Primary malignant rhabdoid tumor of the brain: clinical, imaging, and pathologic findings.

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Primary Malignant Rhabdoid Tumor of the Brain: Clinical, Imaging, and Pathologic Findings

Soheil L. Hanna, James W. Langston, David M. Parham, and Edwin C. Douglass

PURPOSE: To describe the imaging and pathologic findings of malignant rhabdoid tumor (MRT), a rare primary brain neoplasm affecting children. METHODS: The CT and/or MR features, pathologic findings, and clinical records of three children with primary MRT of the brain were retrospectively reviewed. RESULTS: The tumors, large, left-sided cerebral masses, were intraventricular in two cases. MR images in one patient showed T1- and T2-weighted signal intensity isointense with gray matter. Multiple necrotic/cystic foci were present in all cases, with two showing a patchy pattern of enhancement on CT and MR. The diagnosis of MRT was documented by ultrastructural and immunohistochemical studies. All patients had normal abdominal CT scans, excluding the possibility of primary renal rhabdoid tumor metastatic to the brain. The disease progressed rapidly in each case, despite surgery, chemotherapy, and craniospinal irradiation, with serial imaging evidence of tumor regrowth at the primary site and the development of metastatic satellite lesions. CONCLUSIONS: The diagnosis of primary MRT of the brain can be made only pathologically; however, the nonspecific imaging findings in these cases suggest that MRT should be considered in the differential diagnosis of large childhood intracranial neoplasms.

Index terms: Brain neoplasms, in infants and children; Sarcoma; Pediatric neuroradiology

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Malignant rhabdoid tumor (MRT) is an uncommon childhood neoplasm that typically arises within the kidney. It is characterized by an aggressive clinical course. Since its recognition in 1978 (1), six cases of primary intracranial MRT have been reported (2–7). Only two of these included a description of the imaging findings (6, 7). This report presents three additional cases with their clinical, imaging, and pathologic findings.

Materials and Methods

Clinical Findings

We reviewed the clinical, imaging, and pathologic features of three patients with primary MRT of the brain, one boy and two girls, aged 8, 25, and 66 months at the time of presentation. The diagnosis of MRT was established by light and electron microscopy and immunohistochemistry following partial or total tumor resection.

Imaging Findings

CT brain scans before and after intravenous contrast enhancement were obtained preoperatively in two patients. The third patient underwent magnetic resonance (MR) imaging. All patients also underwent contrast-enhanced computed tomography (CT) scans of the abdomen at the time of diagnosis to exclude primary renal tumors. Postoperative follow-up brain imaging was routinely performed using CT or MR to assess the effects of chemotherapy and craniospinal irradiation.

TABLE 1: Summary of clinical findings in patients with primary malignant rhabdoid tumor of the brain

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>F</td>
<td>Lethargy, ataxia, disconjugate vision, fever, and vomiting</td>
<td>Partial resection; chemotherapy,(^a) craniospinal RT (4950 cGy)(^b)</td>
<td>Died 6 months postoperatively</td>
<td>Not performed</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>M</td>
<td>Lethargy, increased irritability, right extremity tremors, and vomiting</td>
<td>Total resection; chemotherapy,(^c) craniospinal RT (5000 cGy)(^b)</td>
<td>Died 15 months postoperatively</td>
<td>Not performed</td>
</tr>
<tr>
<td>3</td>
<td>5.5</td>
<td>F</td>
<td>Diplopia and fatigue</td>
<td>Total resection; chemotherapy,(^d) craniospinal RT (6255 cGy)(^b)</td>
<td>Died 6 months postoperatively</td>
<td>Not performed</td>
</tr>
<tr>
<td>Cases reported in the literature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotelo-Avila et al (2), 1986</td>
<td>13.3</td>
<td>M</td>
<td>Headache, tonic-clonic seizures</td>
<td>Partial resection; RT (3,780 cGy)</td>
<td>Died 3 months postoperatively</td>
<td>Not performed</td>
</tr>
<tr>
<td>Briner et al (3), 1985</td>
<td>0.2</td>
<td>M</td>
<td></td>
<td>Partial resection</td>
<td>Died 2.5 months postoperatively</td>
<td>Frontal meningeal metastases</td>
</tr>
<tr>
<td>Kapur et al (4), 1986</td>
<td>5.8</td>
<td>M</td>
<td>Apathy, hypotonia, hyperirritability, increased head size, and seizures</td>
<td>No treatment</td>
<td>Died 0.5 months following presentation</td>
<td>Tumor extension throughout subarachnoid space with invasion of frontal lobes</td>
</tr>
<tr>
<td>Biggs et al (5), 1987</td>
<td>0.1</td>
<td>M</td>
<td>Lethargy, neck pain, morning vomiting, and squint</td>
<td>Partial resection; chemotherapy; craniospinal RT</td>
<td>Alive 5 months postoperatively</td>
<td>No further follow-up</td>
</tr>
<tr>
<td>Jakate et al (6), 1988</td>
<td>3</td>
<td>F</td>
<td>Lethargy, neck pain, morning vomiting, and squint</td>
<td>Partial resection; chemotherapy; craniospinal RT</td>
<td>Died 9 months</td>
<td>Not performed</td>
</tr>
<tr>
<td>Ho et al (7), 1990</td>
<td>4</td>
<td>M</td>
<td>Headache, poor appetite, and drowsiness</td>
<td>Partial resection; RT (1,340 cGy)</td>
<td>Died 1 month postoperatively</td>
<td>Not performed</td>
</tr>
</tbody>
</table>

