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Clinical Study

Malignant rhabdoid tumor in a pregnant adult female: literature review of central nervous system rhabdoid tumors

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Summary

Rhabdoid tumors of the central nervous system are uncommon, aggressive childhood malignancies. The 13 described adult cases comprise both primary CNS tumors and malignant transformation of previously existing gliomas, meningiomas, and astrocytomas. Central nervous system rhabdoid lesions of adults have been diagnosed as primary malignant rhabdoid tumors, atypical teratoid/rhabdoid tumors, and more recently, rhabdoid glioblastomas. We report a case of a 20-year-old woman in her 30th week of pregnancy who presented with headache, nausea and blurry vision. MRI revealed a large rim-enhancing mass of the right occipital lobe. Gross total resection was achieved via a right parietal-occipital craniotomy. Pathologic evaluation revealed histology, electron microscopy and immunohistochemistry consistent with the diagnosis of malignant rhabdoid tumor. FISH studies were negative for the *INI-1* genetic mutations and chromosome 22q deletion associated with childhood atypical rhabdoid/rhabdoid tumor in 75% of cases. The patient delivered her infant via caesarian section prior to initiating further therapy. We briefly describe the characteristics and current understanding of rhabdoid tumors, and review the literature comparing the 12 other cases of central nervous system rhabdoid tumors in adults. Furthermore, we consider and discuss the implications of this case being the second presentation of MRT during pregnancy in only six adult female patients.

Introduction

Primary rhabdoid tumors of the CNS are rare entities, usually occurring in children and infants less than 2 years of age. The malignancy is named for the typical rhabdoid cell type, with abundant pale eosinophilic cytoplasm, eccentrically placed nuclei and prominent nucleoli. Round, basophilic inclusions are often present, displacing and indenting the nucleus. The typical rhabdoid cells usually compose only part of the tumor, while the remaining tissue consists of a variety of cell types or a pre-existing primary lesion. Tumors with a mixed phenotype including mesenchymal, epithelial, and primitive neuroectodermal cells are characterized as atypical teratoid/rhabdoid tumors (ATRT). These primarily childhood tumors are frequently misdiagnosed as medulloblastomas or primitive neuroectodermal tumors (PNET)[1]. The prognosis is dismal, with most patients surviving less than a year. Rhabdoid transformation has also been described in meningioma [2], astrocytoma [3], and glioma [4], as well as in cases of unknown histogenesis. Recently, rhabdoid glioblastoma has been introduced and characterized as a high-grade pleomorphic malignancy with areas of low-grade glioma, epithelioid glioblastoma and rhabdoid transformation [5]. Whether the rhabdoid features are noted at initial presentation or as a later transformational change, the lesions behave aggressively with frequent leptomeningeal spread, rapid recurrence and growth, and high morbidity and mortality despite treatment with resection, chemotherapy, or radiotherapy.

Multiple molecular and genetic studies have identified the *INI-1* gene on chromosome 22q11.2 as playing an important role in the development of rhabdoid malignancies. *INI-1* is a component of the SWI/SNF chromatin remodeling complex, and functions as a tumor suppressor by positively regulating transcription of a particular set of eukaryotic genes, possibly including the *c-Myc* target genes involved with differentiation and apoptosis [6]. Alterations, deletions, and mutations of *INI-1* and neighboring genes have been identified in rhabdoid tumors presenting in the CNS, kidney, and soft tissues. Children and infants with germline loss of *INI-1* function are predisposed to developing rhabdoid tumors at a very early age, and may present with ATRT [7]. Spontaneous somatic mutations, deletions, and monosomy of chromosome 22 have also been documented in patients without germline mutations, and have been associated with clonal rhabdoid transformation of CNS lesions. However, 15–25% of rhabdoid tumors do not have an identifiable mutation, deletion, or transcription abnormality of *INI-1*, and the presence of positive molecular studies is not required for diagnosis [6].

Case report

History

A 20-year-old woman in her 30th week of pregnancy was referred to Yale-New Haven Hospital with worsening

headache due to an intra-cranial lesion, identified by MRI. Past medical history included mild asthma, gastro-esophageal reflux disorder, and one prior pregnancy without complications. History of present illness included nausea and occipital headache, progressively worsening throughout the pregnancy. Two weeks later she was admitted to the emergency department with symptoms of a severe headache radiating from the occiput to the jaw and forehead, nausea, blurry vision, weakness and tingling of the right face and left extremities, and unsteady gait. She denied vomiting, loss of consciousness, and seizures. Physical exam revealed a left homonymous hemianopsia, left drift, 4/5 strength and increased reflexes of the left extremities. The neurological examination was otherwise normal. The patient was treated with acetaminophen, metoclopromide, and dexamethasone to reduce cerebral edema and promote fetal lung maturity.

