Original Article

A clinicopathological study of atypical teratoid/rhabdoid tumor with review of the literature

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ABSTRACT

Background: Atypical teratoid/rhabdoid tumor (AT/RT) is a rare, aggressive neoplasm of the central nervous system occurring mainly in the early childhood. **Objective:** The objective of the present study was to study the clinicopathologic features of this newly recognized tumor. **Materials and Methods:** A retrospective search of pathology files from a series of brain tumors revealed five patients with features of AT/RT. The clinical, radiological and pathological features were analysed. **Results:** The cases included three boys and two girls with age ranging from 2 years to 15 years. The tumors were located in the infratentorial (three located in the cerebellar hemispheres) and supratentorial areas (two located in the parietal and frontal lobes). One of the cerebellar tumors involved bilateral cerebellopontine (CP) angles, mimicking a primary CP angle tumor (like neurofibroma) with two small deposits in the cerebrum (parietal lobe). Radiologically all the five cases had heterogeneous enhancement with two of them exhibiting cystic change within. Histopathologically, the tumors were composed of rhabdoid cells, undifferentiated small cells, mixed with epithelial, mesenchymal, and neural tumor-like areas. The proportion of each of these elements varied in all the four cases. One of the tumor had predominantly small cells with focal rhabdoid differentiation mimicking a medulloblastoma/primitive neuroectodermal tumor. **Conclusion:** AT/RT is an aggressive tumor with a varied clinical and pathological profile. The present case series helps in creating an awareness of this complex tumor and stresses the importance of correct diagnosis of this neoplasm that tends to have a bad prognosis.

Key words: Atypical teratoid/rhabdoid tumor, central nervous system neoplasm, pediatric brain tumor, rhabdoid tumor

INTRODUCTION

Atypical teratoid/rhabdoid tumor (AT/RT) is a rare, highly aggressive, central nervous system (CNS) malignancy that usually affects very young children. The age at presentation is, usually, <2 years.[1,2] However, it has also been reported to occur in older children and adults.[1] This tumor is typically misdiagnosed as medulloblastoma/primitive neuroectodermal tumor (PNET) primarily because 70% of AT/RTs contain fields indistinguishable from classic PNETs. Separation of these two tumor types is crucial because the prognosis for AT/RT is grim even when treatment includes surgery with or without radio- and/or chemotherapy.[2] Disseminated forms occur in 20-30% of cases. Patients with ATRT typically follow a dismal course, and the median time to death is only a few months after the diagnosis. The neoplasm has characteristic histologic and genetic features which would differentiate from these mimics. However, the clinical and imaging characteristics could be variable and nonspecific. The histological hallmark of AT/RT is the presence of rhabdoid cells; these cells have brightly eosinophilic cytoplasm, large and eccentrically placed nuclei, and a single prominent nucleolus each, with or without fibrillary globoid inclusions.[3] The present case series describes the clinical, pathological, and imaging features observed in this particular neoplastic entity.

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MATERIALS AND METHODS

A retrospective search of pathology files at our institution from 2005 to 2012 revealed five patients with brain tumors exhibiting embryonal/blastemal tumor morphology and rhabdoid features. The records and the slides were retrieved for a detailed clinical, radiological and pathological analysis. The paraffin blocks were subjected to immunohistochemical staining using Ki-67, INI1, synaptophysin, cytokeratin, and

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GFAP. The histopathological details were studied by two pathologists independently, and results analyzed.

RESULTS

The study included five cases that satisfied the features of AT/RT. Three of the patients were males, and two of them were girls. The mean age of these patients was 9.1 years with age ranging from 2 years to 15 years. The main presenting symptoms in these patients were those related to raised intracranial tension/hydrocephalus. The other symptoms included seizures, headache, vomiting and visual changes. One of the cases also presented with extremity weakness, lethargy, extraocular muscle weakness, facial paralysis and decreased gag reflex. There were no neurocutaneous markers observed in any of these tumors. The tumors were located in infratentorial and supratentorial areas. Two of the cases were supratentorial with one in the frontal and the other located in the parietal lobe, while the remaining three infratentorial cases were situated in the cerebellar hemispheres. One of these cerebellar tumors involved bilateral cerebellopontine (CP) angles [Figure 1a], mimicking a primary CP angle tumor with two small deposits in the cerebrum (parietal lobe) [Figure 1c]. The clinical differential diagnoses in these patients were mainly medulloblastoma/PNET, exophytic brainstem glioma and neurofibromatosis 2 Wishart type in the case with bilateral CP angle involvement. All patients underwent surgical excision of the tumor, with gross total resection achieved in only two patients. These patients were referred to a higher oncocenter for chemotherapy. Three of them expired within 1 year and two patients, particularly the adolescent ones have survived for more than 1½ years postdiagnosis. Radiologically all the cases had heterogeneous enhancement with two of them exhibiting cystic change within.

