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Progressive Multifocal Glioblastoma in a Patient with Multiple Sclerosis: Case Report & Management Considerations

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Case Report

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Abstract

Background

Multiple sclerosis is a chronic immune-mediated demyelinating disorder of the central nervous system characterized by blood-brain barrier disruption and lymphocytic infiltration. Glioblastoma is the most common primary malignant brain tumor, marked by aggressive growth, angiogenesis, and invasion, with limited survival despite multimodal therapies. Available literature on the co-occurrence of these disorders is limited to case reports and small series.

Case Presentation:

A 65-year-old woman with a 40-year history of relapsing-remitting multiple sclerosis treated with glatiramer acetate for > 2 decades, presented with new-onset focal seizures. She was found to have multifocal glioblastoma involving the right frontal and temporal lobes. Histopathology confirmed glioblastoma with wild-type isocitrate dehydrogenase and unmethylated *O^6-methylguanine-DNA methyltransferase* promoter. Despite multimodal therapies, including a trial of everolimus, her clinical course was marked by progressive neurologic decline and death.

Conclusions

Detailed radiologic interpretation, timely biopsy of atypical lesions, and individualized treatment strategies are essential for managing concurrent multifocal glioblastoma and multiple sclerosis. This case also highlights treatment decisions to balance tumor control while limiting the risk of exacerbating demyelination. Temozolomide chemotherapy and everolimus, which inhibit the mechanistic target of rapamycin, represent therapies with dual activities against tumor progression and immune-mediated inflammation.

Introduction

The simultaneous occurrence of glioblastoma in multiple sclerosis patients is remarkably uncommon, and the optimal management of this malignancy in the setting of chronic cerebral inflammation is poorly defined. Multiple sclerosis is a chronic immune-mediated inflammatory disorder affecting the central nervous system, impacting nearly 2.8 million individuals globally with an annual incidence rate of 2.1 per 100,000 (1). This disorder is characterized by disruption of the blood-brain barrier and infiltration of autoreactive lymphocytes into the brain, leading to demyelination and axonal damage (1). Acute treatment involves the use of immunosuppressive corticosteroids or cytotoxic chemotherapies, while chronic disease-modifying therapies aim to downregulate immune activation or limit lymphocyte trafficking into the brain to prevent relapses. Conversely, glioblastoma represents the predominant category of malignant primary brain tumors, and this aggressive brain tumor is found with an annual

incidence of 3.2 per 100,000. Clinical hallmarks include growth and proliferation, angiogenesis, and invasion into the adjacent brain parenchyma (2). Despite aggressive combined-modality treatments with external beam radiotherapy, concurrent with cytotoxic temozolomide chemotherapy and followed by adjuvant temozolomide with or without Tumor Treating Fields, median overall survival remains a dismal 19 months and a 5-year survival rate of just 7.2% (3). Since each disorder is relatively uncommon on its own, the actual prevalence of glioblastoma in the multiple sclerosis population is likely extremely low. The existing literature is primarily descriptive, consisting of isolated case reports and small case series. However, population-based studies have not shown an increased risk of glioma among individuals with autoimmune diseases (4, 5).

When both glioblastoma and multiple sclerosis occur in the same patient, survival outcome may be compromised by treatments designed for one disease while exacerbating the other. For example, rapid progressive demyelination from external beam radiotherapy has been observed and documented in patients with multiple sclerosis (6, 7). Improvements in the conformality of radiation delivery to glioblastoma, such as intensity-modulated or volumetric arc radiation therapy, may mitigate this risk (8, 9). Furthermore, immunotherapy has become an essential treatment modality for a wide variety of solid tumors (10). Although the use of ipilimumab for advanced melanoma in a patient with multiple sclerosis resulted in severe demyelinating relapses, the overall rate of multiple sclerosis exacerbation from checkpoint inhibitors is low at 3% (11, 12). Furthermore, checkpoint inhibitors have not been shown to be efficacious against glioblastoma, though other forms of anticancer immunotherapies are under active investigation (13, 14, 15). Lastly, corticosteroids are essential immunosuppressive agents to quell acute inflammation in multiple sclerosis, but they also suppress anti-tumor immunity against glioblastoma (16). Therefore, optimal management of glioblastoma in multiple sclerosis patients requires judicious balance between anti-tumor therapies and anti-inflammatory agents.

In this report, we describe the clinical course of multifocal glioblastoma in a woman who had multiple sclerosis for 40 years and treated with glatiramer acetate for over 20 years. Her rapid and progressive neurologic decline highlights the diagnostic and biological complexities associated with these two concurrent disorders. The choice of drug treatments also deserves a critical analysis of the underlying pharmacologic effects on both neurologic disorders.

Case Presentation

Presentation of Multifocal Glioblastomas

A summary of this patient’s diagnostic and treatment procedures is outlined in Fig. 1. She was a 65-year-old woman, with a longstanding history of relapsing-remitting multiple sclerosis that had started at age 25, experienced an unprovoked seizure on May 10, 2024. Her seizure was witnessed by her husband and started with word-finding difficulty followed by speech arrest, left-gaze deviation, eye jerks and left-sided hemi-body jerks. Emergency medical service personnel arrived at her home, witnessed another seizure, and promptly administered lorazepam and levetiracetam. In the emergency department, a non-contrast