Imaging studies

Magnetic resonance imaging of the brain with and without contrast revealed an irregular rim-enhancing lesion of the right occipital lobe abutting the dura but appearing to arise from the cortex. The lesion was large with a necrotic center, and was noted to cause a significant mass effect on the occipital horn of the right lateral ventricle (Figure 1).

Tumor resection

Gross total resection was planned via a right parietal–occipital craniotomy, with continuous fetal monitoring and an obstetric team available in case fetal distress necessitated emergent caesarian section. At surgery, a large tensely bulging mass with a central cystic cavity in the right occipital cortex was drained. The tumor was found to be large, vascular and extensively cystic. Radical right occipital lobectomy was performed, and all grossly suspicious adjacent foci were resected. There were no intraoperative complications. Post-surgical resection, the patient had a left visual field deficit, and resolution of other symptoms. She was discharged to home after 1 week.

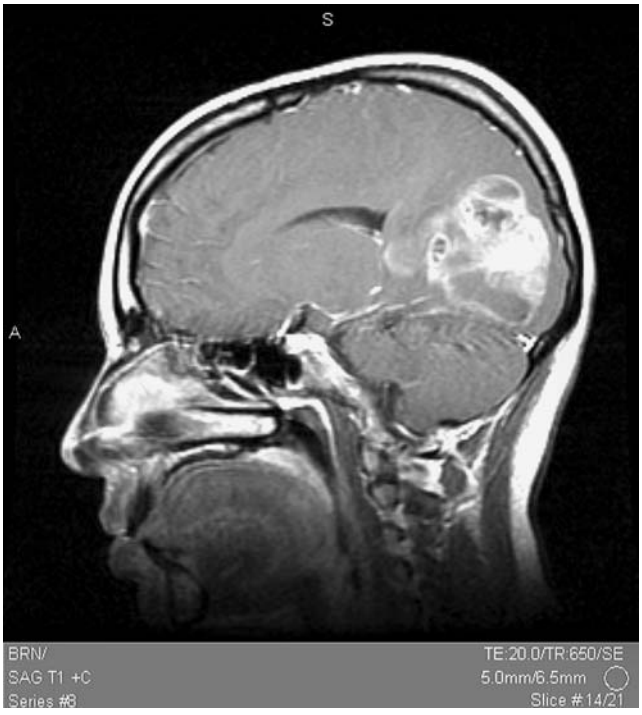

Figure 1. Sagittal T1-weighted MRI image with contrast showing the brain prior to resection with a large rim-enhancing mass with central necrosis within the right occipital cortex.

Treatment

Treatment options and related risks were discussed with the patient and her family. The patient was unwilling to expose her unborn infant to any potential radiation, and opted for early delivery prior to initiating radiotherapy. Caesarian section was performed at 32 5/7 weeks gestation, and a 2155 gm male infant was delivered. To date, the patient is doing well with no evidence of disease recurrence.

Materials and methods

Fresh tissue was fixed in 4% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E). Immunohistochemical stains were performed on formalin-fixed paraffin embedded tissue, and included glial fibrillary acidic protein, vimentin, synaptophysin, cytokeratin AE_1/AE_3, Cam 5.2, melanoma antigen (HMB-45), epithelial membrane antigen, MIB-1, smooth muscle actin, estrogen receptor, progesterone receptor, and epidermal growth factor receptor (EGFR). Fluorescence *in situ* hybridization (FISH) analysis of the *INI-1* gene was performed, as previously described by Bruch et al. [8]. For electron microscopy, tissue was fixed in 2.5% glutaraldehyde in PBS for 24 h, postfixed in buffered osmium tetroxide, *en block* counterstained with 2% uranyl acetate (UA) in veronal acetate buffer for 2 h and embedded in Epon 812. Thin sections were cut on an LKB 8800 ultramicrotome, counterstained with saturated solution of UA in methanol and Reynold's lead citrate, and viewed on a Zeiss EM10B operating at 60kV.

Results

Gross

The fresh tissue specimen comprised the right occipital lobe which was received as two large irregular fragments. The segments measured $8.0 \times 6.0 \times 3.0$ cm and $8.0 \times 6.0 \times 2.0$ cm and consisted of the right occipital cortex surrounding a $5.0 \times 4.5 \times 1.5$ cm area of friable tumor and hematoma. The infiltrative, poorly-demarcated neoplasm was heterogeneous with areas of hemorrhage, necrosis, and firm rubbery foci. The solid portions were translucent to gray, and protruded from the cortex of the occipital lobe into the hemorrhagic cystic area (Figure 2).

