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Laboratory Investigation

Clinicopathologic and cytogenetic analysis of malignant rhabdoid tumor of the central nervous system

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Introduction

Malignant rhabdoid tumor (MRT) is an aggressive neoplasm of infants and children with distinctive light microscopic, immunohistochemical, and ultrastructural features [1, 2]. Originally described in the kidney, the tumor also occurs in the liver [3], soft tissues [4], and paravertebral region [5]. Primary neoplasms of the brain such as primitive neuroectodermal tumors and astrocytomas have been found to arise in some patients with systemic MRTs [6–9]. Recently, primary MRT of the central nervous system (CNS MRT), unassociated with systemic tumors, has been described [1, 2, 10–19]. In the sixteen reported cases for which clinical information is available, these tumors appear to be similar to non-CNS MRTs in that they are aggressive, and usually fatal.

Abnormalities of chromosome 22 have been reported in four of five CNS MRTs in which cytogenetic analysis has been done [14, 20–22]; four of fourteen of the histologically similar non-CNS MRTs have abnormalities of chromosome 22 [3, 5, 22–26]. Because this primary brain tumor has been recognized less than a decade, and the number of karyotyped cases is small, we report three additional cases diagnosed at our pediatric hospital in the last three years. The combined clinical, histological, immunohistochemical, ultrastructural and cytogenetic studies in these three cases add to the evolving body of information about this unusual childhood CNS tumor.

Case histories

Case 1

A previously healthy 3-year-old boy presented with lethargy, vomiting, and weakness of the right arm of one week's duration. On neurological examination, he had mild hemiparesis and right-sided hyperreflexia. Magnetic resonance imaging (MRI) showed a 6 cm inhomogeneous mass, with surrounding edema, in the left frontoparietal area. No other masses were seen on body computerized tomography (CT). The patient underwent a left frontal craniotomy with subtotal tumor resection. Postoperatively, he received 5,400 cGy of cranial irradiation. Follow-up head CR showed no evidence of tumor regrowth or craniospinal metastasis. He remains with mild residual right-sided weakness 3 years after surgery.

Case 2

A previously healthy 5-month-old boy presented with a 2-week history of lethargy, vomiting, and esotropia. On neurological examination, he had a bulging anterior fontanelle, mild right hemiparesis, and downturning eyes. CT and MRI studies showed an inhomogeneous, partially cystic 4 cm mass in the posterior fossa, with dilation of the lateral ventricles. Metastases to the subarachnoid space of the lumbar spinal cord were also present, but there

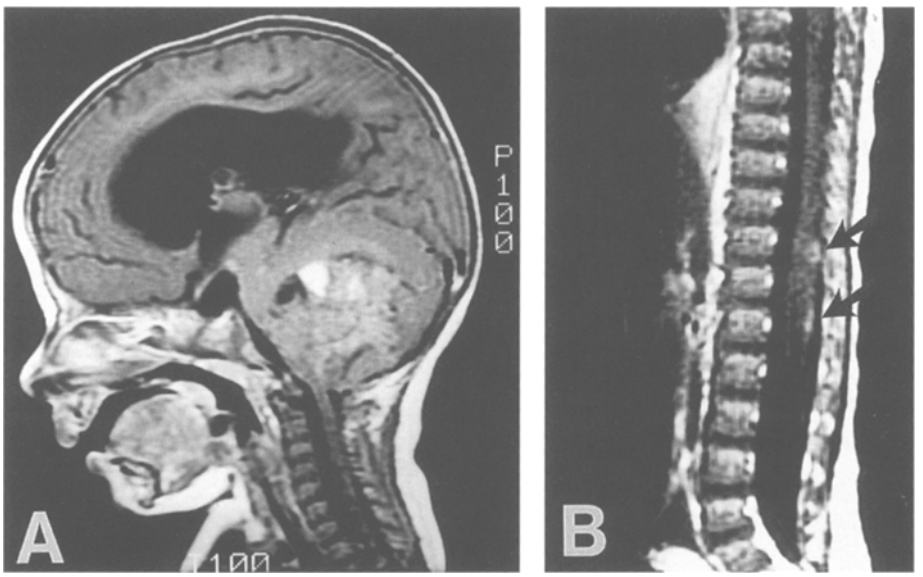


Fig. 1. (A) Parasagittal MRI of brain, Case 2, showing inhomogeneous tumor mass in posterior fossa. (B) Sagittal MRI of spine, Case 2, illustrating metastases to the subarachnoid space of the lumbar spinal cord (arrows).

were no tumor foci outside the craniospinal axis (Fig. 1). The patient underwent craniotomy with subtotal removal of tumor, and ventriculo-peritoneal shunt placement. At surgery, the tumor involved the left cerebellar hemisphere, filled the fourth ventricle, and extended into the medial right cerebellar hemisphere. The tumor was adherent to the brainstem and lower cranial nerves. Postoperatively, the patient was treated with steroids, but developed progressive neurologic impairment, and died two months after surgery. Permission for autopsy was refused.