head computed tomography (CT) revealed a right frontal lobe mass with cerebral edema and effacement of sulci in the right hemisphere. Follow up gadolinium-enhanced magnetic resonance imaging (MRI) of the head showed three relatively homogeneously enhancing lesions, one in the right frontal white matter measuring 1.4 x 1.3 x 1.6 cm, another in the superior right frontal lobe measuring 1.2 x 1.3 x 1.2 cm, and a third in the right temporal white matter measuring 2.3 x 1.8 x 1.9 cm; all lesions were associated with surrounding cerebral edema as shown on (i) fluid attenuated inversion recovery (FLAIR) sequence, (ii) restricted diffusion and (iii) elevated relative cerebral blood volume (rCBV) at 1.5 to 2x the contralateral white matter (Fig. 2). Extensive white matter tract abnormalities were evident, involving the splenium of the corpus callosum as well as bilateral superior longitudinal fasciculi, inferior longitudinal fasciculi and subcortical U fibers. No systemic malignancy was detected on CT of the chest, abdomen and pelvis. Two days after her seizure, the patient underwent an excisional biopsy of the right frontal lesion because it had the highest rCBV measurement. Frozen section of the specimen showed a hypercellular tumor suspicious for a lymphocytic process, consistent with the findings on neuroradiology imaging. However, hematoxylin-and-eosin-stained permanent sections revealed a glial tumor with areas of spindle cell morphology, nuclear atypia, mitoses, endothelial proliferation and focal necrosis, features consistent with glioblastoma. Tumor cells were seen infiltrating into the adjacent brain parenchyma together with lymphocytic perivascular cuffing. By immunohistochemistry, the tumor cells diffusely expressed glial fibrillary acidic protein (GFAP) while being negative for CD45 and isocitrate dehydrogenase-1 (IDH-1 R132H); ATRX was retained, p53 was equivocal with only scatter positivity, and Ki-67 was focally positive up to 25% of tumor nuclei. Molecular analysis did not detect methylation of the *O^6-methylguanine-DNA methyltransferase (MGMT)* promoter.

Her post-operative neurological examination was characterized by an alert mental status and the ability to follow commands readily. She had a Karnofsky Performance Score of 70. Language function was fluent with good comprehension and repetition, but she had occasional naming problems. Her recall was fair. Cranial nerve examination was notable for being equal and reactive to light. Extraocular movements were full without nystagmus. Visual fields were full to confrontation and funduscopic examination revealed sharp disk margins without optic disk pallor. There was no facial asymmetry, and sensation and hearing were normal. Her tongue was midline and there was no dysarthria or abnormality in guttural sounds. Both sternocleidomastoids and upper trapezii functioned within normal limits. Motor function was characterized by normal muscle strength without subtle pronation, drift on outstretched upper extremities or hypertonia. Reflexes were 2 + and symmetrical in the extremities but ankle jerks were absent. Sensation was intact to touch and proprioception. Coordination examination did not reveal appendicular dysmetria. Her gait was steady but tandem walk was difficult for her. She had a slight sway on Romberg testing.

History of Multiple Sclerosis

Her multiple sclerosis symptoms began in her 20’s and consisted of imbalance, dysarthria and extreme fatigue. The diagnosis was made in 1984 primarily based on MRI criteria with FLAIR hyperintensities in

her brain without cerebrospinal fluid analysis for oligoclonal gammopathy or intrathecal synthesis of immunoglobulins. Initially, she was not placed on disease-modifying therapies because her flare-ups were infrequent, occurring at a rate of once per year without any need for hospitalization. However, by 2004 or about 20 years after her diagnosis, she was experiencing 5 to 6 attacks per year, prompting her neurologist to give her glatiramer acetate injections, which attenuated the frequency of attacks to once or twice per year. She had been treated chronically with glatiramer acetate until one year prior to her seizure and diagnosis of glioblastoma.

Multi-modality treatment of multifocal glioblastomas

Treatment consisted of external beam radiotherapy to both the right frontal and temporal lobes as well as the interconnecting uncinate fasciculus (Fig. 3). This was administered in 15 fractions to 4,005 cGy (in 267 cGy per fraction) concurrent with daily temozolomide at a dose of 75 mg/m^2/day. The post-radiotherapy gadolinium-enhanced head MRI showed a mixed response, with interval growth of the right superior frontal tumor from 1.2 x 1.3 x 1.2 cm to 2.4 x 1.8 x 2.1 cm and associated with elevated rCBV to 2x reference white matter, while the right frontal and right temporal lobe tumors shrank. The patient was treated with 1 cycle of adjuvant temozolomide at a dose of 150 mg/m2/day x 5 days. However, she developed neurologic dysfunctions in multiple domains, characterized by drowsiness and poor attentiveness, together with significant cognitive and motor slowing, difficulty with naming, poor short-term recall, decreased vision in the right visual field, left corticospinal tract dysfunction and imbalance. To confirm the sensitivity of her residual tumors to temozolomide, the patient underwent a gross total resection of the right superior frontal glioblastoma for tumor spheroid drug sensitivity testing using the Kiyatec 3D Predict™ Glioma assay (17). The result corroborated sensitivity to temozolomide and everolimus but no in vitro response was noted to lomustine, etoposide, or irinotecan. Postoperative gadolinium-enhanced head MRI confirmed gross total resection of the superior right frontal tumor. The patient continued to deteriorate despite escalation of dexamethasone to 4 mg two to three times and the addition of methylphenidate. A lumbar puncture, performed 1 month after her second neurosurgical procedure and 5 months after her initial seizure and diagnosis, revealed 1 white cell, 0 red cell, 43 mg/dL protein, 60 mg/dL glucose, negative cytology for malignant cells, but 3 oligoclonal bands were present. A request for everolimus was initially denied by her insurer, but the denial was reversed after external review as the reviewer agreed that everolimus could potentially treat and stabilize both the glioblastoma tumor and cerebral inflammation from multiple sclerosis. Bevacizumab infusion was initiated 2 months after her second neurosurgical procedure but her subsequent head MRI scans continued to show progressive enhancements. The patient was provided with hospice care at home and died from her disease 6.7 months after her second neurosurgical procedure, or 10.5 months from the initial diagnosis of her glioblastoma.

