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Case Report

A New Sarcoma Shortly after Treatment for High-Grade Glioma with Adjuvant Chemoradiation: A Case Report

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Keywords
Sarcoma · High-grade glioma · Glioblastoma · Radiation · Complication · Secondary cancer

Abstract

Introduction: High-grade gliomas are central nervous system tumors conventionally treated with surgery followed by adjuvant chemoradiotherapy. Secondary cancer due to radiation therapy is a rare yet established phenomenon that typically occurs years after radiation therapy. ***Case Presentation:*** In this case, we discuss an early presentation of a second cancer adjacent to the radiation field. This case report is of a 52-year-old male who developed a new scalp sarcoma at the site of primary surgery 8 months after radiation therapy. Genetic testing revealed a heterozygous missense variant in the *NF1* gene, a variant of uncertain significance. The report highlights that this case does not conform to the expected criteria for postradiation sarcoma in terms of timing. ***Conclusion:*** Secondary cancers may arise earlier than expected, even in phenotypically normal patients, as they may have unmanifested variants of relevant mutations. The question of pre-radiotherapy screening for radiosensitivity syndromes and diseases requires further study, as current data are limited and do not provide enough insight into the significance of different genetic variants.

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Introduction

Gliomas are central nervous system tumors with histologic features similar to normal glial cells, from which they derive their names. Gliomas are classified according to the World Health Organization (WHO) Classification of Central Nervous System Tumors, revised in 2021 [1].

Tumors arising from precursor or glial cells known as gliomas account for up to 85% of all primary malignant brain tumors [2]. High-grade gliomas include grade 3 tumors (e.g., astrocytoma, oligodendroglioma, and oligoastrocytoma) and grade 4 tumors (e.g., glioblastoma [GBM]) based on their WHO classification [1]. GBM is often treated with maximal safe surgical resection, concurrent chemoradiotherapy, and temozolomide chemotherapy as an adjuvant [3]. Soft tissue sarcomas (STSs) are a rare group of tumors that can develop in any tissue composed of connective tissue, such as muscle, fat, cartilage, nerves, and blood vessels. There are many types of STS, each with a unique clinical presentation, molecular profile, treatment response, and prognosis [4].

The risk of developing a radiation-associated sarcoma is estimated to be very low, at less than 1% in exposed adult populations [5]. Radiation-induced sarcomas (RIS) typically develop many years after radiation therapy. The median time between radiation therapy and diagnosis of an RIS is approximately 12 years [5]. While most develop after 10 years, some have been reported as early as 3 years after radiation therapy [6].

Arlen et al. [7] modified the criteria for diagnosing postradiation sarcoma to distinguish it from primary tumors. The modified criteria included the following: the sarcoma must be located within the radiation field, the sarcoma must be histologically confirmed, the affected tissue must have been normal prior to irradiation, and there must be a latency period of several years between the irradiation and the development of the sarcoma. The latency period is important because it helps rule out the possibility that the sarcoma is a primary tumor that developed independently of radiation therapy. Murray et al. [8] further revised the criteria. The case discussed in the present case study is noteworthy because the patient developed a soft tissue sarcoma in the scalp just 8 months following completion of radiotherapy.

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The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material at https://doi.org/10.1159/000538508. A timeline of the patient's hospital course is illustrated in Figure 1. A 52-year-old male presented with a 2-week history of new-onset headache associated with bilateral blurry vision. He described the headache as a sudden bilateral pain in the temporal region. The headache was severe in intensity and was relieved slightly by over-the-counter analgesics. He denied any history of fever, trauma, syncope, seizure, diaphoresis, facial asymmetry, slurred speech, dizziness, or weakness. The patient was healthy and had no history of surgery or smoking. His parents were first cousins. The patient's brother had died from gastric cancer, and his parental cousin had a history of gastrointestinal cancer. The patient had four healthy children.

The patient was vitally stable, alert, and oriented at the initial assessment, with a Glasgow Coma Scale score of 15/15. The pupils were 3 mm and reactive bilaterally. Extraocular muscle movements were intact with no nystagmus. However, visual field examination revealed a slight decrease in the temporal field of the right eye, with intact remaining fields. The patient reported an increase in headache when the right eye was examined.

