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## Case Report

# Glioblastoma with brainstem leptomenigeal pseudoprogression following radiation therapy

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## ABSTRACT

In brain tumor patients, worsening of imaging findings in the first 6 months after surgical debulking and chemoradiation can occur in the absence of tumor growth, a phenomenon known as pseudoprogression. Awareness of pseudoprogression is important as it can lead to unnecessary additional changes in patient management. In this case, a patient with bilateral frontal glioblastoma presented with new post-treatment brainstem leptomenigeal enhancement which was distant from the original tumor site, concerning for disease progression. However, the patient was asymptomatic and correlation of leptomenigeal enhancement locations with radiation therapy dose maps revealed high doses at the affected site, supporting a diagnosis of treatment effect which was confirmed by resolution on follow-up imaging after treatment with steroids. Parenchymal pseudoprogression in brain tumor patients is well-documented, but worsening leptomenigeal enhancement following therapy may also represent treatment effects. If spatially remote leptomenigeal enhancement occurs, correlation with radiation dose maps may be useful in suggesting a diagnosis of treatment effect over tumor progression.

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## Introduction

Glioblastoma (GBM) is an aggressive grade 4 brain tumor with poor overall prognosis and is the most common malignant primary brain tumor [1]. Standard glioblastoma treatment involves maximal safe resection/surgical debulking of the enhancing tumor followed by chemoradiation with concurrent

temozolomide [2]. Magnetic resonance imaging (MRI) of the brain is used for diagnosis, treatment planning, and subsequent follow-up and monitoring to guide additional decision-making. After surgery and radiation, worsening enhancement on T1 postcontrast imaging and worsening edema/tumor size on T2 fluid attenuation inversion recovery (FLAIR) imaging can be caused by early radiation effects, mimicking tumor progression and often appearing within 90 days of radiation therapy. This phenomenon is well-described for the brain parenchyma

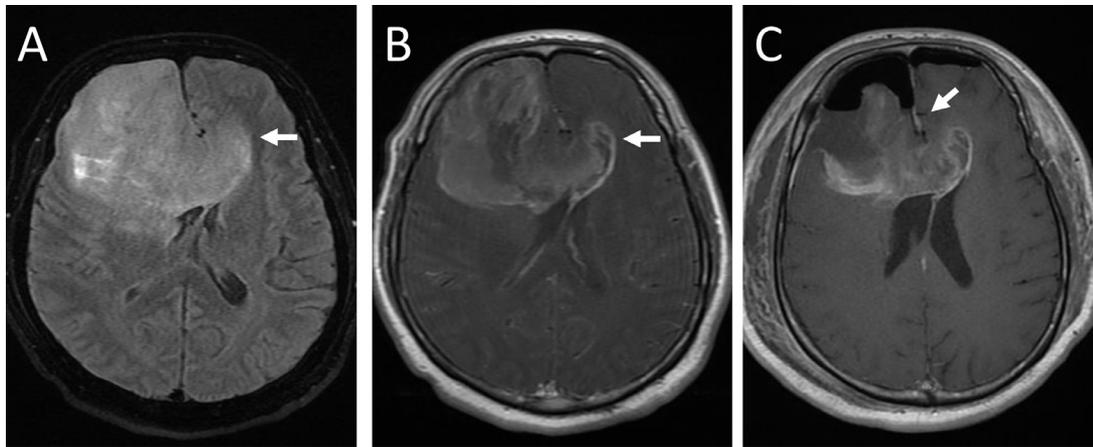
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**Fig. 1** – Preoperative axial T2 FLAIR (A) and T1 postcontrast (B) MRI showing a FLAIR hyperintense (arrow) and enhancing bifrontal mass (arrow) extending along the corpus callosum compatible with glioblastoma. Postoperative axial T1 postcontrast image (C) showing significant debulking of the tumor (arrow).