Post-mortem neuropathology examination

Post-mortem neuropathologic examination of the brain revealed the patient’s known multifocal glioblastomas within a background concurrent and progressive demyelinating plaques from her longstanding multiple sclerosis. On gross examination, a 6.8 cm necrotic mass was identified in the right temporal lobe (Fig. 4A). Microscopy revealed residual high grade tumor with classic glioblastoma morphology in the right frontal lobe (Fig. 4B), characterized by diffusely infiltrative tumor cells with atypia, frequent mitoses, endothelial proliferation, and pseudopalisading necrosis (Fig. 4C). Multiple periventricular white matter lesions demonstrating sharply demarcated myelin-poor, pauci-cellular morphology consistent with chronic inactive plaques. A subset of these plaques contained scattered areas of partial-remyelination, consistent with the colloquially termed "shadow plaques" formation in neuropathology (Fig. 4D). While the infiltrative tumor was found focally within these myelin-poor plaques (Fig. 4E) and throughout the white matter, there was one focus where the tumor cells did not appear to infiltrate into the plaque despite being directly adjacent to it, which may represent an area of spared involvement by tumor (Fig. 4F). H&E stain and CD3 immunohistochemical stain showed small foci of perivascular inflammation composed of CD3 + T lymphocytes indicating chronic inflammation (Fig. 4G, H).

Discussion

Our patient’s glioblastoma arose synchronously in a multifocal fashion within background of inflammation associated with multiple sclerosis (Fig. 4G, H). Both entities are diseases of the brain's white matter. As expected, her prognosis is especially poor because patients harboring multifocal glioblastoma typically have a median overall survival of 7.0 to 8.3 months (18, 19), which is significantly shortened compared to the overall survival of 14.6 to 24 months in those with solitary glioblastoma (20, 21). Importantly, patients with both glioblastoma and multiple sclerosis have a poor outcome. Despite limited data, the overall survival in this rare sub-population is 6.9 months (22).

The initial diagnostic head MRI showed neuroradiological features consistent with lymphoma instead of glioblastoma. These features include homogeneous enhancement on post-gadolinium T1-weighted sequences and restricted water diffusion on diffusion-weighted images. These unusual neuroimaging characteristics could be the result of this patient’s B-cell-biased immune response against the glioblastoma. First, there is evidence of ongoing immune activation, as evidenced by lymphocytic perivascular cuffing in the first histological specimen and oligoclonal bands in her cerebrospinal fluid from a lumbar puncture performed one month after her second neurosurgical procedure. Second, in patients with multiple sclerosis, B cells predominantly mediate the inflammatory response, while T cells and macrophages play a lesser role in the brain (23). This concept is supported by the efficacy of anti-CD20 monoclonal antibodies, such as rituximab, ocrelizumab, ofatumumab, and ublituximab, as cornerstone disease-modifying therapies for multiple sclerosis in the modern era (24). Together, the B-cell-biased immune response in our patient mounted against her glioblastoma could therefore result in an enhancement pattern similar to that for central nervous system lymphoma.

Long-term administration of glatiramer acetate in this patient necessitates further examination. Prior to her diagnosis of glioblastoma, she had been receiving this disease-modifying therapy for her frequently relapsing multiple sclerosis for more than 20 years. Glatiramer acetate facilitates the polarization of macrophages and microglia toward an anti-inflammatory phenotype, thereby contributing to its therapeutic efficacy. Since anti-inflammatory macrophages are also linked to glioma proliferation, angiogenesis, and invasion, it is theoretically possible that this medication may contribute to glioblastoma pathogenesis and progression (25, 26). Despite these concerns, current evidence does not indicate an elevated risk of malignancy associated with extended use of glatiramer acetate, and longitudinal cohort studies have confirmed its long-term safety (27).

Temozolomide can treat both glioblastoma and multiple sclerosis. First, temozolomide's efficacy for newly diagnosed glioblastoma was established in a randomized phase III clinical trial when administered concurrently with radiation and also in the adjuvant phase after radiotherapy (20). The potential benefit of temozolomide in our patient was also confirmed by Kyatec's 3D Predict™ Glioma *in vitro* assay (17). Second, temozolomide may also have efficacy as a disease-modifying therapy for multiple sclerosis, and this is based on its conversion into the active alkylating metabolite 5-(3-methyl triazen-1-yl)imidazole-4-carboxamide (MTIC) spontaneously in physiological pH. Cyclophosphamide is another alkylating agent and a disease-modifying therapy for multiple sclerosis; it is metabolized by the hepatic cytochrome P450 enzymes to 4-hydroxycyclophosphamide, which equilibrates with aldophosphamide and ultimately yields phosphoramide mustard and acrolein as active metabolites (28). Indeed, Flowers reported the use of temozolomide in a young patient with oligodendroglioma and active multiple sclerosis and found no new plaques after 7 years of follow-up (29).