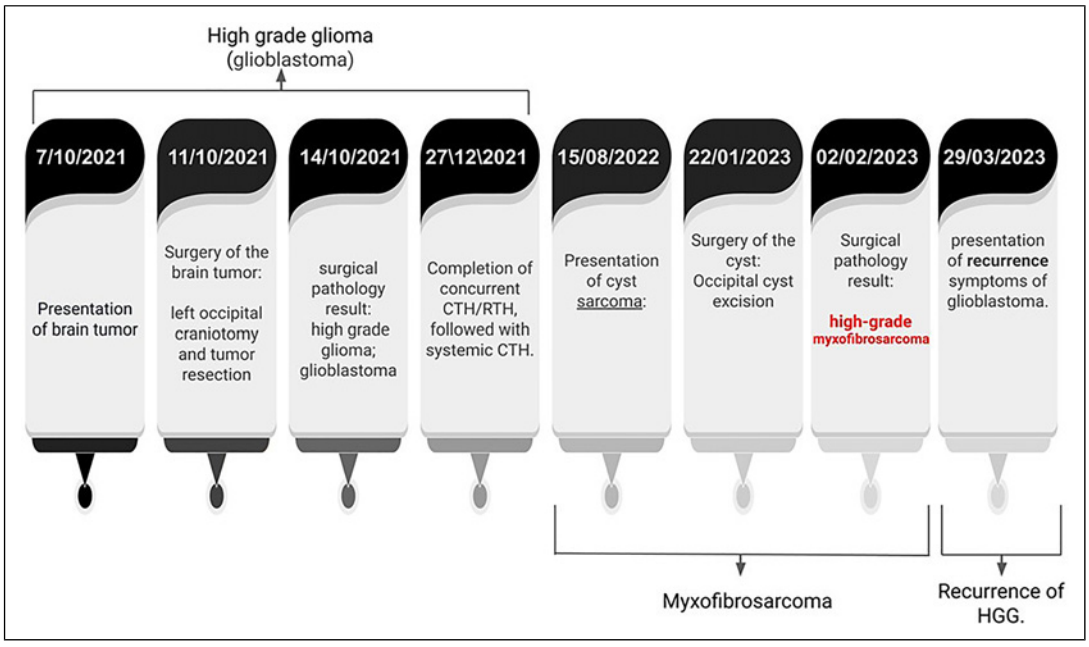

Fig. 1. Timeline of the case.

As part of a full neurological exam, cranial nerve examination showed that CN-5 sensation was decreased on the right side in all three divisions. The examination of the other cranial nerves was intact. The motor examination revealed power in lower limb extension as 4+, and power in other limbs was 5/5. Sensation was intact in all limbs, and reflexes were 2+.

Brain magnetic resonance imaging (MRI) was performed, which revealed a heterogeneously enhancing mass in the left occipital lobe cortical base, measuring 2.8 × 2.5 × 2.2 cm in craniocaudal, anterior-posterior, and transverse diameters, respectively, with disproportionate vasogenic edema and mass effect (Fig. 2a, b). The patient underwent a left occipital craniotomy and tumor resection. The pathology report revealed a high-grade glioma (Fig. 3a, b). Histopathologic examination revealed markedly cellular glial neoplasm, with prominent nuclear pleomorphism, hyperchromatic nuclei, irregular nuclear membranes, and a variety of neoplastic cell patterns. The latter included gemistocytes and spindle, round, and small cells. Geographic necrotic foci were multiple. Immunohistochemistry (IHC) for glial fibrillary acidic protein (Fig. 3c) was strongly positive in the tumor cells. The Ki-67 proliferative index was increased in multiple tumor foci (Fig. 3d).

The mitoses count was variable, measuring in areas up to 5 figures/high-power field. Microvascular proliferation was identified. Ki-67 proliferative index was 25%. IHC for IDH1 R132H was positive, and P53 showed a wild-type reactivity pattern (scattered nuclear staining). IHC for IDH1 and FISH for 1p\19q were negative. Hence, the tumor was classified as GBM, IDH wild-type. For 2021 classification, this can be classified as high-grade glioma, not otherwise specified. The patient received concurrent chemo-radiotherapy with temozolomide and radiation therapy (60 Gy in 30 fractions using volumetric modulated arc therapy, Fig. 2c, d) to the surgical bed and surrounding brain tissue, as per standard radiation oncology protocols for high-grade gliomas, followed by adjuvant chemotherapy.

