

Plasmablastic lymphoma transformation in a patient with Waldenström macroglobulinemia treated with ibrutinib

A 67-year-old female was diagnosed with Waldenström macroglobulinemia (WM) in October 2004. At diagnosis, the patient was asymptomatic and mildly anaemic with a haemoglobin of 10.4 g/dl (normal range 11–14.9 g/dl). A serum immunofixation electrophoresis detected an IgM kappa monoclonal gammopathy. Serum IgM level was 2450 mg/dl (normal range 40–230 g/dl). A bone marrow biopsy showed 60–70% involvement of a diffuse interstitial population of small lymphocytes admixed with lymphoplasmacytic forms, along with Dutcher bodies and mast cells, consistent with lymphoplasmacytic lymphoma (LPL). The patient did not meet the criteria to treat and was monitored with serial examinations, symptom assessment and laboratory testing. In June 2020, the patient (now age 83) reported progressive fatigue, nosebleeds and dizziness. Her haemoglobin level was 10 g/dl and serum IgM level was 5736 mg/dl. Physical examination did not reveal lymphadenopathy or organomegaly. A bone marrow biopsy was recommended for genotyping, but the patient declined. The International Prognostic System for WM score was high-risk. The patient was started on oral ibrutinib 420 mg once a day. Within 2 months of ibrutinib therapy, the patient reported improvement in fatigue. Her haemoglobin level increased to 11.9 g/dl, and serum IgM level decreased to 2428 mg/dl, consistent with a partial response to therapy. She experienced occasional mouth sores and mild, easy bruising, probably related to ibrutinib. In October 2020, the patient presented with 1 week of abdominal distention and bilateral lower extremity oedema. Laboratory studies showed a lower haemoglobin level at 9.8 g/dl, an increased serum IgM level at 5683 mg/dl and a high serum lactate dehydrogenase level at 509 U/l (normal range 135–225 U/l). Abdominal computed tomography (CT) revealed bulky lymphadenopathy encasing the inferior vena cava. Positron emission tomography (PET)/CT showed intensely F-fluorodeoxyglucose (FDG)-avid confluent lymphadenopathy extending from the posterior mediastinum through the retroperitoneum and scattered foci throughout the skeleton (Fig 1). A CT-guided retroperitoneal lymph node biopsy showed lymphoid tissue diffusely effaced by sheets of large cells with ovoid to irregular nuclei, vesicular chromatin, prominent nucleoli and abundant eosinophilic cytoplasm. Immunohistochemical studies showed large cells positive for CD138, MUM1, and MYC (>80%), and negative for PAX5, CD20, CD30, ALK1, EMA, and HHV8. The large cells displayed monotypic cytoplasmic expression of immunoglobulin kappa light chain. CD20 and PAX5 stains highlighted

numerous background small B-cells. *In-situ* hybridization (ISH) for Epstein-Barr virus-encoded RNA (EBER) was negative. The Ki67 proliferative index was approximately 90% in the large cells and <5% in the small-cell areas. The final pathological diagnosis was consistent with large cell transformation with plasmablastic features in the background of lymphoplasmacytic lymphoma (Fig 2). Fluorescent ISH cytogenetic studies detected *MYC* gene rearrangement in 76%, monosomy of *BCL2* in 60% and polysomy of *BCL6* in 30% of the nuclei investigated. Clinical Oncopanel assay showed mutations in the *MYD88* (p.L265P), *ARID1A* (p.P158fs*73), *EP300* (p.A1892D), *KMT2D* (p.S2155L) and *TP53* (c.993+381T>G) genes. Copy number alteration analysis showed low copy number gain of *BCL6* at 3q27.3, single copy deletion of *TP53* at 17p13.1, and single-copy deletion of *BCL2* at 18q21.33. IgH gene rearrangement matching between the LPL and plasmablastic lymphoma (PBL) components was not possible. A diagnosis of stage IV, HIV-negative PBL with *MYC* gene rearrangement was made. The International Prognostic Index (IPI) was high-risk. The patient received one cycle of bortezomib plus cyclophosphamide, doxorubicin, vincristine and prednisone (V-CHOP) as an inpatient, with improvement in abdominal bloating. Given clinical stability, she was discharged, but her medical insurance denied outpatient bortezomib. She received one cycle of CHOP alone. In January 2021, leg oedema, abdominal distention, and pain recurred. CT showed a marked increase in mesentery, retroperitoneal and pelvic lymph nodes with encasement of the retroperitoneal and mesenteric vessels. There was also increased diffuse abdominal wall oedema associated with pleural effusions and ascites. The treating team had an end-of-life discussion with the patient and her daughter. The patient decided not to pursue additional treatment for her PBL and was enrolled in hospice care for pain management. The patient passed away several days later, 3 months after transformation to PBL and 17 years from WM diagnosis.

