PEER REVIEWED LETTER

Malignant Teratoid/Rhabdoid Tumour: Long-Term Survival

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The patient is a previously healthy 19-month-old child who became symptomatic in October 1998 with right hand weakness and cessation of new words with progression of right sided weakness and decreased sensation over the next month. The computed tomography (CT) and magnetic resonance imaging (MRI) scans demonstrated a large, deep, left frontal periventricular enhancing mass with several cystic areas. A left frontoparietal craniotomy was performed and the tumour was grossly resected. The pathological diagnosis was AT/RT. Grossly, the tumour was composed of firm, pink-tan hemorrhagic tissue. Sections showed a densely cellular, infiltrating neoplasm with areas of necrosis (some calcified), fascicular and focal sheets of collagen, and a variable, often prominent reticulin network. There was no endothelial proliferation. Light microscopy with hematoxylin and eosin stain (Figure 1) revealed a varied tumour appearance predominantly composed of larger tumour cells, with randomly dispersed nests of small undifferentiated cells close to the interface of tumour and normal brain tissue. The larger cells had several growth patterns: some were loosely arranged bi- or multi-polar cells forming cords and acinar structures against a faintly basophilic mucinous background, some were elongated cells arranged in coarse follicles or other compact bundles, while others were arranged in sheets or nests with prominent, sometimes glassy eosinophilic and cytoplasmic inclusions and eccentric nuclei (rhabdoid cells). Larger cells had nuclei with vesicular chromatin and prominent nucleoli, and smaller cells had hyperchromatic nuclei. Mitoses were focally numerous with some atypical in form, and cytoplasmic glycogen was inconspicuous. Immunohistochemical studies revealed widespread staining for epithelial membrane antigen (EMA), vimentin (Figure 2), glial fibrillary acid protein (GFAP), groups of cells with membranous patterns of staining for CD99, regional staining for neuron-specific enolase (NSE), scattered staining for transthyretin, and rare staining for actin, cytokeratin, and synaptophysin. The tumour was positive for chromosome 22 monosomy. Electron microscopy showed polygonal cells arranged in ill-defined acini that formed inconspicuous, sometimes entwined short microvillus processes. Variable numbers of intermediate filaments were identified and some cells showed a rudimentary basal lamina. Desmosomes were not seen, and there was no evidence of neural differentiation.

Post operative CT and MRI showed no definite residual tumour, however, the patient had residual right hemiparesis. The infant commenced a course of chemotherapy consisting of: Vincristine (0.05 mg/kg IV), Etoposide (1.5 mg/kg/day IV x 5 days), Carboplatinum (10 mg/kg/day IV x 2 days), and Iphosphamide (60 mg/kg/day IV x 5 days). Pretreatment neuropsychological testing was not performed because of the urgency of the clinical situation. At the end of chemotherapy, 14 months from diagnosis, the child was walking well with a leg brace and had regained limited movement of her right arm. MRI

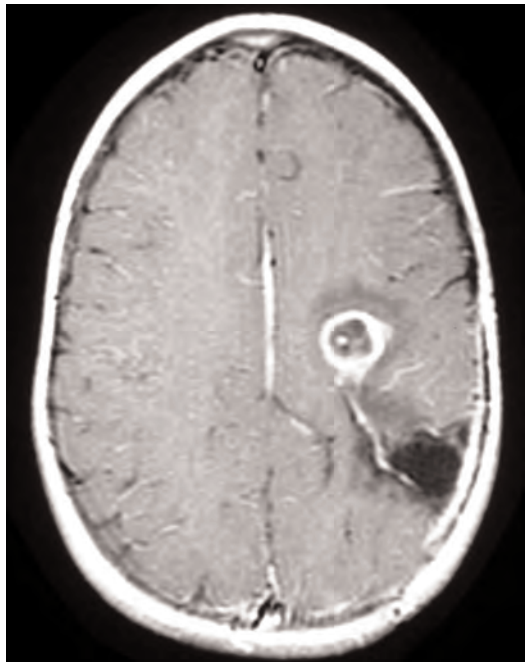

Figure 1. *Axial T1-weighted preoperative MRI image with gadolinium of the left frontal enhancing tumour.*