The patient was followed up regularly with MRI scans, which showed no evidence of recurrent disease. However, 8 months after completion of radiation therapy, the patient presented with left-sided scalp numbness and “fluid-filled” painful swelling at the previous surgical site.

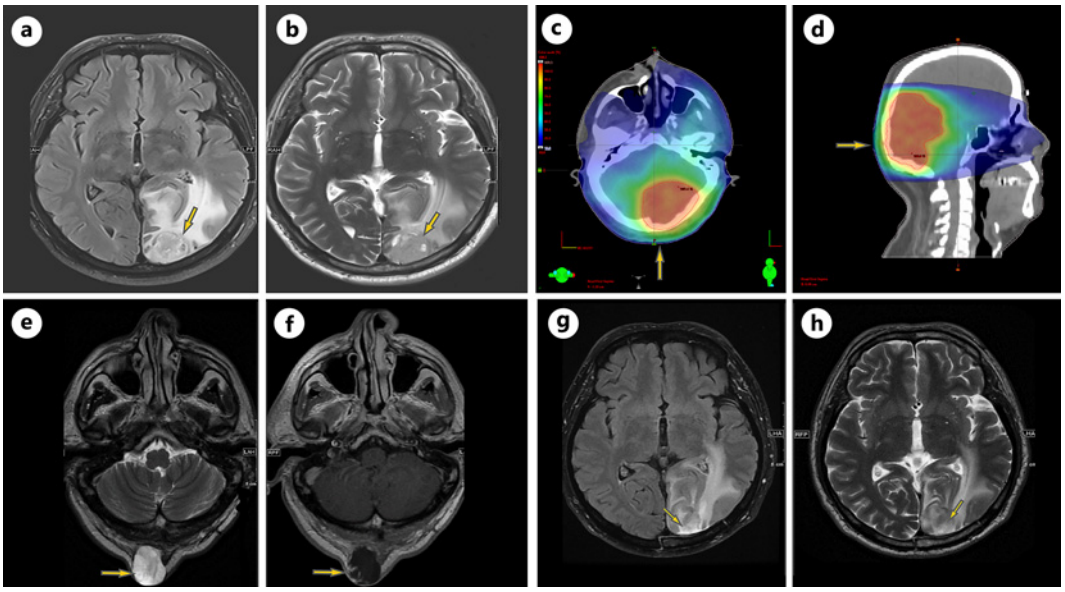

Fig. 2. Axial FLAIR (**a**) and T2WI (**b**) images show a heterogenous left occipital lobe cortical base intra-axial mass that is predominantly high on T2WI. **c**, **d** Radiotherapy plan for high-grade glioma, showing the dose to the what later became an STS. **e**, **f** Interval development of extracranial suboccipital mass demonstrates heterogeneous high-signal intensity on T2 and peripheral enhancement and nodularity on post-contrast T1WI. **g**, **h** Interval progression of the recurrent high-grade left occipital tumor on FLAIR and T2WI.

Physical examination findings showed a 5.5 × 5.5 cm immobile, non-tender occipital cystic mass with a soft consistency. A computerized tomography scan revealed a left occipital hypodensity at the surgical bed; 3 × 2.3 × 2.3 cm, a well-defined occipital/suboccipital with clear fluid collection of cerebrospinal fluid density seen just below the previous inferior-medial occipital craniotomy. A brain MRI revealed there was no associated diffusion restriction to suggest abscess formation, and although there were stable left occipital postsurgical changes without evidence of tumor recurrence, the development of extracranial suboccipital mass demonstrates heterogeneous high-signal intensity on T2 and peripheral enhancement and nodularity on post-contrast T1 (Fig. 2e, f). The patient underwent a re-excision of the lesion after the histopathology confirmed the neoplastic nature of the mass. Physical examination for neurofibromas, café-au-lait macules, and other features was negative.

