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Tumor Recurrence or Radionecrosis: A Clinical Dilemma in Long-Term Survivors of Low-Grade Diffuse Glioma With Drug-Resistant Epilepsy

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Abstract

Low-grade diffuse gliomas with isocitrate dehydrogenase (IDH) mutations predominantly affect young adults and are frequently associated with prolonged survival, requiring extended neuro-oncological follow-up. In these patients, differentiating tumor recurrence from radionecrosis after radiotherapy remains a major diagnostic challenge because both entities may present with overlapping clinical manifestations and conventional imaging findings.

We present the case of a 35-year-old man with an IDH-mutant grade 2 astrocytoma located in the left temporo-parieto-insular region who underwent subtotal surgical resection followed by radiotherapy and adjuvant temozolomide. During follow-up, he developed focal drug-resistant structural epilepsy with progressive seizure burden despite multiple antiseizure medications. Serial MRI demonstrated the appearance and interval growth of a nodular enhancing lesion within the frontal operculum adjacent to the surgical cavity, raising concern for tumor recurrence.

Given the diagnostic uncertainty, 18F-fluoroethyl-L-tyrosine positron emission tomography (18F-FET PET) was performed, demonstrating mild and homogeneous amino acid uptake with a tumor-to-background ratio (TBR) of 1.7 and maximum standardized uptake value (SUVmax) of 2.1, findings favoring treatment-related changes and radionecrosis rather than active tumor progression. Considering the imaging characteristics, eloquent cortical location, and multidisciplinary assessment, a conservative neuro-oncological management approach was favored.

This case highlights the importance of integrating advanced metabolic imaging techniques such as 18F-FET PET into the evaluation of long-term survivors of low-grade gliomas (LGGs) presenting with worsening epilepsy and new enhancing lesions after radiotherapy. Amino acid PET imaging may represent a valuable complementary tool for distinguishing radionecrosis from recurrent tumor activity in complex neuro-oncological cases.

Categories: Neurology, Radiation Oncology, Oncology
Keywords: epilepsy, low-grade diffuse gliomas, neuro-oncology, radionecrosis, tumor activity

Introduction

Low-grade gliomas (LGGs) are diffuse primary brain tumors that predominantly affect young adults and are characterized by a relatively prolonged clinical course compared with high-grade gliomas. According to the 2021 WHO Classification of Central Nervous System Tumors, adult-type diffuse LGGs include IDH-mutant astrocytomas and oligodendrogliomas [1].

These tumors account for approximately 5%-10% of primary brain neoplasms and have an estimated incidence of two to three cases per 100,000 population annually [2]. Their prolonged survival, frequently ranging from several years to decades, has increased the importance of long-term treatment-related complications and surveillance strategies [3].

Epilepsy is one of the most common clinical manifestations of LGGs, particularly in IDH-mutant tumors, and may significantly affect quality of life. Drug-resistant epilepsy is defined by the International League Against Epilepsy (ILAE) as the failure of adequate trials of two appropriately selected and tolerated antiseizure medications to achieve sustained seizure freedom [4]. Approximately 20%-30% of patients with LGGs may develop pharmacoresistant epilepsy during the disease course [5].

Current treatment strategies for LGGs include surgical resection, radiotherapy, chemotherapy, and, more recently, targeted therapies such as vorasidenib, which has recently been approved for selected patients with grade 2 isocitrate dehydrogenase (IDH)-mutant gliomas [6].

Although radiotherapy remains an important therapeutic tool for delaying tumor progression, it may also result in delayed treatment-related complications, including radiation necrosis [7].

Because patients with LGGs frequently experience prolonged survival and require long-term imaging follow-up, differentiating tumor recurrence from radionecrosis represents an increasingly important diagnostic challenge in neuro-oncology. Clinical manifestations and conventional imaging findings often overlap considerably between the two entities, making accurate diagnosis difficult. Advanced neuroimaging techniques, including amino acid PET radiotracers such as 18F-fluoroethyl-L-tyrosine positron emission tomography (18F-FET PET), have emerged as promising tools to improve diagnostic accuracy and guide therapeutic decision-making in these patients [8].

