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Case Report

Atypical teratoid/rhabdoid tumour with leptomeningeal dissemination in an adult

T. Kawaguchi[1], **T. Kumabe**[1], **M. Watanabe**[2], and **T. Tominaga**[1]

[1] Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan
[2] Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan

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Summary

A 22-year-old man presented with a rare case of atypical teratoid/rhabdoid tumour (AT/RT). Magnetic resonance imaging showed a left cerebellar mass with leptomeningeal dissemination. Partial resection was performed. Histological examination revealed AT/RT. Postoperatively, whole neuraxis and local irradiation were performed. Three-drug chemotherapy with ifosfamide, cisplatin, and etoposide, and adjuvant intrathecal administration of methotrexate were repeated. Near complete response was achieved, and no tumour recurrence/progression has been noticed during the follow up of 24 months. Intensive radiochemotherapy can successfully control AT/RT, even with leptomeningeal dissemination.

Keywords: Atypical teratoid/rhabdoid tumour; chemotherapy; leptomeningeal dissemination; radiation.

Introduction

Atypical teratoid/rhabdoid tumour (AT/RT) is a rare disorder which histologically resembles the more common and less aggressive medulloblastoma or primitive neuroectodermal tumour (PNET). AT/RT is characterized by epithelial and mesenchymal components, and rhabdoid cells which contain eosinophilic cytoplasm and eccentric nuclei with prominent nucleoli. AT/RT of the central nervous system has attracted significant interest since the first description in 1987 [14]. AT/RT is a tumour of infancy and childhood with a median age at diagnosis of 16.5 months [18], and 94% of patients are less than 5 years of age [17, 19]. Only eight adult cases of AT/RT have been reported since 1992 [1, 6, 7, 9, 12, 15, 16, 21]. Here we report a case of AT/RT with leptomeningeal dissemination in an adult who was successfully treated with radiochemotherapy.

Case report

A 22-year-old man was admitted to our hospital with a 2-week history of headache and nausea. Neurological examination found slight left facial paresis and truncal ataxia. Magnetic resonance (MR) imaging of the brain showed an approximately 4-cm diameter mass lesion in the left cerebellar hemisphere with relatively homogeneous enhancement (Fig. 1A). Diffusion-weighted MR imaging showed the tumour as a moderately high intensity mass. Proton MR spectroscopy revealed significant elevation of the choline level, but no peaks of creatine or N-acetylaspartate were detected. MR imaging of the spine revealed diffuse leptomeningeal dissemination to the brain stem and the whole spinal cord (Fig. 2A). The preliminary diagnosis was desmoplastic medulloblastoma, anaplastic ependymoma, lymphoma, PNET, or malignant rhabdoid tumour.

Partial resection was performed via a midline posterior fossa approach. The antero-lateral part of the tumour was too hard and too strongly adherent to the lower cranial nerves to be removed (Fig. 1B). A catheter connected to an Ommaya reservoir was inserted into the posterior horn of the right lateral ventricle.

Histological examination of the tumour specimens revealed areas of rhabdoid cells containing eosinophilic cytoplasm and eccentric nuclei with prominent nucleoli (Fig. 3A). Glandular components were also detected in some areas (Fig. 3B). Immunohistochemical staining showed slight immunoreactivity for epithelial membrane antigen (EMA) and pancytokeratin (AE1/AE3), and marked immunoreactivity for vimentin, smooth muscle actin (SMA), synaptophysin, and neurofilament protein (Fig. 4A–C). No immunoreactivity was found for GFAP, except for intermingled reactive astroglia. The labelling index for Ki-67 was 50–60% (Fig. 4D). The histological diagnosis was AT/RT.

