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Case report

Glioblastoma in a fingolimod-treated multiple sclerosis patient: Causal or coincidental association?

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1. Introduction

Fingolimod (Gilenya; Novartis International AG, Basel, Switzerland) (FGL) is a once-daily disease-modifying agent approved to treat relapsing forms of multiple sclerosis (MS). This sphingosine 1 phosphate-receptor modulator selectively and reversibly sequesters CCR7-positive naïve and central memory T-lymphocytes in secondary lymphoid organs, thereby preventing them from circulating to other tissues, including the central nervous system. Because the CCR7-negative effector memory T cells are spared, the immune surveillance is theoretically preserved (Chun et al., 2010). Up to now, apart from cutaneous neoplasms, there is no evidence of an increased risk of malignancy in the fingolimod all-exposure population compared to the MS and general population. However, recent reports discussing the observation of lymphoproliferative disorders in patients treated with FGL reminded us that we should remain vigilant (de Jong et al., 2018; Baharnoori et al., 2019). Here, we present a patient who developed glioblastoma while being treated with FGL.

1.1. Case presentation

A 55-year-old Caucasian woman was diagnosed with relapsing-remitting MS in 1988 at age 26. She was treated at an affiliated hospital with interferon beta − 1b for 14 years. She was treated at an affiliated hospital with interferon beta − 1b for 14 years. In late 2013, she had a spinal cord attack resulting in right-sided weakness and sensory loss, suspended sensory level between T8-10 on the right, and reduced walking distance, from which she recovered partially. At that time, brain MRI showed a new gadolinium enhancing demyelinating lesion in the left occipital lobe, and she was tested positive for neutralizing anti-interferon beta antibodies. Given the persistence of inflammatory activity despite the first-line treatment, she transitioned to FGL in February 2014 by the patient's local neurologist, to stabilize disease activity. Afterward, she had neither relapses nor MRI activity for the next 4 years (EDSS score 4.0). During FGL treatment, the absolute lymphocyte counts ranged from 190 to 577/µl (normal range 1000–3000/µl). Grade 4 lymphopenia (≤ 200 cells/µL) was only observed once during the routine surveillance, but absolute lymphocyte counts were most of the time < 400/µl. Apart from MS, the patient had no significant medical history. During treatment with FGL, MS remained clinically and radiologically stable. In May 2018, she had an MRI of the brain which didn't reveal any new or enhancing lesion (Fig. 1A–C).

In October 2018, 4.5 years after staring FGL therapy, she was admitted to our hospital after developing speech disturbance 2 days ago. In the previous days, she also had transient right hemisensory disturbance. Her medications included fingolimod 0.5 mg daily and levothyroxine 125 µg daily. On admission, examination was notable for mildly impaired speech fluency and mild dysarthria. Neurological examination was otherwise unchanged (EDSS 4.0) and revealed mild gait ataxia, grade 4 right-sided hemiparesis with Babinski sign, right hypoesthesia, and nystagmus. She had no fever and her mental status was not altered. The admission laboratory studies showed fingolimod-induced grade 3 lymphopenia (absolute lymphocyte count 230/µL, with CD4 T cells 23/µl, CD8 T cells 45/µl and CD19 B cells 22/µl) but were otherwise unremarkable. The patient underwent brain MRI which demonstrated a new closed ring contrast-enhancing mass in the left frontal lobe, with surrounding edema (Fig. 1D–E). FGL was discontinued immediately. Tumefactive form of MS relapse, brain abscess, and neoplasm were considered in the differential diagnosis. Ten days after the MRI scan, the patient underwent subtotal resection of the lesion. Histopathologic examination was consistent with a glioblastoma (WHO grade IV) showing increased cellularity consisting of astrocytes with nuclear atypia, high mitosis, microvascular proliferation, and areas of necrosis (Fig. 2A–C). A positive immunohistochemical reaction to the glial marker Glial Fibrillary Acidic Protein confirmed the glial lineage of the tumor (Fig. 2D). Subsequent molecular analyses revealed an unmethylated MGMT and IDH wild-type. The patient was then

