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CASE REPORT

Atypical teratoid/rhabdoid tumour: 7-year event-free survival with gross total resection and radiotherapy in a 7-year-old boy

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Abstract
Case study We report the case of a 7-year-old boy who presented in 1998 a tumour of the left frontal lobe. Initially diagnosed as anaplastic ependymoma, the boy was treated by gross total resection followed by radiotherapy at the operated site. In July 2005, an orbital tumour was discovered and resected. The tumour was composed of sheets of rhabdoid cells which diffusely expressed vimentin and focally epithelial membrane antigen (EMA) and α-smooth actin by immunohistochemistry. The first tumour was re-examined. Small foci of rhabdoid cells were found. Immunohistochemistry anti-INI1 performed on both tumours was negative. Molecular techniques performed on frozen specimen of the orbital tumour confirmed the diagnosis of atypical teratoid/rhabdoid tumour (ATRT).

Discussion We discuss the pathological criteria for diagnosis of ATRT and the usefulness of early radiotherapy in the light of the recent literature.

Keywords Atypical teratoid/rhabdoid tumour · Radiotherapy · Pathology · INI1 immunohistochemistry

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Introduction

Atypical teratoid/rhabdoid tumour (AT/RT) of the central nervous system (CNS) is a rare and aggressive neoplasm of children with a median time to death of few months. Age at presentation is commonly less than 2 years, although cases in adults have been reported [13]. Infratentorial tumours are slightly more frequent than supratentorial tumours. Disseminated forms occurred in 20–30% of cases. Neuroradiological findings are not specific [5]. Diagnosis is based on histological, immunohistochemical and molecular data. The histological hallmark of AT/RT is the presence of "rhabdoid" cells [15].

Vimentin is the most consistently expressed marker while EMA, cytokeratin and α-smooth actin are usually focally positive. Recently, immunohistochemistry (IHC) with antibody baf47 anti-INI 1 protein has been shown to be a useful tool for diagnosis. In AT/RT, all tumour cells exhibit a loss of expression of this protein as the result of biallelic inactivation of the INI1 gene located in 22 q 11.2 [10, 11].

To date, no clinical, histological or molecular prognostic factors have been clearly demonstrated. Optimum treatment is unknown and usually includes surgery, chemotherapy and radiotherapy which is often delayed because of the young age of the patients.

We report an unusual case of AT/RT located in the left frontal lobe in a 7-year-old boy. Initially misdiagnosed as

anaplastic ependymoma, this boy underwent gross total resection followed by focal radiotherapy. No chemotherapy was given. With this treatment, the boy was free of disease for 7 years.

Case report

A 7-year-old boy presented at our hospital in May 1998 after a brief history of progressive headache and asthenia. Magnetic resonance imaging (MRI) of the brain revealed a large contrast-enhancing heterogeneous solid and cystic mass in the left frontal lobe (Fig. 1a). Oedema was prominent. Gross total resection was performed, and pathological diagnosis was "anaplastic ependymoma". The tumour was made of sheets of atypical cells with high nuclear cytoplasmic ratio arranged around vessels (Fig. 1b,c). Cellularity was high and mitosis obvious. Tumour cells were immunoreactive with anti-glial fibrillary acidic protein (GFAP) antibody (Fig. 1f). Post-operative MRI showed no