Note.—RT = radiation therapy.
\(^a\) Intrathecal methotrexate, intravenous nitrogen mustard and vincristine.
\(^b\) Doses are total irradiation delivered to primary tumor area.
\(^c\) Cyclophosphamide, vincristine, cisplatin, and etoposide.
\(^d\) Ifosfamide, etoposide, and carboplatin.

Pathology

Formalin-fixed tissue in paraffin blocks was available in all three tumors. The avidin-biotin-complex (ABC) peroxidase-complex procedure was applied to sections from each tumor, using antibodies including monoclonal antivimentin (VIM), anticytokeratin (CK), antiLeu-7 (LEU), antiepithelial membrane antigen (EMA), antiligil fibrillary acidic protein (GFAP), polyclonal antineuron-specific enolase (NSE), and anti-S100 protein (S100). For negative controls, normal rabbit serum or purified mouse plasmacytoma ascites fluid was substituted for similar dilutions of polyclonal and monoclonal antisera, respectively. Sections of skin, colon carcinomas, brain, colon, and peripheral nerve were used as positive controls. All controls yielded the anticipated reactions.

Material for electron microscopic examination was available in two cases (cases 2 and 3). Preliminary sections were cut at approximately 0.4 μm and stained with toluidine blue, and representative blocks demonstrating tumor were selected. Sections of these blocks were then stained with uranyl acetate and lead citrate and examined with a transmission electron microscope.

Results

Clinical Findings

The clinical findings and postoperative courses of the three patients with MRT are summarized in Table 1. Lethargy, vomiting, and vision disturbances were the predominant presenting symptoms. All patients had large cerebral tumors, with the maximum transverse dimension ranging from 5 to 7 cm. The tumor was left-sided in each case; two tumors were intraventricular, involving the left frontal horn (case 2) and left trigone (case 3). In all three cases, the disease progressed rapidly, resulting in death within 15 months from diagnosis, despite intensive postoperative therapy including irradiation of the primary site (4950-
### Table 2: Imaging findings of primary malignant rhabdoid tumor of the brain

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Unenhanced CT Density</th>
<th>Calcification</th>
<th>MR* T1W</th>
<th>T2W</th>
<th>Enhanced Pattern</th>
<th>Necrosis/ Cyst</th>
<th>Edema</th>
<th>Serial Postoperative CT/MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L parietal</td>
<td>6 x 5 x 5.5</td>
<td>Patchy iso-</td>
<td>None</td>
<td>UA</td>
<td>UA</td>
<td>Patchy</td>
<td></td>
<td></td>
<td>Growth at primary site,</td>
</tr>
<tr>
<td></td>
<td>lobe</td>
<td></td>
<td>hyperdense</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>new frontal satellites</td>
</tr>
<tr>
<td>2</td>
<td>L frontal</td>
<td>7 x 5 x 6</td>
<td>Slightly hyper-</td>
<td>Few flecks</td>
<td>UA</td>
<td>UA</td>
<td>Diffuse</td>
<td></td>
<td></td>
<td>Growth at primary site,</td>
</tr>
<tr>
<td></td>
<td>horn (in-</td>
<td></td>
<td>dense</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>new cerebellopontine</td>
</tr>
<tr>
<td></td>
<td>tranventricular)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>satellites</td>
</tr>
<tr>
<td>3</td>
<td>L trigone</td>
<td>5.5 x 5 x 5</td>
<td>UA</td>
<td></td>
<td>UA</td>
<td>UA</td>
<td>Isointense</td>
<td></td>
<td></td>
<td>Growth at primary site,</td>
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<td></td>
<td>(intran-</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>new cerebellar and</td>
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<tr>
<td></td>
<td>ventricular)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cerebellopontine satellites</td>
</tr>
</tbody>
</table>

