literature.⁷ The hSNF5/INI1 gene encodes for a component of the SWI/SNF Sucrose Non-Fermenting gene number 5 (SNF5) ATP-dependent chromatin remodeling complex that appears to play an important role at the G1/S cell cycle checkpoint.^{6, 7} Most recently, the name *SMARCB1* has been used to correspond to the SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1. The majority of atypical teratoid rhabdoid tumors demonstrate bi-allelic inactivating mutations in the *SMARCB1* gene.⁷

Treatment and Prognosis—Atypical teratoid rhabdoid tumors remain challenging tumors to cure, historically having a median survival of 12-17 months⁸ despite aggressive therapy. There are no definitive treatment guidelines for this highly aggressive malignancy. Diagnosis is made following a surgical partial or gross total resection, although the prognostic significance of tumor location or degree of tumor resection is unclear. Multimodality therapy with multi-agent chemotherapy having backbones of doxorubicin, cyclophosphamide, vincristine, ifosfamide, cisplatin, etoposide and/or high dose chemotherapy with stem cell support has been shown to improve progression-free survival.⁹⁻¹⁵ Chemotherapy has been used in the adjuvant setting and also may help to delay radiotherapy in this young population. Many studies incorporate intrathecal chemotherapy, most commonly methotrexate and previously available mafosfamide^{9, 16} and may be particularly important in the child for whom radiation therapy is not being considered. Recent studies support the use of 3D-conformal treatment plans with focal radiotherapy; pencil beam proton therapy to improve survival and maintain quality of life for the very young child is also an attractive alternative.¹⁷

Newer Investigational Agents—The mainstay of therapy for ATRT now is surgery, radiation and high dose cytotoxic therapy. However, minimizing treatment related morbidity in very young children, along with an increased understanding of the pathogenetics of atypical teratoid rhabdoid tumors comes the promise of effective therapeutic targets including Aurora Kinase, Cyclin D1 and IGF-1R. Aurora Kinase A (AURKA) encodes a protein that regulates the formation and stability of the mitotic spindle and is highly active in atypical teratoid rhabdoid tumors through loss of the INI1. Alisertib (MLN8237) inhibits AURKA in vitro and in vivo; single-agent alisertib has manageable toxicities and modest reductions in tumor burden.¹⁸ Cyclin D1 appears to drive primary atypical teratoid rhabdoid tumors and as such, may be an effective therapeutic target.¹⁹ IGF-1R is more highly expressed in atypical teratoid rhabdoid tumors compared to both normal brain and other childhood CNS malignancies, supporting the ongoing investigations with agents directed at

IGF-1R.²⁰ Specifically targeted agents are all at various stages of clinical development and offer promise for improvement in the control of this challenging malignancy.

2) Embryonal tumor with multilayered rosettes/ Embryonal Tumor with Abundant Neuropil and True Rosettes (ETMR/ETANTR)

As a distinct histopathologic entity, embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a rare subtype of primitive neuroectodermal tumors first reported in 2000 by Eberhart et al, with a few hundred patients being diagnosed to date.²¹ It is generally viewed as a variety of primitive neuroectodermal tumor combining pathologic features of neuroblastoma and ependymblastoma²², with notable areas of fibrillary neuropil admixed with cellular ependymblastic rosettes, occasionally with neurocytic differentiation.²³ These typical histopathologic features are often combined with unique chromosome 19q13.42 amplification²⁴ and/or LIN28 expression²⁵, and are used to confirm the diagnosis. Korshunov and colleagues performed a comprehensive clinical, pathological, and molecular analysis of 97 cases of these rare tumors, including genome-wide DNA methylation and copy number profiling of 41 tumors, and identified uniform molecular signatures in all tumors irrespective of histological patterns, indicating that ETANTR, ependymblastoma and medulloepithelioma comprise a single biological entity.²⁶ This has more recently led to these tumors collectively being referred to as embryonal tumors with multilayered rosettes (ETMR).

Gessi et al. have reviewed the clinical scenarios associated with the highest number of patients to date, 29.²⁷ The tumor almost exclusively occurs in children less than 4 years of age with a clear predominance of females. Tumors appear more prevalent in the supratentorial than in the infratentorial compartment. Clinical symptoms at presentation include raised intracranial pressure, epilepsy, hemiparesis, symptoms of cerebellar involvement, or with cranial nerve involvement. No established management protocol exists. Despite multimodality treatment regimens involving high dose alkylator chemotherapy and radiation therapy, ETMR/ETANTRs are generally considered highly aggressive embryonal neoplasms, and at present, carry a near uniformly lethal outcome. Recent information reported from Jabado and colleagues identified overexpression of a developmental enzyme – DNMT3B- in ETMR/ETANTRs.²⁸ Further research is attempting to control the levels of DNMT3B and correlate this with tumor cell survival in vitro. Such studies hold promise for identifying treatment strategies that may improve survival.

3) Choroid Plexus Tumors

Tumors arising from the choroid plexus producing cerebrospinal fluid are uncommon, accounting for less than 1% of all CNS tumors. Encountered in all age groups, they are more commonly seen in childhood. They may display a benign (choroid plexus papilloma) or malignant (choroid plexus carcinoma) phenotype. Although the cause is unknown, choroid plexus tumors are a feature in patients with Li-Fraumeni syndrome and its variant Li-Fraumeni-like syndrome and the diagnosis should prompt further genetic testing.

