Primary cutaneous Epstein-Barr virus-positive diffuse large B-cell lymphoma (DLBCL) in a patient taking fingolimod

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Abstract

A 55-year-old man with relapsing-remitting multiple sclerosis on fingolimod presented to the dermatology clinic with skin lesions on the left temple and cheek. Histopathology showed a diffuse infiltrate of enlarged, atypical lymphocytes throughout the dermis with an overlying grenz zone and a subpopulation of scattered smaller lymphocytes and plasma cells. Epstein-Barr virus-encoded RNA in situ hybridization stain was positive. Based on the morphologic and immunophenotypic findings, a diagnosis of EBV-positive diffuse large B-cell lymphoma was made. This case aims to raise awareness for the dermatologist that patients on fingolimod may be at increased risk of lymphoproliferative disorders.

Keywords: primary cutaneous lymphoma, primary cutaneous Epstein-Barr virus-positive lymphoma, primary cutaneous diffuse large B-cell lymphoma, diffuse large B-cell lymphoma, primary cutaneous B-cell lymphoma, fingolimod, multiple sclerosis, DLBCL, EBV-positive DLBCL

Introduction

Fingolimod is a sphingosine-1-phosphate receptor modulator approved for use in relapsing–remitting multiple sclerosis (MS). It inhibits normal egress of lymphocytes from lymphoid tissue and it has been associated with an increased risk of infection and lymphoma because of some of these immunoregulatory effects [1].

We report a patient with primary cutaneous Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) who was taking fingolimod for relapsing–remitting MS. To our understanding, only one other incidence of EBV-positive DLBCL has been reported in a patient on fingolimod and that lymphoma, presented in the brain [2].

Case Synopsis

A 55-year-old man with relapsing-remitting MS presented to the dermatology clinic in July 2016 with a two-month history of skin lesions on the left temple and cheek. His MS was managed for four years with interferon beta-1a but because of flu-like symptoms his treatment was changed to fingolimod in March

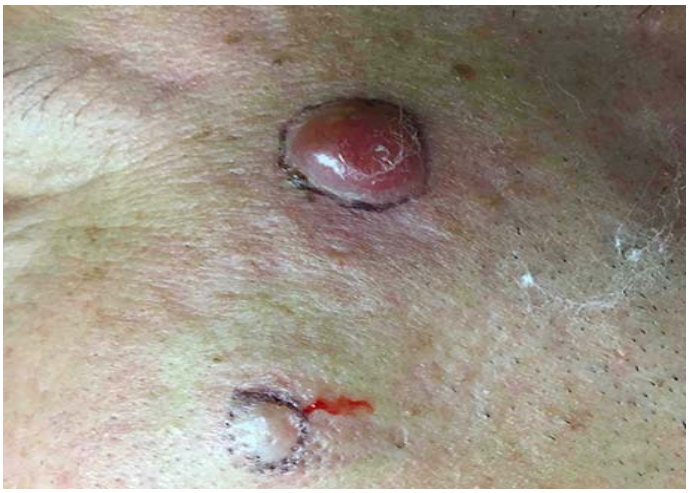

Figure 1. *Two violaceous nodules on the temple and cheek. The inferior lesion is blanched in photo, which was taken after this lesion was anesthetized with lidocaine with epinephrine.*

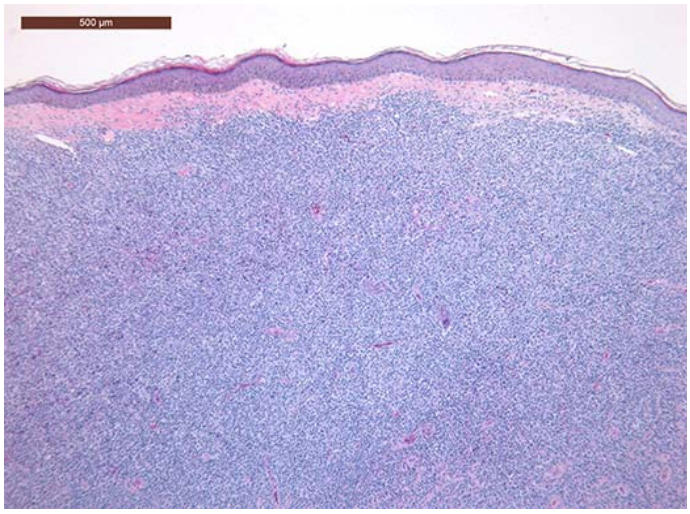

Figure 2. *Skin biopsy demonstrating a diffuse infiltrate of small lymphocytes, larger atypical lymphocytes, and sparing of the epidermis with an overlying grenz zone. H&E, 50×.*

