Gliosarcoma with Extensive Extracranial Metastatic Spread and Familial Coincidence: An Illustrative Case

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Case Report

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Abstract

Gliosarcoma is a rare histopathological subtype of glioblastoma. Metastatic spreading is very unusual. In this report, we illustrate a case of gliosarcoma with extensive extracranial metastases with confirmation of histological and molecular concordance between the primary tumor and a metastatic lesion of the lung. Moreover, the case revealed a family coincidence of glial tumors as the patient's son was diagnosed with a high-grade glioma shortly after the patient's death. By molecular analysis (Sanger and next generation panel sequencing), we could confirm that both patients carried mutations in the *TP53* gene. Interestingly, the detected mutations were located in different exons. According to the current scientific knowledge, even further genetic findings do not explain the aggressive metastatic spread observed in the reported case nor reveal a family tumor syndrome. In conclusion, the molecular mechanisms leading to a metastatic phenotype of gliosarcoma remain unknown and should be studied further.

Introduction

Glioblastoma (CNS WHO grade 4) is the most common primary malignant brain tumor in adults, histopathologically characterized by predominantly astrocytic differentiation and presence of vascular proliferates and/or intratumoral necrosis [1]. Beside histopathological criteria, the detection of homozygous *CDKN2A/B* deletion, *TERT* promoter mutation, *EGFR* gene amplification or +7/−10 chromosome copy number changes lead to the diagnosis of CNS WHO grade 4 in *IDH*-wildtype diffuse astrocytic glioma [1].

A rare histopathological subtype of glioblastoma is gliosarcoma, which contains a glial and a mesenchymal-sarcomatous component [2, 3] and predominantly affects male patients (approx. 71 %) at a median age of 42 years [4]. Genetic alterations show an unanimous profile across the tumor irrespective of the histological area [3]. Molecular gliosarcoma profiling revealed *PTEN* and *TP53* mutations, monosomy of chromosome 10 and homozygous *CDKN2A/B* deletion as well as (rarely) *TERT* promoter mutations, and no genetic changes in *ATRX*, resembling a subtype of *IDH*-wildtype glioblastoma [3, 5 - 7].

Treatment comprises surgery, irradiation, and temozolomide chemotherapy [8 - 10], but biological aggressiveness and systemic dissemination lead to a low median survival of 13 months [4, 11 - 15]. Spreading of gliosarcoma has been reported in singular cases only [16 - 19] and is assumed to occur hematogenously [16].

Here, we present a case of an extracranially metastasized gliosarcoma with confirmation of histological and molecular concordance between primary tumor and a pulmonary metastatic lesion. Interestingly, we report a familial coincidence of a high-grade glioma with *TP53* mutations.

Case Report

A 47-year-old Caucasian male presented with cephalgia, memory impairment and homonymous hemianopsia for 3 weeks. His medical history was unremarkable besides arterial hypertension and smoking. MRI showed a left-sided temporo-occipital lesion of 6.5 cm diameter with marginal enhancement and perifocal edema (Fig. 1 a - d). The patient underwent a gross-total resection of the lesion and histopathological analysis revealed glioblastoma with sarcomatous component (gliosarcoma; CNS WHO grade 4), IDH-wildtype. Concomitant radiochemotherapy with temozolomide according to the Stupp protocol was applied [10]. Seven month later, the patient underwent repeated gross-total resection followed by bevacizumab therapy due to asymptomatic tumor recurrence. Five months after re-resection, a left-sided nuchal lesion was excised and diagnosed as a cutaneous gliosarcoma metastasis. Subsequently, rapid clinical deterioration with cephalgia, nausea, vomiting and cognitive impairment occurred. CSF analysis showed lymphocytic pleocytosis, but no evidence of granulocyte-dominated inflammation or tumor cells. MRI revealed progression of the gliosarcoma at the primary site as well as multifocal meningeal, ependymal, and intracerebral manifestations. Re-irradiation and treatment with lomustine was initiated, but was stopped after application of 32.4 Gy due to further clinical deterioration. CT of abdomen and chest showed multifocal tumor spreading. The patient died shortly after, 15 months after primary diagnosis.

