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Primary cutaneous marginal zone lymphoma in a patient with multiple sclerosis under fingolimod therapy

Thilo Gambichler,[1-3] Sera Selina Weyer-Fahlbusch,[1] Markus Werner,[1] Ulrika Schade,[4] Lieselotte Bissels,[5] Laura Susok[2]

[1]Department of Dermatology, Dortmund Hospital gGmbH, Witten-Herdecke University, Dortmund; [2]Department of Dermatology, Christian Hospital, Unna; [3]Department of Dermatology, Ruhr-University Bochum; [4]Hematopathology Lübeck Center; [5]Department of Neurology, Dortmund Hospital gGmbH, Witten-Herdecke University, Dortmund, Germany

Correspondence: Thilo Gambichler, Dortmund Hospital gGmbH, Witten-Herdecke University, Dortmund, Germany.
E-mail: t.gambichler@klinikum-bochum.de

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Consent for publication: written informed consent for publication of clinical details and clinical images was obtained from the patient.

Availability of data and materials: all data generated or analyzed during this case study are included in this published article.

Dear Editor,

Increased prevalence of cancer, in particular lymphomas, has been observed in patients with multiple sclerosis (MS) treated with fingolimod.[1-7] We report the first case of primary cutaneous marginal zone lymphoma (PCMZL) that developed under long-term fingolimod therapy for MS.

A 54-year-old female presented with a 22-year history of relapsing-remitting MS, initially treated with glatiramer acetate followed by interferon-β1. In 2016, the patient started receiving fingolimod because of progressive disease. In the summer of 2024, she developed several asymptomatic, brownish-erythematous nodules on her upper legs, buttocks, and left upper arm (Figure 1). At this time, she was taking fingolimod 0.5 mg/d, while her MS was graded 6.0 according to the Expanded Disability Status Scale. An elliptical excision of one lesion on the right upper left leg was performed for histological examination. Histopathology revealed a dense, nodular dermal infiltrate, as well as a sparse infiltrate, sometimes organized in follicular structures, sparing the epidermis, consisting of small lymphocytes and plasma cells (Figure 2). The immunohistochemistry stain revealed dense $CD20^+$ B cell aggregates, follicular-like structures with positivity for CD23, and only weak CD10 expression with negativity for Bcl-2. Plasma cells also showed kappa light-chain restriction and reactivity to CD138 (Figure 2). According to the BIOMED-2 protocol, we observed a small Ig kappa (tube A) amplicon of 284 bp and an Ig kappa (tube B) amplicon of 282 bp. Low expression of 10% for Ki-67 was detected. Polymerase chain reaction (PCR) testing was negative for *B. burgdorferi* and positive for Epstein-Barr virus (EBV). However, Epstein-Barr virus-encoded small RNAs (EBER) *in situ* hybridization as well as LMP1 immunohistochemistry of tumor tissue were negative. A diagnosis of PCMZL was made.

Complete blood count revealed severe lymphopenia of 160/µl (110-4500). Serology for *B. burgdorferi* was negative. Immune electrophoresis, including immune fixation, did not reveal evidence for monoclonal gammopathy and Bence Jones proteinuria. A blood smear was unremarkable. Flow cytometry of lymphocytic subpopulations in the peripheral blood was unremarkable. Lymph node ultrasound, neck, thorax, and abdomen computed tomography, and cranial magnetic resonance imaging did not reveal evidence for lymphoma manifestation in other organs but the skin. Because of the indolent nature of PCMZL, we refrained from bone marrow biopsy. Hence, fingolimod was discontinued, and ofatumumab was initiated.