Radiation can potentially precipitate neurologic dysfunction and exacerbate demyelination in patients already affected by multiple sclerosis. These deficits include neurocognitive disturbance, short-term memory loss, ataxia, diplopia, ophthalmoplegia, multiple cranial neuropathies, decreased visual acuity, and corticospinal tract dysfunction, and they occur at a median of 1.0 year after external beam radiotherapy on average to 5,000 cGy in 200 cGy per fraction for low-grade gliomas, meningioma, and pituitary adenomas (7). Additionally, a case report documented a patient irradiated for adenoid cystic carcinoma to 5,000 cGy, also in 25 fractions at 200 cGy per fraction, and developed diplopia, dysarthria, ataxia and limb incoordination. MRI revealed new demyelinating lesions in the brainstem, all within the 50% isodose region of the radiation field (6). However, patients in these cases were treated prior to the availability of image-guided treatment planning. Modern day intensity-modulated and volumetric-arc radiation therapies are the standard of care for glioblastomas, and they are particularly relevant for sparing multiple white matter tracts in our patient, which were already compromised by her longstanding relapsing-remitting multiple sclerosis (8, 9). Moreover, fatigue is the most common and a major debilitating symptom in patients with multiple sclerosis, and this can be exacerbated by radiation (30). Our patient received hypofractionated radiotherapy administered over 3 weeks instead of the standard fractionation over 6 weeks. This shorter-course radiation schedule has been demonstrated in a phase II single-arm clinical trial to improve quality-of-life scores across multiple domains, including fatigue (31).

Therefore, multiple strategies exist to limit potential radiation toxicity in multiple sclerosis patients during treatment for their glioblastoma.

Everolimus was chosen as a second-line therapeutic agent for our patient. It is both a *bona fide* anticancer drug and an immunosuppressant (Fig. 5), marketed by Novartis to oncologists under the brand name Afinitor® and to transplant surgeons under the brand name Zortress® (16). Two separate package inserts are available because the same drug was approved by the United States Food and Drug Administration for patients with cancer (21) and for solid-organ transplant recipients (33).Therefore, everolimus was chosen for the treatment of this patient's glioblastoma while simultaneously providing disease-modifying therapy for her multiple sclerosis. It is notable that the patient's insurer's denial of our request for this drug was overturned after an external review, indicating a sound rationale for our choice of this medication. The mechanism behind this drug's efficacy involves blocking mTOR, which is necessary for the clonal expansion of both malignant and inflammatory cells (34, 35).

Another drug that deserves mention is dimethyl fumarate, which can mediate metabolic reprogramming in both immune and cancer cells. It is approved as a disease-modifying therapy for multiple sclerosis. Dimethyl fumarate and its metabolite monomethyl fumarate activate the anti-oxidant/anti-inflammatory Nrf2 pathway while inhibiting the pro-inflammatory mediator NF-κB (36). Importantly, this drug blocks aerobic glycolysis by targeting the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thereby modulating the immune response and limiting immunologic memory (37). GAPDH is also a potential target for cancer therapy (38). This is because GAPDH is highly dysregulated in multiple cancer types, leading to upregulation of important cancer-related pathways and biological processes (39). Indeed, monomethyl fumarate appears to be synergistic with both radiation and temozolomide in multiple human glioblastoma cell lines, and dimethyl fumarate was subsequently investigated in a phase I trial for newly diagnosed glioblastoma patients. The results showed acceptable toxicities, and the recommended phase 2 dose was 240 mg three times daily (40). Therefore, dimethyl fumarate could be another agent with potentially dual efficacy against glioblastoma tumor growth and multiple sclerosis immune activation (Fig. 6).

This report is constrained by its focus on a single patient, which limits the ability to generalize findings and prevents causal relationships among multiple sclerosis, disease-modifying therapies, biology of glioblastoma and anti-cancer treatment responses. The clinical outcomes are further complicated by the presence of multifocal glioblastoma, which is recognized as an independent adverse prognostic factor, regardless of treatment. The process of making therapeutic decisions necessitated a personalized, non-standardized sequence of multimodal treatments, which restricts the ability to attribute outcomes to any specific intervention. Notably, everolimus was used off-label, started late in the progression of the disease, and administered for a short period amidst significant tumor burden, concurrent corticosteroid treatment, and subsequent bevacizumab therapy. Consequently, the therapeutic effectiveness and potential negative impacts of mTOR inhibition on tumor progression or immune regulation cannot be accurately evaluated and resolved. Still, this drug was chosen based on a sound rationale against glioblastoma tumor growth and multiple sclerosis immune activation. Lastly, the relationships between

long-term exposure to disease-modifying therapies and disease outcomes remain uncertain. As is the case with all case reports, these findings are prone to reporting bias and should be viewed as hypothesis-generating for future research.

Conclusion

This case illustrates an exceptionally rare coexistence of glioblastoma and multiple sclerosis, highlighting the intricate biological and clinical interactions between infiltrative malignant glioma and chronic immune-mediated demyelination. Our post-mortem findings reveal that glioblastoma cells can invade areas of myelin loss; however, tumor infiltration was not uniform across all demyelinating plaques. This suggests that the inflammatory microenvironment associated with multiple sclerosis does not consistently facilitate glioma proliferation and may, in certain regions, hinder tumor infiltration. From a clinical perspective, this case underscores the necessity of maintaining a heightened level of suspicion for neoplastic processes when new or atypical enhancing lesions emerge in patients with a long history of multiple sclerosis. Neuroimaging characteristics may be deceptive in the context of chronic neuroinflammation, thereby reinforcing the importance of prompt histopathologic validation. Lastly, therapeutic decision-making must judiciously weigh the efficacy of tumor-directed treatments against the risk of exacerbating demyelination, particularly with the use of radiotherapy, corticosteroids and immune-modulating agents. Ultimately, this case may prompt real-world N-of-1 evaluation of agents that possess dual activity against both glioblastoma and immune-mediated inflammation for this rare and complex patient population.