Post-mortem examination showed multiple intracranial manifestations and systemic metastases in several organs, including multiple lesions of thyroid gland, peri- and myocardium (Fig. 1 e - g), lung (Fig. 1 h) and pleura, intercostal muscles (Fig. 1 i), diaphragm, thoracic spine (Fig. 1 j), gastric wall and small intestine, kidney, spleen, liver, peritoneal adipose tissue and subcutaneous in the nuchal region. Tumor-induced obstruction of the fourth ventricle with subsequent (tumor-toxic) cardio-pulmonary failure was assumed as cause of death.

11 months later, his 26-year-old son presented at the hospital with mild right-sided facial paresis, confusion and fatigue. MRI showed a left fronto-polar contrast enhancing lesion with diffuse infiltration of the corpus callosum and the brain stem, leading to a midline shift. Gross-total resection was performed and astrocytoma (CNS WHO grade 4), IDH-mutant was diagnosed. The patient underwent concomitant and adjuvant radiochemotherapy with temozolomide. Three and a half years later, local tumor progression was detected. The patient refused any further cancer treatment.

Histopathology

Microscopic analysis of the father’s primary tumor displayed a biphasic tissue pattern, containing a glial as well as a sarcomatous component (Fig. 2 a). The glial tumor component mostly contained round nuclei rich in chromatin, and tumor cells were positive for MAP2c (Fig. 2 c right) and GFAP (Fig. 2 d right). The sarcomatous component demonstrated a spindle cell configured histoarchitecture with elongated nuclei. Reticulin staining highlighted a dense fiber network surrounding single cells (Fig. 2 b left). Tumor cells of the sarcomatous component did not express glial markers like MAP2c (Fig. 2 c left) or GFAP (Fig. 2 d left). Tumor cells of both components showed increased mitotic (Fig. 2 a) and proliferation activity. Approximately 30 % of tumor cell nuclei accumulated p53 protein (Fig. 2 e). Infiltration of the tumor tissue

by lymphocytes and monocytes as well as focal bleeding and calcification were observed. Immunohistochemistry of mutant IDH-1 (R123H) was negative (Fig. 2 f). Microscopic analysis of the nuchal lesion revealed an identical tissue pattern (Fig. 2 g) with a high fraction of p53-accumulating tumor cell nuclei (Fig. 2 h).

Post-mortem analyses confirmed tumor infiltration of the leptomeninges resembling meningeosis gliosarcomatosa (Fig. 2 i, j). Multiple intracranial manifestations were observed at resection site, callosal commissure, midbrain, medulla oblongata, cerebellum and occipital cortex. Every manifestation of the tumor revealed strong nuclear accumulation of p53 protein (Fig. 2 l). Microscopy revealed a near-complete obstruction of the fourth ventricle by tumor tissue (Fig. 2 k). Furthermore, the examined brain tissue showed signs of elevated intracranial pressure such as impression marks of cerebellum and temporal uncus, intravascular stasis and global parenchymal edema.

The son's tumor showed a high-grade astrocytic neoplasm with diffuse infiltration of the adjunct brain tissue, high cellularity and an increased mitotic index as well as microvascular proliferations and palisading necrosis (Fig. 2 m). A sarcomatous component could not be observed in this tumor (Fig. 2 n). More than 50 % of tumor cell nuclei accumulated p53-protein (Fig. 2 o). In contrast to the father's tumor, an *IDH-1* (R123H) mutation was detected immunohistochemically (Fig. 2 p).

Molecular Pathology

Comparative molecular analysis did not show increased methylation of the *MGMT* promoter in both cases. To analyze whether the appearance of two high-grade gliomas within one family reveal a genetic equivalent of a family tumor syndrome, we first tested both, father's and son's tumor tissue for constitutional DNA mismatch repair deficiency (CMMRD) by immunohistochemistry. Thereby, no evidence for a loss of the DNA mismatch repair proteins MLH1, MSH2, MSH6 or PMS2 was found. Next, considering hereditary mutations within the tumor suppressor gene *TP53*, we performed Sanger sequencing of *TP53*, exons 4 to 9, in the tumor tissue. We were able to detect mutant *TP53* sequences in both tumors, but tumors of father and son did not carry the same mutations. Whereas the father's *TP53* point mutation was found in exon 7 (p.R248Q; Fig. 2 q), his son carried two point mutations in exon 5 (p.S127F and p.K132R; Fig. 2 r). Post-mortem, one of the father's pulmonary metastases was also analyzed molecularly showing the identical *TP53* point mutation (p.R248Q) as found in the cerebral primary tumor.