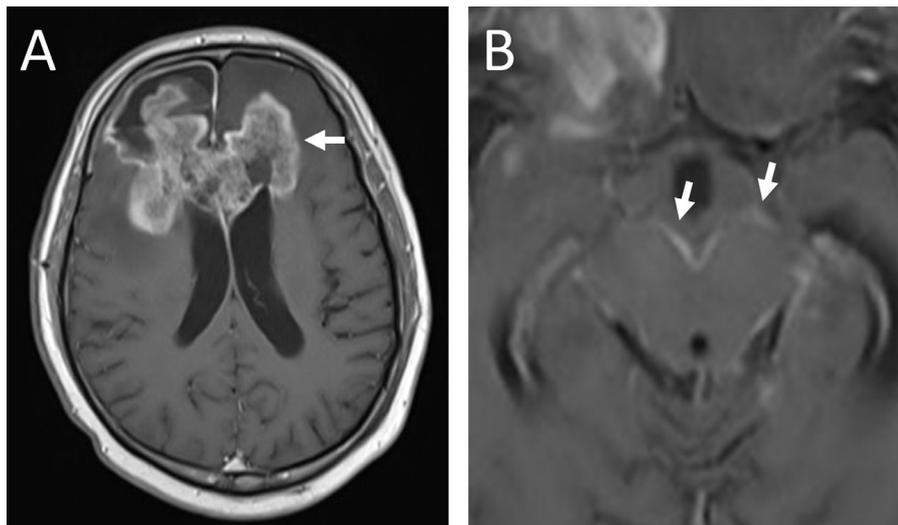
and has been termed pseudoprogression [3]. However, some features, such as remote distance from the tumor site or leptomeningeal involvement have not been frequently described with pseudoprogression. This case report highlights a unique situation of a glioblastoma patient who developed leptomeningeal enhancement surrounding the midbrain in the immediate postradiation period.

### Case report

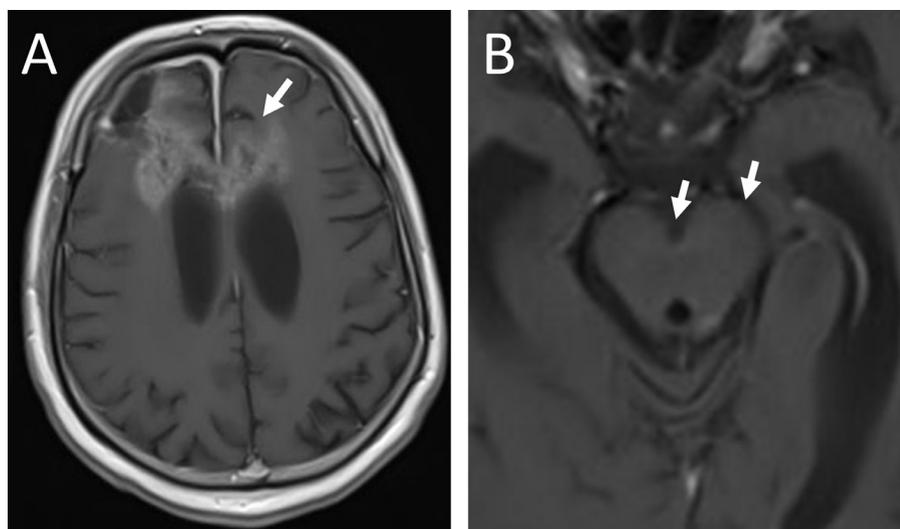
A 40-year-old Asian male with no past medical history presented with 1 month of worsening headache, acute nausea/vomiting, urinary incontinence, and a new episode of seizure. A computed tomography of the head revealed

a mass in the frontal lobes. A subsequent MRI revealed a heterogeneous, enhancing bifrontal lobe mass with T2 FLAIR signal hyperintensity crossing at the genu of the corpus callosum concerning for glioblastoma (Fig. 1). The patient was treated with surgical debulking, confirming a diagnosis of glioblastoma [isocitrate dehydrogenase (IDH) mutant, 1p19q wildtype, O6-methylguanine-DNA methyltransferase (MGMT) methylated], followed by radiation with concurrent temozolomide beginning 1 month after surgery.

One month after completing chemoradiation, the patient was in stable condition with mild fatigue and no new seizures or neurological symptoms. MRI at this time (Fig. 2) revealed worsening enhancement and T2 FLAIR signal hyperintensity at the tumor site, including across the corpus callosum, suggesting pseudoprogression given the location of imaging changes near the treatment field. New brainstem lep-



**Fig. 2** – Post-treatment MRI 1 month after completing radiation. T1 postcontrast image through the frontal lobes (A) shows worsening extensive enhancement at the primary tumor site (arrow). However, an image through the midbrain (B) shows extensive linear and nodular leptomeningeal enhancement surrounding the midbrain and involvement of the interpeduncular cistern and cerebral peduncles (arrows) not seen on pretreatment imaging.