2015. His subsequent course was complicated by herpes zoster involving the left side of his face in December 2015, which was treated with acyclovir.

On physical examination, two violaceous, telangiectatic, nodules were present on the left temple, measuring 1.2cm and left cheek, measuring <1cm (**Figure 1**). A punch biopsy of each lesion was obtained.

Histopathology revealed similar findings in both specimens, showing a diffuse infiltrate of enlarged, atypical lymphocytes throughout the dermis, with an overlying grenz zone and without epidermal involvement. There was a subpopulation of scattered smaller lymphocytes and plasma cells (**Figures 2, 3**). The large, atypical cell population stained positively with CD20, CD30, and BCl-6, whereas BCl-2 showed weak, patchy positivity (**Figure 4**). Multiple myeloma oncogene 1 and c-Myc were positive in about 20% of cells; Ki-67 stained over 90% of the large cells. The atypical cells were negative for CD10, CD3, CD5, CD34, and Tdt. Epstein-Barr virus-encoded RNA in situ hybridization stain (EBER-ISH) was positive for EBV (**Figure 4**). Plasma EBV PCR was undetectable. Based on the morphologic and immunophenotypic findings, a diagnosis of EBV-positive diffuse large B-cell lymphoma was made.

Complete blood count was normal other than elevated peripheral monocytes (19.5%; reference range 3.5-9.0) and decreased peripheral lymphocytes (9.5%; reference ranges 18.0-42.). Positron emission topography showed a 1.1cm subcutaneous nodule along the left temporal scalp, corresponding to the previously noted cutaneous lesion. There was no evidence of metastatic disease.

Fingolimod was discontinued in September 2016 and the patient was treated with three cycles of modified CH(O)P (cyclophosphamide, adriamycin, and prednisone) followed by 36Gy radiation in 18 fractions over 30 days. Vincristine was not used owing to his history of MS and rituximab was deemed inappropriate because of a positive antibody titer for JC virus and a prior JC DNA titer of

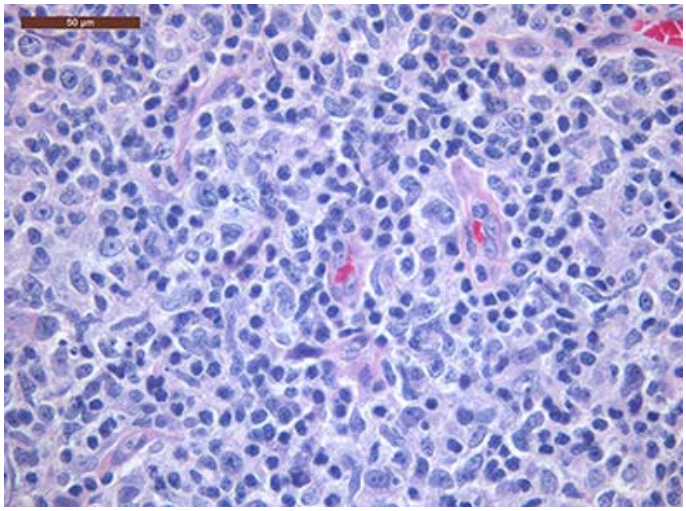

Figure 3. *High magnification demonstrating both small lymphocytes, as well as scattered large atypical lymphocytes with convoluted nuclei and distinct nucleoli. H&E, 400×.*

