

Atypical Teratoid/Rhabdoid Tumor: An Unusual Variant of a Rare Entity

J Jaggon, K Bishop, M Pedican, W Halliday, R Melbourne-Chambers, J Tapper

Citation

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Abstract

Atypical teratoid/rhabdoid tumors (AT/RTs) of the central nervous system (CNS) are distinctive, malignant neoplasms of uncertain histogenesis. They are thought to be embryonal and are usually composed of varying amounts of rhabdoid-type cells, small primitive neuroepithelial cells, epithelial tissue and neoplastic mesenchyme. Diagnosis may be difficult due to this morphologic variability and usually depends on demonstrating the presence of a specific mutation on chromosome 22 (the hSNF5/INI1 gene) or by visualizing ultrastructural whorled masses of intracytoplasmic intermediate filaments. The prognosis is poor with the majority of patients dying within one year of diagnosis. We describe a case of an AT/RT in an 8 year old boy who died shortly after presentation and whose tumor at autopsy showed unusual gross and histologic features. Diagnosis was only made after electron microscopy and immunohistochemical stains revealed the characteristic features.

INTRODUCTION

Malignant rhabdoid tumors were first described in the kidney in the late 1970's as a variant of Wilms tumor (1), however, it soon became clear that the two were different entities (2). Subsequently, rhabdoid tumors were reported in a variety of extrarenal sites such as the brain, skin, liver, thymus and orbit and this was followed by widespread debate about whether these tumors all shared the same underlying genetic abnormality or whether they were a heterogeneous group with morphologic similarities (3, 4).

AT/RTs were first described in 1987(5), but it was not until 1996 that Rorke et al defined the group as a distinct entity (6). Since then it has been shown that rhabdoid tumors of the central nervous system, kidney and soft tissues are characterized by monosomy 22 or a partial deletion of chromosome band 22q11.2, which contains the hSNF5/INI1 gene (7-9).

AT/RTs are highly malignant embryonal central nervous system neoplasms (World Health Organization Grade IV) that arise in children most commonly those less than two years of age. They occur primarily within the cranial vault where up to two thirds are in the posterior fossa. There is often CNS dissemination at the time of diagnosis and they do not respond well to therapy.

We report a case of AT/RT in an eight year old boy which grossly showed mucinous features and histologically appeared to be a mucinous/chordoid type tumor. A definitive diagnosis was reached only after immunohistochemical and ultrastructural studies were performed. This case is quite interesting as this morphology, though usually present focally in many AT/RTs, is rarely the predominating pattern. Differentials such as chordoid gliomas or meningiomas would therefore have to be ruled out.

CASE REPORT

This 8 year old boy with no known chronic illnesses presented to hospital with a two month history of vomiting, which was irregular and intermittent at first, but after one month became regular and occurred daily. At about the same time he developed twisting of the face to the right associated with slurred speech and a few days later started to have headaches which were primarily in the occipital area. He subsequently developed weakness in the legs with inability to walk unsupported and, shortly before presentation, uncontrolled, uncoordinated movements of both arms and legs.

Examination revealed bilateral papilloedema, multiple cranial nerve deficits on the left, right hemiparesis and cerebellar signs. A non-contrast computed tomography (CT)

scan revealed a hypodense, ill-defined mass arising from the left cerebellar hemisphere extending into mid-brain, with displacement of the fourth ventricle to the right. There was evidence of ventricular dilatation involving the lateral and third ventricles. Hyperdense lesions noted within the mass were thought to be due to hemorrhage. Loss of gyral folds was also noted. Differential diagnoses at the time included pilocytic astrocytoma versus a high grade glioma; a medulloblastoma was thought to be less likely. The patient however died two days after admission before a definitive diagnosis was made.

At autopsy, the brain was markedly edematous weighing 1520g (normal for age 1273 g) (10). There was a 7x6x2 cm lobulated, hemorrhagic, myxoid mass that appeared to arise from the left cerebellar hemisphere in the region of the inferior vermis with extension to involve the brainstem ventrally as well as the left cerebellopontine angle. The mass appeared to be separate from the fourth ventricle which was compressed; there was dilation of the aqueduct as well as the third and lateral ventricles (Figs. 1 & 2).