**Fig. 3 – Post-treatment MRI 2 months after completing radiation. T1 postcontrast image through the frontal lobes (A) shows improvement of enhancement at the primary tumor site (arrow). Image through the midbrain (B) shows essentially complete resolution of leptomeningeal enhancement (arrows).**

tomeningeal enhancement was identified along the midbrain remote from the tumor treatment site. These findings were concerning for leptomeningeal spread of disease with pseudoprogression considered less likely given the location and leptomeningeal predominance. Infectious and aseptic meningitis, neurosarcoidosis, and tuberculosis were considered unlikely given lack of infectious signs, history, and clinical course [4].

Because of the patient's clinical stability and lack of new symptoms, the patient was maintained on dexamethasone but no alteration in treatment was made. Lumbar puncture was considered to assess for tumor cells in cerebrospinal fluid (CSF) but was deferred in lieu of short-term follow-up imaging. MRI 1 month later (Fig. 3) demonstrated slight improvement in enhancement and T2 FLAIR signal hyperintensity at the primary site most consistent with pseudoprogression. The abnormal brainstem leptomeningeal enhancement resolved completely. The patient was later started on bevacizumab to treat pseudoprogression at the primary right frontal site. Further follow-up contrast enhanced brain MRIs have shown gradual improvement of pseudoprogression in the right frontal lobe with no further abnormal enhancement in the leptomeninges or brainstem over a 6-month time period [5].

Radiation dose maps were obtained and registered to the 1 month postradiation follow-up MRI (Fig. 4). Despite perceived distance from the primary radiation bed, doses to the leptomeninges around the midbrain were within the 40-50 Gy range. These levels of radiation are likely high enough to explain the transient treatment effects/pseudoprogression which were seen at this site.

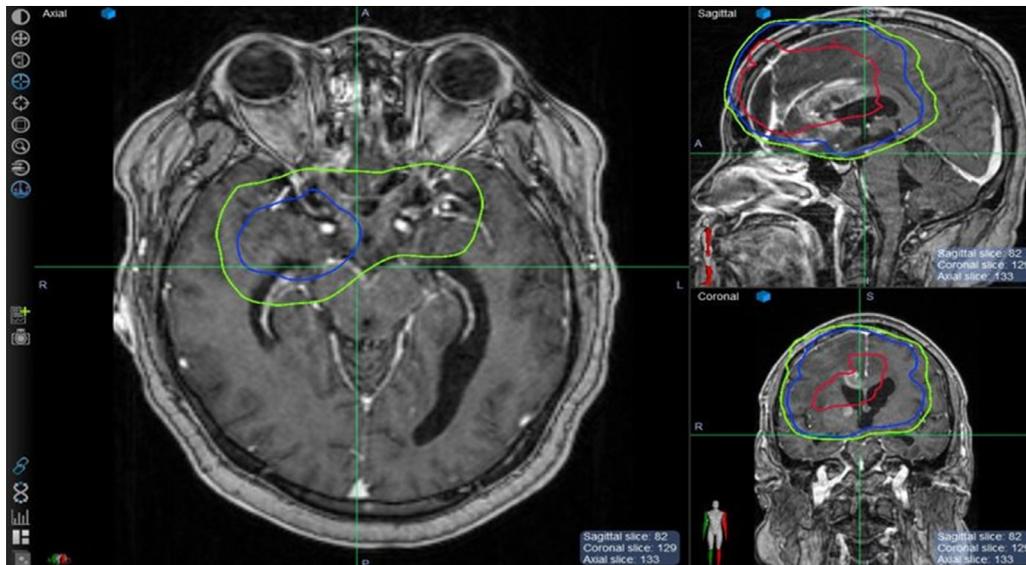
## Discussion

Pseudoprogression, or early treatment-related imaging changes, is a well-described phenomenon after radiation

therapy for glioblastomas. It is most frequently characterized by expansion of parenchymal FLAIR signal and worsening enhancement. It occurs in 20%-30% of cases and is more frequent in tumors with MGMT methylation [6]. Pseudoprogression presents a diagnostic conundrum because patients already have low expected survival, and early worsening of tumor could precipitate a change in management, such as addition of a new chemotherapy agent or reoperation.

