

Secondary meningioma in a long-term survivor of atypical teratoid/rhabdoid tumour with a germline *INI1* mutation

A. C. J. Ammerlaan · M. P. W. A. Houben ·
C. C. Tijssen · P. Wesseling · T. J. M. Hulsebos

Received: 21 December 2007 / Published online: 31 January 2008
© The Author(s) 2008

Abstract

Objective We report on a patient who developed a meningioma more than two decades after removal at a young age of an atypical teratoid/rhabdoid tumour (AT/RT), which was due to a germline *INI1* mutation, and radio- and chemotherapy.

Materials and methods We present genetic evidence that the meningioma is not a recurrence or metastasis of the AT/RT and not due to the *INI1* mutation, but is a radiation-induced tumour.

Conclusion This is the first case illustrating that improved survival of young patients with an AT/RT after aggressive treatment may be gained at the cost of an increased risk for the development of radiation-induced, non-*INI1*-related tumours.

Keywords Meningioma · Radiation therapy · Atypical teratoid/rhabdoid tumour · Genetic predisposition · *INI1*

Introduction

We previously reported on a family in which four cousins developed an atypical teratoid/rhabdoid tumour (AT/RT) at

young age, due to inheritance of a germline G>A mutation in the donor splice site of exon 4 of the tumour suppressor gene *INI1* [2]. More than 20 years after resection of the AT/RT, the oldest of the four cousins developed an intracranial meningioma and, after an additional year, a myoepithelioma of the lip. In addition to the constitutional *INI1* mutation and loss of the normal *INI1* allele, we detected an identical rearrangement in the *NF2* gene, not affecting its coding regions, in the AT/RT and myoepithelioma of the patient and concluded that they both originated from a common precursor cell. However, the rearrangement in *NF2* and loss of the normal *INI1* allele could not be demonstrated in the meningioma. Despite this, the development of the meningioma may be the consequence of the presence of the constitutional *INI1* mutation, because mutations in this gene have been identified in meningiomas [8]. Alternatively, the meningioma could be induced by the radiation therapy, which our patient received after removal of the AT/RT and which is a well-known consequence of this treatment [1]. We investigated the meningioma for the presence of genetic changes reported in radiation-induced meningiomas and performed a comparative loss of heterozygosity (LOH) analysis to demonstrate that such radiation-induced genetic changes are absent in the AT/RT and myoepithelioma of our patient.

Materials and methods

Tumour samples and DNA isolation

DNA from the AT/RT and the myoepithelioma was isolated from formalin-fixed and paraffin-embedded tumour material, and DNA from the meningioma was isolated from a fresh frozen tumour sample using commercially available kits (Qiagen, Venlo, The Netherlands).

A. C. J. Ammerlaan · T. J. M. Hulsebos (✉)
Department of Neurogenetics, Academic Medical Center,
Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands
e-mail: t.j.hulsebos@amc.uva.nl

M. P. W. A. Houben · C. C. Tijssen
Department of Neurology, St. Elisabeth Hospital,
Tilburg, The Netherlands

P. Wesseling
Department of Pathology,
Nijmegen Center for Molecular Life Sciences,
Radboud University Nijmegen Medical Centre,
Nijmegen, The Netherlands

SNP analysis

A genome-wide single nucleotide polymorphism (SNP) analysis of normal and meningioma DNA was conducted with the Affymetrix GeneChip Human Mapping 10K Array Xba 142 2.0. The array contains 10,204 SNPs distributed across the genome. The GeneChips were processed by an authorised Affymetrix Service Provider using standard Affymetrix protocols (Service XS, Leiden, The Netherlands). LOH regions were identified by comparing the SNP profiles of normal and meningioma DNA and scoring heterozygous SNP markers (AB) in the normal DNA that were reduced to homozygosity (AA or BB) in the meningioma DNA. Intervals were determined on the basis of locations of SNP markers in the UCSC Genome Browser, March 2006 Build, at <http://genome.ucsc.edu/>.

LOH analysis

Loss of heterozygosity (LOH) analysis was performed with microsatellite markers as described previously [3] using primer sequences and conditions for polymerase chain reaction given by The Genome Database at <http://www.gdb.org/>. Because of rather extensive degradation of DNA extracted from the AT/RT, only markers generating PCR fragments smaller than 150 bp were used.