Declarations

Competing interests:

The authors declare no competing interests.

Consent for publication:

Informed consent for publication was obtained from the patient’s spouse.

Ethics approval and consent to participate:

This work was performed in accordance with the Declaration of Helsinki and under an institutional review board approved protocol #218622 for retrospective patient data analysis at Brown University Health.

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None.

Author Contribution

NK, LES, AN and ETW helped with data collection, data analysis, and writing the manuscript. RT, CC, EW, TR, HCC, CCC, AF, JAG, HE, SS provided patient care, interpretation of patient data, and writing the manuscript. AN, JD, MP and JD performed the gross and microscopic post-mortem examination. All authors reviewed the manuscript

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Data availability:

All primary data will be available upon request.

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Figures

Figure 1

Timeline of intervention from diagnosis to treatment and from disease progression to hospice.

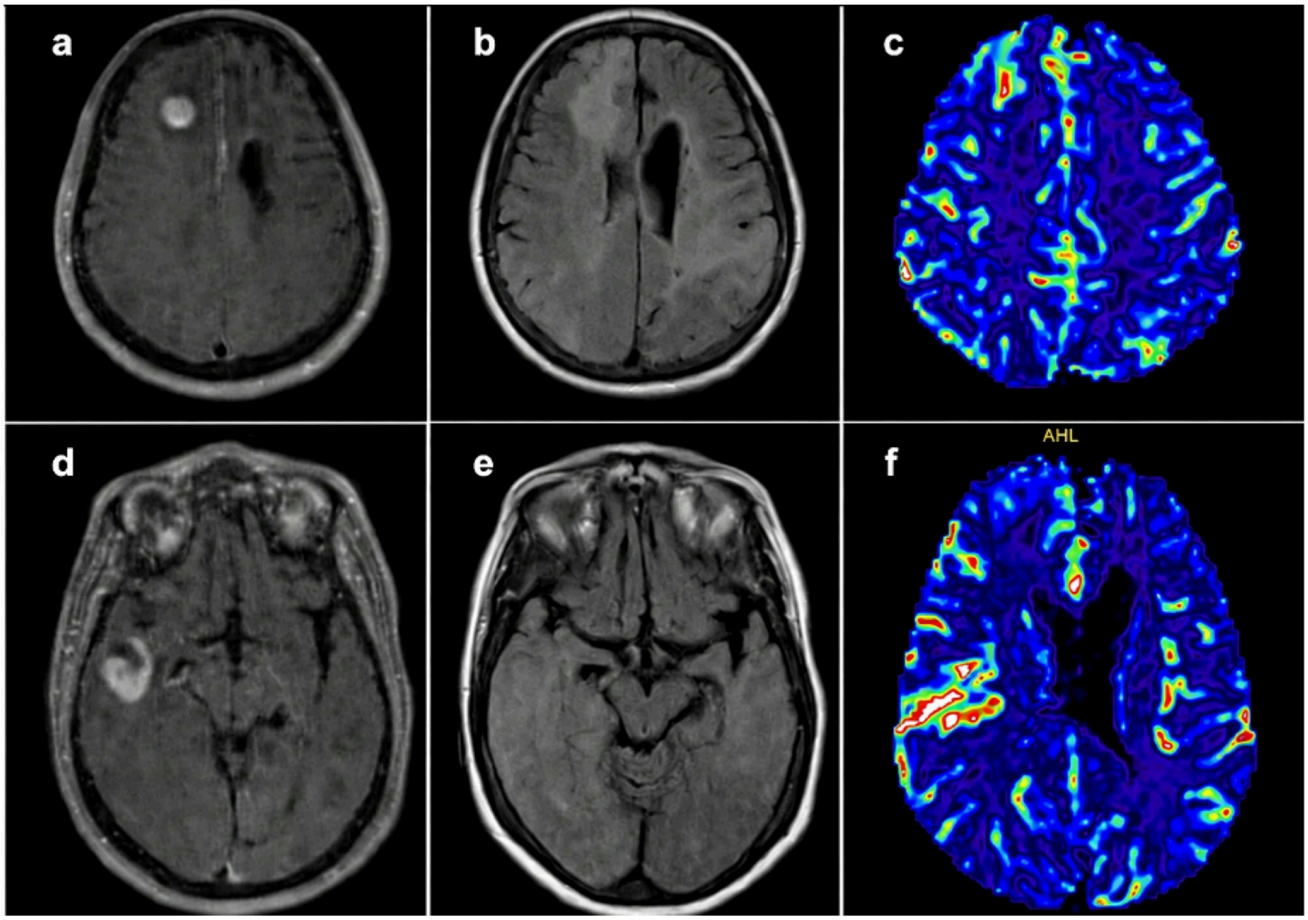

Figure 2

Gadolinium-enhanced head MRI at initial diagnosis. (a) A homogeneously enhancing mass was identified in the right frontal white matter, together with (b) extensive hyperintensities seen on the FLAIR sequence in both hemispheric white matter and (c) increased rCBV. (d) Another homogeneously enhancing mass in the right temporal pole with an open ring sign typically seen in multiple sclerosis, together with (e) extensive FLAIR hyperintensities and sulcal effacement and (f) increased rCBV.

