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Authors

Majd, Pejman

O'Connell, Daniel E

Kim, Ronald C

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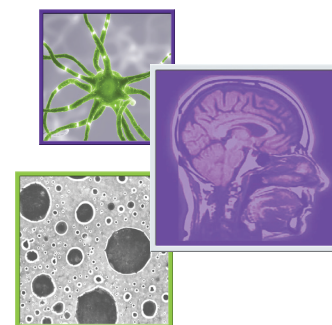
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Case of glioblastoma patient treated with tumor treating fields therapy at recurrence degenerating to sarcoma

Pejman Majd¹, Daniel E O'Connell², Ronald C Kim², Daniela A Bota² & Jose A Carrillo^{*2}

Practice points

- Optune® system (Novocure Ltd.) is a US FDA approved treatment strategy for glioblastoma (GBM) that emits alternating electrical fields or tumor treating fields (TTF).
- TTF in the kilohertz range results in cytoskeleton disruption by exerting its effects on GBM via cell cycle mitosis disruption and cytokinesis.
- We describe a patient with recurrent GBM who had disease progression following initial standard surgical treatment and concomitant chemoradiotherapy.
- After initiation of TTF electrical device therapy with bevacizumab, the patient's GBM was found to have sarcomatous transformation.
- GSM progressing into pure sarcomas of the central nervous system is exceptionally rare.
- Upon tumor progression, the patient underwent surgical resection that revealed transformation into a GFAP-negative, reticulin-positive sarcoma with rhabdomyoid features.
- The possibility of a causal connection between the Optune therapy and sarcomatous transformation needs to be further evaluated.
- No such case of apparent sarcoma formation in the CNS following chemoradiotherapy and/or electrical current treatment for GBM has been reported in the literature.

Optune® treatment is a US FDA-approved treatment for glioblastoma (GBM) that employs alternating electric fields. Tumor treating field (TTF) therapy can exert its effects on GBM via cell cycle mitosis disruption and cytokinesis. We describe a patient with recurrent GBM who had disease progression following standard surgical treatment and concomitant chemoradiotherapy, and was found to have sarcomatous transformation after initiation of TTF therapy with bevacizumab. Upon tumor progression, repeat surgical resection revealed transformation into a GFAP-negative, reticulin-positive sarcoma with rhabdomyoid features. The possibility of a causal connection between TTF therapy and sarcomatous transformation needs to be further evaluated. No such case of apparent sarcoma formation in the CNS following chemoradiotherapy and/or TTF treatment for GBM has been reported.

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¹University of California, Irvine School of Medicine, 1001 Health Sciences Rd, Irvine, CA 92617

²University of California, Irvine Medical Center, 200 S. Manchester Ave, Suite 206, Orange, CA 92868, USA

*Author for correspondence: Tel.: +1 714 456 7214; Fax: +1 714 456 6894; Carrilj2@hs.uci.edu

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• Optune® • recurrence
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Intermediate-frequency, low-intensity alternating electrical fields selectively eliminate or arrest the growth of rapidly dividing cancer cells by inhibiting the proper formation of the mitotic spindle and causing rapid membrane breakdown during cytokinesis [1]. The physical and electrical properties of cancer cells differ from cells that proliferate normally; cancer cells exhibit a lower membrane electrical potential compared with normal proliferating cells and increased membrane fluidity affecting ease of deformation [2]. The Optune® System (Novocure Ltd.) is an approved anti-mitotic nonionizing radiation treatment for patients with recurrent glioblastoma (GBM). GBMs are highly malignant and currently the most common primary brain tumor in adults. They generally follow with a poor prognosis with a mean survival time of 6–12 months following diagnosis [3]. Established standard of care is radiotherapy plus concomitant and adjuvant temozolomide [4]. Tumor treating field (TTF) has been shown to treat GBM by emitting alternating electric fields in the kilohertz range. The cancer cells are subject to alternating electric fields in the frequency of 100–250 kHz resulting in cytoskeleton disruption, specifically during mitosis in the metaphase-to-anaphase transition. These cells then undergo a phase of violent blebbing followed by asymmetric chromosome segregation.

This process causes aneuploidy, which ultimately results in cell apoptosis.

