Introduction

Central nervous system primitive neuroectodermal tumors: still a useful classification?

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The terminology for small, round, blue cell tumors of the CNS has been confusing from the beginning. The initial description of medulloblastoma by Baily and Cushing[1] in 1925 suggested that the cell of origin was the medulloblast, a cell type now considered not to exist. Because of phenotypic similarities, Hart and Earle,[2] in 1973, lumped a group of pediatric brain tumors previously known as medulloblastoma, pineoblastoma, cerebral neuroblastoma, and so on into a group of tumors they called primitive neuroectodermal tumors (PNETs). Since this time, much has been written about PNETs, their cell of origin, molecular biology, clinical behavior, and prognosis. Of note, these CNS PNETs are entirely different from the peripheral nervous system PNETs characterized by a translocation between chromosomes 11 and 22.

With the advent of molecular biology techniques including transcriptional profiling, exon-array, and single-nucleotide polymorphism–array technologies, the distinctions between cerebellar medulloblastoma and supratentorial PNETs have become better defined. In 2002, Pomeroy and colleagues[5] used transcriptional profiling to show that supratentorial PNETs and atypical teratoid tumors were distinct from each other and quite distinct from medulloblastomas. In addition, they showed that these 3 groups of tumors had distinctly different prognoses. Prior to this work, 2 different, mutually exclusive genetic alterations had been described in medulloblastoma by Raffel and coworkers.[6,9] One group had mutations in the sonic hedgehog pathway, the other in the Wnt pathway. The work of Pomeroy and colleagues also suggested that medulloblastoma may encompass more than a single tumor type, as the tumors with sonic hedgehog pathway alterations were distinguishable from other medulloblastomas by their gene expression pattern.[5] Building on this work, Dr. Michael Taylor and his group have shown that medulloblastomas can be divided into at least 4 subtypes based on their gene expression profiles. The age at presentation and prognosis are distinct for each subtype, suggesting that these are really different tumors.[4] These authors suggest that the differences may result from differing cells of origin giving rise to each tumor type, a hypothesis supported by the others.[7,8] Interestingly, the Group C subtype seems to carry an especially grim prognosis, being responsible for most cases of CSF dissemination and death in the medulloblastomas as a whole. Information about nonmedulloblastoma PNETs has been more scarce. For example, Li et al.[3] have recently reported on the use of advanced genetic strategies to identify frequent amplification of a microRNA polycistron on chromosome 19 in aggressive PNETs. Overall, the work on the subclassification of these tumors suggests that the term PNET may have outlived its usefulness for CNS tumors and that each different tumor previously included in the classification should be identified by its unique name.

In this issue of *Neurosurgical Focus*, 3 papers on PNETs are published. In the first paper, the authors present 2 cases of intraspinal tumors. One tumor is intramedullary, and the other, occurring in the region of the conus medullaris, appears to be intradural, extramedullary in location. Of note, both patients underwent appropriate workup to ensure that the spinal tumors did not represent drop metastases from a medulloblastoma. Although drop metastases into the CSF have been well reported, intramedullary metastases, usually in the cervical spinal cord, have been reported and hypothesized to be caused by cells falling into the central canal of the cord. This article provides a comprehensive review of the topic, including a discussion of the molecular changes seen in PNETs, along with the incidence and special features of intraspinal tumors.

In the second paper in the issue, the authors present 2 cases of the recently described "embryonal tumor with

abundant neuropil and true rosettes" (ETANTR). These tumors, classified within the PNETs, are clearly a distinct tumor type. An ETANTR is a malignant tumor presenting in young children, and the authors describe the case of a patient who survived for 7 years, the longest period yet reported for this rare tumor. The authors provide an excellent review of this rare, recently described tumor type, with careful presentation of the ETANTR's clinical outcomes, cytogenetic changes, and relationships with medulloblastoma and ependymoblastoma.

The third paper in this issue of *Neurosurgical Focus* focuses on a case of supratentorial PNET appearing in a patient after radiotherapy was performed for a craniopharyngioma. As mentioned in the paper, 4 criteria are needed to identify a tumor as being likely induced by radiotherapy: 1) the tumor in question must arise in the irradiated field, 2) sufficient time must have elapsed between the irradiation and the appearance of the tumor in question, 3) the patient cannot have a syndrome that predisposed him/her to the tumor in question, and 4) the tumor in question must be easily differentiated from the initial tumor for which the irradiation was delivered. The case presented in this paper seems to meet these criteria because the PNET arose in the field of irradiation delivered to treat the initial craniopharyngioma, the PNET presented 8 years after radiotherapy, the patient was not known to have any of the syndromes associated with the development of PNETs, and the 2 tumors were distinctly different. Although other reports of radiation-induced PNETs exist and are referenced in this paper, the current case is of interest because the patient was treated with radiation therapy without adjuvant chemotherapy, a common combination in other reports of radiation-induced PNETs, indicating that irradiation alone may in rare cases cause the PNET. *(DOI: 10.3171/2011.1.FOCUS.Intro)*

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Primitive neuroectodermal tumors of the spine: a comprehensive review with illustrative clinical cases

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Primary spinal primitive neuroectodermal tumors (PNETs) are uncommon malignancies that are increasingly reported in the literature. Spinal PNETs, like their cranial counterparts, are aggressive tumors and patients with these tumors typically have short survival times despite maximal surgery, chemotherapy, and radiation. Because no standard management guidelines exist for treating these tumors, a multitude of therapeutic strategies have been employed with varying success. In this study the authors perform a comprehensive review of the literature on primary spinal PNETs and provide 2 new cases that highlight the salient features of their clinical management. (DOI: 10.3171/2010.10.FOCUS10217)

PRIMITIVE neuroectodermal tumors are a heterogeneous group of malignant neoplasms that occur mostly in childhood and early adulthood. Histologically the PNET cells exhibit a primitive, poorly differentiated morphology with varying degrees of pleomorphism and occasional evidence of neuroectodermal differentiation. Primary spinal PNETs represent a small percentage of these tumors. Like all PNETs, they can fall into 1 of 2 categories: CNS PNETs or central PNETs, and Ewing sarcoma/PNETs or peripheral PNETs. Due to the low incidence of these tumors, the available epidemiology is likely unreliable, and there are currently no standard clinical guidelines outlining their management. In addition, the existing literature on primary spinal PNETs consists mostly of case reports with a variety of clinical presentations, management recommendations, and outcomes data indicating a need for further study.

In this paper we present 2 illustrative cases demonstrating the clinical management of patients with primary spinal PNETs followed by a comprehensive review of the literature on these tumors. To our knowledge, our report contains the first account of an acutely presenting hemorrhagic cervical intramedullary PNET. While most authors describe spinal PNETs as "very rare," we identified 82 cases (including ours) in the literature, 41 more than the highest reported number to date.[3,40,43]

Abbreviations used in this paper: GTR = gross-total resection; PNET = primitive neuroectodermal tumor; STR = subtotal resection.

Case Illustrations

Case 1

Presentation. This 27-year-old man with no significant medical history presented to the emergency department of a different hospital complaining of rapidly progressive ascending weakness and sensory changes involving the lower extremities, chest, and upper extremities over a period of hours. The patient described new-onset, bilateral, lower extremity numbness starting 9 days prior to his emergency department arrival and mild bilateral lower-extremity weakness and gait instability for 2 days prior to his emergency department arrival. The patient's condition continued to progress and he became quadriplegic with complete sensory and motor loss below the shoulders (C-5) without evidence of cardiopulmonary compromise. An MR image of the spine demonstrated a 1 × 4 cm expansile intramedullary lesion partially obliterating the spinal canal from the C-5 to the C-7 vertebrae (Fig. 1A). The lesion was hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging sequences with minimal contrast enhancement (Fig. 1A-C). Gradient echo MR imaging suggested the presence of blood products within the lesion (Fig. 1D). Ependymoma, astrocytoma, and hemangioblastoma were considered in the differential diagnosis. The patient was urgently transferred to our institution at the request of his family. Upon arrival in our neurological intensive care unit 24 hours after the onset of complete
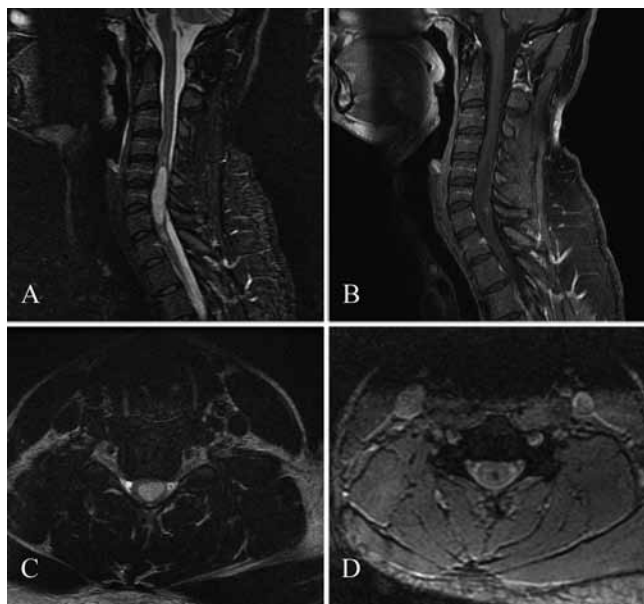
FIG. 1. Preoperative MR imaging in Case 1. **A and C:** Sagittal **(A)** and axial **(C)** T2-weighted images demonstrating a hyperintense cervical intramedullary lesion. **B:** Sagittal T1-weighted postcontrast image demonstrating a hypointense lesion with a small inferior region of enhancement. **D:** Axial T2*-weighted gradient echo image demonstrating central cord hypointensity consistent with blood products.
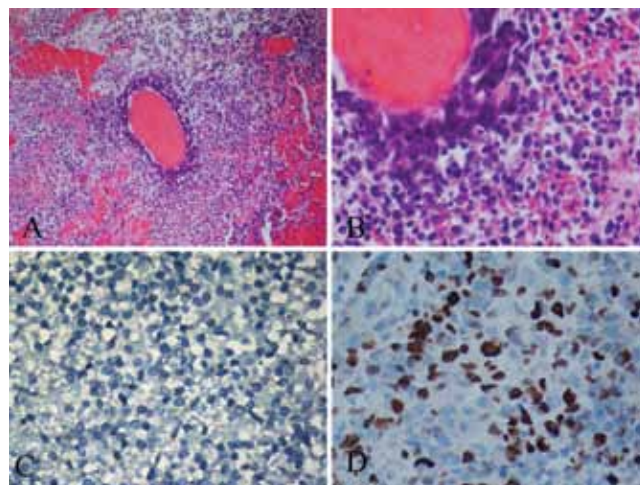

FIG. 2. Photomicrographs obtained in Case 1. **A and B:** Tissue sections demonstrating primitive cells with scant cytoplasm in a hemorrhagic background. H & E, original magnification × 10 **(A)**, × 40 **(B)**. **C and D:** Immunoperoxidase stains show that tumor cells are CD99 negative **(C)** and have a high Ki 67 proliferation index **(D)**. Original magnification × 40.

quadriplegia, his physical examination was significant for 0/5 strength in both upper and lower extremities, complete sensory loss below the C-5 dermatome, and absence of all reflexes. He began receiving dexamethasone and underwent preparation for emergency spinal decompression and possible lesion biopsy.

Surgery. Laminectomies of the C-4 to T-1 vertebrae were performed with preservation of the facet joints. The dura was opened in the midline and tented laterally, revealing a grossly expanded cord, particularly marked at the C5–6 levels. Using microsurgical techniques the arachnoid was opened and a midline myelotomy was made extending just rostral and caudal to the expanded cord. The underlying tissue was diffusely hemorrhagic and discolored. The hematoma was allowed to express itself and tissue was sent for pathological analysis. Resection of grossly abnormal tissue was performed while taking care not to disrupt what appeared to be a ventral plane between the hemorrhagic tissue and more normal-appearing cord. The patient was successfully extubated and transferred to the neurological intensive care unit.