Case 3

A 6-year-old boy was evaluated for a two-month history of severe bifrontal headaches and vomiting. The neurological examination was within normal limits. Cranial MRI revealed a 5 cm paramedian frontoparietal mass involving the corpus callosum and crossing the midline. The mass could only be partially resected because of invasion of septal structures and adhesion to ventricular walls. The patient subsequently received 5,207 cGy of cranial irradiation. He has an unremarkable neurological exam 22 months after surgery. Sequential MRI scans have shown a decreasing residual mass in the roof of the left lateral ventricle.

Materials and methods

Light microscopy

Tissue at the time of craniotomy was fixed in 10% neutral buffered formalin, and embedded in paraffin. Five micron sections were stained with hematoxylin-eosin (H&E). Selected sections were stained with periodic acid-Schiff (PAS) with and without diastase digestion, and with modified Gomori (reticulin) stain.

Immunohistochemistry

Immunohistochemical studies were performed on paraffin-embedded sections using a peroxidase technique [27] with polyclonal antibodies to keratins AE1/AE3 (Dako Corp., Santa Barbara, CA, 1:150 dilution), and glial fibrillary acidic protein (GFAP, Dako Corp., 1:500), and with monoclonal antibodies to epithelial membrane antigen (EMA, Dako Corp., 1:40) and vimentin (Dako Corp.,

