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CASE REPORT

Relapse of a group 4 medulloblastoma after 18 years as proven by histology and DNA methylation profiling

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Abstract

Background Recent studies on medulloblastomas (MB) suggest that a large fraction of tumors appearing as late recurrence turn out to be secondary malignancies, e.g., malignant gliomas, after thorough molecular investigation.

Results Here, we report of a patient with a group 4 MB that developed a distant recurrence after more than 18 years. The recurrent tumor was confirmed by histology and genome-wide DNA methylation profiling.

Conclusion Our case not only illustrates the potential of very late recurrences after seemingly cured group 4 MB, but also illustrates that detailed molecular analyses are indispensable in patients with a history of a previous malignancy.

Keywords Medulloblastoma · Group 4 · Late recurrences · Genome-wide DNA methylation

Background and importance

Medulloblastoma (MB) remains the most common malignant brain tumor in children [3]. Several studies looking at the long term follow-up of patients with MB have reported of high mortality due to long term side effects of the initial therapy [7] as well as secondary malignancies [7, 8, 12, 13]. In contrast, recurrences from the initial MB that appear after 5 years or even after a decade are very rare. In line with this observation, recent reports that have analyzed potential recurrences by novel molecular approaches have discovered that such tumors often turn out to be malignant gliomas [9]. In fact, it is well known that malignant gliomas may appear with histological features of embryonal tumors and that discrimination without molecular analyses may be hard, if not impossible. Therefore, it appears unclear, which percentage of MB "relapses" after more than 5 years are truly MB and how long patients have to be afraid of true relapses instead of secondary malignancies. We report here on a bona fide relapse of a group 4 MB after more than 18 years that has been proven both by histology and molecular pathology.

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Clinical presentation

Patient history

At the age of 13, the patient was diagnosed with classic MB WHO°IV at the vermis cerebelli (Fig. 1a). Patient tumor samples and MRI scans were obtained as approved by the local medical ethics committee. Unfortunately, the initial diagnostic procedure used up all tumor material. The patient underwent surgery being subtotal resected without metastasis and received radiotherapy of the craniospinal axis of 35.2 Gy with a boost to the posterior cranial fossa totaling 55.2 Gy. Subsequent chemotherapy consisted of cisplatin, lomustine, and vincristine according to HIT-91 protocol.

Fifteen years after completing radiotherapy she was diagnosed with a meningioma WHO°I at the left frontotemporal region (Fig. 1b), while being free of any MB foci.