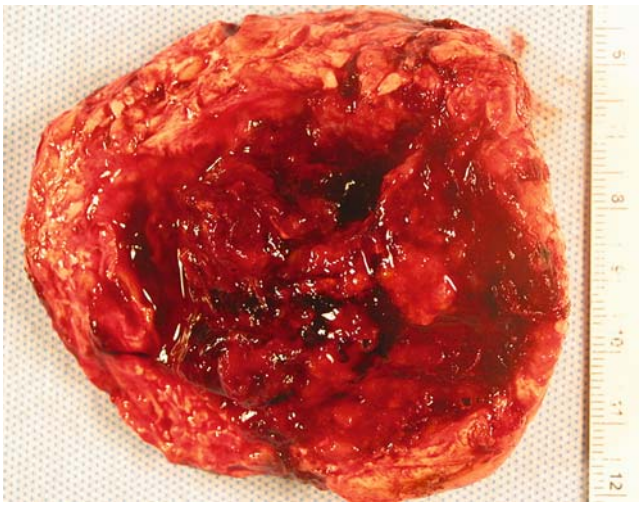

Figure 2. Gross photograph of the surgical specimen showing the right occipital lobe with cystic hemorrhage and necrosis of the tumor mass.

Histopathology

H&E staining revealed a tumor mainly composed of sheets of polygonal neoplastic cells with abundant pale eosinophilic cytoplasm and irregular nuclei. Several areas consisted of typical rhabdoid cells, identified by their abundant pale eosinophilic cytoplasm and ovoid or convex eccentrically located nuclei with prominent nucleoli. Many of the rhabdoid cells contained a single large round basophilic cytoplasmic inclusion body, displacing and indenting the nucleus. The tumor was extremely heterogeneous; necrosis, chondroid differentiation, solid areas, and myxoid areas were identified (Figures 3 and 4).

Immunohistochemistry

The tumor showed strong focal positivity for GFAP and vimentin, while the rhabdoid cell inclusions were strongly immunoreactive throughout. SMA, EMA, and Cam 5.2 staining showed only rare positive inclusion body staining. The proliferation index measured by MIB-1 (Ki-67) was 40% in the areas of highest mitotic activity. Immunohistochemical staining was negative for HMB 45, cytokeratin AE_1/AE_3, and synaptophysin. ER, PR, and EGFR staining were entirely negative (Table 1).

FISH study

Fluorescence *in situ* hybridization studies failed to reveal any abnormalities in the *INI-1* region of chromosome 22q11.

Transmission electron microscopy

By TEM, rhabdoid cell nuclei were often grooved and contained prominent nucleoli. The cytoplasm was filled with loose bundles of intermediate filaments. Rare cells