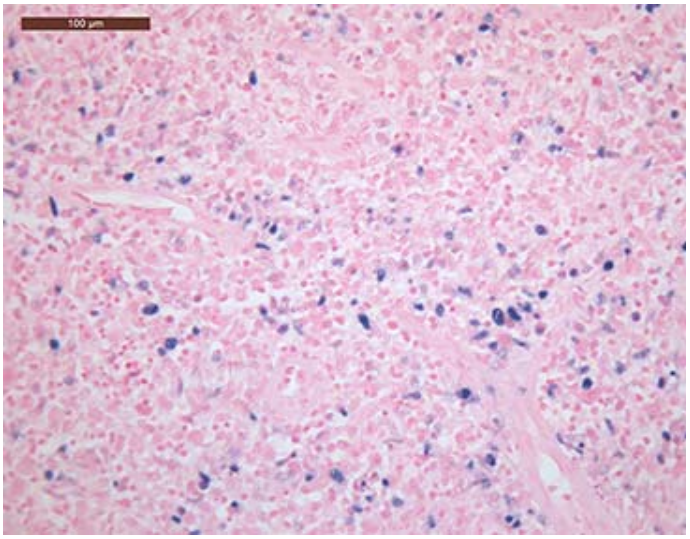

Figure 4. *Large atypical cells positive (blue stain) for EBV-encoded RNA in-situ hybridization stain. EBER-ISH, 200×.*

Table 1 *Comparison of two cases of EBV-positive DLBCL associated with fingolimod use.*

	Age	Sex	Race	Duration on fingolimod	Treatment	Response
Our patient	55	Male	Caucasian	16 months	None (Diagnosed at autopsy)	N/A
CNS lymphoma patient	42	Male	Unknown	9 months	Modified R-CH(O)P	Complete clinical remission

1.56. JC virus is a polyomavirus present in the majority of the population that can reactivate in cases of profound immunosuppression and cause a devastating leukoencephalopathy. A post-treatment PET in November 2016 showed a complete response. He remains in clinical remission, **Table 1**.

Case Discussion

Epstein-Barr virus-positive DLBCL is one of several EBV-associated lymphoproliferative disorders [3]. Lymph node involvement occurs in up to 70% of patients and primary or secondary extranodal disease may involve the skin and soft tissue, bone and bone marrow, nasal and oropharyngeal cavities, lung, tonsils, and gastrointestinal system [3].

Owing to its broad immunomodulatory effects, fingolimod may increase the risk of certain infections. In clinical trials with fingolimod, the most commonly reported adverse events were upper respiratory tract infections, nasopharyngitis, and sinusitis. Bronchitis, influenza, and herpes viral infections occurred more frequently in patients treated with fingolimod versus placebo [1, 4]. Several incidences of reactivation of latent viral infections during fingolimod treatment have been reported, including hepatitis C, EBV, and varicella zoster virus [5, 6]. It is currently recommended that varicella zoster virus titers be checked and that patients with low titers be immunized prior to initiation of treatment [7]. Relevant to dermatologic care of patients on fingolimod, basal cell carcinoma was reported with higher incidence than placebo in a randomized controlled trial studying fingolimod for MS, with a relative risk of 3.9 [1].

Furthermore, numerous cases of lymphoma and lymphoproliferative disorders in patients taking fingolimod have been reported, including the aforementioned EBV-positive B-cell lymphoma of the brain [2]. Whereas that case of EBV-positive B-cell lymphoma in a patient on fingolimod presented in the brain in a 42-year-old man who had received nine months of continuous fingolimod therapy, the case reported herein presented after 16 months of fingolimod exposure while the patient was still receiving treatment and with disease limited to the skin. The diagnosis in the former case was made at autopsy, approximately one year after discontinuing fingolimod owing to a serious MS relapse. In the present case, remission of the cutaneous lymphoma was achieved with drug cessation followed by lymphoma treatment.

Conclusion

Herein we report a case of primary cutaneous EBV-associated DLBCL occurring in association with fingolimod use. Given the recognized link between fingolimod and skin cancers, dermatologic monitoring is warranted. This case aims to raise awareness for the dermatologist that these patients may also be at increased risk of lymphoproliferative disorders [1, 7, 8]. We also hope this will serve as a reminder that fingolimod has numerous immunomodulatory actions, which raise the risk of varicella zoster virus, among other infections.

Potential conflicts of interest

The authors declare no conflicts of interests.

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