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Clinical Study

Primary malignant rhabdoid tumor of the central nervous system – a comprehensive review

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Summary

This paper presents the case of an eight-year-old girl who presented with headache and vomiting and was found to harbor a right fronto-temporo-parietal, partially cystic and centrally solid tumor that measured 11 × 8 × 7 cm. This vascular tumor was gross totally removed. The initial histopathologic diagnosis was hemangiopericytoma and the patient received a total dose of 5330 cGy of external cranial radiation. Twelve months later, the patient presented with left lower quadrant pain and limping and the spinal MR scans showed metastases at T4-5, T7, T12-L1 and L3 levels. The voluminous lesion at T12-L1 was surgically removed. Histopathological examination of both specimens revealed that both tumors in fact were malignant rhabdoid tumor (MRT). The patient did not benefit from spinal surgery and died 4 months later. A review of the literature has shown that since Briner et al'. first report in 1985 [Pediatr Pathol 3: 117–118, 1985], 100 MRT cases have been published. More than two-thirds of reviewed cases presented with local recurrence or subarachnoid spread after a mean period of 6.9 months after diagnosis and died two months later. Infratentorial and pineal location and surgery limited to biopsy were poor prognostic indicators. Twenty-two cases remained alive at a mean period of 24.5 months. The longest survival with an intracranial MRT was 65 months. Of those remaining alive, 15 had no evidence of disease (NED). Our case is the first MRT case immunopositive for HMB-45 and has also shown that the MRT cells grow aggressive over time as demonstrated by a four-fold increase in MIB-1 labeling index.

Introduction

Malignant rhabdoid tumor (MRT) is an uncommon and highly aggressive childhood neoplasm originally described in the kidney as the ''rhabdomyo-sarcomatoid'' variant of Wilms tumor during the evaluation of National Wilms' Tumor Study results [1]. Fortunately accounting only for 2% of renal neoplasms of childhood, renal MRT usually develops within the first two years of life and carries an extremely poor prognosis [2]. The term rhabdomyosarcomatoid (and later rhabdoid in short) described tumor's close resemblance to rhabdomyosarcoma under the light microscope consisting of tumor cells with eccentric nuclei and prominent bulging eosinophilic cytoplasm. Soon after its recognition as a separate entity [3], it became evident that MRTs were not confined to kidney. Examples of extra-renal primary MRTs arising from a variety of sites, including the chest wall, thymus, heart, liver, pelvis, uterus, vulva, prostate, bladder, soft tissues, skin and paravertebral region have been reported [4].

First described by Briner et al. in 1985 [5], primary MRT of the the central nervous system (CNS) is an extremely rare and aggressive tumor. Despite its rarity, somehow CNS is still the most frequent anatomic location for an extrarenal MRT as compared to other locations. We herein present the case of a child who underwent surgery for an intracranial MRT, received postoperative cranial radiation, returned in one year with seeding at spinal levels and died 4 months after surgery and spinal radiotherapy.

Case report

History

An 8-year-old girl presented with one-month history of headache and vomiting. Neurological examination on admission revealed minimal left hemiparesis and bilateral papilledema and significantly decreased vision. Computed tomography (CT) showed centrally solid huge cystic tumor that occupied most of the right hemisphere and measured 11 × 8 × 7 cm (Figure 1a, b). The solid central portion was hyperdense on non-enhanced CT scan, included multiple linear calcifications and enhanced homogenously after contrast injection. On MR scans, the solid portion appeared isointense on both T1- and T2- weighted images while the cystic part appeared isointense with the cerebrospinal fluid (CSF) (Figure 2a–c). MR verified that there was a septum between the cystic part and the right lateral ventricle. MR angiograms showed that the right middle cerebral artery (MCA) directly

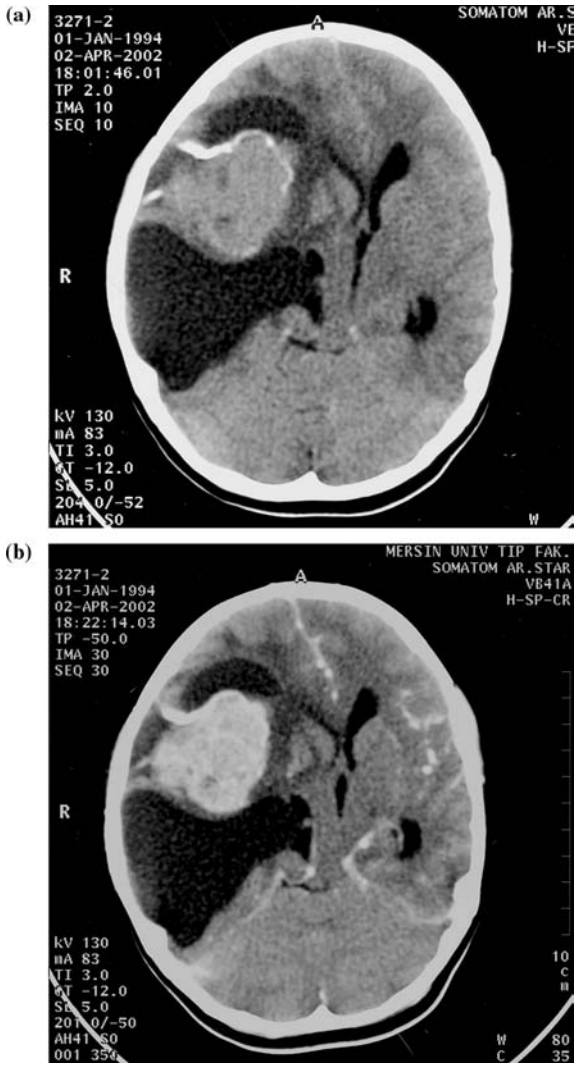

Figure 1. Non-enhanced axial CT scan (a) demonstrates a right-sided fronto-temporoparietal tumor with a solid center and cystic components both anterior and posterior to this solid portion. The periphery of the solid portion is marked with linear calcification. The solid part of the tumor is attached to the dura along a 1-cm strip. There is significant trans-falcine shift but only minimal edema in the surrounding brain. After contrast injection the solid center enhanced markedly (b).

entered and fed the solid portion (Figure 2d). Preoperative diagnosis was between primitive neuroectodermal tumor (PNET), cystic ganglioglioma, cystic astrocytoma and cystic meningioma. At surgery, the tumor was found to be rubbery and extremely vascular. It had only a 1 cm^2 contact with the parietal dura without significant supply from the dura. The main MCA trunk as a whole was entering and feeding the solid portion. MCA was double clipped and tumor was gross totally removed (Figure 3a).

