

CASE STUDY

BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA IN A PATIENT TREATED WITH FINGOLIMOD FOR MULTIPLE SCLEROSIS – A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

The aim: Multiple sclerosis (MS) is a disease of the central nervous system (CNS) characterized by inflammation and demyelination, which leads to chronic progressive disability. Fingolimod is the first registered oral disease-modifying drug (DMD) approved for the treatment of highly active relapsing-remitting multiple sclerosis (RRMS). Fingolimod statistically significantly reduced the number of relapses, clinical and radiological disease activity and disability progression. However, fingolimod can be associated with an increased risk of cancer. This study is aimed to underline how important is regular specialist follow-up during fingolimod therapy.

Materials and methods: The literature review was conducted using the key words: "fingolimod", "multiple sclerosis", "fingolimod and cancer", "relapsing-remitting multiple sclerosis", "fingolimod adverse effects", "basal cell carcinoma fingolimod", "squamous cell carcinoma fingolimod". The study is based on the case report of a 67-year-old male patient with metachronous skin cancer treated with fingolimod. The drug had an influence on the inhibition of clinical and radiological activity of the disease. Despite the control of the underlying disease, skin cancers occurred during treatment. Basal cell carcinoma and squamous cell carcinoma were diagnosed at an early stage when complete resection was possible and negative (R0) margin resection was achieved.

Conclusions: Dermatological examination should be performed at the beginning and during treatment with fingolimod. Patients need to be informed about the risk of malignancy. Patient education are crucial during treatment, which allows achieving a good therapeutic effect, thus minimizing the risk of malignancy and enabling its early detection and cure.

KEY WORDS: multiple sclerosis, basal cell carcinoma, squamous cell carcinoma, fingolimod, metachronous skin cancer, relapsing- remitting multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is a multifactorial chronic disease of the central nervous system (CNS) characterized by inflammation and demyelination, which leads to chronic progressive disability, thus impairing the quality of life.

The disease predominantly affects young adults between 20 and 40 years of age. It is more prevalent in the Caucasian population. Women are more frequently affected [1-4].

The current treatment of MS consists primarily of disease-modifying drugs (DMDs). The therapy includes first-line agents (β -interferons, pegylated interferon beta 1a, glatiramer acetate, dimethyl fumarate) and second-line agents (fingolimod, natalizumab, ocrelizumab, cladribine). The latter group of drugs is indicated in rapidly progressive severe disease or when the first-line treatment is not effective [5].

Fingolimod was approved by the Food and Drug Administration (FDA) for the treatment of MS in 2010 [5-7]. It is an oral immunosuppressive drug which binds to the sphingosine-1-phosphate receptor located on immune cells [7, 8]. By modulating the function of S1P receptors on lymphocytes, it inhibits their migration from lymph nodes

to the peripheral blood and the central nervous system [9, 10]. The drug reduces their autoimmune activity in the CNS, which is the pathogenesis of MS lesions.

As with other drugs, the use of fingolimod is also related to the risk of adverse effects. The most commonly reported side effects include headache, flu-like symptoms, diarrhea, nausea, cough, back pain, sinusitis, and rhinitis. In addition, elevated liver enzymes (ALT, GGT, AST) are also reported [6, 7, 10, 11].

Furthermore, the use of fingolimod can be associated with an increased risk of cancer [8]. FDA and the European Medicine Agency (EMA) list lymphomas as a potential adverse effect of fingolimod therapy. Additionally, EMA pays attention to the possibility of developing skin cancer during therapy [9].

Studies reported that patients treated with fingolimod developed basal cell carcinoma, squamous cell carcinoma, cutaneous melanoma, Kaposi's sarcoma, squamous cell carcinoma of the palatine tonsil related to human papillomavirus infection, breast cancer, primary cutaneous CD30+ anaplastic large-cell lymphoma (PCALCL), or Merkel cell skin cancer [4, 6, 7, 11-19].

THE AIM

The purpose of this study is to highlight the need for regular specialist follow-up during fingolimod therapy and to indicate the relationship between treatment with this drug and skin cancer occurrence based on our case report and on the literature review.

MATERIALS AND METHODS

Polish and English-language publications were found according to the given keywords: “fingolimod”, “multiple sclerosis”, “fingolimod and cancer”, “relapsing-remitting multiple sclerosis”, “fingolimod adverse effects”, “basal cell carcinoma fingolimod”, “squamous cell carcinoma fingolimod” in the databases of the PubMed and Google Scholar.