In this report, we present the case of a young patient with IDH-mutant diffuse LGG who developed worsening drug-resistant epilepsy and a progressive enhancing lesion after radiotherapy, generating a complex diagnostic dilemma between tumor recurrence and radionecrosis.

Case Presentation

A 35-year-old male patient was diagnosed in 2019 with an IDH-mutant grade 2 astrocytoma located in the left temporo-parieto-insular region. The patient was initially treated with surgery (subtotal planned resection due to proximity to eloquent brain areas), followed by 54 Gy of radiotherapy and adjuvant 12 cycles of temozolomide.

In 2022, the patient developed focal structural drug-resistant epilepsy, defined by persistent seizures despite multiple adequately dosed antiseizure medications, including oxcarbazepine, lamotrigine, clobazam, brivaracetam, levetiracetam, and lacosamide. Seizures consisted predominantly of focal impaired-awareness episodes characterized by speech arrest and behavioral arrest, occasionally progressing to bilateral tonic-clonic seizures. Electroencephalographic (EEG) studies demonstrated epileptiform activity predominantly involving the left frontotemporal region, concordant with the tumor location and surrounding perilesional changes. Follow-up MRI studies initially demonstrated a stable residual lesion without evidence of progression.

In January 2024, the patient presented with left periventricular (peritumoral) and right cerebellar ischemic strokes. A comprehensive diagnostic evaluation for stroke in a young patient, including vascular imaging and angiography, revealed no evidence of large-vessel vasculopathy. Differential considerations included radiation-induced vasculopathy and cardioembolic phenomena. A patent foramen ovale was identified and subsequently surgically corrected.

At the three-month follow-up, MRI revealed a new 2 mm nodular enhancing lesion within the frontal operculum adjacent to the surgical cavity, while the known caudal remnant remained stable (Figure *1*). Subsequent MRI and PET imaging demonstrated interval growth of the lesion, which increased to approximately 7 × 8 mm over six months (Figure *2*). Clinically, seizure frequency worsened during this period despite multiple antiseizure medication adjustments, raising concern for tumor progression according to Response Assessment in Neuro-Oncology (RANO) criteria [9].

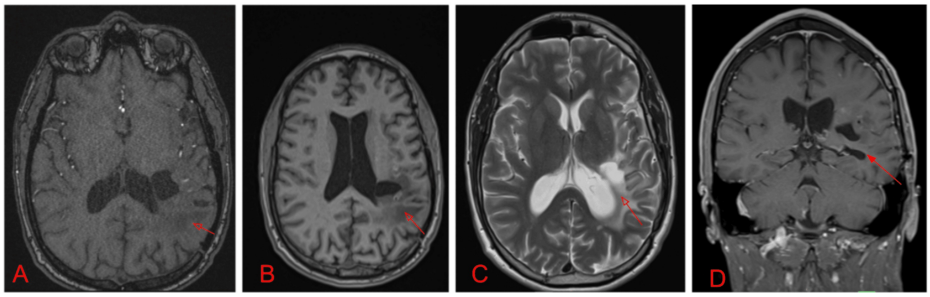


FIGURE 1: MRI demonstrating a small nodular enhancing lesion within the left frontal operculum adjacent to the surgical cavity (arrows), while the caudal residual lesion remained stable.

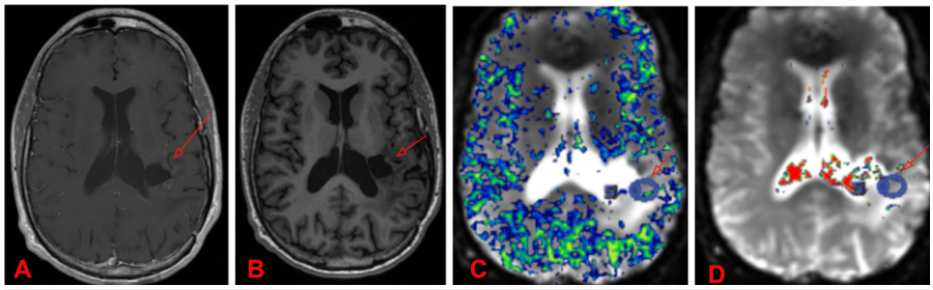


FIGURE 2: Diffusion and perfusion MRI demonstrating interval growth of the left frontal opercular lesion to approximately 7 × 8 mm with associated perfusion abnormalities.