Histopathology

The initial neuropathological diagnosis was a hemangiopericytoma, Grade III (WHO, 2000). Postoperative radiation therapy was considered necessary and a total dose of 5330 cGy of external cranial radiation was given over a 6 week period using a Co60 source. Reviewing the histopathological slides, the pathology department at the radiotherapy center came up with the suggestion of a malignant melanotic schwannoma. At a third consultation, long after completion of radiotherapy, the neuropathologist came with the diagnosis of malignant rhabdoid meningioma. Finally after four consultations, diagnosis of malignant rhabdoid tumor of the brain was reached (Figure 3b–e). Histologically, the tumor tissue was composed of smaller round to fusiform cells with pleomorphic nuclei and scanty cytoplasm and larger round to polygonal cells with eccentric nuclei. Cells were dispersed monotonously in an edematous stroma. Rhabdoid cells had eosinophilic glassy cytoplasm that contained round hyaline-like inclusions. The whole tumor cell population displayed pleomorphism, atypia, abundant mitotic figures, sheeting and micronecrosis. Except for the presence of small cells, there was no clear-cut epithelial, neuroectodermal or mesenchymal component. Lymphocytes and psammoma as well as pseudopsammoma bodies were present. Of note, there were few tumor cells containing melanin. Conventional histochemical techniques showed pericellular and perivascular reticulogenesis as well as the presence of diffuse intracytoplasmic PAS-positive material. Immunohistochemically, rhabdoid cells showed strong cytoplasmic staining for vimentin. The tumor cells were immunonegative for epithelial membrane antigen (EMA), cytokeratin, glial fibrillary acidic protein (GFAP), synaptophysin and S-100. There were few GFAP positive cells at the periphery of the tumor corresponding to reactive astrocytes seen with light microscopy. Few melanin-containing cells stained positive for HMB-45. Proliferative index as determined by MIB-1 was 17%. Electron microscopy, cytogenetic and molecular studies were not carried out.

Clinical course

Post-operative MR scans confirmed gross total excision and the return of the midline structures to their normal configuration (Figure 4). Initial surveillance imaging did not reveal any bone, lung or internal organ metastasis or local recurrence. Cytological examination of the CSF did not reveal any abnormal cells. Four months after cranial surgery, the patient presented with further decrease of the remaining vision and intermittent headaches. A catheter connected to a subgaleal Ommaya reservoir was placed within the tumor cavity for CSF pressure measurements as well as for cytological analysis. Regular sampling failed to show any increase in the CSF pressure or any malignant cells at cytological analysis. At 12 months postoperatively, the patient presented with left lower quadrant pain which progressed to limping and left leg weakness in less than two weeks. Spinal MR showed tumor seeding at T4-5, T7, T12-L1 and L3 levels. The lesion at T12-L1 was significantly distorting the spinal cord (Figure 5). Surgical decompression of the spinal cord was considered and subtotal excision of this voluminous and relatively vascular intradural tumor was accomplished. The seedings

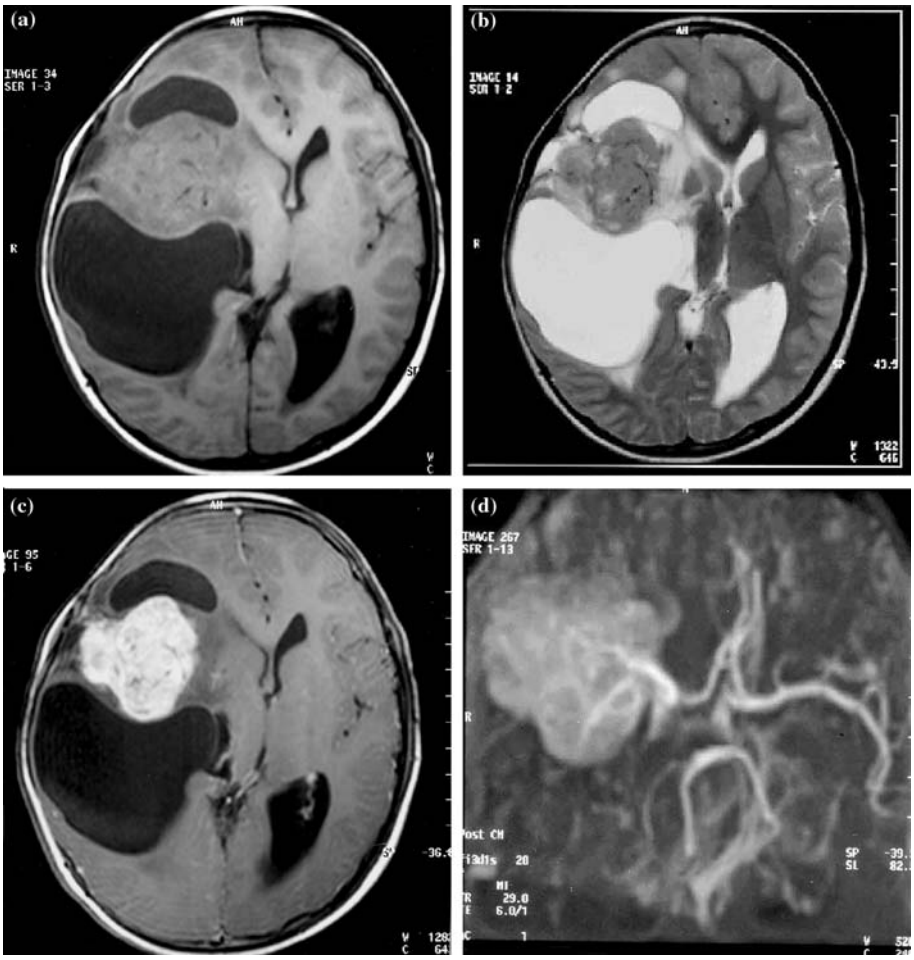

Figure 2. The solid portion appears iso-intense on both axial T1-weighted (a) and T2-weighted MR images (b) and enhanced homogenously with Gd-DTPA (c). MR angiography showed that the right middle cerebral artery (MCA) trunk directly enters and feeds the solid portion (d).

within the dura was found to form a web through multiple contacts between arachnoid and pia. The spinal tumor had identical histomorphologic and immunophenotypic characteristics with the original tumor. In addition to previous immunohistochemistry panel, the cells were also tested for CD34 and smooth muscle actin alpha (SMAA). The tumor cells were immunonegative for CD34 but stained strongly positive for SMAA. MIB-1 labeling index for the seeding tumor cells was 80%, more than four times that of the original tumor. Staining for p53 for the primary tumor showed minimal expression (staining of less than 1/3 of the cells), whereas immunostaining of the metastatic tumor showed moderate (staining of 1/3–1/2 of the tumor cells) expression of p53 protein.