The average size of these lesions was 3.5 cm in its greatest dimension. All tumors showed marked heterogeneity on both computed tomography (CT) scans and magnetic resonance images (MRIs). One of them showed foci of calcifications. Three of the tumors showed both cystic and solid areas [Figure 1b]. The cystic areas were usually eccentric. The walls of the eccentric cysts showed varying degrees of enhancement. The solid component of the masses was heterogeneous and showed varying degrees of increased signal intensity on T2-weighted images, decreased signal intensity on T1-weighted images. The solid portion in two of the cases also showed evidence of necrosis. Preoperatively these neoplasms appeared greyish yellow, vascular, friable and exhibited a poor plane with the normal structures. Microscopically, the cerebellar folia/cerebrum was seen infiltrated by the tumor. The tumor consisted of solid sheets of malignant cells with a mixture of small, embryonal type cells and large cells

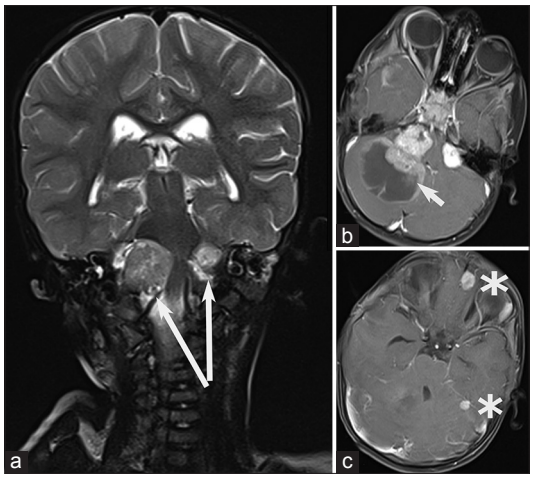

Figure 1: (a) Magnetic resonance image (MRI) showing a heterointense mass involving bilateral cerebellopontine angles (arrows). (b) MRI showing a cerebellar cystic lesion with a mural nodule. (c) MRI showing two cerebral nodules (asterix*) with a larger mass in the cerebellum (primary)

with abundant cytoplasm [Figure 2e]. The small cells had indistinct outlines, sparse cytoplasm, and dense nuclei. These cells, at some of the foci, were arranged in a nested pattern within a delicate fibrovascular stroma (vague nodularity) giving a trabecular or alveolar/organoid/glandular pattern of appearance. These cells constituted the teratoid component of the tumor [Figure 2a-d]. One of the cases had a predominant small cell component almost forming the entire volume of the tumor. The large cells had eccentric vesicular pleomorphic nuclei with a prominent nucleolus. The cytoplasm appeared homogeneous bright pink with an inclusion like appearance. These cells comprised the rhabdoid component of the neoplasm [Figure 2e]. One of the cases had a predominant rhabdoid component [Figure 2f]. Aberrant mitotic activity was observed with necrosis. There were cytokeratin positive cells in the teratoid areas [Figure 2g]. INI1 done on these tumors showed absent nuclear staining in three of them, cytoplasmic staining in one and patchy nuclear staining in the other [Figure 2h and i].

Glial fibrillary acidic protein highlighted the normal brain parenchyma infiltrated by the tumor. All the tumors satisfied the diagnosis of AT/RT (WHO grade IV).

DISCUSSION

Atypical teratoid/rhabdoid tumor is a rare and highly malignant tumor of the CNS that tends to occur in infancy and early childhood.[1] A CNS tumor of rhabdoid cells was first described in 1985, but its clinical and pathological features were not well defined until 1995-1996. Rorke *et al.*, first characterized this tumor as "AT/RT," based on the disparate combination of rhabdoid, primitive neuroepithelial, epithelial, and mesenchymal components.[2]