CASE REPORT

A 67-year-old male patient was admitted to the Department of Otorhinolaryngology and Oncological Laryngology in Zabrze in early March 2020 due to a skin tumor of the right nasal vestibule. The patient reported impaired nasal patency on the right side, which worsened over a short period of time. Anterior rhinoscopy revealed a nodular lesion obstructing the right nasal passage.

In July 2019, the patient had undergone resection of a skin tumor of the left nasal wing. Histological evaluation showed basal cell carcinoma. Total resection of the lesion was performed and the patient underwent a periodic follow-up.

The patient's medical history included surgical removal of a skin tumor of the left thigh in 2019 and resection of a neck skin tumor in 2018. Postoperative histological assessment showed keratoacanthoma and basal cell carcinoma, which was resected completely.

The patient started to be under the care of the department of neurology due to relapsing-remitting MS (RRMS) in May 2009. In 2009, the patient developed limb weakness on the right side and right-sided hypoesthesia. Similar symptoms also occurred in 2000. Outpatient brain magnetic resonance imaging (MRI) showed no pathological lesions. However, MRI of the cervical spinal cord showed a single demyelinating lesion at the C6-C7 level. The symptoms resolved spontaneously. Except for urinary incontinence, the patient had no other complaints. In 2009, contrast-enhanced MRI of the brain showed diffuse supratentorial and infratentorial demyelinating lesions with one active lesion in the cervical region without radiological progression. Visual evoked potentials showed bilateral visual pathway damage. After glucocorticoid treatment, the neurological condition of the patient improved. In February 2010, the patient had another relapse in the form of right limb paresis. As a result, interferon-beta-1 b was administered. The patient was given subcutaneous injections of recombinant interferon-beta-1b for 3 years. During the third year of treatment, other relapses of moderate intensity occurred (June and July 2013). The neurological status was assessed according to the Expanded Disability Status Scale (EDSS = 4.5). In September 2013, a follow-up MRI of the brain

showed progression of demyelinating lesions with the presence of 3 new lesions on T2-weighted sequences. The patient met the inclusion criteria for treatment with fingolimod (two moderate relapses during the first-line therapy and lesions on MRI).

In September 2013, the patient was qualified for treatment with fingolimod after undergoing basic and additional tests (including tests for the presence of antibodies against hepatitis B virus) and cardiac, ophthalmological and dermatological assessment. The treatment was initiated without complications. During therapy, no relapses were observed and the patient's neurological condition improved (EDSS = 2.0). Follow-up brain MRI examinations, which were performed in September 2014 and 2015, showed no radiological progression. In September 2016, a reduction of two demyelinating lesions was found on MRI with no enhancement following contrast administration. In subsequent years, follow-up MRI examinations showed no progression of demyelinating lesions. The patient was on oral fingolimod 0.5 mg for 7 years.

The subject was also diagnosed with peptic ulcer disease and had a gastric perforation which was surgically treated in 2017. As a result, the patient was on pantoprazole (20 mg/day). Other medications taken by the patient included zopiclone (3.75 mg/day), and bisoprolol (2.5 mg/day).

The patient was retired and did not work. He had previously been employed in a gas plant but had very little exposure to ultraviolet radiation.

The patient had a 50-year history of smoking (10-20 cigarettes/day) and his family history was positive for cancer (brothers diagnosed with hepatic cancer and multiple myeloma, while father died of gastric cancer).

In March 2020, the patient was admitted to the Department of Otorhinolaryngology for surgery. An excisional biopsy of the lesion was performed. Histological examination showed keratinizing squamous cell carcinoma (G1) without angioinvasion or neuroinvasion. Cancer infiltration was found in the surgical margins. Therefore, the patient was referred for radical surgery. On April 16, 2020, a lateral rhinotomy was performed under general anesthesia. After injecting the incision site with marcaine and epinephrine, an incision was made around the right nasal wing, the flap was inverted, the skin scar of the nasal vestibule from the previous surgery was located and removed with a wide margin of surrounding tissue. Surgical margins were collected and the specimen was sent for histological examination. Subcutaneous and skin sutures were placed. A seton with the ointment was placed to the right nasal passage. Histological findings showed keratinizing squamous cell carcinoma (G1) (maximum size of 0.6 cm; infiltration depth of 0.2 cm). No vascular or nerve invasion was found. The lesion was completely resected with surgical margins (the transverse margins were 0.3 cm, longitudinal margins were 0.4 cm, and the deep margin was 0.1 cm). The surgical margins which were additionally referred for assessment were free of tumor tissue. R0 resection was achieved in the patient. Due to histological findings, the administration of fingolimod was discontinued.

