Histopathological findings were consistent with herpesvirus infection. Polymerase-chain-reaction testing confirmed the diagnosis of varicella–zoster virus (VZV) infection; serologic testing was positive for IgM antibodies to VZV, but there was no IgG response. The patient had no documented lymphocytopenia (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Because his medical history mentioned chickenpox during childhood, we made the diagnosis of generalized VZV infection.

The DMF treatment may have reactivated the VZV infection in this patient, because the infection developed 2 months after the initiation of treatment, he never received ultraviolet-light therapy, and he did not use topical glucocorticoids. This case suggests that patients treated with DMF may have an increased risk of viral infection, even in the absence of lymphocytopenia.

Marloes S. van Kester, M.D., Ph.D.
Jan N. Bouwes Bavinck, M.D., Ph.D.
Koen D. Quint, M.D., Ph.D.
Leiden University Medical Center
Leiden, the Netherlands
m.s.van_kester@lumc.nl

No potential conflict of interest relevant to this letter was reported.

1. Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. N Engl J Med 2015;372:1476-8.

DOI: 10.1056/NEJMc1506151

DR. NIEUWKAMP AND COLLEAGUES REPLY: We agree with Balak and Hajdarbegovic and with van Kester et al. that patients receiving DMF are at risk for opportunistic infections even without severe lymphocytopenia, and we believe that these letters support the viewpoints expressed in our letter. An additional patient with PML and the immune reconstitution inflammatory syndrome after DMF treatment with only a modest case of lymphocytopenia was reported recently.[1] Because the number of patients treated with DMF has increased rapidly since the approval of delayed-release DMF as first-line treatment for relapsing–remitting multiple sclerosis, PML or other opportunistic infections may develop in more patients. We think that safety monitoring of patients treated with DMF is crucial, because opportunistic infections can occur in patients without severe lymphocytopenia. Further studies concerning safety monitoring and new methods for identification of patients at risk are therefore urgently needed.

Dennis J. Nieuwkamp, M.D., Ph.D.
Jean-Luc Murk, M.D., Ph.D.
University Medical Center Utrecht
Utrecht, the Netherlands
d.nieuwkamp@umcutrecht.nl
Bob W. van Oosten, M.D., Ph.D.
VU University Medical Center
Amsterdam, the Netherlands

Since publication of their letter, the authors report no further potential conflict of interest.

1. Hoepner R, Faissner S, Klasing A, et al. Progressive multifocal leukoencephalopathy during fumarate monotherapy of psoriasis. Neurol Neuroimmunol Neuroinflamm 2015;2(3):e85.

DOI: 10.1056/NEJMc1506151

MYD88 Mutations and Response to Ibrutinib in Waldenström's Macroglobulinemia

TO THE EDITOR: Whole-genome sequencing identified the *MYD88* L265P variant as the most prevalent mutation in patients with Waldenström's macroglobulinemia (WM), a type of non-Hodgkin's lymphoma.[1] In 93 to 97% of patients with this disorder, allele-specific polymerase-chain-reaction (AS-PCR) assays identified *MYD88* L265P, which results from a T→C transversion at position 38182641 on chromosome 3p22.2. Signaling studies showed that the mutant protein that is encoded by *MYD88* L265P triggers tumor growth through the activation of nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) by Bruton's tyrosine kinase. This kinase is targeted by ibrutinib, a drug that is widely used in the treatment of B-cell cancers. In addition, *CXCR4* WHIM mutations (associated with a syndrome called WHIM [warts, hypogammaglobulinemia, infections, and myelokathexis]) that were found almost exclusively in patients with WM who have the *MYD88* L265P variant were found to convey resistance to ibrutinib.