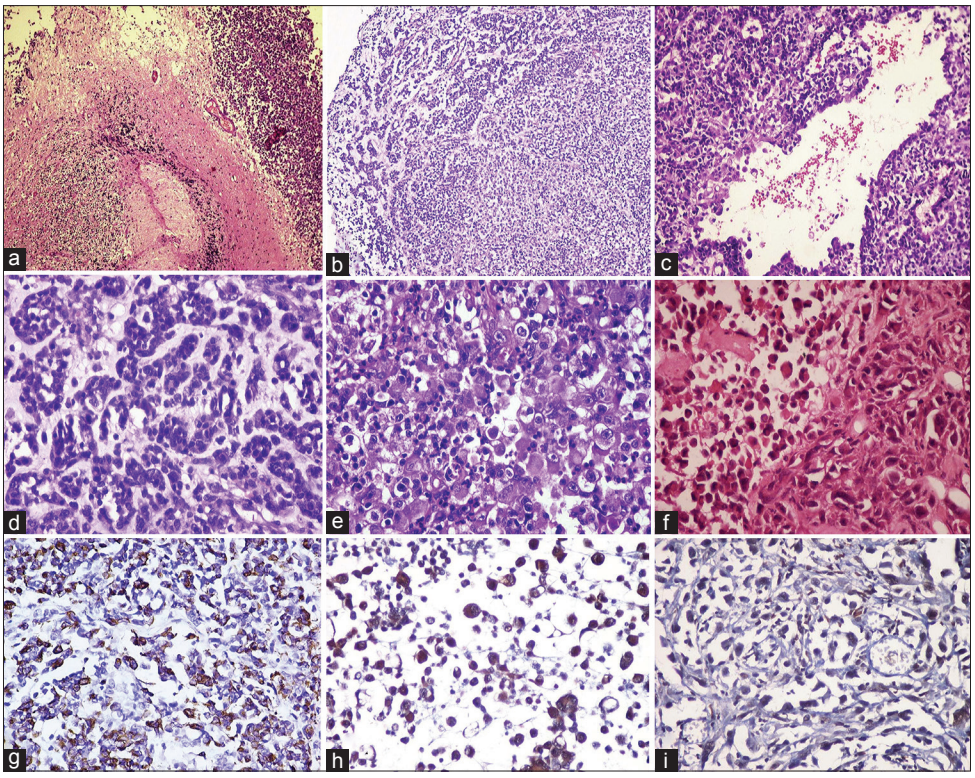

Figure 2: (a) Microphotograph showing a small round cell tumor infiltrating the cerebellum (H and E, ×40). (b) Microphotograph showing small cells arranged in a nested pattern (H and E, ×100). (c) Microphotograph showing small cells forming glandular structures/spaces (H and E, ×100). (d) Microphotograph showing small cells forming small glandular structures and nests (H and E, ×200). (e) Microphotograph showing a mixture of small embryonal and large rhabdoid cells (H and E, ×400). (f) Microphotograph showing predominantly rhabdoid cells (H and E, ×400). (g) Microphotograph showing cytokeratin positive staining of the tumor cells. (h) Microphotograph showing cytoplasmic staining of the INI1. (i) Microphotograph showing absence of nuclear staining of INI1

It is believed that AT/RT accounts for approximately 1-3% of pediatric brain tumors with a slight male predominance (male to female ratio of 1.6:1).[3,4] The present series had a 3:2 male to female ratio. This neoplasm is extremely rare in adulthood. The age at presentation is, usually, <2 years, however, some older children and even adults with AT/RT have been described.[5-7] Two of the patients in the present series were adolescents (11 and 15 years) suggesting that the occurrence in older childhood and adolescence may not be very uncommon. In view of a very small sample size (cases), the mean age may not be reliable. This differs from medulloblastoma, which has a peak occurrence at 7 years of age.[8] Koral *et al*. described that the mean age of presentation of ATRT was lower than that of medulloblastoma, that is, 1.32 years versus 6.52 years.[9]

The majority of these tumors (approximately two-third) occur in the posterior fossa, especially cerebellar hemisphere.[4,10,11] Other areas reported to be affected include the cerebral hemispheres, suprasellar, pineal region and the spine.[10,12] Three out of the five cases in the present study had the neoplasm located in the posterior fossa with one of them involving bilateral CP angle. This CP angle involvement is not uncommon as compared to medulloblastoma and is observed in about 15% of the patients.[2]

The clinical symptoms, signs and the radiological appearance of AT/RT appear to be similar to those of PNET- medulloblastoma, which frequently misleads AT/RT to a preoperative diagnosis of PNET/medulloblastoma.[4] In medulloblastoma of childhood, the tumor usually arises from the vermian area and grows into the fourth ventricle, but AT/RT may arise from the cerebellar hemisphere and grow into the adjacent cisternal space instead of filling the fourth ventricle. Compression and displacement of the fourth ventricle by mass effect of the tumor is very unusual in medulloblastoma as compared to AT/RT. Also radiologically, AT/RT tends to be relatively more heterogeneous on CT and MRI with an inhomogeneous enhancement. Calcification, cyst formation, and hemorrhage are frequently associated.[13] The other clinical differential point is the patient's age. Medulloblastoma is rare in infants and the median age for diagnosis is about 6 years.[2] Cerebellar hemispheric location and aggressive growth pattern could be considered as gross morphologic characteristics of this tumor.[4]