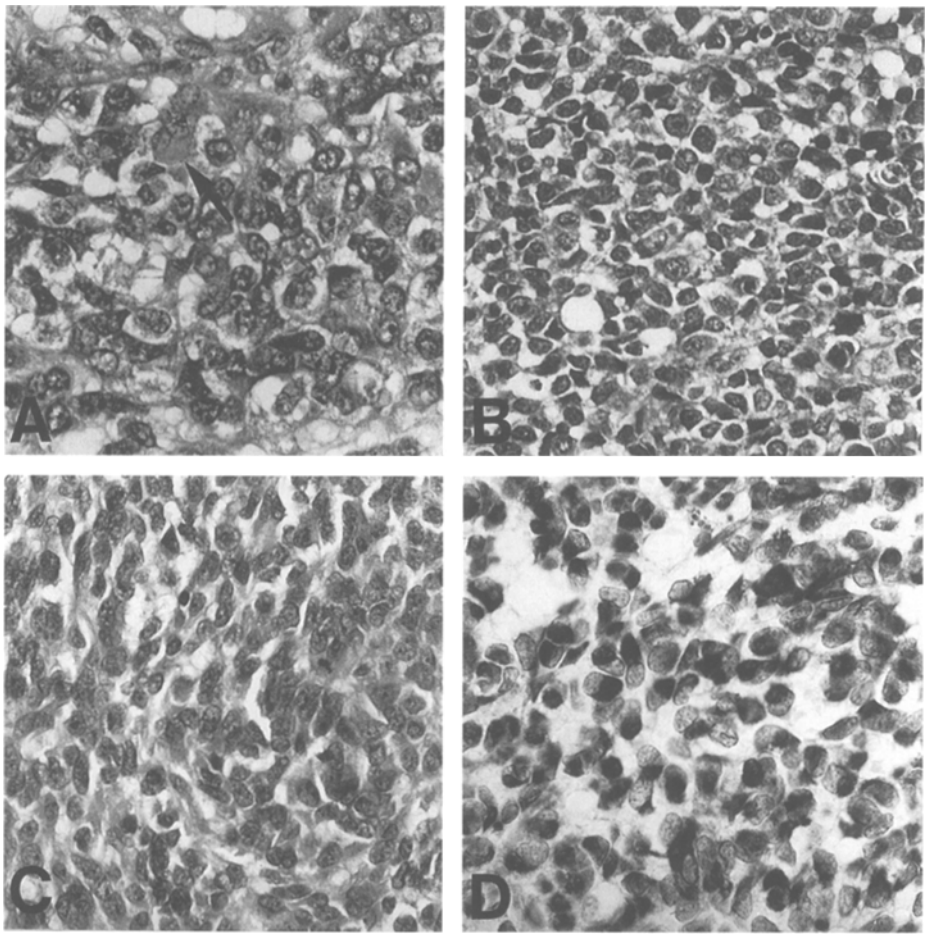


Fig. 2. Representative histology from posterior fossa mass, Case 2, showing globular cytoplasmic inclusion (arrow) (H&E, × 1680). (B) Representative histology from left hemisphere tumor, Case 1 (H&E, × 1320). (C) Representative histology from cerebral tumor, Case 3 (H&E, × 1320). (D) Tumor from Case 3, stained with monoclonal antibodies to vimentin, showing cytoplasmic immunoreactivity in a discrete, globular pattern (Anti-vimentin 1:100, × 1680).

1:100). Studies using an alkaline-phosphatase technique (Biogenics Basic Universal Kit) were performed with antibodies to desmin (Signet Labs, Dedham, MA), and myoglobin (Biogenix Labs, San Ramon, CA). Parallel-run sections of each tumor were incubated with normal serum instead of antibody solutions, and served as negative controls. Parallel-run sections of tissues appropriately specific for each antibody were positive controls (mesothelioma for keratins AE1/AE3 and EMA, gliotic spinal cord for GFAP, dermal nevus for vimentin and skeletal muscle for desmin and myoglobin).

Electron microscopy

Fresh tissue was fixed in a glutaraldehyde-paraformaldehyde solution, post-fixed in 1% osmium tetroxide, dehydrated, and embedded in epoxy resin. One micron sections were stained with toluidine blue, and selected embedded tissue was thin-sectioned on an LKB Ultra-Microtome. The sections, double-stained with uranyl acetate and lead citrate, were examined with a Phillips 300 electron microscope.

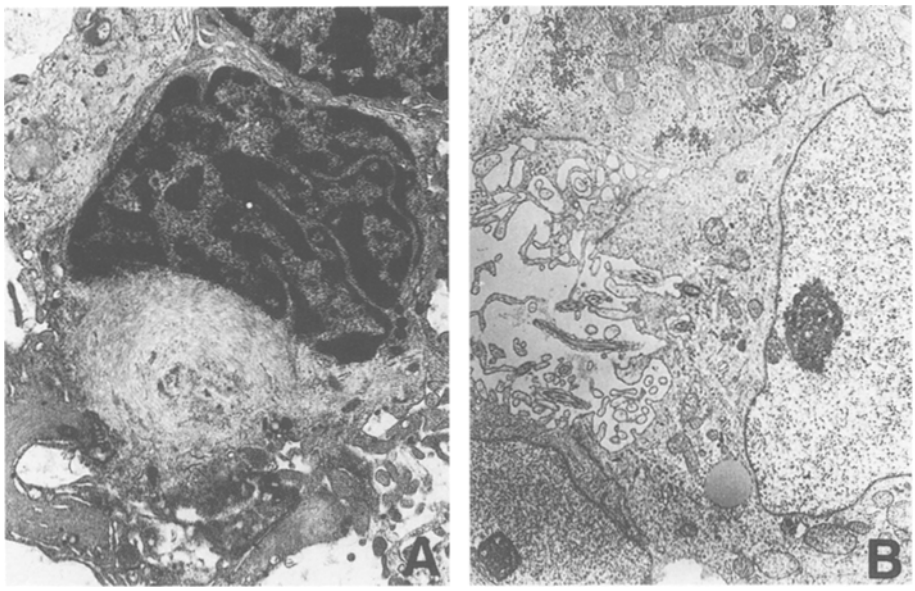


Fig. 3. (A) Electron micrograph from Case 3, showing tumor cell containing whorl of intermediate filaments indenting the nucleus (× 8640). (B) Electron micrograph from Case 2, showing tumor cell with open chromatin and prominent nucleolus, cilia, and intercellular junctions (× 5702).

Cytogenetics

Fresh tissue from all three tumors was disaggregated, cultured for 2–4 days, harvested and stained for karyotype analysis according to standard methods [28]. A minimum of 10 metaphases were analyzed from each tumor.

Results

Light microscopy

The tumors were composed of sheets and lobules of cells; in some areas, groups of cells were separated by abundant collagenous connective tissue. The tumor cells had irregular, hyperchromatic nuclei, which were often eccentric, and varying amounts of cytoplasm (Fig. 2). Many cells contained abundant eosinophilic cytoplasm with globular hyaline inclusions which failed to stain with PAS. The mitotic rate was high in all cases (average count: nine mitotic figures per ten high power microscope fields, range 7–14 per ten high power fields). In one of the tumors (Case 1), there were broad zones of necrosis with focal calcification. Increased vascular density without multilayered endothelial cell proliferation was also noted in Case 1.