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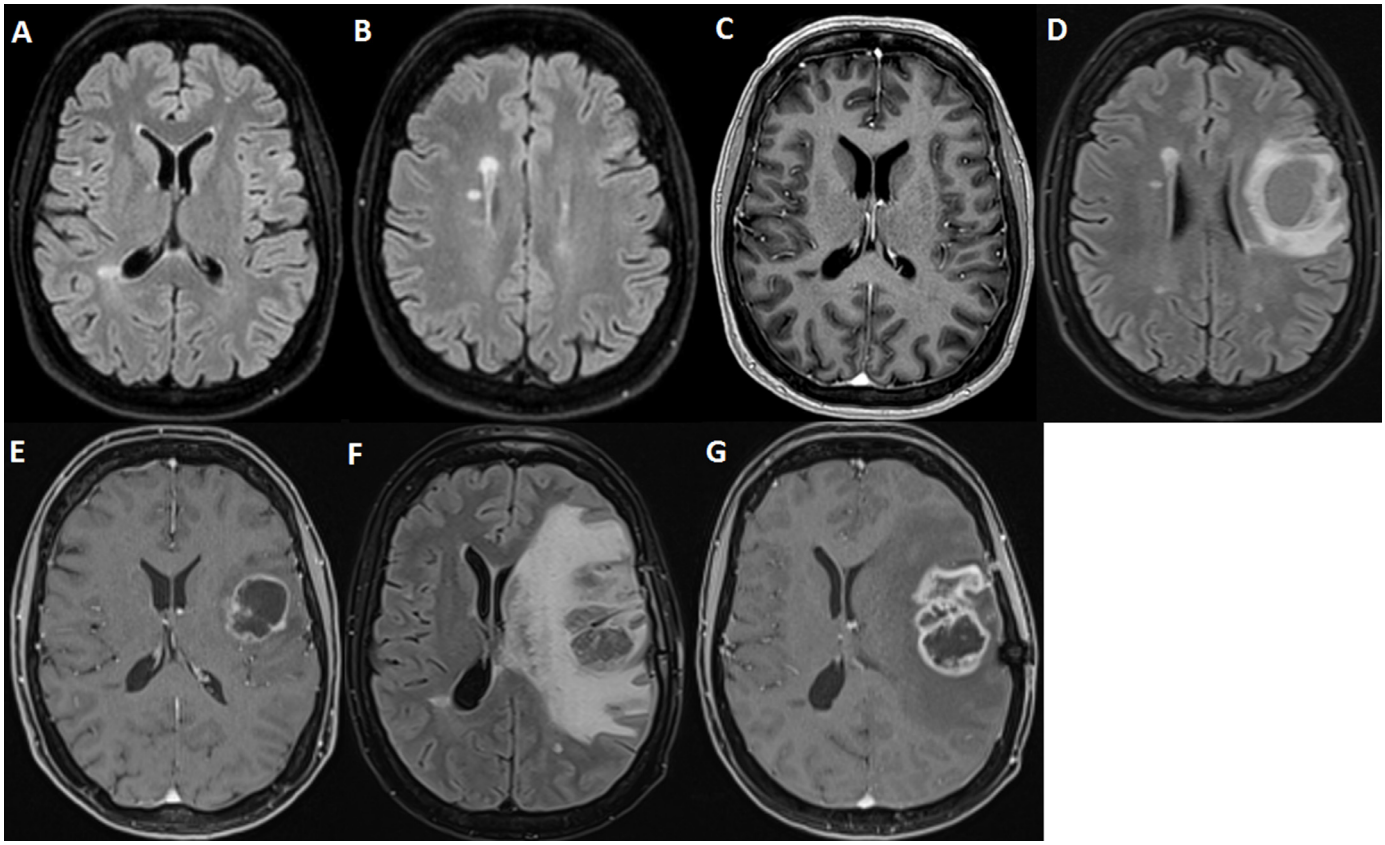