Atypical teratoid/rhabdoid tumors are histologically-mixed tumors that contain a "rhabdoid" element plus a variable amount of PNET-like areas. The medulloblastoma/PNET resembling areas contain small, primitive looking neuronal cells with hyperchromatic nuclei and anaplasia.[2] Importantly, the tumor is characterized by the presence

of a distinct cell type which is called the rhabdoid cell. Recognition of the rhabdoid element by the pathologist is critical because this is the characteristic feature of AT/RT and the presence of rhabdoid cell phenotype correlates with a significantly worse prognosis than the classic PNET/medulloblastoma histology.[2,14,15] The rhabdoid cells have been described as medium to large cells with eccentrically placed vesicular (i.e. lightly staining chromatin) nucleus, prominent nucleolus and a brightly eosinophilic cytoplasm (which contains whorled cytoplasmic intermediate filaments).[16] The rhabdoid cells of ATRTs are always immunopositive for vimentin, which is highlighted in the cytoplasmic filamentous inclusions. The large majority of tumors (95%) are also positive for EMA, and 75% are positive for smooth muscle actin. Variable immunopositivity is seen for a variety of other markers including epithelial markers (cytokeratins) and neuroectodermal markers, for example, GFAP.[8]

In addition, some AT/RTs may have mesenchymal and epithelial components. Because of this morphologic variability, AT/RTs have been often misclassified.[5,6,12,17,18] The rhabdoid component was present in all the four cases in the present series, except one, where the rhabdoid cells were focal and was picked up only on thorough sampling. It is not surprising that such AT/RTs in the posterior fossa with a very sparse rhabdoid component may be misdiagnosed as medulloblastoma during frozen section, intraoperatively or when the tissue is not adequately sampled. This distinction will be a real difficult in a small or nonrepresentative biopsy featuring only the small cell component. In such instances, the application of a panel of immunohistochemical stains would be needed.

A mutation or deletion in the INI1/hSNF5 gene occurs in the majority of AT/RT tumors. Absence of nuclear expression of INI1 is a critical tool for accurate AT/RT diagnosis and antibody to INI1 can be used to confirm.[19] However, INI1 staining maybe absent in many high-grade brain tumors.[20] The INI1 was unstained in three of our cases, but however one case showed cytoplasmic staining and the other with incompletely retained nuclear staining, a similar observation in some reports.[21] This can be explained by the fact that a wide spectrum of mutation has been found spanning the entire length of the INI1 protein. Some of these mutations can lead to nuclear export of the INI1 protein leading to a cytoplasmic localization of the protein or a missense mutation leading on to a nonfunctional expression of the protein in the nucleus (retained nuclear staining).[22,23] This mutation may have to be confirmed by a cytogenetic workup. As far as histogenesis is concerned, there is a great deal of controversy. Many proposals highlight the histiocytic, mesenchymal, meningeal, neuroectodermal or even germ cell lineage of AT/RT.[3,24]

The optimal treatment for AT/RT remains unclear. Until date, the role of surgery for AT/RT has not been well defined. While surgery is effective in reducing the mass, children who receive surgery without adjuvant therapy can die within a month.[25] The role of the extent of surgery in different locations is also unclear. To achieve gross total resection, some authors have recommended aggressive surgical excision, including second surgery where feasible.[26] Chemotherapy also has a part to play in treatment of this tumor, especially in children younger than 3 years of age, in whom radiation therapy needs to be delayed due to its deleterious effect on the developing CNS. They are refractory to PNET and germ cell chemotherapy. Older children with ATRT tend to have better outcomes than that of their younger counterparts. Apart from malignant local invasion, up to one-third of patients have CSF dissemination at the time of diagnosis.[8] One of the case, in the present series, had deposits in the cerebral hemisphere and disseminated forms have been reported to occur in 20-30% of cases.[1,26]

Patients with ATRT typically follow a dismal course and the median time to death is only a few months after the diagnosis.[3,26-28] This is especially true for children below 3 years of age. Moreover, children of this age group are more likely to have dissemination at diagnosis and have a faster rate of progression.[26] The death rate from the disease is 84%, despite aggressive therapy including chemotherapy and radiotherapy.[29] On the contrary, the 5-year survival rates for PNET/medulloblastoma have achieved 90% or greater with advances in neurosurgery, chemotherapy and radiotherapy.[14]

CONCLUSION

The lack of therapeutic response and a dismal prognosis requires that AT/RT be distinguished from tumors of the PNET/medulloblastoma group. Cellular neoplasms (particularly small cell tumors) arising in the cerebellum of infants and children naturally suggest the differential diagnosis of medulloblastoma. Indeed, this was the initial diagnosis in three of our cases in the present series. This series also highlights the varied clinicopathological and radiological spectrum of AT/RT which has to be considered in the differential diagnosis of posterior cranial fossa pediatric tumors to avoid misdiagnosis and erroneous prognostication. The important radiological cues to be considered are heterogeneous mass lesions with calcifications, eccentric cysts, invasive pattern of tumor growth and off midline location in the posterior fossa particularly in children younger than 2 years.

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