Cases reported in the literature

- Soto-Avila et al (2), 1986: L temporal lobe, 5 x 4
- Briner et al (3), 1985: L parietal lobe, large (into lateral ventricle)
- Kapur et al (4), 1986: Cerebellum
- Biggs et al (5), 1987: Cerebellum
- Jakate et al (6), 1988: L cerebellum, large (into fourth ventricle)
- Ho et al (7), 1990: Multifocal, dense

Note—L = left; UA = unavailable; T1W = T1-weighted; T2W = T2-weighted.

* T1- and T2-weighted tumor signal characteristics compared to normal gray matter.

* Unenhanced CT tumor density compared to normal gray matter.

* Size of largest necrotic/cystic focus.

6255 cGy) and multiagent chemotherapy (see Table 1).

**Imaging Findings**

Imaging results are given in Table 2. The unenhanced preoperative CT scans in cases 1 and 2 showed a varying density pattern, ranging from iso- to slight hyperdensity in relation to normal gray matter (Figs. 1A and 2A). There were a few scattered flecks of calcification present in one tumor (case 2). The signal characteristics of the solid tumor component of the single case imaged by MR (case 3) paralleled those of normal gray matter on T1- and T2-weighted images (Figs. 3A and 3B).

The contrast-enhanced preoperative CT and MR scans showed a patchy pattern of enhance-
Fig. 1. Case 1: 25-month-old girl with left parietal primary MRT.
A, Unenhanced transverse CT image shows a large left supraventricular, parafalcine mass of mixed density and prominent adjacent edema.
B, Contrast-enhanced image at the same level shows intense patchy peripheral enhancement and central necrosis.
C, Postoperative contrast-enhanced CT image obtained 1-month following partial resection shows tumor regrowth about the primary site and a new frontal tumor satellite (arrow).

Fig. 2. Case 2: 8-month-old boy with frontal intraventricular primary MRT.
A, Unenhanced transverse CT image shows an intraventricular slightly dense tumor centered about the left frontal horn and crossing to the opposite horn.
B, Contrast-enhanced image at the same level shows intense diffuse tumor enhancement with several 1.5-cm necrotic/cystic areas.
C, Posttreatment contrast-enhanced CT image obtained 10 months later shows a large extraaxial cerebellopontine tumor satellite.
D, Electron micrograph of tumor cell demonstrating a prominent cytoplasmic inclusion composed of tightly packed whorls of intermediate filaments (F = filaments, N = nucleus; X12,400).
Fig. 3. Case 3: 66-month-old girl with left lateral intraventricular primary MRT.

A and B, Transverse T1-weighted (520/15) (A), and T2-weighted (2500/90) (B) images obtained at the same level show a large mass predominantly isointense with gray matter centered about the trigone of the left lateral ventricle. There is moderate associated parenchymal edema consistent with brain invasion.

C and D, Postcontrast transverse (C) and sagittal (D) T1-weighted (520/15) images show patchy tumor enhancement with small central nonenhanced necrotic areas.

E, Postcontrast transverse T1-weighted (520/15) image obtained 2 weeks after surgery shows linear enhancement about the margins of resection consistent with gliosis without evidence of residual tumor. Note also, smooth dural postoperative enhancement.

F, Transverse contrast-enhanced T1-weighted image (520/15) at the same level as E obtained 1.5-month later shows nodular (solid arrow) and thick irregular enhancement (open arrows) about a portion of the surgical margins consistent with tumor recurrence.
Fig. 3. Continued. G, Coronal contrast-enhanced T1-weighted image (700/30) obtained 4 months after F shows continued tumor growth at the primary site (arrowheads) and interval development of enhancing metastases (white arrows).

H, Photomicrograph illustrating tumor composed of diffuse sheets of cells with eccentric nuclei (straight black arrows), prominent nucleoli (white arrows), abundant cytoplasm, and discrete cytoplasmic inclusions (curved arrows) (hematoxylineosin, ×450).

