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Letter to the Editor

Melanoma during fingolimod treatment for multiple sclerosis

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Dear Editor,

The immunosuppressant drug fingolimod (FTY720) inhibits lymphocyte egress from lymphoid organs and is indicated in relapsing-remitting multiple sclerosis (MS).

To date very few cases of melanoma development have been described during fingolimod treatment. We report a new case and provide review of the literature.

A 51-year-old woman was referred to our department in October 2018 for stage I melanoma. Her mother died from a melanoma. She had a type I phototype with fair skin, blond hair and freckles and reported frequent sunburns during childhood. She was treated with the anti–alpha-4 integrin mAb natalizumab between 2009 and 2013 (42 infusions) for a very active MS. In August 2013, because the patient presented a high anti-John Cunningham virus (JVC) antibody index and as natalizumab is associated with the risk of progressive multifocal leukoencephalopathy caused by JCV, natalizumab was interrupted. And the patient was started on fingolimod 0.5 mg/d. She had a dermatological follow-up every 2 years, and her full body examination in 2016 was considered normal. In 2017, she reported pruritus on a mole of her back, and her husband noticed that this mole

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Table 1
Cases of melanoma after fingolimod treatment for multiple sclerosis.

Source	Patient sex/age	Diagnosis, melanoma Type/Breslow index	Delay (months)	Skin type	Fingolimod (mg/day)	Evolution
Kappos *et al.* [1]	1 case (0.2%)	NA	24	NA	1.25	Treatment stopped
Comi *et al.* [2]	1 case	NA	36	NA	1.25	NA
Cohen *et al.* [3]	3 cases (0.7%)	NA	NA	NA	0.5	NA
Conzett *et al.* [4]	F/41	Second annual full-body skin examination revealed a new pigmented macule Melanoma ex naevo 0.9 mm Ulceration NA	57	Skin type II, without freckles or sun damage	1.25	Treatment stopped Sentinel node biopsy specimens negative
Havla *et al.* [5]	M/51	Right knee SSM pT1a	48	NA	0.5	Treatment stopped
Lublin *et al.* [6]	1 case (0.3%)	NA	NA	NA	0.5	NA
Haebich *et al.* [7]	F/41	Left ankle: soreness naevus, change of size and colour SSM 1.5 mm Not ulcerated	2	NA	0.5	Treatment stopped Wider excision, no evidence of residual tumour
Robinson *et al.* [8]	F/52	Back: change of colour and size SSM 2.1 mm Ulceration	61	>50 naevi No history of skin cancer	0.5	Treatment stopped Sentinel lymph node biopsy negative
Killestein *et al.* [9]	F/44	Right upper arm: change of colour and size SSM 0.8 mm No ulceration	32	NA	NA	Treatment NA Sentinel lymph node biopsy negative
	F/38	Left upper arm: change of colour and size nevus SSM 0.5 mm No ulceration	15	NA	NA	Treatment NA
	F/44	Interscapular: change of size at screening SSM 0.6 mm No ulceration	12	NA	NA	Treatment NA
	M/32	Interscapular: change of aspect, not specified SSM 0.9 mm No ulceration	31	NA	NA	Treatment NA
	F/45	Right scapula: change of colour and irritating SSM 2.3 mm No ulceration	20	NA	NA	Treatment NA Sentinel lymph node biopsy negative
Present case	F/51	Back: mole became pruritus, and crust was noticed by husband Nodular melanoma 1.1 mm No ulceration	48	Melanoma of her mother Type skin 1	0.5	Treatment stopped Sentinel lymph node biopsy negative

F: female; M: male; MS: multiple sclerosis; SSM: superficial spreading malignant melanoma; NA: not applicable; d: day.

had changed in colour and size. An excision biopsy was performed, revealing a 1.1-mm thick nodular melanoma. The patient underwent a wide local excision with 2-cm margins, and sentinel lymph node biopsy was negative. Full body computed tomography scan did not show any distant metastasis. Fingolimod treatment was suspected to have a role in melanoma emergence and was stopped.

To date, 15 cases of melanoma during fingolimod treatment have been reported (Table 1) [1–9]. The responsibility of this drug in melanoma occurrence is still debated because clear evidence is still lacking, because no cases of melanoma were reported in a 2-year follow-up of 160 patients and a 1-year follow-up of 328 patients [10].

Another potential factor in our patient is the previous treatment with natalizumab, also known as a possible trigger for melanomas [11]. This was also the case in 4 of 5 patients reported in a recent study [9].

Fingolimod is also associated with an increased incidence of other skin malignancies: basal-cell carcinoma, Bowen disease [1,3] as well as the rarer skin cancers such as Kaposi sarcoma, Merkel cell carcinoma or cutaneous lymphoma. This was also found in a phase II clinical study of fingolimod in MS where the cases of skin cancers were higher than expected [12].

From the mechanistic point of view, phosphorylated fingolimod activates sphingosine 1-phosphate (S1P) receptors resulting in functional S1P antagonism with inhibition of lymphocyte egress from lymph nodes and secondary lymphoid tissues [13] associated with decreased number of circulating lymphocytes. One can hypothesise that such lymphocyte decrease might eliminate or neutralise melanoma-specific lymphocytes and counteract cancer immune surveillance. An alternative hypothesis is a pro-oncogenic effect of fingolimod via activation of the IL6/JAK/STAT3 pathway [14]. Conversely, other preclinical data suggest a potential antitumoural effect of fingolimod via activation of tumour suppressor protein phosphatase 2A has been reported [15].

In conclusion, we report a new case of melanoma diagnosed after 4 years of fingolimod, suggesting a possible link with the immunosuppressive drug. Physicians should be aware of this possible link, and we recommend a regular self-examination of the skin every 3 months and annual full-body skin examination in such patients. It is possible, that fingolimod could facilitate melanoma in melanoma predisposed patients, like in the present case with a patient presenting both constitutional and acquired melanoma risk factors. Thus, it seems reasonable to conduct larger studies with longer follow-up and to advise a specific dermatologic follow-up for patients with melanoma skin factors who are treated with fingolimod.

Conflict of interest statement

Caroline Robert has acted as a consultant of BMS, Pierre Fabre, Merck, Novartis and Roche. Emilie Routier has acted as a consultant of BMS and Roche. Catherine Lubetzki served on the scientific advisory board for Vertex, Biogen, Novartis, Genzyme and Roche; was an associate editor for Brain; served on the editorial board for MSJ and MSJ and Related Disorders; has consulted for Biogen, Roche, Genzyme and Vertex; had scientific collaboration with EMD Serono and received research support from EMD, Serono and Vertex. Charles Velter, Marina Thomas M, Andrea Cavalcanti A, Marie Bastien and Florence Chochon declare no competing interests.

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