However, 18F-FET PET imaging (Figure *3*) demonstrated mild, diffuse, homogeneous uptake with a maximum standardized uptake value (SUVmax) of 2.1 and a tumor-to-background ratio (TBR) of 1.7, findings below commonly reported thresholds associated with active tumor recurrence and therefore more suggestive of treatment-related inflammatory changes and radionecrosis rather than neoplastic progression. The coexistence of progressive seizures and radiological evolution generated a significant diagnostic dilemma between recurrent tumor activity and radionecrosis.

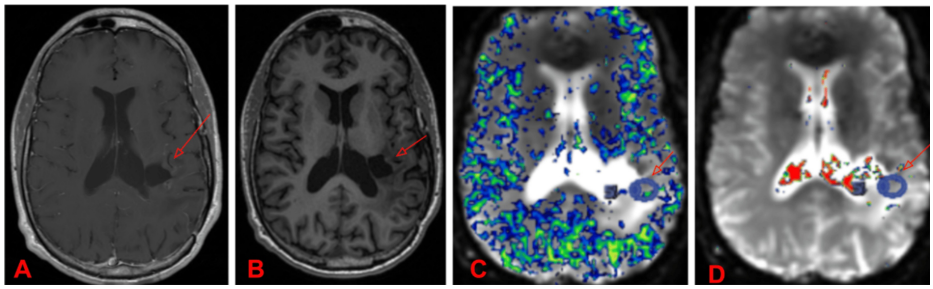


FIGURE 3: MRI and 18F-FET PET/CT correlation demonstrating mild and homogeneous amino acid uptake within the lesion (SUVmax 2.1; TBR 1.7), favoring treatment-related changes rather than active tumor recurrence.

18F-FET PET: 18F-fluoroethyl-L-tyrosine positron emission tomography; SUVmax: maximum standardized uptake value; TBR: tumor-to-background ratio

Given the proximity of the lesion to eloquent cortical regions involved in language and motor function, resective epilepsy surgery was considered high risk and ultimately deemed unfeasible. The patient was, therefore, considered a candidate for vagus nerve stimulation (VNS).

To manage suspected radiation necrosis, the epileptology team initiated a course of corticosteroid therapy, resulting in temporary seizure freedom for approximately three months. Given the imaging characteristics, metabolic profile on FET-PET, and clinical stability outside seizure recurrence, a conservative neuro-oncological approach was favored. At the most recent follow-up, the patient continued to experience an average of two seizures per month but remained functionally independent with preserved quality of life.

Discussion

Radiation necrosis represents one of the most important delayed complications of radiotherapy in patients with diffuse gliomas, particularly among long-term survivors of IDH-mutant LGGs. Because these patients frequently experience prolonged survival and undergo extended imaging surveillance, distinguishing treatment-related changes from true tumor recurrence has become an increasingly relevant challenge in neuro-oncology practice [10].

The present case illustrates the complexity of this diagnostic dilemma, and the main clinical, radiological, and pathological findings are summarized in Table *1*. The patient developed progressive drug-resistant epilepsy associated with the appearance and interval growth of a new enhancing lesion adjacent to the surgical cavity several years after completion of radiotherapy. Clinically and radiologically, these findings

raised significant concern for tumor progression according to RANO criteria. However, the metabolic characteristics observed on 18F-FET PET imaging favored radionecrosis rather than active neoplastic disease.

