**INTRODUCTION**

The current World Health Organization (WHO) classification of tumors of the central nervous system (CNS) released in 2016 introduced the integration of both histomorphologic tumor features and molecular genetic aspects as essential parts in brain tumor classification.\(^1\) By this approach, the underlying tumor biology and altered molecular pathways are taken into consideration for advanced individualized treatment planning.

Within the last years, epigenomic tumor classification by applying DNA methylation profiling emerged as a valuable tool in brain tumor classification.\(^2\-\,6\) One impressive example is the epigenomic analysis of highly malignant glioblastoma (WHO Grade IV).\(^2\) While glioblastoma show homogeneous phenotypical hallmarks with pleomorphic glial tumor cells, mitoses, microvascular proliferation, and necroses, methylation profiling revealed six molecular subtypes that are linked with patient age, location, and outcome.\(^2\) Based on these findings, methylation profiling was applied on medulloblastoma,\(^7\) ependymal tumors,\(^4\) and meningioma\(^3\) leading to a DNA methylation-based classification of CNS tumors.\(^8\) This approach revealed 82 distinct molecular tumor entities.\(^8\)

Gangliogliomas are rare glioneuronal tumors that represent only 1.3% of all tumors of the central nervous system.\(^1\) These tumors show a high degree of association with epilepsy...
and are typically found in younger patients. Gangliogliomas show slow growth and good outcome. Thus, most gangliogliomas are classified as WHO grade I tumors.

Here, we report on a malignant brain tumor with glioblastoma genotype morphologically mimicking ganglioglioma that was revealed by in-depths DNA methylation-based classification.

2 | CASE PRESENTATION

A 55-year-old male Caucasian patient presented with headache, vertigo, and visual problems persisting for months, followed by a single bilateral tonic-clonic epileptic seizure. On clinical examination, no other focal neurological deficits were recorded. Magnetic resonance imaging (MRI) showed a right frontal parafalcine intracranial mass with subtle, diffuse contrast enhancement (Figure 1A,B). A [18F] fluoroethyltyrosine (FET)-PET CT showed pathological uptake of the tracer with a maximum standardized uptake value (SUVmax) of 3.4 (Figure 1C,D). Subsequently, the patient underwent microsurgical gross total tumor resection with immediate postoperative MRI showing no residual contrast enhancement. A 3-month follow-up MRI and FET-PET CT scan showed no residual contrast enhancement (Figure 1E,F) but an increased FET uptake was recorded at the caudal margin of resection cavity (Figure 1G,H). A concomitant radiochemotherapy with Temozolomide and a cumulative dose of 60 Gy analogous to EORTC/NCIC protocol was accomplished. Ten months after initial tumor resection and 3 months after completion of concomitant radiochemotherapy, the patient showed radiological signs of progressive disease. The MRI revealed increased contrast enhancement (Figure 1I–L). After interdisciplinary consultation, a second-line chemotherapy with Bevacizumab and Irinotecan was then administered.

3 | PATHOLOGICAL FINDINGS

Histological examination of the specimen on H&E stain showed a tumor with glial and neuronal elements with increased cellularity and pleomorphic neoplastic cells as well as dystrophic calcifications (Figure 2A), extensive perivascular lymphoid infiltrates (Figure 2B) and intermingles partially multinucleated, atypical ganglionic cells without polarization.

![Figure 1](image_url)

**Figure 1** Radiological findings. Pre-surgical MRI showed an intracranial mass of the right frontal parafalcial cortex with subtle, diffuse contrast enhancement A, B, with FET-PET CT showing pathological uptake of the tracer with SUVmax of 3.4 C, D. Three-month follow-up imaging showed no contrast enhanced E,F, but an increased FET-uptake G, H. Last follow-up MRI (10 months after initial tumor resection) revealed progressive disease with midline infiltration and contralateral hemisphere affection typical for glioblastoma I-L.
FIGURE 2  Histological and immunohistochemical findings. In H&E stained sections the tumor showed glial and neuronal elements with increased cellularity and pleomorphic neoplastic cells with only sparse mitoses, dystrophic calcifications (A), extensive perivascular lymphoid infiltrates (arrow, B), and intermingled atypical ganglionial cells (arrows, C). Immunohistochemical stains showed GFAP (D), and MAP2 (E), positive tumor cells. Dysmorphic ganglionial cells were positive for NeuN (F), and synaptophysin (G), with some CD34 positive tumor cells (H). Nuclear expression of ATRX was retained (I). There was no nuclear accumulation of the P53 protein (J). Ki67 proliferation index was low with only 5% positive cells (K), and there were only single PHH3 (H3S10p) positive cells (L). There was no mutant IDH1 R132H (M), H3.3 K27M (N), and BRAF V600E (O) protein detectable. Scale bar: 500 µm A, 100 µm B, 50 µm C-O