Pathology. The pathology specimens consisted of sheets and vague groups of the tumor cells in a hemorrhagic background (Fig. 2A). The tumor cells were mainly grouped around vessels without a distinct histoarchitecture (Fig. 2B). Individual cells had a primitive appearance with large, pleomorphic nuclei and scant cytoplasm. Nuclear molding was prominent in several areas. Abundant karyorrhectic debris was present together with the tumor cell aggregates (Fig. 2B). Immunohistochemical stains revealed that a small subset of tumor cells stained positively for glial fibrillary acidic protein and synapto-

physin (not shown), suggesting some degree of glial and neuronal differentiation. The tumor cells did not express CD99, a relatively specific marker for Ewing sarcoma/PNET (Fig. 2C). The MIB-1 (Ki 67) proliferation index was approximately 30% to 40% (Fig. 2D). Fluorescence in situ hybridization analysis using the EWSR1 break apart probe did not reveal a chromosome 22q12 rearrangement. These findings are most consistent with a diagnosis of a CNS PNET.

Postoperative Course. Within hours of being transferred from the operating room to the neurological intensive care unit the patient required reintubation due to respiratory difficulty believed to be secondary to postsurgical cord edema. Further imaging workup did not reveal metastases or other possible primary lesions. A tracheostomy was performed and the patient was subsequently discharged to a skilled nursing facility with quadriplegia (American Spinal Injury Association Grade A) and was ventilator-dependent but otherwise stable. He was treated with 6 cycles of vincristine, cyclophosphamide, carboplatin, and etoposide (COPE). At a follow-up visit 28 months after surgery, the patient remained progression free and stable.

Case 2

Presentation. This 35-year-old man with no significant medical history was first examined in an office consultation for progressive back and leg pain of 6 months duration. The leg pain was radicular in nature and particularly notable around the knees. His back pain was reported to awaken him at night. On physical examination his motor function, sensory function, gait, and reflexes were intact. Magnetic resonance imaging was obtained, which showed a 1.4 × 4.7 cm intradural mass that extended from the level of the T12–L1 intervertebral space to the L1–2 intervertebral space, with the rostral aspect of the

mass abutting the conus medullaris. The mass appeared isointense on T1-weighted sequences and moderately hyperintense on T2-weighted sequences (Fig. 3). Contrast-enhanced images were not available. Myxopapillary ependymoma and nerve sheath tumor were considered in the differential diagnosis. Elective surgical intervention was recommended with the goal of GTR.

Surgery. Bilateral laminectomies from T-12 to L-2 with preservation of the facet joints were performed. The dura was opened in the midline and tented laterally, exposing the nerve roots of the cauda equina. Using microsurgical techniques, the arachnoid was incised and a dissection plane was identified between the roots of the cauda equina and the tumor. The highly vascular and friable tumor was well circumscribed without a true capsule, but there was intricate association with, and attachment to, the rootlets of the cauda equina. The tumor was internally debulked and the margins carefully delivered into the surgical field. Intricate tumor attachments to the surrounding rootlets were removed piecemeal. A radical resection (but not GTR) was achieved as there remained small tumor remnants inferiorly that could not be safely resected. The patient was extubated and transferred to the recovery unit uneventfully.

Pathology. On microscopic examination the specimen was highly cellular and predominantly arranged in patternless sheets of cells (Fig. 4A and B). Primitive-appearing, medium-sized cells with indistinct cell borders were present. The nuclei of the neoplastic cells were round-to-oval with stippled or compact chromatin and occasional nucleoli. Nuclear molding was evident. Occasional ill-defined rosettelike structures were noted (not shown), resembling Homer-Wright rosettes. Many mitotic figures and karyorrhectic bodies were noted (Fig. 4B). Vast areas of tumor ne-
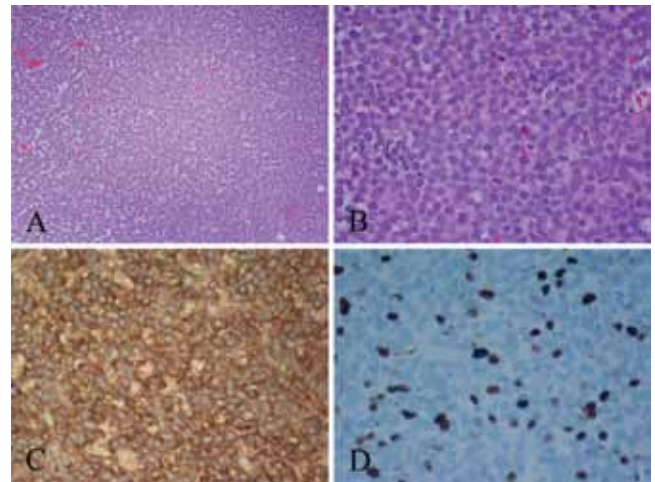

FIG. 4. Photomicrographs obtained in Case 2. **A and B:** Tissue sections shows densely packed sheets of primitive appearing cells. H & E. Original magnification × 10 **(A)**, × 40 **(B)**. **C and D:** Immuno-peroxidase stains show strong membranous CD99 immunoreactivity highlighting cell borders **(C)** and an elevated Ki 67 proliferation index **(D)**. Original magnification × 40.

crosis were observed (not shown). In immunohistochemical preparations the neoplastic cells diffusely and strongly expressed CD99 (Fig. 4C). The neoplastic cells did not express synaptophysin or glial fibrillary acidic protein (not shown). The MIB-1 (Ki 67) proliferation index was 20%–30% (Fig. 4D). Fluorescence in situ hybridization analysis revealed a chromosome 22q12 rearrangement. These findings are consistent with a diagnosis of Ewing sarcoma/PNET.

Postoperative Course. The patient awoke from surgery neurologically intact. His preoperative back pain resolved but his leg pain remained, and he subsequently began receiving gabapentin. Postoperative MR imaging of the spine demonstrated a 9-mm residual nodule at the inferior portion of the resection. Further imaging workup did not reveal metastases or other possible primary lesions. A protocol of focal external beam radiation therapy and chemotherapy was recommended, but the patient returned to his home country and was lost to follow-up approximately 2 months following surgery.

Discussion

History and Classification

Primary spinal PNETs are histologically indistinguishable from other neural axis PNETs. The earliest recognized case report of a spinal PNET is from a paper by Smith et al. published in 1969.[87] Their use of the term PNET is problematic, however, because the nomenclature and criteria for diagnosing PNET were not formally introduced until 1973 by Hart and Earle,[35] and therefore it is unclear whether or not the tumor they reported actually met the criteria for a PNET. The original classification scheme for PNETs arose from the hypothesis that all tumors of this category share a common progenitor cell. However, in 1993 the WHO determined that this claim could not
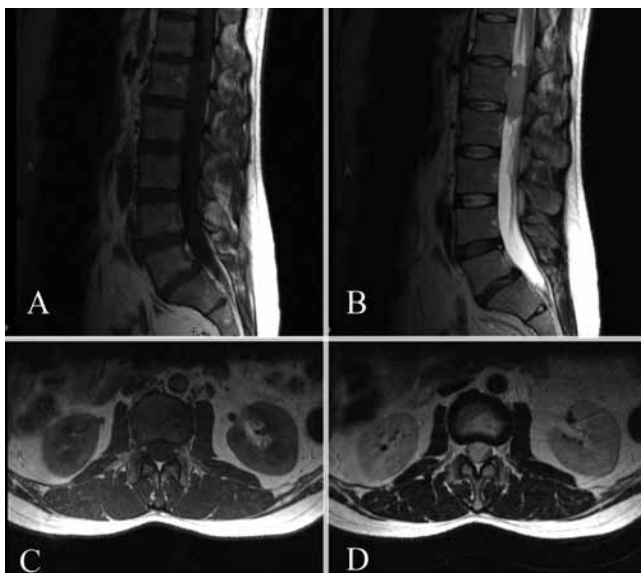

FIG. 3. Preoperative MR imaging in Case 2. **A and C:** Sagittal **(A)** and axial **(C)** T1-weighted images demonstrating a subtle isointense lumbar intraspinal lesion. **B and D:** Sagittal **(B)** and axial **(D)** T2-weighted images demonstrating a slightly hyperintense intradural lesion abutting the conus.

be substantiated.[53,83] The WHO description of PNETs has evolved such that several tumors once included under this nomenclature are now understood as distinct diagnoses, including such notable examples as medulloblastoma, atypical teratoid/rhabdoid tumors, and pineoblastomas.[54,55,64] In addition, tumors that exhibit more extensive differentiation are considered to be distinct diagnoses, including neuroblastomas, ganglioneuroblastomas, medulloepitheliomas, and ependymoblastomas.[55,64] Similarly, it has been argued that embryonal tumor with abundant neuropil and true rosettes represents a distinct entity as well.[21,30,64]

Those tumors currently understood as PNETs are further divided into 2 categories: CNS PNETs and Ewing sarcoma/PNETs. They can both be found anywhere along the neural axis. Genetic and immunohistopathological analyses are used to distinguish these 2 subtypes, but the clinical significance of this segregation continues to remain unclear.

Epidemiology

Little reliable information is available on the incidence of primary spinal PNETs.[64,85] A recent large series of patients indicates that PNETs represent less than 1% of primary spinal tumors.[22] However, whereas primary spinal PNETs are rare, they are perhaps more common than has been previously recognized. Our review of the literature yielded 82 cases (including ours) reported since 1969 (Table 1). Interestingly, the majority of these cases were reported within the last decade, possibly indicating an increased awareness of the diagnosis (Fig. 5). The assertion that primary spinal PNETs are most prevalent in the pediatric and young-adult populations and are observed more commonly in males than in females is supported by our analysis of reported cases.[40,45,48] The median age at the time of diagnosis was 24 years (range 0.25–70 years) and there was a nearly 2:1 male sex preponderance (Table 1).

Genetics

Much of the revision of the classification schema for PNETs has resulted from advances in their genetic characterization. It is important to note that there is currently

no known genetic distinction between cranial/supratentorial PNETs and spinal PNETs; thus genetic analyses from intracranial PNETs may also inform our understanding of spinal PNETs.[64] This idea is supported by the fact that both CNS PNETs and Ewing sarcoma/PNETs can each be found either intracranially or intraspinally. Thus, anatomical location cannot be used to distinguish PNETs.

Cytogenetic analysis of CNS PNETs has revealed several notable alterations. These include RASSF1A promoter methylation, expression of the Neuro D family of basic helix-loop-helix transcription factors (bHLH), and expression of achaete scute, a transcription factor with homology to Neuro D.[64] Using fluorescence in situ hybridization analysis of 30 patients with PNETs, Behdad and Perry[7] identified several *MYC* gene amplifications, including MYCN and MYCC, and found that polysomies of chromosomes 2 and 8 are significant prognostic indicators of poor survival in adult patients with PNET. In addition, the *NOTCH1* gene, neuroglial differentiation gene *SOX2*, and the bHLH suppressor gene *ID1* have been shown to be upregulated in supratentorial PNETs.[80] Several studies have demonstrated that chromosomal deletions at 16p and 19p are common in CNS PNETs.[12,41] Interestingly, CNS PNETs generally lack the i(17)q abnormality present in 30%–50% of medulloblastoma specimens, a feature greatly responsible for their reclassification into distinct entities.[29,55,64]

Ewing sarcoma/PNETs demonstrate the characteristic translocation (11;22) (q24;q12) in more than 90% of cases.[6,15,67] Most commonly, this involves a rearrangement of the *EWS* and *FL1* genes (85%) or *EWS* and *ERG* genes (10%).[6,16,88,98] The presence of an (11;22) (q24;q12) translocation is therefore the strongest diagnostic tool in identifying Ewing sarcoma/PNET. The presence of this translocation may be confirmed by either fluorescence in situ hybridization or reverse transcription polymerase chain reaction. Upregulation of the *MIC2* gene, which encodes the surface protein CD99, is also usually present in Ewing sarcoma/PNETs and is another useful diagnostic indicator. The membrane proteins HNK1 and CAV1 have been implicated in Ewing sarcoma/PNET as well.[62]

Histopathology and Immunohistochemistry

Central nervous system PNETs are generally characterized by poorly differentiated, often densely packed cells with high nuclear-to-cytoplasmic ratios.[64] Both nuclear pleomorphism and molding are often observed, as demonstrated in Case 1. Individual cells may exhibit differentiation along neuronal, astrocytic, or ependymal lineages with corresponding nuclear and cytoplasmic features. Tumor cells can be arranged in a number of patterns, including parallel streams, palisades, and/or single file. Homer-Wright rosettes are often present, but not definitive. Degenerate regions usually show calcification and many tumors demonstrate vascular-endothelial proliferation.