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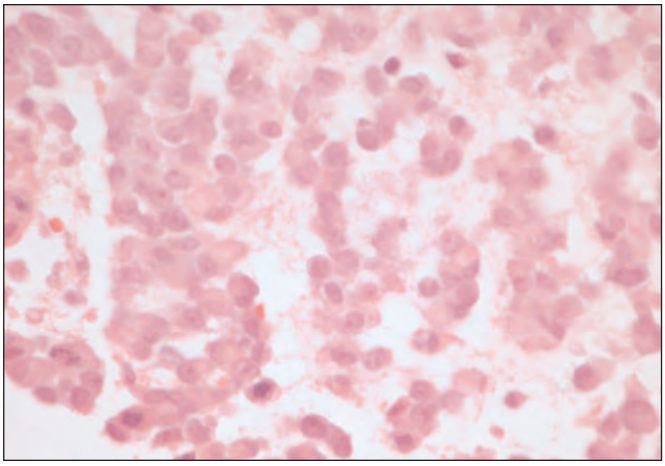

Figure 2. *Hematoxylin and eosin stain (original magnification x600).*

of the brain at 17 months, however, disclosed new focal enhancing nodular lesions suspicious for tumour recurrence at the anterior and left resection margins. Resection was attempted, however, the area of recurrence could not be reached with safety, biopsies were negative. The MRI six months later showed further growth of the residual anterior mass. Surgical removal was again attempted and the mass was grossly resected.

Unfortunately, an MRI two months later revealed a further new ring-enhancing mass within the resection cavity suspicious for recurrence (Figure 1). The MRI spine was unchanged and cerebrospinal fluid cytology was negative. The child (now age 4) commenced another course of chemotherapy consisting of Vincristine, Etoposide, and Carboplatinum and focal radiation to 54 Gy/30 fractions with in the hope that the tumour would respond and become resectable. However, further surgery was unnecessary as the tumour responded well to radiotherapy and the second course of chemotherapy. The child is currently doing well and remains in radiographic remission 86 months from the time of diagnosis.

Discussion

Compared to other malignant CNS tumours in this age group, AT/RT displays unique clinical, histopathological, immunohistochemical, and cytogenic features that ultimately led to its definition as a distinct entity in 1987.[1-7] The World Health Organization classification of tumours of the CNS currently lists AT/RT as a malignant embryonal tumour. Primitive neuroectodermal tumour/medulloblastoma (PNET-MB) was a frequent misdiagnosis.[4,6] In response, in 2001 a National Cancer Institute workshop delineated the criteria required to diagnose AT/RT.[4]

Light microscopy and immunohistochemistry are mandatory for diagnosis.[4] AT/RT displays nests or sheets of rhabdoid cells adjacent to, or surrounded by variable combinations of neuroectodermal, mesenchymal, and epithelial cell regions.[1-4,7] The areas of neuroectodermal cells are indistinguishable from PNET in 70% of cases if examined in isolation from the rhabdoid regions.[1,8] This is in contrast to most malignant rhabdoid tumours (MRTs) that have more discrete cellular elements dispersed on a predominantly rhabdoid cell background. The mesenchymal and epithelial regions occur in approximately one quarter to one third of AT/RT cases, another feature not observed in MRT. The rhabdoid cells in AT/RT have variable morphologic features, but are primarily plump, homogeneous, and may contain dense, round inclusions. Nuclei are eccentric and round with prominent nucleoli. Immunohistochemical stains characteristic for AT/RT include EMA, vimentin, and smooth muscle antigen. GFAP, keratin, and neurofilament protein may also be expressed. Ultrastructural features of AT/RT are variable and sample-dependent. Cytogenic studies have identified a rhabdoid suppressor gene (INI1/hSNF5) at 22p11.2, with mutations predisposing children to AT/RT.[3] There is considerable variation in the cytogenic findings from different studies, however, which raises the possibility that multiple genetic pathways may underlie the AT/RT phenotype.[9] Abnormalities on chromosome 22, therefore, are not sufficient for diagnosis of AT/RT.

