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Clinical Study

Spinal metastasis of gliosarcoma: Array-based comparative genomic hybridization for confirmation of metastatic spread

Genevieve Schindler [a,c,*], David Capper [b], Andrey Korshunov [b], Kirsten Schmieder [a,c], Christopher Brenke [a,c]

[a] Department of Neurosurgery, University Medical Center Mannheim, Mannheim, Germany
[b] Department of Neuropathology, Institute of Pathology, University Hospital Heidelberg and Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[c] Department of Neurosurgery, Knappschafts-Krankenhaus Bochum-Langendreer, Ruhr-University of Bochum, In der Schornau 23-25, 44892 Bochum, Germany

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ABSTRACT

We report a 64-year-old woman who underwent craniotomy and gross total resection of a left frontal lobe tumor initially diagnosed as glioblastoma. Multiple wound revisions were necessary due to repeated wound healing disorders under concomitant radio-chemotherapy. After 9 months there was local cranial tumor recurrence, requiring re-operation. Thereafter, temozolomide monotherapy was implemented. Histologically, a shift from glial to mesenchymal differentiation was observed in the recurrent tumor, resulting in the diagnosis of gliosarcoma. A further 9 months later a thoracic spinal tumor occurred requiring emergency tumor resection. Analysis showed a mesenchymal tumor without definite glial component. Being resistant to local radiation therapy, symptomatic local spinal tumor progression was observed within 1 month requiring re-resection. There was no response to chemotherapy with bevacizumab and irinotecan. Considering the pronounced sarcoma-like differentiation, a sarcoma chemotherapy regime with doxorubicin was initiated. This was also to no avail; the disease progressed and recurred at both the spinal and cerebral locations, respectively. This ambiguous tumor characteristic and therapy resistance encouraged us to retrospectively perform molecular and array-based comparative genomic hybridization (aCGH) analysis on the extirpated cerebral and spinal tumors. Tumors from both locations showed a consistent cytogenetic signature of gain of chromosome 7, and losses of chromosomes 10 and 13. This novel report of aCGH analysis of spinal gliosarcoma metastasis and the correlation to the clinical disease course shows that genotypic profiling may serve as a supplementary diagnostic tool in improving our knowledge of the biologic behavior of rare tumor variants.

1. Introduction

Over the past decade the treatment options for intracranial glioblastoma, the most common and most aggressive primary brain tumor [1], have improved. Standard treatment currently comprises surgical resection followed by radiation plus concomitant and adjuvant chemotherapy (CT) with temozolomide (TMZ) [2], with the mean overall survival amounting to 14.6 months [3]. Furthermore, molecular targeted therapy is refining therapy decisions [4]. In particular, the expression and activity of the DNA repair enzyme O(6)-methylguanine DNA methyltransferase (MGMT) is purported to be linked to the sensitivity of treatment with alkylating agent CT [5]. Unfortunately, these improvements only apply to cranial tumor manifestation. With an incidence of 2% [6] spinal glioblastoma spread is rare. This might change in the future as primary tumor therapy improves. Factors predisposing to metastatic spread include invasion of the dural veins [7,8], dural disruption following surgical procedures [9], and presence of mesenchymal differentiation, most commonly seen in gliosarcomas (GS) [10–12]. Spinal tumor spread often escapes early diagnosis as symptoms such as back pain, gait disorder, autonomic dysfunction, and motor and sensory deficits become evident in only about 2% of patients [1,13]. Despite salvage CT and radiation of the neuroaxis, patient survival remains poor. Often these patients are of middle age and are still in good clinical condition when presenting with glioblastoma metastasis [14]. Surgical debulking plays a pivotal role in allowing symptom control by decompression of the spinal cord, enabling diagnosis through acquisition of a specimen for histopathological (HP) and molecular analysis [4]. However this benefit is limited and spinal glioblastoma manifestation in the disease course often conveys a dismal prognosis for

* Corresponding author. Tel.: +49 234 2998 0255; fax: +49 23 4299 3609.
E-mail address: genevieve.schindler@gmail.com (G. Schindler).

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the patient, as there still are no recommendations for adjuvant therapy [15]. The lack of appreciation of the metastatic potential of the primary intracranial tumor results in delayed diagnosis and treatment. Better prognosis might be obtained by distinct diagnosis and treatment of tumor metastases [16].

The diagnosis of disseminated high-grade gliomas (HGG) is based on pathognomonic features and HP characteristics. Array-based comparative genomic hybridization (aCGH) analysis of cranial glioblastoma [17] and GS [12] has given insight to their genetic alterations. To our knowledge there are no reports of such investigations for spinal manifestations or metastasized HGG.

Our report of a patient with recurrent and disseminated GS is novel for its HP and molecular and genetic profile analysis of the cerebral and spinal tumors which correlate with the clinical course.