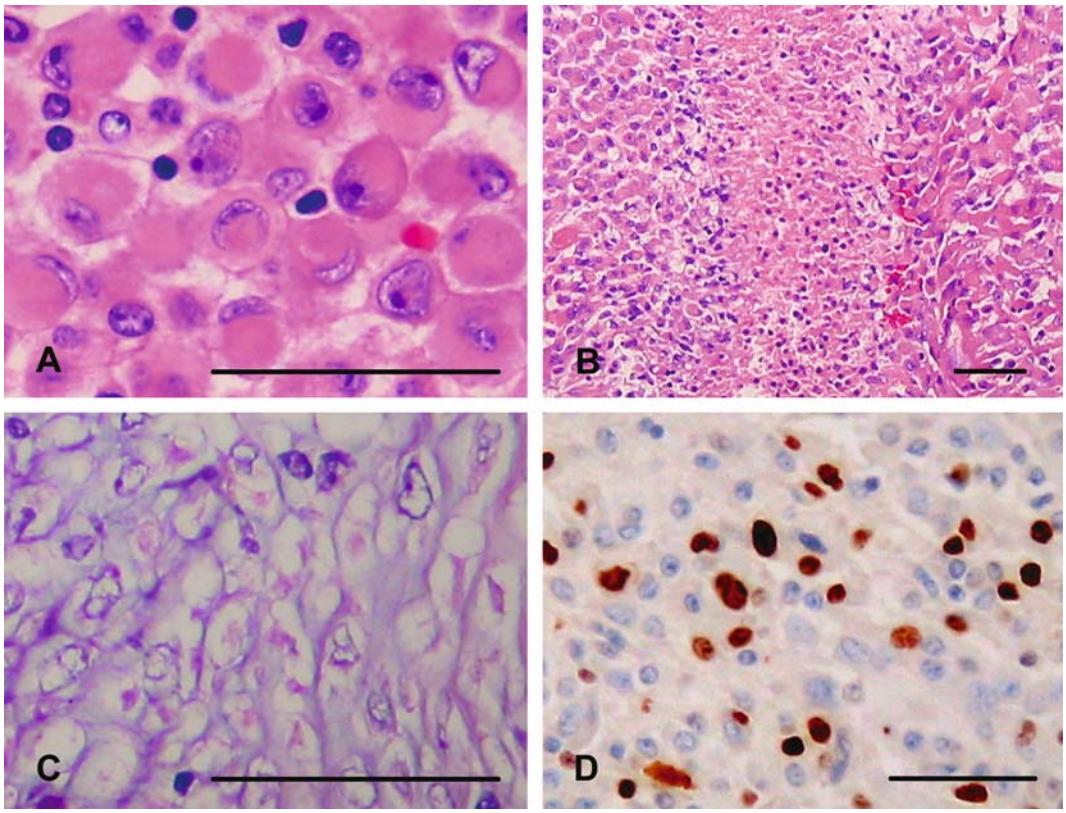

Figure 3. (A) Neoplastic cells show typical rhabdoid features including round to ovoid cytoplasmic inclusions and eceentrically located nuclei. Bar = 50 μm. Hematoxylin and eosin stain. (B) Focal necrosis is also present in the tumor. Bar = 50 μm. Hematoxylin and eosin stain. (C) Minute islands of chondroid tissue are rarely spotted in the tumor. Bar = 50 μm. Hematoxylin and eosin stain. (D) Numerous neoplastic cells are immunopositive for Ki-67, as demonstrated by dark nuclear staining in this figure. Bar = 50 μm. Ki-67 immunohistochemistry.