The postoperative course was uneventful. Whole neuraxis (30 Gy) and accelerated hyperfractionated local irradiation (30 Gy) was given. Three-drug chemotherapy was administered at 3-week intervals for a total of three cycles. Each cycle consisted of ifosfamide (900 mg/m^2), cisplatin (20 mg/m^2), and etoposide (100 mg/m^2) administered on day 1 to day 5. Intrathecal chemotherapy via the Ommaya reservoir with methotrexate (10 mg) was administered three times. MR imaging showed marked decrease of the residual tumour and leptomeningeal dissemination. The patient was discharged home without neurological deficit. Additional three cycles of the same three-drug chemotherapy were administered

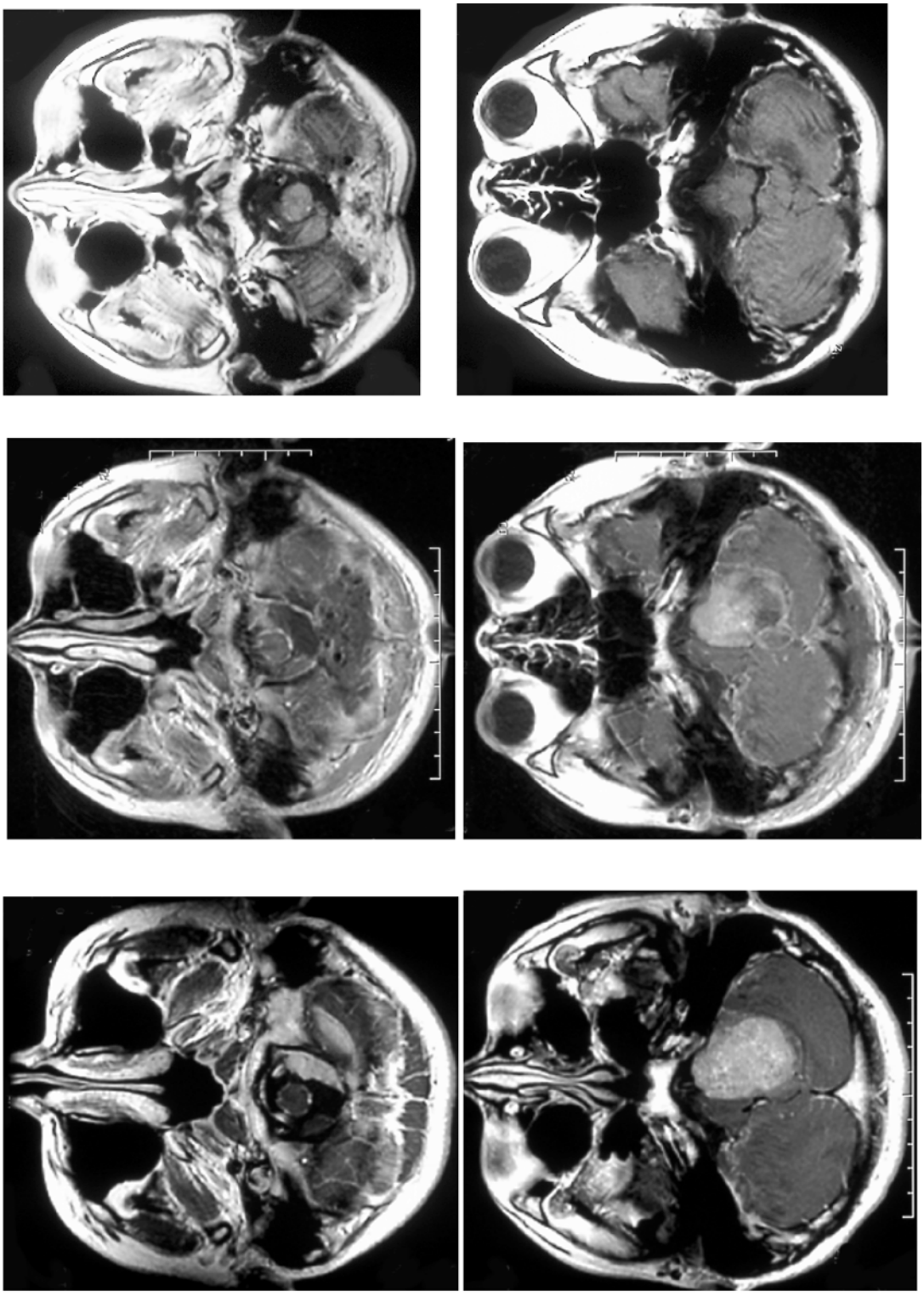

Fig. 1. Axial T1-weighted magnetic resonance (*MR*) images with gadolinium-diethylenetriamine-penta-acetic acid. (A) Preoperative MR images revealing a relatively homogeneously enhanced lesion in the left cerebellar hemisphere. (B) Postoperative MR images revealing residual tumour. (C) MR images 18 months after the surgery revealing disappearance of the tumour