Transformation to aggressive lymphoma is a rare occurrence in patients with WM, with an incidence rate of 1–4%.^{1,2} The most common aggressive histology at transformation is diffuse large B-cell lymphoma (DLBCL). Other histological entities have seldom been reported.³ To the best of our knowledge, this is the first report of a transformation event from WM to PBL. PBL is a rare and aggressive CD20-negative lymphoma characterised by a high recurrence rate and short survival with standard regimens.⁴ We, and others,

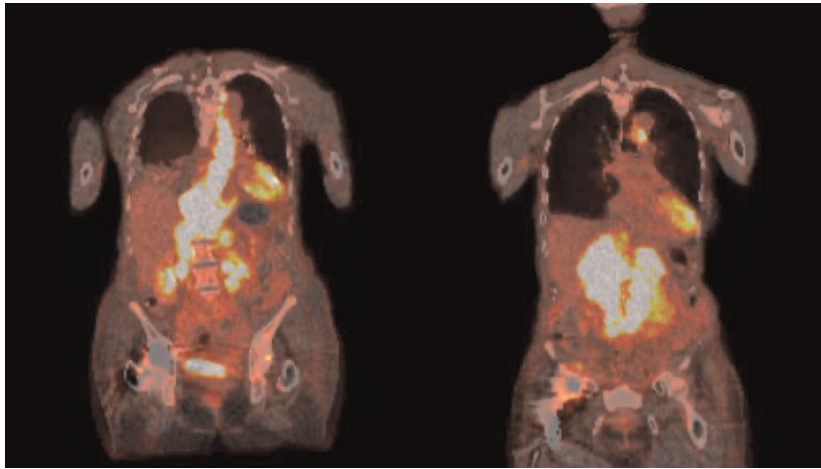


Fig 1. Selected PET/CT scan images at the time of plasmablastic lymphoma transformation. PET/CT, Positron emission tomography/computed tomography.