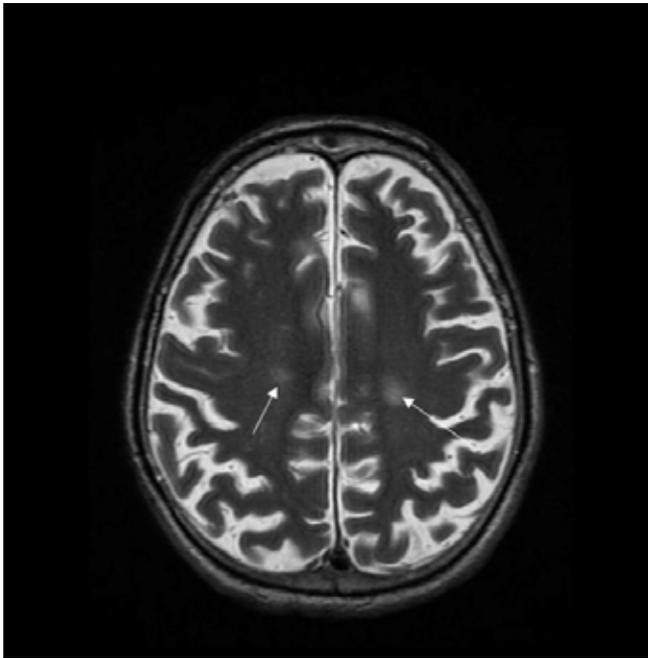


Fig. 1. Magnetic resonance imaging (MRI) after fingolimod treatment shows a reduction of demyelinating lesions. Axial MRI, T2- weighted image showing periventricular lesions and subcortical foci in the centrum semiovale (arrows).

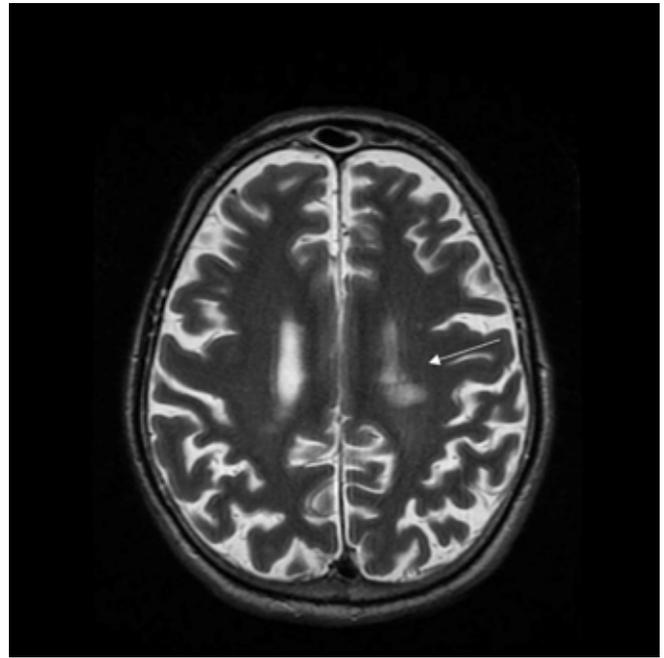


Fig. 2. Magnetic resonance imaging (MRI) after fingolimod treatment shows a reduction of demyelinating lesions. Axial MRI, T2- weighted image showing periventricular lesions and subcortical foci in the centrum semiovale (arrows).

