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Atypical teratoid/rhabdoid tumor of the brain in an adult with 22q deletion but no absence of INI1 protein: a case report and review of the literature

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Abstract

We report a case of atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system (CNS) in an adult and its immunological phenotype and chromosomal DNA imbalance characteristics, as detected by comparative genomic hybridization (CGH). The immunohistochemical characteristics showed that atypical rhabdoid cells were positive for epithelial membrane antigen, vimentin, desmin, and glial fibrillary acidic protein, but there was no absence of INI1 protein. The CGH results identified the imbalances of the case to be the loss of 1p, 5q, 12q, 15q, 19q and 22q and the gain of 9q. Our discovery raises the question whether INI1 is implicated in all cases and whether its deletion is necessary in the pathogenesis of AT/RT, and also whether additional genetic pathways might exist. These data will offer useful information for further research on AT/RTs.

Key words: *atypical teratoid/rhabdoid tumor, comparative genomic hybridization, loss of 22q, INI1 protein.*

Introduction

Atypical teratoid/rhabdoid tumors (AT/RTs) are highly malignant brain tumors predominantly occurring in young children [10], typically containing rhabdoid cells, often with primitive neuroectodermal cells and with divergent differentiation along epithelial, mesenchymal, neuronal or glial lines. The INI1 gene locus on chromosome 22q11.2 was also called hSNF5 or SMARCB1. It was thought that alterations of the *INI1* gene which resulted in the protein expression loss were a possible novel pathogenesis of AT/RT [7]. However, to date, no clinical, histological or molecular prognostic factors have been clearly demonstrated. In the 1990s, it was observed that AT/RT often demonstrates a loss of all or part of chromosome 22 [2,14]. But to our knowledge, AT/RTs have been reported in adults only in rare cases in the literature [11,13,15-17], and only a few cases of AT/RTs have been investigated by comparative genomic hybridization (CGH) [4,18]. Studies have shown that the wide absence of recurrent genomic alterations other than SMARCB1 aberrations was recently confirmed in whole exome sequencing [9]. A small subset of these tumors dis-

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plays a loss of INI1 but has the atypical histopathological features of AT/RT [3]. The preservation and expression of the INI1 gene in a small population of AT/RTs therefore exists. We report here one case of AT/RT of the central nervous system (CNS) with loss of some of 22q but no absence of INI1 protein expression in adults, which is rare for this tumor, and these data offer useful evidence concerning its unique clinical, histological and molecular biological features.

Case report

A 38-year-old male patient complained of headache and vomiting for 12 days. Magnetic resonance imaging (MRI) showed an iso/hypointense mass on T2WI and isointense on T1WI with strong contrast enhancement in the occiput (Fig. 1). Surgical resection of the mass was performed. Radiotherapy was applied after the operation. Unfortunately, the patient died after three months following tumor recurrence.

