RADIATION ONCOLOGY CASE

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Subclinical recurrence of anaplastic astrocytoma: Demonstrating the difficulty in distinguishing progression from pseudoprogression

Howard E. Morgan, BS; Maxwell C. McDonald, MD; J. Ben Wilkinson, MD

CASE SUMMARY

A 47-year-old Caucasian man presented with progressive headaches over 6 months. A 4.3 cm x 3.4 cm mass was seen in the right cerebellum compressing the brainstem (Figure 1). Pathology after a near-total resection was consistent with a WHO grade III anaplastic astrocytoma with MGMT methylation, an IDH1 (isocitrate dehydrogenase) mutation, and KI-67 of 15%. Adjuvant intensity-modulated radiation therapy (IMRT) was delivered to the areas surrounding the tumor resection cavity (59.4 Gy/33 fractions) with concurrent temozolomide (TMZ) followed by adjuvant TMZ for 1 year.

Over the next 20 months, the patient reported no neurologic symptoms and had no notable physical examination findings. Follow-up MRIs showed a gradually enlarging septated lesion with limited areas of enhancement surrounding the cystic post-therapy changes.

*Prepared by **Mr. Morgan,** medical student at LSU Health Science Center, Shreveport, LA; **Dr. McDonald,** medical oncologist, Willis-Knighton Health System, Shreveport; and **Dr. Wilkinson,** radiation oncologist, Willis-Knighton Health System.*

IMAGING FINDINGS

MRIs showed slight peripheral enhancement that was gradually expanding: 1.6 x 1.4 cm at 3 months post-IMRT (Figure 2A) to 4.1 x 3.5 cm at 19 months post-IMRT (Figure 2C). However, no progressive nodular enhancement was noted at any interval. MRI spectroscopy and perfusion were considered but not obtained, as significant hemosiderin deposits in the area were felt to prohibit accurate test results. A positron emission tomography (PET) scan with brain protocol (Figure 3) showed overall decreased uptake in the right cerebellum with a faint line of increased fludeoxyglucose F 18 (FDG) avidity in the center; however, this area of uptake did not correspond to the area of thickened enhancement seen on the MRIs. Differential diagnosis for the area of progressive enhancement included tumor recurrence vs. pseudoprogression.

CLINICAL RESOLUTION

At 20 months post-IMRT, the patient began noticing nontender drainage from his prior suboccipital incision site. Due to concern for subclinical osteomyelitis and an enlarging cystic structure within the posterior fossa, a repeat craniotomy with subtotal resection was completed. Pathology revealed acute osteomyelitis and recurrent vs. persistent WHO grade III anaplastic astrocytoma with radiation changes. Ki-67 of the persistent disease was decreased to < 1%. Due to the presence of residual tumor cells in the re-excision specimen, the patient has restarted on temozolamide, and is being followed clinically with MRIs every 3 months.

DIAGNOSIS

Persistent vs. recurrent WHO grade III anaplastic astrocytoma with radiation changes.

DISCUSSION

Cerebellar gliomas are rare, comprising 1.8% of all gliomas, with the majority arising in the frontal (25.6%), temporal (19.6%), and parietal (13.8%) lobes.[1] As showed in this case, general presenting symptoms of anaplastic astrocytomas (AA) include headaches (53%) and visual symptoms (23%), in addition to seizures (56%), memory loss (26%), and weakness (25%).[2] However, this patient's recurrence was atypical, in that he showed no signs of clinical progression in the midst of a gradually expanding cystic lesion. In a retrospective cohort of grade III and IV gliomas,

