



Case Report

Response to Ibrutinib of a Refractory IgA Lymphoplasmacytic Lymphoma Carrying the *MYD88* L265P Gene Mutation

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Abstract. In 2014 a 66-year-old woman presented with anemia and an IgAk monoclonal spike. Bone marrow (BM) biopsy showed 80% lymphocytes and lymphoplasmacytoid cells. Computed Tomography (CT) scan documented neither adenopathy nor splenomegaly. Diagnosis of IgA lymphoplasmacytic lymphoma was made. After three lines of treatment, progressive disease with adenopathies, splenomegaly, and ascites were documented on a CT scan. Our patient developed thrombocytopenia, transfusion-dependent anemia, and clinical deterioration. We performed genetic studies of peripheral blood lymphocytes with the NGS approach. Given the identification of *MYD88* L265P mutation, in February 2018 our patient started ibrutinib off-label. Hb and PLT improved from day +35. In July 2018 no ascites and 50% reduction of adenopathies and spleen were shown on a CT scan. In April 2019 the patient was still on ibrutinib with transfusion independence and good performance status.

Keywords: IgA-secreting lymphoplasmacytic lymphoma; Ibrutinib; *MYD88*.

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Introduction. Lymphoplasmacytic lymphoma (LPL) is a rare chronic lymphoproliferative neoplasm characterized by the proliferation of B lymphocytes with varying degrees of plasmacytic differentiation involving bone marrow (BM), lymph nodes, or spleen.¹ Waldenstrom macroglobulinemia (WM) is a subset of LPL that has a detectable level of monoclonal IgM gammopathy, with BM involvement by LPL.^{2,3} Indeed in over 95% of LPL cases, the malignant clone produces an IgM paraprotein consistent with WM.⁴ However, the remaining LPL cases do not fulfill the

diagnostic criteria of WM. These conditions are mainly represented by rare cases of primary nonsecretory lymph node-based presentations of LPL or by lymphoplasmacytic B-cell proliferation in the BM associated with IgA or IgG gammopathies.^{1,5} Accurate diagnosis of LPL can be difficult because of the absence of morphologic, immunophenotypic, or chromosomal markers, especially in non-WM cases where there is no IgM gammopathy to support the diagnosis.¹ The identification of the *MYD88* L265P gene mutation represented a major advance in the

diagnosis of LPL^{3,5} although the real incidence of this mutation in LPL patients is unknown and a small number of WM patients with unmutated *MYD88* exist. Indeed in a study by Treon et al.⁶ about 90% of WM or LPL have *MYD88* L265P mutation and a small subgroup of patients with marginal zone lymphoma (MZL) were shown to carry this genetic lesion.⁶ In contrast, *MYD88* L265P mutation was absent in tissue samples from patients with myeloma, including samples from patients with IgM secreting myeloma.⁶ *MYD88* L265P mutation may, therefore, be useful in distinguishing LPL from B-cell disorders showing partially overlapping clinicopathological features.⁶ Few cases of non-IgM LPL have been reported demonstrating the presence of *MYD88* L265P.^{5,7-11}

MYD88 L265P triggers survival signaling through BTK and HCK, and *MYD88* L265P expressing cell lines undergo apoptosis in response to ibrutinib, which targets both of these kinases.⁴ Moreover, Ibrutinib has demonstrated significant activity in patients with relapsed/refractory B-Cell malignancies.^{12,13} In 2015, the FDA and the EMA approved ibrutinib for the treatment of symptomatic WM but not for LPL, based on a clinical trial in previously treated patients. The patients with LPL not fulfilling the diagnostic criteria of WM were excluded from WM trials and should be treated as the other indolent lymphoproliferative neoplasms, while recent guidelines¹⁴⁻¹⁷ included

recommendations on the usage of ibrutinib specifically for WM. For these reasons, the use of ibrutinib in non-IgM LPL has not yet been reported. We present here the first report of a patient with *MYD88*-mutated IgA LPL who underwent salvage therapy with ibrutinib.