Ofatumumab is a fully human IgG1 monoclonal anti-CD20 antibody. It is approved for the treatment of MS with a subcutaneous dose of 20 mg at weeks 0, 1, and 2, followed by 20 mg once monthly from week 4.[7]

The result of a recent meta-analysis demonstrated that the pooled prevalence of malignancies in MS patients who received fingolimod was 2%.[1] About 20 cases of fingolimod-induced lymphoma in MS patients have been published, the majority represented by T cell lymphomas, in particular, primary cutaneous $CD30^+$ anaplastic large T cell lymphoma, lymphomatoid papulosis, and mycosis fungoides.[1] Hence, most lymphoproliferative diseases were observed in the skin but more rarely also in the bladder, eye, mediastinum, and central nervous system. To the best of our knowledge, this is the third published case of a primary cutaneous B-cell lymphoma developing during fingolimod therapy.[2,5,6] In the present case, lymphoma development was relatively late. However, regarding the timing of onset of fingolimod-induced lymphomas in MS patients, there is great variability. Interestingly, a potential causal relationship between drug administration and lymphoma development has been suggested, as lymphomas have not only emerged during fingolimod therapy but, in one case report, also showed spontaneous regression following fingolimod discontinuation, though the reported follow-up was limited to only four weeks.[4] Moreover, animal models have demonstrated that fingolimod predisposes to lymphoma development by reducing immune surveillance of neoplastic lymphoid clones in the periphery through modulation of the peripheral T lymphocytic microenvironment.[3] Fingolimod is capable of inhibiting lymphocyte egress from lymph nodes through the modulation of sphingosine-1-phosphate receptors and thereby prevents lymphocyte migration to peripheral tissues. Furthermore, fingolimod is capable of inducing differentiation of peripheral T cells towards a regulatory T lymphocyte phenotype and blocks antigen presentation by inhibiting Langerhans cell migration to lymph nodes. However, it is unclear why fingolimod appears to be most frequently associated with primary cutaneous $CD30^+$ T cell lymphomas rather than other extranodal lymphoproliferative diseases also known to originate from tissue-resident memory T cells.[3]

Given the established association between fingolimod and cutaneous malignancies, regular dermatologic surveillance is recommended. This case underscores the importance of raising awareness among dermatologists that patients receiving fingolimod may also be at increased risk for developing cutaneous B-cell lymphomas, in addition to the more commonly reported T-cell variants.

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Figure 1. A slightly reddish palpable subcutaneous nodule on the thigh of a patient with multiple sclerosis and primary cutaneous marginal zone lymphoma developed under fingolimod therapy.

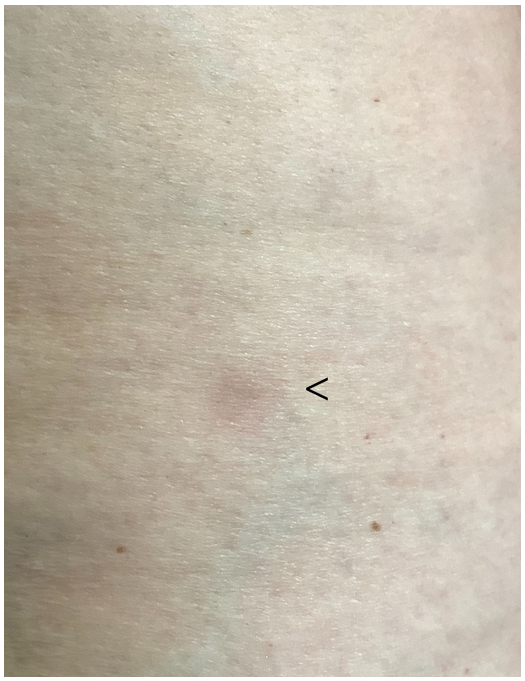

Figure 2. Hematoxylin-eosin stain of a skin biopsy revealed a sparse infiltrate sometimes organized in follicular structures (**a**, magnification x100) consisting of small lymphocytes and plasma cells (**b**, magnification x250; **c**, magnification x400). Immunohistochemically (**c**), the infiltrating lymphocytes were strongly positive for kappa (**d**) and only partially positive for lambda (**e**, magnification x100).