The headaches returned after spinal surgery and CT scans showed increased ventricular volume but no solid recurrence or relapse. CSF pressure was 17 cm H_20 without any cells at cytological analysis, so a ventriculoperitoneal (VP) shunt insertion was considered. After the shunt, the headaches soon subsided and the patient eventually received a total dose of 35 Gy spinal radiation treatment. Chemotherapy was considered after spinal irradiation but the child never regained strength to tolerate the treatment. She remained paraplegic and blind until she died at home 4 months after the diagnosis of the spinal metastases and 16 months after the initial presentation.

Discussion

An overview on histogenesis

The histological origin of rhabdoid cells of MRTs still remains an enigma. Early immunohistochemical and ultrastructural studies clearly excluded a myogenous differentiation and confirmed that MRTs were totally unrelated to rhabdomyosarcoma or Wilms' tumor [2–4]. First set of evidence pointing to a neuroectodermal origin came with the observation of a greater than expected association between renal MRTs and PNETs of the central nervous system. Bonnin et al. [6] reported six childhood MRTs of the kidney in association with primary tumors like medulloblastoma (MB), pineoblastoma, PNET, malignant subependymal giant cell astrocytoma and cerebellar medulloepithelioma. Later, in a review of 111 patients with renal MRT, Weeks et al. [7] discerned that upto 13.5% ($n = 15$) developed a brain tumor all histologically different than MRT.

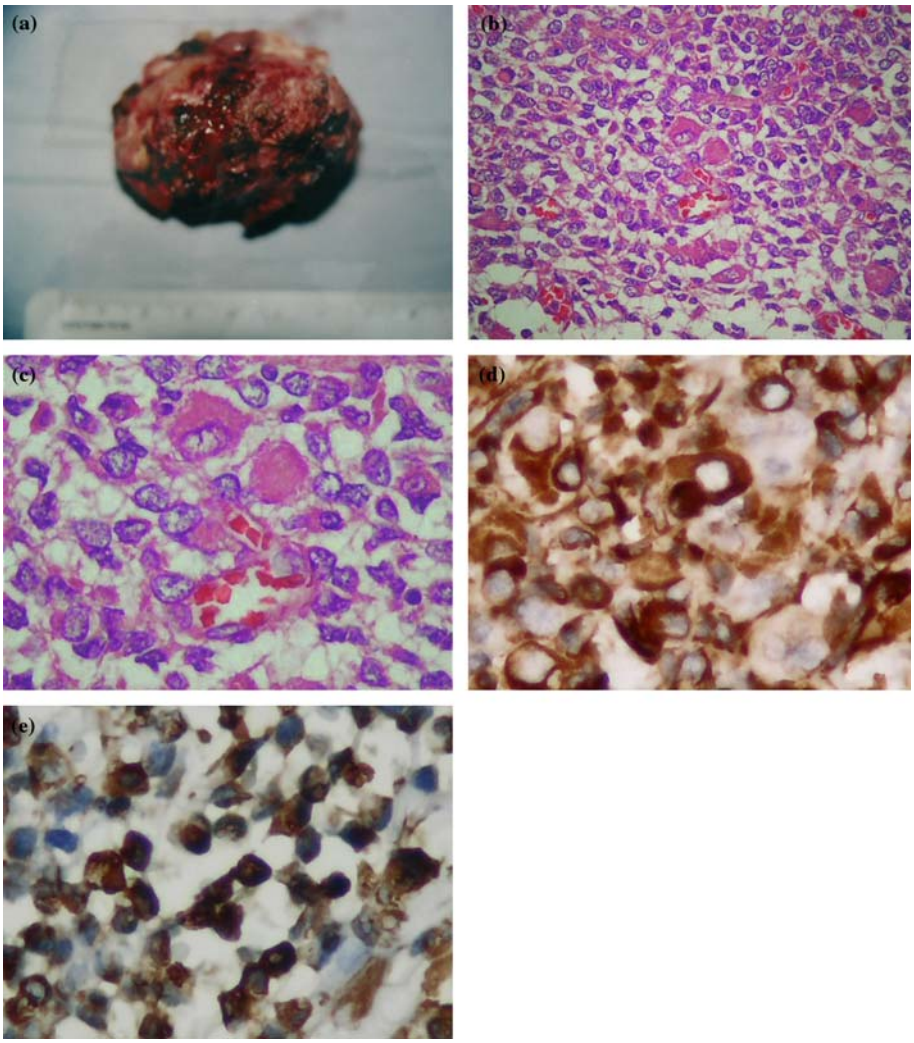

Figure 3. (a) Macroscopic examination of extirpated solid portion of the tumor. (b) On microscopy the tumor is composed of two different cell types. Small cells with scant cytoplasm are predominant component, whereas the cells with large and eccentric nuclei and abundant cytoplasm are the eye-catching features of this tumor (H & E, 200 × original magnification). (c) Higher magnification shows rhabdoid cells with eccentric and prominent nuclei, abundant eosinophilic cytoplasm and paranuclear inclusions (H&E, 400 × original magnification). (d) Tumor cells show diffuse cytoplasmic immunoreactivity for vimentin (Streptavidin, 400 × original magnification). (e) Tumor cells also demonstrate cytoplasmic immunoreactivity for smooth muscle actin alpha (Streptavidin, 400 × original magnification).

