The Loss of 1p as a Reliable Marker of Progression in a Child with Aggressive Meningioma: A 16-Year Follow-Up Case Report

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Established Facts

- Already known fact: A deletion of the short arm of one chromosome 1 through a translocation between chromosomes 1 and 11 (t[1; 11]) as well as partial or complete monosomy of chromosomes 2, 6, 7, 11, 13, and 22 are already known to be associated with an aggressive course of the disease.

Novel Insights

- New information: The meningioma is one of the best cytogenetically examined tumors. The loss of 1p and monosomy 14 are markers for tumor progression and recurrence for these tumors. Also, *SMO* and *AKT1* are markers for a poor clinical course of these tumors, especially in the olfactorius region, as in our case.
- However, this is not the case in childhood meningiomas.
- Interestingly, in our case, the loss of 1p-represents to be a potential marker for the poor clinical course of our child meningioma and remains to be a stable marker over the course of 16 years.

Keywords

Meningioma · Deletion of 1p · *SMO* and *AKT1* mutations · Chromosomes · Genetic progression

Abstract

Background: Here, we present the case of a 32-year-old female with a progressing history of meningioma for 16 years starting with an ethmoidal lesion in 2002. The initial tumor specimen of this patient showed a deletion of the short arm of chromosome 1 through a translocation between chromosomes 1 and 11 (t[1; 11]) as well as additional chromosomal

aberrations, including partial or complete monosomy of chromosomes 2, 6, 7, 11, 13, and 22. These molecular characteristics were already known to be associated with an aggressive course of the disease, and the patient was, therefore, included in a strict follow-up regime. From 2003 to 2019, the patient suffered multiple relapses and consecutive tumor resections. **Methods:** Tumor specimen from 2017 was examined using a genome-wide methylation analysis as well as a whole-genome sequencing. **Results:** These analyses confirmed the findings of 2002 and proved genetic alteration in the meningioma to be very stable over the time. Yet *SMO* and *AKT1* mutations, which have been described to be

paradigmatic in frontobasal meningioma, could not be found. **Conclusions:** Genetic characteristics seem to be very stable during progression of the disease. The loss of 1p represents to be a potential marker for the poor clinical course of our child meningioma. In 2019, our patient passed away due to the progress of her meningioma disease.

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Introduction

Meningiomas are mostly benign tumors that originate from the coverings of the brain and spinal cord and represent around 33.8% of all intracranial tumors [1]. In a study from Holleczer et al. [2], the mean age of the patients at diagnosis was 63 years, and 70, 28, and 3% had WHO grades I, II, and III meningiomas, respectively. Ten-year observed and relative survival of all patients combined was 72 and 91%, respectively. Tumor-related mortality varied by sex and increased with age at diagnosis and the WHO grade of the tumor. The overall 10-year cumulative incidence of meningioma recurrence was 9%. In adults, meningioma occurs twice more frequent in female than in male patients, and around 95% of all meningiomas represent WHO grade I whereas only a minor percentage of these tumors is of WHO grades II and III [2]. The most frequent somatic chromosomal aberration in adult meningiomas is a monosomy of chromosome 22 [3, 4]. Cytogenetic findings associated with progression to atypical and anaplastic meningiomas are hypodiploidy and, in rare cases, hyperdiploidy beyond monosomy 22 as well as deletions on the short arm of one chromosome 1 [5–9]. The loss of heterozygosity on chromosome 22q with biallelic inactivation of the NF2 tumor suppressor gene reflects an early step in meningioma tumorigenesis [10]. These tumors rarely occur in children, pediatric, and juvenile cases represent <2% of all meningiomas [11]. In pediatric and juvenile cases, these tumors can be associated with von Recklinghausen neurofibromatosis (type 1) or, on rarer occasions, with neurofibromatosis type 2 [12]. Due to the low incidence of meningiomas in pediatric patients, to date, only one study with 40 included patients screened these patients systematically for genetic alterations [13]. In 2017, Boetto et al. [14] and Strickland et al. [15] published data which showed that *SMO* mutation status and *AKT1* mutation status are paradigmatic in anterior skull base meningiomas. This was the reason for us to reevaluate the once published case report for the follow-up of the clinical history as well as analyzing

the molecular characteristics including *SMO* and *AKT1* with newly available techniques.

In this article, we would like to present the case of a 32-year-old woman. We already presented this patient, whose history of meningioma commenced with a first ethmoidal lesion, with its cytogenetic and molecular data in a case report 16 years ago [16].

Methods

850k – Chip Array for Methylation Analysis

All tissue samples were snap-frozen after tumor removal and stored at –80°C before the analysis. DNA was extracted from tumors and analyzed for genome-wide methylation patterns using the Illumina Human Methylation 850 EPIC BeadChip (850k) array, and processing of DNA methylation data was performed as previously described [17, 18]. DNA methylation patterns were assigned to subgroups as described previously [19]. Copy number profiles were generated using the “conumee” package for R (<https://www.bioconductor.org/packages/release/bioc/html/conumee.html>).

