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Long-term Survival in a Patient With Transformation of Waldenström's Macroglobulinemia into DLBCL

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Abstract. *Background/Aim: Waldenström's macroglobulinemia (WM) is a rare slow-growing B-cell lymphoma that is characterized by lymphoplasmacytic bone marrow infiltration and the production of monoclonal immunoglobulin M (IgM) paraprotein. In 5-10% of patients, WM undergoes transformation into diffuse large B-cell lymphoma (DLBCL), which is more aggressive, with poor prognosis and a low survival rate. Case Report: A 69-year-old woman was diagnosed with WM in 2009. She received six cycles of chemoimmunotherapy and a remarkable remission was achieved. However, in 2013 the disease transformed into DLBCL. The patient received chemotherapy and after the completion of the first cycle of therapy, the disease was significantly minimized. At the end of the therapy, there was no evidence of disease, and the patient remains disease-free. The cytogenetic profile of the patient did not reveal expression of BCL2 apoptosis regulator, BCL6 transcription repressor, Epstein–Barr virus small RNA, syndecan 1 nor cyclin D1. According to a staging system based on the platelet count, lactate dehydrogenase and previous treatment for WM, the described patient was classified as being at intermediate risk with an expected 2-year survival probability of 47% after WM transformation into DLBCL. However, the patient unexpectedly exceeded these prognostic indications. Conclusion: The findings for this patient are of great interest compared with the existing literature which suggests that the survival and prognosis for patients with transformed DLBCL are not favorable.*

Waldenström's macroglobulinemia (WM) is a rare type of B-cell non-Hodgkin lymphoma that is characterized by lymphoplasmacytic bone marrow infiltration and the production of monoclonal immunoglobulin M (IgM) paraprotein (1). WM accounts for 1-2% of all patients with hematological malignancies and the median overall survival is approximately 8 years (2, 3). In rare cases, in 5-10% of patients with WM, the disease may undergo transformation into diffuse large B-cell lymphoma (DLBCL) and this can occur at any time in the course of the disease (4, 5). DLBCL that arises from histological transformation (HT) of WM has worse prognosis compared with de novo DLBCL, with a median survival of less than 3 years (5-7).

In this case report, we present a woman with DLBCL which developed following WM who has remained disease-free over the past 10 years after completion of chemotherapy.

Case Report

In February 2009, a 69-year-old woman (approval number 375/ 21-05-2019), with a history of anemia worsening over the previous 6 months, presented with a remarkably low hemoglobin level of 8 g/dl. The physical examination revealed paleness, enlargement of the spleen and absence of lymphadenopathy. Abdominal computed tomography confirmed these findings, while fundoscopy indicated lesions compatible with hyperviscosity syndrome. The laboratory examinations showed a remarkably level low of hemoglobin=7.3-8.9 g/dl, white blood cell count of 17.3×10^3/μl (24% neutrophils, 60% lymphocytes), high IgM level of 9,110 mg/dl, abnormal high lactate dehydrogenase (LDH)=376 U/l and β2 microglobulin=3,500 μg/l. In

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addition, the bone marrow examination revealed 40-50% infiltration by monoclonal lympho-plasma cells and immunofixation was positive for IgM kappa monoclonal protein; thus, the diagnosis of WM was established.

The patient received a combination of dexamethasone at 20 mg on day 1, 375 mg/m^2 rituximab on day 1 and cyclophosphamide at 100 mg/m^2 twice daily for 5 days (DRC) every 21 days for 6 months. Erythropoietin and filgrastim were administered as supportive measures. The regimen was well tolerated, with no clinically significant major adverse events. Following eight cycles of chemoimmunotherapy, hematological partial response was achieved. The laboratory findings were improved as follows: hemoglobin=12.3 g/dl, white blood cell count of 5.2×10^3/µl (63% neutrophils, 28% lymphocytes), IgM=2,620 mg/dl, LDH=137 U/l and β2 microglobulin=1,668 µg/l. The performance status of the patient was excellent and maintenance treatment with rituximab monotherapy was given every 2 months for 1 year. During a follow-up period of 3 years, the IgM level showed a constant decrease, and the laboratory findings were unremarkable.

However, during a routine follow-up visit in 2013, the physical examination revealed a gluteal mass and swelling of ipsilateral inguinal lymph nodes. A biopsy of the lymph node was performed, and immunohistochemistry demonstrated expression of CD20, CD30, paired box 5, CD79a, multiple myeloma oncogene-1, CIgM(κ) and p53, while there was no evidence of BCL2 apoptosis regulator (BCL2), BCL6 transcription repressor (BCL6), Epstein–Barr virus small RNA, syndecan and cyclin D1 expression; hence, the pathology report findings were suggestive of DLBCL. Staging with whole-body computed tomography did not reveal any other disease foci. The patient started treatment immediately with 660 mg rituximab, 1,300 mg cyclophosphamide, 80 mg doxorubicin, 2 mg vincristine and 100 mg prednisone (R-CHOP regimen) for six cycles. Importantly, the disease showed a rapid clinical response to treatment. At the beginning of the second cycle, the gluteal mass shrank at such an extent that it was no longer palpable during physical examination and the inguinal lymphadenopathy was significantly improved according to the imaging studies. After the third cycle, restaging was performed with computed tomography and showed complete response to treatment. The patient completed six cycles of treatment. She tolerated treatment well with no infusion-related reactions or other major toxicities to report. Diarrhea of grade one, grade one alopecia and a grade two thromboembolic event were reported, according to Common Terminology Criteria for Adverse Events. The laboratory hematological findings were unremarkable. Restaging after completion of therapy was also negative for residual disease. The patient has been followed up since then at regular time intervals with clinical, hematological, and imaging assessments. At 10 years after the completion of salvage chemotherapy for transformed DLBCL, there are no signs or symptoms of disease recurrence in terms of both DLBCL and WM.