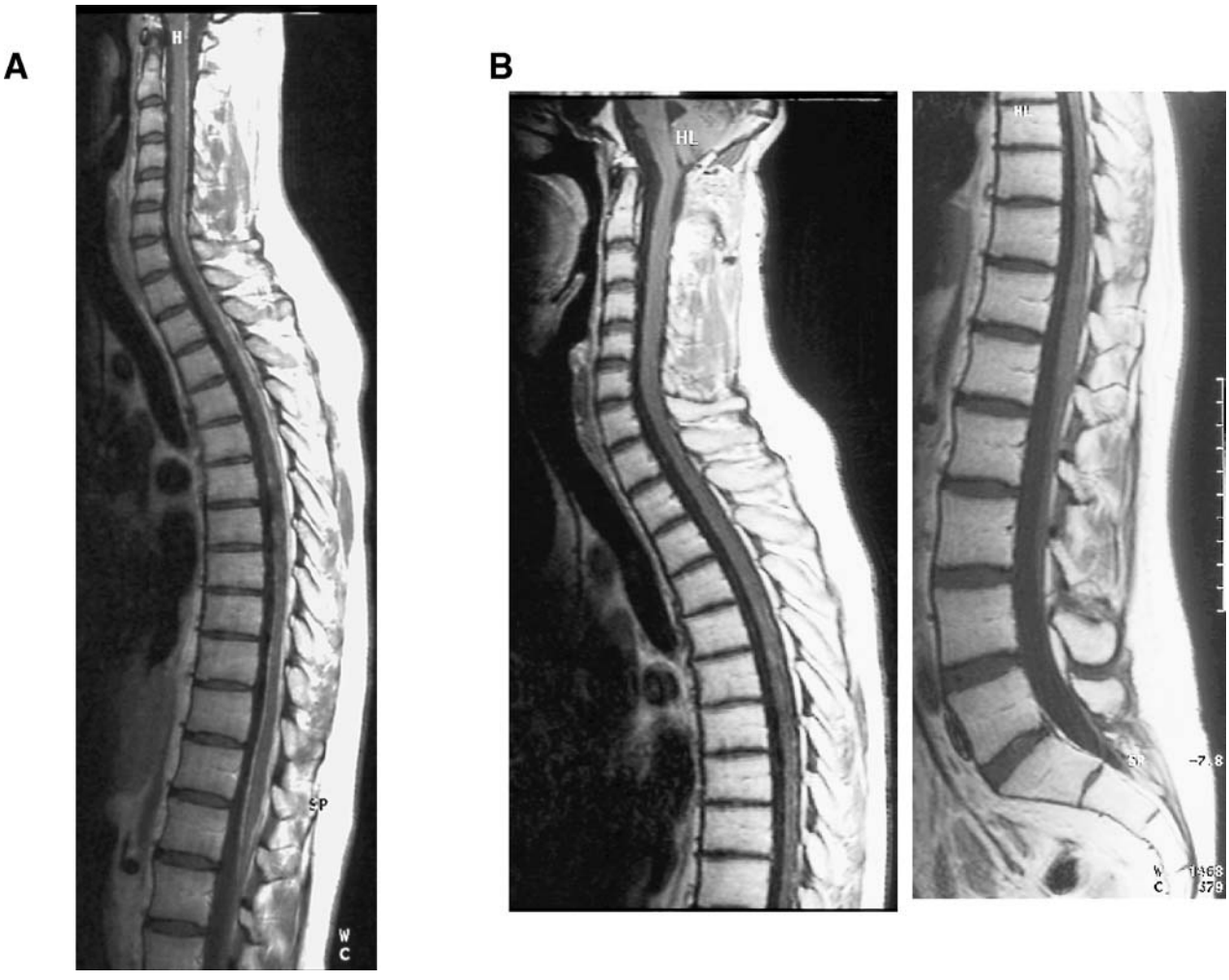

Fig. 2. Sagittal T1-weighted magnetic resonance (*MR*) images with gadolinium-diethylenetriamine-penta-acetic acid. (A) Preoperative MR image revealing diffuse leptomeningeal dissemination to the whole spinal cord. (B) MR images 18 months after the combined therapy revealing complete disappearance of the dissemination

