BRIEF COMMUNICATION

Glioblastoma in natalizumab-treated multiple sclerosis patients

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Abstract

We present two natalizumab-treated multiple sclerosis patients who developed glioblastoma multiforme (GBM) with variable outcomes. One patient had an isocitrate dehydrogenase (IDH)-wildtype GBM with aggressive behavior, who declined treatment and died 13 weeks after symptoms onset. The other patient underwent resection of an IDH-mutant secondary GBM that arose from a previously diagnosed grade II astrocytoma. He is still alive 5 years after the diagnosis of GBM. JC virus was not detected in either case. Whether natalizumab played a role in the development of GBM in those patients deserves further investigation.

Introduction

We present two patients with multiple sclerosis (MS) who developed glioblastoma multiforme (GBM) while being treated with natalizumab. GBM is the most common primary intracranial malignancy in adults. Despite multiple therapeutic approaches, only a few patients survive beyond 5 years.[1] MS is characterized by recurrent bouts of multifocal autoimmune inflammatory demyelination of the central nervous system, followed by gliotic scarring.[2] Natalizumab is a humanized monoclonal antibody to alpha-4 integrin that reduces relapse rates and disability in patients with relapsing-remitting MS. There are few reports of neoplasia occurring in natalizumab-treated patients.[3–10]

Natalizumab-induced impairment of immune surveillance in the central nervous system is thought to be one possible explanation for the incidence of neoplasias.[11,12]

Patient One

A 67-year-old woman with long-standing history of relapsing-remitting MS presented with left upper and lower extremity weakness. She received intravenous corticosteroids without improvement. She had been diagnosed with MS more than 25 years earlier. She was treated with glatiramer acetate for 12 years, followed by dimethyl fumarate for 2 years before starting monthly natalizumab infusions 2 years prior to her current presentation.

She underwent an MRI of the brain 3 weeks after symptom-onset at another institution, which showed new contrast-enhancing lesions in the right frontoparietal area (Fig. 1A and B). A lumbar puncture was performed to investigate progressive multifocal leukoencephalopathy. CSF analyses were normal including undetectable JCV DNA. She developed focal seizures treated with levetiracetam. She underwent plasma exchange to remove natalizumab from her bloodstream. Shortly thereafter, she developed dysarthria and a left visual field cut. An MRI of the brain 6 weeks after symptom-onset showed increased number and size of right frontoparietal expansive lesions, with associated 9.5 mm midline shift (Fig. 1C and D). Repeat CSF analysis was unremarkable. She was treated with intravenous corticosteroids and immunoglobulins without improvement of her symptoms.
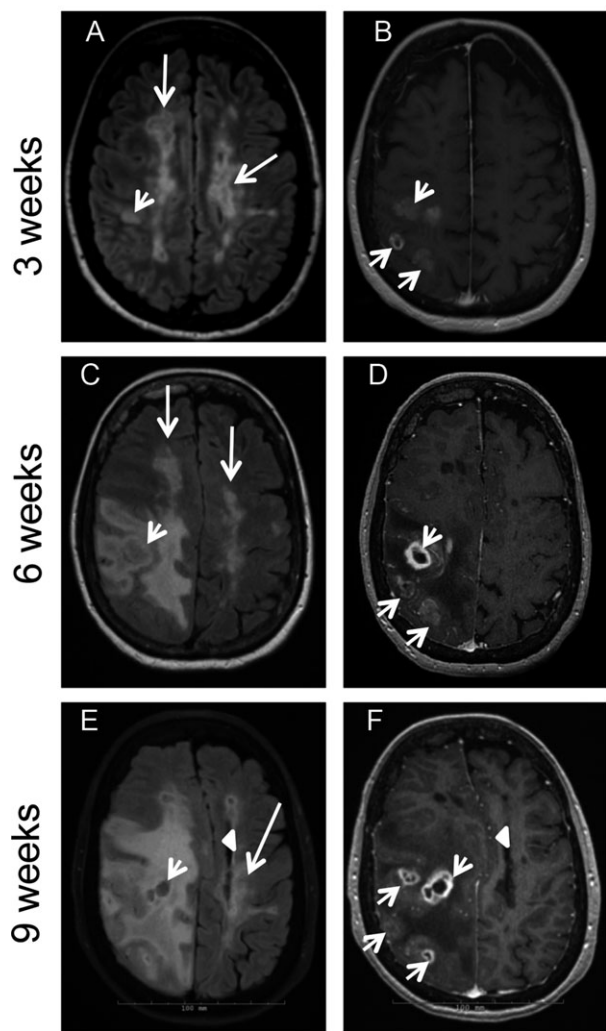
Evolution of MRI findings after symptoms onset