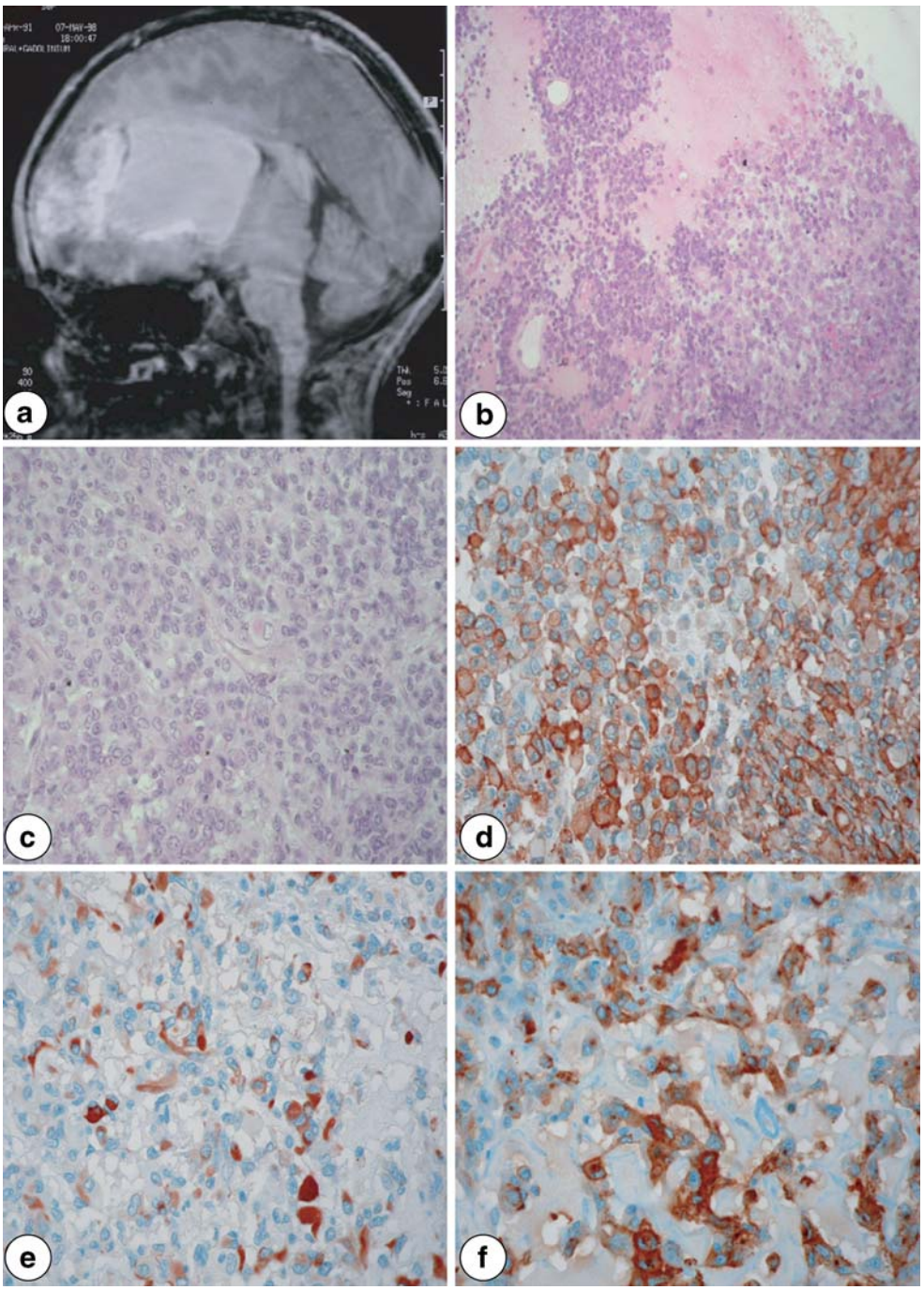

Fig. 1 **a** MRI T1-weighted sequence: Large hemispheric frontal tumour enhanced after Gadolinium injection. **b** Histology: Densely cellular tumour with cells arranged around vessels. High nuclear cytoplasmic ratio on the *left*. On the *right*, the cells have more abundant cytoplasm (Hematoxylin and eosin stain. Magnification ×100). **c** Histology: In this small area, cells are rhabdoid with prominent nucleolus and abundant eosinophilic cytoplasm (Hematoxylin and eosin stain. Magnification ×250). **d** Immunohistochemistry: Tumour cells were diffusely positive with anti-vimentin antibody (Magnification ×400). **e** Immunohistochemistry: EMA antibody stained both membrane and cytoplasm of few cells (Magnification ×400). **f** Immunohistochemistry: A few cells were also GFAP positive (Magnification ×400)