Immunopositivity for NSE, S-100, neurofilaments and GFAP among MRTs of the brain in 30–50% of reported MRT cases is additional set of evidence to support a neuroectodermal origin [8,9]. Ultrastructural identification of neurosecretory granules in rhabdoid cells of CNS MRTs as well as detection of hormonal activity in renal MRTs also contribute to neuroectodermal origin theory [9,10]. Alternatively, an epithelial differentiation from a meningothelial precursor cell was suggested [11]. The meningothelial precursor cell is embryologically equivalent to the serosal mesothelial precursor cell surrounding the kidney and the occurrence of primary intracranial MRTs where there are abundant meningothelial infoldings like the frontal base dura, Sylvian fissure, falx cerebri, the tentorium and the falx cerebelli may support a leptomeningeal origin. In addition to location, immunohistochemical positivity for vimentin and epithelial markers in MRTs [8,9] is also similar to meningiomas and their cell of origin, the meningothelial or arachnoidal cell. Moreover it may be more than co-incidence that both MRTs and meningiomas share anomalies of chromosome 22, namely monosomy of chromosome 22. In addition to these theories, the variety of primary sites reported for MRT as well as the immunohistochemical and ultrastructural demonstration of aggregated vimentin filaments in rhabdoid cells also makes a mesenchymal origin likely for the rhabdoid cell.

Nomenclature

As more and cases with renal as well as extra-renal MRTs were being diagnosed and reported, it became evident that CNS MRTs contained fewer rhabdoid cells than the renal MRTs. Moreover, CNS MRTs represented a heterogeneous group that not only included pure (or classic) MRTs but also rhabdoid tumors composed of a combined population of neuroectodermal, epithelial or mesenchymal elements partially admixed with rhabdoid cells [4]. To selectively cover the

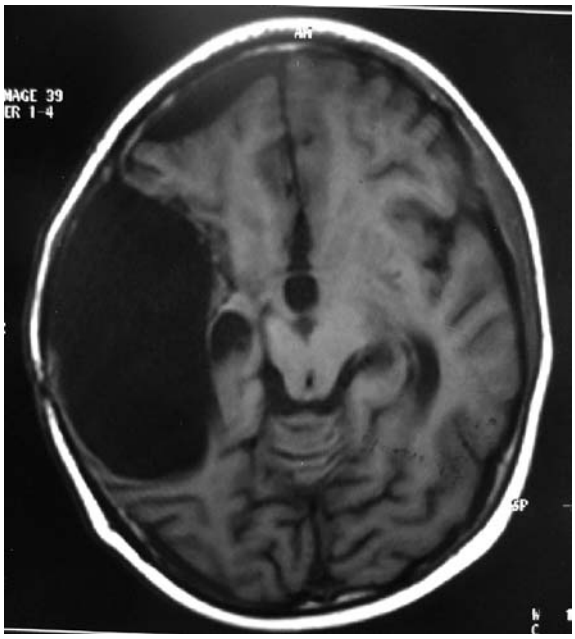

Figure 4. Postoperative MR scan confirms gross total excision.

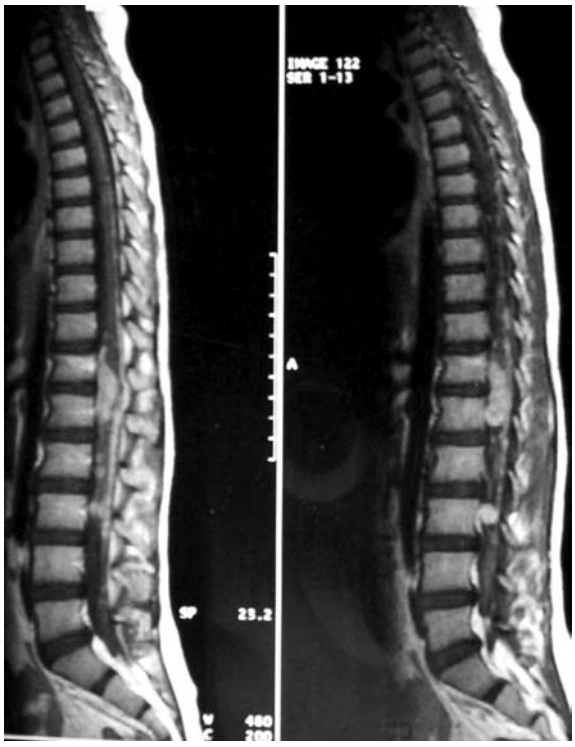

Figure 5. Contrast enhanced sagittal (left) and left parasagittal (right) spinal MR image demonstrate a voluminous seeding at T-12-L1 accompanied by other seeding foci at L3 and mid-to-upper thoracic segments.

latter group of tumors with mixed cellular population, Lefkowitz et al. [12] initially suggested use of the term atypical teratoid tumor (ATT) of infancy. Although extremely useful in differentiation between pure MRTs and other tumors that contain rhabdoid cells, this term somehow did not receive the popularity that it deserved. In 1995, Rorke et al. [13] based on data from 52 infants and children, proposed the term atypical teratoid/rhabdoid tumor (AT/RT) of infancy and childhood, which theoretically unified the the concepts of classic CNS-MRT and of ATT of infancy. AT/RTs included a unique combination of PNET-like, epithelial and mesenchymal features in addition to rhabdoid cells. The AT/RT concept quickly gained popularity and was included in WHO 2000 classification of CNS tumors as a malignant embryonal CNS tumor manifesting in children and composed of rhabdoid cells with or without cells resembling a classical PNET, epithelial tissue and neoplastic mesenchyme [14]. Yet, Rorke et al. [13,15] in original description of AT/RT stated that only 13% of their 52 cases had pure rhabdoid morphology. While both MRT and AT/RT may be similar in terms of aggressivity, new AT/RT concept clearly blurred the differences between an AT/RT and a MRT and although AT/RT appears to be a distinct entity, it is not necessarily the same entity as the MRT.

Brief review of MRT cases

With additional cases on top of the reviews made on the topic MRT by Weiss et al. [16] and Ronghe et al. [17], we were able to trace a total of 100 cases of MRT of the CNS published since 1985 [18–41]. In comparison to published MRT cases, we also found approximately 200 cases of published AT/RT cases [42–55], but AT/RT cases were deliberately excluded from this comprehensive review. The correct use of the term MRT for many cases published even after description of AT/RT clearly shows that there are many scientists who do share our concern that these two tumors are not the same. Ironically enough, the term AT/RT was erroneously used for cases that included only rhabdoid cells without any PNET, mesenchymal and epithelial components [56]. Our review has shown that there were MRT cases reported repeatedly. Two cases initially reported by Behring et al. [8] were later re-reported by both Weiss et al. [16] and by Reinhardt et al. [36], therefore these two patients were included in our review only once.