Figure 1. Progression of lesions in the right frontoparietal region on brain MRI. Axial fluid-attenuated inversion recovery (FLAIR) (A, C, E) and postcontrast T1-weighted images (B, D, F) demonstrate multiple irregular enhancing lesions (short arrows) with extensive surrounding edema. There is associated mass effect with leftward midline shift (arrow head). Multiple sclerosis lesions are present in the white matter of both hemispheres (long arrows).

She was evaluated at our institution for brain biopsy. A repeat MRI of the brain 9 weeks after symptoms onset revealed an increase in size and number of the right frontoparietal tumefactive lesions (Fig. 1E and F). There were new areas of enhancement with surrounding extensive edema, 13 mm midline shift. MR spectroscopy showed decreased N-acetylaspartate and increased choline within the lesions and increased lactate within the center of the lesions. These findings were most consistent with GBM. After considering all options, the patient and her family

decided to abstain from further diagnostic work up, including brain biopsy, and opted for transfer to hospice care. They consented for a postmortem exam. The patient died 13 weeks after symptoms onset.

Autopsy showed an infiltrating neoplasm centered on the right frontoparietal lobe, causing blurring of gray-white matter boundaries, infiltrating the deep basal ganglia, and containing areas of necrosis. Histologic sections showed a GBM with areas of necrosis and endothelial proliferation (Fig. 3A). The tumor cells were negative for isocitrate dehydrogenase (IDH) mutations (immunohistochemistry and target sequencing). There was loss of nuclear staining for alpha thalassemia/mental retardation syndrome X-linked (ATRX) in the tumor cells (ATRX mutant pattern) (Fig. 3C). JCV immunostaining and PCR on the brain tissue were negative.

Patient Two

A 26-year-old man with a history of relapsing-remitting MS underwent a routine surveillance MRI, which showed a right superior frontal lobe mass at the cortical surface (Fig. 2A and B). He had been diagnosed with MS 4 years earlier. He was treated with interferon beta 1a IM for 3 years before starting natalizumab infusions 7 months prior to the discovery of the mass. The lesion increased in size on serial imaging studies and he underwent a brain biopsy that showed diffuse astrocytoma, IDH-mutant, WHO grade II (Fig. 3C), followed by craniotomy and lesion resection a few weeks after the diagnostic MRI. He developed focal seizures after surgery and was treated with levetiracetam with optimal seizure control. He continued monthly natalizumab infusions and was clinically and radiographically stable for 5 years. An MRI of the brain obtained after he developed new left-sided weakness showed a recurrence of the right frontal lobe lesion (Fig. 2C, D, E and F). He underwent a second craniotomy and tumor resection, which he tolerated well and without complications. Histopathology showed GBM with primary neuroectodermal tumor (PNET)-like component, IDH-mutant, WHO grade IV (Fig. 3D). By immunohistochemistry, the tumor was positive for *IDH1* (R132H) mutation, and had loss of ATRX nuclear staining (ATRX mutant pattern) (Fig. 3E and F). JCV immunostaining was negative. The patient was treated with temozolomide and radiation therapy which were well tolerated. At the last clinical evaluation, 5 years after the diagnosis of GBM and 10 years after diagnosis of astrocytoma, he showed no evidence of tumor recurrence, and he continues monthly natalizumab injections for MS and daily levetiracetam treatment for seizure prophylaxis.