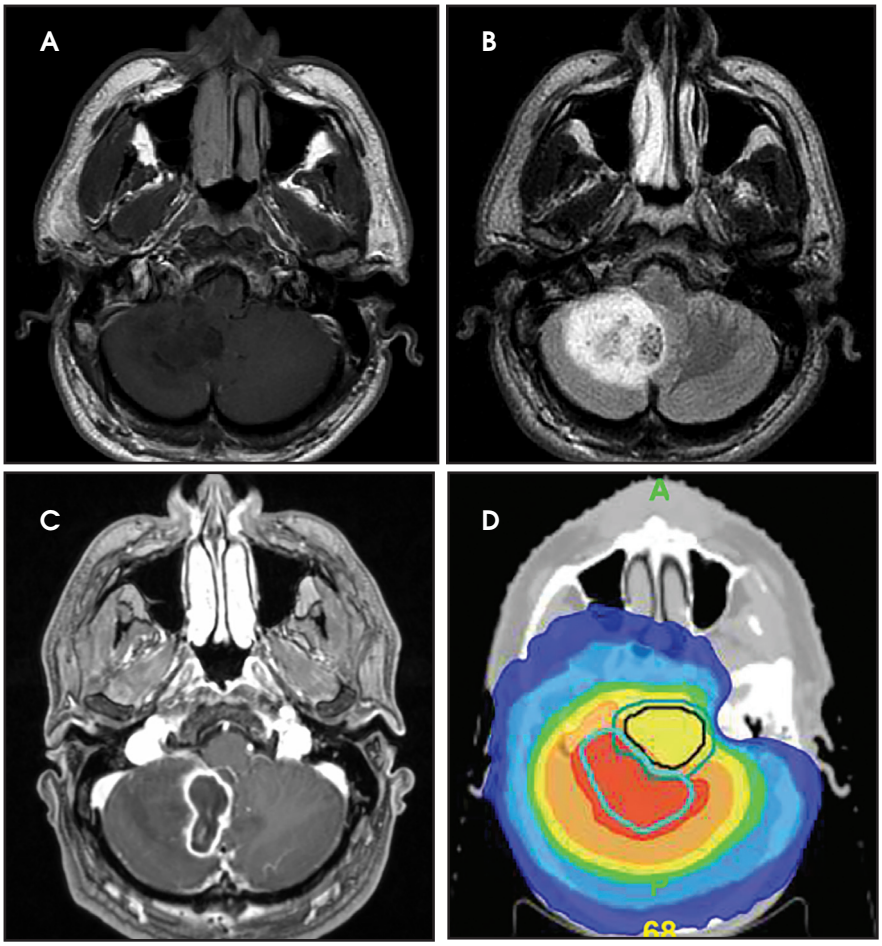

FIGURE 1. *Pre-resection, a 4.3 cm x 3.4 cm mass is visualized in the right cerebellar lobe with T1-weighted MRI plus contrast (A) and FLAIR (B). (C) At 2 weeks postresection, a 3.4 cm x 1.7 cm rim-enhancing lesion is noted in the right cerebellum. (D) IMRT plan to deliver 59.4 Gy over 33 fractions to resection cavity.*

67% with early progression showed neurological deterioration within 4 weeks of imaging findings (n = 18).[3] Although imaging in this case showed mild peripheral enhancement, strong nodular enhancement is more characteristic with recurrence.[4] This incongruent picture, in addition to the equivocal findings on PET, distinguished between progression and pseudoprogression that was unclear during surveillance, a growing problem that complicates the decision of when to intervene.

Pseudoprogression is an obstacle in the surveillance of brain neoplasms, since it mimics MRI findings of recurrence within the field of radiation without representing true disease. It is reported to occur in approximately 20% of malignant gliomas following chemoradiotherapy, with 50% of those showing early MRI findings of recurrence within 4 weeks to actually be pseudoprogression.[3] Pseudoprogression should not be confused with radiation necrosis or pseudoresponse. Pseudoprogression is distinguished by being an early and transient treatment-related effect, with T1-weighted, MRI postcontrast findings of increased enhancement, usually appearing within 3 months post-treatment and subsiding in 6 months.[5] In contrast, radiation necrosis is a late and irreversible treatment-related effect, with MRI findings appearing > 3 months post-treatment but never completely