Histopathological examination revealed a high-grade myxofibrosarcoma. The tumor showed a multinodular growth pattern with scattered fibrous septa. The background was predominantly myxoid, with scattered elongated blood vessels. The tumor cells were arranged in short fascicles and exhibited large hyperchromatic nuclei, irregular nuclear membranes, high mitotic activity (including atypical mitotic figures), and foci of necrosis (Fig. 3e, f). The immunohistochemistry studies showed that the tumor cells were negative for pan-CK (AE1/AE3), SMA, *DESMIN*, *CD34*, S100, *synaptophysin*, glial fibrillary acidic protein (Fig. 3g), and Neu-N. Ki-67 proliferation index was markedly high (~50%) (Fig. 3h). This histomorphology and immunohistochemistry were consistent with high-grade myxofibrosarcoma. FDG-18 PET-CT was done, and no other masses were identified.

During routine follow-up, the patient was found to have GBM progression and recurrence in February and March 2023. The patient presented with slurred speech, generalized weakness, visual disturbance, and dizziness. MRI findings revealed an interval progression of the recurrent high-grade left occipital tumor (Fig. 2g, h).

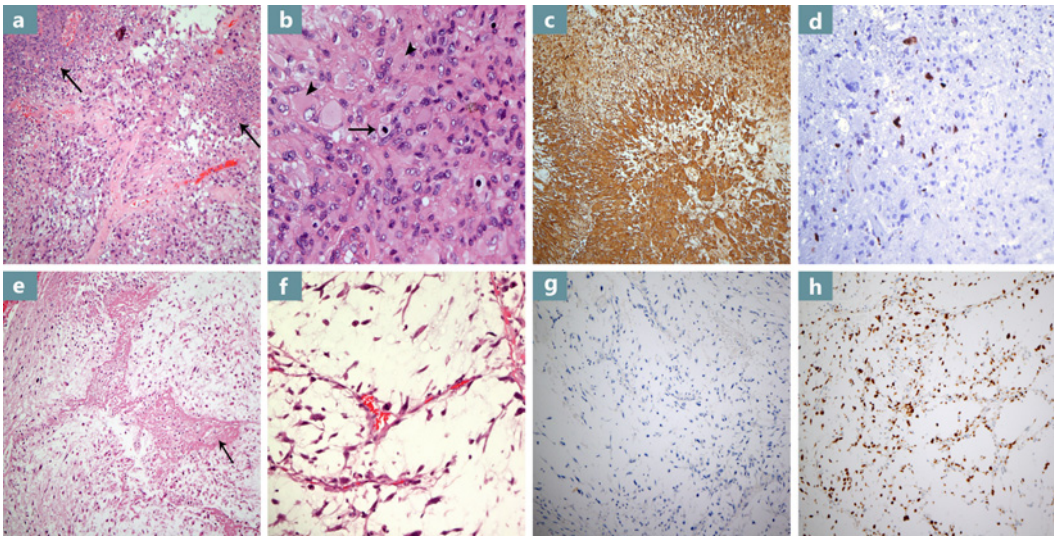

Fig. 3. **a** The first tumor is a hypercellular astrocytic neoplasm that exhibits hyperchromatic, pleomorphic, and irregular nuclei. The tumor cells show infiltration of the brain tissue with scattered foci of necrosis (arrows, H&E. ×100). **b** This malignant glioma exhibits many gemistocytic cells with abundant eosinophilic cytoplasm (arrowheads) and easily detectable mitoses (arrow, H&E. ×400). **c** GFAP immunohistochemical study highlights the tumor cells (GFAP, ×400). **d** The Ki-67 proliferative index is increased in multiple tumor areas (Ki-67, ×100). **e** The second tumor is a soft tissue neoplasm with cellular and hypocellular areas, abundant myxoid background, and areas of necrosis (arrows). The cells are pleomorphic and exhibit round-to-spindle, hyperchromatic, and atypical nuclei (H&E. ×100). **f** A High-power view of the tumor shows a rich myxoid stroma and elongated curvilinear thin blood vessels and has easily detectable mitoses (H&E. ×200). **g** GFAP immunohistochemical study is negative (GFAP, ×100). **h** This tumor's Ki-67 proliferative index is markedly high (Ki-67, ×100).