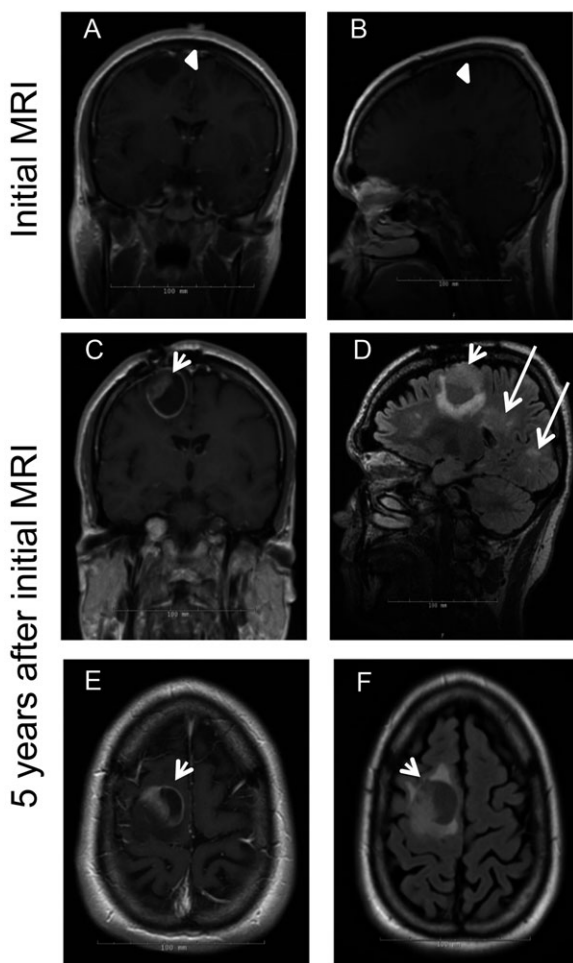## Evolution of imaging findings after initial MRI

Figure 2. Initial MRI demonstrates a lesion (arrow head) without associate enhancement on coronal and sagittal postcontrast T1-weighted images (A, B). Coronal and axial postcontrast T1-weighted images (C, E) as well as sagittal, axial fluid-attenuated inversion recovery (FLAIR) (D, F) demonstrate irregular enhancing lesion (short arrows) with surrounding edema. Multiple sclerosis lesions are visible in the subcortical white matter (long arrows).

Discussion

We describe two cases of GBM in patients treated with natalizumab. Natalizumab is the most effective treatment for reduction in relapses in MS patients. According to the long-term safety study of natalizumab treatment, the most frequently reported serious adverse events were infections (4%), gastrointestinal disorders (2%), and neoplasms (2%).[10] The concurrent use of natalizumab in the present cases raises questions regarding a possible relationship between the impaired immune surveillance caused by natalizumab and the development of GBM. Patients with

gliomas show a systemically impaired immune response and pathologic examination exhibits, in most cases, little tumor-associated inflammatory infiltrate, suggesting that immune suppression plays a pivotal role in tumor progression.[13] Natalizumab prevents trafficking of all white blood cells in the CNS, which will prevent immune surveillance against tumor development, which may, in rare cases, lead to development of glioma.