The exact incidence of AT/RT is unknown, however, a previous Children's Cancer Group study of children less than three years of age with known malignant brain tumour proposed a 10-15% incidence rate of AT/RT.[1,4-5] There is no clear gender predilection. The posterior fossa appears to be the most common location for AT/RT.[1-2,5,10-12] AT/RT has also been noted in suprasellar, pineal, temporal, spinal cord, and extramedullary regions.[1] Clinical behavior is usually consistent with tumour location. Synchronous tumours cannot be excluded with AT/RT[5], and leptomeningeal dissemination at the time of initial diagnosis has been reported at rates ranging between 15-40%.[1,4] Typical radiographic features of AT/RT are non-specific on CT and MRI: prominent cystic/necrotic areas associated with an inhomogeneous contrast-enhanced solid component.[4,13-14] Unusual appearances have been described elsewhere.[15]

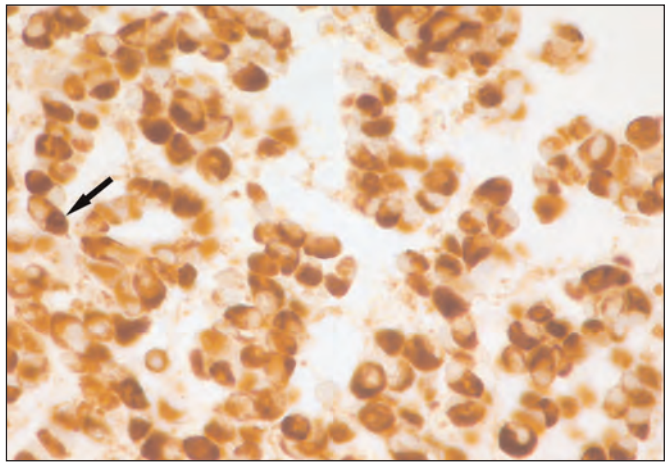

Figure 3. *Intense vimentin staining of cytoplasmic inclusions in tumour cells (original magnification x 600)*

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Treatment outcomes for infants with AT/RT are poor, with an average survival time of less than one year following diagnosis.[1-5,8] AT/RT is resistant to most forms of therapy, and owing to its low incidence, there is no consensus on an optimal treatment strategy. There is now evidence, however, that more aggressive multi-modality management of AT/RT can lead to longer survival times,[3] as was seen in the present case.

In their report of 42 patients enrolled in a registry for children with AT/RT, Hilden[3] et al recommended an aggressive surgical approach, including second-look surgery to achieve gross total resection when possible. They reported median event-free survival (EFS) times of 14 months for patients who had gross total resection compared to 9.25 months for patients who had only partial resection.

Chemotherapy is often used as an alternative to radiotherapy in infants.[16] The relative value of individual agents for treatment of AT/RT, however, is unknown. Hilden et al[2] suggest that AT/RT is indeed chemosensitive, in light of the fact that 12 of 22 patients in their registry achieved at least a partial response after receiving predominantly platin- and alkylator-based regimens. The combination of carboplatin, etoposide, and high-dose methotrexate has been highly active in pediatric patients with CNS embryonal tumours.[16]

Radiation has recently been recommended to be included in the developing Children's Oncology Group (COG) protocol for CNS AT/RT. A good response to radiation was seen in the present case, negating the need for further surgery. In the AT/RT registry, 8 of 14 children who achieved long-term survival (median EFS = 42 months) received radiotherapy, although this group had an older median age of 47 months at diagnosis. In MRT, longer survival times have been associated with the inclusion of radiotherapy, and craniospinal irradiation has been suggested to increase disease control similar to results seen in medulloblastoma.[17] Radiotherapy, although controversial, should be considered in appropriate cases of AT/RT for its potential to increase disease control and prolong survival.

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