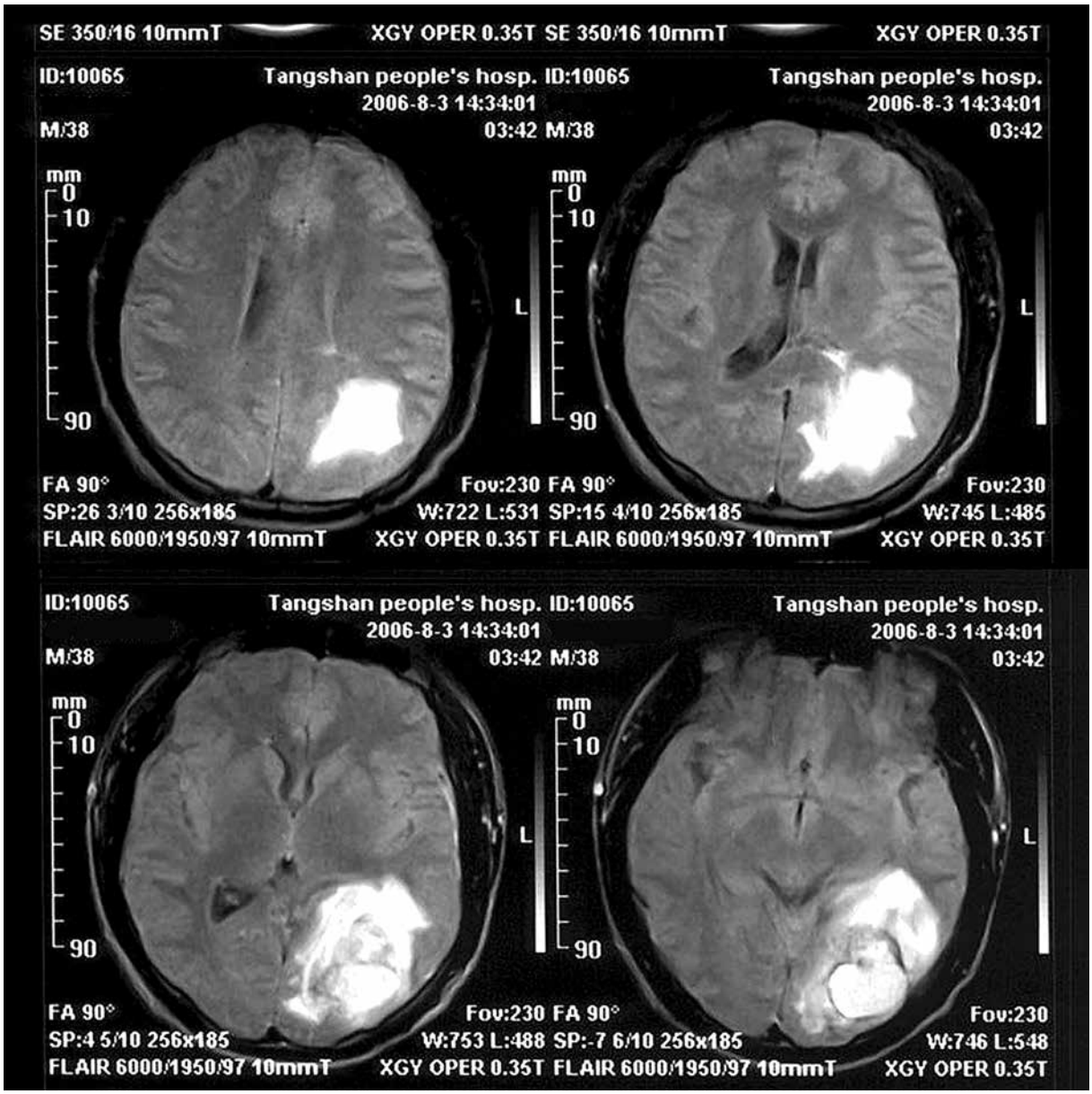

Fig. 1. Magnetic resonance (MR) images of one case of atypical teratoid/rhabdoid tumor. The fluid-attenuated inversion recovery (FLAIR) axial MR images show a temples-parietal-occipital borderline mass with a cystic component of hyperintensities and a solid contrast-enhanced component (A1-A4) and with peripheral edema.

Material and methods

INI1 antibody was obtained from DAKO (catalogue no. A-0150, Dako, Denmark), and other antibodies (include epithelial membrane antigen – EMA, vimentin – Vim, desmin – Des, glial fibrillary acidic protein – GFAP) for immunohistochemical (IHC) staining were purchased from Beijing Zhongshan Golden Bridge Biotechnology Co. Ltd. The reagents for CGH were from Invitrogen and Roche companies.

Tumor samples were observed by hematoxylin and eosin staining and immunohistochemical staining. Comparative genomic hybridization was performed according to the procedure described by Mohapatra *et al*. [12] to detect chromosomal DNA imbalances. The images then obtained for the analysis of the signals were analyzed using Leica CW4000 Karyo software.