I, Antivimentin stain illustrating strong brown (arrows) cytoplasmic immunoreactivity (ABC method, ×450). This correlates with the filamentous bundles detected by electron microscopy and is a characteristic feature of rhabdoid tumors at all sites.

J, Antiepithelial membrane antigen stain illustrating brown (arrows) membranous immunoreactivity (ABC method ×450). Epithelial membrane antigen reactivity is also a characteristic feature of rhabdoid tumors at all sites.

K, Antineuron-specific enolase stain illustrating moderate to weak brown (arrows) cytoplasmic immunoreactivity (ABC method, ×450). Immune reaction for this antigen may be indicative of neural differentiation or histogenesis.

ment of the solid tumor component in two cases (Figs. 1B, 3C, and 3D) and a uniform pattern in one (Fig. 2B). All tumors showed multiple necrotic/cystic foci of 1.0 to 2.5 cm diameter. Images of two tumors revealed moderate to marked adjacent brain edema; the other lesion (case 2) was entirely intraventricular and caused only interstitial edema secondary to obstructive hydrocephalus (Fig. 2). Serial CT and/or MR imaging following either total or partial tumor resection indicated tumor regrowth at the primary site (Figs. 1C, 3E, and 3F) and new, rapidly
TABLE 3: Light microscopic and immunohistochemical features of primary malignant rhabdoid tumors of the brain

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Light Microscopy</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>2</td>
<td>1+</td>
<td>3+</td>
</tr>
<tr>
<td>3</td>
<td>3+</td>
<td>3+</td>
</tr>
</tbody>
</table>

Note.—N = typical nuclei; C = typical cytoplasm; I = cytoplasmic inclusions on routine staining; P = histologic pattern according to Weeks et al (8); Cl = classical pattern; Sp = spindled pattern; Sc = sclerosing pattern; Ep = epithelioid pattern; VIM = vimentin; CK = cytokeratin; EMA = epithelial membrane antigen; GFAP = glial fibrillary acidic protein; NSE = neuron-specific enolase; LEU = Leu-7; S100 = S100 protein; 0 = no tumor cells positive; 1+ = <10% of tumor cells positive; 2+ = 10-50% of tumor cells positive; 3+ = >50% of tumor cells positive.

growing meningeal masses consistent with metastases (Figs. 1C, 2C, and 3G).

Pathology

On routine stains, the cases contained cells with typical "rhabdoid" features, ie, eccentric nuclei, prominent "owls-eye" nucleoli, abundant brightly eosinophilic cytoplasm, and discrete cytoplasmic hyaline inclusions (Fig. 3H). Areas of "spindled" pattern were predominant in cases 2 and 3, whereas case 1 contained areas with the classic diffuse pattern (8) (see Table 3). Epithelioid areas were present in cases 1 and 3, and a minor component of sclerosis was present in case 2.

Areas of vimentin immunoreactivity were the most consistent immunohistochemical finding (Table 3), and revealed cytoplasmic inclusions not recognizable on routine stains (Fig. 3J). Cytokeratin immunoreactivity and varying degrees of membranous staining for epithelial membrane antigen (Fig. 3J) were present in all cases. Case 3 exhibited moderate cytoplasmic staining with anti-GFAP. The neural markers NSE, Leu-7, and S100 were variably present, but did not appear to follow a discernable pattern (Fig. 3K).

Electron microscopy, available in cases 2 and 3, revealed intermediate filaments within numerous cells in both cases. Case 2, in particular, had characteristic compact whorls of intermediate filaments (Fig. 2D). Cytoplasmic lipid vacuoles were present in case 2 and abundant in case 3. Cytoplasmic processes were present in both cases studied. Case 3 contained occasional aggregates of neurosecretory granules and parallel arrays of 25-nm microtubules. Both cases also contained numerous primitive intercellular junctions, especially in areas of process formation.

Discussion

MRT is a rare and extremely aggressive malignancy, originally regarded as a "rhabdomyosarcomatoid" variant of Wilms tumor associated with a poor prognosis (1). Since that early description, there have been several reports of primary extra-renal MRTs arising from a variety of sites, including the paravertebral region (9), chest wall (10), heart (11), liver (12), pelvis (13), uterus (14), vulva (15), prostate (16), soft tissues (17), and brain (2–7). Of six previously documented cases of primary MRT of the brain, imaging findings (CT) have been presented for only two (6, 7). Our series of three cases provides an opportunity to evaluate the tumor's clinical, imaging, and pathologic features.