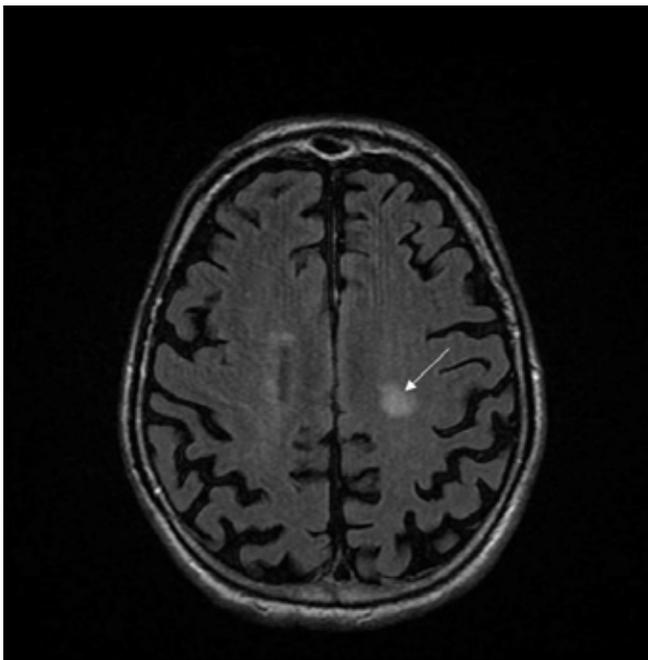


Fig. 3. Magnetic resonance imaging (MRI) after fingolimod treatment shows a reduction of demyelinating lesions. Axial MRI T2/FLAIR images show periventricular demyelinating plaques (arrows).

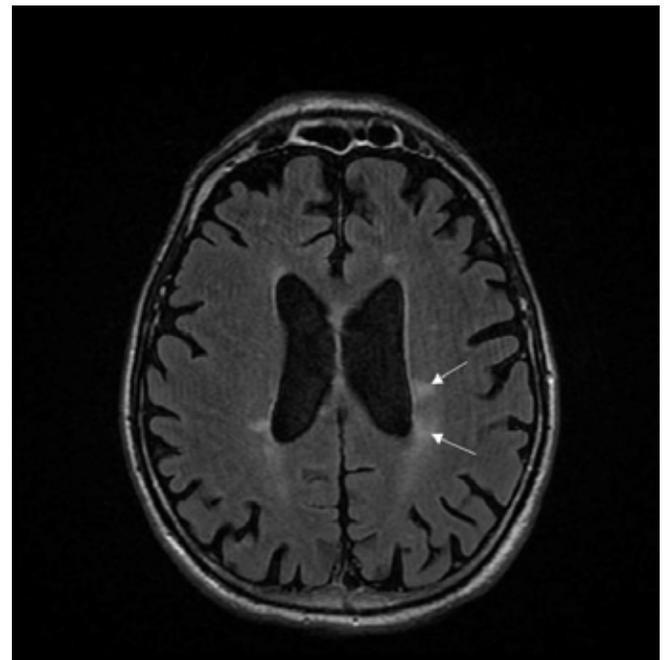


Fig. 4. Magnetic resonance imaging (MRI) after fingolimod treatment shows a reduction of demyelinating lesions. Axial MRI T2/FLAIR images show periventricular demyelinating plaques (arrows).

REVIEW AND DISCUSSION

Baharnoori et al. showed that most epidemiological studies reported a lower incidence of malignancies in patients with MS compared to the general population. However, they stressed that the data had been collected before the introduction of new immunomodulatory drugs into therapy [5].

Bahmanyar et al. emphasized that cancer risk in MS patients was lower compared to the general population, the exception being brain and urinary tract tumors, which are more prevalent in MS patients. According to Bahmanyar et al., a lower prevalence of tumors in MS patients might be due to an increase in systemic autoimmune responses

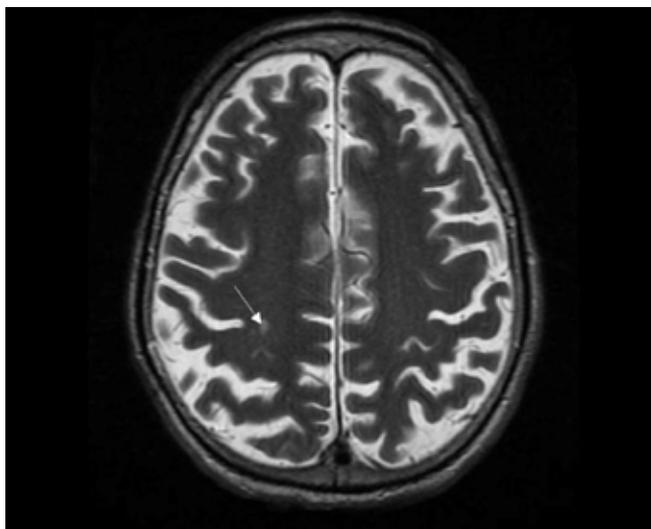


Fig. 5. Magnetic resonance imaging (MRI) after fingolimod treatment shows a reduction of demyelinating lesions. Axial MRI, T2- weighted image showing periventricular lesions and subcortical foci in the centrum semiovale (arrows).