Results

The hematoxylin and eosin (H&E) sections of the case showed that the histopathological features revealed rhabdoid cells which are characteristic features of an AT/RT. The immunohistochemical profile revealed that the rhabdoid cells characteristically showed positive for EMA, Vim, Des, and GFAP, but also no absence of INI1 protein. The MIB-1 proliferation index was 19.84% (Fig. 2). The results of the CGH analysis were obtained from high quality figures of CGH profiles. The common imbalances of this case were losses of 1p, 5q, 12q, 15q, 19q and 22q and the gain of 9q (Fig. 3).

Discussion

Atypical teratoid/rhabdoid tumors are rare, highly aggressive tumors of childhood, particularly under the age of 3 years. They are extremely rare in adults. The diagnosis is challenging, as there may be significant histological overlap with other embryonal tumors [1]. It usually occurs in very young children, although it has been reported in adults as well [11], but it rarely occurs in adults, and the true incidence of it is not yet known. Atypical teratoid/rhabdoid tumor is composed of rhabdoid cells entirely or in part with a combination of primitive neuroectodermal, mesenchymal and epithelial cells. The appearance of rhabdoid cells typically falls along a spectrum ranging from this rhabdoid phenotype to cells with less striking nuclear atypia and large amounts of pale eosinophilic cytoplasm. These rhabdoid cells

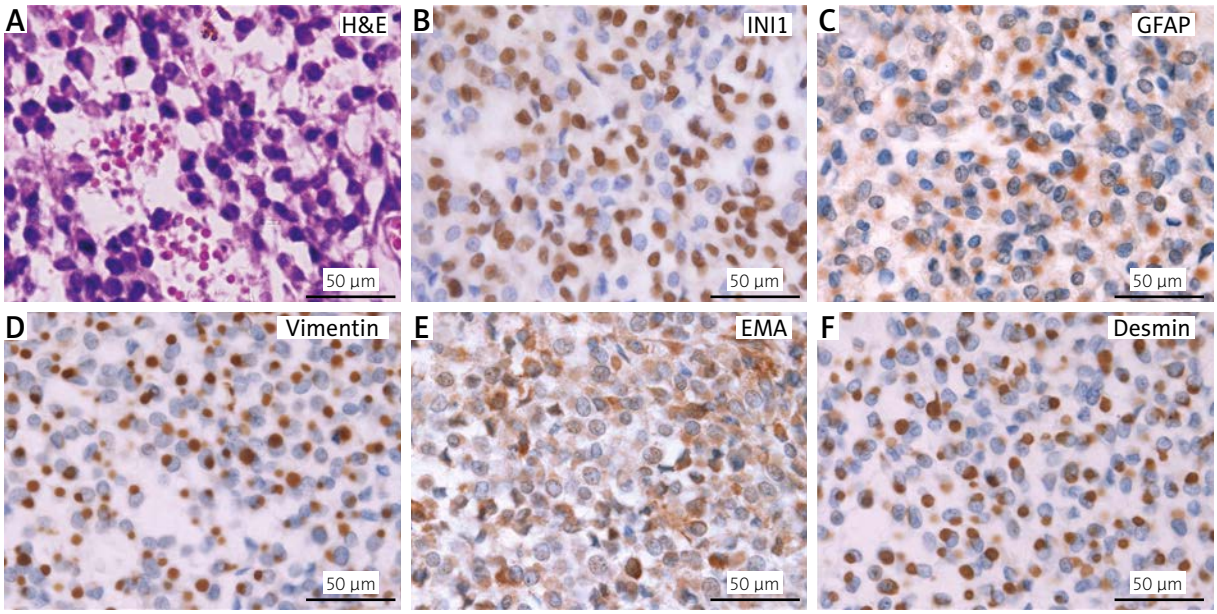

Fig. 2. Hematoxylin and eosin stain (H&E) and immunohistochemical features of the case. The H&E sections show the histopathological feature being composed of rhabdoid cells (**A**). The immunohistochemical analysis demonstrated atypical rhabdoid cells partially positive for INI1 (**B**), partially positive for glial fibrillary acidic protein (GFAP) (**C**), positive for vimentin (Vim) (**D**), partially positive for epithelial membrane antigen (EMA) (**E**) and positive for desmin (Des) (**F**).