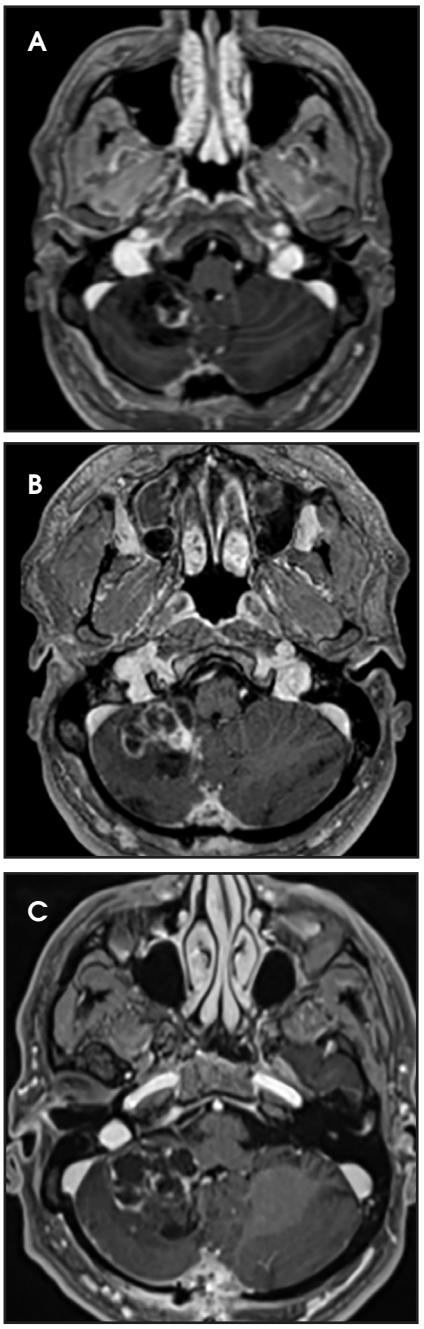

FIGURE 2. *T1-weighted MRI images showing an evolving cystic lesion in the right cerebellum. (A) At 3 months postradiation, the postsurgical cavity has decreased to 1.6 cm x 1.4 cm, and shows mild rim enhancement when compared to Figure 1C. (B) At 10 months postradiation, the cavity increased to 3.3 cm x 3.5 cm with increased rim enhancement. (C) At 19 months postradiation, the cavity increased to 4.1 cm x 3.5 cm, with extension to middle cerebellar peduncle.*

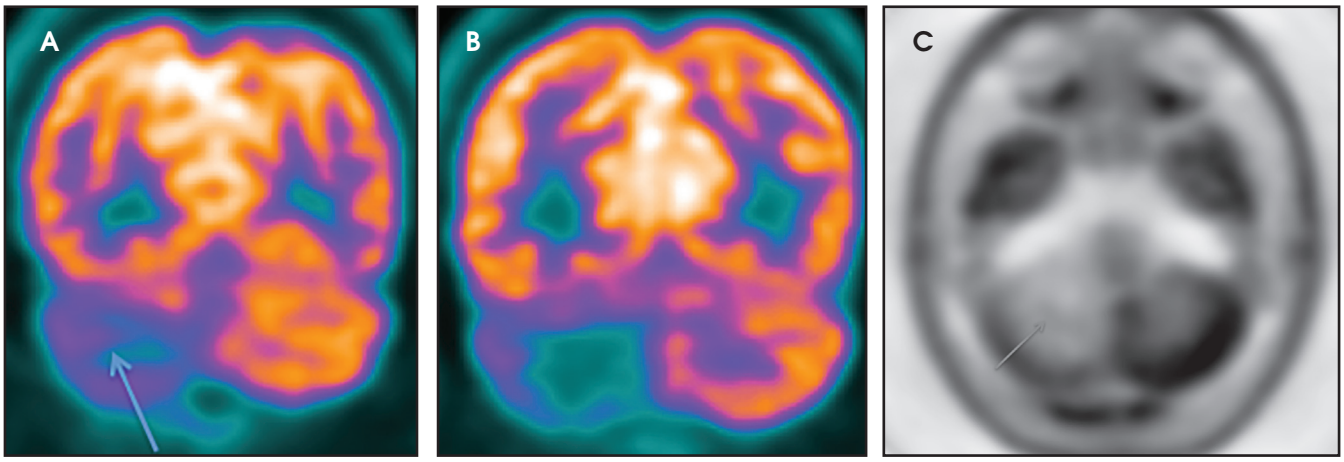

***FIGURE 3**. At 14 months postradiation, an FDG-PET scan showed decreased uptake of FDG in the right cerebellum (coronals A and B, and axial C). A faint linear area of increased FDG uptake was found in the middle of the lesion (blue arrow), but did not correspond with septations when superimposed on the MRI.*