Electron microscopy of CNS PNETs often reveals scant cytoplasmic organelles and reflects individual lineage differentiation. Compact arrays of cytoplasmic glial filaments suggest glial differentiation, while the presence of growth cones would support ganglionic differentiation.

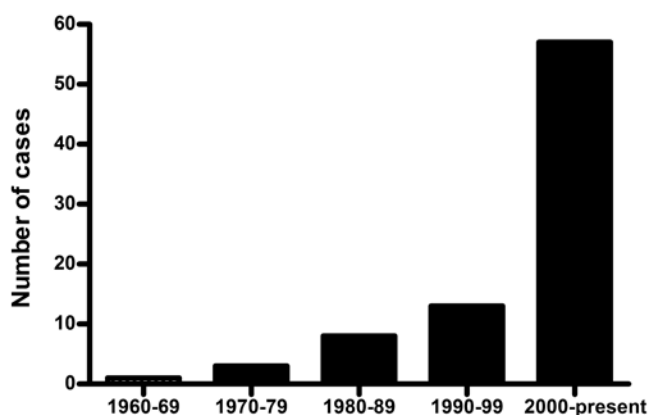The immunohistochemical profile of CNS PNETs is

FIG. 5. Distribution of spinal PNET case reports by decade. Since the original description of a spinal PNET in 1969 there has been a steady increase in the number of reports, and since the year 2000 there have been at least 57 reports, the most in any decade.

TABLE 1: Clinical characteristics of reported spinal PNET cases*

Case No.	Authors & Year	Age (yrs), Sex	Duration of Symptoms (wks)	Survival (mos)	PNET Location
1	Smith et al., 1969	24, M	NA	10	intradural-extramedullary
2	Kosnik et al., 1978	NA	NA	<12	NA
3		NA	NA	<12	NA
4		NA	NA	<12	intramedullary
5	Kepes et al., 1985	24, M	NA	18	intradural-extramedullary
6		56, M	NA	alive at 36	intradural-extramedullary
7		39, M	NA	42	intradural-extramedullary
8	Liu et al., 1987	26, F	NA	alive at 6	extradural
9	Sevick et al., 1987	26, M	NA	36	intradural-extramedullary
10	Jaksche et al., 1988	15, F	NA	18	intramedullary
11		26, M	NA	36	intramedullary
12	Freyer et al., 1989	7, M	NA	20	intramedullary
13	Ogasawara et al., 1992	16, F	8	29	intramedullary
14	McDermott et al., 1994	47, M	72	16	intradural w/ extradural extension
15	Kwon et al., 1996	0.25, F	1	0.5	intramedullary
16	Deme et al., 1997	22, F	2.5	alive at 15	intramedullary
17	Hisaoka et al., 1997	14, M	12	alive at 3	intradural-extramedullary
18	Mottl & Koutecky, 1997	NA, F	NA	alive at time of study	NA
19	Miller et al., 1997	NA	NA	NA	intramedullary
20		NA	NA	NA	intramedullary
21	Meltzer et al., 1998	25, M	NA	60	intramedullary
22	Papadatos et al., 1998	23, F	52	alive at 12	intradural-extramedullary
23	Koot et al., 1998	2, F	3	several days	intradural w/ extradural extension
24	Dorfmüller et al., 1999	17, M	3	alive at 23	extradural
25		32, M	16	29	intradural w/ extradural extension
26	Isotalo et al., 2000	52, M	24	alive at 12	intradural-extramedullary
27	Weil et al., 2001	21, M	24	alive at 30	intramedullary
28	Izycka-Swieszewska et al., 2001	13, F	4	alive at 31	extradural
29	Mawrin et al., 2002	69, M	20	3	intramedullary
30	Virani & Jain, 2002	5, M	4	alive at 8	intramedullary
31	Yavuz et al., 2002	18, F	8	alive at 25	intradural-extramedullary
32	Reihani-Kermani & Amizadeh, 2002	22, F	4	alive at 9	intradural-extramedullary
33	Mawrin et al., 2002	38, M	NA	18	intramedullary
34	Albrecht et al., 2003	29, F	NA	17	intramedullary
35	Albrecht et al., 2003	49, F	NA	23	intradural-extramedullary
36	Izycka-Swieszewska et al., 2003	26, M	52	3	intradural-extramedullary
37	Harimaya et al., 2003	12, F	0.57	32	extradural
38		10, M	1.28	22	extradural
39		30, F	6	14	intradural-extramedullary
40		14, M	12	alive at 67	intradural-extramedullary
41	Aydin et al., 2004	16, M	24	alive at 7	extradural
42	Akyüz et al., 2004	31, F	12	2	intradural-extramedullary
43	Kim et al., 2004	17, M	4	alive at 4	intramedullary
44	Weber et al., 2004	26, M	3	alive at 16	extradural
45	Bohn Sarmiento et al., 2005	37, M	NA	6	intradural-extramedullary
46	Kampman et al., 2006	3, M	2	0.25	intramedullary
47	Jain et al., 2006	54, F	4	NA	intramedullary
48	De Tommasi et al., 2006	38, M	8	18	intramedullary

(continued)

TABLE 1: Clinical characteristics of reported spinal PNET cases* *(continued)*

Case No.	Authors & Year	Age (yrs), Sex	Duration of Symptoms (wks)	Survival (mos)	PNET Location
49	Fabre et al., 2006	70, M	16	alive at 12	intradural-extramedullary
50	Koudelová et al., 2006	28, F	NA	alive at 24	extradural
51	Nutman et al., 2007	19, F	8	alive at 24	intradural-extramedullary
52	Kumar et al., 2007	9, F	8	alive at 18	possibly intramedullary
53		8, M	20	alive at 8	intradural w/ extradural extension
54		18, M	16	alive at 6	intramedullary
55	Perry et al., 2007	27, M	32	alive at 72	intradural w/ extradural extension
56		16, F	12	alive at 5	intradural-extramedullary
57	He et al., 2007	8, F	8	10	extradural
58	Sahu et al., 2007	11, M	NA	NA	intradural-extramedullary
59	Feng et al., 2008	24, M	4	alive at 14	extradural
60	Han et al., 2008	17, M	2	24	intramedullary
61		40, F	38	alive at 8	intramedullary
62	Musahl et al., 2008	27, M	4	alive at 24	extradural
63	Cai et al., 2008	3, M	4	6	extradural
64	Hrabálek et al., 2009	29, M	12	4	intradural-extramedullary
65	Theeler et al., 2009	28, F	52	alive at 2	extradural
66	Kiatsoontorn et al., 2009	25, M	2–3	alive at 6	extradural
67	Otero-Rodríguez et al., 2009	1.58, M	24	alive at 6	intramedullary
68	Jingyu et al., 2009	19, F	6.5	alive at 10	intradural-extramedullary
69		46, M	0.6	alive at 14	intradural-extramedullary
70		58, M	2.1	alive at 25	extradural
71		14, M	16	alive at 6	intradural-extramedullary
72	Chang et al., 2010	15, F	4	alive at 12	extradural
73	Alexander et al., 2010	45, M	16	alive at 13	intradural-extramedullary
74	Duan et al., 2010	24, M	16	30	extradural
75		14, M	NA	NA	extradural
76		26, F	NA	NA	extradural
77		7, M	NA	NA	extradural
78		8, M	NA	NA	intradural-extramedullary
79		25, M	NA	NA	intradural-extramedullary
80		34, M	NA	NA	extradural
81	present study, Case 1	27, M	1.28	alive at 28.4	intramedullary
82	present study, Case 2	35, M	24	alive at 2	intradural-extramedullary

* NA = not available.

variable. Cells exhibiting neuronal differentiation express synaptophysin, Class III β-tubulin, and neurofilament protein and have recently been shown to overexpress the oncogenic transcription factor Y-box-binding protein-1.[31,93] These cells may also express S100, neuron-specific enolase, and Leu-7 (CD-57).[82] Glial fibrillary acidic protein is expressed in tumors with astrocytic differentiation. Mitotic activity is highly variable. In general, intertumor variability is too high to base diagnosis on a single antigen expression pattern.[64]

Ewing sarcoma/PNETs are histologically characterized by sheets of primitive-appearing cells with thin rims of periodic acid-Schiff positive, diastase-sensitive, glycogen-rich cytoplasm.[25] Some degree of cytoplasmic clearing may also be evident. Homer-Wright rosettes are sometimes present. Most tumors stain at least focally with neuronal markers such as synaptophysin and neuron-specific enolase. Cytokeratin stains are usually negative.[64]

The membrane proteins FLI1, HNK1, and CAV1 are commonly expressed in Ewing sarcoma/PNETs.[18,26,27,63,69–71,91] In addition, upregulation of the *MIC2* gene in Ewing sarcoma/PNET results in a high degree of expression of the transmembrane glycoprotein CD99. Conversely, CD99 is generally not expressed in CNS PNETs.[4,95] In a study of 402 confirmed cases of Ewing sarcoma/PNET, Llombart-Bosch et al.[62] found that 99% expressed CD99 either focally or globally. However, MIC2/CD99 is also highly expressed in a number of other tumors including ependy-

momas, low-grade astrocytomas, glioblastomas, choroid plexus carcinomas, and rarely, in CNS PNETs.[14,32,36,64,89,95] Thus, while CD99 immunopositivity can be useful in differentiating CNS PNETs and Ewing sarcoma/PNET, it is not specific. The presence of an (11;22) (q24;q12) translocation is necessary for definitive diagnosis.

Clinical Presentation

As demonstrated by our 2 case illustrations, the clinical presentation of spinal PNETs is variable. The development of pain, paresthesias, weakness, or incontinence over several weeks to months is nonspecific but commonly observed (Table 1). Conversely, intratumoral hemorrhage resulting in acute neurological decline, such as that observed in our first case, has not been previously reported. Our second case represents a more typical subacute presentation.

Radiographic Findings

The radiographic findings of spinal PNETs vary from patient to patient and are generally not helpful in differentiating them from other primary spinal lesions such as ependymoma or astrocytoma. Magnetic resonance imaging with and without Gd contrast is the imaging modality of choice in detecting spinal PNETs. As demonstrated by our reported cases, spinal PNETs are typically hypo- to isointense on T1-weighted MR imaging and iso- to hyperintense on T2-weighted imaging. There is often minimal contrast enhancement and, less frequently, the appearance of cystic regions. Fluorine-18–labeled fluorodeoxyglucose PET-CT is another useful adjunct in guiding the management of patients with these tumors; in particular, it can be helpful in detecting metastatic disease and tumor progression.[20,68,94] Determining that the tumor is restricted to the spine is important because spinal PNETs can be metastatic from extraspinal primary lesions at presentation. Conversely, primary spinal PNETs may metastasize extraspinally (Table 2).

Diagnosis

A definitive diagnosis of PNET can only be made after tumor tissue is obtained from a limited biopsy or a radical resection specimen. The specific diagnostic criteria used are as described in the clinical cases and in the section on histopathology. In terms of subtyping, in our first case the diagnosis of CNS PNET was based on characteristic histology, supportive immunohistochemistry revealing a lack of tumor cell CD99 expression, and cytogenetics demonstrating normal chromosomal arrangement. Conversely, in our second case, a Ewing sarcoma/PNET was diagnosed based on characteristic histology, robust tumor cell expression of CD99, and cytogenetic analysis revealing a chromosome 22q12 translocation.

The segregation of primary intraspinal PNETs into their respective subtypes has not been systematic throughout the literature. Of the 82 total cases in our review of the literature, only 16 (19.5%) included chromosome 22 rearrangement analysis while 37 (45.1%) reported on tumor cell expression of CD99 (Table 2). Although it has been suggested that there are differences with regard to the clinical evolution and the optimal medical manage-

ment of PNET subtypes, there is a paucity of data available in the literature to confirm that this is indeed the case.[48,49,75,96] We therefore advocate that all spinal PNET specimens undergo standard subtyping analyses to facilitate advancements in our understanding of these tumors.