Immunohistochemistry

All tumors stained positively with vimentin, predominantly as a discrete cytoplasmic globule. The staining was diffuse in one case (Case 3), and focal in the other two cases (Fig. 2D). One of the tumors (Case 2) also stained diffusely with epithelial membrane antigen (EMA), while the other tumors were negative. All tumors were negative for cytokeratin and markers of muscle differentiation (desmin in Cases 1 and 3, and myoglobin in Cases 1 and 2). The tumor cells in all cases were negative for GFAP. Rare large cells with cytoplasmic processes and strong staining for glial fibrillary acidic protein (GFAP) seen in two cases (Cases 1 and 2) were interpreted as entrapped reactive astrocytes.

Electron microscopy

The tumor cells from two of the cases (Cases 1 and 3) contained moderate amounts of cytoplasm and

primitive intercellular junctions. In both cases, many cells contained bundles of intermediate filaments closely apposed to the nucleus. In some cells, the intermediate filaments formed a discrete whorl which indented the nucleus (Fig. 3A). No evidence of neural, neuroendocrine, or skeletal muscle differentiation was seen in the tumor cells. The tumor from Case 2 contained cells with moderate amounts of cytoplasm and cytoplasmic aggregates of intermediate filaments similar to those seen in the other two cases. Some cells had well-developed intercellular junctions and cilia, as well as intracytoplasmic and intercellular lumina with microvilli (Fig. 3B); the nuclear features of these cells resembled those of tumor cells rather than entrappped ependymal cells.

Cytogenetics

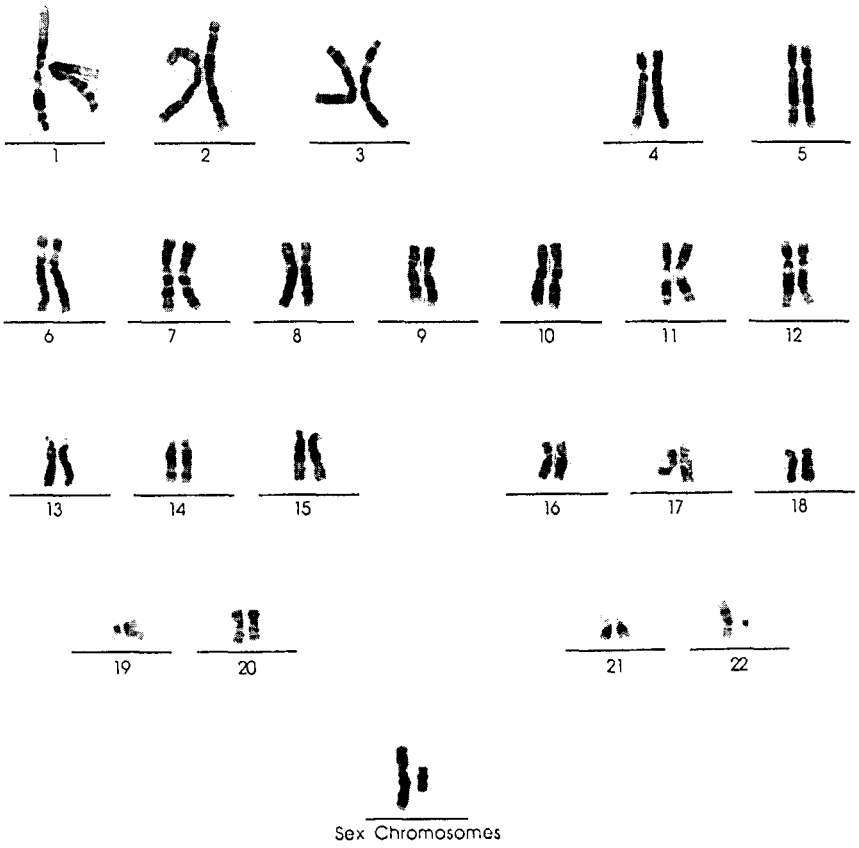
In Case 1, ten of eleven metaphases analyzed had the karyotype 46, XY, add(22)(p11), del(22)(q11). The net effect of the derivative chromosome 22 and deleted chromosome 22 is a loss of genetic material from the chromosome 22 long arm (Fig. 4A). In Case 2, six of sixteen metaphases analyzed had a clonal karyotype 45, XY, – 22 (Monosomy 22) (Fig. 4B). The remaining metaphases were 46, XY. In Case 3, thirteen of fourteen metaphases analyzed had a karyotype of 47, XY, + der(1)t(1;1)1qter→-1p12::1q22→1qter), effectively resulting in two extra copies of chromosome 1q material. Both copies of chromosome 22 were karyotypically normal (Fig. 4C).