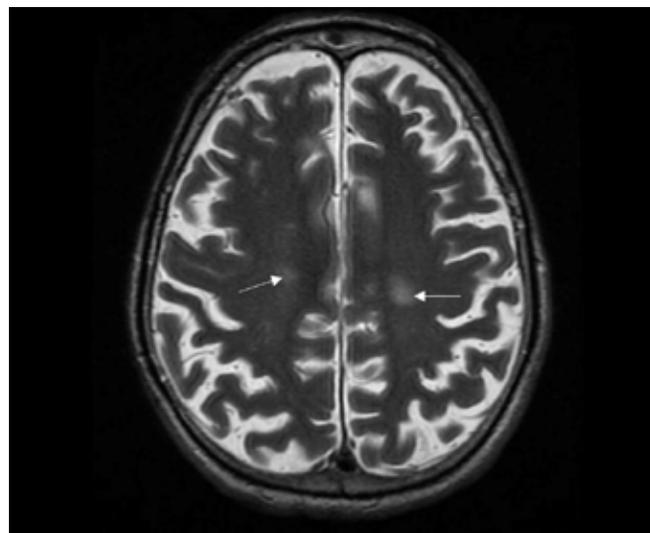


Fig. 6. Magnetic resonance imaging (MRI) after fingolimod treatment shows a reduction of demyelinating lesions. Axial MRI, T2- weighted image showing periventricular lesions and subcortical foci in the centrum semiovale (arrows).

during the course of the disease, which could be a protective mechanism against the formation of some tumors. Additionally, lifestyle changes in patients after diagnosis of MS are listed as cancer protective factors [20].

However, Lebrun and Rocher found that the number of cancer cases in MS patients could be underestimated. According to them, physicians do not systematically report the incidence of cancers in MS patients. It is likely that the incidence of cancer is underestimated as regards previously used DMDs [4].

Fingolimod is the first registered oral DMD approved for the treatment of highly active RRMS. The advantage of fingolimod is related to the way of administration. The recommended dose is one capsule (0.5 mg/day) [6]. The efficacy of fingolimod has been confirmed in multicenter FREEDOMS and TRANSFORMS trials, which demonstrated that the drug statistically significantly reduced the number of relapses and significantly reduced clinical and radiological disease activity [3, 8, 21, 22]. These trials showed its superiority over interferon beta-1a, which is the first-line drug [21]. In addition, the FREEDOMS trial also highlighted that fingolimod reduced disability progression [6, 23].

The drug interferes with the immune system, thus resulting in a reduction in the peripheral blood lymphocyte count to 20%-30% of the baseline value. The low lymphocyte count is maintained during long-term use of the drug [8]. Chronic intake of fingolimod also leads to a reduction in the number of neutrophil granulocytes to about 80% of the baseline value [10]. The influence on the number of circulating lymphocytes is due to their sequestration in lymph nodes and not due to lymphotoxicity, and hence the effect of the drug is reversible [6].

It is known that immunosuppression promotes the development of cancer [6, 12, 24]. Cohen et al. in the

LONGTERM study showed that the effect of fingolimod on the immune system may be associated with an increased risk of malignancy, as with other immunomodulatory drugs. The analysis showed that solid organ cancers or hematologic malignancies were rare. However, skin cancers, including basal cell carcinoma and squamous cell carcinoma, were more prevalent.

The INFORMS phase III trial, conducted between 2008 and 2011 in which patients (n= 336) were on fingolimod (0.5 mg/day) and placebo (n=487), showed that basal cell carcinoma and squamous cell carcinoma were more prevalent in the group of patients on fingolimod. [25]

In turn, the FREEDOMS double-blind randomized trial, which lasted 24 months and involved 425 patients on fingolimod 0.5 mg/day, 429 patients on fingolimod 1.25 mg, and 418 patients on placebo, did not show significant differences in the incidence of malignant melanoma in these groups. The FREEDOMS II trial showed that the incidence of skin cancers was similar between the groups on fingolimod and placebo, with the exception of basal cell carcinoma whose incidence was higher in patients on fingolimod [21].

The TRANSFORMS study compared the use of fingolimod with interferon beta in RRMS for 12 months. In this study, Cohen et al. found a higher risk of malignancy in patients on fingolimod 1.25 mg (2 cases of basal cell carcinoma and 2 cases of breast cancer) and fingolimod 0.5 mg (3 cases of basal cell carcinoma, 3 cases of malignant melanoma and 2 cases of breast cancer) compared to interferon beta (2 cases of basal cell carcinoma). [22]

There are also other case reports of cancer in patients treated with fingolimod, including lung, brain, hematopoietic, and lymphatic cancers. However, many cases are related to various types of skin cancer [14, 24].