Next generation sequencing (NGS) examining 41 glioma-associated genes confirmed *TP53* mutations in both cases. *RB1* mutation (allele variant fraction: 54.4 %), *PTEN* mutation (allele variant fraction: 54.2 %) and *TERT* mutation within the promoter region (C228T, allele variant fraction: 20 %) were detected in the father's tumor, and analysis of a lung metastasis showed the identical results as the primary gliosarcoma. In contrast, the son's tumor DNA carried a *PIK3R1* mutation (allele variant fraction: 45.1 %), whereas *TERT* promoter analysis revealed wildtype alleles.

Discussion

Although metastatic spread of gliosarcoma is rare, it occurs more frequently than in glioblastoma (up to 1.1 % versus 0.5 %) [20, 21]. Here, we report a case of gliosarcoma with fulminant multi-organ spreading, the entire extent of which was only revealed during autopsy and considerably wider compared to other reports [16 - 19]. According to the affected organs (mostly lung, heart, liver, spleen, bone and muscle system), we assume hematogenous spreading. However, nuchal metastases were located in the area of surgical approach for primary resection, rendering local cutaneous and subcutaneous spread by surgical instruments plausible as assumed in a case by Bekar et al. [22].

Besides surgery, the patient's treatment included first-line radiochemotherapy with temozolomide, followed by re-resection, re-irradiation, bevacizumab and lomustine treatment upon progression. While recommended treatment of gliosarcoma encompasses the same standardized approach used in glioblastoma, supporting evidence is limited given its rarity [13]. *MGMT* promoter methylation, bearing an established prognostic and predictive value in glioblastoma [23], is rare in gliosarcoma, which might explain the poor response of gliosarcoma to alkylating chemotherapy [6, 11, 24].

Whereas gliosarcoma is composed of two tissue components, both reveal identical mutations in the tumor suppressor gene *TP53* [5]. To confirm the metastases' origin, we analyzed one lung lesion for *TP53* mutations and detected the exact same point mutation as observed in the cerebral primaries, as well as the same genetic alterations in NGS panel testing. Although the patient's son was diagnosed with astrocytoma (CNS WHO grade 4), IDH-mutant soon afterwards, no indication for presence of a familial tumor syndrome, such as Li-Fraumeni syndrome or constitutional DNA mismatch repair deficiency, was detected. However, less frequent familial tumor syndromes should still be considered.

NGS analysis uncovered genetic alterations (*TP53*, *PTEN* and RB1) commonly observed in gliosarcoma [25], while *TERT* mutations are rare, reported in only 0.2% of gliosarcoma cases [25]. According to current scientific knowledge, these genetic findings do not explain the aggressive metastatic spread observed.

In conclusion, further studies are warranted to unravel the molecular mechanisms leading to a metastatic phenotype in gliosarcoma and we recommend to treating physicians to take into consideration potential extracranial metastases, even at an early disease stage.

Abbreviations

ATRX	Alpha thalassemia/mental retardation syndrome X-linked protein
CDKN2A/B	Cyclin dependent kinase inhibitor 2A/B
CNS	Central nervous system
CSF	Cerebrospinal fluid

CT	Computer tomography
EGFR	Epidermal growth factor-receptor
FLAIR	Fluid attenuated inversion recovery
GFAP	Glial fibrillary acidic protein
H&E	Hematoxylin and eosin
IDH	Isocitrat dehydrogenase
MAP2c	Microtubule-associated protein 2c
MGMT	O6-methylguanin-DNA methyltransferase
MRI	Magnetic resonance imaging
NGS	Next generation sequencing
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1
PTEN	Phosphatase and tensin homolog
RB1	Retinoblastoma protein 1
TERT	Telomerase reverse transcriptase
WHO	World Health Organization

Declarations

Ethical approval Patient inclusion and sample analyses at the University Hospital Bonn were approved by the local ethics committee of the University Hospital Bonn (vote AZ 026/22).