GBM is the most aggressive of primary tumors of the brain. Patients with GBM have a median survival of less than 1 year and only 2% of patients survive 3 years.[1] These two MS patients had GBM with different histopathologic characteristics. One had an IDH-wildtype tumor, consistent with a de novo primary GMB with aggressive behavior. The second patient had an IDH-mutant secondary GBM that arose from a grade II astrocytoma. The excellent outcome of this patient, who is still alive 5 years after the diagnosis of GBM, correlates with the favorable prognosis of IDH-mutant GBM compared to IDH-wildtype tumors. IDH mutation is thought to be an early event in the development of low-grade astrocytomas. It is found in secondary glioblastomas but is essentially absent in primary glioblastomas, supporting this hypothesis.[14,15] In addition, the second patient was younger than age 40 and had a secondary glioblastoma, which is also associated with a favorable prognosis. To the best of our knowledge, there is only one other case of GBM reported in a natalizumab-treated patient, which was diagnosed after 4 months of natalizumab monotherapy. This patient was treated with a combination of surgery, radiation therapy, and chemotherapy and died 1 year after GBM diagnosis. Histological and immunohistochemical features were not described.[16]

It is difficult to establish a causal relationship between natalizumab and GBM based on those cases. Gliomas may be underdiagnosed in patients with MS. Frequently, new neurological symptoms and MRI changes are attributed to reactivation of disease and further work up is not pursued. Alternatively, new brain lesions different from MS in natalizumab-treated patients may be considered to be caused by PML, even if JC virus PCR is negative in CSF. Postmortem verification may not be done in those cases. This emphasizes the need for continued vigilance in natalizumab-treated patients. It is especially important since natalizumab is now being used in combination with other agents for the experimental treatment of various neoplasms, including GBM. Indeed, natalizumab inhibits binding of leukocytes to vascular endothelial cell adhesion molecule 1 (VCAM-1) by blocking $\alpha4\beta1$ or $\alpha4\beta7$ integrin receptors on leukocytes. This may be a potential therapeutic target to influence chemotherapy responsiveness in resistant disease.[17–19]
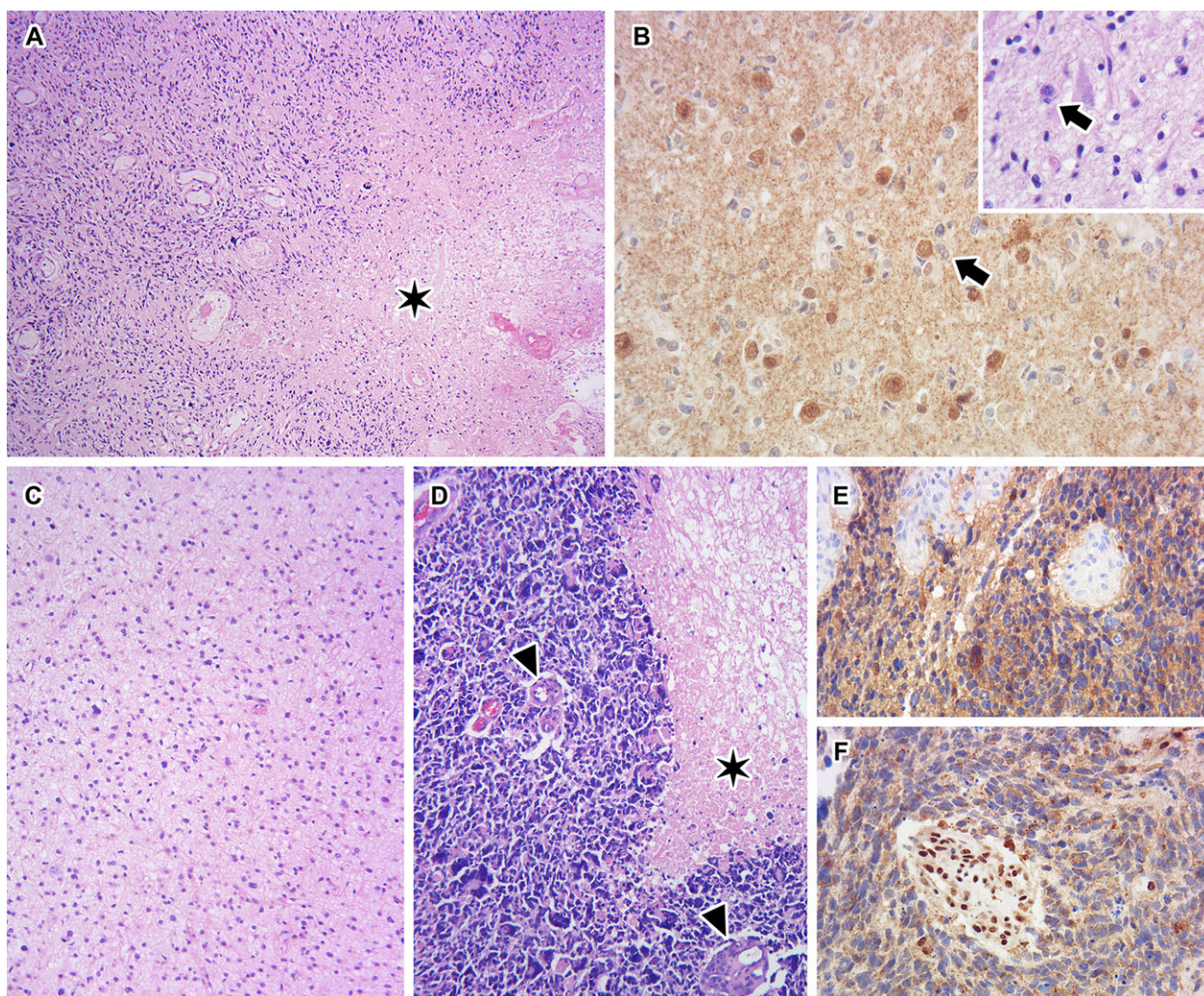