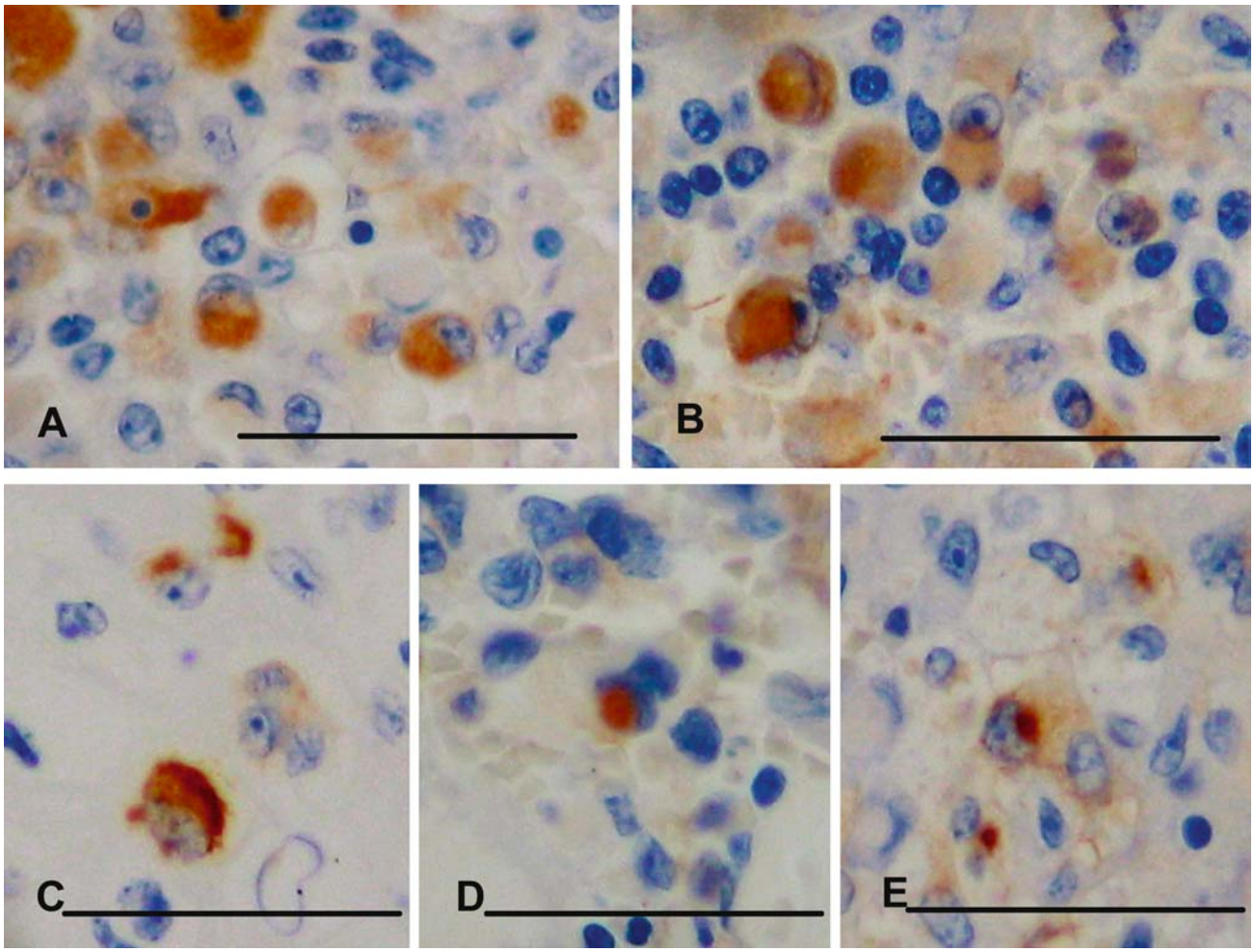

Figure 4. Enhanced cytoplasmic staining indicates immunopositivity with various antibodies. (A) Glial fibrillary acidic protein, (B) Vimentin, (C) Keratin (CAM5.2), (D) Epithelial membrane antigen, (E) Smooth muscle antigen. Bar = 50 μm. Immunohistochemistry.

Table 1. Immunohistochemical staining results in tumor cells

GFAP	+ +
Vimentin	+ +
EMA	+
SMA	+
CAM 5.2	+
Synaptophysin	-
Keratin, AE1/AE3	-
ER	-
PR	-
HMB45	-
Ki-67	40%

Diffusely positive: + +; Scattered cells postive: +; Negative: –.

contained more dense arrays of intermediate filaments. Condensation of cytoskeletal elements was focally identified adjacent to microvilli. No caveolae, lumen formation or other signs of polarity were detected. Intercellular junctions were mainly represented by zonulae adherence.

Literature review

Twelve cases of primary rhabdoid tumors of the CNS have been reported in adult patients [3,4,9–17], ranging from 18 to 35 years of age (Table 2). Three cases of rhabdoid tumors have been described in adolescents age 16 and 17 years [3,5,18]. Including the patient presented here, 10 of 16 (62.5%) were male, and 6 (37.5%) were female. One other female patient was pregnant when she presented with symptoms [14], (two of six, 33%). Three cases were diagnosed as ATRT, 10 cases as primary malignant rhabdoid tumor (MRT), two cases as rhabdoid glioblastoma, and one case simply as 'rhabdoid tumor'. The diagnoses were confirmed by histologic appearance and immunohistochemical staining in 13 cases. In three cases, molecular studies were also used to confirm the diagnosis. Bruch et al. [8] identified a clonal heterogeneous 22q deletion in a 21-year-old female, and a partial 22q deletion involving the *bcr* gene in a 34-year-old female [11]. Wyatt-Ashmead et al. [4] describe a rhabdoid glioblastoma with monosomy of chromosome 22 [4]. The patient described here was diagnosed with malignant rhabdoid tumor based on the histologic and immunohistochemical features of the rhabdoid tumor cells. FISH analysis was negative for mutations and deletions on chromosome 22.

The average age of adult presentation was 26.2 years, with a median age of 27 years. Including 16 and 17 year old patients, the average age at presentation was 24.4. The average survival after diagnosis was 19.3 months,

Table 2. Age and gender of adult patients, rhabdoid tumor diagnosis and location, treatment, survival, associated genetic mutation and staining characteristics as reported in the literature