subsiding.[5,6] The MRI findings of radiation necrosis can be broad, with peripheral enhancement resembling a "spreading waveform" (98%) vs. nodular (2%), internal enhancement with a "soap bubble" appearance (90%), cystic components (75%), and central necrosis (89%).[7] On the other hand, pseudoresponse is characterized by decreasing enhancement on MRI during treatment with anti-angiogenic medications such as bevacizumab, which may be confused with a positive response to treatment.[5]

Despite increasing awareness of these treatment-related effects, no reliable method distinguishes them from real progression on MRI,[8] aside from a pathological diagnosis as shown in this case. Pseudoprogression may not be recognized until gradual dampening of enhancement by 6 months and radiation necrosis may be further confused by the persistent presence of enhancing lesions > 6 months post-treatment.[5,6] In addition, the lack of a significant difference between neurological complaints of real progression (67%) and pseudoprogression (33%)[3] further complicates their distinction, as clinical correlation may not be reliable. National Comprehensive Cancer Network (NCCN) guidelines for surveillance of malignant gliomas after chemoradiotherapy include obtaining the first MRI 2-6 weeks after therapy completion, then at 2-4 month intervals for 2-3 years before lengthening.[9] To reflect the growing awareness of treatment-related effects, the Macdonald Criteria–imaging criteria for assessing treatment response–have recently been revised to avoid diagnosing progression at < 3 months after therapy within the 80% isodose lines of radiation, a time with high incidence of pseudoprogression.[10]

Although MRI has not been reliable in distinguishing pseudoprogression, other modalities have shown promise, including FDG-PET, C-Met-PET, MR spectroscopy, and MR perfusion.[8] In our case, FDG-PET showed a faint area of FDG uptake in the center of the resection cavity and not overlapping with the area of enhancement. Although FDG PET has higher accuracy than MRI, its sensitivity (77%) and specificity (78%)[11] still limit its utility in equivocal cases. A recent study examining the parameters of PET and CT perfusion in predicting progression has suggested that it is not the magnitude of uptake but the ratio of uptake to blood flow that correlates best with progression. They proposed that poorly perfused lesions may show reduced FDG uptake overall, while still being more metabolically active due to an increased extraction of FDG per volume of blood encountered.[12]

In addition to imaging, the molecular profile has also shown promise in stratifying those at increased probability of pseudoprogression. MGMT promoter methylation, a marker for increased response to TMZ treatment, has been associated with an increased incidence of pseudoprogression,[13] and when combined with MRI findings, increases the accuracy of identifying pseudoprogression in glioblastomas.[14] A positive prognostic marker 1p19q codeletion has been linked to a decreased incidence of pseudoprogression (3% with codeletion vs. 31%) in grades II and III oligoastrocytomas and oligodendrogliomas.[15] IDH1 mutation, a positive prognostic marker, was suggested to be associated with a higher incidence of pseudoprogression in a smaller study (n = 28, with 3 cases of pseudoprogression), but likely needs confirmation with larger sample sizes.[16] In this case, the histology was MGMT-methylated, which may have contributed to the increased risk of pseudoprogression mixed with recurrent vs. persistent glioma.

CONCLUSION

Determining when a malignant glioma progresses on MRI after chemoradiotherapy has become increasingly difficult with the growing awareness of treatment-related effects. While the

most definitive way of differentiating these entities is biopsy or surgical resection, noninvasive means are needed to lower time to intervention for those progressing. Many such noninvasive measures have shown promise, including FDG-PET as discussed in this report, and molecular markers for risk stratification, with MGMT being the most studied. Close clinical observation with short-interval MRIs, even in the presence of negative advanced imaging studies, is a reasonable clinical strategy. In our experience, continued growth of a septated or cystic lesion without true nodular enhancement can be a sign of disease persistence or recurrence, and warrants repeat craniotomy or a change in therapeutic management depending on the patient's condition.

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