Management

From a clinical perspective, there are no standard protocols employed in the management of spinal PNETs. Instead, most treating physicians use empirical and often kitchen-sink type approaches. Furthermore, as the literature on these tumors consists mainly of case reports with short follow-up times, it is difficult to draw conclusions regarding the appropriateness of any single strategy. In general most centers employ surgical biopsy or resection, chemotherapy, and radiation therapy in their treatment protocols.

Surgery

The surgical treatment of spinal PNETs, as with most spinal tumors, is guided by the principles that one should: 1) decompress neural elements to prevent further neurological decline, 2) obtain an adequate tissue sample for pathological examination, and 3) resect as much tumor as can be safely removed. Exposure over the entire rostrocaudal extent of the tumor is generally necessary to accomplish these goals. While a standard laminectomy with preservation of the facet joints is usually performed in adults, laminoplasty may be considered in pediatric patients.

In our review of 82 reported cases, 81 underwent some form of open surgical procedure and 1 underwent stereotactic biopsy (Table 2). Of those cases from which the information could be extracted, GTR was achieved in 35% (20 of 57), STR was achieved in 51% (29 of 57), and biopsy only was achieved in 14% (8 of 57).

Adjuvant Therapy

Evidence of benefit from adjuvant therapy in treating spinal PNETs is anecdotal at best. Nevertheless, both radiation and chemotherapy are commonly used. The optimal radiation strategy, the necessity of full neural axis radiation in the setting of localized disease, and dosing are all controversial topics in the treatment of primary spinal PNETs.[94] In the cases we reviewed, 65 (83%) of 78 patients received radiation therapy (Table 2). Total doses ranged from 30 Gy to 60 Gy. Some authors advocate for hyperfractionated radiotherapy, but there is currently no data to suggest any benefit to this strategy.[2]

Much like the variety of radiation strategies employed, a multitude of chemotherapeutic agents have been advocated for use in patients with spinal PNETs (Table 2). Regimens that combine high-dose chemotherapy and autologous stem cell rescue in addition to surgery and radiation have shown promising results in several reports.[75,96]

Follow-Up and Prognosis

The prognosis in most cases of spinal PNETs appears to be poor with a median patient survival of 1 to 2 years.[48,59] Approximately one-third of patients will exhibit cerebrospinal dissemination of their tumor.[39] Extraneural

TABLE 2: Disease extent, intervention, and pathological markers*

Case No.	Authors & Year	Extraspinal Metastases	Op	Chemotherapy Agents	Radiation	CD99	t(11;22)
1	Smith et al., 1969	lung	yes	none	yes	NA	NA
2	Kosnik et al., 1978	NA	resection	methotrexate, vincristine, lomustine	4000–6000 rads	NA	NA
3		NA	resection	methotrexate, vincristine, lomustine	4000–6000 rads	NA	NA
4		lung, bone marrow, lymph node, brain	resection	methotrexate, vincristine, lomustine	4000–6000 rads	NA	NA
5	Kepes et al., 1985	NA	yes	none	yes	NA	NA
6		NA	yes	none	yes	NA	NA
7		NA	yes	none	yes	NA	NA
8	Liu et al., 1987	NA	yes	none	yes	NA	NA
9	Sevick et al., 1987	NA	yes	none	yes	NA	NA
10	Jaksche et al., 1988	none	yes	methotrexate, vincristine, lomustine, cisplatin	craniospinal	NA	NA
11		brain	STR	yes	craniospinal	NA	NA
12	Freyer et al., 1989	none	yes	yes	yes	NA	NA
13	Ogasawara et al., 1992	brain	STR	ranimustine, cisplatin, etoposide	36 Gy to spine, 20 Gy to brain metastasis	NA	NA
14	McDermott et al., 1994	none	min resection	yes	yes	NA	NA
15	Kwon et al., 1996	brain	biopsy	vincristine, cisplatin, procarbazine, hydroxyurea, lomustine, cytosine arabinoside, cyclophosphamide	none	NA	NA
16	Deme et al., 1997	none	GTR	etoposide, carboplatin, iphosphamide	craniospinal	NA	NA
17	Hisaoka et al., 1997	NA	resection	NA	NA	+	+
18	Mottl & Koutecky, 1997	none	biopsy	vincristine, carboplatin, cyclophosphamide, etoposide	30 Gy	NA	NA
19	Miller et al., 1997	NA	NA	NA	NA	NA	NA
20		NA	NA	NA	NA	NA	NA
21	Meltzer et al., 1998	brain	resection	vincristine, lomustine	craniospinal	NA	NA
22	Papadatos et al., 1998	none	STR	cyclophosphamide, cisplatinum, etoposide	36 Gy w/ 9 Gy boost	NA	NA
23	Koot et al., 1998	NA	yes	none	yes	NA	NA
24	Dorfmüller et al., 1999	none	GTR	vincristine, doxorubicin, ifosfamide, actinomycin D	49 Gy hyperfractionated	+	+
25		brain	GTR	cisplatin, vincristine, actinomycin D, ifosfamide, doxorubicin	craniospinal	+	+
26	Isotalo et al., 2000	none	STR	none	38.5 Gy craniospinal, 17.5 Gy to tumor	+	NA
27	Weil et al., 2001	none	NA	NA	NA	+	+
28	Izycka-Swieszewska et al., 2001	lung	biopsy	carboplatin, epirubicin, etoposide, vincristine, ifosfamide, actinomycin, trofosfamid, idarubicin	33 Gy	+	+
29	Mawrin et al., 2002	none	STR	none	50.4 Gy	NA	NA
30	Virani & Jain, 2002	mediastinal	GTR	none	yes	NA	NA
31	Yavuz et al., 2002	none	STR	vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide	34 Gy craniospinal, 20 Gy to tumor	NA	NA
32	Reihani-Kermani & Amizadeh, 2002	none	GTR	none	craniospinal	NA	NA
33	Mawrin et al., 2002	none	yes	yes	yes	NA	NA
34	Albrecht et al., 2003	none	biopsy	doxorubicin, etoposide, cyclophosphamide	53.2 Gy total w/ 35.2 Gy boost	NA	−

TABLE 2: Disease extent, intervention, and pathological markers* *(continued)*

Case No.	Authors & Year	Extraspinal Metastases	Op	Chemotherapy Agents	Radiation	CD99	t(11;22)
35	Albrecht et al., 2003	none	GTR	vincristine, cisplatinum	50.4 Gy initially, 32.4 Gy to recurrence	+	NA
36	Izycka-Swieszews-ka et al., 2003	NA	STR	none	craniospinal	−	−
37	Harimaya et al., 2003	mediastinal	STR	vincristine, doxorubicin, cyclophospha-mide, actinomycin D, carboplatin, etoposide (w/ autologous stem cell rescue)	30 Gy	NA	NA
38		lung	STR	vincristine, doxorubicin, ifosfamide, actinomycin D	30 Gy	NA	NA
39		none	STR	vincristine, doxorubicin, ifosfamide, actinomycin D	50 Gy	NA	NA
40		none	GTR	vincristine, doxorubicin, ifosfamide, ac-tinomycin D, carboplatin, etoposide, ifosfamide (w/ autologous stem cell rescue)	none	NA	NA
41	Aydin et al., 2004	none	GTR	vincristine, cyclophosphamide, doxo-rubicin	yes	NA	NA
42	Akyüz et al., 2004	brain	STR	vincristine, lomustine, cisplatin, vincristine	52.8 Gy hyperfraction-ated	+	NA
43	Kim et al., 2004	none	STR	none	50.4 Gy craniospinal	+	NA
44	Weber et al., 2004	none	GTR	vincristine, ifosfamide, doxorubicin, etoposide, actinomycin, cyclophos-phamide	63 CGE fractionated protons to tumor, 36 Gy craniospinal	+	NA
45	Bohn Sarmiento et al., 2005	rib cage, liver, lung, spleen, testicles, bone marrow	STR	none	30 Gy	+	NA
46	Kampman et al., 2006	none	STR	none	none	−	NA
47	Jain et al., 2006	none	STR	none	craniospinal w/ boost to tumor	−	NA
48	De Tommasi et al., 2006	none	biopsy	vincristine, chloroethylnitrosourea, cis-platinum	none	NA	NA
49	Fabre et al., 2006	none	STR	doxorubicin, ifosfamide, cisplatin, vin-cristine	30 Gy	+	+
50	Koudelová et al., 2006	NA	yes	yes	yes	NA	NA
51	Nutman et al., 2007	none	GTR	vincristine, cyclophosphamide, carbo-platin, thiotepa, etoposide (w/ auto-logous stem cell rescue)	craniospinal w/ 9 Gy boost	+	NA
52	Kumar et al., 2007	none	STR	yes	yes	NA	NA
53		none	GTR	none	none	NA	NA
54		none	biopsy	yes	yes	+	NA
55	Perry et al., 2007	none	GTR	cyclophosphamide, doxorubicin, vin-cristine, ifosfamide, etoposide, topo-tecan, temozolomide, thiotepa, car-boplatin (w/ autologous stem cell rescue)	45 Gy hyperfractionated	+	−
56		none	STR	cyclophosphamide, doxorubicin, vin-cristine, etoposide, ifosfamide	45 Gy	+	+
57	He et al., 2007	lung	STR	cyclophosphamide, doxorubicin, vin-cristine	50 Gy	+	NA

(continued)

TABLE 2: Disease extent, intervention, and pathological markers* *(continued)*

Case No.	Authors & Year	Extraspinal Metastases	Op	Chemotherapy Agents	Radiation	CD99	t(11;22)
58	Sahu et al., 2007	none	STR	ifosfamide, etoposide, cyclophosphamide, doxorubicin, vincristine, actinomycin D	55 Gy fractionated	+	NA
59	Feng et al., 2008	none	GTR	none	45 Gy hyperfractionated	+	−
60	Han et al., 2008	NA	STR	yes	yes	NA	NA
61		NA	GTR	yes	yes	NA	NA
62	Musahl et al., 2008	lung, lymph node	GTR	vincristine, doxorubicin, cyclophosphamide	yes	NA	NA
63	Cai et al., 2008	lung	GTR	none	none	+	NA
64	Hrabálek et al., 2009	none	STR	vincristine, ifosfamide, doxorubicin, etoposide	none	+	+
65	Theeler et al., 2009	none	stereotactic biopsy	vincristine, cyclophosphamide, doxorubicin, ifosfamide, etoposide	yes	+	+
66	Kiatsoontorn et al., 2009	none	GTR	ifosfamide, cisplatin, etoposide	45 Gy fractionated	+	NA
67	Otero-Rodríguez et al., 2009	none	STR	cisplatin, carboplatin, etoposide, cyclophosphamide, methotrexate	none	NA	NA
68	Jingyu et al., 2009	none	STR	cyclophosphamide, temozolomide	craniospinal	NA	NA
69		none	GTR	vincristine, cyclophosphamide, doxorubicin	yes	NA	NA
70		none	GTR	none	none	NA	NA
71		none	GTR	cyclophosphamide, temozolomide	craniospinal	NA	NA
72	Chang et al., 2010	none	STR	none	none	+	NA
73	Alexander et al., 2010	none	STR	none	54 Gy	+	+
74	Duan et al., 2010	lung	biopsy (w/ some hemorrhage)	vincristine, doxorubicin, cyclophosphamide	50 Gy fractionated	+	NA
75		none	resection	yes	35 Gy	+	NA
76		lung	resection	yes	50 Gy	+	NA
77		none	resection	none	30 Gy	+	NA
78		none	resection	yes	30 Gy	+	NA
79		none	resection	yes	50 Gy	+	NA
80		none	resection	none	none	+	NA
81	present study, Case 1	none	STR	cyclophosphamide, vincristine, carboplatin, etoposide	none	−	−
82	present study, Case 2	none	STR	none	none	+	+

* CGE = cobalt gray equivalent; min = minimal; + = positive; − = negative.

metastases to bone, liver, and cervical lymph nodes have also been reported, thus follow-up with MR imaging and possibly FDG PET scanning are important.[8,64]

Conclusions

Primary spinal PNETs are devastating malignancies that appear to be more common than has previously been reported. The clinician should give consideration to the possibility of this diagnosis, especially in the setting of a young adult or child with an intraspinal mass. While there are no widely accepted standards for the manage-

ment of spinal PNETs, we advocate complete resection when possible with the goals of neurological stabilization and obtaining sufficient tissue for accurate diagnosis. This should then be followed by an individualized combination of chemotherapy and/or radiation. As much remains to be learned about these tumors, especially regarding the prognostic implication of PNET subtyping, pathological samples should be analyzed for CD99 immunoreactivity and the (11;22) (q24;q12) translocation. Only by carefully delineating primary intraspinal PNET subtypes, as was completed in the 2 case illustrations we presented, will the clinical differences and optimal management strategies become apparent for these aggressive tumors.