Gliosarcoma (GSM), a malignant neoplasm containing morphologic features of both GBM and sarcoma, was first described by Strobe in 1895 but did not gain recognition until 1955 when Feigin and Gross reported in detail on three patients with this malignancy [5]. Previous studies by Feigin *et al.* [5,6] and Rubinstein [7,8] have recorded an occurrence of mixed GBM and sarcoma, or GSM. The WHO defines GSM as a rare variant of GBM showing biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation [9]. It is particularly difficult to distinguish between GBM and GSM, often requiring further exploration of the mesenchymal elements in the tumors [10]. Macroscopically, a boundary between the glial and sarcomatous components is not observed; distinction requires microscopic examination. Due to its low occurrence and small patient numbers, reports in the literature are overall limited; however, Han *et al.* have identified several pathological markers that attempt to distinguish GSM from GBM [11]. The malignant mesenchymal component of GSM can include cartilaginous, osseous, myoblastic and lipomatous elements not present in the glial component, or in GBM. The glial and mesenchymal elements can be truly intermingled or distinctly separable [12]. To date, there is no consensus as to how much of a mesenchymal component would qualify a neoplasm as GSM [13] and no minimal histologic criterion defined for how much atypical mesenchymal spindle cell proliferation needs to be present to classify sarcoma [14].

Despite their different characteristics, GSM is typically managed like GBM; surgical resection followed by adjuvant radiotherapy. GSM has similar survival characteristics (6–14.8 months) [15] although there have been reported cases with long survival up to 22 years [15]. GSM progressing into pure sarcomas of the central nervous system are exceptionally rare and most CNS sarcomas show fibrous, 'fibrohistiocytic', or indeterminate differentiation. While the prognosis for high-grade sarcomas seems more favorable than that of GBM, with a 28% survival rate of 5 years for high grade sarcomas reported in one case series [16], the 5-year actuarial disease-free survival in irradiation-induced sarcoma patients is even more promising at 60% [17]. We here present a case of a 35-year-old female who presented with a right superior medial temporal lobe and parietal lobe

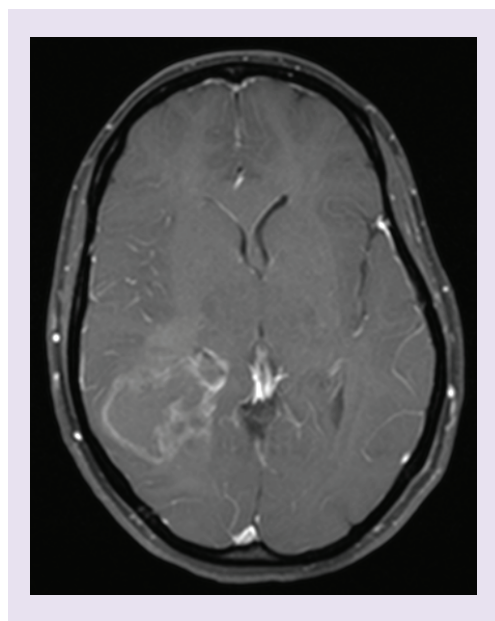


Figure 1. Pre-operative MRI T1 axial with gadolinium contrast. MRI showing typical contrast enhancement pattern in GBM prior to surgery.

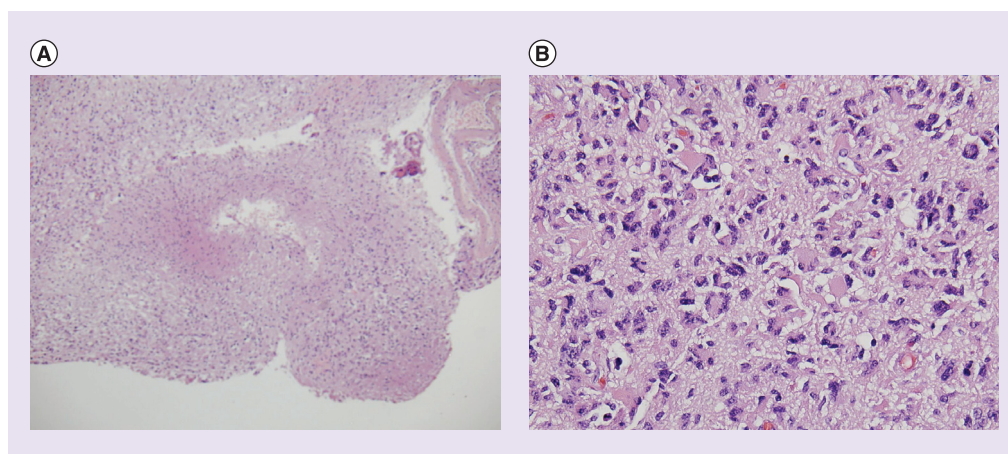


Figure 2. (A) Necrosis with pseudopalisading, Hematoxylin and eosin (H&E) stain at 10x. (B) Pink astrocyte, H&E stain at 40x.

mass consistent with GBM (WHO grade IV) and after the third recurrence showed evidence of transformation to a sarcoma with rhabdomyoid features, without any GSM component.