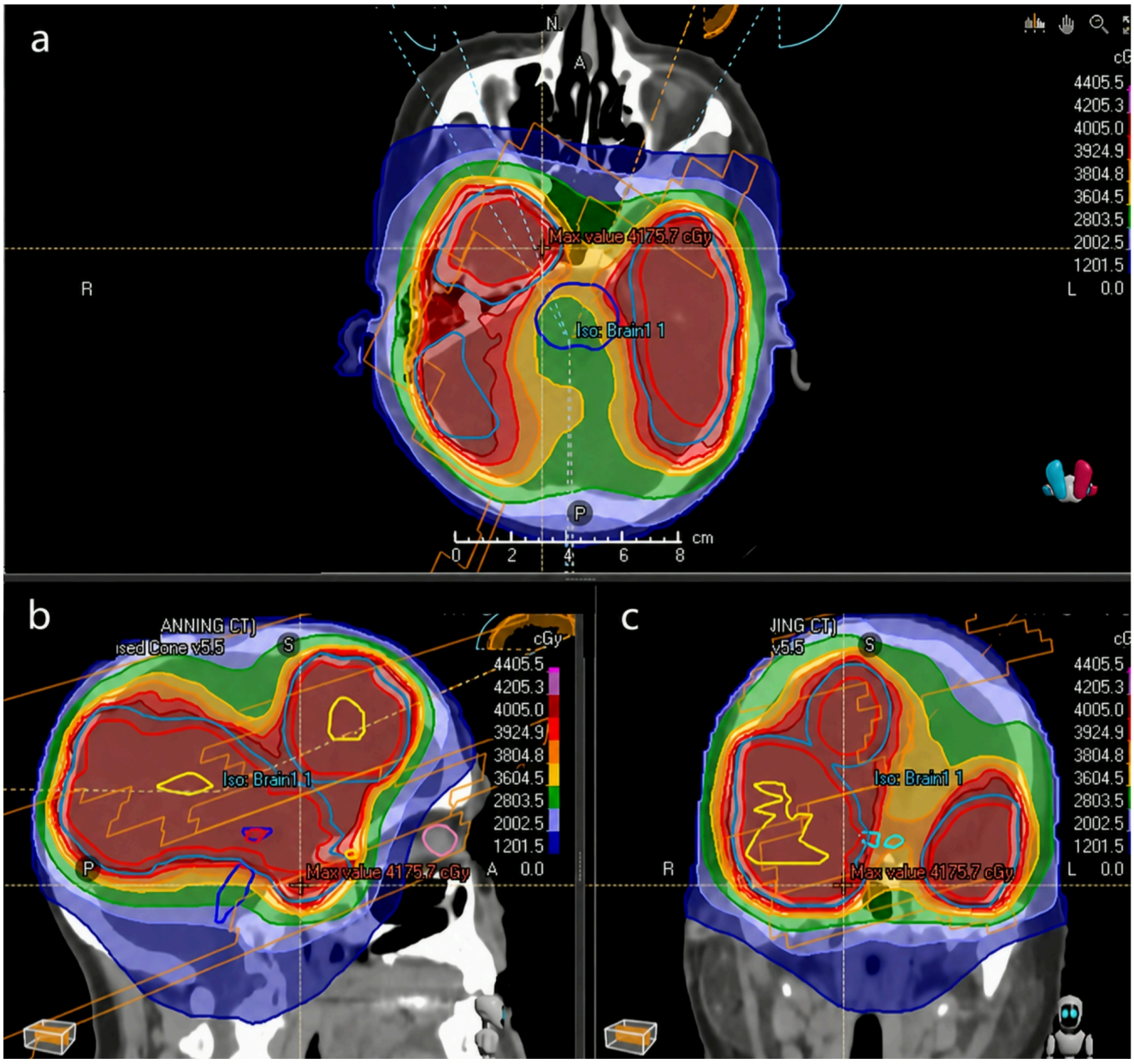

Figure 3

Radiotherapy treatment planning for the multifocal glioblastomas showing isodose distribution in axial (a), sagittal (b) , and coronal views (c).