Figure 1

Figure 1: Formalin fixed brain showing large lobulated myxoid tumor in the region of the left cerebellar pontine angle. Note the extensive intratumoral hemorrhage

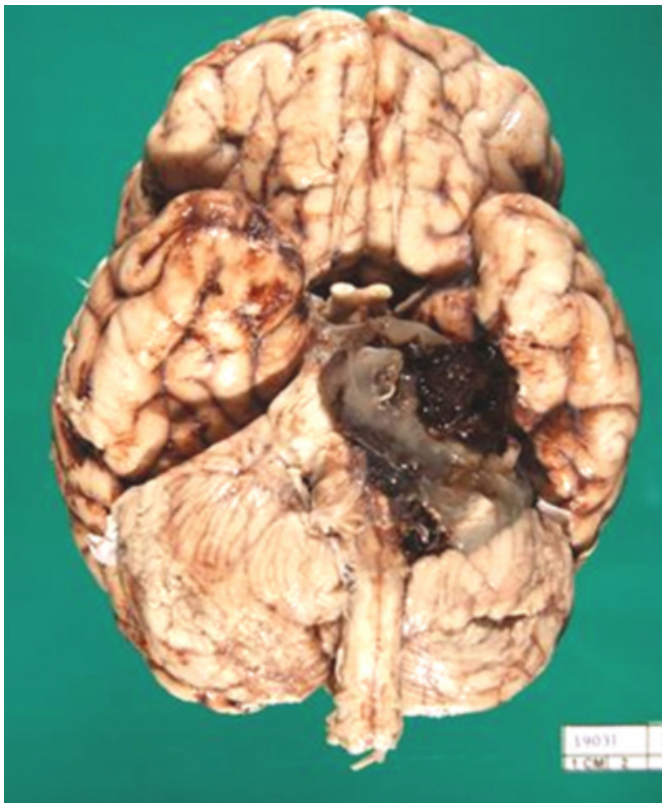


Figure 2

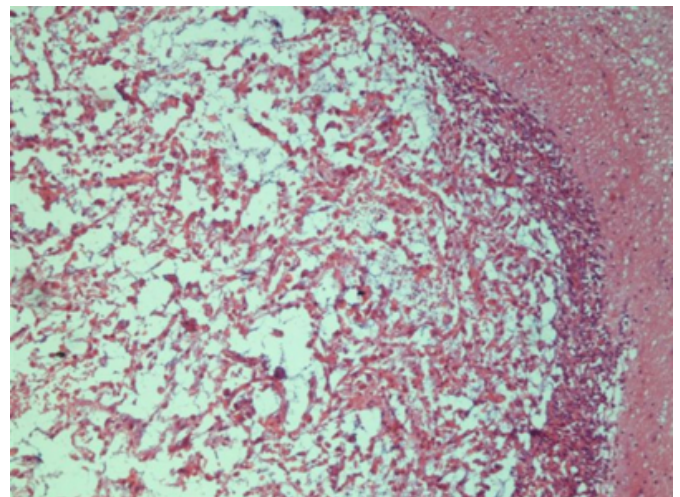
Figure 2: Sagittal section showing the tumor mass separate from and compressing the fourth ventricle; aqueductal dilation can also be seen.



Histologically, the tumor was disposed in two main patterns: the majority of the tumor was arranged in cords in a mucinous background while on the periphery the cells were more compact and spindly and formed solid nests in places (Fig. 3).

Figure 3

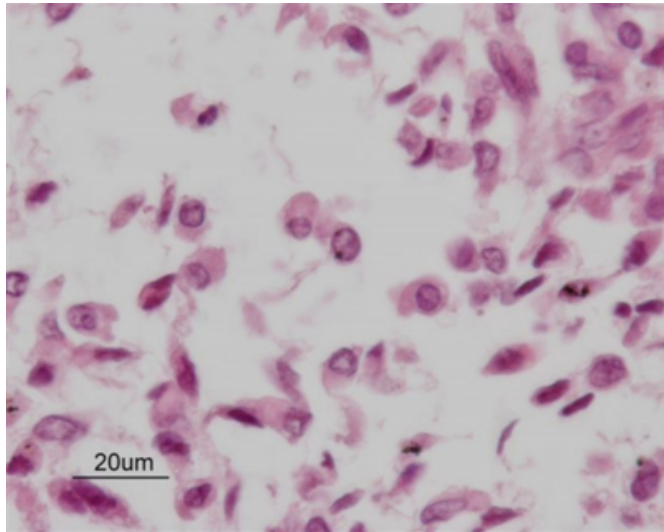
Figure 3: Low power view showing two patterns – solid nests on the periphery while centrally the tumor was composed of cords of cells in a mucinous background. H&E. (x 10).