Age at presentation for PMRT cases varied between 14 days and 45 years (mean 6.76 years, median 3.6 years). Female to male ratio was 1.26: 1. Interestingly a steadily increasing number of adult patients have been reported [23,28,29,31,32,34,39,57–59]. Reports of more and more adult MRT cases do suggest that MRT may not necessarily be a tumor confined to infancy or early childhood. During the early years after Biggs et al.'s [60] first fully documented report, the majority of new reported cases had infratentorial MRTs and this had created an initial false sense that MRTs occurred predominantly in the infratentorial compartment and mimicked PNET-medulloblastomas of the infratentorial compartment. In contrast to this early view, our review has shown that 58% of the reviewed cases had their MRTs in the supratentorial compartment. Five cases had pineal region tumors and only 34 patients had infratentorial tumors. Three patients had their primary

MRT in the spinal canal [8,20,26]. Of 58 cases with supratentorial MRTs, the tumor was intraventricular in 7 patients, within the 3rd ventricle in three [9,36,41] and in the lateral ventricles in the remaining four patients [10,58,61]. In addition to pure intraventricular location, a significant number of MRT cases occurred in a paraventricular location. Both intraventricular and paraventricular locations support the hypothesis that MRTs might have arised as a result of oncogenetic events affecting centrally placed neural primordia [10]. In cases with both renal and brain MRTs, the tumor in the brain is often considered as the metastasis of the renal tumor although it is difficult to disprove a simultaneous and multifocal growth [62,63]. Likewise, rare cases with simultaneous occurrence of both brain and spinal MRTs also exist [26,35,62], and in these cases predicting a primary site is also difficult and speculative. In addition to their propensity to spread through the CSF, MRTs have been found capable of eroding through the bone. Naso-ethmoidal and/or orbital extension of basal frontal MRT [64] or internal auditory canal enlargement in a case of a cerebello-pontine angle MRT [65] have been described. On a rare occasion, the tumor caused skull erosion [38]. That child presented with a subcutaneous lump in the head and neuroimaging confirmed the extracranial extension of the intracranial tumor that had penetrated through the eroded skull [38].

Associated anomalies/diseases

Cases with associated diseases and/or malignancies are of interest. Beigel et al.'s [62] first case, a 6 month old baby boy and the 8 month old boy reported by Cohn et al. [63] had simultaneous occurrence of a renal and a cerebellar MRT. The autopsy case of Chang et al. [66], a 14-day-old boy had a solitary MRT of the liver in addition to a large CNS MRT. Bouffet et al.'s [67] interesting case had Rendu-Osler disease, an autosomal dominant disease endemic at the origin of the publication. This patient who presented with a metastatic MRT at the age of 12, had undergone previous surgery for a cerebellar astrocytoma at the age of 3. The patient did not receive any radiation before the diagnosis of MRT.

Radiological features of MRT

Primary CNS MRTs often appear as slightly hyperdense heterogenous lesions on non-enhanced CT (NECT) scans. MRTs, especially when they are supratentorial, tend to be very large and lobulated lesions. Of those cases with documented size of the tumor, the length and the width of supratentorial MRT varied between 6 and 10 cm, being 7 cm on average [9,10,35,37,40,58]. Parasagittal MRTs or MRTs involving the motor strip were often smaller (3 cm in daimeter) and round [24,34,36]. Excluding cases with bihemispheric and/or midline lesions, the left hemisphere was involved in 73% of the cases. Punctate or flecks of calcification(s) as seen in our case often accompanied the NECT image [10,25,26,35,39]. Dense central calcification is rare [35]. A significant number of cases had large tumor-associated cysts [17,24,26,33,34, 37,39,56,64]. Tumor associated cysts are often marginal cysts but rare central cysts can also occur. No similar case to our case with cavitation and cyst-like cavity formation along an arterial territory secondary to continuous steal was previously reported. Diffuse hyperdensity on NECT is attributed to highly cellular nature of MRTs. The enhancement pattern on contrast-enhanced CT scan (CECT) is usually diffuse and homogenous [10,25,27,30,35,41,57,65,67] except for very large lesions when central necrotic area would not enhance and only a peripheral nodular enhancement would be seen [10].

As for MR appearance, MRTs that do not contain calcification and/or hemorrhage as initially detected by NECT, are uniformly isointense to grey matter on both T1- and T2-weighted images (WI) [10, 25,26,33,35,37,56]. Areas of hyperintensity on T1-WI should suggest previous hemorrhage and special sequences would be useful in demonstrating the blood-breakdown products [25]. In contrast to the usual bright signal intensity of most CNS tumors on T2-WIs, isointensity on T2-WIs suggests less free water than many other tumors pointing to dense cellularity and a high nuclear/cytoplasma ratio. The calcified areas appeared hypointense on both T1 and T2-WI whereas necrotic and cystic portions are often hypointense on T1- and hyperintense on T2-WIs [37,56]. Peritumoral edema is often inappropriate to the size of the tumor with minimal to moderate edema even in large tumors [9,10,23,56]. Only centrally necrotic tumors are exception to this statement. These findings suggest that since MRTs are embryonal tumors, the brain's response to the growing embryonal cells remains minimal compared to brain's repsonse to other CNS tumors. Depending on the vascularity, low signal blood vessels can be depicted on T2-WI as also shown in our case [33]. MRTs often enhance markedly and homogenously on MR scans but depending on the presence of a cyst or necrosis, heterogenously or peripherally enhancing lesions were also described [23]. Our review has shown that if the tumor was less than 3 cm in diameter the enhancement pattern was often homogenous. MR angiogram (MRA) was not used for any of the previously reported MRT cases. MRA and our surgical findings clearly prove that as the MRT in our case grew bigger, it stole more of the blood destined for the brain and eventually caused encephalomalacia and cavitation along the right MCA territory. As for MR technology in progress, Huisman et al. [33] reported their MR spectroscopy (MRS) findings in a case with MRT. Quantitative ^{1}H spectroscopy of a large partially cystic and partially solid lesion showed increased concentration of choline within the solid portion. This was interpreted by the authors as an indication of increased membrane turnover. In addition, an absent creatine and acetyl-aspartate peak was found confirming lack of neuronal differentiation of the tumor cells. The authors suggested that further series of ^{1}H MRS were needed to prove whether these findings or "fingerprint" were characteristic for MRT or not [33].