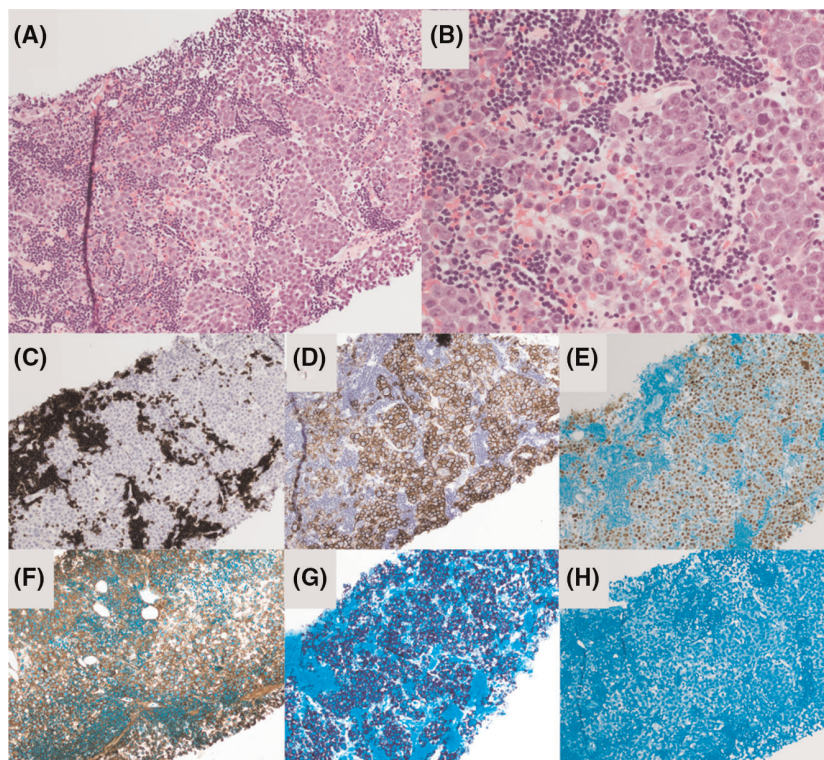


Fig 2. Hematoxylin and eosin stain of the patient's retroperitoneal lymph node biopsy at $\times 200$ (A) and $\times 400$ total magnification (B). CD20 (Clone L26) highlights strong positivity in numerous small B cells with no significant staining in large cells at $\times 200$ total magnification (C). CD138 (Clone B-B4) highlights multiple large cells at $\times 200$ total magnification (D). c-MYC (Clone Y69) highlights $>80\%$ of large cells with no significant expression in small cells at $\times 200$ total magnification (E). Immunohistochemical study for IgM (polyclonal) showing variable surface and cytoplasmic staining in large and small neoplastic cells $\times 200$ total magnification (F). *In-situ* hybridization study for immunoglobulin kappa light chain highlights kappa restriction in large and small neoplastic cells at $\times 200$ total magnification (G). *In-situ* hybridization study for EBV-encoded RNA (EBER) is negative at $\times 200$ total magnification (H).

have reported potential benefits on response and survival with the addition of the proteasome inhibitor bortezomib to chemotherapy.^{5,6} Biologically, PBL is characterized by morphology that mimics DLBCL and an immunophenotype akin to myeloma, though with genomic abnormalities that differ

from DLBCL.^{7,8} Therefore, the use of an anti-myeloma agent in combination with chemotherapy is a reasonable approach in this hard-to-treat disease. Despite an initial response to the first cycle of bortezomib plus CHOP, bortezomib was not covered by insurance. Therefore, therapy continued with

CHOP alone, with disease progression shortly after the second cycle. It is difficult to determine whether continued bortezomib would have favorably impacted this patient's outcome. There were numerous adverse factors for this patient. The IPI score was high (age ≥ 60 years, ECOG ≥ 2 , elevated serum LDH level, stage IV and ≥ 2 sites of extranodal disease), and genomic studies detected *MYC* gene rearrangements and multiple point mutations in *MYD88*, *ARID1A*, *EP300*, *KMT2D* and *TP53* genes, as previously described in EBV-negative PBL.⁸ These genomic anomalies are associated with poor outcomes in PBL and other lymphoproliferative disorders.^{9–14} Mutations in JAK-STAT-related genes have been described in EBV-positive PBL and were not detected in this case.⁸ Previous exposure to nucleoside analogs and *MYD88* wildtype status have been associated with a higher risk of aggressive transformation in PBL,^{15,16} but these factors were not present in this patient.

Herein, we report a unique case of transformation from WM to PBL in a patient responding to ibrutinib therapy. The expression of IgM and κ light chain by both the indolent and the aggressive processes and presence of mutated *MYD88* rather supports a *bona fide* clonal transformation, though the emergence of a secondary primary is possible.

Author contributions

JJC designed the study and drafted the manuscript. JJC, CAF, SS and SPT provided clinical care to the patient. JL and OP performed the pathological evaluation of the case. All the authors critically reviewed the draft and approved the final manuscript.

Conflict of interest

JJC received research funds or honoraria from Abbvie, Beigene, Janssen, Pharmacyclics, Roche and TG Therapeutics. SPT received research funds or honoraria from Beigene, BMS, Pharmacyclics and X4. All other authors have no conflict of interest to disclose.

Jorge J. Castillo^{1,2} 

John LaMacchia^{2,3}

Catherine A. Flynn¹

Shayna Sarosiek^{1,2} 

Olga Pozdnyakova^{2,3}

Steven P. Treon^{1,2} 

¹Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, ²Harvard Medical School and ³Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA.