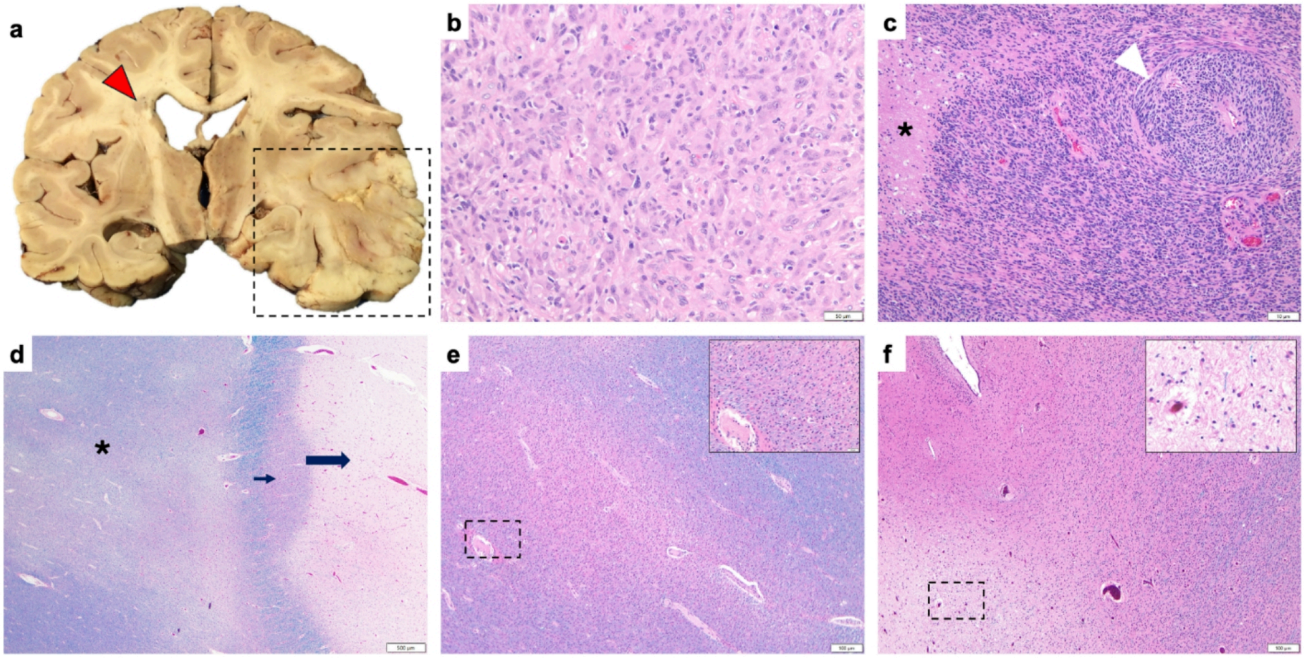

Figure 4

Post-mortem neuropathologic findings. (a) Coronal section of the cerebral hemispheres showing a necrotic right temporal lobe mass (box) and left periventricular plaque (red arrowhead). (b) High power image of previously resected right frontal lobe glioblastoma (hematoxylin & eosin 200x, scale bar=50 μm). (c) Right temporal lobe mass demonstrating atypia, pseudopalisading necrosis (asterisk) and prominent focus of endothelial proliferation (white arrowhead) (hematoxylin & eosin and Luxol fast blue 100x, scale bar=100 μm). (d) Chronic plaque in the left occipital lobe with a rim of remyelination (small arrow), consistent with shadow plaque (large arrow), adjacent to area containing numerous additional small foci of white matter pallor (asterisk) (hematoxylin & eosin and Luxol fast blue 20x, scale bar=500 μm). (e) Tumor infiltrating myelin poor foci, right occipital lobe with high power inset highlighting tumor cells (hematoxylin & eosin and Luxol fast blue 20x, scale bar=500 μm). (f) Periventricular plaque with adjacent tumor cells. High power inset highlights areas of complete demyelination without evident tumor present (hematoxylin & eosin and Luxol fast blue 40x, scale bar=100 μm).

