



Case Report

Drug-resistant high grade glioma-related epilepsy surgery for focal motor status epilepticus localized by CT-PET imaging

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ARTICLE INFO

Article history:

Received 2 June 2021

Revised 5 September 2021

Accepted 8 September 2021

Available online 15 September 2021

Keywords:

Epilepsy surgery

Glioblastoma

FDG-PET

ABSTRACT

Tumor-related epilepsy is a frequent complication of glioblastoma with seizures often representing the first manifestation of the malignancy. Though tumor resection is associated with improved seizure control, extensive surgery is not always feasible if eloquent cortex is involved in seizure generation and early propagation. We describe a case of a patient with glioblastoma with drug-resistant focal status epilepticus where fluorodeoxyglucose positron emission tomography imaging was successfully used to localize the seizure-onset and optimize tumor resection. This led to successful resection of hypermetabolic tumor tissue and resolution of focal status epilepticus without damage to eloquent cortex.

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1. Introduction

Seizures are a frequent complication of primary and metastatic brain tumors with up to 80% of patients with primary brain tumors and up to 24% of patients with brain metastases experiencing at least one seizure during the course of their illness [1–3]. Seizure incidence varies depending on factors such as tumor histology, location, and size [4,5]. Incidence of seizures is estimated as 30–62% in patients with glioblastoma multiforme (GBM) [1,6,7]. While most patients with brain tumor-related epilepsy (BRE) are successfully managed with antiseizure medications, drug-resistant epilepsy can occur in the setting of high-grade and low-grade glioma [6,7]. Surgical resection can be curative in the setting of drug-resistant BRE, but not always possible due to factors such as involvement of eloquent cortex and multifocal tumor [7–9].

Successful surgical resection requires accurate localization of epileptogenic zone and delineation of eloquent cortex, if any. Electroencephalogram (EEG) and magnetic resonance imaging (MRI) representing the most common modalities utilized as part of epilepsy surgery evaluation [8,9]. In addition, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging of brain glucose metabolism is a widely accepted technique for epileptogenic focus localization, identifying areas of focal glucose hypometabolism and assisting in surgical decision-making

[10,11]. Here, we present a case where FDG-PET imaging led to identification of a hypermetabolic focus guiding tumor resection with resolution of focal motor status epilepticus previously resistant to multiple antiseizure medications in a patient with GBM.

2. Case description

A 23-year-old woman presented with a first lifetime tonic-clonic seizure. Upon evaluation, an MRI brain identified a non-enhancing left parietal convexity hyperintensity with associated vasogenic edema, consistent with a glioma (Fig. 1A, 1B). Functional MRI demonstrated tumor predominantly involving primary sensory cortex. Scalp EEG obtained during initial evaluation recorded multiple left temporal onset ictal discharges associated with focal aware (gustatory aura) and focal impaired awareness seizures (gustatory aura → automatisms with loss of awareness). She became seizure-free on combination therapy with lacosamide and levetiracetam. While surgical planning was in progress, the patient developed recurrent fronto-central onset seizures characterized by paraesthesias in the right arm, right side of her face and word finding difficulty (Fig. 2 A). Valproic acid, topiramate and lorazepam were serially added to levetiracetam and lacosamide in an attempt to achieve control. Her language function declined and she became somnolent due to a combination of frequent seizures and multiple antiseizure medications. FDG-PET identified cortical hypermetabolism at the confluence of the posterior portion of the long gyrus of the insula, postcentral gyrus, and