Recent findings have implicated Notch3 signaling, the transcription factor TWIST1, platelet-derived growth factor receptor, and the tumor necrosis factor-related apoptosis-inducing

ligand pathway in choroid plexus papilloma tumorigenesis.²⁹ While generally considered benign, choroid plexus papillomas and the even rarer atypical CPP subset interestingly harbor a number of chromosomal abnormalities.³⁰ Surgical resection remains the standard of care, affording most patients excellent long term survival. Multimodality therapy including chemotherapy and radiotherapy is generally reserved for recurrent and/or metastatic lesions.

Unlike its benign counterpart, choroid plexus carcinomas are diagnosed histopathologically by transgression of the ependymal lining and invasion into adjacent brain parenchyma, and nuclear atypia in conjunction with Ki67/MIB1 labeling consistent with cellular proliferation. Somatic mutations in TP53 are observed in up to 60% of choroid plexus carcinomas. Though they rarely metastasize outside the central nervous system, dissemination throughout the cerebrospinal fluid pathway is not uncommon.

Both choroid plexus papillomas and choroid plexus carcinomas result in overproduction of cerebrospinal fluid, often leading to hydrocephalus and signs of raised intracranial pressure. Aggressive surgical treatment with gross total resection significantly impacts prognosis. For choroid plexus carcinomas, particularly in the setting of Li-Fraumeni syndrome, post operative radiation therapy is used judiciously and is generally reserved for patients who underwent a subtotal resection, children >3 years of age, or patients with leptomeningeal spread. Finlay and colleagues recently reported a series of 12 children with choroid plexus carcinoma (median age of 19.5 months) treated with high dose multi-agent chemotherapy regimens alone: 10 patients had >95% surgical resection, and 3 patients had disseminated disease at diagnosis. Ten patients completed consolidation of whom five are alive, irradiation and disease free at 29, 43, 61, 66 and 89 months from diagnosis. Seven patients experienced tumor recurrence/progression at a median time of 13 months (range 2–43 months). Five patients received irradiation, one for residual disease and four upon progression or recurrence, of whom one is alive at 61 months. The 3- and 5-year progression-free survivals are 58% and 38% and overall survivals 83% and 62%, respectively. Late deaths from disease beyond 5 years were also noted.³¹ Such chemotherapy-only strategies may produce long-term remission in young children with newly diagnosed choroid plexus carcinoma with avoidance of cranial irradiation. In the relapsed or progressive setting, however, long-term survival remains poor.³²

4) Pleomorphic Xanthoastrocytoma

Although this rare tumor may be encountered at any age, pleomorphic xanthoastrocytomas most commonly affect children and young adults. Rare morphologic variants exist, with characteristic histological features of pleomorphic xanthoastrocytoma including pleomorphic, giant and spindle-shaped tumor cells, with pale and intensively eosinophilic granular bodies; degrees of anaplasia may be present.³³ Known chromosomal imbalances include losses of 9p21.3 and p16 expression.³⁴ pleomorphic xanthoastrocytomas are now readily classified by the presence of BRAFV600E mutations in combination with the lack of IDH-1 mutations.³³ pleomorphic xanthoastrocytomas have been noted to have the highest frequencies of BRAFV600E mutation among primary CNS neoplasms.³⁵⁻³⁷ This mutation, present in the majority of tumors, can be readily identified by immunohistochemistry and is an attractive therapeutic target.

Significant progress has been made to expand our knowledge on the natural history and molecular features of pleomorphic xanthoastrocytoma.³⁸⁻⁴⁰ Ida and colleagues have provided one of the most comprehensive studies correlating histopathology, cytogenetics and natural history of the disease.³³ Patients most commonly presented with a supratentorial contrast enhancing tumor, with seizures representing the most common clinical symptom at diagnosis. Confirmed in a number of studies, patients with a favorable prognosis include those with low mitotic index, lack of tumor necrosis and/or anaplasia and presence of BRAFV600E mutation. Given the limited role for chemotherapy and radiation therapy, gross total surgical excision significantly correlates with improved survival.^{33, 41}

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Figure 1.
Histology demonstrating classic pathologic features of rhabdoid cells of atypical teratoid rhabdoid tumors.

TABLE 1

Rare Histologies Encountered in Pediatric CNS Tumors

Histologic Type
Embryonal
Atypical Teratoid /Rhabdoid Tumor
Embryonal Tumor Multilayered Rosettes
- Embryonal Tumor Abundant Neuropil True Rosettes
-Ependymoblastoma
- Medulloepithelioma
Medulloblastoma
Neuronal Tumors
Ganglioglioma
Gangliocytoma
Neurocytoma
Dysembryoplastic Neuroepithelial Tumor
Choroid Plexus Tumors
Choroid Plexus Papilloma
Anaplastic Choroid Plexus Tumor
Choroid Plexus Carcinoma
Pituitary Adenomas
Other
-Gliosarcoma
-Hemangiopericytoma
-Pilomyxoid astrocytoma
-Pleomorphic xanthoastrocytoma