The patient underwent a second surgery, a left occipital craniotomy, and tumor resection. The case was presented to a tumor board that discussed the patient's case and recommended close observation without immediate radiotherapy or additional chemotherapy. However, it was agreed that chemotherapy would be further discussed.

After the STS diagnosis, WES was sent for to assess for hereditary predisposition conditions, which was carried out on a blood sample and came back with a heterozygous missense variant in *NF1*. This was classified as a variant of uncertain significance per American College of Medical Genetics and Genomics guidelines [9].

Discussion

Incidence is in the range of 0.03–0.2% at 10 years. RIS incidence can be 40% higher when compared to the general population [10]. Occurrence is related to multiple factors, such as the cumulative dose of ionizing radiation, the patient's age at initiation of treatment, total exposure time, time since exposure, and genetic factors [11].

Although RIS is attributable to radiation exposure, it is not readily distinguishable from spontaneous tumors. Behjati et al. [12] demonstrated identifying two signatures of ionizing radiation [12], but their used method is not accessible to our institution. Treatment for RIS depends on the size and grade of the tumor; however, the main modality of treatment consists of surgical resection, and in some reports, less than 1 third of patients received chemotherapy or radiotherapy [13].

The prognosis for RIS is variable. However, the overall survival rate for RIS is less than 35% at 5 years. Patients with low-grade tumors and those with complete surgical resection of the tumor have improved prognosis [14].

The present case study demonstrates an extremely rare case: a second cancer less than a year following radiation exposure. The patient's genetic whole exome sequencing analysis revealed a heterozygous missense variant in *NF1*. Germline variation in the *NF1* gene is associated with multiple phenotypes: juvenile myelomonocytic leukemia (#OMIM: 607785), familial spinal neurofibromatosis (#OMIM: 162210), neurofibromatosis type 1 (*NF1*) (#OMIM: 162200), neurofibromatosis-Noonan syndrome (#OMIM: 601321), and Watson syndrome (#OMIM: 193520). *NF1* is an autosomal dominant disorder characterized by cafe-au-lait spots, Lisch nodules in the eye, and fibromatous skin tumors. Individuals with the disorder have increased susceptibility to developing benign and malignant tumors, such as glioma, malignant peripheral nerve sheath tumors, and undifferentiated pleomorphic sarcoma [15]. In the present case study, and as described earlier, the patient had no morphological findings or indications in the clinical history or a family history supportive of *NF1*.

Conclusion

This case report highlights the potential complications of radiation related to duration and site specificity. In our case, a myxofibrosarcoma diagnosed as early as 8 months after treatment conflicts with the generally accepted understanding that cancer is a late complication of radiation. The myxofibrosarcoma developed in the scalp at the surgical site after primary surgery and concomitant treatment of GBM. The patient had no phenotypic signs or symptoms of *NF1*. Further testing for signatures of ionizing radiation could be helpful in asserting the relationship between the sarcoma and the radiation therapy given to the brain tumor. However, this may have little impact on the prognosis of the patient. Advanced, fast genetic testing for possible radiation-sensitive diseases could help guide the management of patients, but its benefit remains in question, as some variants are of uncertain significance with currently available data.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

Abdossalam M. Madkhali put together the general structure, managed the writing, oversaw the development of the manuscript, wrote the abstract, and carried out the final reviewing and editing prior to submission. Mohammed H. Alnajeim wrote the manuscript, made edits and changes, and constructed the medical history from the patient's record. Hasah F.F Alaluan wrote the manuscript, made edits and changes, and created figures. Eyad F. Al Saeed reviewed the manuscript and was the patient's primary radiation oncologist. Abdulrazag M. Ajlan reviewed the manuscript and provided technical insight. Ahmed Abdelwarith reviewed the manuscript and is the primary oncologist for the patient. Ali Abduh conducted a radiological review of the case and provided the radiological images and captions. Saleh Albanyan reviewed the manuscript and contributed pertinent sections to the genetic testing sections. He was the geneticist on the case. Ashwag Alqurashi reviewed the manuscript and was the primary neurosurgeon for the patient's initial presentation. Hisham Alkhalidi reviewed the manuscript, contributed to the pathology section, conducted a pathology review of the case, and provided the needed images and captions.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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