Case report

History

Our patient was diagnosed with a tumour in the fourth ventricle and right cerebellar hemisphere at the age of 4.5 years. Resection of the tumour was incomplete. The tumour was originally classified as anaplastic ependymoma WHO grade III, but upon extensive genetic analysis and histopathological re-evaluation, reclassified as AT/RT [2]. He received adjuvant chemotherapy (methotrexate, vincristine and prednisolone) followed by craniospinal radiotherapy (3,300 cGy in 22 doses) with a boost of 2,100 cGy on the location of the tumour. Fifteen years later, a brain CT without contrast showed no signs of recurrent disease or of other new pathology. Almost 6 years later, 20.5 years after initial diagnosis, he presented again with bifrontal headaches, increasing ataxic gait disturbances and fatigue. CT examination showed a large isodense space-occupying lesion in the left temporal region with oedema, midline shift and contrast enhancement. One year after resection of this tumour, he developed a myoepithelioma of the upper lip. The patient is alive at 29 years of age.

Table 1 LOH regions in the meningioma, as determined by SNP analysis

Chromosome region	Exact interval (Mb)
1pter-p34.3	0–38.90
1p33-p33	46.99–51.09
1p32.2-1p31.3	58.19–65.50
2pter-p12	0–79.28
3p26.1-cen	6.11–88.84
7q36.1-qter	150.04–158.66
16pter-p12.1	0–22.75
16q23.1-q23.3	73.46–81.33
17cen-q21.31	23.09–40.35
19pter-p13.2	0–8.83

Histological findings

Histopathological examination of the left temporal tumour revealed an atypical meningothelial meningioma WHO grade II with many vessels and up to six mitoses per 2 mm².

SNP and LOH analysis Radiation-induced meningiomas usually display a complex karyotype [1]. To determine the genetic changes, we performed a genome-wide scan by SNP analysis of the meningioma and corresponding normal DNA. The identified chromosomal regions displaying LOH are listed in Table 1. Next, we tested several markers from within each of the five largest deleted regions by conven-

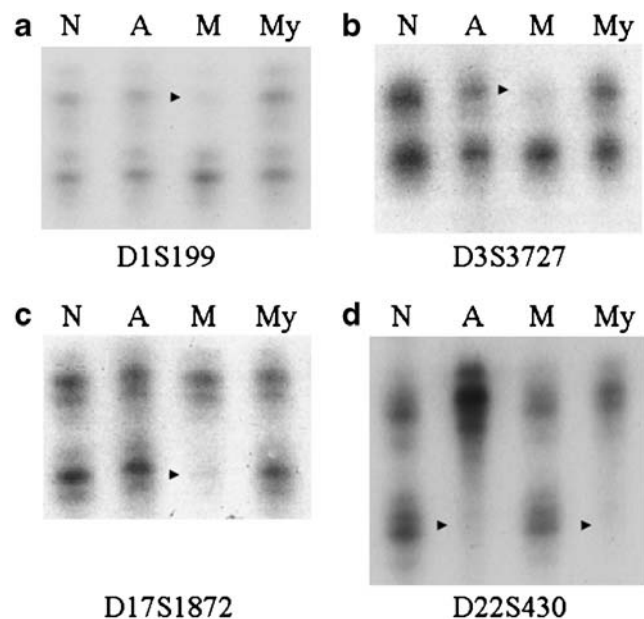


Fig. 1 LOH analysis using markers from chromosome regions **a** 1pter-p34.3 (*DIS199*), **b** 3p26.1-cen (*D3S3727*), **c** 17qcen-q21.31 (*D17S1872*) and **d** 22q (*D22S430*) of AT/RT (*A*), meningioma (*M*) and myoepithelioma (*My*) DNAs of the patient. *N* denotes normal DNA derived from the patient's blood leucocytes. Arrowhead indicates position of lost allele

tional microsatellite analysis to determine their LOH status in the meningioma and in the AT/RT and myoepithelioma. Presence of LOH in the meningioma, but absence of LOH in AT/RT and myoepithelioma was found for *DIS199* in 1pter-p34.3 (Fig. 1a), *D2S327* in 2pter-p12, *D3S3727* in 3p26.1-cen (Fig. 1b), *D16S3020* in 16pter-p12.1 and *D17S1872* in 17qcen-q21.31 (Fig. 1c). In contrast, as determined previously [2] and exemplified by marker *D22S430* in Fig. 1d, there was LOH for chromosome 22 markers in the AT/RT and myoepithelioma, but not in the meningioma.