Age	Gender	Diagnosis	Tumor location	Alterations of 22q	Surgery	Treatment	Survival	Immunohistochemisty staining positivity	Author	Publication date
18	Male	Rhabdoid Tumor	Left Frontal	Not reported	Total Resection	Chemotherapy	18 months	Vimentin, EMA, Keratin	Cossu et al.	1993
18	Male	Rhabdoid Glioblastoma, originating in glioma	Supretentorial	Monosomy 22	Partial	Chemotherapy and Radiation	5 months	Vimentin, EMA, Keratin, S100, SMA, CD99	Wyatt-Ashmead et al.	2001
20	Female Pregnant*	Rhabdoid glioblastoma	Right Occipital	Negative	Total Resection	Chemotherapy and Radiation	10 months +	GFAP, Vimentin, EMA (rare)	Clark et al.	
20	Male	Malignant Rhabdoid Tumor	Left Parietal	Not reported	Total Resection	Radiation	2 years +	Keratin, EMA, Vimentin, S100	Arrazola et al.	2000
21	Female	Atypical Teratoid/ Rhabdoid Tumor	Spinal Cord	22q deletion	Not Reported	Not reported	6 months	Not Reported	Bruch et al., Fuller et al.	2001
21	Male	Malignant Rhabdoid Tumor	Left Temporal	Not reported	Partial	Local 60 Gy CF	6 years	Vimentin, EMA, alpha 1 chymotrypsin	Horn et al.	1993
27	Male	Malignant Rhabdoid Tumor	Pineal	Not reported	Partial	Local, 60 Gy CF and Chemotherapy	2 years	Vimentin, EMA, Synaptophysin, NSE, S100, SMA	Sugita et al.	1999
30	Female Pregnant*	Atypical Teratoid/Rhabdoid Tumor	Cerebellum	Not reported	Total Resection	Local, 54 Gy AHF	11 months	Vimentin, EMA, Keratin, GFAP, NFP, S100	Lutterbach et al.	2000
31	Female	Malignant Rhabdoid Tumor	Right Parieto-rolandic	Not reported	Partial	Local 20 Gy CF and Chemotherapy	6 months	GFAP, S100, Vimentin, alpha1-antichymotrypsin, alpha1-antitrypsin, NFP, CD68, HHF35	Pimentel et al.	2003
32	Male	Malignant Rhabdoid Tumor	Left Frontal	Not reported	Biopsy	None	5 months	Vimentin, GFAP, S100	Fisher et al.	1996
34	Female	Atypical Teratoid/ Rhabdoid Tumor	Parietal	*bcr* deletion	Not Reported	Not reported	6 months	Not Reported	Bruch et al., Fuller et al.	2001
34	Male	Malignant Rhabdoid Tumor	Left Parietal	Not reported	Biopsy	Local, 56 Gy CF	6 months	Vimentin	Ashraf et al.	1997
35	Male	Malignant Rhabdoid Tumor	Left Temporal	Not reported	Partial	Local, 54 Gy CF	5 years	Vimentin, EMA, Keratin	Byram	1999

Female patients pregnant at the time of diagnosis; + indicates the patient was surviving at the time of publication.

with a range of 1 month to 6 years. Including adolescents, the survival was 17.6 months. Two patients were still living at the time of publications, including our patient and a 20-year-old male still alive after 24 months as reported by Arrazola et al. [10]. Tumor location, treatment protocols, and immunohistochemical positivity were variable.

Discussion

Malignant rhabdoid tumors (MRT), first described as rare aggressive childhood neoplasms of the kidney, have since proven to share both a poor prognosis and a similar phenotype with rhabdoid tumors at several extrarenal sites, including skin, soft tissue, and the central nervous system. In neonates and infants intracranial rhabdoid tumors are often related to the somatic or germline loss of the 22q11.2 locus. Because of the associated surrounding morphology, these lesions are diagnosed as 'atypical teratoid/rhabdoid tumors' (ATRT), first described as an entity by Rorke et al. in 1995 [19]. The distinct presence of rhabdoid cells in a teratoid background as well as the associated chromosomal abnormality have allowed better differentiation of ATRT from primitive neuroectodermal tumors (PNET) in children. However, not all malignant rhabdoid tumors show the *INI-1* gene loss, and rarely, these tumors appear in adolescents or adults. The origin and significance of these malignancies which share a similar rhabdoid phenotype but differing immunohistochemical, genetic, and histological characteristics, has led to significant controversy and debate over the appropriate categorization and identification of these entities. The relationship between development of rhabdoid transformation, the *INI-1* gene alterations, and the subsequent associated aggressive behavior is also poorly understood.

Adult presentation

In addition to the case presented here, 12 cases of adult rhabdoid tumors of the CNS have been described in the literature. All cases described had positive immunohistochemical staining for vimentin, and the majority were positive for EMA, GFAP, and SMA. The average survival in adult patients was 19.3 months, possibly indicating a better prognosis for adult patients than for children. However, the longer survival of adults may simply be related to the completeness of surgical resection and the ability to use radiotherapy levels usually not tolerated by small children. Standard treatment protocols have yet to be developed, due to the rare occurrence of the tumor.

Additionally, several of the cases including that described here failed to show the teratoid features of PNET or the mesenchymal components typically associated with childhood ATRT. It is unlikely that adults carry a germline mutation of the *INI-1* gene, due to the high potential for early malignancy. Instead, adult cases of rhabdoid tumors often were associated with a preexisting lesion, or were found at presentation to have features of mature associated glial tumors, as in the recently described rhabdoid glioblastomas [4]. These factors suggest that malignant transformation of the rhabdoid cells in adults may be occurring in susceptible areas of a pre-existing neoplasm rather than as a primary lesion. For example, rhabdoid transformation occurring in meningioma has been well described and in some cases associated with deletions of the 22q12 region near the *INI-1* gene locus [2]. 'Rhabdoid meningioma' was described by Perry et al. in 1998 as a highly aggressive variant of meningioma with histologic rhabdoid transformation often occurring in recurrent disease [20]. Rhabdoid transformation has also been described in atypical and papillary meningiomas of children [21,22].