The term "rhabdoid" was applied to these tumors because of their light microscopic resemblance to rhabdomyosarcoma. However, subsequent ultrastructural and immunohistochemical studies did not substantiate myogenous differentiation, indicating instead that MRT is a unique neoplasm of undetermined histogenesis, unrelated to either rhabdomyosarcoma or Wilms tumor (18, 19). Our cases fulfill the criteria for the diagnosis of MRT, including the presence of cytoplasmic aggregates of intermediate filaments, and keratin and vimentin immunoreactivity. Of particular interest is the finding of neural differentiation by both immunohistochemistry and electron microscopy. A prominent early theory held that renal MRTs were neuroectodermal in origin (20). Support for this theory comes from evidence of hormonal activity (21) and the observation of a greater than expected association between renal MRTs and primitive neuroectodermal tumors of the central nervous system (22, 23). This theory might explain the intraventricular location of two of our tumors, given the central location of the primordial neurons.

When MRT is diagnosed in the brain, an occult renal primary must be considered. In our three cases, abdominal CT scans demonstrated normal kidneys. Given the relentlessly progressive course of these tumors, it is highly unlikely that renal
MRT or other intraabdominal primaries would be clinically undetected.

The mean age of our patients (2.7 years) was similar to that of previously documented primary MRTs of the brain (2–7) listed in Tables 1 and 2. Two of our patients were female, whereas five of six previous cases have been in males. All of our patients had left cerebral tumors; locations in the previous cases were left cerebral (2, 3), posterior fossa (4–6), and multifocal (7). Two tumors in our series were intraventricular, whereas two of the four previous cases with sufficient surgical data (3, 6) indicated ventricular invasion. Serial postsurgical imaging in our patients revealed not only relapse at the primary site but also the development of rapidly growing meningeal masses consistent with leptomeningeal metastases. The latter finding was present in two of the previously reported cases (3, 5) and was likely responsible for the initial multifocal presentation of the tumor in another (7).

Our patients had a mean survival of 9 months from the time of surgery. The previous cases had even poorer outcome (median survival, 2.5 months). This discrepancy could reflect the aggressive postsurgical therapy used in our patients, including irradiation of the primary site. Of the six previous cases, one died prior to treatment (5) and one had surgery alone (3); only three patients had received chemotheraphy and/or irradiation following surgery (2, 6, 7). No treatment information was reported for the remaining patient (4).

Although the preoperative imaging findings described here are nonspecific, there was some consistency among the three cases. All tumors were large and had multiple necrotic/cystic foci 1.0 to 2.5 cm in diameter. Two tumors had a patchy pattern of enhancement on CT and MR and were associated with moderate to marked adjacent parenchymal edema consistent with the aggressive nature of the tumor. The fact that two tumors in our series were located within the lateral ventricle suggests consideration of primary MRT in the differential diagnosis of large childhood lateral ventricular masses, which includes choroid plexus papilloma/carcinoma, primitive neuroectodermal tumor, and teratoma (24). The presence of enlarged ventricles and cisterns that are not mechanically obstructed by the tumor may favor choroid plexus papilloma, but the remaining diagnoses have CT findings similar to those seen with MRT.

In case number 3 in our series, no specific MR features were demonstrated. Although the T1- and T2-weighted signal characteristics of the solid tumor component were similar to those most commonly encountered with meningioma (25, 26), the enhancement pattern was distinctly different. Histologically, the T1- and T2-weighted tumor isointensity with gray matter was found to reflect prominent tumor cellularity characterized by diffuse sheets of round-to-oval tumor cells.

In summary, MRT of the brain is a rare, rapidly fatal primary brain tumor that should be considered in the differential diagnosis of large childhood intracranial neoplasms. The imaging findings in our series, although nonspecific, reflect the aggressive nature of the tumor. The striking tendency of this tumor to relapse and spread via the leptomeninges indicates the need for contrast-enhanced MR in the initial and serial assessments of disease extent.

Acknowledgments

We are grateful to Drs Tom Callihan and Olga Lassiter for loaning us the paraffin blocks on cases 1 and 2, to Hallie Holt for the immunohistochemical stains, and to Alice Slusher and Vicki Denison for electron microscopy assistance.

References