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Case Report

Signet-Ring Cell Adenocarcinoma of the Lung Associated with Fingolimod Treatment in a Patient with Multiple Sclerosis

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Abstract

Fingolimod is a selective sphingosine-1-phosphate (S1P) receptor modulator approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) as monotherapy, in cases of first-line treatment failure, or as a first option in aggressive forms. The appearance of neoplasms is among the infrequent side effects of treatment. This is a case report on an MS patient treated with Fingolimod who developed pulmonary signet-ring cell adenocarcinoma of the lung and features a discussion of the drug's possible involvement in the development of these types of neoplasms.

***Keywords:** Fingolimod Treatment; Lung, Headache; Signet-Ring Cell Adenocarcinoma; Multiple Sclerosis*

Introduction

Idiopathic intracranial hypertension (IIH) is a neurological disease characterized by clinical manifestations of increased Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by inflammation, demyelination, glial scar formation, and neuro-axonal damage. Fingolimod is a selective sphingosine-1-phosphate (S1P) receptor modulator approved by the Spanish Agency for Medicines and Health Products for the treatment of relapsing-remitting MS (RRMS) as monotherapy, in cases of first-line treatment failure, or as a first option in aggressive forms[1]. The drug acts as an antagonist at the lymphocyte level, preventing lymphocyte egress from lymphoid tissues and thereby redistributing and reducing migration to the central nervous system, lessening inflammation and tissue damage[2]. The appearance of neoplasms is among the infrequent side effects of treatment. The rare association with basal cell carcinoma of the skin and the very uncommon association with lymphomas are also described in the technical file[3]. In a recent retrospective observational study on the use of Fingolimod in Spain which included 804 patients treated in 56 hospitals, neoplasms appeared in 5 patients, or 0.6% of the sample, including breast cancer, cervical cancer, Merkel cell carcinoma, renal cancer, and papillary thyroid cancer[4]. The case report below is of an MS patient being treated with Fingolimod who developed signet-ring cell adenocarcinoma and features a discussion of the drug's possible involvement in the development of these types of neoplasms.

Case Presentation

A 35-year-old non-smoker, a Berber and military professional with no medical history of interest who was first evaluated in 2010 at age 29 for hemiparesis in the right half of the body along with distal onset involving ascending tingling in the same extremities and dysmetria. At the age of 25, the patient had suffered several falls due to numbness in his right foot that was resolved in a few days, hence the failure to consult with a physician. The following was observed on exploration at the time: left papillary pallor in the fundus of the eye, right-beating nystagmus, hemiparesis in the right half of the body with dysmetria that did not prevent ambulation, global hyperreflexia and positive Babinski response on the right. An MRI of the neuraxis was performed, with results showing more than 12 demyelinating lesions distributed throughout the juxtacortical, periventricular, infratentorial and cervical cord levels, of which one showed contrast. The cerebrospinal fluid analysis showed the presence of oligoclonal IgG bands. Treatment with Interferon beta-1a, 44 micrograms subcutaneously 3 times per week, was initiated.

In 2011, the patient suffered right optic neuritis with severe visual impairment and, weeks later, a new medullar outbreak with paraparesis of the lower limbs. The sequelae impairments of both outbreaks persisted, despite treatment with intravenous steroids at high doses, to give an EDSS score of 5.5. It was agreed to replace the treatment with Fingolimod 0.5 mg once daily. Treatment was initiated according to protocol and was effective and well-tolerated for 52 months with no new outbreak. Serial blood cell counts every 3 months showed lymphopenia never lower than 200 cells / microliter and mean numbers of between 600 and 800 cells / microliter. The patient's body mass index was 31.

In March 2016, the patient consulted due to an outbreak, presenting with dysarthria and an increase in basal paraparesis that prevented him from walking. The patient had no fever or systemic symptoms. On examination, bulbar dysarthria, left internuclear ophthalmoplegia and tetraparesis predominated in the lower limbs. The patient was admitted for reevaluation. A complementary study was performed with a lymphocyte count of 900 cells / microliter. Brain and spinal MRI showed an increase in lesion load in the brainstem, with a contrast-enhanced lesion in the cervical cord and, as a casual finding, an image suggestive of metastatic lesion (Figure 1A) in the D1 vertebral body that was not present in MRI performed 6 months before. A chest CT showed a nodule in the upper segment of the lower left lobe and left hilar adenopathy and mediastinal prevascular area. A PET scan with 18F-fluorodeoxyglucose showed hypermetabolic areas suggestive of neoplasms in all suspicious lesions (Figure 1B) with no extra-thoracic presence. A thoracotomy was performed by transbronchial needle aspiration for the adenopathy study, which was conclusive for mucosecretory adenocarcinoma with signet-ring cells (Figure 1C). The tissue showed positivity to the TTF-1 marker (nuclear marker of pulmonary origin).