Many authors have classified adult rhabdoid tumors simply as 'malignant rhabdoid tumor', while others have identified them as ATRT. In cases where rhabdoid transformation is clearly associated with another lesion the designation has indicated both, for example rhabdoid meningioma or rhabdoid glioblastoma.

Women/pregnancy

The ratio of men to women with rhabdoid tumors in this review was 10:6, indicating a slight male preponderance, similar to that seen in children. Interestingly, two of the six women (33%) described were pregnant at the time of diagnosis. The significance of this observation is unknown. Special staining done to evaluate for hormonal receptors or production were negative in both cases, and a relationship between the state of pregnancy and the incidence of CNS rhabdoid tumors has never been described. However, meningiomas are known to be sensitive to progesterone and have an increased incidence in pregnant women. The *INI-1* component of the SWI/SNF complex associated with rhabdoid tumors has been shown to interact with steroid hormones [6,7]. Cytokeratin 8, a component of the inclusion bodies and also associated with genetic mutations in rhabdoid tumors, has also been shown to undergo phosphorylation after stimulation with epidermal growth factor [23], which has been shown to cooperate as a transcription factor to induce cellular proliferation [24]. The effects of pregnancy on tumor growth are likely complex and subtle, and may involve both the unique hormonal state as well as associated physiologic alterations [25].

Both the woman described here and the patient described by Lutterbach et al. underwent surgical resection during pregnancy and later delivered healthy infants. Stovall et al. have described a technique to effectively use radiotherapy during pregnancy while limiting exposure of the fetus to less than 0.1 Gy [26]. The patient described by Lutterbach underwent postoperative radiotherapy, and delivered her infant by caesarian section at 36 weeks gestation [14]. The patient described here opted to have caesarian section at 33 weeks gestation before beginning postoperative radiotherapy.

ATRT background

In children, the central nervous system rhabdoid malignancy most often diagnosed is ATRT, first de-

scribed by Rorke et al. in 1995 [27]. Atypical teratoid/rhabdoid tumor of the central nervous system is a rare aggressive neoplasm usually occurring in children less than 2 years of age. The tumor is histologically similar to rhabdoid tumors of the kidney seen in infants and to extrarenal rhabdoid tumors of children and adults. Central nervous system presentation is often misdiagnosed as medulloblastoma or primitive neuroectodermal tumor (PNET) [28], but is associated with a worse prognosis and a median 6-month survival [27]. The tumors lack features of malignant teratomas, but frequently show teratoid areas of mesenchymal, primitive neuroepithelial, glandular, and epithelial populations as well as the typical rhabdoid cells. Cells can be round, polygonal, spindled or undifferentiated, and are arranged in alveolar, trabecular, solid, or angiocentric patterns. Mitosis, necrosis, hemorrhage, and cystic changes have been described [1]. Immunohistochemical staining is widely variable, with most tumors staining for vimentin, EMA, and SMA, and often for GFAP, keratin, and NFP [29].

The characterization of ATRT is becoming more sophisticated as molecular studies increase our understanding of the genetic alterations on chromosome 22q associated with the development of this tumor. In addition, the availability of FISH analysis is increasingly improving the diagnosis of these patients, especially those with ambiguous histology.

The role of INI-1 as a tumor suppressor

Several studies have tried to elucidate the function and role of the *hSNF5/INI-1* gene in the development of rhabdoid malignancies. Patients with germline *INI-1* defects are predisposed to malignancy, thus implicating the gene as a tumor suppressor. Molecular experiments have shown that *INI-1* participates in forming the functional center of the ATP-dependent chromatin-remodeling complex, SWI/SNF [6,30]. This complex affects transcription by reorganizing nucleosomes associated with specific eukaryotic cellular genes. *INI-1* is thought to interact with c-Myc which recognizes the E-box motif of the promoter region. The c-Myc family acts as sequence specific transactivators, repressing transcription by recruiting negative regulators and possibly activating transcription by recruiting SWI/SNF [6]. In addition, *INI-1* has been shown to interact with other diverse proteins affecting apoptosis, differentiation, replication, transcription, and tumor suppression [6]. For example, the SWI/SNF complex has been shown to interact with C/EBP-beta, HRX, steroid hormone receptors, and erythroid Kruppel-like factor. Animal studies have demonstrated that the *INI-1* component of SWI/SNF plays a critical role in the development of various tissue types by regulating of cell growth and proliferation [31]. Versteege et al. demonstrated that wild type ectopic *hSNF5/INI-1* expression inhibits cell entry in to the S phase and causes cell cycle arrest by down-regulating E2F targets such as *cylcinA, E2F1* and *CDC6* [32]. Similarly, Reincke et al. showed that adenovirus transduction of MRT cell lines with different isoforms of *INI-1* suppressed cell growth and upregulated senescence proteins [33].