Discussion

We present three cases of primary malignant rhabdoid tumor of the brain in children, with clinical, pathologic, and cytogenetic findings. Including our three cases, a total of 19 cases of CNS MRT with clinical and pathologic features have been reported. The mean age at diagnosis was four years (range, 3 months to 21 years) [1, 2, 10–19] (Table 1). CNS MRT is an aggressive neoplasm; 14 of 19 patients died of disease. The median length of survival among all cases was 8 months from diagnosis (range, 2 weeks to 2 years); in one unusual case, a 21-year-old patient survived for 6 years before succumbing to repeated recurrences [12]. About half of the cases involved the cerebral hemispheres, including all lobes, and half involved the posterior fossa, with six cases reported as specifically involving the cerebellum. The tumor was often difficult to resect at presentation due to extensive infiltration of the brain parenchyma. Leptomeningeal involvement, including metastases to the spinal meninges, was frequent, occurring in 8 of 19 cases (42%).

The histologic features of CNS MRT are a relatively monomorphous population of intermediate-sized cells with vesicular nuclei, whorls of intermediate filaments seen ultrastructurally, and immunoreactivity for vimentin. The sixteen previously reported cases of rhabdoid tumor of the brain showed similar findings (Table 1). An unusual finding in one of our cases (Case 2) is the ultrastructural finding of cilia and cytoplasmic lumina containing microvilli, not previously reported in CNS MRT. This finding is in keeping with the immunohistochemical evidence of epithelial differentiation in this tumor, highlighted by EMA immunoreactivity. Other tumors in the differential diagnosis of MRT include ependymomas and medulloblastomas. However, distinction of MRT from these relatively common tumors is made readily on routine light microscopy. The relationship of MRT to 'atypical teratoid tumors' of the brain, which have histologic features of rhabdoid tumors with neuroepithelial, peripheral epithelial, and mesenchymal elements, is unclear [29].

Previous reports of rhabdoid tumor of the brain have described cytogenetic abnormalities of chromosome 22, as seen in two of our cases (Table 2) [14, 21, 22]. These abnormalities, either monosomy, deletion or translocations involving the long arm (22q), were present in four of only five previously reported karyotypes of primary MRTs of the brain and in one tumor involving the spinal canal and retroperitoneum. Two of our cases (Cases 1 and 2) showed abnormalities of chromosome 22. One of our cases (Case 3) showed a different cytogenetic abnormality, an isolated gain of chromosome 1 material in the form of a derivative chromosome 1, similar to an isochromosome 1q; this finding is similar