residual disease nor spinal dissemination. Cerebrospinal fluid (CSF) did not contain tumour cells. Focal radiotherapy was provided with a total dose of 50 Gy in 28 fractions. The patient did well until 14 years old when he consulted for a ptosis and oedema of the left orbit in June 2005. A firm nodule in the internal left canthus was present at palpation. MRI showed a single round tumour measuring 1 cm in diameter in the soft tissues with contrast-enhancing on T1-gadolinium sequence (Fig. 2a). The lacrimal gland was intact. No bone lysis nor hemispheric tumour was observed. No other location was found on neuroaxis MRI. A gross total resection was achieved by an ipsilateral superciliary approach. Part of the tumour was frozen in liquid nitrogen and kept at −80°C for molecular analysis. The remaining specimens were fixed in formalin, and all paraffin-embedded for histological and immunohistochemical analysis. Automated IHC was performed with avidin–biotin–peroxidase complex on a Ventana 320 Device (Tucson, AZ, USA) with a Ventana kit (Strasbourg, France) including 3-Amino-9-ethylcarbazole (AEC) reagent. The following antibodies were used for both tumors: EMA (Dako, clone 29, diluted to 1/30), keratin (AE1/AE3, Ventana non-diluted; KL1, IT diluted to 1:50), GFAP (Dako, polyclonal, diluted to 1:2000), α-smooth actin (Dako, clone 1A4 prediluted), vimentin (IT, clone V9, diluted to 1:2000), PS100 (IT, polyclonal diluted to 1:400), Baf 47(BD transduction laboratories, clone25, diluted to 1:100), desmin (Microm, clone D33, prediluted), myogenin (Microm, clone F5D, diluted to 1:5), neurofilament (Dako, clone 2F11, diluted to 1:100). Heat antigen retrieval with citrate buffer was used for all the antibodies except AE1/AE3, GFAP, α-smooth actin, PS100. Protease pre-treatment was used for AE1/AE3 only. On microscopic examination, we observed strands and cords of cells with rhabdoid features, abundant eosinophilic cytoplasm and clear eccentric nucleus in a collagenic stroma (Fig. 2b). No other component [primitive neuroectodermal tumors (PNET), epithelial or mesenchymal] was present. By IHC, the cells diffusely expressed vimentin and PS100. Marked positivity was observed with EMA, α-smooth actin and GFAP. Focal immunostaining was found with cytokeratin (AE1, AE3), while KL1 was negative. IHC anti-INI 1 showed lack of nuclear expression in tumour cells, whereas endothelial cells were positive (internal positive control). The cells were also negative for desmin, myogenin and neurofilament. Diagnosis of AT/RT was made on recurrence.

Slides of the first tumour were re-examined, and limited fields of "rhabdoid" cells intermixed with a poorly differentiated component were found. IHC was also performed and showed a profile identical to the recurrence such as diffuse vimentin (Fig. 1d) and focal EMA positivity (Fig. 1e).