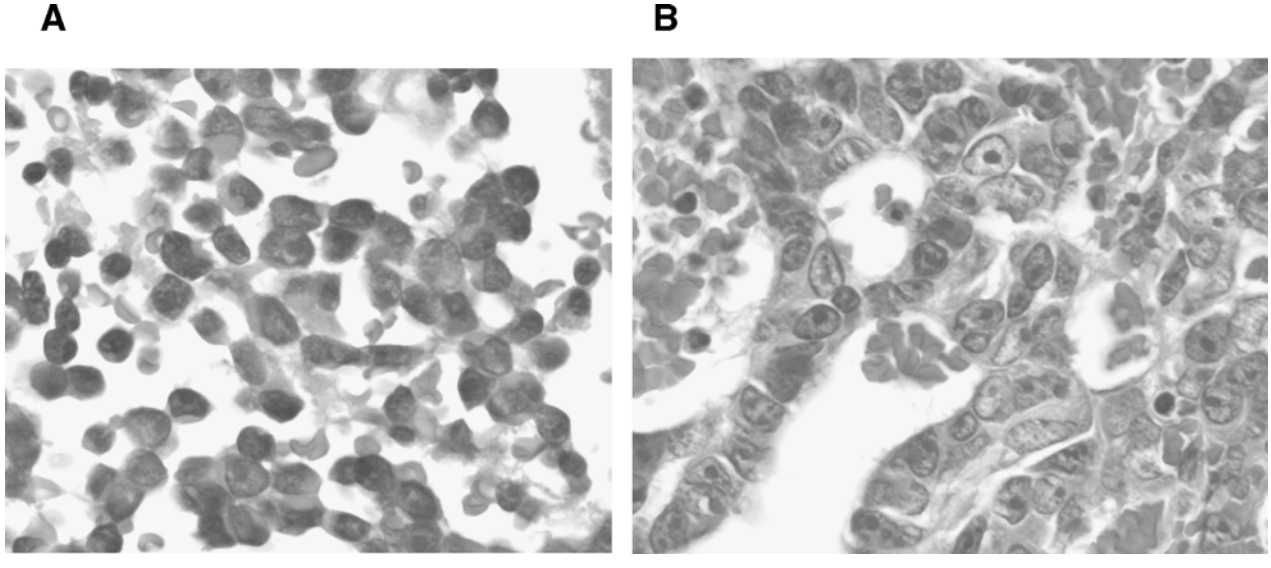

Fig. 3. Photomicrographs of the surgical specimen of the tumour (H&E, original magnification ×200). (A) The tumour consists of rhabdoid cells with eosinophilic cytoplasm and prominent nucleoli. (B) Glandular components are present