The cells were medium-sized to large and some contained nuclei with clumped chromatin and little cytoplasm; some, however, contained ample perinuclear eosinophilic cytoplasm reminiscent of rhabdoid cells. Cytoplasmic inclusions were not appreciated on hematoxylin and eosin (H&E) stain (Fig. 4) nor were rosettes and gland-like structures identified.

Figure 4

Figure 4: Higher power showing cells with rhabdoid features – intracytoplasmic inclusions are however, not appreciated. (H&E.)



Immunohistochemistry revealed widespread reactivity for S100, vimentin and CD 99. There was scattered positivity for smooth muscle actin. The tumor cell nuclei were clearly negative for BAF47 (INI1 protein) (Fig. 5). Ultrastructural studies showed that the cytoplasm of the tumor cells contain masses of tightly compacted, whorled intermediate filaments (Fig. 6).

Figure 5

Figure 5: Negative nuclear staining for the INI1 protein (BAF47 stain) is characteristic of AT/RTs. Positive staining of inflammatory cells (arrowheads) act as positive controls.

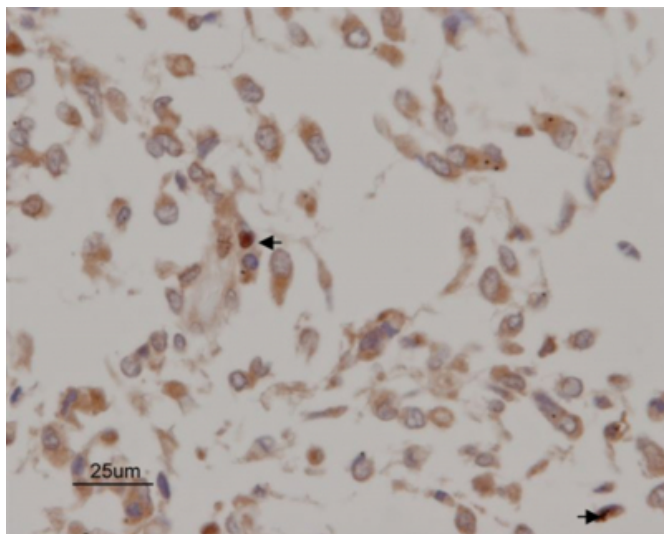
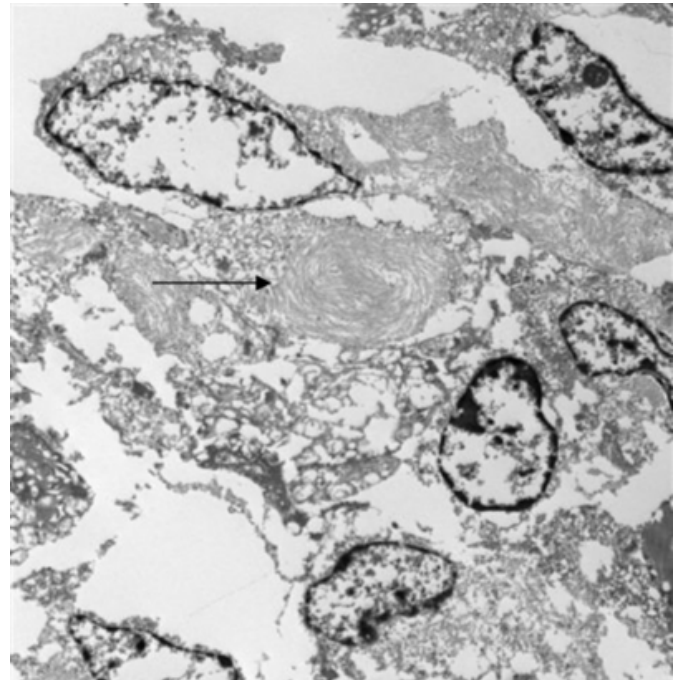