Consent for publication The manuscript was written after the patient's death without including any specific information suitable to reveal the patient's identity.

Availability of data and materials The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions The authors TT, SJE, EH, CL[6], UH and BG were involved in the clinical treatment of the patient. LLF, CL[5], GK, TG, AW, TP, MG, GHG performed the (either diagnostic or post mortem) analysis of the tumor tissue. LLF, TT, JW, GHG mainly contributed to the preparation of this manuscript. All authors read and approved the final manuscript.

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References

1. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23:1231–1251.
2. Galanis E, Buckner JC, Dinapoli RP, Scheithauer BW, Jenkins RB, Wang CH, O'Fallon JR, Farr GJr. Clinical outcome of gliosarcoma compared with glioblastoma multiforme: North Central Cancer Treatment Group results. J Neurosurg. 1998;89:425–430.
3. Reis RM, Könü-Leblebicioglu D, Lopes JM, Kleihues P, Ohgaki H. Genetic profile of gliosarcomas. Am J Pathol. 2000;156(2):425–432.
4. Pietschmann S, von Bueren AO, Kerber MJ, Baumert BG, Kortmann RD, Muller K. An individual patient data meta-analysis on characteristics, treatments and outcomes of glioblastoma/ gliosarcoma patients with metastases outside of the central nervous system. PLoS One. 2015;10:e0121592.
5. Biernat W, Aguzzi A, Sure U, Grant JW, Kleihues P, Hegi ME. Identical mutations of the p53 tumor suppressor gene in the gliomatous and the sarcomatous components of gliosarcomas suggest a common origin from glial cells. J Neuropathol Exp Neurol. 1995;54:651–656.
6. Lee D, Kang SY, Suh YL, Jeong JY, Lee JI, Nam DH. Clinicopathologic and genomic features of gliosarcomas. J Neurooncol. 2012;107:643–650.
7. Oh JE, Ohta T, Nonoguchi N, Satomi K, Capper D, Pierscianek D, Sure U, Vital A, Paulus W, Mittelbronn M, Antonelli M, Kleihues P, Giangaspero F, Ohgaki H. Genetic Alterations in Gliosarcoma and Giant Cell Glioblastoma. Brain Pathol. 2016;26(4):517–522.
8. Damodaran O, van Heerden J, Nowak AK, Bynevelt M, McDonald K, Marsh J, Lee G. Clinical management and survival outcomes of gliosarcomas in the era of multimodality therapy. J Clin Neurosci. 2014;21:478–481.
9. Jin MC, Liu EK, Shi S, Gibbs IC, Thomas R, Recht L, Soltys SG, Pollom EL, Chang SD, Hayden Gephart M, Nagpal S, Li G. Evaluating Surgical Resection Extent and Adjuvant Therapy in the Management of Gliosarcoma. Front Oncol. 2020;10:337.
10. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO, European Organisation for R, Treatment of Cancer Brain T, Radiotherapy G, and National Cancer Institute of Canada Clinical Trials G. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987–996.