So far no more data on MR spectroscopy of MRTs have appeared.

Surgical treatment of MRTs

The first-line treatment is surgery and the goal should be gross total excision. Detailed data on surgical treatment existed for 82 of the reviewed cases. Of these 82 cases, 25 underwent gross-total, 24 underwent subtotal and another set of 24 patients underwent partial excision. Nine patients were considered only for a biopsy. VP shunt insertion was usually considered for cases with an infratentorial MRT and coexisting obstructive hydrocephalus [9,22,41,68,69]. Velasco et al.'s [69] unique 3-year-old case with neoplastic hydranencephaly and MRT of the whole cranial vault underwent VP shunt surgery at six weeks of age with the diagnosis of congenital hydrocephalus. Our literature review has also shown that elevated CSF pressure usually coincided with a positive CSF cytology [59] and late hydrocephalus often coincided with late subarachnoid spread [8,9,65].

Metastasis of MRTs

The frequent close relation to the ventricular system and the subarachnoid spaces do explain tumor's tendency for leptomeningeal spread. CSF seeding may occur spontaneously or postoperatively. Few patients who had multifocal cranial MRTs on admission have proven that spontaneous subarachnoid spread may occur even before surgical spillage [35,64,68]. Slightly more than one-third of all cases (39.4%) developed subarachnoid spread postoperatively either as subarachnoid spread, distant seeding and/or carcinomatous meningitis. As for distant seeding, spinal metastasis from a brain MRT was more common [11,32,36,62,65], although cranial (upward) metastasis from a primary spinal cord MRT [8] was also described. Few of the cases with spinal metastasis were treated with spinal irradition often with no benefit [36,59,65]. No case with spontaneous or postoperative spinal metastasis was considered for surgery. If the surgeon (IHT) had known earlier that our patient harbored a MRT, we would probably have proceeded with palliative irradiation to the spine instead of surgery. All the patients receiving palliative radiation for spinal metastasis died within 4 months a survival figure exactly matching to our case [36,59,65].

Metastasis beyond the CNS occurred in 3 patients. An extracerebral subgaleal metastasis occurred along the needle trajectory in an adult patient who underwent CT-guided biopsy. The growth of the seeded tumor occurred despite radiation therapy for the cerebral lesion [23]. Extracranial metastasis from cranial MRTs occurred in 2 patients. The final autopsy examination of Velasco et al.'s [69] case who presented with abdominal ascites 3 years after placement of a shunt showed a peritoneal mass consisting of MRT cells that surrounded the distal tip of shunt. This extracranial metastasis evidently occurred through the shunt tubing. The third case was an example of hematogenous spread in an adult MRT case reported by Sugita et al. [31] and a lung metastasis was histologically diagnosed eighteen months after pineal MRT surgery.

Histopathologic and ultrastructural features of MRTs

Although numerous pathologists who consulted our case had considerable difficulty in reaching the exact and correct diagnosis of MRT, histopathological diagnosis of CNS MRT should be straighforward especially if the pathologist and/or the surgeon have some experience with these rare tumors. On light microscope, MRTs are composed of medium to large round or polygonal cells with prominent eosinophilic cytoplasm, eccentric and round nuclei with prominent nucleoli. Often there is a prominent stroma. Vacuolated cells, either as isolated or in groups may appear as a reminiscent of a "starry sky" [22] or "ground glass" [58]. Mitosis is fairly frequent and there are often many foci of necrosis. Chordoid differentiation within a MRT is rare but has been described in two instances [14,31]. Our review has shown that in at least three cases, the pathologist(s) had similar difficulty in reaching the correct diagnosis of MRT. The initial diagnosis was malignant small cell tumor [65], fibrosarcoma [36] or ostesarcoma [57] in these three cases.

Immunohistochemistry (IHC) in MRTs provides supportive evidence of rhabdoid character especially when ultrastructural evaluation is not available. MRTs are well known for immunopositive reaction to the triad of vimentin, EMA and cytokeratin (CK). The most consistent of these has been vimentin immunoreactivity seen in 99% of cases. It is the intracytoplasmic hyaline inside large polygonal cells that do stain positive for vimentin. General belief is that negative vimentin immunoreactivity is not compatible with the diagnosis of MRT even though other parameters do suggest MRT. Second most consistent marker for MRT is EMA (85%). However, the absence of EMA immunopositivity does not exclude a MRT and there are numerous cases in the literature with EMA immunonegativity [8,16,21,23, 27,60,69]. Third important IHC marker is CK and a significant majority of the reviewed MRT cases had tumors that stained positive for cytokeratin (75%). In few cases, the rhabdoid cells may not stain with cytokeratin and our review has shown that these were almost always the cells that also did not stain with EMA. This is easy to understand since both EMA and CK are epithelial markers. Our review also revealed few odd cases with EMA immunonegativity and CK immunopositivity [8,21,27] as well as cases with EMA immunopositivity and CK immunonegativity [31,39,40]. The fourth most common immunohistochemical reaction is with antibodies against smooth muscle actin (SMA) [9,16,17,31–33,52]. SMA positivity is a non-specific sign of differentiation and does not necessarily point to a smooth muscle cell origin. As for differential diagnosis from rhabdomyosarcomas, MRTs are expected to be immunonegative for myoglobin, desmin and myosin. Desmin [9] and myoglobin [9,33] immunopositivity in MRTs is exceedingly rare. Approximately half of the reviewed cases also