Manouchehri et al. described a female patient with MS

who had been treated with fingolimod for 2 years and developed cutaneous anaplastic lymphoma during treatment. After discontinuation of the drug, the symptoms of lymphoma resolved, which could indicate a direct link between the development of this malignancy and the drug intake.

A similar case was reported by Papatthemeli et al. Cutaneous anaplastic lymphoma was diagnosed in a patient treated with fingolimod and resolved shortly after discontinuation of treatment. The authors highlighted that primary cutaneous lymphomas should be considered a potential adverse effect in patients on fingolimod and should be taken into account during patient examination [11, 18].

Baharoori et al. described a female patient on fingolimod who developed lymphoplasmacytic lymphoma located in the left frontal lobe. After discontinuation of the drug, the size of the tumor decreased, despite the absence of additional treatment, which may suggest that fingolimod may contribute to lymphoproliferative diseases [5].

In the summary of product characteristics of fingolimod, basal cell carcinoma is listed as a common adverse effect. Malignant melanoma is uncommon (1:100), squamous cell carcinoma is rare (1:1000), whereas Kaposi's sarcoma is very rare (1:10,000).

In the general population, basal cell carcinoma accounts for approximately 80% of all non-melanoma skin cancers. It is also the most prevalent skin cancer among Caucasians [26]. The incidence of this cancer is related to the latitude. The highest incidence is found among men over 60 years of age. It is characterized by slow growth and a low propensity to metastasize. [27]. High exposure to ultraviolet radiation is reported as a major risk factor for the disease. Additionally, immunosuppression is also a predisposing factor [28]. Surgical removal of the lesion with margins of healthy tissue is the treatment of choice, which provides the highest cure rate [27].

Squamous cell carcinoma is the second most prevalent skin cancer and accounts for approximately 20% of all cases, with the head and neck region being the most common location. It is characterized by faster tumor growth and a greater propensity to metastasize to lymph nodes compared to basal cell carcinoma [28]. It often arises from precancerous lesions. However, it can also arise from normal skin, and the lesions are often localized at the border of skin and mucosa [29]. The major risk factors for its occurrence include significant exposure to ultraviolet radiation, exposure to chemicals (such as arsenic, coal tar, soot, nitrogen mustards, aromatic polycyclic compounds - biphenyl derivatives, psoralen), HPV infections, smoking, and genetic factors. The prevalence of this cancer increases with age.

Immunosuppression significantly increases the risk of its occurrence. The course of the disease is more aggressive. Lesions are often multifocal and involvement of lymph nodes is more frequent. Surgical resection is the mainstay of treatment for squamous cell carcinoma. Adjuvant radiotherapy may be indicated in patients with the aggressive course of the disease [28]. It is applied to treat clinically advanced lesions, including cases with lymph node and/or CNS involvement.

A surgical margin of no less than 6 mm is recommended in the cases of SCC. When it is difficult to obtain such a margin due to the location of the lesion and the subsequent cosmetic effect, achieving a margin negative resection (R0) is considered satisfactory. Systemic therapy is warranted when the disease is advanced, recurrent and multifocal. However, there are no conclusive data which confirm the efficacy of chemotherapy in the treatment of squamous cell carcinoma [28, 29].

Considering the above case and the presented data, it seems reasonable to recommend careful monitoring of patients treated with fingolimod. Dermatological examination should be performed at the beginning and during treatment [4, 7, 15, 16].

Prior to disease-modifying therapy (DMT), next to dermatological assessment, gynecological consultation should be performed. Additionally, X-ray of the lungs should be performed in smoking patients. Fecal occult blood testing should be done in patients over 50 years of age [4].

Patients need to be informed about the risk of malignancy. They should also be provided with the detailed information on alarming symptoms and on skin lesions that require medical attention, which can allow early detection of lesions at an earlier stage, thus increasing the chances of cure. Screening and specialist consultations are also crucial [3, 4, 7, 17]. Most DMDs are contraindicated in patients with a history of malignancy. However, this does not apply to patients with a history of basal cell carcinoma [4].

In our patient, fingolimod resulted in very good control of the underlying disease and even led to the resolution of lesions on MRI. Considering the prevalence of basal cell carcinoma in the general population, especially in individuals over 60 years of age and usually very good surgical results and good prognosis, the benefits of treatment with fingolimod seemed to outweigh the risks in our patient.