2. Materials and methods

2.1. Radiographic analysis

High-resolution MRI was performed routinely; T1-weighted images were acquired before and after administration of a contrast agent. Certified radiologists performed and analyzed all images. Disease progress and recurrence was assessed according to the Response Assessment in Neuro-Oncology (RANO) criteria [18]. Lesions were classified as enhancing or non-enhancing based on the presence of hyperintensity on post-contrast T1-weighted MRI. T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences were used to assess for peritumoral edema. The extent of resection was assessed by comparing the MRI T1-weighted enhanced lesion before, and 48 hours after, surgery.

2.2. Tumor specimen collection and processing

Tumor resection was performed using standard microsurgical navigation assisted procedures (Brainlab, Feldkirchen, Germany). All samples obtained at the time of surgery were immediately frozen in liquid nitrogen, and continuously stored at −80 °C until used for further analysis.

2.3. Histological, immunohistochemical and molecular analysis

All HP diagnostics were performed by neuropathologists from formalin fixed and paraffin embedded surgical specimens, according to the current edition of the World Health Organization Classification of Tumors of the Central Nervous System [19]. Histological examination of tissues stained with hematoxylin and eosin was used for diagnostic purposes, and morphological features, including the cytoplasmic, cellular, necrotic, vasculature and infiltrative archetype throughout the lesions were described. Immunohistochemical staining for glial fibrillary acidic protein (GFAP) and the isocitrate dehydrogenase (IDH) 1 mutation R132H were performed under standard conditions. Further, Ki-67 proliferation index was determined for all samples. The MGMT promoter methylation status was analyzed by methylation-specific polymerase chain reaction from formalin-fixed paraffin-embedded tissue as previously described [20].

2.4. Nucleic acid isolation and aCGH

Extraction of high molecular weight DNA from frozen tumor samples was carried out as previously described [21,22]. aCGH was carried out as reported before [23,24]. Selection of genomic clones, isolation of bacterial artificial chromosome DNA, performance of degenerated oligonucleotide primer polymerase chain reaction, preparation of microarrays, labeling, hybridization, and washing procedures were performed as stated elsewhere [23,24].

3. Results

3.1. Clinical report

Approval for the acquisition and use of patient data and material was obtained from the Ethics Committee of the University Hospital in Mannheim, Germany where the patient was treated. The patient gave an informed consent for all procedures and investigations performed.

A 64-year-old woman presented clinically with headache. Neuroimaging demonstrated a 3 × 2 cm ring-enhancing lesion (Fig. 1). Gross total tumor resection was achieved via craniotomy. The initial tumor showed a biphasic tissue pattern with alternating areas of glial and mesenchymal differentiation with histological characteristics for HGG including necrosis, high cell proliferation, and pathological vessels, with a Ki-67 proliferation index of about 20%. Immunohistochemical staining for GFAP was positive whereas IDH-1 R132H was negative (Fig. 2). MGMT promoter methylation status was also negative. This led to the initial diagnosis of glioblastoma with a sarcomatous component. Post-surgical management was commenced with standard radiotherapy (RT) and concomitant TMZ CT. This had to be interrupted due to wound healing disorders, requiring several surgical procedures for local wound revision. At the fourth revision a titanium mesh cranioplasty was implanted. Having paused for 2 months, the adjuvant therapy with TMZ was resumed. The patient presented during this whole period in a very good clinical condition; her Karnofsky Performance Status (KPS) score was 100. Hence, upon local tumor recurrence after a period of 9 months, cranial re-operation was performed. Mesenchymal differentiation predominated over the glial aspects in the recurrent cranial tumor, contrasting with the more balanced initial biphasic pattern seen in the primary tumor (Fig. 2). This supported the GS diagnosis. Thereafter, standard post-RT TMZ was prescribed for 5 days every month and the local tumor region was stereotactically irradiated. Radiographic tumor progression was seen 2 months after stereotactic RT, leading to a change of CT regime to TMZ 250 mg/day. Unfortunately, the patient presented 18 months after initial cranial glioblastoma diagnosis with lower limb neurological deficits of paresthesia and paralysis. On emergency diagnosis of a thoracic mass at level T10/T11 with accompanying spinal cord compression, surgical resection and spinal cord decompression was performed immediately. Histological analysis now showed almost complete loss of the glial tumor components of the tumor (Fig. 2). Stereotactic RT with 50 Gy to T9–T12 was initiated. Due to local tumor recurrence after only 30 days of ongoing RT (having received 14 Gy), spinal cord decompression was again necessary. However, there was no evidence of infectious or tumor cells in the cerebrospinal fluid examinations performed at the two spinal surgeries.

At this time, cranial MRI showed no signs of tumor progression, with no enhancing lesions on either post-contrast T1-weighted or FLAIR sequences (Fig. 1). The clinical condition of the patient had declined; she presented with a KPS of 70. HP analysis of the recurrent spinal tumor mainly depicted characteristics of sarcoma, with a total loss of the glial differentiation (Fig. 2). Salvage CT with bevacizumab and irinotecan was implemented, without success. There was tumor progression and recurrence at the spinal and cerebral sites, respectively. Analogous to sarcoma therapy, CT with doxorubicin was performed, but to no avail. At further clinical deterioration (KPS 40), no further specific cancer therapy was undertaken. The patient died within 8 months after initial spinal dissemination detection and at an overall survival of 23 months.