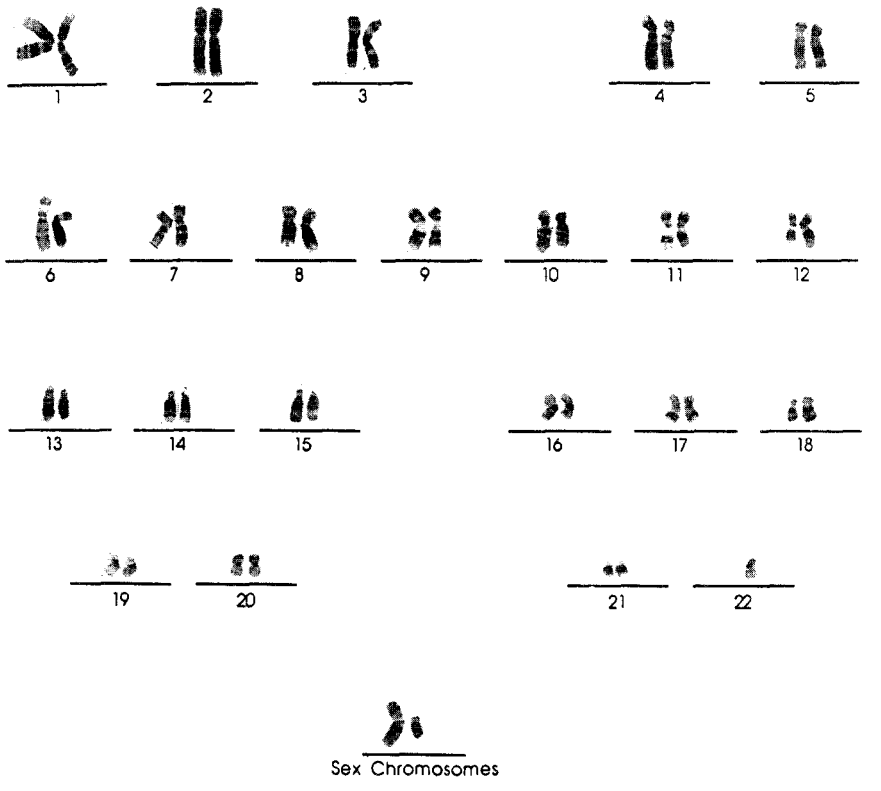


A

Fig. 4. (A) Karyotype from Case 1, showing 46,XY,add(22)(p11),del(22)(q11).

to an i(1q) present in a previously reported CNS MRT as well as a renal MRT [21, 25]. In the current case, however, both copies of chromosome 22 were karyotypically normal (see Fig. 4C). To our knowledge, this is the second reported karyotype of a primary MRT of the brain with a structurally normal chromosome 22 [20]. Although the finding of chromosome 22 abnormalities has been a consistent finding four of the five previously karyotyped CNS MRTs, it is neither specific for nor diagnostic of this tumor. Chromosome 22 monosomy, deletion or loss of genetic material have been reported in meningiomas, acoustic neuromas, and atypical teratoid tumors [14, 30–32]. Two recently reported cases of ependymomas in children also had abnormalities of chromosome 22 [33]. As for other CNS tumor types, only one of 21 karyotyped primary pediatric brain tumors (a cerebral astrocytoma) and none of seven medulloblastomas showed chromosome 22 abnormalities [32, 34].

The finding of monosomy, deletion and translocation involving the long arm of chromosome 22 in most malignant rhabdoid tumors of the brain suggests that loss of a specific gene or genes in this region may be involved in rhabdoid oncogenesis. However, as seen in one of our cases (Case 3), a karyotypic chromosome 22 abnormality is not a necessary finding in a brain tumor with the rhabdoid phenotype. Chromosome 22 abnormalities may in fact define a subset of CNS MRT, possibly with different clinical features. Alternatively, cases of CNS MRT with and without chromosome 22 abnormalities may be related at a molecular level, sharing a loss of genetic material which may be submicroscopic in some cases. An analogous phenomenon is seen in chronic myelogenous leukemia, in which cases lacking a Philadelphia chromosome have molecular evidence of bcr-abl rearrangement [35].



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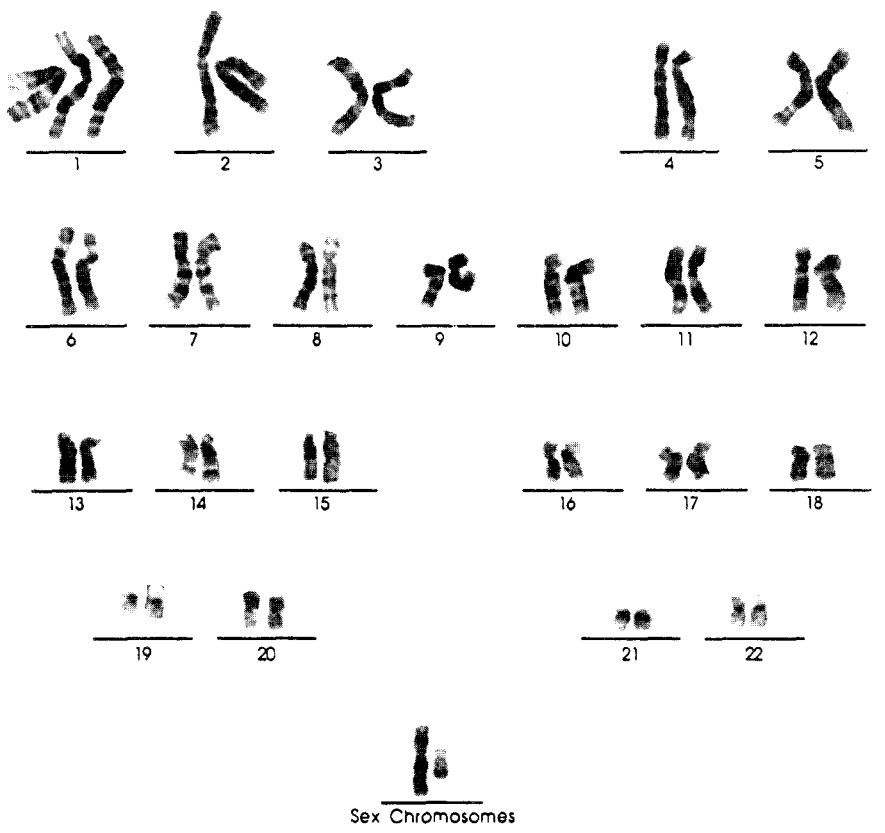