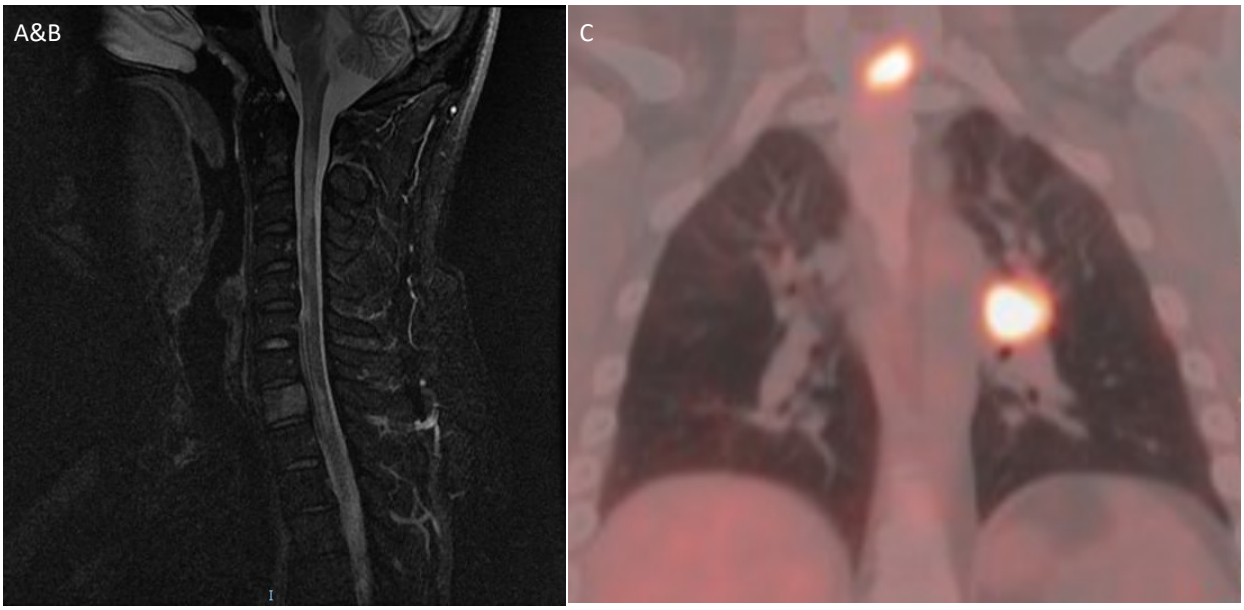

Figure 1: A*) Cervical spinal cord STIR MRI sequence. Intra-axial demyelinating lesions and hyperintense lesion in the D1 vertebral body are observed;* ***B)*** *PET scan with 18F-fluorodeoxyglucose showing hypermetabolic areas in hilar adenopathy and in the vertebral body;* ***C)*** *Pathologic anatomy of hematoxylin-eosin-stained signet-ring cells.*

Fingolimod treatment was discontinued and chemotherapy and radiotherapy for the vertebral lesion was proposed.

Discussion and Conclusion

The association of neoplasms with the use of Fingolimod treatment for MS is infrequent. Nevertheless, patients receiving immune-suppressing medication such as Fingolimod are known to experience an increased risk of lymphomas and other malignant cancers, particularly of the skin. Side effects like neoplasms are rare and could take a long time to develop or be detected. A review of the scientific and medical literature identified two published patient medical reports (case reports), three medical research studies on human participants (clinical trials), and four safety reviews that describe cases of neoplasms in patients treated with Fingolimod[5]. Moreover, in the FREEDOMS II study, participants receiving Fingolimod had a higher occurrence of skin cancers and neoplasms than those who did not[6].

In this particular case, discovery was by chance and in the context of the neuroimaging requested due to an aggressive outbreak, which meant that stage IV carcinoma was diagnosed. In this patient, the Fingolimod-induced prolongation of cellular and humoral immunosuppression for 52 months, an expected pharmacodynamical treatment effect, could have affected the adenocarcinoma pathogenesis. The transient suspension of Fingolimod treatment is recommended even if the patient is asymptomatic to lymphopenia with a cell count of less than 200 cells / microliter to prevent opportunistic infections, even though the peripheral blood lymphocyte count does not reflect the total lymphocyte population due to the drug's action mechanism[7]. There is no association data for sustained lymphopenia with prolonged use of the drug and appearance of neoplasms.

The appearance of adenocarcinoma with pulmonary signet-ring cells in this patient could be associated with Fingolimod's action as an S1P receptor modulator. Adenocarcinoma with pulmonary signet-ring cell pattern is an uncommon entity: 0.14-1.9% of lung carcinomas. It is a subtype of mucin that produces adenocarcinoma characterized by the presence of round cells with a large cytoplasmic vacuole that displaces the nucleus to the periphery, adopting the seal ring phenotype[7]. This cell pattern has an aggressive clinical behavior and some studies suggest that the S1P signalling pathway could promote an increase of epidermal growth factor receptor (EGFR) expression in lung adenocarcinoma cells, thus enhancing EGF-stimulated colony formation, proliferation and invasion of lung adenocarcinoma cells[8].

Fingolimod is a selective S1P receptor modulator and several lines of evidence suggest that S1P mediated signalling pathways are closely linked to the carcinogenesis of various human cancers[9-10]. Concretely, a recent study has shown that the S1P-mediated signalling pathways could be involved in the development of human lung adenocarcinoma, leading to increased cell proliferation and invasion. Hence the potential link between use of Fingolimod and abnormal tissue growth (neoplasms) should be monitored.

Conflict of Interest

The authors declare there is no conflict of interest to disclose.

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