Case presentation

A 35-year-old female patient initially presented with bilateral hand numbness and persistent nausea. She subsequently underwent imaging which revealed a complex superior medial temporal lobe mass extending posteriorly (Figure 1). The mass was a heterogeneous with a nonenhancing component and an irregular necrotic cystic area with prominent surrounding contrast enhancement.

The patient then underwent a right temporo-parietal craniotomy with evacuation of the necrotic and cystic area of the tumor. After tumor resection, pathological examination of the tumor confirmed the diagnosis of GBM (Figure 2). Subsequent to surgery, chemoradiotherapy was initiated consisting of radiation with concurrent temozolomide.

During the midst of concomitant chemoradiotherapy, she developed severe headache, nausea and vomiting. Repeat MRI showed that the residual solid tumor component area progressed into an irregularly enhancing and necrotic 3.9 × 3.1 cm mass with more mass effect and increased surrounding vasogenic edema. Surgical re-exploration was carried out by a right fronto-parietal craniotomy with further tumor resection, and the patient subsequently resumed concurrent radiotherapy with temozolomide in 12 fractions at 2.5 Gy per fraction (30 Gy total). The patient went on to complete radiation

therapy totaling 75 Gy and had completed two cycles of adjuvant temozolomide before she developed radiographic progressive of disease per 2010 RANO criteria [18] and was subsequently started on bevacizumab/irinotecan.

Five months after initial diagnosis, the patient developed recurrence again and a therapy regimen of one cycle of carboplatin as well as bevacizumab was initiated and also began treatment with the TTF system [19]. The patient

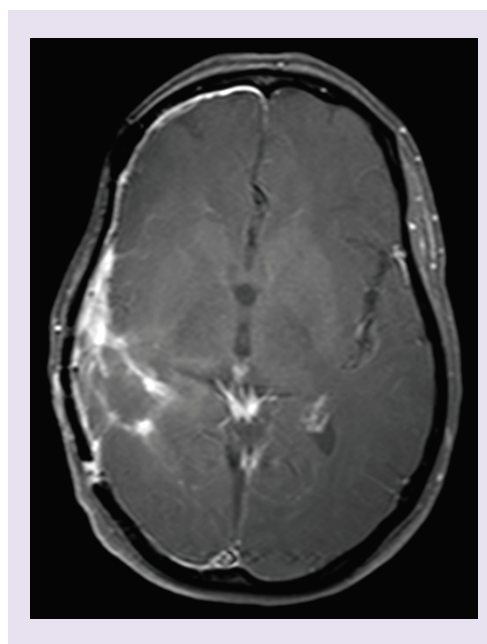


Figure 3. T1 axial with gadolinium contrast showing right temporo-parietal progression with dural involvement. MRI with enhancing progression with new dural extension of disease.

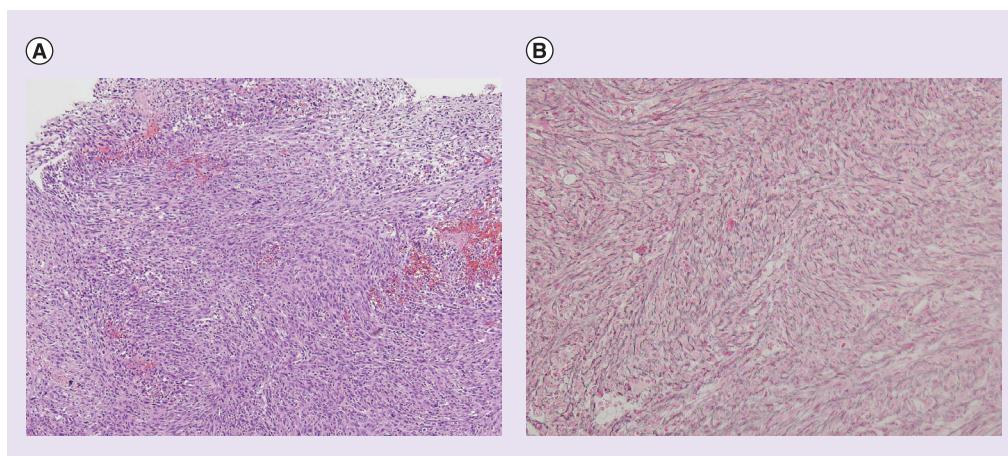


Figure 4. (A) H&E stain at 10x. (B) Reticulin stain at 10x.

continued to show changes on neuroimaging with progression in her right temporal lobe and temporo-parietal junction (Figure 3).