C

Fig. 4. (B) Karyotype from Case 2, showing 45,XY, monosomy 22. (C) Karyotype from Case 3, showing 47,XY,+ der(1)t(1;1)(1qter→1p12::1q22→1qter). Both copies of chromosome 22 are normal.

Conversely, other tumors with structural abnormalities in the long arm of chromosome 22, but without the rhabdoid phenotype, may have additional as yet undetermined molecular defects influencing their morphology and biologic behavior. Clearly, karyotypic data and molecular analysis of chromosome 22 on many more cases of CNS MRT are needed to clarify these issues.

The immunophenotype of CNS MRT (positivity for vimentin and often EMA) and predilection for leptomeningeal spread have led some authors to suggest a meningothelial origin of this tumor [2]. The similar cytogenetic findings of loss of chromosome 22 material in CNS MRT and in meningiomas also support an association between these tumors. However, only one reported case of MRT appears to have arisen from the meninges of the skull base [12]. Furthermore, the anaplastic histologic appearance, aggressive clinical course of these tumors, and almost exclusive occurrence in children contrast sharply with the bland histology, clinical behavior, and incidence of meningiomas, which are indolent neoplasms of adults. The finding of luminal microvilli in Case 2, a possible marker of ependymal differentiation, and the occurrence of chromosome 22 abnormalities in ependymomas may indicate a histogenetic relationship between MRT and ependymoma. One recently reported case of CNS MRT showed immunohistochemical and ultrastructural evidence of neuroglial differentiation [19]. Thus, CNS MRTs may represent a group of tumors with a shared phenotype, but with heterogeneous histogenesis.

Malignant rhabdoid tumor occurring outside the central nervous system is a well-recognized entity, occurring primarily as renal tumors in children, but also occurring in the liver and soft tissues [4, 6, 36]. Although histologically identical to CNS MRT, they have heterogeneous cytogenetic aberrations (Table 2) [3, 5, 22–26]. Four of fourteen of these systemic MRTs contain abnormalities of chromosome 22, with three of the four involving the long arm. Thus, a subset of systemic MRTs appear to be related to the CNS MRTs both histologically and cytogenetically, implying a common molecular mechanism in their origin. There is an intriguing associ-

Table 1. Summary of case reports of malignant rhabdoid tumor of the brain

Authors	Age	Sex	Location of tumor	Survival after diagnosis	Immunohistochemistry
Current cases (1995)	3 years	M	Left frontoparietal	Alive at 3 years	+ Vim (a)
	5 months	M	Posterior fossa, SAS (b)	DOD (c) at 2 months	+ Vim, EMA (d)
	6 years	M	Median frontoparietal	Alive at 22 months	+ Vim
Weeks *et al.* (1994)	26 months	M	Left frontoparietal	DOD at 7 months	+ Vim, GFAP (e), NSE (f), EMA
Cossu *et al.* (1993)	18 years	M	Left frontal lobe	DOD at 8 months	+ Vim, EMA, ± CK (g)
	14 years	F	Right tempero-occipital	DOD at 2 years	+ Vim, EMA, ± GFAP
	7 years	M	Left parietal lobe	Alive at 2 years	+ Vim, EMA
Agranovich *et al.* (1992)	2.5 years	M	Left hemisphere, SAS	DOD 8 months	+ Vim, NSE
Horn *et al.* (1992)	21 years	M	Left temporal fossa	DOD at 6 years	+ Vim, EMA
Chou *et al.* (1991)	18 months	F	Cerebellum, SAS	DOD at 8 months	+ Vim, EMA
	5 years	M	Cerebellum, SAS	DOD at 3 weeks	+ Vim, EMA
Perilongo *et al.* (1991)	6 years	F	Left occipital lobe	DOD at 1 year	+ Vim, EMA
Biegel *et al.* (1990)	1 year	F	Posterior fossa, SAS	DOD at 5 months	+ Vim, EMA, ± CK
	6 months	M	Cerebellum, SAS (h)	DOD at 1 month	+ Vim, EMA, ± CK
Ho *et al.* (1990)	4 years	M	Posterior fossa	DOD at 1 month	Not reported
Jakate *et al.* (1988)	3 years	F	Cerebellum	Alive at 5 months	+ Vim, EMA, + CK
Biggs *et al.* (1987)	3 months	M	Cerebellum, SAS	DOD at 2 weeks	+ Vim
Briner *et al.* (1985)	3 months	M	Left parietal lobe, SAS	DOD at 10 weeks	Not reported
Kapur *et al.* (1985)	5 years	M	Cerebellum	Not reported	Not reported