Targeted Next-Generation Sequencing

Molecular barcode-indexed ligation-based sequencing libraries were constructed using 200 ng of sheared DNA. Paired-end sequencing employing the brain tumor panel developed at the Dept. of Neuropathology, Heidelberg, was performed using the NextSeq 500 (Illumina). Sequence data were mapped to the reference human genome using the Burrows-Wheeler Aligner and were processed using the publicly available SAM tools as described previously [20].

Case Report

The Initial Case

The initially 16-year-old patient underwent resection of a lesion of the ethmoidal region with extension into the nasal vault and the right orbit by combined intracranial-transbasal and transnasal approach in 2002 (Fig. 1a, b). A postoperative MRI showed no residual tumor (Fig. 2a, b). The histological examination showed a meningioma with partial activity loss of alkaline phosphatase and an elevated Ki-67 index. The tumor was, therefore, classified as WHO grade II. The karyotype in 2002 was 43, XX, –1, –11, +der (1) t (1; 11) (p11; q11), del (2) (p12), del (6) (q28), der (7) dic (7; 22) (p12; q11), –13, –22 (cp8) (Fig. 3). On the basis of these aberrations with deletion of the short arm of one chromosome 1, the karyotype of this meningioma was classified to be progression associated, with an increased risk of recurrence. The patient was consecutively incorporated into an intensified schedule of postoperative surveillance, with MRI every 6 months. These data were already presented 16 years ago in a case report [16].

History since 2003

Three years later in 2005, a second resection at the initial tumor region was necessary due to a local recurrence. Radiotherapy with

Fig. 1. a, b Initial contrast-enhanced axial (a) and coronal (b) MRI scans. Tumor of the ethmoidal region with expansion into the nasal vault and the right orbit.

Fig. 2. a, b Axial MRI scans (a, b) 2 months after surgery depicting total removal of the tumor. KM, Contrast medium.

54 Gy was administered to the same site in 2006. From 2009, MRI controls revealed multiple meningiomas occurring at many different sites. In 2010, a space-occupying frontobasal recurrence had to be resected with postresectional implantation of a frontal titan plastic. Because of the continually arising new meningiomas, a systemic target therapy with Imatinib, a tyrosine kinase inhibitor, was initiated in December 2011 and aborted in March 2012 because of adverse effects. Bevacizumab as an angiogenesis inhibitor, which works by slowing the growth of new blood vessels by inhibiting vascular endothelial growth factor-A, was administered between 2012 and 2013. In 2014 vision of the right eye deteriorated, therefore, a decompression of the right optical nerve with resection of adjacent tumor tissue was conducted. A systemic target therapy with peptide receptor radionuclides (PRRT) was conducted in 2015. In 2016, multiple meningiomas at the right and left convexity, nasal region, and at the right sphenoid were resected (Fig. 4). In 2017, a space-occupying meningioma with a sphenopetroclival part with contact to the right orbita was removed. Also 2017, a new meningioma right pterional was resected (Fig. 5a, b). All of the specimen acquired during the previously mentioned resection revealed a neuropathological finding of WHO grade II chordoid meningioma. Our patient was in a very good condition until she developed progressive dysphagia in September 2018. Further clinical history is available until January 2019 (Fig. 6).

New Molecular Results

The specimen acquired during the resection of the frontobasal lesion with contact to the right orbita in 2017 was applied for the abovementioned analysis. In comparison to the previous cytogenetic analysis of 2003, the current sample showed the same genetic profile. Especially, the losses on chromosomes 1 and 22 were also detectable in the probes of 2017 (Fig. 3). The DNA methylation profile indicated that the tumor is allotted to the meningioma methylation class intermediate-A, which is associated with an increased recurrence. Panel sequencing did not reveal any relevant mutation, particularly no mutation in the meningioma-related genes *AKT1*, *SMO*, *KLF4*, *TRAF7*, *PIK3CA*, *SUFU*, and – despite monosomy 22 – *NF2* (Fig. 7).

Discussion

Genetic and chromosomal alterations associated with meningioma, in general, are a deletion of chromosome 22 and a mutation in the *NF2* gene [3, 4, 6]. There is a huge correlation between a chromosomal anomaly on chromosome 22 and neurofibromatosis as the *NF2* tumor suppres-

Fig. 3. Example of GTG-banded karyotype. Chromosomal examination showed deletion of the short arm of chromosome 1 as well as additional chromosomal aberrations, including a translocation between chromosomes 1 and 11 and deletion of chromosomes 2, 6, 7, 11, and 13.

Fig. 4. Initial contrast-enhanced axial MRI scans showing multiple meningiomas, which occurred in 2016.

Fig. 5. a, b Contrast-enhanced axial MRI, which highlights the area of tumor resection in 2017 with a massive sphenopetroclival meningioma with contact to the right orbita and the posterior fossa. Specimen of this tumor was used for further analysis.

Fig. 6. The diagram shows the time course of the tumor disease with the therapies carried out.

sor gene is located on 22q12 [10]. Additionally, chromosomal losses have been recognized on 1p, 22q, 14q, 18q, 10q, and 6q, with gains identified on 20q, 12q, 15q, 1q, 9q, and 17q, whereas in grade III meningiomas, common losses have been recognized on 6q, 10q, and 14q [1, 5–7, 10].