E-mail: jorgej_castillo@dfci.harvard.edu

Keywords: Waldenström's macroglobulinaemia, plasmablastic lymphoma, ibrutinib

First published online 6 August 2021
doi: 10.1111/bjh.17759

References

- Castillo JJ, Gustine J, Meid K, Dubeau T, Hunter ZR, Treon SP. Histological transformation to diffuse large B-cell lymphoma in patients with Waldenström macroglobulinemia. *Am J Hematol*. 2016;**91**(10):1032–5.
- Zanwar S, Abeykoon JP, Durot E, King R, Perez Burbano GE, Kumar S, et al. Impact of MYD88(L265P) mutation status on histological transformation of Waldenström macroglobulinemia. *Am J Hematol*. 2020;**95**(3):274–81.
- Owen RG, Bynoe AG, Varghese A, de Tute RM, Rawstron AC. Heterogeneity of histological transformation events in Waldenström's macroglobulinemia (WM) and related disorders. *Clin Lymphoma Myeloma Leuk*. 2011;**11**(1):176–9.
- Castillo JJ, Furman M, Beltrán BE, Bibas M, Bower M, Chen W, et al. Human immunodeficiency virus-associated plasmablastic lymphoma: poor prognosis in the era of highly active antiretroviral therapy. *Cancer*. 2012;**118**(21):5270–7.
- Castillo JJ, Guerrero-García T, Baldini F, Tchernonog E, Cartron G, Nin-kovic S, et al. Bortezomib plus EPOCH is effective as frontline treatment in patients with plasmablastic lymphoma. *Br J Haematol*. 2019;**184**(4):679–82.
- Fernandez-Alvarez R, Gonzalez-Rodriguez AP, Rubio-Castro A, Gonzalez ME, Payer AR, Alonso-Garcia A, et al. Bortezomib plus CHOP for the treatment of HIV-associated plasmablastic lymphoma: clinical experience in three patients. *Leuk Lymphoma*. 2016;**57**(2):463–6.
- Castillo JJ, Bibas M, Miranda RN. The biology and treatment of plasmablastic lymphoma. *Blood*. 2015;**125**(15):2323–30.
- Ramis-Zaldivar JE, Gonzalez-Farre B, Nicolae A, Pack S, Clot G, Nadeu F, et al. MAP-kinase and JAK-STAT pathways dysregulation in plasmablastic lymphoma. *Haematologica*. 2021. <https://doi.org/10.3324/haematol.2020.271957>
- Pastore A, Jurinovic V, Kridel R, Hoster E, Staiger AM, Szczepanowski M, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol*. 2015;**16**(9):1111–22.
- Salido M, Baró C, Oscier D, Stamatopoulos K, Dierlamm J, Matutes E, et al. Cytogenetic aberrations and their prognostic value in a series of 330 splenic marginal zone B-cell lymphomas: a multicenter study of the Splenic B-Cell Lymphoma Group. *Blood*. 2010;**116**(9):1479–88.
- Xu-Monette ZY, Wu L, Visco C, Tai YC, Tzankov A, Liu WM, et al. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. *Blood*. 2012;**120**(19):3986–96.
- Aukema SM, Hoster E, Rosenwald A, Canoni D, Delfau-Larue M-H, Rymkiewicz G, et al. Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network. *Blood*. 2018;**131**(4):417–20.
- Qu X, Li H, Braziel RM, Passerini V, Rimsza LM, Hsi ED, et al. Genomic alterations important for the prognosis in patients with follicular lymphoma treated in SWOG study S0016. *Blood*. 2019;**133**(1):81–93.
- Ferrero S, Rossi D, Rinaldi A, Brusca A, Spina V, Eskelund CW, et al. KMT2D mutations and TP53 disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study. *Haematologica*. 2020;**105**(6):1604–12.
- Leleu X, Soumerai J, Roccaro A, Hatjiharissi E, Hunter ZR, Manning R, et al. Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenström macroglobulinemia treated with nucleoside analogs. *J Clin Oncol*. 2009;**27**(2):250–5.
- Treon SP, Gustine J, Xu L, Manning RJ, Tsakmakis N, Demos M, et al. MYD88 wild-type Waldenström macroglobulinemia: differential diagnosis, risk of histological transformation, and overall survival. *Br J Haematol*. 2018;**180**(3):374–80.