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.

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


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. 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.

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


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. 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.
MYD88 mutations that are uncommon in patients with WM, they make up one quarter of all MYD88 mutations in patients with DLBCL. 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. 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.

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.

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