In a recent series of 775 meningiomas, Clark et al. [21] described Sonic Hedgehog (*SHH*) pathway-related meningiomas harboring *SMO* gene mutations. These tumors were mostly WHO grade I, meningiomas, and located at the anterior skull base, suggesting a possible link

Fig. 7. The DNA methylation profile indicated that the tumor is allotted to the meningeoma methylation class intermediate-A, which is associated with an increased recurrence. Panel sequencing did not reveal any relevant mutation, particularly no mutation in the meningeoma-related genes *AKT1*, *SMO*, *KLF4*, *TRAF7*, *PIK3CA*, *SUFU*, and – despite monosomy 22 – *NF2*.

between this potential driver mutation and anatomical site of origin. Indeed, *SMO* mutations alter the *SHH* pathway, which plays a critical role in craniofacial patterning during embryonic development, and consequently in the development of meninges at this location [14, 21]. However, it is not clear whether meningeoma tumorigenesis is induced by early prenatal deregulation of meningeal embryogenesis or by dedifferentiation of mature cells into a stem-like state [22]. On the other hand, the loss of one chromosome 22 is considered as an early event in tumorigenesis of meningeoma, which is followed by an loss of one short arm of one chromosome 1 and monosomy 14 [1, 5–7, 10].

Cases of pediatric meningeoma present in parts similar characteristics according to Battu et al. [23]. Pediatric meningeomas can be associated with NF-gene mutations. In sporadic cases, the majority of juvenile meningeomas also harbor a monosomy of chromosome 22. Some cases also presented a chromosome 1 and 14 deletion. A mutation of *AKT*, *SMO*, *KLF4*, *TRAF7* (exon 17), and *pTERT* was in contrast to adult cases, not described [23].

Already in 1922, Cushing published on behavior of meningeomas at different intracranial locations [24]. He

demonstrated that different intracranial meningeoma localizations result in different prognosis regarding survival and relapse. Cytogenetic aberrations of meningeomas have been shown to be significantly associated with the tumor location as well [25]. In adult cases of meningeoma of the frontal cranial base, mutations of the genes *SMO* and *AKT1* are described. A mutation of *SMO* was significantly associated with a larger tumor volume compared to wild-type *SMO* meningeomas. Due to these genetical aberrations, which are not found in meningeomas of the convexity, Cornelius et al. [26] state a genetic difference on principle between the different tumor locations. These findings are supported by the results of Boetto et al. [14] who found in the majority of 79 patients with olfactory groove meningeoma either a mutation of *SMO* or *AKT1*.

Based on these publications, we examined our patient's nasoethmoidal meningeoma for the mutations described above, hoping to get an additional answer concerning the aggressive biological behavior of the given tumor. From a prognostic and therapeutical point of view, it was shown that *SMO* mutation is associated with poorer prognosis and late recurrences [21, 22] and that *SMO* inhibitors are under clinical evaluation for *SHH*-

mutated medulloblastoma [27] and routinely used in metastatic basal cell carcinoma [28]. Further intention was to use next-generation sequencing techniques to gain a deeper insight into the genetic characteristics of the once presented case and compare these findings with the initial analysis of 2003.

Interestingly, the genetic characteristics in this case showed to be remarkably stable. Analyzed with the newly available tools like next-generation sequencing, the genetic distinctiveness of the probes of 2003 and 2017 were similar. Particularly, the losses on the short arm of one chromosome 1 and the monosomy 22 were found in both specimens.

However, the abovementioned mutation in the meningioma-related genes *AKT1* and *SMO* were not present in our patient suggesting that the meningioma of our patient does not follow the *SHH* pathway activation. These results are in line with the findings from Battu et al. [29] and coworker who found that the characteristic *AKT/SMO*, *KLF4/TRAF7*, and *PTERT* genetic alterations seen in adults were distinctly absent in pediatric meningiomas.

In summary, this case shows that the biological behavior and course of the meningiomas are not easy to predict. In addition to the known genetic aberrations and the above described *SHH* pathway, we found the deletion of the short arm of one chromosome 1, which is a very typical somatic aberration pattern in our patient, which despite all efforts has repeatedly led to recurrences. Our patient died in January 2019.

Acknowledgements

We wish to thank Mr. R. Koop for expert technical assistance and Prof. Reith for his help in the neuroradiological diagnosis, and Lilli Charlotte Urbschat for helpful discussions.

Statement of Ethics

The parents have given their written informed consent for publication of data and images.

Conflict of Interest Statement

The authors have no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Funding Sources

The authors did not receive any funding.

Author Contributions

H.S. collected patient data and wrote parts of the paper. S.C. collected patient data and wrote sections of the paper. F.S. did the panel sequencing and wrote a part of the paper. U.S. did the cytogenetic analysis and wrote parts of the paper. J.O. is head of the department and supervised the treatment of our patient and did surgery. R.K. did surgery, wrote sections of the paper, and revised the draft. All authors read and approved the final manuscript.

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