11. Castelli J, Feuvret L, Haoming QC, Biau J, Jouglar E, Berger A, Truc G, Gutierrez FL, Morandi X, Le Reste PJ, Thillays F, Loussouarn D, Nouhaud E, Crehange G, Antoni D, Vauleon E, de Crevoisier R, Noel G. Prognostic and therapeutic factors of gliosarcoma from a multi-institutional series. J Neurooncol. 2016;129:85–92.
12. Kozak KR, Mahadevan A, Moody JS. Adult gliosarcoma: epidemiology, natural history, and factors associated with outcome. Neuro Oncol. 2009;11:183–191.
13. Smith DR, Wu CC, Saadatmand HJ, Isaacson SR, Cheng SK, Sisti MB, Bruce JN, Sheth SA, Lassman AB, Iwamoto FM, Wang SH, Canoll P, McKhann GM 2nd, Wang TJC. Clinical and molecular characteristics of gliosarcoma and modern prognostic significance relative to conventional glioblastoma. J Neurooncol. 2018;137:303–311.
14. Pietschmann S, von Bueren AO, Henke G, Kerber MJ, Kortmann RD, Muller K. An individual patient data meta-analysis on characteristics, treatments and outcomes of the glioblastoma/gliosarcoma patients with central nervous system metastases reported in literature until 2013. J Neurooncol. 2014;120:451–457.
15. Zhang Y, Ma JP, Weng JC, Wang L, Wu Z, Li D, Zhang JT. The clinical, radiological, and immunohistochemical characteristics and outcomes of primary intracranial gliosarcoma: a retrospective single-centre study. Neurosurg Rev. 2021;44:1003–1015.
16. Beaumont TL, Kupsky WJ, Barger GR, Sloan AE. Gliosarcoma with multiple extracranial metastases: case report and review of the literature. J Neurooncol 2007;83(1):39–46.
17. Choi MG, Lee JH, Lee MS, Suh SJ, Lee YS, Kang DG. Primary Gliosarcoma with Extracranial Metastasis. Brain Tumor Res Treat. 2020;8:53–56.
18. Demirci S, Akalin T, Islekel S, Ertan Y, Anacak Y. Multiple spinal metastases of cranial gliosarcoma: a case report and review of the literature. J Neurooncol. 2008;88:199–204.
19. Mesfin FB, Deshaies EM, Patel R, Weaver S, Spurgas P, Popp AJ. Metastatic gliosarcoma with a unique presentation and progression: case report and review of the literature. Clin Neuropathol. 2010;29:147–150.
20. Frandsen S, Broholm H, Larsen VA, Grunnet K, Møller S, Poulsen HS, Michaelsen SR. Clinical Characteristics of Gliosarcoma and Outcomes From Standardized Treatment Relative to Conventional Glioblastoma. Front Oncol. 2019;9:1425.
21. Lah TT, Novak M, Breznik B. Brain malignancies: Glioblastoma and brain metastases. Semin Cancer Biol. 2020;60:262–273.
22. Bekar A, Kahveci R, Tolunay S, Kahraman A, Kuytu T. Metastatic Gliosarcoma Mass Extension to a Donor Fascia Lata Graft Harvest Site by Tumor Cell Contamination. World Neurosurg. 2010;73:719–721.
23. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 1995;352:997–1003.

24. Saadeh F, El Iskandarani S, Najjar M, Assi HI. Prognosis and management of gliosarcoma patients: A review of literature. Clin Neurol Neurosurg. 2019;182:98–103.
25. AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discov. 2017;7:818–831.