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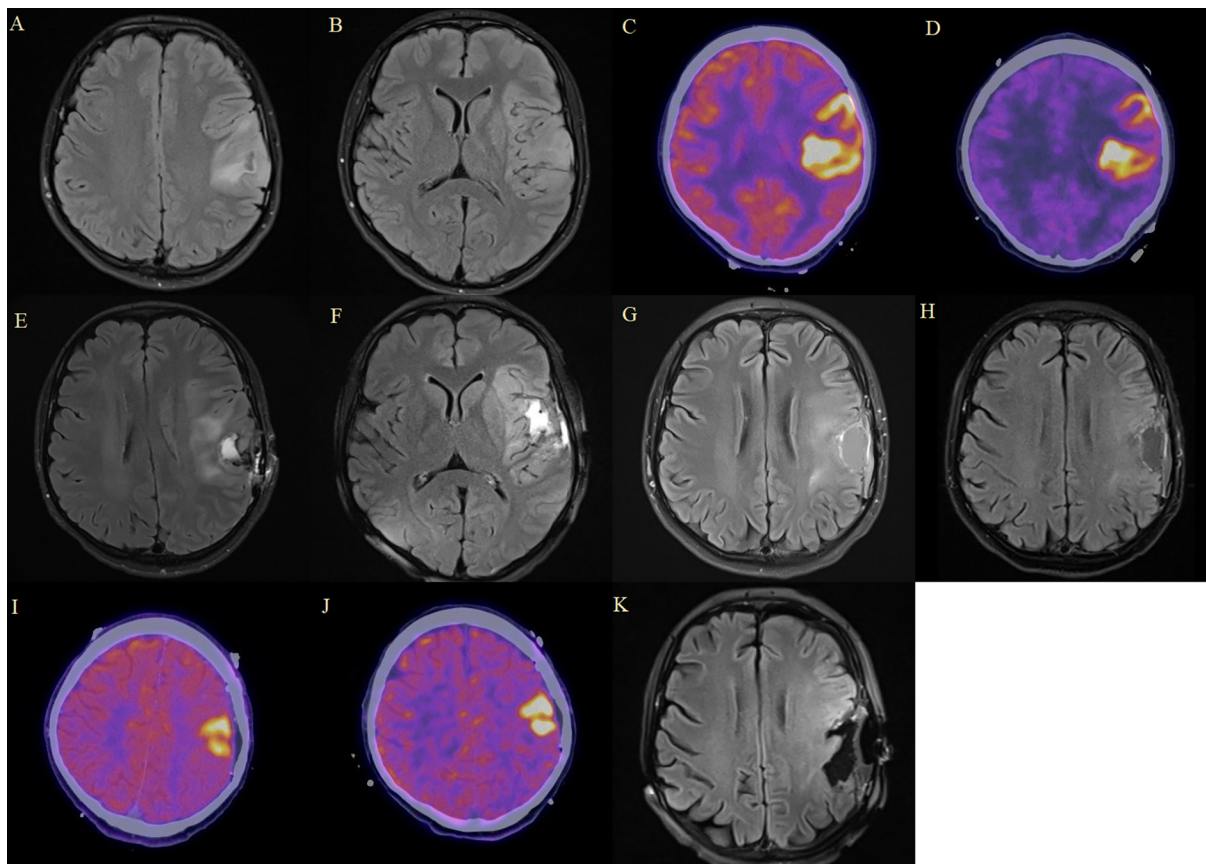


Fig. 1. A: Axial MRI brain T2 FLAIR image demonstrating left parietal convexity hyperintensity with associated vasogenic edema. B: Axial MRI brain T2 FLAIR image demonstrating additional areas of tumor involvement. C: Axial fused FDG:PET CT image demonstrating hypermetabolic region of tumor in setting of increased seizure activity prior to patient's initial surgery. D: Axial fused FDG:PET CT image obtained with 6-hour delay demonstrating persistent hypermetabolic activity prior to initial surgery. E: Post-operative axial MRI brain T2 FLAIR image demonstrating subtotal resection from first part of two-step resection. F: Post-operative axial MRI brain T2 FLAIR image demonstrating additional area of resection from second part of the procedure. G: Axial MRI brain T2 FLAIR image after completion of chemoradiation demonstrating increased hyperintensity in the treatment area. H: Axial MRI brain T2 FLAIR image demonstrating stable hyperintensity despite increased seizure frequency. I: Axial fused FDG:PET CT image demonstrating hypermetabolic region of tumor in setting of increased seizure activity after surgery and completion of chemoradiation. J: Axial fused FDG:PET CT image obtained with 6-hour delay demonstrating persistent hypermetabolic activity in setting of increased seizure activity after surgery and completion of chemoradiation. K: Axial MRI brain T2 FLAIR image demonstrating additional resection for seizure focus.

frontal operculum (Fig. 1C) with persistent FDG uptake at 6-hour delay (Fig. 1D). She underwent craniotomy for a two-part subtotal resection of the tumor with post-operative MRI demonstrating residual non-enhancing left frontoparietal tumor (Fig. 1E, F). The hypermetabolic focus identified on FDG-PET was removed. Due to involvement of eloquent cortex, further resection was not attempted. Awake craniotomy was considered, but patient was not a candidate due to very frequent seizures associated with word-finding difficulty, speech arrest, and baseline aphasia related to tumor. Following subtotal resection, seizure frequency decreased and lorazepam was discontinued. Pathology was consistent with glioblastoma, isocitrate dehydrogenase (*IDH*) wildtype by genetic sequencing, O^6 -methylguanine-DNA methyltransferase (*MGMT*) methylation status indeterminate due to discordant result from two laboratories (Fig. 3). Further molecular profiling of the tumor identified histone H3.3G34R and platelet-derived growth factor receptor alpha (*PDGFRA*) alterations. Patient underwent standard of care radiation therapy with temozolomide chemotherapy as per Stupp protocol [12].