Figure 6

Figure 6: Electron microscopy reveal that the tumor cells contain whorls of intracytoplasmic intermediate filaments (arrow)



DISCUSSION

AT/RTs show a broad histologic spectrum ranging from lesions which consist exclusively of typical rhabdoid cells to those that are primarily small cell in composition mimicking at times primitive neuroectodermal tumors (PNETs). Typical rhabdoid cells have eccentric nuclei with prominent nucleoli and intracytoplasmic hyaline inclusions. Most AT/RTs are however, architecturally complex and appear somewhat jumbled due to the mixture of small cells with larger cells, the latter usually showing a variable degree of rhabdoid features. Others may sometimes take on a mesenchymal quality with a fascicular architecture appearing in the more compact areas. Rarely, as in our case, the majority of the tumor is composed of small cells forming cords in a mucoid matrix reminiscent of a chordoma.

It is this architectural and morphologic variety that makes AT/RT one of the most difficult tumors to diagnose. They may show a wide variation of immunohistochemical staining patterns which can vary from tumor to tumor; all AT/RTs however, tend to show widespread positive staining for vimentin and epithelial membrane antigen (EMA), while there may be patchy positive staining for smooth muscle actin (SMA), glial fibrillary acid protein (GFAP), neurofilament protein (NFP), S100, CD99 and keratin. Negative staining of tumor cell nuclei for the INI1 gene

product (BAF47 stain) in combination with ultrastructural studies which show characteristic whorls of intermediate filaments within the cytoplasm are now thought to be confirmatory for AT/RTs. A recent study out of Austria (11) found that PNET-like tumors without rhabdoid features which lacked INI1 showed a more aggressive clinical course similar to that seen in typical AT/RTs.

AT/RTs, because of their morphological variety, have a long list of differential diagnoses. This list is normally topped by tumors such as medulloblastomas, PNETs, choroid plexus carcinomas and some germ cell tumors. In the case presented here, because the majority of the tumor showed cords of cells in a myxoid background, the differential list differed and included entities such as chordoid meningioma, chordoid glioma and chordoma, even though the latter two were unlikely considering the age of the patient and the location of the tumor. An accurate diagnosis would have been essential in order to determine proper treatment and prognostication had the patient not died, as all the differentials in this case are regarded as WHO Grade II lesions or, in the case of a chordoma, a locally aggressive but relatively benign tumor.

The prognosis for AT/RTs has historically been poor and large studies have been difficult due to the rarity of the tumor. Therapy remains quite varied and controversial. A central nervous system AT/RT Registry was set up in 2004 (12) and enrollment is ongoing. This group has reported so far that older children diagnosed with this disease have a better prognosis. They also reported that more aggressive therapy, including surgery, chemotherapy, intrathecal chemotherapy, craniospinal radiotherapy and high-dose chemotherapy with stem cell rescue have shown mild improvements in survival.

These tumors are both difficult to diagnose and treat. The major difficulty in diagnosis comes from the fact that AT/RTs show wide morphologic variability; however, now with the advent of more specific immunohistochemical stains as well as ultrastructural studies, more and more cases will be accurately diagnosed and thus the full morphologic

spectrum of this entity will soon be known. At the same time, it is hoped that with future advances in medicine and technology, a more effective treatment regime will be discovered and implemented.

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Author Information

Jacqueline R Jaggon, MBBS, DM (Path)

Lecturer and Consultant Pathologist, Department of Pathology, University Hospital of the West Indies

Karen L Bishop, MBBS, DM (Path)

Lecturer and Consultant Pathologist, Department of Pathology, University Hospital of the West Indies

Mandi C Pedican, MBBS

Resident in Pathology, Department of Pathology, University Hospital of the West Indies

W Halliday, MD

Staff Neuropathologist, FRCP Professor, Division of Neuropathology, The Hospital for Sick Children

Roxanne Melbourne-Chambers, MBBS, DM (Paed)

Lecturer, Department of Obstetrics, Gynecology and Child Health, University Hospital of the West Indies

Judy M Tapper, MBBS, FRCPC

Associate Lecturer, Department of Obstetrics, Gynecology and Child Health, University Hospital of the West Indies