Figures

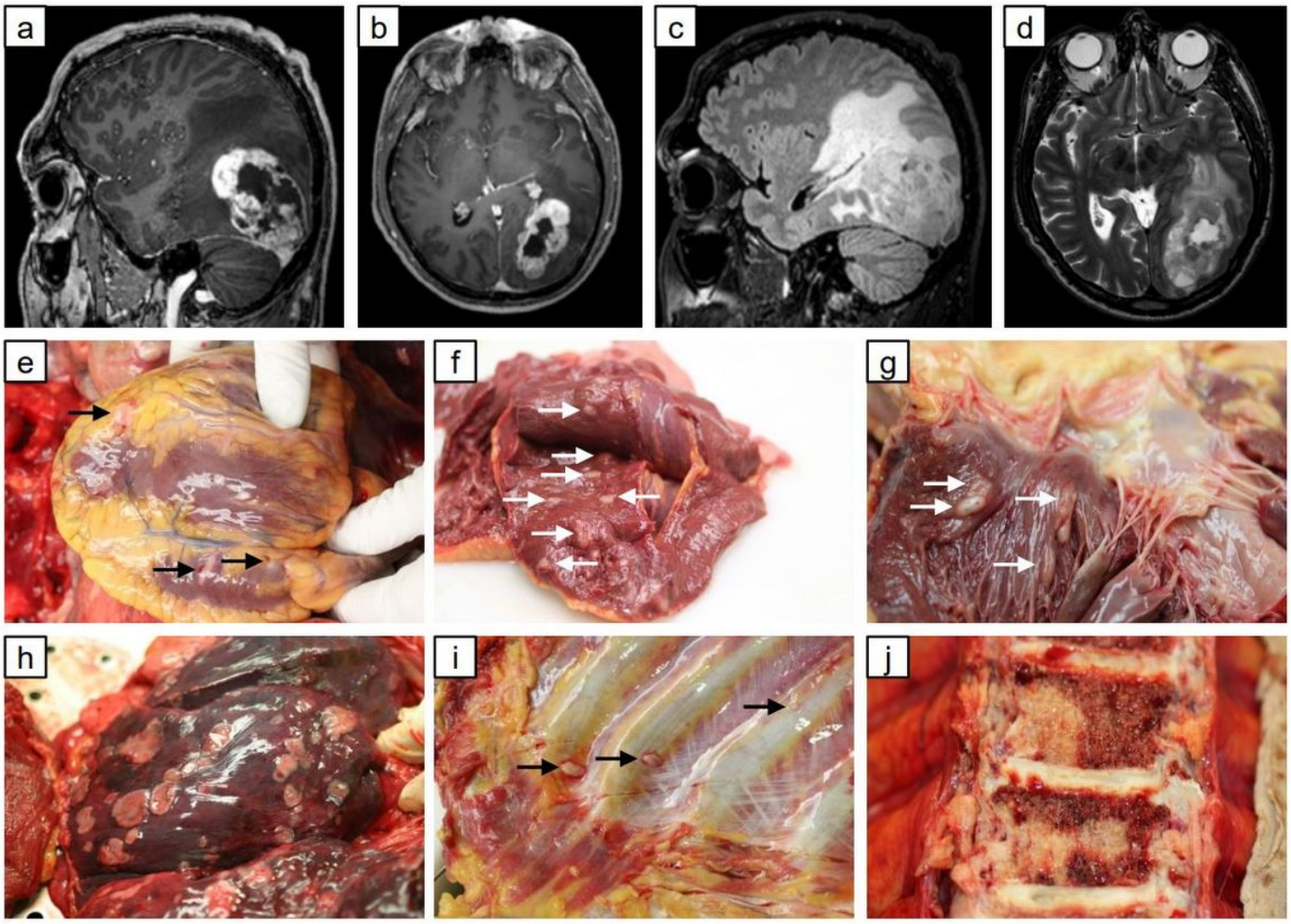

Figure 1

Neuroradiological and post-mortem pathological analysis MRI revealed a left-side temporo-occipital lesion with inhomogeneous marginal contrast enhancement and distinct perifocal edema (A - D): Sagittal (A) and axial (B) T1-weighted images with contrast agent, sagittal FLAIR (C) and axial T2-weigthed images (D). Post-mortem examination showed multiple systemic metastases (E - J): Pericardium (E), cor, intramural (F), cor, right ventricle (G), lung and visceral pleura (H), parietal pleura (I) and thoracic spine at level T3/4 (J). Arrows point at metastatic lesions (E - G, I).