During the course of radiation therapy with concomitant temozolomide chemotherapy, the patient experienced recurrent focal aware seizures characterized by aphasia and right arm and face clonic activity. Addition of clobazam resulted in seizure-freedom for two-months and she successfully completed her radiation therapy with concomitant temozolomide as well as first cycle of adju-

vant temozolomide. Post-radiation therapy MRI brain demonstrated increased FLAIR signal change with no new areas or enhancement or hyperperfusion, consistent with treatment-related changes (Fig. 1G).

Prior to her second cycle of adjuvant chemotherapy, focal aware seizures recurred. These were characterized by aphasia and clonic activity affecting the right side of her face, right arm and leg followed by right arm weakness. These became resistant to various combinations of antiseizure medications. She became sedated, her memory declined and she could no longer participate in physical therapy. Video-EEG recorded brief, stereotyped events characterized by rhythmic movements of the right cheek and forehead with preserved awareness occurring 12–15 times per hour consistent with focal motor status epilepticus (epilepsia partialis continua) (Fig. 2C). There were no associated scalp EEG changes with these brief seizures except rhythmic myogenic artifact over the right hemisphere derivations (Fig. 2B). An MRI brain demonstrated post-operative and post-radiation therapy changes with stable residual tumor volume and no clear evidence of tumor recurrence or progression (Fig. 1H). Repeat functional MRI was attempted, but study was nondiagnostic due to patient's clinical status and inability to participate in paradigm acquisition. However, repeat delayed FDG-PET identified a margin along the posterior medial aspect of the tumor bed with increased FDG perfusion (Fig. 1I) maintained on repeat imaging with six-hour delay (Fig. 1J). FDG uptake at 1