Discussion

In a previous study, we provided evidence for the involvement of *INI1*, by constitutional mutation and independent somatic loss, in the development of both the AT/RT and the myoepithelioma of our patient. Moreover, we could demonstrate that these tumours originated from an identical precursor cell [2]. Although involvement of *INI1* has been described in sporadic meningiomas [8], until now meningiomas have not been reported to occur as a consequence of the inheritance of an *INI1* mutation. However, this might be due to the extreme rarity of families with an inherited *INI1* mutation, with only four published cases so far [2, 5, 6, 11]. In this context, it is interesting to note that (as demonstrated before and exemplified by marker *D22S430* in Fig. 1d) the meningioma of our patient has no LOH 22 and the retained *INI1* allele carries no additional inactivating mutation [2], indicating that this tumour is not the result of inheritance of the mutated *INI1* gene. In contrast, the meningioma displayed genetic changes that are characteristic for radiation-induced meningiomas [1, 7, 9], such as a complex karyotype, as evidenced by the SNP analysis (Table 1), including extensive losses on chromosome arm 1p, but no loss of chromosome 22, and no mutation in the *NF2* gene [2]. The genetic changes found in the meningioma proved not to be present in the AT/RT or myoepithelioma (Fig. 1a–c, and data not shown), demonstrating that the meningioma is genetically not related to these tumours and should not be considered as a late and more differentiated recurrence or metastasis of the AT/RT.

In conclusion, the clinical and genetic characteristics of the meningioma clearly indicate that the tumour developed as a consequence of the radiation therapy. Recent evidence suggests that long-term survival of patients with a childhood AT/RT can occur especially after aggressive treatment including radiotherapy [10, 12]. The possible late effects of radiation therapy have been considered as serious drawbacks of this treatment. This is the first case in literature in which such a possible consequence in the form of a radiation-induced meningioma is actually documented in a

long-term survivor of an AT/RT. Compared to sporadic meningiomas, radiation-induced meningiomas are more aggressive and have a higher chance to recur [1]. Because of this unfavourable prognosis, continuous medical surveillance of our patient is warranted.

Acknowledgement We gratefully acknowledge the financial support from the Dutch Cancer Society, grants KUN 2003-2975 (PW) and UVA 2001-2561 (TH).

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

- Al Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ (2004) Radiation-induced meningiomas: clinical, pathological, cytogenetic, and cytogenetic characteristics. *J Neurosurg* 100:1002–1013
- Ammerlaan ACJ, Ararou A, Houben MPWA, Baas F, Tijssen CC, Teepeen JLJM, Wesseling P, Hulsebos TJM (2007) Long-term survival and transmission of *INI1*-mutation via nonpenetrant males in a family with rhabdoid tumour predisposition syndrome. *Br J Cancer*, DOI 10.1038/sj.bjc.6604156
- Bijlsma EK, Voesten AM, Bijleveld EH, Troost D, Westerveld A, Merel P, Thomas G, Hulsebos TJM (1995) Molecular analysis of genetic changes in ependymomas. *Genes Chromosomes Cancer* 13:272–277
- Harrison MJ, Wolfe DE, Lau TS, Mitnick RJ, Sachdev VP (1991) Radiation-induced meningiomas: experience at the Mount Sinai Hospital and review of the literature. *J Neurosurg* 75:564–574
- Hulsebos TJ, Plomp AS, Wolterman RA, Robanus-Maandag EC, Baas F, Wesseling P (2007) Germline mutation of *INI1/SMARCB1* in familial schwannomatosis. *Am J Hum Genet* 80:805–810
- Janson K, Nedzi LA, David O, Schorin M, Walsh JW, Bhattacharjee M, Pridjian G, Tan L, Judkins AR, Biegel JA (2006) Predisposition to atypical teratoid/rhabdoid tumor due to an inherited *INI1* mutation. *Pediatr Blood Cancer* 47:279–284
- Ragel BT, Jensen RL (2005) Molecular genetics of meningiomas. *Neurosurg Focus* 19:E9
- Schmitz U, Mueller W, Weber M, Sevenet N, Delattre O, von Deimling A (2001) *INI1* mutations in meningiomas at a potential hotspot in exon 9. *Br J Cancer* 84:199–201
- Shoshan Y, Chernova O, Juen SS, Somerville RP, Israel Z, Barnett GH, Cowell JK (2000) Radiation-induced meningioma: a distinct molecular genetic pattern. *J Neuropathol Exp Neurol* 59:614–620
- Squire SE, Chan MD, Marcus KJ (2007) Atypical teratoid/rhabdoid tumor: the controversy behind radiation therapy. *J Neurooncol* 81:97–111
- Taylor MD, Gokgoz N, Andrulis IL, Mainprize TG, Drake JM, Rutka JT (2000) Familial posterior fossa brain tumors of infancy secondary to germline mutation of the *hSNF5* gene. *Am J Hum Genet* 66:1403–1406
- Tekautz TM, Fuller CE, Blaney S, Fouladi M, Broniscer A, Merchant TE, Krasin M, Dalton J, Hale G, Kun LE, Wallace D, Gilbertson RJ, Gajjar A (2005) Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. *J Clin Oncol* 23:1491–1499