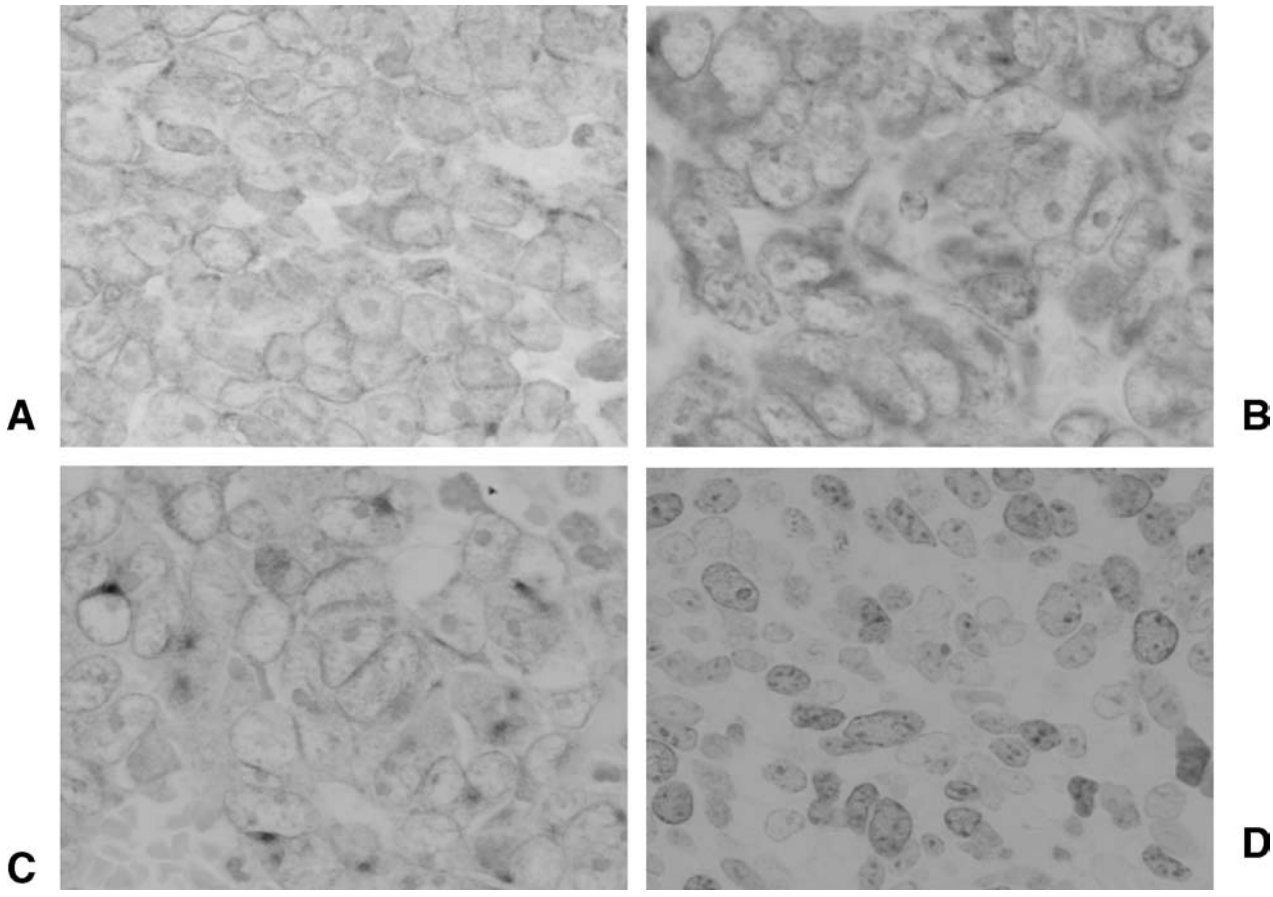

Fig. 4. Photomicrographs of immunohistochemical staining showing that most of tumour cells were positive for smooth muscle actin (A), vimentin (B), and synaptophysin (C). The labelling index for Ki-67 was 50–60% (D). Original magnification ×200

at 3-month intervals, and intrathecal administration of methotrexate (10 mg) was repeated every month. The patient has remained in good condition with no tumour recurrence/progression during the follow up of 24 months (Figs. 1C and 2B).

Discussion

AT/RT must be differentiated from medulloblastoma or PNET because AT/RT requires more intensive treatment. AT/RT exhibits variations in cell type and histological pattern [13]. Therefore, immunohistochemical investigation is helpful and important for definitive diagnosis. The three antibodies of greatest value are vimentin, EMA, and SMA. In addition, positive reactions can sometimes be observed for glial fibrillary acidic protein, neurofilament protein, cytokeratin, synaptophysin, and S-100 protein. Ninety percent of cases of AT/RT demonstrate monosomy or deletion of chromosome 22 [3]. This change is rare in medulloblastoma and PNET [2, 4, 18]. Therefore, fluorescence in situ hybridization and/or loss of heterozygosity studies should be used routinely.

The 5-year survival of patients with medulloblastoma treated by adjuvant therapy varies from 25% to 70% [20]. Patients with PNET generally survive less than 24 months in spite of surgery, radiotherapy, and chemotherapy [8]. AT/RT appears to be non-responsive to adjuvant therapy and most children survive for less than 12 months after diagnosis [5, 18]. The mean survival time is 3 months after only surgical intervention and 8 months with adjuvant radiochemotherapy [10]. Leptomeningeal dissemination can be seen from the very early stage in one third of cases [5, 18]. There is no generally accepted treatment for AT/RT, but intensive therapy can change the natural history of AT/RT. Two children were successfully treated with high-dose chemotherapy and autologous bone-marrow transplant [11].