A review of primitive neuroectodermal tumors of the spine

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Embryonal tumors with abundant neuropil and true rosettes: 2 illustrative cases and a review of the literature

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Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a recently identified variant of primitive neuroectodermal tumor, with fewer than 50 cases reported in the literature to date. Histologically, this tumor has features of ependymoblastoma and neuroblastoma, demonstrating areas of fine fibrillary neuropil intermingled with ependymoblastic rosettes and zones of undifferentiated neuroepithelial cells. However, ETANTR is distinguished pathologically from other embryonal tumors by the striking abundance of neuropil. Clinically, ETANTRs have shown high malignant potential and poor clinical outcome despite aggressive treatment. The authors describe 2 illustrative surgical cases of ETANTR, one involving the longest reported survival in the literature to date. The other had a poor outcome despite high-dose adjuvant chemotherapy with sequential autologous hematopoietic stem cell rescue. The authors review the natural history and treatment strategies available for this unusual malignant pediatric brain tumor. (DOI: 10.3171/2010.10.FOCUS10226)

KEY WORDS   •   embryonal tumor with abundant neuropil and true rosettes   •   primitive neuroectodermal tumor   •   WHO classification   •   neuropil   •   ependymoblastoma   •   brain tumor

EMBRYONAL tumor with abundant neuropil and true rosettes (ETANTR) has been identified as a histologically distinctive CNS PNET. It has mixed histological features of ependymoblastoma and neuroblastoma. This new subtype was first reported in 2000 by Eberhart and colleagues.[6] The most distinctive and consistent features of ETANTR are the presence of undifferentiated neuroepithelial cells and ependymoblastic rosettes arising abruptly in a paucicellular background of abundant neoplastic neuropil.

The classification of CNS PNETs has long been controversial. In 2007, the WHO classified CNS PNETs as one of 3 histological subtypes of primitive embryonal tumors, the other 2 subtypes being medulloblastoma and atypical teratoid/rhabdoid tumor (AT/RT).[14] The WHO recognizes 5 PNET subtypes including PNET not otherwise specified (NOS), medulloepithelioma, neuroblastoma, ganglioneuroblastoma, and ependymoblastoma. ETANTR appears similar to ependymoblastoma and neuroblastoma but has unique histological, immunohistochemical, and ultrastructural features. The WHO classifies ependymoblastoma and neuroblastoma as separate entities, while ETANTR is currently considered only a variant.[14] Whether ETANTR should be split off as a distinct pathological entity is a topic currently under debate.

ETANTR is associated with a high potential for malignancy and a dismal prognosis. The paucity of reported cases and lack of treatment guidelines prompted us to explore the pathology and management of this unusual lesion.

Case Reports

Case 1

History and Presentation. This 4-year-old boy presented with right-sided headaches that became progressively worse over 3 weeks. The headaches became severe 4 days prior to admission and awakened him from sleep in the morning. Examination was remarkable for macrocrania and no lateralizing neurological deficits.

Imaging Evaluation. Cranial CT showed a large intraaxial right parietal brain tumor with slight calcification and significant mass effect. Magnetic resonance imaging delineated the intraaxial tumor, which was hypointense on T1-weighted images and heterogeneous on T2-weighted images, with prominent vessels within the mass. There was minimal contrast enhancement (Fig. 1).

Operation. The patient underwent right parietal craniotomy and radical resection of the tumor. The tumor presented at the cortical surface and was adherent to the dura in some areas. It appeared as a fleshy, reddish-gray intraaxial mass that was highly vascular. Thrombosed vessels were observed within the mass. Medially, the tumor extended to the sagittal sinus and falx cerebri, which were visualized at the end of the resection. A radical tumor resection was achieved.

Postoperative Course and Findings. Postoperatively the patient had no focal neurological deficits. The biopsy showed ETANTR, strongly positive for neuropil and synaptophysin (Fig. 2). The pathological diagnosis was confirmed by external review. Postoperative MR imaging confirmed radical resection of the tumor (Fig. 3). An MR imaging study of the spine showed no evidence of disseminated disease. Cerebrospinal fluid cytology was negative for tumor.

Adjuvant Therapy and Follow-Up. The patient was treated with radiation and chemotherapy at Mott Children's Hospital, University of Michigan. Craniospinal radiation was administered over 6 weeks, with 36 Gy to the brain and spinal cord and a boost to 55.8 Gy to the tumor bed. Chemotherapy was administered according to Children's Cancer Group Protocol 99701, although the patient was treated off-study. This was a Phase I trial of the use of carboplatin as a radiation sensitizer. The patient received carboplatin at the maximum tolerated dose (cumulative dose 1050 mg/m^2) and vincristine concurrently with radiation therapy. This was followed by cis-platinum (cumulative dose 450 mg/m^2), vincristine (cumulative dose 30 mg/m^2), and cyclophosphamide (cumulative dose 11.5 mg/m^2) over a period of 6 months (Arm B). Surveillance MR imaging was performed 4 times a year for 1 year, then 3 times a year for 1 year, then twice a year for 1 year, and then yearly thereafter. Follow-up MR imaging of the brain 7 years after surgery showed no evidence of recurrent tumor (Fig. 4). Spine imaging was performed serially during the first 4 postoperative years but not thereafter. No spinal disease was noted.

Seven years following surgery, the patient remains neurologically intact except for mild high-pitched hearing loss in the right ear. He is mainstreamed (in regular classes) in the fifth grade. He has some cognitive delay and receives assistance in mathematics. He is active physically and plays baseball and tackle football. He recently completed a 50-mile bicycle ride. He does have short stature and hypothyroidism for which he receives treatment with growth hormone and levothyroxine.

Case 2

History and Presentation. This 17-month-old previously healthy boy presented with a 3-day history of progressive lethargy, vomiting, and left-sided weakness affecting his upper extremity followed by his lower extremity, which proceeded to an acute deterioration of mental status with extensor posturing.

Imaging Evaluation. Cranial CT showed a 7-cm–diameter intraaxial lesion in the right hemisphere with edema and 12 mm of midline shift. Magnetic resonance imaging showed a prominent, globoid, weakly enhancing, partially cystic mass, with scattered foci of nodularity. The mass was hypointense on T1-weighted sequences. It was located in the suprasylvian region and occupied a substantial portion of the right hemisphere (Fig. 5).

First Operation, Postoperative Course, and Adjuvant Therapy. The patient underwent an emergent craniotomy and radical resection of the tumor. Postoperative MR imaging showed no significant residual tumor (Fig. 6). Pathological specimens showed ETANTR. Postoperatively, the patient did well following a course of rehabilitation. He was able to ambulate independently with a steady gait. His hemiparesis improved but did not resolve. He received adjuvant chemotherapy with cyclophosphamide, etoposide, and methotrexate.

Second Operation, Postoperative Course, and Adjuvant Therapy. Four months after surgery, he developed irritability and had frequent falls. Repeat MR imaging showed recurrence of tumor within the operative bed (Fig. 7). The patient underwent repeat tumor resection, and postoperative MR imaging again showed no residual tumor. He was started on myeloablative chemotherapy using thiotepa and carboplatin, with autologous stem cell rescue. There was initial regression of tumor on MR imaging after completion of 2 cycles of stem cell rescue, and he subsequently received a third infusion of autologous stem cells. He developed severe leukopenia and bacteremia with *Klebsiella*, *Pseudomonas*, *Acinetobacter*, and *Enterobacter* that responded to antibiotic therapy. Repeat MR imaging 1 year following the initial surgery showed a new right occipital metastatic lesion adjacent to the transverse sinus. Palliative intensity modulation radiation therapy was recommended, but the family declined further treatment and the child died shortly thereafter (Fig. 8).

Discussion

Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a histologically distinctive malignant brain tumor of childhood. Since its initial description a decade ago, there have been fewer than 50 cases cited in the literature. In the present report, we describe 2 children with supratentorial ETANTR who each presented with a short history and rapid progression of clinical symptoms. In each case, the tumor was very large and exhibited mass effect. The patient in Case 1 was treated with radical surgery, craniospinal radiation, and chemotherapy, and he is alive without clinical or radiological evidence of active disease 7 years after presentation. This represents the longest reported survival for a patient with ETANTR to date.

The explanation for this long survival is not entirely clear. The tumor was hemispheric, and we were able to achieve a radical resection. Adjuvant therapy included both craniospinal radiation and chemotherapy. The PNETs as a group show better response to radiation than chemotherapy. The use of high-dose carboplatin as a radiation sensitizer may have played a role in achieving disease con-
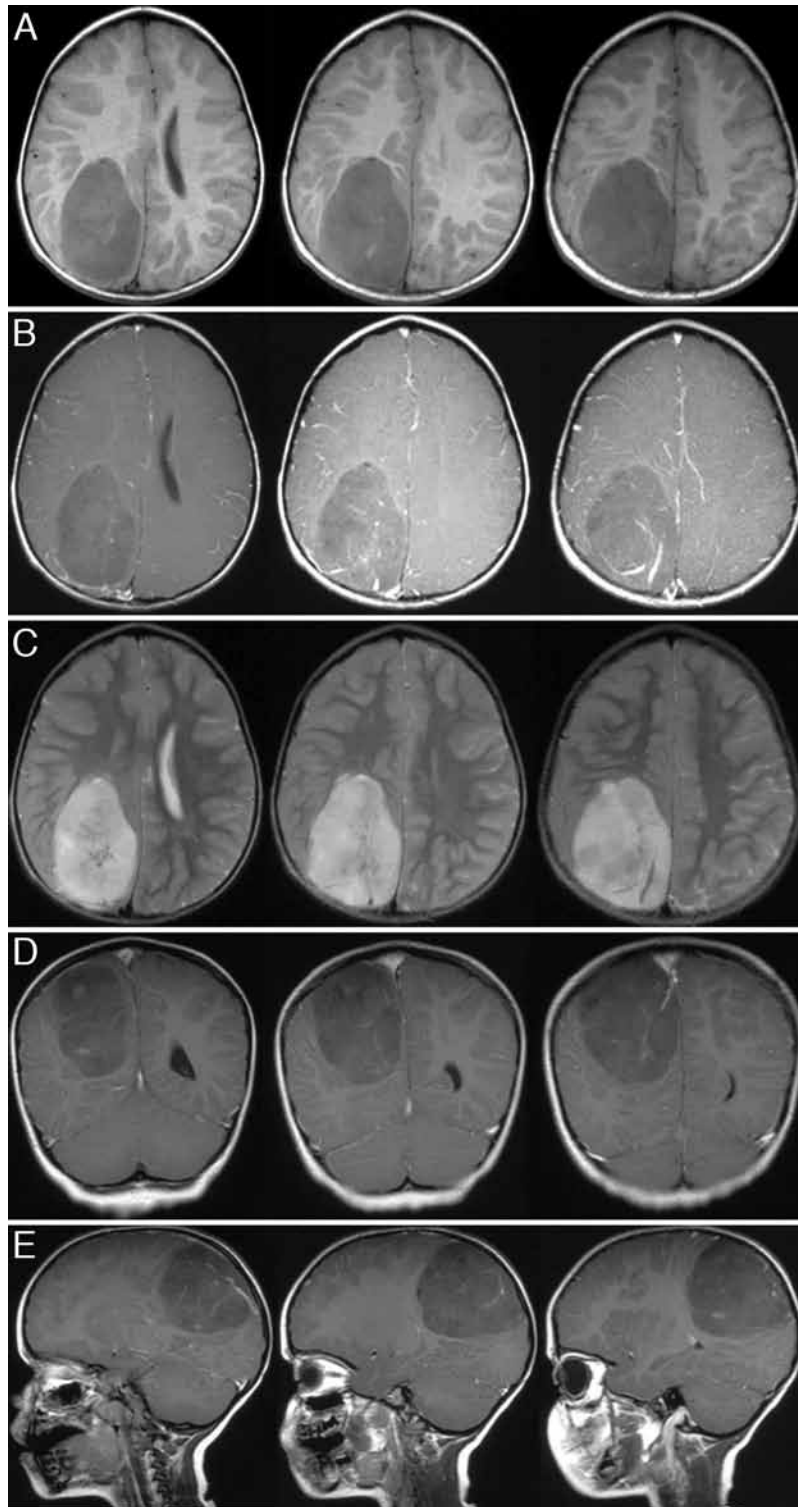
Fɪɢ. 1. Case 1. Preoperative MR imaging. **A:** Axial T1-weighted images obtained without contrast enhancement. **B:** Axial T1-weighted Gd-enhanced images. **C:** Axial T2-weighted images. **D:** Coronal Gd-enhanced T1-weighted images. **E:** Sagittal Gd-enhanced T1-weighted images.

trol. Other long-term survivors may exist, but, since most reported series are in pathology journals, this information is not easily available.