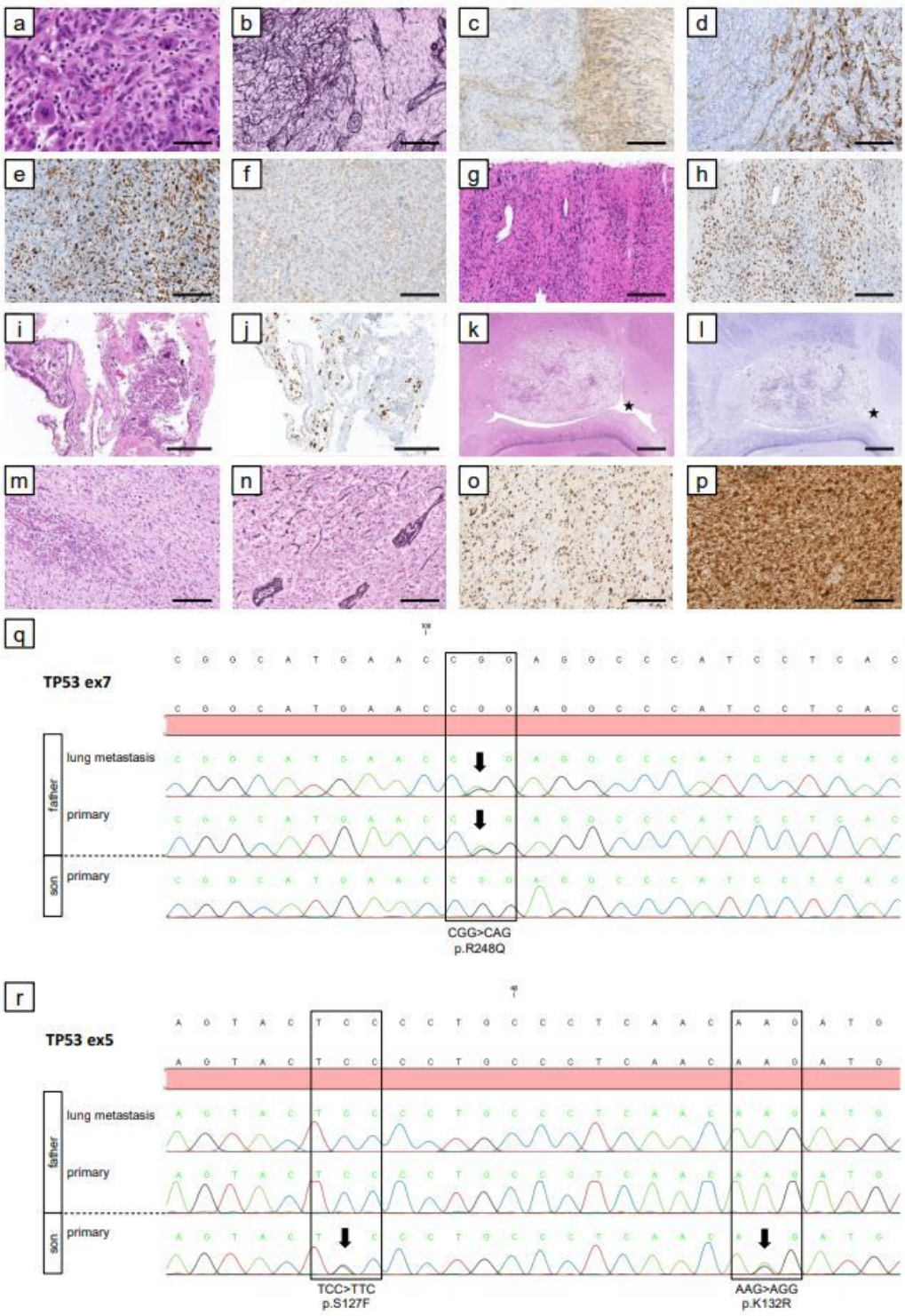

Figure 2

Histopathological and molecular analysis Microscopic analysis of the patient's primary tumor (A - F) displayed the typical biphasic histomorphology of gliosarcoma: H&E stain (A), reticulin staining (B), MAP2c (C), GFAP (D) p53 protein (E), IDH-1 (R123H) protein (F). A later occurred and resected nuchal lesion (G, H) showed the same tissue pattern as the primary tumor and was the first confirmed extracranial metastasis of the gliosarcoma recognized: H&E stain (G), p53 protein (H). Microscopic post-

mortem examination of the leptomeninges (I, J) confirmed a meningeosis gliosarcomatosa: H&E stain (I), p53 protein (J). Post-mortem analysis of the pontine area (K, L) revealed tumor-induced obstruction of the fourth ventricle (star symbol) as cause of death: H&E stain (K), p53 protein (L). 11 month after the patient's death, his son was diagnosed with an astrocytoma (CNS WHO grade 4), IDH-mutant. Microscopic analysis of the son's primary tumor (M - P): H&E stain (M), reticulin staining (N), p53 protein (O), IDH-1 (R132H) protein (P). Sanger sequencing of *TP53* (Q, R): Whereas the father carried a point mutation in exon 7 (Q), his son carried two point mutations in exon 5 (R). Arrows indicate the detected mutations (Q, R). Scale bars equate to 60 µm (A), 200 µm (B - J, M - P) or 1000 µm (K, L).