Importantly, the patient had also other risk factors for malignancy (i.e., long-term smoking, a positive family history of cancer, age). Of note, the patient developed two different nasal skin malignancies within a short period of time. Additionally, the patient underwent surgical excision of basal cell carcinoma of the neck in 2018 and keratoacanthoma of the left thigh in 2019. Interestingly, the incidence of cancer increased significantly after a 5-year treatment with fingolimod, which may be related to the cumulative drug dose. This observation seems to support the observation of Lebrun and Rocher who found that the possibility of cancer during MS treatment was more connected with duration and the cumulative dose of the DMD than with a specific immunosuppressive drug [4]. However, in the case of fingolimod, the LONGTERMS trial showed that such a relationship was not found [8].

Due to its more aggressive course and a greater propensity to metastasize, the diagnosis of squamous cell carcinoma, particularly in immunocompromised patients, was the indication to discontinue the administration of fingolimod.

Good effect of MS treatment with fingolimod should be considered when the safety of the drug is taken into consideration. Patient-doctor compliance, careful assessment

of patient condition, and patient awareness of drug-related risks are of paramount importance. ENT assessment of patients with MS also remains to be considered.

CONCLUSIONS

Fingolimod is a highly effective drug for the treatment of RRMS. In our case, the drug had an influence on the inhibition of clinical and radiological activity of the disease. Despite the control of the underlying disease, skin cancers occurred during treatment, which may be strongly related to the use of the drug, as shown by many studies. Basal cell carcinoma and squamous cell carcinoma were diagnosed at an early stage when complete resection was possible and negative (R0) margin resection was achieved.

Therefore, it is crucial to highlight the recommendations for regular specialist follow-up during fingolimod therapy. ENT assessment of patients with MS seems to be warranted. Patient compliance and patient education are crucial during treatment, which allows achieving a good therapeutic effect, thus minimizing the risk of malignancy and enabling its early detection and cure.