(a) + = Positive result, Vim = Vimentin. (b) Subarachnoid spread of tumor. (c) Dead of disease. (d) Epithelial membrane antigen. (e) Glial fibrillary acidic protein. (f) Neuron-specific enolase. (g) ± = Equivocal result, CK = Cytokeratin. (h) Patient had a concurrent renal rhabdoid tumor.

ation between primitive tumors of the brain that do not have the appearance of rhabdoid tumors, and rhabdoid tumors of the kidney and liver [6–9]. Pineoblastoma, primitive neuroectodermal tumors, and astrocytomas have been described, either preceding or following diagnosis of the systemic rhabdoid tumor. Cytogenetics have not been reported in these combined cases of systemic rhabdoid tumors and associated non-rhabdoid brain tumors. If shared karyotypic abnormalities were found in the CNS and systemic tumors in these cases, this would support a common genetic origin of systemic MRTs and primitive CNS neoplasms, including both CNS MRTs and non-rhabdoid brain tumors.

In summary, the pathologic and clinical findings of our three cases of CNS MRT broaden the spectrum of characteristics of this recently recognized primitive tumor. Two of our cases contain a structural abnormality of chromosome 22, similar to four of five previously reported karyotypes of CNS MRT. One of our cases has an abnormality of chromosome 1, as did a previously reported CNS MRT [21]. Further study, such as molecular analysis of CNS MRTs with a karyotypically normal chromosome 22 (as in our case 3) may be useful in determining the relationship, if any, of karyotypically inapparent chromosome 22 loss to the rhabdoid phenotype. The definition of CNS MRT as a distinct nosologic entity, as opposed to a subtype of known primary CNS tumor with a particular phenotype, will depend on clinical, immunophenotypic and cytogenetic data from a larger number of these tumors.

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Table 2. Cytogenetics in malignant rhabdoid tumor

Authors	Location of tumor	Cytogenetics
	Brain tumors	
Current cases (1995)	Left frontoparietal lobes	add(22)(p11), del(22)(q11)
	Posterior fossa	Monosomy 22
	Frontoparietal	+der(1)t(1:1)(p12;q22) (a)
Karnes *et al.* (1992)	Brain	der(2), del(16), ins(17), der(19) del(20) (a)
Biegel *et al.* (1992)	Left occipital lobe	− 9, − 22 + i(1q), + der(22)t(9;22)(p13;q11)
Biegel *et al.* (1990)	Posterior fossa	Monosomy 22
Biegel *et al.* (1990)	Cerebellum (b)	Menosomy 22
Douglass *et al.* (1990)	Brain	Monosomy 22, del 22(q11), + 20
	Systemic tumors	
Shashi *et al.* (1994)	Kidney	+ i(1)(q10), der(8)t(8;22)(q12; q11.2), der(22)t(8;22)(q23;q11.2)
Ota *et al.* (1993)	Kidney	del(22)(q11.2), − 22, t(2q;10q), t(4q;15q)
Karnes *et al.* (1991)	Spinal canal, retroperitoneum	t(11;22)(P15.5;q11.23)
Foschini *et al.* (1991)	Liver	t(1;8)(p36;q24)
Gansler *et al.* (1991)	Kidney	Normal
Douglass *et al.* (1990	Kidney (4 cases)	All normal
	Kidney (1 case)	del(13)(q14)
	Liver (1 case)	Normal
	Liver (1 case)	del(1)(q12), del(3)(p21)
	Soft tissue (1 case)	t(8;15)(q12;p11)
Handgretinger *et al.* (1990)	Intraspinal dura	t(18;22)(q21;p11.2)

(a) Simplified karyotype. (b) Patient had a concurrent renal rhabdoid tumor, karyotype not reported.

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