Fig. 1. Brain MRI. Axial T2 fluid attenuated inversion recovery (A,B) and T1 post-contrast (C) images performed 5 months (May 2018) before the diagnosis of glioblastoma, and showing no evidence of malignancy. Axial T2 fluid attenuated inversion recovery (D) and T1 post-contrast (E) images of the tumor at initial presentation (October 2018). Axial T2 fluid attenuated inversion recovery (F) and T1 post-contrast (G) images of the tumor 3 months after diagnosis. Periventricular lesions suggestive of multiple sclerosis can be observed (A, B, D).

treated with radiotherapy plus concomitant and adjuvant temozolomide. MRI follow-up at 3 months showed tumor progression (Fig. 1G–H). Despite addition of lomustine to temozolomide and radiotherapy, the patient's condition rapidly worsened. Palliative care was given at home and the patient died 5 months after diagnosis.

2. Discussion

We describe here a case of rapidly fatal glioblastoma while on FGL. Glioblastoma is the most common primary malignant brain tumor in adults. The prognosis of patients with glioblastoma remains dismal due to its infiltrating nature, even after surgery, radiation and chemotherapy. After searching in PubMed and Scopus, we found only one confirmed case of glioblastoma developed in an MS patient treated for 2.5 years with FGL (Sharim et al., 2016). However, when we checked VigiBase (http://www.vigiaccess.org/), the World Health Organization global database for adverse drug reactions, we found 12 cases in addition to our case which have already been reported anonymously to the Belgian centre for Pharmacovigilance (BCPH).

Besides its remarkable effectiveness in reducing disease activity in relapsing MS, current data suggest that FGL has additional therapeutic applications. An anti-cancer effect of FGL has been described in various *in vitro* and *in vivo* cancer models including glioblastoma, suggesting the potential use of FGL as a therapeutic agent in a wide variety of tumors. FGL reduces migration and invasion of glioblastoma cell by inhibiting the PI3K/AKT/mTOR/p70S6K signaling pathway (Zhang et al., 2014) and induces apoptosis, autophagy and necroptosis in human glioblastoma cell lines, both *in vitro* and *in vivo* animal studies (Zhang et al., 2015). Furthermore, FGL has been shown to sensitize glioblastoma cells to the DNA alkylating chemotherapeutic temozolomide by inhibiting the Nrf2/ARE pathway (Zhang et al., 2017). However, these data must be interpreted with caution, mainly because the stunning *in vitro* effect of FGL was weaker *in vivo* (Brunkhorst et al., 2014). Moreover, these anti-cancer properties of FGL have been observed with decisively higher doses than those used in MS patients, at concentrations that might not be reached *in vivo*. Finally, down regulation of sphingosine-1-phosphate receptor, which is induced by FGL, has been associated with poor survival in glioblastoma multiforme (Walters et al., 2011).

Our patient had profound and prolonged lymphopenia, (circulating lymphocytes counts $< 400/\mu l$ most of the time), it is therefore possible that lymphocyte sequestration had impaired cancer surveillance. Indeed, previous experiments in mouse models for myeloma and B-cell lymphoma have shown that FGL can reduce immuno surveillance, resulting in cancer development (Lovrik et al., 2012). However, mice were treated with higher doses of FGL than those used in MS patients

In conclusion, there is currently no direct evidence determining causality of FGL, but this observation advocates the need for continued vigilance in FGL-treated patients, especially in patients older than 50 years who appear to be at higher risk of infections and malignancies due to the effects of natural immuno senescence in conjunction with long-term effects of fingolimod on the immune system. This also underscores the importance of gathering real world evidence on the long-term safety of MS patients on disease-modifying treatments. Physicians should be encouraged to systematically report the occurrence of malignancies in patients with MS exposed to disease-modifying treatments to help answer whether FGL confers any tumor-promoting effect.

