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Glioblastoma following treatment with fingolimod for relapsing-remitting multiple sclerosis

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Abstract

Glioblastoma is a rare and aggressive primary brain tumor with incidence of 5 per 100,000 annually. We report a 50-year-old woman diagnosed with glioblastoma within 3 years of induction of fingolimod therapy for relapsing-remitting multiple sclerosis. Fingolimod, an immunomodulating agent used in the treatment of relapsing-remitting multiple sclerosis, has also been suggested to impart a cardioprotective role in heart failure and arrhythmia via activation of P21-activated kinase-1 (Pak1). In the brain, Pak1 activation has been shown to correlate with decreased survival time amongst patients with glioblastoma. A molecular mechanism underlying a link between fingolimod use and glioblastoma development may involve activation of Pak1. To our knowledge, this is the first report of a potential association between fingolimod use and glioblastoma development.

Keywords

Fingolimod; Glioblastoma; P21-activated kinase

1. Introduction

Fingolimod (commercially known as Gilenya, Novartis Pharmaceuticals, UK) is an immunomodulating agent used in the prevention of relapses in relapsing-remitting multiple sclerosis (RRMS) [1]. Its efficacy has been shown to be superior to that of intramuscular interferon beta-1a in the prevention of relapses as well as in the reduction of lesion size and number on MRI [2]. Fingolimod acts as sphingosine-1-phosphate (S1P) receptor modulator on lymphocytes, inducing receptor internalization and subsequent cellular insensitivity to signals necessary for egress from the lymph node [2,3]. This leads to sequestration of

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Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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lymphocytes in the thymus gland and lymph nodes, thereby reducing levels of auto-aggressive circulating lymphocytes that might attack the central nervous system.

This report describes a 50-year-old woman with RRMS treated with fingolimod, who subsequently developed glioblastoma involving the splenium of the corpus callosum. We review molecular mechanisms underlying a potential association between fingolimod and glioma development.

2. Case report

A 50-year-old woman diagnosed with RRMS in 1998 was treated with fingolimod 0.5 mg per day for 2.5 years prior to presentation with altered mentation and seizures. Her only other regular medication at the time was pantoprazole 40 mg/day. Three months prior to presentation, the patient was evaluated by her neurologist for complaints of memory loss as well as development of increasing burning in both feet and painful tingling and numbness in her hands. MRI at that time revealed new thickening and mild T2 enhancement of the splenium of the corpus callosum, a lesion presumed to be a new tumefactive plaque of multiple sclerosis. One month later, she presented with a generalized tonic-clonic seizure associated with a febrile illness. She was treated with levetiracetam and 3 days of intravenous methylprednisolone with a subsequent dexamethasone taper. White blood cell count was normal at 6.6×10^3 cells per microliter, but with lymphopenia of 0.4×10^3 lymphocytes per microliter. At this time fingolimod was discontinued. She did not report additional seizures, but her cognitive function continued to decline. MRI 1 month later demonstrated further progression of the splenial lesion to 7×3 cm in size with lobulation and central necrosis (Fig. 1). On examination, the patient was oriented to person, but not place or time; her speech was slow and hypophonic; comprehension was intact, but delayed recall absent. Stereotactic biopsy was done, revealing histopathological features consistent with glioblastoma (Fig. 2). The neoplasm was diffusely glial fibrillary acidic protein and focally p53 immunoreactive, negative for isocitrate dehydrogenase 1 R132H mutation, and with Ki-67 proliferative index of 10–15%. Temozolomide and radiation therapy were subsequently initiated.

3. Discussion

Fingolimod has been shown to be superior to interferon in randomized controlled trials studying the prevention of relapses for patients with RRMS [2]. Reported adverse effects associated with fingolimod use include bradycardia/atrioventricular block, hypertension, macular edema, and elevated liver enzyme levels [1,2]. Cases of progressive multifocal leukoencephalopathy, disseminated varicella zoster, and herpes encephalitis have also been reported [2], possibly related to its immunosuppressive effects.

This report describes a 50-year-old woman who was diagnosed with glioblastoma within 3 years of induction of fingolimod therapy for RRMS. A causal link between immunosuppression and malignancy has been previously described [4]. The patient was lymphopenic at the time of original presentation, suggesting that immunosuppression may have played a potential role in glioma development. In addition to its immunosuppressive

effect, fingolimod may target signaling pathways leading to glioma development: at the molecular level, fingolimod activates P21-activated kinase-1 (Pak1) which may impart a cardioprotective role in heart failure and arrhythmias [5,6]. Pak1 is a serine/threonine protein kinase that also is a mediator of small guanosine triphosphatases, which are involved in the proliferation, survival, and invasiveness of cancer cells. Pak1 activation in the cytoplasm of neoplastic glial cells has been shown to correlate with shorter survival time amongst patients with glioblastoma [7]. While the activating effects of fingolimod on Pak1 have previously been described in the myocardium [5,6], fingolimod is a highly lipophilic molecule readily crossing the blood–brain barrier [2], suggesting that it may have similar effects on Pak1 activation in the central nervous system.

The pathway described above however is in contrast to previous *in vitro* studies and *in vivo* animal studies that have shown fingolimod to cause apoptosis of neoplastic glial cells [8]. Pathways implicated include the inactivation of the ERK-MAP kinase pathway [9], the reactive oxygen species-c-Jun N-terminal kinase-protein 53 (ROS-JNK-p53) pathway [10], and the direct of functional S1P antagonism itself [11]. While we acknowledge the reported antineoplastic properties of fingolimod, it is possible that in different cases, individual pathways play varying roles in cell proliferation and survival. Moreover, *in vitro* studies may not reflect the complex *in vivo* environment.

Given the current lack of understanding of the biological foundations of glioblastoma, treatment is limited and prognosis remains poor [12]. Although a causal link between fingolimod use and glioma development cannot be made based on a single case, this report identifies a possible association of which we feel treating providers should be aware.

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Highlights

- Fingolimod is an immunomodulating agent used in the treatment of relapsing-remitting multiple sclerosis
- We present a patient with glioblastoma within 3 years of induction of fingolimod therapy
- To our knowledge, is the first case identifying a potential association between fingolimod and glioblastoma
- A molecular mechanism underlying fingolimod use and glioblastoma development may involve activation of P21-activated kinase-1

Fig. 1. Axial T1-weighted MRI showing a large heterogeneous rim enhancing mass crossing the splenium of the corpus callosum.

Figure 0002

Figure 0003

Figure 0005

Fig. 2.

Histological examination. The tumor was composed of cells with eosinophilic, fibrillary cytoplasm and pleomorphic, ovoid to spindled nuclei (hematoxylin and eosin, original magnification $\times 100$) (A), and mitotically active with frequent mitotic figures (hematoxylin and eosin, original magnification $\times 200$) (B). The neoplasm was strongly and diffusely immunoreactive with glial fibrillary acidic protein (original magnification $\times 100$) (C). Ki-67 nuclear labeling index was elevated, approaching approximately 15% in some foci (original magnification $\times 40$) (D).