In addition to the characterization of *INI-1* as a tumor suppressor, the specific mutations and deletions of *INI-1* are being clarified. Beigel et al. used interphase FISH, PCR based microsatellite, heteroduplex and sequence analysis to analyze the *INI-1* locus of 100 primary malignant rhabdoid tumors from different sites [7]. They found a variety of abnormalities, including germline mutations, deletions or insertions leading to novel stop codons, single base pair nonsense mutations, and intragenic deletions [7]. Interestingly, 25% of the histologically confirmed rhabdoid tumors did not show *INI-1* deletions or mutations [7]. This finding is consistent with other studies which report detectable chromosome 22 defects in only 75 to 85% of cases [6,34–37]. While the current consensus agrees that *INI-1* plays an important role in most rhabdoid tumors, it is evident that not all tumors with a rhabdoid phenotype have monosomy 22 or *INI-1* gene mutation. Likewise, not all tumors with this genetic loss display histologic rhabdoid transformation [6,34–37]. Some authors propose that *INI-1* defects uniquely characterize true malignant rhabdoid tumors; however, the presence of a genetic abnormality is not presently required for diagnosis.

Phenotype vs. genotype

An issue yet to be resolved in the characterization of rhabdoid malignancy is whether the rhabdoid tumor represents a unique entity or a non-specific phenotypic change. It remains unclear whether adult and childhood rhabdoid tumors share a common cell of origin, pathogenesis, and set of genetic alterations, or conversely, are the common result of advanced dedifferentiation in tumor progression. Fuller et al. attempted to clarify the nature of various tumors with rhabdoid features using FISH analysis to test for deletions of the 22q11.2 locus in atypical teratoid rhabdoid tumors, extrarenal malignant rhabdoid tumors, and composite extrarenal rhabdoid tumors (CERTs), including sarcoma, carcinoma, or melanoma with rhabdoid features [37]. They found that 77% of ATRTs and 75% of MRTs demonstrated *INI-1* loss, while only 13% of the CERTs had the same finding. These results show that tumors other than MRT are capable of developing a rhabdoid-like phenotype without acquiring the *INI-1* gene mutation [37]. Wharton et al. performed comparative genomic hybridization on three ATRT cases, and found that one case showed a loss of 8p instead of the expected *INI-1* mutations, suggesting that other genetic abnormalities may be involved in rhabdoid tumor development [36].

While chromosome 22 defects in relation to rhabdoid inclusion bodies are poorly understood, other genetic alterations have been correlated with this phenotype. Rhabdoid cells have an eccentric nucleus displaced by a cytoplasmic inclusion body consisting of whorled bundles of 10 nm intermediate filaments. These inclusions possibly represent failure of normal cytoskeleton formation with resultant disorganization of vimentin and cytokeratin. Shiratsuchi et al. analyzed rhabdoid tumors

and epithelioid sarcoma using immunohistochemistry. They found that while epithelioid sarcomas are diffusely positive for many cytokeratin subunits, rhabdoid cell inclusion bodies were immunopositive for only vimentin, CK8 and CK18 [38,39]. Further evaluation by three-dimensional confocal imaging showed that vimentin is diffusely distributed, but CK 8 and 18 focally form conglomerates consistent with the bundles of whorled intermediate filaments seen by electron microscopy [40]. Direct sequencing of the CK8 gene *(KRT8)* in seven malignant rhabdoid tumors showed missense mutations in all of them. The genetic defects involved regions known to participate in protofilament-to-protofilament linkage as well as a phosphorylation site known to affect filament organization [39].

Conclusion

In summary, the patient presented here represents one of the few adults with MRT and one of two women who were pregnant at the time of diagnosis. The literature describes only six women with MRT, indicating that 33% of the described cases occurred during pregnancy. The mechanism of pregnancy related effects on the development of malignant rhabdoid tumors is unknown. Malignant rhabdoid tumors of the central nervous system remain a complex and poorly understood entity, especially in adult patients. While the associated chromosome 22 defects and *INI-1* mutations have been recently characterized by several studies, questions remain as to how genetic alterations are related to the observed phenotype, how to classify tumors without these associated genetic alterations, and how diagnosis and treatment of these patients should progress. The preferred diagnosis of these has changed over time and needs careful consideration, especially in adult patients who may not have *INI-1* mutations. Because ATRT is particularly associated with infancy, we suggest that adult tumors be recognized simply as malignant rhabdoid tumors.

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