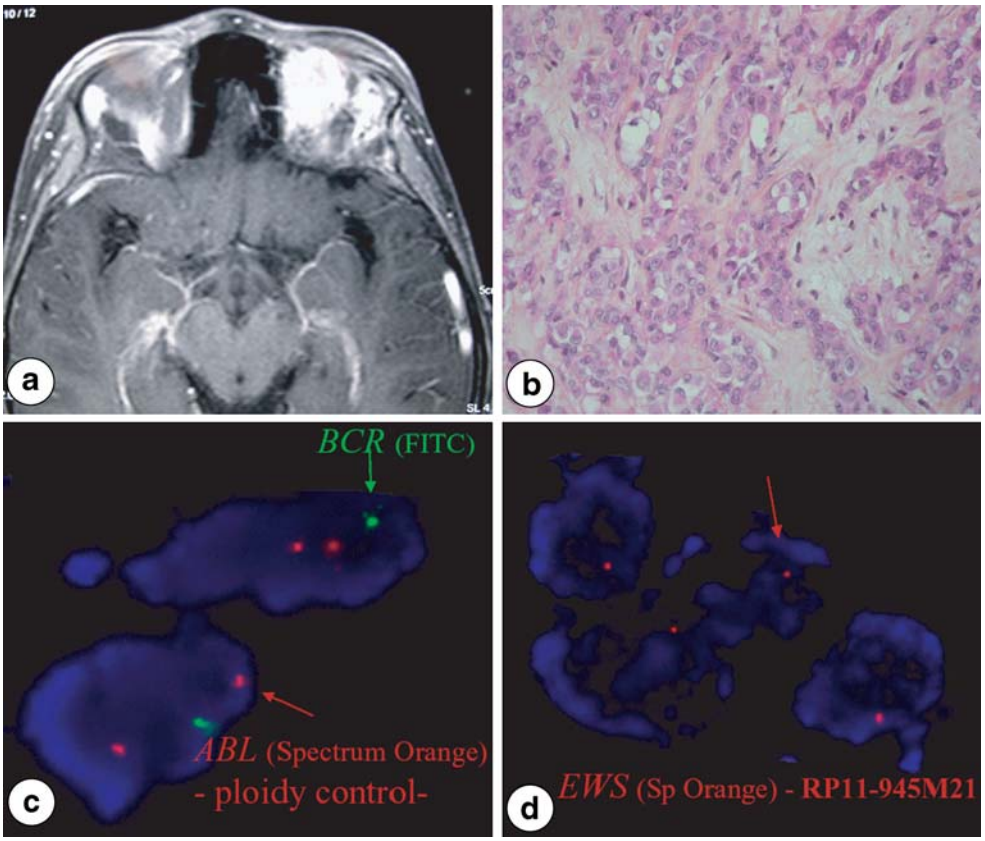

Fig. 2 **a** MRI: T1 weighted sequence. Left orbital tumour with gadolinium uptake. **b** Histology: Tumour was only composed of strands and cords of rhabdoid cells (Hematoxylin and eosin stain. Magnification ×400). **c** and **d** INI1 flanking regions studied by interphase FISH technique. **c** Interphase FISH analysis with the BCR-ABL probe showing heterozygous deletion of *BCR* locus in a diploid cell (ABL locus is conserved). **d** Interphase FISH analysis with the EWS probe showing heterozygous deletion of *EWS* locus

Frozen tumour was available for the recurrence only. Fluorescence in situ hybridization (FISH) was performed according to standard protocols. Fluorescence signals were detected by fluorescence microscopy with a charge-coupled device (CCD) camera on a Zeiss photomicroscope (Axiophot Imager.Z1, Zeiss, Germany). Locus-Specific FISH probes were used to characterize 22 q chromosomal region. We studied chromosomal regions flanking the *INI1* gene by using two loci: the *BCR* (breakpoint cluster region) locus at 22 q11.2 corresponding to the flanking centromeric region of *INI1* and the *EWS* (Ewing Sarcoma) locus at 22 q12 corresponding to its telomeric region. The following probes were used: BCR-ABL FISH DNA Dual Color ES and a bacterial artificial chromosome (BAC) clone RP11-945M21 labeled with Spectrum Orange. BAC clone was obtained from BAC/PAC Resources, Children's Hospital Oakland Research Institute, CA, USA. A heterozygous deletion of *BCR* and *EWS* loci which lay around INI1 gene was found (Fig. 2c,d). This meant either monosomy 22 or deletion for 22 q.

Mutational analysis and sequencing of the nine exons of INI1 gene was performed as previously reported [16] and showed deletion of a single pair of bases (codon 383) in exon 9 and hemizygotous deletion of the whole gene in the tumor recurrence, while no alteration was found for constitutional DNA. Molecular data confirmed the diagnosis of AT/RT. Then polychemotherapy was undertaken (oncovin, adriamycin, endoxan, etoposide) and radiotherapy of the recurrence field. One year after the end of the treatment of the recurrence, the boy is alive and free of disease.

Discussion

Primary intracranial AT/RT has a dismal prognosis with a median overall survival of less than 1 year. Given the poor prognosis of AT/RT, a trimodality treatment including surgery, chemotherapy and radiotherapy, often delayed because of the young age of the children, is indicated. Survival up to 6 years after diagnosis is rarely achieved, and in these case reports, intensive chemotherapy is always performed [2, 12, 14, 18]. For the first time, we report the case of a boy presenting with a left frontal AT/RT with an event-free survival (EFS) of 7 years after gross total resection and external cranial radiotherapy only.

To date, the role of surgery has not been clearly addressed in the literature. No clinical studies showed that extent of surgery was statistically correlated to overall survival.