Case Report. In September 2014 a 66-year-old woman presented with symptomatic anemia (Hemoglobin, Hb: 9 g/dl), with IgA/k monoclonal spike (1.6 g/dl) (**Figure 1**) and an otherwise unremarkable serum chemistry profile. A Computed Tomography (CT) scan documented neither adenopathy nor splenomegaly. BM biopsy showed an 80% infiltrate by lymphocytes and lymphoplasmacytoid cells with admixed atypical plasma cells (25%). Flow cytometry showed a kappa-restricted B-cell population (strong sIg kappa positivity) that expressed CD20, CD19, CD22, CD38, CD138, FMC7, and was negative for CD5, CD3, CD10, CD56, CD79a, CD23. The malignant plasma cells showed IgA+ kappa-restriction. The karyotype on BM cells was normal and so, no t(4,14), t(14,16), t(11,14), or del(17p) aberrations were detected by fluorescence in situ hybridization (FISH) using a probe-panel for multiple myeloma (MM); a deletion of 13q14 DLEU was detected by FISH using a 5 probe-panel for CLL (13q14, chromosome-12 centromere, 11q22, 17p13, 6q21). A diagnosis of IgA-secreting LPL was made.

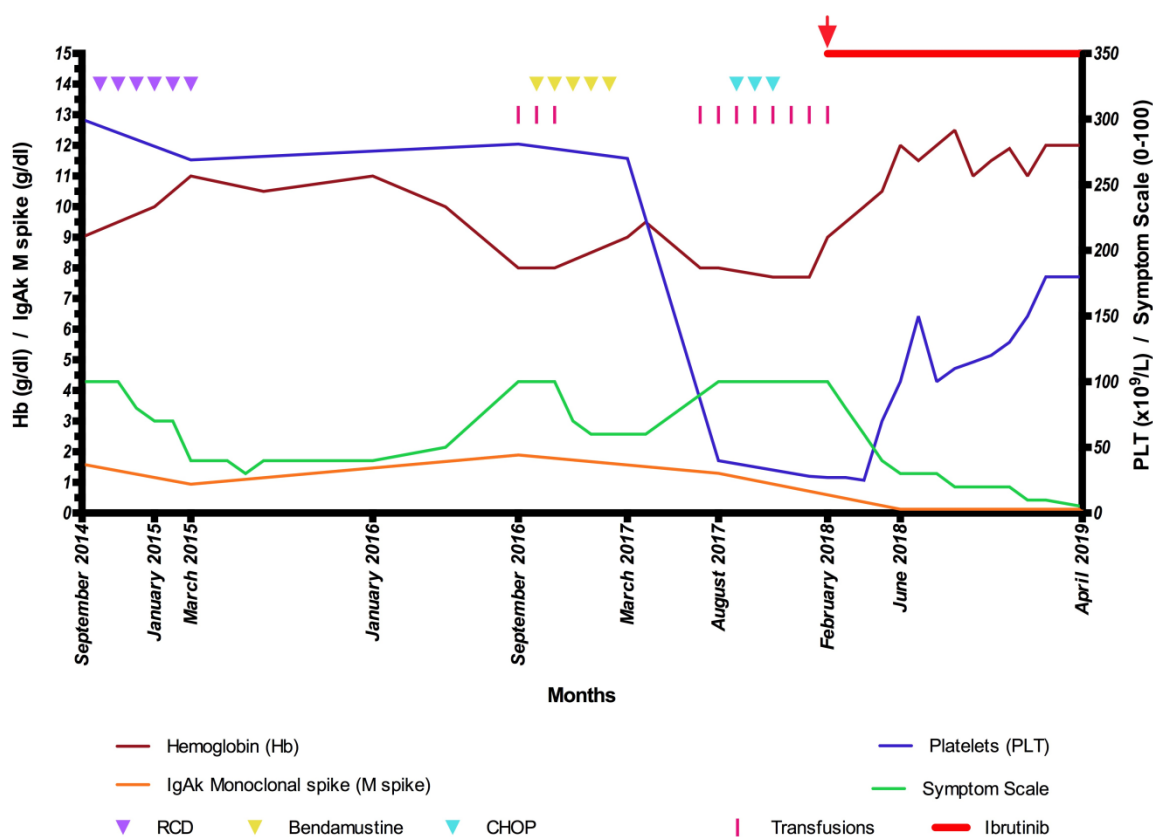


Figure 1. The diagram illustrates modifications in hemoglobin (Hb) and IgAk monoclonal spike (left Y axis), platelets (PLT) and symptoms (right Y axis) by treatment in our patient. Symptom Scale: 0–100-point scale, based on patient’s reported symptoms. Higher scores indicate more severe symptoms. RCD: Rituximab-Cyclophosphamide-Dexamethasone; CHOP: Cyclophosphamide-Doxorubicin-Vincristine-Prednisone. Red arrow: initiation of ibrutinib.

The patient was treated with rituximab-cyclophosphamide-dexamethasone (RCD regimen) with Partial Response (PR)¹⁸ (**Figure 1**). Eighteen months later the patient, who presented with progressive disease (PD) (Hb 8 g/dl, lymphocytes 3.56 x 10⁹/L with 80% lymphoplasmacytic cells, IgAk monoclonal spike 1.9 g/dl), was treated with bendamustine. In January 2017, after five cycles, the BM aspirate showed 90% lymphoid cells and adenopathies, splenomegaly and ascites were noted on a CT scan. Thus, cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) was started and, after three cycles, the patient developed thrombocytopenia (Platelets, PLT: 30 x 10⁹/L), transfusion-dependent anemia (Hb 7.7 g/dl), persistent lymphocytosis (Lymphocytes: 7.15 x 10⁹/L) in the peripheral blood (PB) and clinical deterioration (**Figure 1**). We performed genetic studies of PB lymphocytes (after separation over a Ficoll gradient, yielding >80% clonal B lymphocytes) with a targeted NGS approach detecting mutations