(Figure 2C). There were only single mitoses, no microvascular proliferations and no necroses.

Immunohistochemical workup performed on a Ventana Benchmark Ultra System with standard protocols showed GFAP (glial fibrillary acidic protein, Figure 2D) and MAP2 (microtubule-associated protein, Figure 2E) positive tumor cells. Dysmorphic ganglionial cells were positive for NeuN (neuronal nuclei, Figure 2F) and synaptophysin (Figure 2G). Immunohistochemical stains with antibodies against CD34 marked atypical neuronal and satellite cells (Figure 2H). Nuclear expression of ATRX (nuclear immunopositivity for α-thalassemia/mental-retardation-syndrome-X-linked) was retained (Figure 2I). Antibodies against P53 did not show an accumulation of the P53 protein within the tumor cells (Figure 2J). Proliferation was low with 5% Ki67 positive cells (Figure 2K). There were only single PHH3 (phosphorylated histone H3, H3S10p) positive cells (Figure 2L). Mutation-specific antibodies did not show expression of mutant IDH1 (isocitrate dehydrogenase) R132H (Figure 2M), mutant histone H3.3 K27M (Figure 2N) or mutant BRAF (B-Rapidly Accelerated Sarcoma) V600E protein (Figure 2O). Thus, the tumor showed morphology of ganglioglioma with no signs of anaplasia. This classification was confirmed by reference pathology suggesting Ganglioglioma WHO Grade I based on histology.

Molecular genetic analysis was performed as previously described. Analysis showed a mutation of the TERT promoter region (C228T) and a PTPN11 p.G60R mutation (Figure 3A). There was no mutation at the further analyzed 52 genes (Figure 3B). Due to the unusual detection of TERT promoter mutation and BRAF wildtype status, methylation profiling was performed using the Illumina Infinium EPIC bead chips according to the manufacturer’s protocol. Arrays were scanned on the Illumina NextSeq 550DX. Data analysis was performed using the Molecular Neuropathology bioinformatics pipeline of the German Cancer Research Center (DKFZ). Interestingly, the tumor clustered to the class of glioblastoma IDH wildtype (score 0.97), subclass mesenchymal (score 0.95; Figure 3C).
As glioneuronal tumors, gangliogliomas are composed of both glial and neuronal components with dysmorphic ganglion cells as a characteristic feature of the histological picture. In more than 95% of ganglioglioma, the tumors do not show signs of malignant behavior and a very favorable outcome. In the presented case, we found a brain tumor morphologically mimicking ganglioglioma: The tumor was composed of glial and neuronal elements with dystrophic calcifications, extensive perivascular lymphoid infiltrates and intermingles atypical ganglionic cells (Figure 2). There were only single mitoses, no microvascular proliferation, and no necrosis. Immunohistochemistry was well in line with histology: The tumor cells expressed GFAP and MAP2, dysmorphic ganglionic cells expressed NeuN and synaptophysin and satellite cells expressed CD34 (Figure 2). Proliferative activity was low (Figure 2).

Molecular workup revealed a TERT (C228T) promoter mutation and DNA methylation profiling allocated the tumor to the molecular group of glioblastomas, mesenchymal subclass (Figure 3). The detection of a PTPN11 mutation and a homozygous CDKN2A/B deletion (Figure 3) also indicates malignant behavior: PTPN11 mediates gliomagenesis and CDKN2A/B deletions are associated with spontaneous tumor development.