In this case, the patient developed worsening imaging findings on the 1-month postradiation follow-up MRI. While the primary tumor site was relatively typical for pseudoprogression, there was new leptomeningeal enhancement along the midbrain, a site distant from the primary treatment site. Leptomeningeal enhancement is characterized by focal, nodular, or diffuse enhancement of the pial or pial-arachnoid surfaces of the brain, which is most commonly seen as enhancement along the gyral surfaces of the brain parenchyma [7]. In this case, the pial surfaces of the midbrain and adjacent cranial nerves were involved. There is a broad differential for abnormal leptomeningeal enhancement which includes malignancy, infection, inflammatory disease, and surgical intervention.

In this patient, the most worrisome possibility was leptomeningeal spread of glioblastoma, which has an estimated prevalence of 4% and typically occurs 8-14 months after diagnosis [8]. Proximity of the original tumor to cerebrospinal fluid, older age, and male gender have been associated with increased incidence of leptomeningeal metastasis. Patients often have worsening nonspecific symptoms such as headache, nausea, gait disturbance, confusion, and altered mental status. Abnormal cells found on CSF sampling can help confirm this diagnosis and would have been indicated in this patient if imaging findings did not improve or new symptoms occurred. Chemotherapy and, particularly, radiation have been shown to provide some benefit, but progression is nearly universal with an estimated 2 to 3-month survival after diagnosis of leptomeningeal disease [9].



**Fig. 4 – Radiation dose contours overlaid on the 1 month postcontrast MRI. Blue contour = 50 Gy, Green = 40 Gy. Dose at the green marker intersection was 44 Gy.**

Other causes of abnormal leptomeningeal enhancement [10] were considered in this case. Meningitis and encephalitis, especially in a postoperative patient, are possibilities. In addition to typical viral and bacterial pathogens, unusual etiologies such as fungal or tuberculous meningitis can have similar imaging findings. However, this patient had no signs of systemic infection or new neurologic symptoms. Inflammatory diseases such as sarcoidosis and vasculitis may also present with leptomeningeal enhancement. Systemic malignancies such as breast and lung carcinomas as well as hematologic malignancies (lymphoma and leukemia) can also present with leptomeningeal disease. This patient had no history of other illnesses or symptoms to point to these other possibilities.

Given the patient's relative stability and unexpected nature of these findings, the patient was maintained on steroids and a short interval follow-up was performed. This follow-up demonstrated resolution of the leptomeningeal disease and improvement of imaging findings elsewhere in the brain. Furthermore, review of radiation dose maps confirmed that the area in question had relatively high radiation doses. No other cause was identified, and the patient continued to do clinically well, further supporting the diagnosis of leptomeningeal pseudoprogression.

Radiation-induced leptomeningeal pseudoprogression is a rare phenomenon, which has not been widely described in the literature. The likely explanation of this leptomeningeal pseudoprogression is radiation-induced disruption of the blood-brain barrier in the region, resulting in leakage of contrast and leptomeningeal enhancement [11]. Transient cortical leptomeningeal enhancement in the peri-ictal period has also been confused for tumor progression in brain tumor patients with seizures [12,13]. Differentiating pseudoprogression from true progression to the leptomeninges has important implications both for patient management and prognosis, as no further therapy was required in this case. Advanced MRI tech-

niques, such as dynamic susceptibility contrast perfusion [dynamic susceptibility contrast (DSC)-perfusion] have been proposed to differentiate between true progressive disease and radiation effects, with radiation effects having relative hypoperfusion. However, perfusion imaging is not likely to be useful in evaluating leptomeningeal disease given the abnormality only affected small linear regions along the surface areas of the brain, which are areas that are normally avidly perfused [14]. In many cases, the true outcome is not known until one or more follow-up imaging exams have been performed.

This case illustrates the importance of being aware of the possibility of leptomeningeal pseudoprogression after radiation therapy in brain tumor cases. In a clinically stable patient where these findings appear shortly after completion of radiation, reasonable exclusion of other causes and correlation with radiation dose maps confirming that the area in question received a significant radiation dose all provide support for making this diagnosis. In these cases, it may be worthwhile to delay changes in management until a short-term follow-up examination can be performed.

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