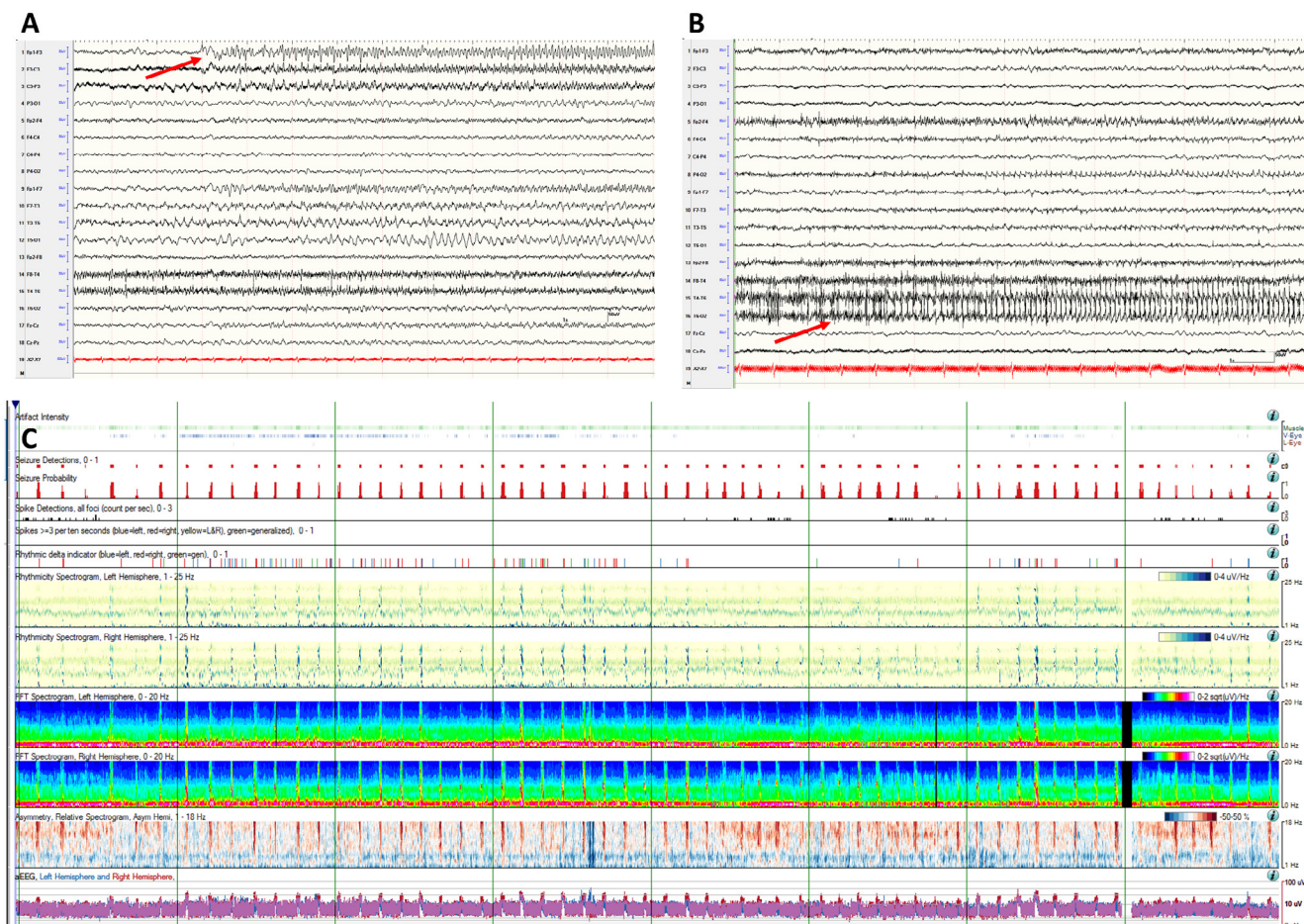


Fig. 2. A. Left fronto-central (F3,C3) onset ictal discharge; rhythmic low voltage beta activity (arrow); Bipolar montage (Sen. 10 μv/mm, LFF 1.6 Hz, HFF 70 Hz) B. Brief focal aware seizures without scalp EEG changes except rhythmic myogenic artifact in the right temporal derivations (arrow) Bipolar montage (Sen. 10 μv/mm, LFF 1.6 Hz, HFF 70 Hz) C. Composite of rhythmicity spectrogram, FFT spectrogram, amplitude averaged EEG over eight hours when patient was in focal motor status (epilepsia partialis continua).

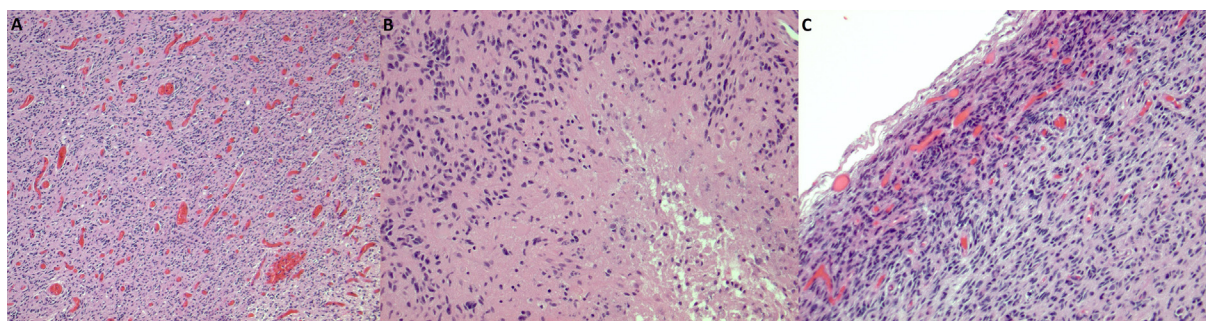


Fig. 3. A. H&E 10x image demonstrating hypercellular tumor with microvascular proliferation; B. H&E 20x image demonstrating area of necrosis; C. H&E 20x image with evidence of subpial tumor infiltration. Findings are consistent with a diagnosis of glioblastoma.

hour was 8.2 SUV max and at 6 hours was 14.0 SUV max. Dynamic analysis showed small margin along the posterior medial aspect of the tumor bed with increased FDG perfusion, representing a new area of hypermetabolism that was not present on the initial PET study. Based on this localization, decision was made to resect the hypermetabolic region in an attempt to resolve the drug-resistant focal motor status epilepticus (Fig. 1K). Post-operatively, patient became seizure-free and her antiseizure medication regimen was simplified from six to three medications (lacosamide, levetiracetam and valproate). Patient’s language function and cognition improved and she was regaining ability to ambulate inde-

pendently. She has since resumed chemotherapy with no reported seizures at follow up one month after repeat surgery.