Figure 3. Histology findings in patient #1 (A–B). (A) Glioblastoma multiforme, IDH1-wildtype, WHO Grade IV with endothelial proliferation and necrosis (star) (H&E, 200x). (B) ATRX immunohistochemistry showing loss of nuclear staining in tumor cells (arrow), while retained nuclear staining in normal neurons (400×). Insert shows H&E of same area (H&E, 400×). Histology findings in patient #2 (C–F). (C) Diffuse astrocytoma, IDH1-mutant, WHO Grade II from 2007 (H&E, 200×). (D) Glioblastoma multiforme with PNET-like component, IDH1-mutant, WHO Grade IV showing necrosis (star) and endothelial proliferation (arrowhead) (H&E 200×). (E) IDH1 R132H mutant staining showing strong cytoplasmic staining in the tumor cells and negative staining in the endothelial cells (400×). (F) ATRX immunostaining showing retained nuclear staining in the endothelial cells and loss of nuclear staining in the tumor cells (400×).

A few studies have shown that the incidence of malignancies associated with natalizumab was similar to that of the general population.[20,21] Overall age-adjusted incidence rates for all gliomas range from 4.67 to 5.73 per 100,000 persons. The true incidence of gliomas in MS patients is difficult to define. A systematic study of 402,462 patients with autoimmune diseases from Sweden found no increased or decreased risk for gliomas in patients with MS.[22] The concurrence of MS and gliomas is rare. To the best of our knowledge, there are fewer than 60 cases of glioma associated with MS reported in the literature to date.[23] Nevertheless, physicians should be aware that new

lesions occurring during natalizumab treatment may be caused by glioma in patients with negative CSF JC Virus PCR, and that a brain biopsy should be considered. Indeed, tissue diagnosis followed by surgical intervention was clearly beneficial in patient two.

It is important to mention that further follow-up is required to evaluate the risk of neoplasias with longer natalizumab exposure. Physicians should report adverse events in natalizumab-treated patients to pharmacovigilance initiatives such as FDA Adverse Event Reporting System (FAERS) and Tysabri Outreach Unified Commitment to Health (TOUCH).

Acknowledgments

Conflict of Interest

The authors have no additional financial relationships or conflicts of interest relevant to this article to disclose.

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