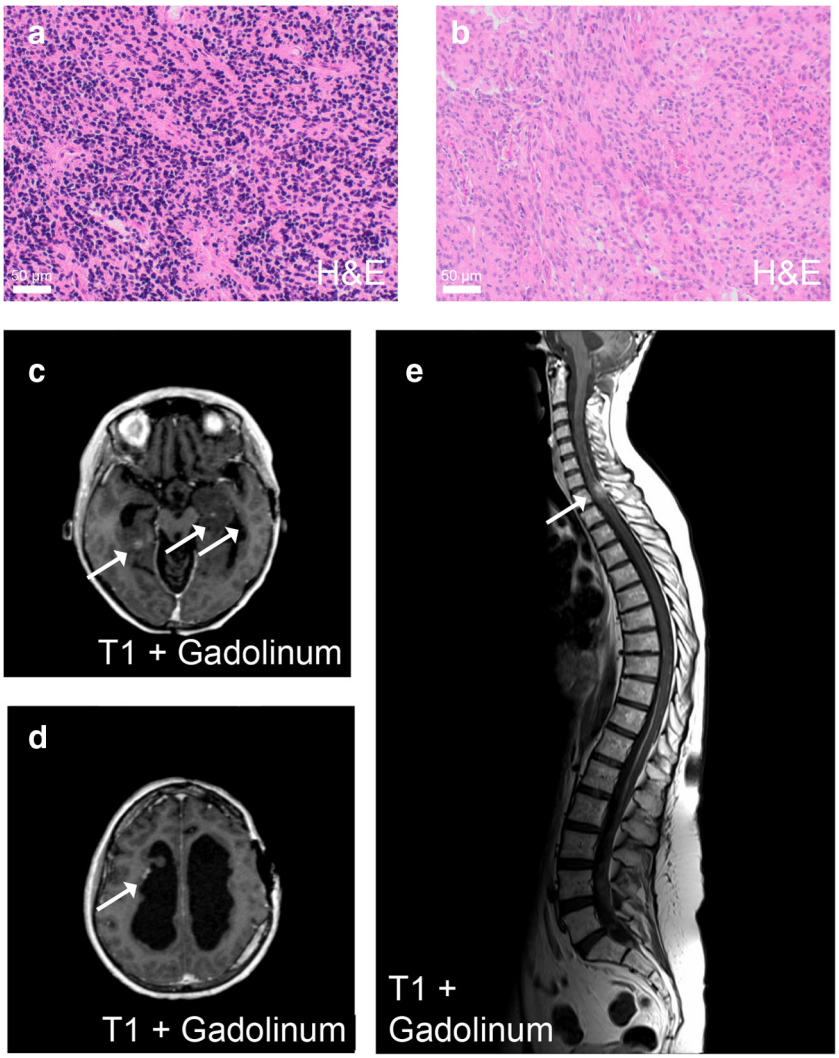


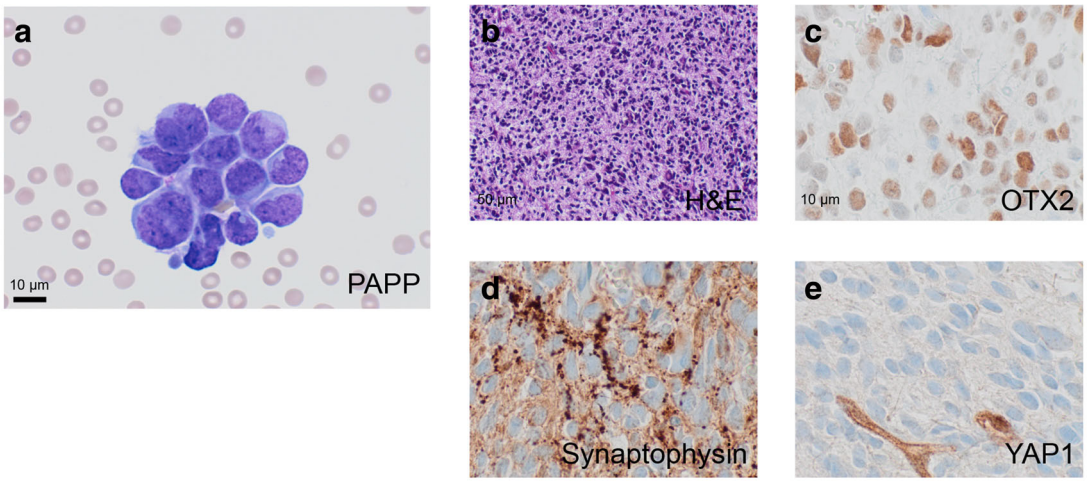
Fig. 1 Histology of previous tumor samples and current MRI. **a** H&E stain of the initial tumor sample revealing typical features of medulloblastoma. **b** H&E stain of the meningioma operated 14 years after radiation. **c**–**e** Current MRI scans of the cranium (**c**, **d**) and spine (**e**) showing multiple contrast-enhancing foci (arrows) along the cranio-spinal axis