ETANTR was first described by Eberhart and col-leagues[6] in 2000, when they reported 7 cases as a distinctive form of CNS PNET. They initially called the lesion "pediatric neuroblastic tumor with abundant neuropil and true rosettes" (PNTANTR).[7,8] The finding of micro-
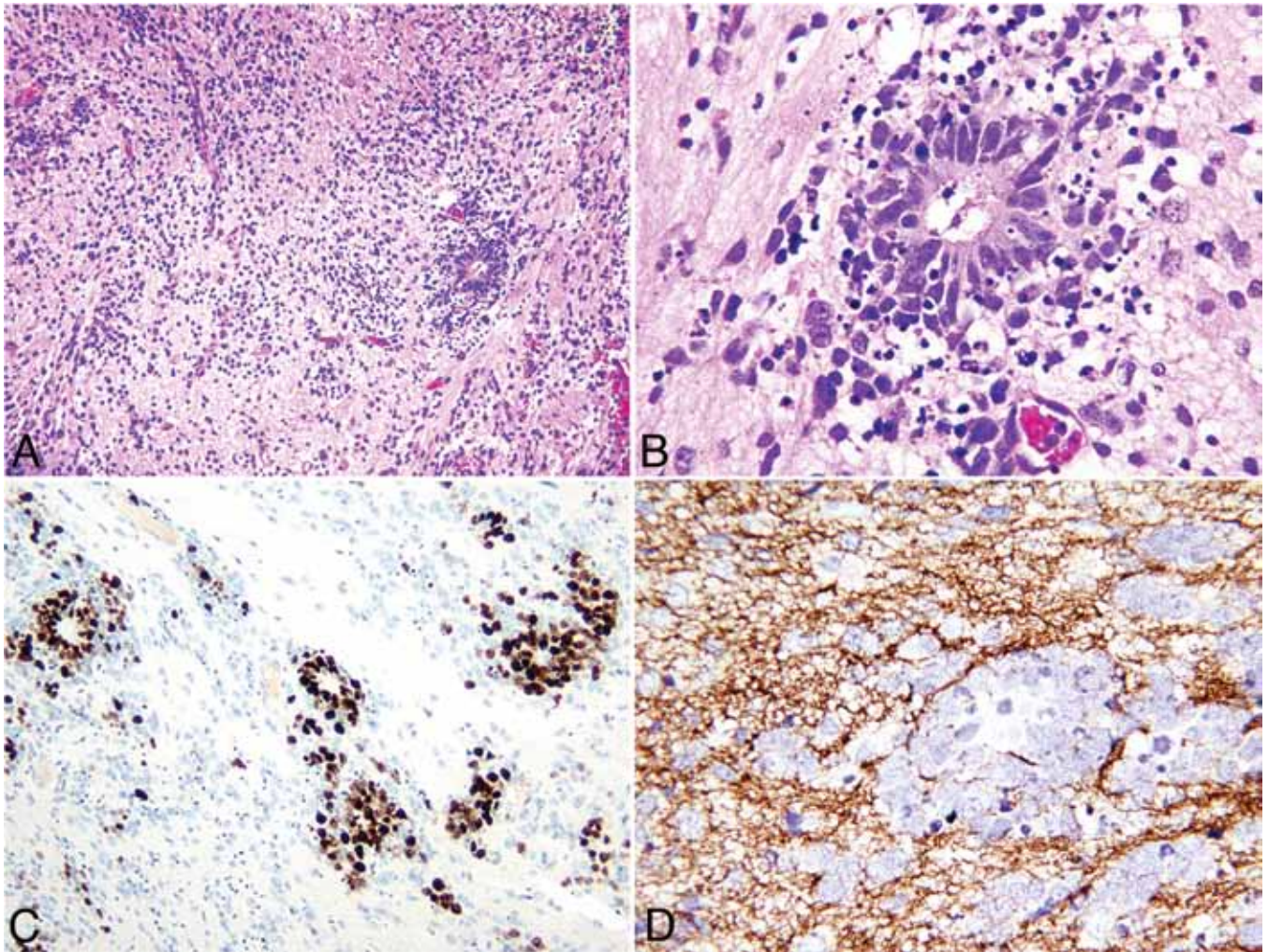
Fig. 2. Case 1. Histopathological features of ETANTR. **A:** Low-power photomicrograph demonstrating abundant neuropil containing occasional true rosettes. H & E. **B:** High-power photomicrograph of true rosettes demonstrating multilayering of pleomorphic nuclei. H & E. **C:** Low-power photomicrograph obtained after immunostaining for Ki 67, which highlights the proliferative activity of cells comprising the true rosettes. **D:** Photomicrograph obtained after immunostaining for synaptophysin. The neuropil separating the true rosettes is highlighted, but the cells comprising the rosettes are not stained. Original magnification × 100 **(A and C)**, × 200 **(D)**, and × 400 **(B)**.

tubules and tumor cells with neurosecretory granules suggested to them a neuroblastic nature of the tumor and accounted for the diffuse synaptophysin immunostain positivity. Occasional glial differentiation of the tumor explained the GFAP positivity. However, the name was subsequently changed to "embryonal tumor with abundant neuropil and true rosettes" (ETANTR) after other groups reported 17 similar cases. Subsequently, Eberhart
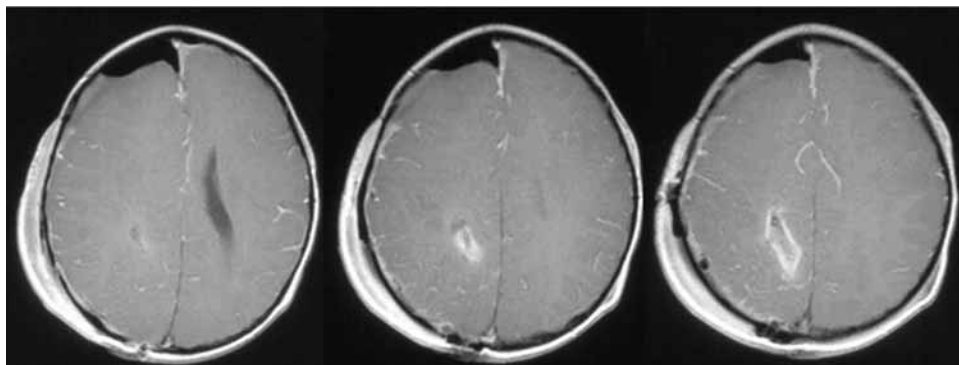
Fig. 3. Case 1. Immediate-postoperative Gd-enhanced MR images showing radical tumor resection.
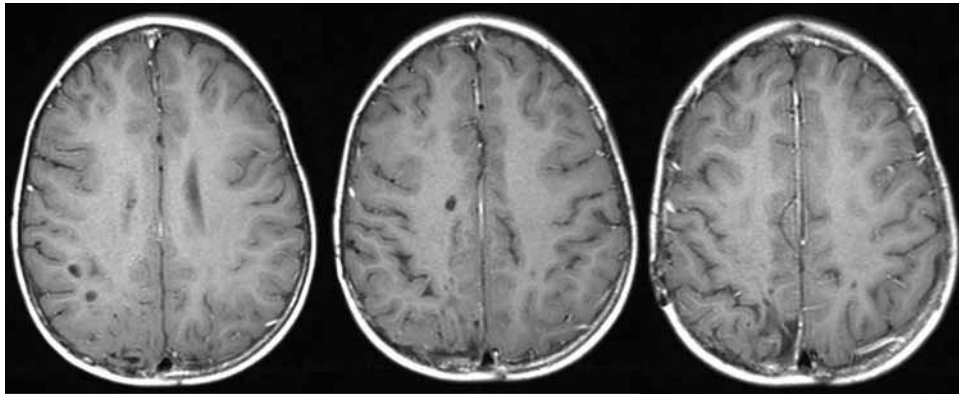
Fig. 4. Case 1. Follow-up Gd-enhanced MR images obtained 7 years after surgery showing absence of recurrent tumor.

and colleagues reported an additional 22 cases in 2009, thus making a total of 46 cases of ETANTR reported in the literature to date.[1,3,5–9,11,13,15]

ETANTR has been identified as a histologically distinctive CNS PNET. It is characterized by the presence of undifferentiated neuroepithelial cells resembling those of the classic PNET as well as broad zones of well-differentiated neuropil and ependymoblastic rosettes arising abruptly from paucicellular regions of neoplastic neuropil. The rosette-forming cells form a multilayered (pseudostratified) wall in which both mitoses and karyorrhectic debris are seen, typically without a luminal basement membrane. Homer Wright rosettes (pathognomonic of neuroblastic differentiation in medulloblastoma) may also be present. A well-defined internal limiting membrane is a hallmark of these lesions, with the outer cells of the rosette merging into the adjacent neuropil and embryonal cells.[9] Medulloblastoma, on the other hand, shows classical Homer-Wright rosettes, and medulloepithelioma shows a canalicular growth pattern with an intact luminal basement membrane and divergent differentiation. Medulloblastoma itself is a very heterogeneous neoplasm with several variants such as classic, desmoplastic, large-cell anaplastic, melanotic, and medullomyoblastoma. These lesions show divergent neuronal differentiation with neuroblastic rosettes, epithelial, glial, and retinoblastoma-like differentiation.[4,10,13] Anaplastic ependymomas, however, show perivascular pseudorosettes that carry a sharp distinction from true rosettes (Table 1).[4,10,16]

The diagnosis of ependymoblastoma is controversial and has been debated since its initial description in 1926.

Recently this subcategory has been considered to be neither precise nor specific.[11] Ependymoblastic rosettes, once considered the hallmark of ependymoblastoma, are no longer considered pathognomonic for this tumor. Judkins and Ellison[11] reviewed 14 cases that had been diagnosed previously as ependymoblastoma and reclassified 8 of them as ETANTR on the basis of the embryonal nature of the cells. They noted that ependymoblastic rosettes were more frequently encountered in ETANTR than in other CNS embryonal neoplasms. They went on to suggest withdrawing the diagnosis of ependymoblastoma from the classification of CNS tumors.