A decision was made to continue with re-exploration via right frontotemporal craniotomy for resection of areas of suspected GBM recurrence. Postoperatively, pathological evaluation of the suspected GBM tumor revealed transformation from a malignant glioma to a sarcoma with rhabdomyoid features (Figure 4). This neoplasm was histologically different in that the tumor resected from the first procedure, which stained diffusely for GFAP, while this tumor was clearly negative for GFAP (Figure 5).

The GFAP stain is a useful marker for glial cells however it is not present in mesenchymal cells. We subsequently found that the stains for CD31 and CD34 were negative in the sarcomatous region with a strong positive reaction to desmin. As per a previously described sarcoma treatment regimen by Arndt *et al.* [20],

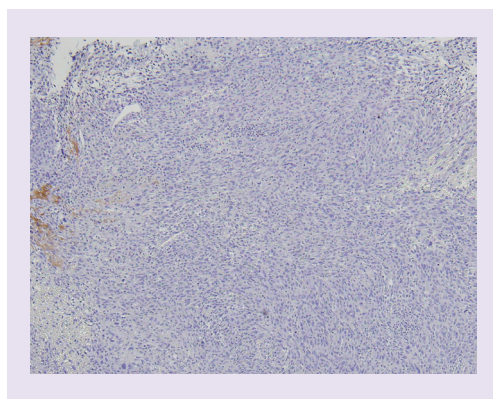


Figure 5. GFAP Immunohistochemistry stain at 10x.

the patient underwent chemotherapy with cyclophosphamide, vincristine, doxorubicin and bevacizumab.

Discussion

Here, we describe the case of a patient with GBM (WHO grade IV) which, after subsequent chemoradiotherapy and surgical resection, progressed and transformed into a sarcoma with rhabdomyoid features, and not a GSM. Initial clinical symptoms presented by the patient were consistent with GBM. The current study goes beyond previous reports and presents the first case of GBM with complete transformation to an undifferentiated sarcoma with rhabdomyoid features.

The exact mechanism that causes the malignant transformation of GBM into sarcoma remains controversial. In the past, the generally accepted theory, the monoclonal origin hypothesis, has been based on immunohistochemical studies that sarcoma develops due to the induction of malignant transformation by one of the components of the hyperplastic blood vessels' endothelium within the GBM, astrocytic elements themselves or fibrohistiocytic cells [10]. Smooth muscle actin reactivity in sarcomatous areas also suggests potential histogenesis in some tumors from the smooth muscle within GBM. Recently, a study by Ohgaki *et al.* has contested the vascular origin of the sarcoma and proposed that the sarcomatous portion results from dedifferentiation within a pre-existing glioma with secondary loss of GFAP positivity and acquisition of mesenchymal characteristics [21]. This is otherwise known as the polyclonal hypothesis. It proposes that glial and sarcomatous lineages develop independently with sarcoma arising

from dedifferentiated vascular adventitia or pluripotent glial cells surviving radiotherapy.

Retrospective analysis has demonstrated significant intratumoral cytogenetic heterogeneity in GBM that could lead to varying survivability [22]. Heterogeneous cancer cells with sizes and shapes outside the typical GBM range may have increased potential to survive radiotherapy and proliferate, pluripotent or not. Recent studies have demonstrated *in vivo* that some differentiated GBM tumor cells may have the ability to dedifferentiate and acquire a stem-like phenotype ('plasticity') in response to microenvironmental stressors such as hypoxia, radiation therapy or temozolomide administration [23]. Although ionizing radiation was studied in these reports, data highlight the existence of a new mechanism of radio resistance in GBM cells through a cellular adaptation of the surviving cancer cells after treatment leading to a stem-like state. Radio-resistant GBM cell subpopulations abundantly express CD133, CD117, CD71 and CD45 surface markers with the capacity for extensive proliferation, self-renewal and pluripotency [24].

GBM is a genetically unstable tumor that has dedifferentiated components with different responses to differing treatment modalities. Our case is also unique due to the fact that our patient was wearing the TTF device leading up to the transformation. It remains possible that the sarcomatous components of GSM grow and

come to dominate the tumor entirely and our case lacks the evidence, although more than plausible, of a GSM intermediary. It is also possible that TTF are disrupting a disproportionate number of glial cells while having less of an effect upon mesenchymal cells that persist as the bulk of tumor burden. The differential effects of TTF at the various cancer cell subtypes mandate further study.

Conclusion

We provide the first case of early transformation from glioblastoma directly to rhabdomyoid sarcoma, without gliosarcoma component on histopathology, after use with NovoTTF therapy.

Financial & competing interests disclosure

JA Carrillo is a consultant for NovoCure. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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