in 20 genes frequently mutated in CLL (*ATM, BIRC3, BRAF, CDKN2A, PTEN, CDH2, DDX3X, FBXW7, KIT, KLHL6, KRAS, MYD88, NOTCH1, NRAS, PIK3CA, POT1, SF3B1, TP53, XPO1, ZMYM3*). The *MYD88* L265P mutation was identified in 65.7% of the reads. Given the identification of *MYD88* L265P in the peripheral blood, ibrutinib appeared a reasonable option. In February 2018, our patient started ibrutinib off-label, 420 mg once daily (**Figure 1**). Hb and PLT improved from day +35 (Hb 10-12 g/dl, PLT > 100 x 10⁹/L). In July 2018 no ascites and 50% reduction of adenopathies and spleen were shown on a CT scan. In April 2019, the patient was still on full dose ibrutinib with transfusion independence and good performance status.

This patient is unique in that it represents - to the best of our knowledge - the first reported case of response to ibrutinib in symptomatic aggressive IgA secreting LPL with *MYD88* mutation refractory to multiple lines of treatment. Guidelines for treatment of WM pose indication for ibrutinib in relapsed or untreated patients who are not candidates for chemoimmunotherapy.¹⁴⁻¹⁷ Our case clearly indicates that ibrutinib may represent a valuable therapeutic option for chemorefractory LPL not fulfilling the diagnostic criteria of WM. Our patient had previously been exposed to alkylators, immunomodulators, anti-CD20 monoclonal antibodies and steroids. Her therapeutic options at the time of her most recent relapse were limited and given the identification of the *MYD88* L265P mutation in the peripheral blood, ibrutinib appeared as a reasonable option. In our patient, ibrutinib produced a response within 4–6 weeks, that is a typical time-frame during which a response is usually observed. The partial response has been sustained for approximately 15 months at the time of this report. The kinetics of response in different disease compartments (blood, nodal, extranodal, spleen) were similar to those observed in WM patients^{15,19} and CLL patients on single-agent ibrutinib²⁰ with few treatment emergent adverse events consisting in grade 1 bruising, arthralgias and diarrhea, which improved and resolved with continued treatment.

In conclusion, we present the case of a heavily pretreated patient with *MYD88*-mutated IgA LPL, who has obtained a partial response to ibrutinib that is ongoing after more than one year of therapy. This observation suggests that ibrutinib appears to be potentially effective in this difficult-to-treat-condition.

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