Clinical admittance

Eighteen years after the initial diagnosis, the patient was admitted to the University Medical Center Hamburg due to an increased walking disorder that aggravated within 4–6 weeks. MRI scans of the craniospinal axis revealed multiple contrast-enhancing foci in close relation to the ventricles or the spinal canal (Fig. 1c–e). Concurrent spinal taps revealed tumorous cells that were suggestive for MB (Fig. 2a). Through brain biopsies of the left temporal contrast enhancing foci definite histology was achieved (Fig. 2b–e), showing a small-, blue-, and round-cell tumor with strong expression of OTX2 and synaptophysin. YAP1 protein was restricted to blood vessels. Tumor cells were negative for GFAP and OLIG2 (data not shown). In addition, we performed genome-wide DNA methylation profiling using an 850k Illumina EPIC array. Tumor classification was performed by the DKFZ brain tumor classifier as previously reported (https://www.molecularneuropathology.org) [1]. Results revealed high similarities of the analyzed lesion with MB, subclass group 4 (Fig. 2f), which is the most common molecular subtype of MB (~40% of cases) [6]. Knowing from the literature that MB recurrences virtually never change their molecular subgroup, we assume that the initial MB in this patient was also a group 4 tumor [10]. The analyses of copy number variations (CNV) showed an isochromosome 17 as well as a loss on chromosome 8. Amplifications at the *MYC* or *MYCN* locus were not detectable. In summary, the recurrent tumor was diagnosed as a classic medulloblastoma (WHO°IV, group 4) (Fig. 2g).

Discussion

According to the current literature, about 20–30% of MB relapse under modern treatment regimens [4, 8, 11] usually within 2 years [13]. In fact, within the cohort of more than 1000 patients that had been included in the HIT2000 MB clinical trial in Germany, we identified only three patients with a relapse after more than 10 years. The longest interval after radiation was 11 years (data not shown). Of note, these tumors



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Family Score	Methylation Family
0.9998	MTGF_MB_G3G4
0.0001	MTGF_GBM
0.0001	MTGF_MB_SHH
0.0001	MTGF_PLEX_T
0.0001	MTGF_IDH_GLM

Class Score	Methylation Class
0.9998	MB, G4
0.0001	MB, SHH CHL AD
0.0001	MB, G3
0.0001	PLEX, PED B
0.0001	GBM, RTK1