showed positive reactions to S-100, NSE and neurofilament protein and synaptophysin. As for markers of germ cell lineage, MRTs are almost always immunonegative for markers like alpha feto protein (AFP), human chorionic gonadotropin (HCG) and placental alkaline phosphatase (PLAP). Only 2 cases with immunopositivity for AFP [8,9] exist in the literature. Immunoreaction with alpha-1 antitrysin and alpha-1 antichymo-tyripsin was positive in the majority of tumors tested [9,39,57] and was negative only in 2 cases [65,70]. The immunohistochemistry panel for the reviewed cases included HMB-45 in 6 patients with MRT [9,31,34,37,66] and all MRTs were immunonegative to this antibody. Our case appears to be the first HMB-45 immunopositive MRT although interpretation of this finding is difficult. Though nearly all the MRT cases included mitosis and necrosis as part of the histologic picture and some were even described to include "numerous" or "extremely high" MIB-1 positively staining nuclei [39], MIB-1 indicis were numerically displayed in only few patients with MRT. MIB-1 labeling index (LI) was 8.4% in Horn et al.'s case [57] and 28.4 and 33.4% in Bergmann's [9] first and second cases. A significantly higher MIB-1 LI values were reported for AT/RTs as compared to MRTs. Lutterbach et al.'s [45] adult AT/RT case had a LI of 80%. Of 11 cases of AT/RT reported viewed by Ho et al. [44] MIB-1 LI ranged between 35.3 and 97.1 (mean 63.9). A correlation between MIB-1 LI and survival was analyzed only by Ho et al. [44]. The mean survival of patients with MIB-1 LI < 55 was found to be 38 months as opposed to 5.4 months for those with LI > 55.

Ultrastructural and cytogenetic studies may significantly contribute to the diagnosis of MRT or to the differential diagnosis of MRT. Key features found by electron microscopy in MRT cells include absence of intercellular junctions and tightly packed whorls of cytoplasmic intermediate filaments, 8–10 nm in thickness [10,57]. Ultrastructural studies are particularly useful in differentiation from rhabdomyosarcoma (which has characteristic Z-bands and a basal lamina as the signs of skeletal muscle differentiation) or rhabdoid meningiomas [27]. When the diagnosis of MRT is in question and when there is no glutaraldehyde-fixed tumor tissue, ultrastructural examination of MRT can be done by treatment of the paraffin embedded tissue as summarized by Bergmann et al. [9] although the quality of images may not be as good as in glutaraldehyde-fixed specimens.

Cytogenetic features

In 1990, Biegel et al. [62] made a significant contribution to our understanding of MRTs with their initial report on cytogenetic characteristics of MRTs. All the patients in their report had monosomy 22. Although monosomy 22 is not a specific genetic abnormality, these initial findings suggested that loss of a gene or genes on chromosome 22 could have been involved in the initiation of MRTs and that this abnormality could be useful in the diagnosis of these rare lesions. Subsequent cytogenetic and molecular analyses have shown that the deletion of region 11.2 of the long arm of chromosome 22 (22g11.2) was a recurrent genetic characteristic of MRTs, indicating that this locus might even encode a tumor supressor gene. In 1998, a group of French researchers mapped these deletions and somatic mutations to the *hSNF5/INI1* gene from band 22q11.2 [70]. The *hSNF5/INI1* gene spans a 50-kilobase region from which 1839-base-pair complementary DNA is derived. The encoded protein is part of a multiprotein complex involved in chromatin remodeling. Only a year later, Biegel et al. [71] have shown that both germ-line and acquired mutations occurred in AT/RTs in locus *INI1* further confirming that *INI1* was the tumor supressor gene involved in MRTs of the brain, kidney and other extra-renal sites. In a unique case with both a CNS ATT and a renal MRT, Biegel et al. [72] also showed identical mutations in exon 7 of the *INI1* rhabdoid tumor supressor gene in both tumors. This unique property adds to our differentiating power since the chromosomal abnormality in PNET-MB cases often lies in 17q and an abnormality in chromosome 17 has yet not been found in MRTs [73]. That is why flourescence *in situ* hybridization (FISH) detection of chromosome dosage is now an accepted tool in differentiating MRTs from PNET-MBs [74]. The non-random association of monosomy 22 with rare cases of PNET-MBs is still under investigation and may suggest another tumor supressor gene mapped to this chromosome [75]. Fernandez et al. [76] recently reported on monozygotic twins with a congenital disseminated MRT in one and a cerebellar tumor mimicking medulloblastoma in the other. The molecular analysis of the tumor specimens revealed intersting findings. There were similar alterations for both MRT and MB: a deletion of exon 7 of the *hSNF5/INI1* gene in one allele and a point mutation in the same exon in the other allele.

Outcome and survival with MRTs

Our review has shown that the prognosis for patients with MRT was poor. Excluding 10 patients with no outcome data, 68 patients presented with relapse after a mean period of 6.9 months (range 1–18) and died after a mean period of 8.9 months after diagnosis (range 0.1–72 months). Only 22 patients were reported alive [17,24,26,34,35,56,64,67–69,77–79]. Mean survival for these 22 patients was 24.5 months (Table 1). In search of factors that may have contributed to survival statistics, we analyzed age, tumor location and surgery as possible factors. The mean age of those remaining alive was 6.0 (range 1.16–20) and was not statistically different than the whole patient population. Majority of the survivors had supratentorial tumors (20/22, 90.9%). Infratentorial and pineal location was a poor prognostic factor. No case with pineal MRT survived (5/5, 100%) while 30/34 (91%) of those with infratentorial tumor succumbed to their disease. Chance of survival with a supratentorial tumor was approximately 34.5% (20/58) as opposed to 5.8% (2/34) for those with an infratentorial tumor. Survival as related to the extent of surgical

Table 1. A summary of patients remaining alive with central nervous system malignant rhabdoid tumor