In an effort to further distinguish ETANTR, some investigative groups have recently performed cytogenetic studies on pathological specimens. Fuller and colleagues[8] found abnormalities on chromosome 17 in 2 cases (isochromosome 17q in 1 tumor and polysomy of 17 in the other), anomalies that are typical of medulloblastoma. This suggests that ETANTR, despite arising at locations outside the cerebellum, may be more closely related to cerebellar medulloblastomas than supratentorial PNETs. Subsequently, Gessi and colleagues[9] found extra copies of chromosome 2 in both of the 2 cases in which they performed cytogenetic testing. Buccoliero and colleagues[3] also found chromosome 2 polysomy in 1 case, as did Pfister and colleagues in 1 case.[15] Although duplication of genetic material on chromosome 17 and loss of genetic material on chromosome 22 has been well documented in embryonal CNS tumors, chromosome 2 polysomy may be a differentiating feature of ETANTR.[2]
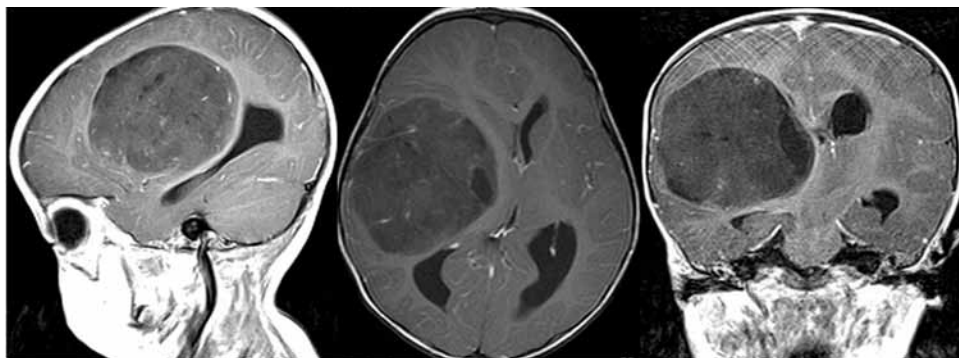
Although ETANTR shows some cytogenetic features

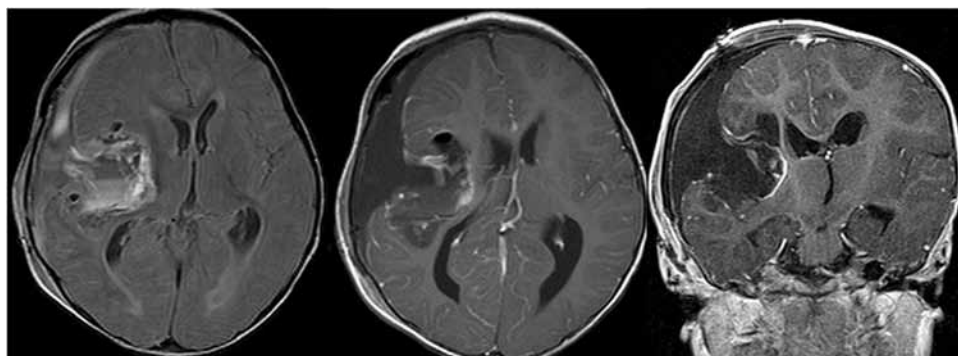**Fig. 5.** Case 2. Preoperative Gd-enhanced sagittal, axial, and coronal MR images.

Fig. 6. Case 2. Immediate postoperative MR images showing radical resection.

resembling medulloblastoma, recent molecular studies have also demonstrated analogies between ETANTR and ependymoblastoma. Pfister and colleagues,[15] who noted the chromosome 2 polysomy in ETANTR, also found a high-level amplification on chromosome 19 at position 19q13.42 causing an upregulation of microRNA clusters and several protein-coding genes. This molecular aberration had not been described in any other brain tumor, further supporting the hypothesis that ETANTR was a distinct tumor entity.

Subsequently, Korshunov and colleagues[12] used fluorescence in situ hybridization to evaluate tumors that had been diagnosed morphologically as either ETANTR or ependymoblastoma. They demonstrated focal genomic amplification at 19q13.42 in 37 of 40 samples (93%). Among tumors harboring this amplification, 19 samples were identified as ETANTR and 18 as ependymoblastoma. This suggests that ETANTR and ependymoblastoma may be closely related.

The natural history of ETANTR is similar to that of other malignant pediatric brain tumors. ETANTRs occur in the pediatric population, usually in children 4 years of age or younger, with a slight female preponderance compared with other PNETs. Although these neoplasms are found in supra- and infratentorial locations, there seems to be a predilection for the supratentorial space, especially the frontal and parietal lobes, where they tend to occur as large, cystic, sometimes calcific intraaxial masses. The radiological differential diagnosis of these lesions includes desmoplastic infantile ganglioglioma, PNET, and supratentorial ependymoma. Gessi and colleagues[9] reported one case with leptomeningeal dissemination that responded to intrathecal chemotherapy. Infantile lesions, in general, are highly malignant and generally associated with a poor clinical outcome, despite aggressive surgical and adjuvant therapy. Like PNETs, these tumors appear to be less sensitive to chemotherapy. The patient in our illustrative Case 2, a 17-month-old child, fared poorly. He was treated with chemotherapy without radiation because of his young age. Both of our patients presented with a short history of rapid clinical deterioration over weeks, suggesting a fast-paced progression of this neoplasm.
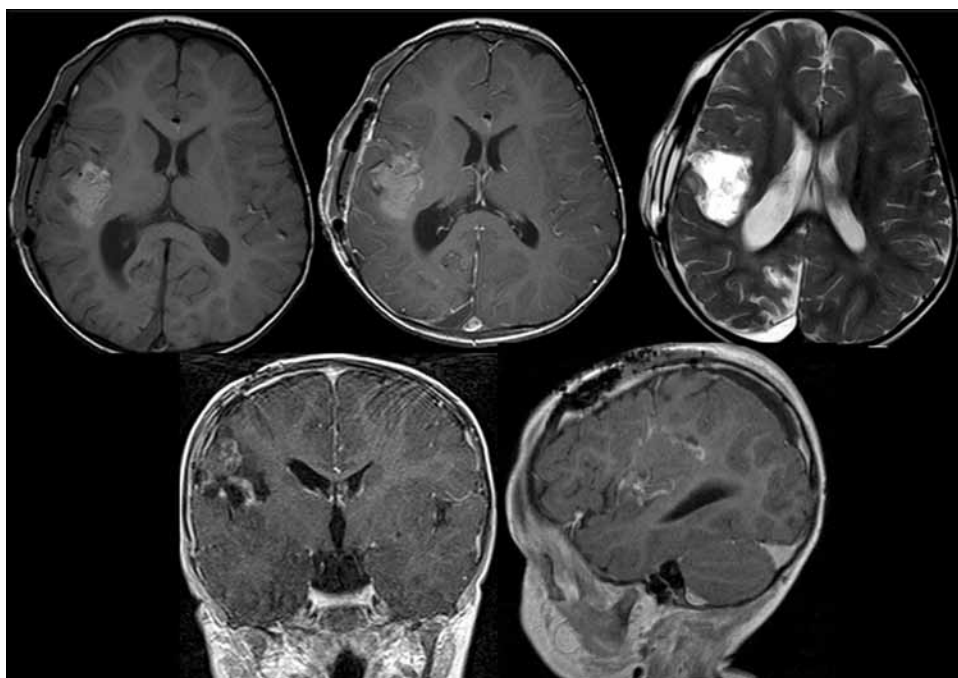

Fig. 7. Case 2. Follow-up MR images obtained 4 months after initial surgery showing tumor recurrence.
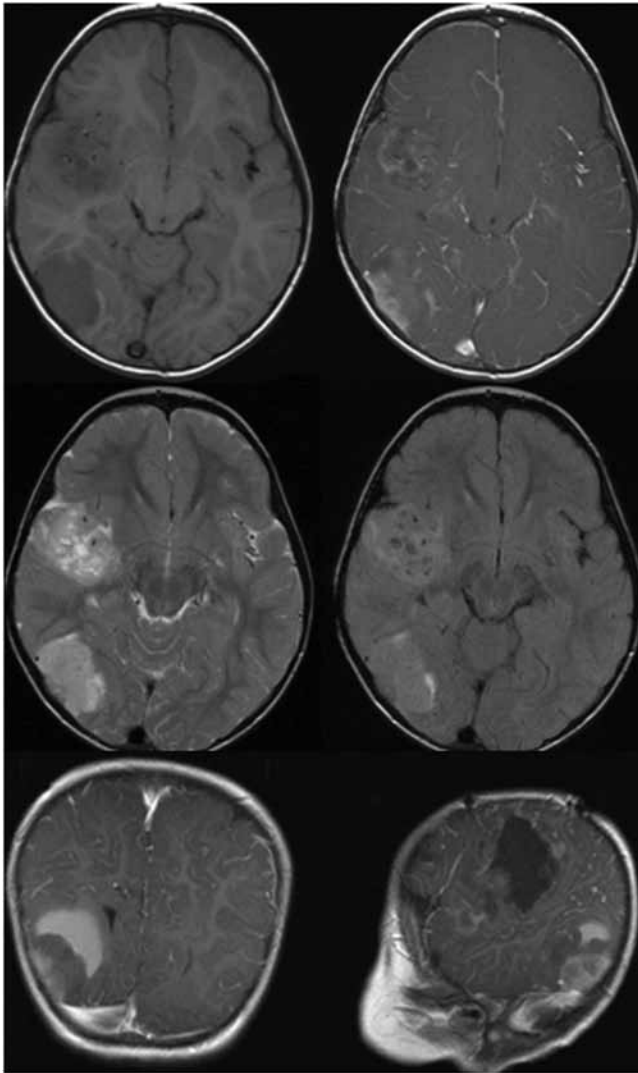
FIG. 8. Case 2. Follow-up MR images showing tumor recurrence after the second resection of the ETANTR, radiation, chemotherapy, and stem cell rescue.

TABLE 1: Histological differential diagnosis of ETANTR and characteristic features

Tumor Type	Histological Characteristics
ETANTR	multilayered true rosettes lacking a luminal basement membrane
medulloblastoma	Homer-Wright rosettes
medulloepithelioma	canalicular growth pattern; luminal basement membrane; divergent differentiation
anaplastic ependymoma	perivascular pseudorosettes; monolayered true rosettes

Of the 46 cases of ETANTR reported to date, the clinical outcome has been poor, with the longest survival found to be only 42 months. The largest series was reported by Gessi and colleagues,[9] who described 29 patients (7 cases from Eberhart and colleagues in 2000 and an additional 22 cases in 2009). Their patients ranged in age from 9 to 48 months. Older patients, who were treated with resection, chemotherapy, and radiation had a better outcome than younger infants, who had only resection and chemotherapy. The longest infant survival was 18 months. Al-Hussain and Dababo[1] reported on a 2-year-old girl with a vermian ETANTR tumor. She underwent near-total resection followed by chemotherapy but developed a recurrence in 6 months. In 2010, Buccoliero and colleagues[3] described a 2-year-old girl with a bihemispheric lesion of the parietooccipital lobes that was completely removed in 2 stages. In 2007, Dunham and colleagues[5] reported on a 2-year-old boy with a partly calcified cystic left temporoparietal hemispheric ETANTR who underwent near-total resection with no adjuvant therapy. He developed a poste-

rior fossa tumor recurrence after 11 months necessitating urgent debulking. The parents declined further treatment. In 2006, Fuller and colleagues[8] reported on 2 patients, a boy and girl, each 4 months old. The boy had a minimally enhancing, large, midpontine lesion that was debulked and subsequently treated with radiation and chemotherapy. He had stable disease at 19 months' follow-up. The girl, who had a left parietooccipital lesion, underwent 3 debulking procedures followed by high-dose chemotherapy and radiation but died within 6 months of the initial diagnosis. In 2006, La Spina and colleagues[13] reported on a 4-year-old boy with a nonenhancing partly cystic intrinsic brainstem ETANTR. Following resection, he underwent hyperfractionated craniospinal radiation and aggressive multiagent chemotherapy and was alive and disease-free 34 months after surgery. In 2009, Pfister and colleagues[15] described a 2-year-old girl with a vermian mass who underwent subtotal resection followed by chemotherapy, stem cell transplantation, and radiation therapy, with stabilization of disease at 16 months follow-up. In 2010, Ferri Niguez and colleagues[7] reported on 2 girls aged 9 and 23 months who both underwent resection and chemotherapy. The latter patient received radiation therapy also. However, both died after 10 months.

Conclusions

ETANTR has been identified as a histologically distinctive, PNET of the CNS. Ependymoblastic rosettes, previously felt to be diagnostic of ependymoblastoma, are more frequently seen in ETANTR than other embryonal tumors. Since the initial description of ETANTR in 2000, the limited reports in the literature have shown a female predominance. The patients are usually young children, presenting before the age of 4 years. ETANTR has unique cytogenetic features including focal genomic amplification of 19q13.42 as well as chromosome 2 polysomy. The treatment strategy is similar to that of PNETs, including resection, systemic chemotherapy, and craniospinal radiation when possible. Although this tumor has a high potential for malignancy and has been associated with a dismal prognosis, it appears that long-term survival is possible following radical surgery and adjuvant therapy, as we have reported in Case 1. As we learn more about the molecular and genetic basis of this malignant neoplasm, it may be possible to develop targeted and more effective therapies.