REFERENCES

- Brownlee WJ, Hardy TA, Fazekas F, et al. Diagnosis of multiple sclerosis: progress and challenges. *Lancet* 2017;389(10076):1336-1346, doi:10.1016/s0140-6736(16)30959-x
- Howard J, Trevick S, Younger DS. Epidemiology of Multiple Sclerosis. *Neurol Clin*. 2016 Nov;34(4):919-939;
- La Mantia L, Tramacere I, Firwana B. Fingolimod for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2016 Apr 19;4:CD009371, doi: 10.1002/14651858.CD009371.pub2.
- Lebrun C, Rocher F. Cancer Risk in Patients with Multiple Sclerosis: Potential Impact of Disease-Modifying Drugs *CNS. Drugs*. 2018 Oct;32(10):939-949, doi: 10.1007/s40263-018-0564-y.
- Baharnoori M, Mahajan R, Solomon IH, et al. Fingolimod-Associated Intracerebral Lymphoproliferative Disorder *Am J Ther*. Jul/Aug 2019;26(4):e481-e484, doi: 10.1097/MJT.0000000000000694.
- Juszczak M, Gierach P, Głabiński A. Fingolimod w leczeniu stwardnienia rozsianego, *Aktualn Neurol*. 2010;10(3):145-151.
- Robinson CL, Guo M. Fingolimod (Gilenya) and melanoma, *BMJ Case Rep* 2016 Dec 21;2016:bcr2016217885, doi: 10.1136/bcr-2016-217885.
- Cohen JA, Tenenbaum N, Bhatt A, et al. Extended treatment with fingolimod for relapsing multiple sclerosis: the 14-year LONGTERMS study results, *Ther Adv Neurol Disord*. 2019 Sep 25;12:1756286419878324, doi: 10.1177/1756286419878324
- Alping P, Askling J, Burman J, et al. Cancer Risk for Fingolimod, Natalizumab, and Rituximab in Multiple Sclerosis Patients. *Ann Neurol*. 2020;87:688-699, doi: 10.1002/ana.25701.
- Bartosik- Psujek H, Selmaj K. Fingolimod w leczeniu stwardnienia rozsianego — aspekty praktyczne. *Pol Przegl Neurol*. 2015;11(1):36-43.
- Manouchehri N, Mirmosayyeb O, Badihian S, et al. Cutaneous anaplastic large cell lymphoma in a multiple sclerosis patient receiving fingolimod. *Mult Scler Relat Disord*. 2018 Jan;19:121-123, doi: 10.1016/j.msard.2017.11.012.
- Benedetti MD, Marangi A, Bozzetti S, et al. HPV-related papillary squamous cell carcinoma of the tonsil during treatment with fingolimod. *Mult Scler Relat Disord*. 2018 Jul;23:24-26, doi:10.1016/j.msard.2018.04.018.
- Carbone ML, Lacial PM, Messinese S, et al. Multiple Sclerosis Treatment and Melanoma Development, *Int J Mol Sci*. 2020 Apr 22;21(8):2950, doi: 10.3390/ijms21082950.
- Connolly A, Grandi V, Stefanato CM, et al. Primary cutaneous CD30 + anaplastic large-cell lymphoma associated with fingolimod. *Br J Dermatol*. 2018 Dec;179(6):1400-1401, doi: 10.1111/bjd.17003
- Haebich G, Mughal A, Tofazzal N. Superficial spreading malignant melanoma in a patient on fingolimod therapy for multiple sclerosis. *Clin Exp Dermatol*. 2016 Jun;41(4):433-4, doi: 10.1111/ced.12770.
- Killestein J, Leurs CE, Hoogervorst ELJ, et al. Five cases of malignant melanoma during fingolimod treatment in Dutch patients with MS. *Neurology*. 2017 Aug 29;89(9):970-972, doi: 10.1212/WNL.0000000000004293
- Mahajan KR, Ko JS, Tetzlaff MT, et al. Merkel cell carcinoma with fingolimod treatment for multiple sclerosis: A case report. *Mult Scler Relat Disord*. 2017 Oct;17:12-14, doi: 10.1016/j.msard.2017.06.004.
- Papathemeli D, Gräfe R, Hildebrandt U, et al. Development of a primary cutaneous CD30(+) anaplastic large-cell T-cell lymphoma during treatment of multiple sclerosis with fingolimod *Mult Scler* 2016 Dec;22(14):1888-1890, doi:10.1177/1352458516645868. Epub 2016 Apr 26.
- Velter C, Thomas M, Cavalcanti A, et al. Melanoma during fingolimod treatment for multiple sclerosis *Eur J Cancer*. 2019 May;113:75-77, doi:10.1016/j.ejca.2019.03.011.
- Bahmanyar S, Montgomery SM, Hillert J, et al. Cancer risk among patients with multiple sclerosis and their parents. *Neurology* 2009; 72:1170-1177, doi: 10.1212/01.wnl.0000345366.10455.62.
- Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:545-556, doi: 10.1016/S1474-4422(14)70049-3.
- Cohen JA, Khatri B, Barkhof F, et al. TRANSFORMS (TRial Assessing injectable interferoN vS. FTY720 Oral in RRMS) Study Group. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study *J Neurol Neurosurg Psychiatry*. 2016 May;87(5):468-75. doi: 10.1136/jnnp-2015-310597.
- Kappos L, O'Connor P, Radue EW. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial. *Neurology*. 2015 Apr 14;84(15):1582-91.
- De Jong BA, van Kempen ZLE, Wattjes MP, et al. Intracerebral lymphoproliferative disorder in an MS patient treated with fingolimod *Neurol Neuroimmunol Neuroinflamm*. 2018 Sep;5(5), doi: 10.1212/NXI.0000000000000483.
- Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2016;387:1075-1084. doi: 10.1016/S0140-6736(15)01314-8
- Rubin A, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med*. 2005 Nov 24;353(21):2262-9, doi: 10.1056/NEJMra044151.
- Girardi FM, Wagner VP, Martins MD, et al. Factors associated with incomplete surgical margins in basal cell carcinoma of the head and neck. *Braz J Otorhinolaryngol* Apr 8;51808-8694(20)30032-X, doi: 10.1016/j.bjorl.2020.02.007.
- Tam S, Gross ND. Cutaneous Squamous Cell Carcinoma in Immunosuppressed Patients *Curr Oncol Rep*. 2019 Jul 29;21(9):82, doi: 10.1007/s11912-019-0831-1

29. Wray J, Morris CG, Kirwan JM, et al. Mendenhall WM Radiation therapy for nasal vestibule squamous cell carcinoma: a 40-year experience. *Eur Arch Otorhinolaryngol* 2016 Mar;273(3):661-9, doi: 10.1007/s00405-015-3603-z.

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Conflict of interest:

The Authors declare no conflict of interest.

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