Declaration of Commpeting Interest

The authors declare no conflict of interest regarding this case report.

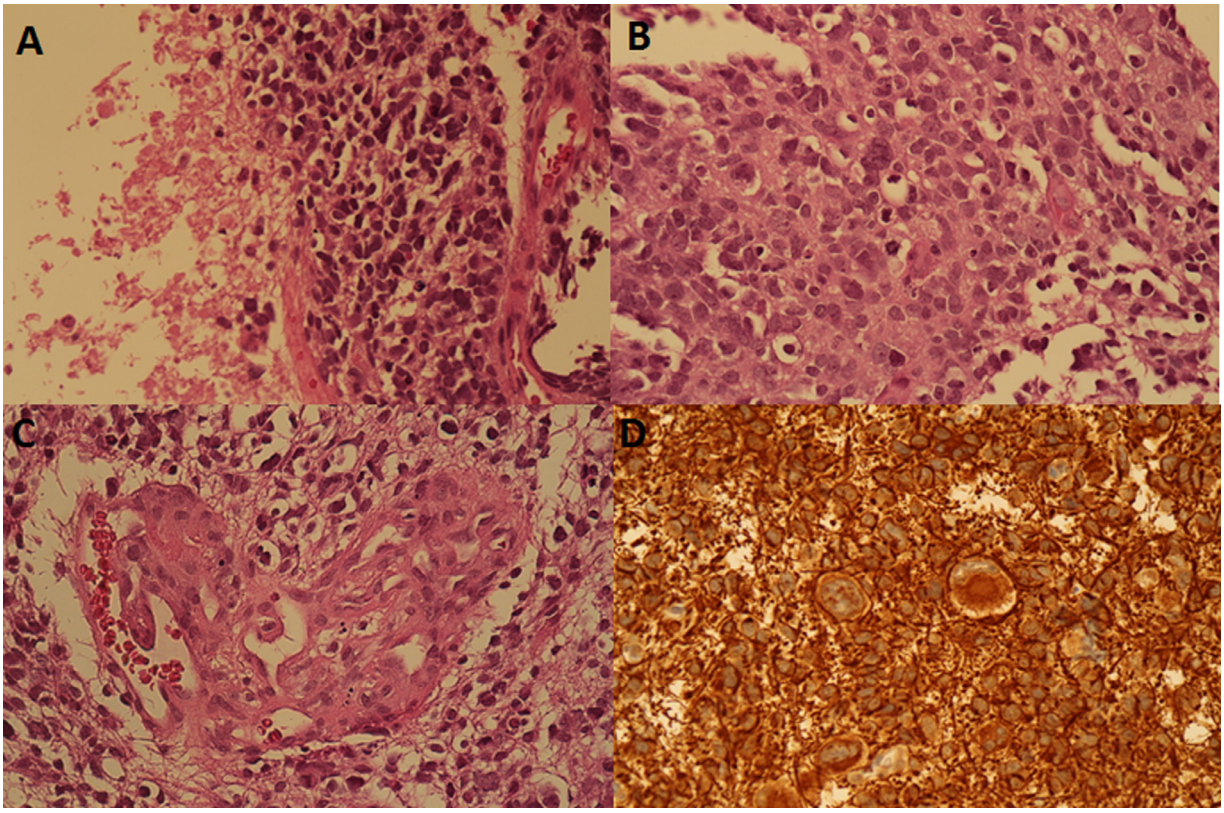

Fig. 2. Histological examination. Hematoxylin and eosin stains of the tumor, showing necrosis at 40x (A), mitotic figures at 40x (B), and microvascular proliferation at 40x (C). The lesion was strongly and diffusely immunoreactive with glial fibrillary acidic protein (40x) (D).

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