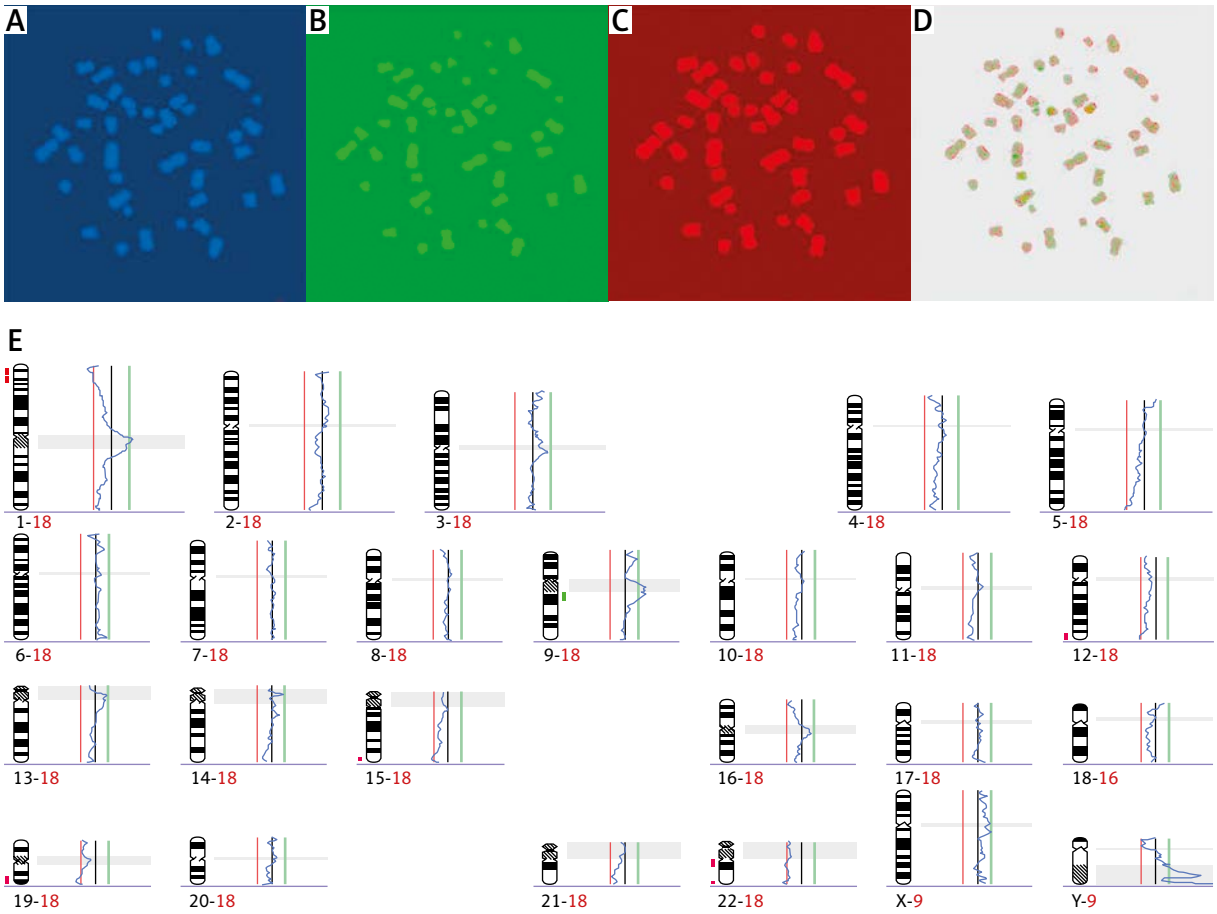

Fig. 3. Results of comparative genomic hybridization (CGH) analysis. The figure of above the blue represented chromosomes by DAPI (4',6-diamidino-2-phenylindole) staining (**A**). The green represented chromosomes by biotin-labeled tumor DNA generating green fluorescence (**B**). The red represented chromosomes digoxigenin-labeled normal reference DNA generating red fluorescence (**C**). Computer coincidence figure of A, B and C (**D**). The curve under represented the diagram auto-generated by the computer of the chromosomes gain or loss. Losses are indicated by the red line on the left of each chromosome scheme, whereas the green line on the right represents gains. The genomic DNA imbalances of both cases contain –1p, –5q, –12q, –15q, –19q, –22q and +9q.

may be arranged in nests or sheets and often have a jumbled appearance [10]. Rhabdoid tumors, in contrast, usually possess a distinctive genetic signature that accompanies the rhabdoid morphology, the INI1 mutation, or a deletion at the 22q11.2 locus. Multiple studies have also demonstrated that a loss of INI1 protein expression caused by homozygous deletions or truncating mutations of INI1 is associated with rhabdoid tumors.

In this case, light microscopy revealed a tumor composed of diffuse sheets of typical "rhabdoid" cells with eccentric nuclei, brightly eosinophilic cytoplasm and microvascular proliferation. The immunohistochemical features supported the reliability of our original diagnosis of AT/RT, but the INI-1 protein immunostaining was positive. This result was consistent with a recent published case report which illustrated an INI1+ AT/RT case in a 9-month-old boy from Los Angeles, and which showed retained INI1/SMARCB1 staining on immunohistochemical analysis [6]. The cellular origin of AT/RT is still unknown, but inactivating mutations of the hSNF5/INI1 gene located on chromosomal region 22q11.2 are regarded as a crucial step in their molecular pathogenesis [5]. The reports in the literature have demonstrated that AT/RT is often associated with characteristic genetic abnormalities, which include either monosomy 22 or deletion involving the hSNF5/INI1 gene located on