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Primitive neuroectodermal tumor after radiation therapy for craniopharyngioma

Case report

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The authors report a case of primitive neuroectodermal tumor induced by radiation therapy of craniopharyngioma. This African-American male patient originally presented with craniopharyngioma, for which he underwent resection and whole-brain radiation therapy. Eight years later, at the age of 20 years, he returned with a left facial droop and left hemiparesis. A right basal ganglia mass was identified and resected. Histopathological examination identified the lesion as primitive neuroectodermal tumor.

Although radiation therapy has shown to be beneficial in decreasing the recurrence rate in subtotally resected craniopharyngioma, the risks of radiation treatment should be clearly communicated to the patients, their families, and neurosurgeons before starting such treatment. This report expands the spectrum of reported radiation-induced neoplasms in the CNS. *(DOI: 10.3171/2010.11.FOCUS10224)*

KEY WORDS   •   craniopharyngioma   •   radiation-induced neoplasm   •   whole-brain radiation therapy   •   primitive neuroectodermal tumor

WHOLE-brain radiation therapy is part of the treatment for craniopharyngioma. One of the rare side effects of radiation therapy is the evolvement of tumors, including malignancies such as sarcomas, gliomas, and benign neoplasms such as meningiomas and schwannomas. Few cases of postradiotherapy PNET have been described in the literature. The majority of these rare cases occurred in patients who undergone WBRT for the treatment of acute leukemia, lymphoma, or astrocytoma. This paper is the first description of the development of a postradiotherapy PNET after resection of craniopharyngioma.

Case Report

History and Presentation. This young African-American man was initially treated in our institution in 1994 (at the age of 12 years) for craniopharyngioma (Fig. 1). At that time, he presented with left hemiparesis and a

Abbreviations used in this paper: GFAP = glial fibrillary acidic protein; PNET = primitive neuroectodermal tumor; WBRT = whole-brain radiation therapy.
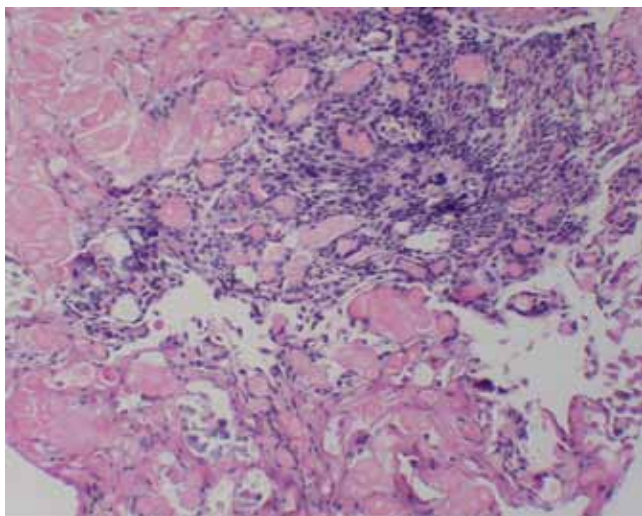
history of similar, transient episodes during the previous few months with deterioration during the last week. The patient denied having headache, nausea, vomiting, ataxia, or seizures. He underwent resection of the mass and was treated with 6 weeks of WBRT. During that time, he suffered from panhypopituitarism and blindness.

He returned in 2002, at the age of 20 years, with new-onset left facial droop and left hemiparesis.

Neuroimaging. An MR imaging study of the brain demonstrated a 2.5-cm enhancing lesion that was hypointense on T1-weighted images and hyperintense on T2-weighted images. The lesion involved the right basal ganglia, the genu of the internal capsule, and the posterior internal capsule (Fig. 2 left). The mass was not noted to involve the sellar region (Fig. 2 right). The tumor was noted to exert mass effect on the right lateral ventricle.

Operation and Postoperative Course. A brown-grayish necrotic tumor was subtotally resected via a right frontotemporopterional craniotomy.

The patient recovered from surgery with some improvement of motor strength. Histopathological examination of the tumor demonstrated a highly cellular neoplasm

Fig. 1. Photomicrograph of an H & E–stained section of the initial pathological specimen demonstrating craniopharyngioma. Original magnification × 400.

Fig. 3. Photomicrographs of sections of the second specimen (PNET) obtained 8 years after radiotherapy. **A:** An H & E–stained section demonstrating a highly cellular neoplasm composed of cells featuring round-to-oval nuclei and scanty cytoplasm, with significant pleomorphism. **B:** Synaptophysin immunoreactive staining of the PNET specimen demonstrating widespread immunoreactivity of tumor cells. **C:** Staining for GFAP showing focal immunoreactivity. **D:** Results of staining with Ki 67 proliferation marker showing staining in over 30% of tumor cells in the PNET specimen. Original magnifications × 400 **(A–C)** and × 200 **(D)**.

composed of cells with round-to-oval nuclei and scanty cytoplasm (Fig. 3A). Tumor cells showed widespread immunoreactivity for vimentin, neuron-specific enolase, and synaptophysin (Fig. 3B), and focal immunoreactivity for GFAP (Fig. 3C) and neurofilament protein. The results of immunohistochemical evaluation for keratin markers (AE1/AE3, CK7, CK20), carcinoembryonic antigen, Melan-A, epithelial membrane antigen, desmin, leukocyte common antigen, and smooth muscle–specific actin were negative. Mucicarmine staining was also negative. The Ki 67 proliferation marker stained over 30% of the tumor cells (Fig. 3D). The final diagnosis was a WHO Grade IV PNET. Postoperative imaging showed no residual mass (Fig. 4A).

Two months later, follow-up MR imaging of the brain demonstrated that the mass in the right basal ganglia was now 3.5 cm (Fig. 4B). Another follow-up MR imaging study 3 weeks later revealed that the mass was larger still, at 5.2 × 4.4 × 5.8 cm (Fig. 4C).

The patient's records are incomplete, but the reports indicate that he received a full regimen of radiotherapy in 1994 for his craniopharyngioma; thus he was no longer a candidate for radiation therapy. A chemotherapy regimen consisting of vincristine, lomustine, and prednisone treatment was initiated. The patient was subsequently lost to follow-up.

Discussion

Primitive neuroectodermal tumor is a rare type of tumor in the adult population, and cases of radiation-induced PNET are especially rare.[7,11] Possible risk factors for these tumors include young age at time of irradiation, genetic predisposition to malignancies, and genetic polymorphism in certain metabolic enzymes.[12] The case presented here meets all the requirements for a radiation-induced neoplasm as described by Cahan et al. in 1948.[3,5] These criteria are: 1) tumor originating from areas that were previously irradiated; 2) elapsed time between radiation treatment and the appearance of the radiation-induced lesion; 3) no other pathological conditions that will predispose to tumor development; and 4) the histological characteristics must be different from those of the primary lesion that prompted the radiation treatment.[3,5] In our patient, the PNET was found in the field of irradiation almost 9 years after the initial treatment, and showed histopathological characteristics that were markedly different from those of the initial tumor. Eleven of the 12 reports of radiation-induced PNET involved pediatric patients who had undergone combination treatment with methotrexate and whole-neuraxis irradiation. A supratentorial PNET was reported 12 years after irradiation for a Grade II
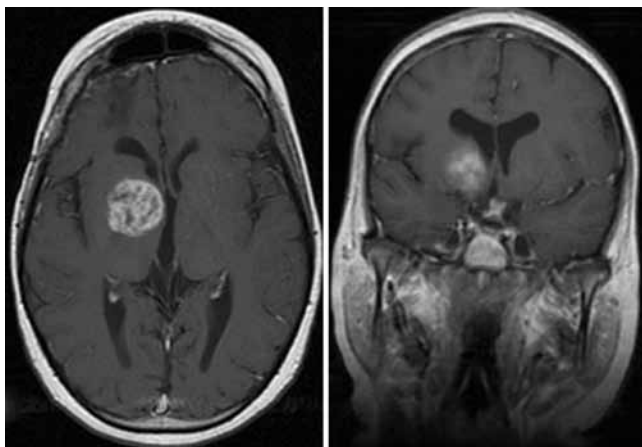

Fig. 2. Preoperative contrast-enhanced T1-weighted MR images. **Left:** Axial image showing a right enhancing lesion measuring 2.5 cm in diameter. **Right:** Coronal view demonstrating the lack of sellar involvement.
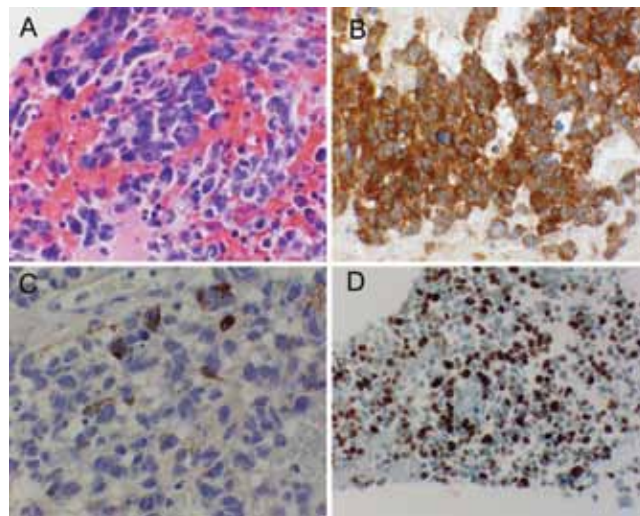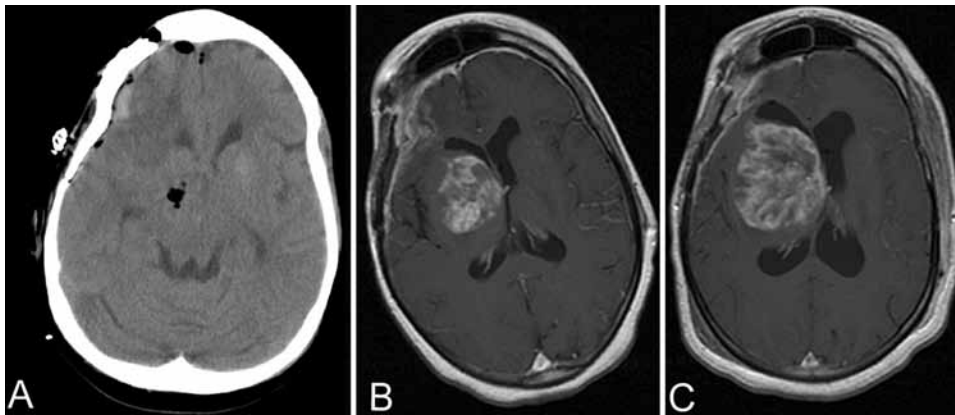
FIG. 4. Postoperative neuroimages. **A:** Noncontrast head CT obtained immediately after resection of the PNET, demonstrating no residual tumor. **B:** Axial contrast-enhanced T1-weighted MR image obtained 1 month postoperatively demonstrating a recurrent lesion measuring 3.5 cm in diameter. **C:** Axial contrast-enhanced T1-weighted MR image obtained 2 months postoperatively showing interval enlargement of the lesion, which is 5.8 cm in diameter in this image.

astrocytoma.[4] Multiple cases of postradiotherapy PNET were reported following initial diagnoses of pilocystic astrocytoma, ependymoma, and low-grade astrocytoma.[5,6,9] This is the first reported case of PNET after radiation therapy for the treatment of craniopharyngioma.

In the past, an association was found between mutation in the *K-ras* protooncogene and the development of PNET, implicating the combination of methotrexate and radiation therapy.[1,2,6] The current case report indicates that acute lymphocytic leukemia, lymphoma, and the combination of methotrexate and radiation therapy are not necessary for PNET development, but rather radiation alone can induce PNET. Even though radiotherapy is clearly beneficial in decreasing the recurrence rate in cases of subtotally resected craniopharyngiomas, the risks should be clearly articulated to the families and neurosurgeons before starting such treatment.[10,13] In the past, WBRT and proton beam therapy were used for the treatment of craniopharyngiomas.[8] In the modern era, single- or multifraction stereotactic radiosurgery would probably be employed.[14]

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Chan. Drafting the article: Chan, Herrera, Wallace. Critically revising the article: Neckrysh, Valyi-Nagy, Charbel. Reviewed final version of the manuscript and approved it for submission: Valyi-Nagy, Charbel.

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