Feature	Tumor recurrence	Radionecrosis
Clinical course	Progressive neurological deterioration	Fluctuating or subacute symptoms
Seizure pattern	Progressive increase in seizure burden	May worsen secondary to cortical injury/inflammation
MRI enhancement	Nodular or progressive enhancement	Variable enhancement, often treatment-related
Perfusion MRI	Increased relative cerebral blood volume (rCBV)	Reduced perfusion/rCBV
Diffusion imaging	Restricted diffusion may be present	Variable diffusion changes
Amino acid PET uptake	Increased focal uptake	Mild or diffuse uptake
Tumor-to-background ratio (TBR)	Frequently >1.9–2.0	Frequently <1.9–2.0
Evolution on follow-up	Persistent progression	Stabilization or response to corticosteroids
Histopathology	Viable tumor cells	Necrosis, gliosis, and inflammatory changes

TABLE 1: Differential features between radionecrosis and tumor recurrence in low-grade glioma patients following radiotherapy.

Radiation necrosis may occur months to years after treatment and can present with seizures, cognitive impairment, focal neurological deficits, or radiological findings that closely resemble tumor recurrence [11]. Conventional MRI alone is frequently insufficient to reliably differentiate between both entities, particularly in patients with LGGs who often demonstrate prolonged post-treatment imaging abnormalities. Advanced neuroimaging modalities, therefore, play an increasingly important role in this setting.

Several MRI-based techniques, including diffusion-weighted imaging (DWI), intravoxel incoherent motion imaging (IVIM), dynamic susceptibility contrast perfusion MRI (DSC-MRI), and magnetic resonance spectroscopy (MRS), have demonstrated potential utility in differentiating recurrent tumors from radionecrosis [12].

However, amino acid PET tracers such as 18F-FET have emerged as particularly valuable tools because of their lower physiological uptake in normal brain tissue and their improved lesion-to-background contrast compared with FDG-PET [13].

In this patient, 18F-FET PET demonstrated mild and homogeneous uptake with a TBR of 1.7 and SUVmax of 2.1. Previous studies have suggested that lower TBR values, generally below 1.9-2.0, favor treatment-related inflammatory changes rather than active tumor recurrence [14]. These findings were particularly relevant in the present case because the progressive seizure burden and interval lesion growth initially raised concern for recurrent disease. The integration of clinical evolution, advanced MRI findings, and amino acid PET imaging ultimately supported a conservative neuro-oncological approach.

Another relevant aspect of this case is the relationship between radionecrosis and pharmacoresistant epilepsy. Seizure worsening in patients with previously treated gliomas may represent either recurrent tumor activity or treatment-associated cortical injury. In our patient, the epileptogenic zone was located adjacent to eloquent cortical regions involved in language and motor function, limiting the feasibility of resective epilepsy surgery. Consequently, management focused on medical optimization, corticosteroid therapy, and consideration of VNS [15].

This case also highlights the importance of multidisciplinary evaluation in neuro-oncology patients presenting with worsening seizures and new enhancing lesions after radiotherapy. The integration of epileptology, neuro-oncology, neuroradiology, and nuclear medicine findings was essential to avoid potentially unnecessary invasive interventions and to guide individualized management decisions.

Although a single case report cannot establish definitive diagnostic algorithms, it illustrates the potential clinical utility of advanced metabolic imaging techniques such as 18F-FET PET in distinguishing

radionecrosis from recurrent tumor activity in long-term survivors of LGG [16].

Conclusions

Radionecrosis should be considered in the differential diagnosis of new or worsening drug-resistant epilepsy in long-term survivors of LGG following radiotherapy. Distinguishing treatment-related changes from true tumor recurrence remains a major clinical challenge because both entities may present with overlapping clinical manifestations and conventional imaging findings.

In the present case, the integration of advanced metabolic imaging with 18F-FET PET, together with clinical and radiological assessment, favored the diagnosis of radionecrosis and allowed a conservative management approach, avoiding potentially unnecessary invasive interventions. Although this report represents a single clinical experience, it highlights the potential utility of amino acid PET imaging as a complementary diagnostic tool in complex neuro-oncological cases with diagnostic uncertainty between radionecrosis and tumor progression.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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