22q11.2, thus leading to the absence of INI1 protein [8]. However, inactivation of INI1 may not be specific for rhabdoid tumors. So far, only a few adult AT/RTs cases have been investigated by CGH, showing the expected loss of 22q, as well as additional losses on chromosomes 1p, 4p, 16p, 19p and 8p [4,18]. This case, as detected by CGH, indicated the losses of 1p, 5q, 12q, 15q, 19q and 22q and the gain of 9q. These divergent CGH results reflect the complicated pathogenesis of AT/RTs. Until now, most AT/RT studies have focused on DNA mutation or deletion. The posttranscriptional regulation of INI1 is still obscure. This case has 22q chromosomal deletion but no absence of INI1 protein. This similarly discrepant result was indicated by both CGH and IHC results. Nevertheless, CGH is a molecular cytogenetic method that is capable of detecting and mapping the relative DNA sequence copy number and identifying fragment gains or losses of DNA, and can thereby act as a screening method for chromosomal alterations. In the present case of AT/RT, the CGH result indicated deletion of part of 22q, but the INI1 gene protein was positive according to IHC, so we think that it was not the fragment of *INI1* gene location loss. This demonstrates that there is another gene related to the genesis of AT/RTs. Despite this assay being limited by the fact that there is not an adequate number of cases of AT/RTs, only occasionally occurring, we hypothesized that these results should be regarded as an exception of INI1 expression and genetic background. Whether or not INI1 proves to be implicated in all cases, our data suggest that apart from monosomy 22q, a better understanding of additional genetic pathways and the clinical and biological roles of these genes is greatly needed, and our data will offer useful information for further research in AT/RT. We speculate that the molecular biological features occurring in adults will differ from those occurring in children. It is therefore necessary to conduct further research on AT/RTs.

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Disclosure

The authors report no conflict of interest.

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