Table 1. Rate of Response to Ibrutinib in Patients with Waldenström's Macroglobulinemia, According to Mutation Status.*

Response Rate	Mutated *MYD88* and Wild-Type *CXCR4* (N=36)	Mutated *MYD88* and *CXCR4* WHIM (N=21)	Wild-Type *MYD88* and *CXCR4* (N=5)	P Value†
		percent		
Overall	100	85.7	60	0.005
Major	91.7	61.9	0	<0.001

* Responses were assessed in 62 previously treated patients with Waldenström's macroglobulinemia for whom both *MYD88* and *CXCR4* mutation status had been determined. *MYD88* status was determined by means of Sanger sequencing of the entire gene. *CXCR4* mutation status was determined by means of Sanger sequencing and allele-specific polymerase-chain-reaction assay for *CXCR4 S338X* C→G and C→A mutations in CD19-selected bone marrow cells.[2] A major response was defined as a partial or very good partial response. No complete responses were observed.[2] WHIM denotes warts, hypogammaglobulinemia, infections, and myelokathexis.

† P values are for the overall comparison among the three groups and were calculated with the use of Fisher's exact test.

These findings prompted a clinical trial of ibrutinib in previously treated patients with WM, which showed fewer overall and major responses among patients with wild-type *MYD88* and *CXCR4* than in those with the *MYD88* L265P variant and either wild-type *CXCR4* or *CXCR4* WHIM.[2] However, of the seven patients with wild-type *MYD88* and *CXCR4*, two had a major response to ibrutinib. Using Sanger sequencing, we found that both of these patients harbored *MYD88* mutations that were not amenable to AS-PCR analysis for *MYD88* L265P. One patient had a G→A transversion at position 38182292, which predicted the *MYD88* S243N variant, and the other had a TG→CT substitution at position 38182641, which predicted the *MYD88* L265P variant. The updated response rates for this trial are notable for the lack of major responses in patients with wild-type *MYD88* on Sanger sequencing (Table 1).

We also performed Sanger sequencing in tumor samples obtained from 12 additional patients with WM who had undetectable *MYD88* L265P on AS-PCR. A T→C transversion at position 38182259, which predicted the *MYD88* M232T variant, was identified in 1 patient. Patients with wild-type *MYD88* on Sanger sequencing had histopathological features that were similar to those in patients with mutated *MYD88*, although the median burden of bone marrow disease at baseline in patients with wild-type *MYD88* was considerably lower than that found in patients with the *MYD88* L265P variant (17.5% vs. 40.0%), as was the serum IgM level (1115 mg per deciliter vs. 3270 mg per deciliter).[3] Despite the lower disease burden in patients with wild-type *MYD88*, their median overall survival was shorter than that in patients with mutated *MYD88* (4.7 years vs. >10 years) with similar follow-up.[3]

All the *MYD88* mutations were also observed in patients with diffuse large B-cell lymphoma (DLBCL), particularly the ABC subtype.[4] Although *MYD88* mutations other than L265P are uncommon in patients with WM, they make up a quarter of all *MYD88* mutations in patients with DLBCL.[4] The *MYD88* mutations that are found in patients with WM (*MYD88* L265P, *MYD88* S243N, and *MYD88* M232T) all show high levels of NF-κB transactivation in transduction studies.[4] Like the *MYD88* L265P variant, *MYD88* S243N triggers the activation of NF-κB by Bruton's tyrosine kinase in WM cells, whereas *MYD88* M232T signaling in WM remains to be investigated. Unlike patients with WM, patients with DLBCL show no association between *MYD88* mutation status and the response to ibrutinib. In such patients, the response may be related to mutations that affect the signaling of B-cell and T-cell receptors, such as *CD79A/B* and *CARD11*.[5]

In conclusion, our findings support the association between *MYD88* mutations and a response to ibrutinib therapy in patients with WM. Moreover, these results highlight the need for studies to address the genetic basis and development of targeted therapies for patients with WM who have wild-type *MYD88*.

Steven P. Treon, M.D., Ph.D.
Lian Xu, M.S.
Zachary Hunter, Ph.D.
Bing Center for Waldenström's Macroglobulinemia
Boston MA
steven_treon@dfci.harvard.edu

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med 2012; 367:826-33.
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CORRECTION

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (July 16, 2015;373:232-42). In Table 1, in the "Intention-to-treat analysis" portion of the table (page 239), the value given for Acute pancreatitis in the "no. per 100 person-yr" column under "Placebo" should have been 0.06, rather than 0.11. The article is correct at NEJM.org.

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