Since 94% of patients are diagnosed at less than 5 years of age [17, 19], only eight adult cases of AT/RT have been reported since 1992 [1, 6, 7, 9, 12, 15, 16, 21] (Table 1). Four of the eight adult patients survived longer than 1 year, thus AT/RT in adults is considered to be less aggressive than in children. Our case maintained

Table 1. *Clinical summary of 9 cases with AT/RT in adult*

Case	Age/sex	Tumour location	Resection	Radiotherapy	Chemotherapy	Survival after diagnosis
Horn *et al.* (1992)	21y/M	lt. temporal	partial	60 Gy	no detail information	6 years
Cossu *et al.* (1993)	18y/M	lt. frontal	complete	No	no detail information	18 months
Fisher *et al.* (1996)	32y/M	lt. frontal	biopsy	No	No	1 month
Ashraf *et al.* (1997)	34y/M	lt. parietal	biopsy	56 Gy	No	6 months
Oulab Ben Taib *et al.* (1999)	17y/M	lt. temporal	partial	No	No	3 weeks
Byram *et al.* (1999)	35y/M	lt. temporal	partial	54 Gy	No	5 years
Sugita *et al.* (1999)	27y/M	pineal region	partial	60 Gy	ACNU	2 years
Lutterbach *et al.* (1999)	30y/F	cerebellum	complete	54 Gy	temozolomide	11 months
present case	22y/M	lt. cerebellar hemisphere	partial	whole neuraxis 30 Gy + local 30 Gy	ifosfamide, cisplatin, etoposide + methotrexate (intrathecal)	24 months (alive)

M Male; *F* female.

a near complete response for more than 24 months to radiation and combination chemotherapy. Horn *et al.* reported a 21-year-old man with skull base AT/RT who received chemotherapy for recurrent AT/RT with a maximum survival of 6 years following the initial diagnosis [12]. In these adult patients with AT/RT including our case, karyotypic analysis was not carried out. So the relation between the status of chromosome 22 and prognosis is still uncertain at this point.

In our case, MR imaging of the spine revealed dissemination at diagnosis. Although leptomeningeal dissemination is considered to indicate a poor prognosis, whole neuraxis radiotherapy, and repeated systemic and intrathecal chemotherapy achieved good control of both the primary lesion and the dissemination.

The present case of AT/RT in an adult shows that although the prognosis of AT/RT is extremely poor, this tumour can be well controlled for more than 24 months by radiation and multimodal chemotherapy.

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Comments

A case of atypical teratoid/rhabdoid tumor (AT/RT) arising in a 22-year old man is described. Partial resection was followed by irradiation, systemic multimodal and intrathecal methotrexate chemotherapy, resulting in near complete response for 24 months. Given the very poor prognosis of the much more common infantile AT/RT, this is a relatively long period. The present case is of interest because prognosis and adequate therapy are still unclear in these extremely rare adult AT/RT cases.

From the biological point of view, an intriguing question is whether AT/RT in adults genetically corresponds to infantile AT/RT, or merely reflects dedifferentiation of other tumor types going along with rhabdoid transformation, i.e. whether it represents a so-called composite rhabdoid tumor. This issue could be addressed by studying chromosome 22 and hSNF5/INI1 gene aberrations, both reflecting genetic hallmarks of infantile AT/RT, in the previously published adult AT/RT cases, which can be retrospectively performed using routine paraffin materials. The results would be of great biological and therapeutic interest, and the authors of this case report are encouraged to initiate an international effort.

W. Paulus
Münster

This manuscript is very interesting because, besides the rarity of the case, it provides the message that even aggressive and diffuse tumours can be successfully treated by a multimodal and aggressive therapy. Too many times, neurosurgeons, oncologists, neurologists and radiotherapists face diffuse tumours (e.g. lymphomas, metastases, etc.), with scepticism. For example, very few centres use intraventricular chemotherapy via an Ommaya reservoir. Today 3–4 brain metastases can be treated by the combination of surgery, for the biggest and life-threatening ones, and radiosurgery for the small deep-seated lesions, depending on the prognosis on the stage and stability of the primary disease.

I think the philosophy the authors advocate should be disseminated widely among the scientific community.

Maurizio Iacoangeli
Italy

Correspondence: Toshihiro Kumabe, M.D., Department of Neurosurgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, 980-8574, Japan. e-mail: kuma@nsg.med.tohoku.ac.jp