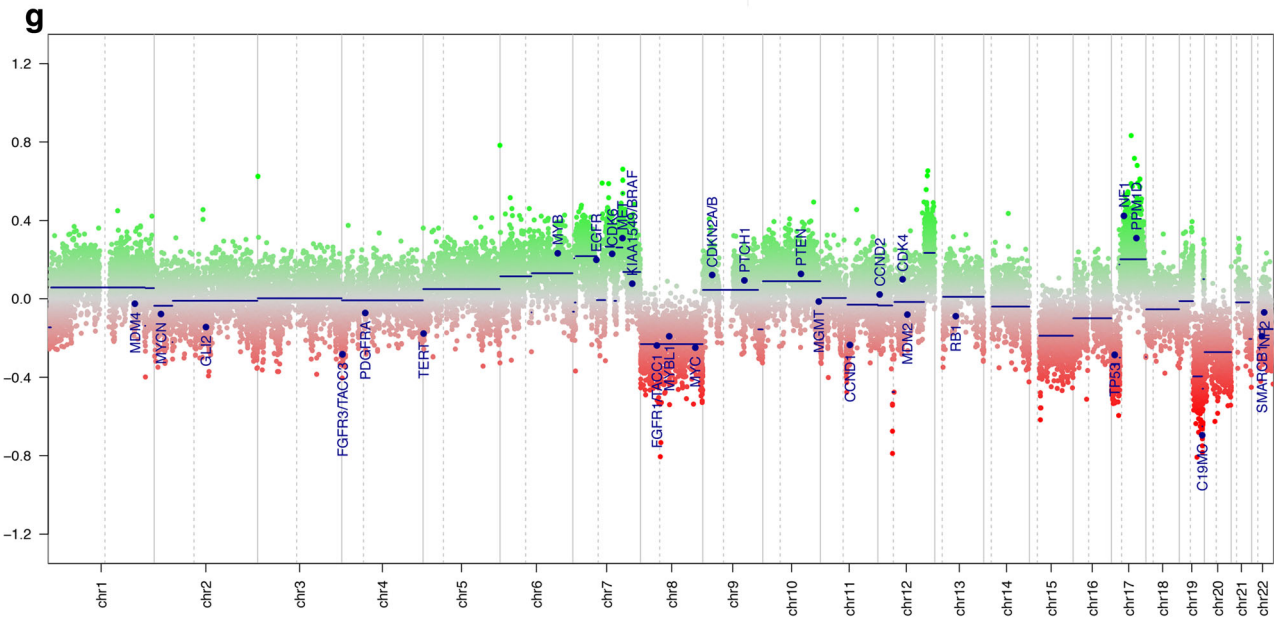

Fig. 2 Histological and genome-wide DNA methylation analysis of the recurrent tumor. **a** Pappenheim-stain (PAPP) of cells isolated from a lumbar puncture reveals cell clusters very suggestive for medulloblastoma cells. **b–e** Histopathology of tumor tissue of a right temporal brain biopsy reveals a cell dense undifferentiated tumor with expression of OTX2 and synaptophysin, as typically seen in group 3/4 medulloblastomas. YAP-1 was restricted to blood vessels. **f** Genome-wide DNA methylation profiling of the tissue reveals a high similarity to the group 3/4 MB methylation family (left) with a definite methylation class being MB group 4 (right). **g** Analysis of copy number variations (CNV) shows an isochromosome 17 and a loss of chromosome 8, but no amplifications at the *MYC* or *MYCN* locus. Oncogenes and tumor suppressors frequently altered in brain tumors are annotated

and most other reported MB relapses have not been characterized by DNA methylation profiling or other molecular tools. For example, 10% of relapses were reported to occur more than 5 years after first diagnosis in a long-term evaluation of the HIT91 trial. However, at that time, only a minority of relapses were re-biopsied and confirmed by histopathological

or available biological assessments [12]. So, it is tempting to speculate that a fraction of these tumors might even turn out to be malignant gliomas after extensive molecular work-up. A very recent report indeed realized that four out of five tumors occurring more than 5 years after the diagnosis of a medulloblastoma had molecular features of a malignant glioma [9]. Another recent publication reported on the genetic landscape of malignant glioma as a secondary disease after radiation of diverse primary tumors and demonstrated five cases with the initial diagnosis of medulloblastoma and a median interval of 11 years after radiation [5]. This is well in line with the assumption that tumors appearing 5 or more years after radiation are highly likely to represent secondary malignancies, e.g., glioma, even if the histopathological appearance may look like small-, blue-, round-cell tumors. Therefore, our reported case appears exceptional. First, the interval between the primary diagnosis and the second tumor is extremely long. Only one single case, which has not even been characterized by immunohistochemistry, was reported with a longer interval, i.e., 23 years [2]. Second, our tumor was molecularly characterized and proven to be a MB recurrence in multiple ways. Through genome-wide methylation profiling, we were able to classify this MB as a group 4 tumor, which is interesting, since the longest interval between a MB and its "true" recurrence in the cohort of Phi et al. was also seen in a group 4 MB [9]. Similarly, Ramaswamy et al. previously used a series of over 200 recurrent MB to show that group 4 MB have the longest time to recurrence [10] compared to all other MB subgroups.

Conclusion

In conclusion, this study highlights the potential for very late recurrences, and group 4 MB may indeed be of relatively high risk in this regard. Therefore, continued follow-ups of patients with MB seem justified to detect secondary malignancies, but also late recurrences. If detected, detailed molecular analyses of the late-occurring tumor, e.g., genome-wide methylation profiling, appear indispensable in order to safely discriminate between these two differential diagnoses.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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