First author	Age	Sex	Tumor site	Surgery	Systemic Chemotherapy						Intrathecal therapy	ABMT	Cycles	Outcome	Survival	Radiotherapy
Jakate	3	F	Cerebellum	PTR	"8 in 1"									NED	5	CrSpXRT-Dose?
Perilongo	5.83	F	L-TO	GTR	CYC	VP-16	CIS-PLAT	VCR						NED	6	CrSpXRT-36 + boost
Weinblatt	NS	F	F	Resection				VCR	ACTI-NO	DOXO	Triple IT			NED	60	CrXRT-Dose?
Bouffet	12	M	R-FP	GTR		VP-16	CIS-PLAT						×4	NED	19	CrSpXRT 27/27/36
Cossu	7	M	L-P	PTR	No detail								×5	NS	25	Yes–No detail
Hasserjian	3	M	L-FP	STR	No chemotherapy									NED	36	No
Hasserjian	6	M	FP	STR	No chemotherapy									ED	22	CrXRT
Olson	1.5	F	R-F	PTR	CYC	VP-16	CIS-PLAT	VCR	ACTI-NO	DOXO	Triple IT			NED	60	CrSpXRT-24 Gy
Olson	2	M	L-CPA	STR	CYC	VP-16	CIS-PLAT	VCR	ACTI-NO	DOXO	Triple IT			NED	24	CrXRT-26 Gy
Olson	5	F	R-T	GTR	CYC	VP-16	CIS-PLAT	VCR	ACTI-NO	DOXO	Triple IT			NED	9	CrSpXRT-25 Gy
Howlett	5	F	L-FP	Debulking	No chemotherapy									NED	48	CrXRT-Dose?
Bhattacharjee	6.5	M	L-P (rolandic)	STR	No chemotherapy									ED	30	Local-46 Gy
Bhattacharjee	7	M	Parasagittal	STR	Aggressive multiagent chemotherapy									NED	12	No
Kumar	3	M	L-T	PTR		VP-16	CIS-PLAT	VCR					×6	ED	8	CrSpXRT-24 Gy
Zuccoli	1.75	NS	R-FP	PTR	CYC	VP-16	CIS-PLAT	VCR						ED	12	No
Arrazola	20	M	L-P (post-central)	GTRX2	No chemotherapy									NED	24	CrSpXRT-Dose?
Yoon2	15	M	R-F	GTR	No detail									NED	6	Yes–No detail
Yoon4	4	F	L-T	GTR	No detail									ED	3	Yes–No detail
Yoon5	6	F	4thV + vermis	PTR	No detail									NED	13	Yes–No detail
Evans	7	F	L-P	GTR	No detail									NS	NS	Awaiting XRT
Ronghe	1.16	F	R-PO & R-cerebellar	STR	IFOS	VP-16	CAR-BOPL	VCR	ACTI-NO	EPI	Triple IT	ABMT[a]	×9	NED	52	No
Ronghe	5	F	L-PO	STR	IFOS	VP-16	CAR-BOPL	VCR	ACTI-NO	EPI	Triple IT		×9	NED	65	CrSpXRT-35/20 Gy

ABMT – Autologous Bone Marrow Transplantation; ACTINO – D-actinomycin; CARPOPL – Carboplatin; CISPLAT – Cis-Platin; CYC – Cyclophosphamide; DOXO – Doxorubicin; ED – Evidence of disease; EPI – Epirubicin; F – Female; GTR – Gross total removal; IFOS – Ifosphamide; M – Male; NED – No Evidence of Disease; NS – Not Specified; PTR – Partial Tumor Removal; STR – Subtotal Tumor Removal; SURVIVAL – In Months; VCR – Vincristine; VP-16 – Etoposide; XRT – Radiotherapy

[a] After Busulphan/thiotepa.

removal also showed a statistical difference between a biopsy and tumor (partial, subtotal or gross total) removal. Those undergoing simple biopsy survived only for a mean period of 1.5 months. There was no meaningful inter-group difference among those who had undergone partial (PTR), subtotal (STR) and gross total resections (GTR) [GTR mean 12.6 months, STR mean 12.7 months and PTR mean 15.1 months]. Postoperative radiotherapy (XRT) protocols were extremely heterogenous. Several patients received only local XRT [24,28,64] or only cranial XRT [9,11,23,26,31,37,39, 57,61,64,78,79]. Some authors considered cranial irradiation only after the diagnosis of relapse [32,58,62]. Only less than one-fourth of the patients undergoing irradiation received proper craniospinal coverage.

In-depth review of all the survivors of MRT has shown that one case had no solid data on survival [38] and another was alive at 8 months in a "do not resuscitate" condition [30]. These two cases were exempted from further analysis. Of the remaining 20 patients, a total of 15 patients were reported as having no evidence of disease (NED) [17,24,26,30,34,35,38,56,58,64,67, 68,77–79]. The mean survival for those with NED was 26.7 months (range 6–65). Among these 15 patients, only two had infratentorial tumors on admission. Of these 15 patients, 10 underwent craniospinal ($n = 6$) or cranial ($n = 4$) irradiation. Eleven patients with NED received chemotherapy. Both radio- and chemotherapy were employed in eight patients with NED. The common denominator of effective chemotherapy regimens in patients with NED was intensive combined modality therapy (Table 1) that included various combinations of vincristine, ifo-/cyclophosphamide, etoposide, *cis*-platin (or carboplatin), actinomycin-D, doxorubicin (or epirubicin) and triple intrathecal (IT) chemotherapy consisting of methotrexate, cytarabine and hydrocortisone. As chemotherapy regimens became more sophisticated and more effective, we came to understand that MRTs were in fact chemosensitive. Poor penetration of chemotherapeutics into the CSF may have been the Achilles heel of serious chemotherapy regimens so effective IT therapy is an invaluable addition to increase local drug concentrations. The literature data clearly show that IT chemotherapy using only methotrexate may not be enough to alter the natural course of the disease [10,11,65]. Triple IT therapy protocol successfully used by Olson et al. [64] that consists of methotrexate, cytosine arabinoside and hydrocortisone was part of intergroup rhabdomyosarcoma (IRS) regimen that is normally used to treat parameningeal sarcomas with intracranial extension. The chemotherapy regimen used by Ronghe et al. [17] was based on the SIOP malignant mesenchymal tumor (MMT-95) protocol with addition of triple IT chemotherapy (UKCCSG MMT 953 Arm B). Insertion of an Ommaya reservoir often creates easy access for IT chemotherapy [17,64]. Intensified and IT therapy complemented with autologous bone marrow transplantation (ABMT) was reported to have boosted the survival with NED. Ronghe et al. [17] successfully used high dose busulphan and thiotepa therapy with ABMT as an alternative to radiotherapy in a 14 month old baby girl for whom radiation was found inappropriate [17]. This patient was alive with NED at 52 months from diagnosis. Long-term morbidity of radiotherapy was mentioned by Ronghe et al. [17] for their second case, the patient with the longest survival (65 months) after treatment for a CNS MRT. The girl who received craniospinal irradiation after nine courses of chemotherapy was 10.5 years old at the time of publication and showed some signs of growth retardation although her neuropsychological assessment was within normal limits.

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