In the series reported by Hilden et al. [9], longer EFS was found for patients with gross total versus partial resections: 14 months compared to 9.25 months.

The efficiency of radiotherapy is also controversial. Conventional radiotherapy is usually used for children older than 3 years or with evidence of meningeal spread. For younger children, radiotherapy is often delayed because its side effects are devastating. Tekautz et al. [17] reported improved survival for children aged 3 years or older when combined radio and chemotherapy were used. More recently, Chen et al. [4] also showed in a series of 17 patients that a significant relationship existed between overall survival and the time interval between surgery and the initiation and also the end point of radiotherapy. They recommend using radiotherapy in children >3 years old soon after surgery and before chemotherapy. Although definitive conclusions cannot be drawn from isolated cases, our observations (and few others in the literature) illustrate the usefulness of gross total resection and early radiotherapy for local control of the disease.

The location of the tumor, frontal hemispheric and "old" age of the patient may have also contributed to a better prognosis in part because they allow maximum local treatment: complete surgery and radiotherapy. In the series reported by Haberler et al. [8] two long survivors, 8 and 11 years, were respectively 6 and 9 years old. Both also had supratentorial tumors. It might also be assumed that AT/RT in younger patients are biologically distinct and are a more aggressive disease with higher frequency of disseminated forms and tendency to develop earlier recurrence often refractory to any therapy.

For our patient, the location of the recurrence in orbital soft tissue is quite intriguing. Although it occurred on the same side as the first tumor, there was no continuity with the initial operating site, and in particular no bone defect was seen on imaging or preoperatively. On the hypothesis of a second rhabdoid tumor occurring in orbital soft tissue, constitutional DNA was investigated to search for a "rhabdoid predisposition syndrome" [16]. Recently, a case of a multicentric tumor was reported in an infant with an AT/RT occurring in the eye and fourth ventricle. In this case, constitutional alteration of INI1 gene was present [7]. No INI1 alteration was found in constitutional DNA in our patient. Recurrence rather than second tumour was the diagnosis adopted.

Microscopic diagnosis of AT/RT is not always easy especially when the typical rhabdoid component is rare or absent. AT/RT can be misdiagnosed as PNET [6], choroid plexus carcinoma or less often as anaplastic ependymoma [11] as in our case. IHC with anti-INI1 antibody, now commercially available, is a very useful tool allowing accurate retrospective diagnosis especially in cases in which frozen material is not available for molecular studies. In addition, lack of INI1 is obvious in all tumour cells whatever the histological component: PNETs, epithelial, mesenchymal or rhabdoid, while EMA positivity or α-smooth actin, are focal [11]. Inactivation of INI1 gene is the genetic hallmark of AT/RT but is found in only 70% of

cases [1]. An additional 20–25% of tumours have reduced expression at the RNA or protein level meaning that IHC anti-INI1 could be more relevant for diagnosis. Recently, Haberler et al. showed that lack of INI1 protein by IHC in CNS embryonal tumours without rhabdoid features are the hallmarks of a group of patients who are resistant to therapy and for whom prognosis is poor. They recommend routinely performing IHC with anti-INI1 antibody in all malignant paediatric embryonal CNS tumours to identify patients who are likely to benefit from intensified treatment.

The INI1 protein is a component of the mammalian SWI/SNF complex which functions in an adenosine triphosphate (ATP)-dependent manner to alter chromatin structure. The specific function of INI1 and its role in malignant transformation is unknown. Somatic mutations or intragenic deletions of INI1 gene have been documented in association with deletion or monosomy 22. CNS AT/RT have a high frequency of monosomy 22. Previous studies have shown that FISH analysis could accurately identify 22 q deletion [3] as in our case. Although mutations have been observed throughout the coding sequence, exons 5 and 9 appear to be two potential hot spots [1]. Although prolonged survival was reported in a case with a mutation in exon 9 as in our case [2], no genotype/phenotype correlations have yet been reported [1].

Prospective multi-institutional clinical trials are needed to improve our knowledge of genetic and clinical behaviour of AT/RT in order to set up the most appropriate treatment. As we have shown in our report, early focal radiotherapy may be of interest to achieve local control.

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