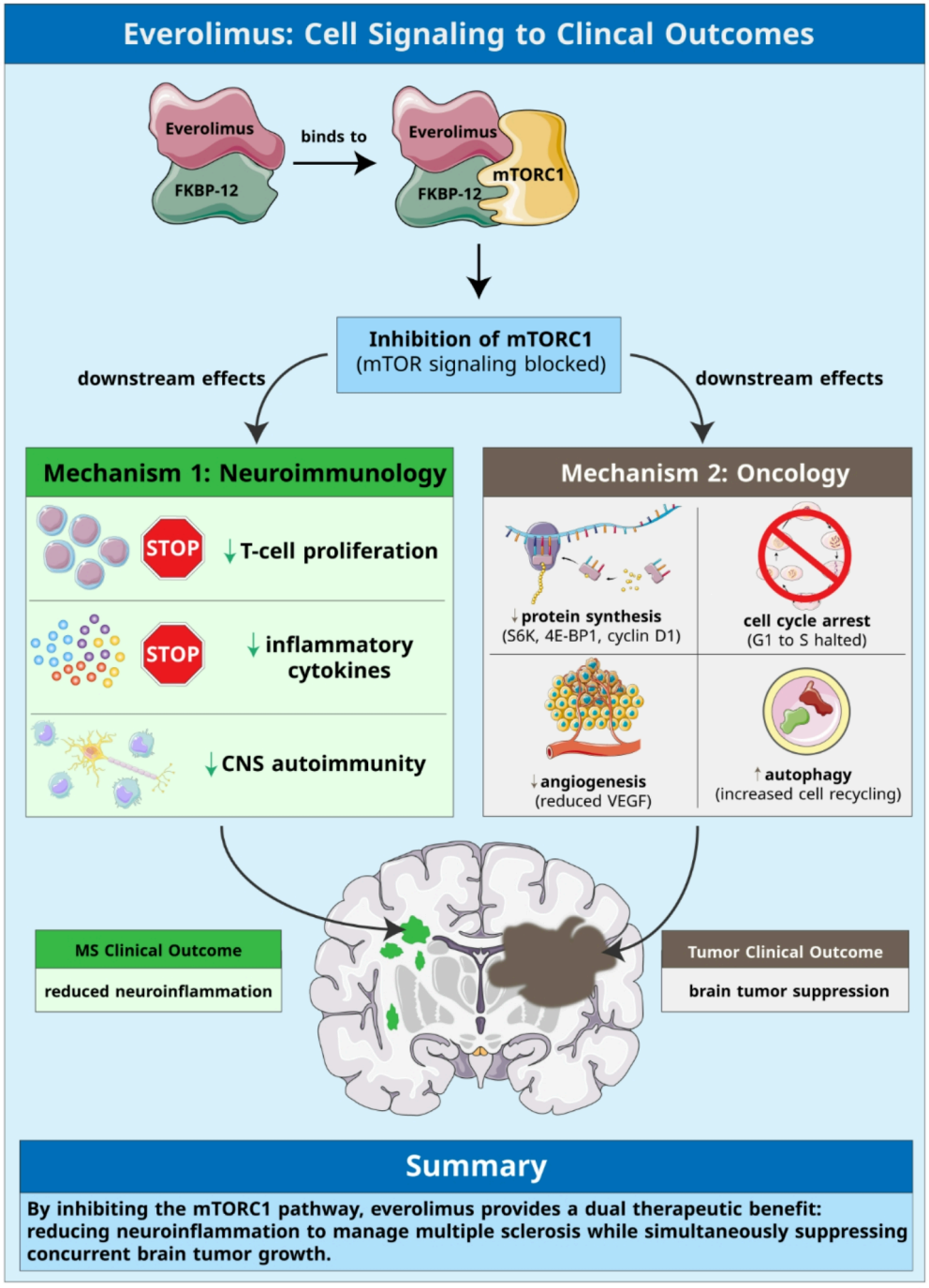

Figure 5

Everolimus' mechanisms of action. Abbreviations: 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; CNS, central nervous system; FKBP12, FK506-binding protein 12; MS, multiple sclerosis; mTORC1, mechanistic target of rapamycin complex 1; S6K, S6 kinase; VEGF, vascular endothelial growth factor.

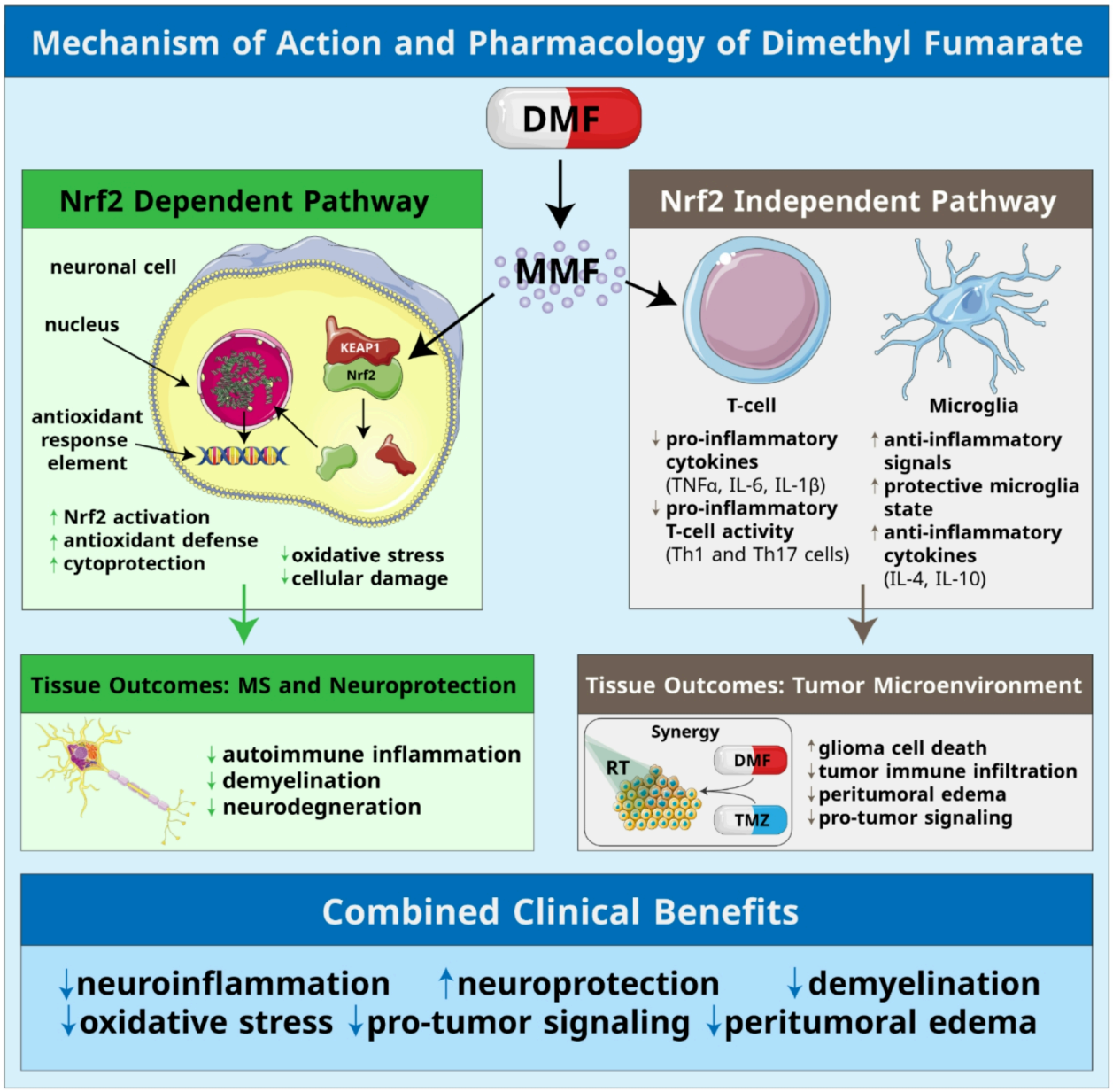

Figure 6

Dimethyl fumarate's mechanisms of action. Abbreviations: CNS, central nervous system; DMF, dimethyl fumarate; IL, interleukin; KEAP1, kelch-like ECH-associated protein 1; MMF, monomethyl fumarate; MS, multiple sclerosis; Nrf2, nuclear factor erythroid 2-related factor 2; RT, radiation therapy; Th, T helper; TMZ, temozolomide; TNF-α, tumor necrosis factor-alpha.