3. Discussion

BRE is a frequent complication of GBM and complete resection of epileptogenic areas may not be possible due to tumor location [6,7]. H3 mutations in general are frequent in pediatric high-grade gliomas and associated with a dismal prognosis [13]. H3.3G34R alteration in particular is associated with supratentorial tumor location and older age of onset, consistent with characteris-

tics of our patient's tumor [13,14]. *PDGFRA* mutations have been described in up to 50% of H3.3 G34R mutant high-grade gliomas, an alteration also found in our patient's tumor [15]. In general, histone-mutant gliomas are challenging to treat with paucity of proven interventions and disease typically refractory to conventional chemotherapy, immunotherapy, and kinase inhibitors [13]. This case was further complicated by drug resistant seizures in the setting of limited initial resection due to involvement of eloquent cortex and patient's inability to undergo awake craniotomy due to her neurologic status.

After initial sub-total resection of the peri-Rolandic GBM, the patient developed focal motor status epilepticus resistant to several antiseizure medications requiring epilepsy surgery evaluation. While radiation therapy is a noninvasive approach that may target epileptogenic region near eloquent cortex, in this case, patient's seizures worsened during radiation therapy and again in the setting of adjuvant chemotherapy [16]. As such, a precise and minimal resection was crucial as the putative epileptogenic zone was surrounded by eloquent cortex. Typical non-invasive (phase I) pre-surgical modalities utilized in conventional epilepsy surgery including seizure semiology, scalp EEG and MRI brain provided incomplete and discordant data in this case. Seizure semiology pointed to the left mesial temporal and perisylvian region (gustatory aura and face and arm clonic movements) although this was not supported by ictal EEG findings. In fact, there were no scalp EEG changes in association with brief focal aware seizures [17] except rhythmic muscle artifact, which became apparent after clinical onset. While immediate post-radiation therapy MRI demonstrated increase in T2 FLAIR hyperintense areas, serial MRIs did not demonstrate any new areas of enhancement or hyperperfusion consistent with tumor progression. Initial increase in T2 FLAIR signal was therefore consistent with treatment-related changes [18]. PET-CT was left as the only other readily available non-invasive modality to localize the epileptogenic zone. PET-CT has been shown to be effective in localizing non-convulsive seizures and focal status epilepticus due to non-tumor etiology [19–21]. PET-CT is also a well-established non-invasive tool in the phase I pre-surgical workup of non-lesional epilepsy [22]. Typically, in patients with BRE, PET is employed to guide resection as a means to achieve seizure freedom however, if complete resection is not feasible due to surrounding eloquent cortex, like the present case, attempting lesionectomy of the hypermetabolic brain region as suggested by PET can be successfully utilized [10,11,22]. Based on the presented case, we suggest that PET imaging should be considered a diagnostic tool in the workup of select patients with tumoral epilepsy who develop drug resistant seizures or status epilepticus.

4. Limitations

Several limitations of this case report are noted. First, this is a single retrospective case report and findings are not necessarily generalizable. While the case highlights the utility of FDG-PET imaging in localization of seizure focus, it is noted that hypermetabolism secondary to recurrent seizures can be difficult to distinguish from hypermetabolism related to high-grade primary brain tumors or metastatic tumors. In addition, while resection guided by PET imaging led to prolonged seizure freedom in this case, this non-invasive modality may not be able to localize the seizure focus in all cases of BRE and intracranial EEG may be necessary in appropriate cases.

5. Conclusions

This case exemplifies a potential role of FDG-PET in non-invasively localizing the abnormalities in tumor-related focal epi-

lepsy when MRI brain, seizure semiology and scalp EEG are non-diagnostic thus avoiding intracranial (invasive) EEG evaluation. Furthermore, in our patient, PET also allowed successful and precise resection of the seizure focus, which was surrounded by eloquent cortex, and minimized the risk of post-surgical neurological deficits. In select patients with focal motor status due to BRE, FDG-PET imaging may potentially help guide pre-surgical decision making.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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