To our knowledge, this is the first reported case of a genotypically glioblastoma phenotypically mimicking WHO Grade I ganglioglioma that was revealed by epigenome wide methylation profiling with documented clinical course emphasizing malignant behavior.

A literature search revealed that there are only sparse reported cases of WHO grade I ganglioglioma with malignant transformation into glioblastoma. In 1987 Kalyan-Raman et al. analyzed a cohort of 10 gangliogliomas with one patient developing a glioblastoma 5 years after primary tumor resection. Jay et al. reported in 1994 a ganglioglioma in a 10–year-old boy showing three recurrences at four, 12, and 36 months after primary resection with the third recurrence revealing a massive midline tumor with highly increased cellularity and many multinucleated tumor cells and mitoses.

Hayashi et al. published in 2001 one case of gangliocytoma/ganglioglioma in a 16–year-old woman that showed two recurrences after 8 and 9 years, the cellularity increased in these recurrences finally resulting in glioblastoma diagnosis.

In 2004, Luyken et al. published a report on 184 patients with supratentorial gangliogliomas, in five patients the tumor recurred between 7 months and 3 years after primary tumor resection with three patients showing histological signs of malignant progression; two even displayed hallmarks of glioblastoma. The outcome in these three patients was very poor with two patient fatalities 1–3 years after recurrence and one patient with progression free survival for 1.5 years. Pandita et al. reported on a 20–year-old woman in 2007 with large, contrast enhancing lesions with perilesional edema and midline shift in MRI. The tumor was resected and histological workup revealed a well-differentiated component compatible with WHO grade I ganglioglioma and a malignant component with pleomorphic tumor cells and a proliferative index of 9%–20%. The patient died 18 months after primary resection.

In 2007, Stevens et al. published a case of a 45–year-old woman with two separate lesions in the temporal lobes. While one of these lesions was classified as ganglioglioma the other was classified as malignant ganglioglioma/glioblastoma variant by the authors. In the clinical course, the lesion classified as malignant ganglioglioma/glioblastoma showed...
multiple recurrences and was subjected to several resections, irradiation, and chemotherapy.13

With the emergence of newly developed sophisticated in depths molecular genetic analysis of brain tumors, there are emerging cases of phenotype-genotype mismatch. Cases with ambiguous and non-informative histology can be classified according to molecular hallmarks that represent the biological behavior of the tumor. Jaunmuktane et al18 reported on methyleme profiling of brain tumors and found that in 25% the histological diagnosis was changed and in 48% refined due to methyleme analysis, only in 25% of cases, the diagnosis was confirmed. But already the study published by Capper et al. in 2018 showed some severe phenotype-genotype mismatches in the cohort of 2801 analyzed cases.8 Thereby, the change of the underlying analysis platform from the Illumina 450 k bead chip covering >450,000 CpG that was used by Capper et al8 in 2018 to the Illumina 850 k/EPIC bead chip covering >850,000 CpGs10,18 enables on the one hand side to include previously data by using powerful computational pipelines and also to refine epigenomic profiling. Thus, we assume that there will be an increasing number of phenotype-genotype mismatches in the future with increasing availability of molecular profiling techniques.

In summary, this is a very impressive example of phenotype-genotype mismatch and to our knowledge the first glioblastoma mimicking ganglioglioma that was revealed by epigenomic profiling. While histology showed a ganglioglioma WHO Grade I, the molecular workup revealed a glioblastoma WHO Grade IV. Well in line with this molecular profile was the clinical course: The tumor showed a rather aggressive behavior with progressive disease in follow-up MRI. Thus, this case emphasizes the urgent need for advanced workup of glial and glioneuronal tumors including histology, genetic and epigenomic characterization for advanced patient care and refined individualized medicine.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
TFJK: planned the work, performed histological assessment, analyzed data, wrote the manuscript; KS: planned the work; HUS: performed histological assessment; BZ: performed molecular analysis, analyzed data; ED: performed molecular analysis, analyzed data; LM contributed radiological findings; JP, CS, BL, MS, ARA, and PAW contributed clinical data; all authors discussed the manuscript.

ETHICAL APPROVAL
All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

PATIENT'S CONSENT
Yes.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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