Discussion

Chronic lymphocytic leukemia/small lymphocytic lymphoma carry a risk for progression to DLBCL, which is known as Richter's syndrome (4). WM can also undergo transformation into DLBCL. Since transformation of WM to a more aggressive type of lymphoma was described for the first time in the 1960s, similar cases have been recorded (8, 9). Transformation into DLBCL is the most common type of high-grade lymphoma, while transformation into immunoblastic lymphoma, peripheral T-cell lymphoma, Hodgkin-type lymphoma and a plasma-type neoplasm have also been observed (10-13). In a retrospective study, Castillo *et al*. found that the risk of transformation of WM into DLBCL is 1% at 5 years, 2.4% at 10 years and 3.8% at 15 years (5).

When the disease involves transformation events that include mutations of *MYC, BCL2* and/or *BCL6*, it is known as a 'double hit' or 'triple hit' lymphoma, according to the World Health Organization classification (14). When overexpression of MYC, BCL2 and BCL6 proteins is present without chromosomal translocation, it is called 'double-expressor' lymphoma. Moreover, these genes are considered as prognostic indicators (14). Hence, it is recommended that all patients with DLBCL should be tested for *MYC, BCL2* and *BCL6* rearrangements (14). Our patient was negative for Immunohistochemical expression of BCL2 and BCL6, while expression of MYC was not investigated.

Progression of WM to DLBCL is associated with poor prognosis. Lin *et al*. observed that eight out of nine (89%) patients died within 10 months of diagnosis of DLBCL, while one patient achieved complete response and remained alive after 8 months from the time of HT (4). The reported median survival was 5 months (4). In another study, Durot and colleagues found that among 77 patients with HT of WM to DLBCL the median progression-free survival and overall survival were 9 and 16 months, respectively (11). In another retrospective study, the median survival was 2.7 years after transformation to DLBCL(5). Taking all this into consideration, our patient had an outstanding clinical course and has remained alive for at least 10 years after the progression of WM to DLBCL with no evidence of disease recurrence.

The median time for WM transformation into DLBCL reportedly ranges from 4 to 6 years; HT is considered a complex and heterogeneous phenomenon and prognostic factors are still not well clarified (10, 15). According to the literature, there is debate whether the transformation into DLBCL should be considered as being clonal-related or an independent second malignancy (16–18). Shiseki *et al*. found a complementarity-determining region 3 (CDR3) in the

immunoglobulin heavy chain gene common to both DLBCL and WM cells, implying a probable clonal evolution as the etiological pathway of the transformation (16). In addition, a whole-exome sequencing study demonstrated recurrent mutations of Pim-1 proto-oncogene, serine/threonine kinase *(PIM1),* FRY-like transcription coactivator (*FRYL)* and hepatocyte nuclear factor-1-beta (*HNF1B*) *ge*nes present in transformed cells, indicating cooperation and interaction between the cell clones responsible for HT (19). The researchers also found a higher rate of mutations in the *CD79B* gene in patients with transformation into DLBCL, suggesting that it might be an indicator for HT (19). Concerning etiology unrelated to clonality, Epstein–Barr virus was described to have a critical role in the development of DLBCL in a patient with WM (20). However, other studies revealed that the majority of patients with transformed DLBLC were negative for Epstein–Barr virus, confirming the heterogeneity and complexity of DLBCL transformed from WM (4, 5, 11). An elevated LDH level, absence of response to treatment and time to progression of more than 5 years from WM diagnosis were also found to be negative prognostic factors (11). In our case, the patient had an LDH level of 691 U/l at the time of transformation, the progression occurred in less than 5 years from diagnosis of WM, and she had had a complete response to first-line salvage treatment. In order to make their prognostic model more accurate, Durot *et al*. developed a prognostic index for 2-year survival after WM transformation based on three unfavorable parameters: Platelet count $<100\times10^9$/l and previous treatment for WM, each scoring 1 point, and elevated LDH, scoring 2 points (21). Patients were classified as having a low transformation risk with zero or 1 point, intermediate risk with 2 or 3 points, and a high risk with 4 points, with 2-year survival rates being 81%, 47% and 21%, respectively (21). Our patient would be classified as having an intermediate risk (previously treated, 1 point; platelet count $=287\times10^9$/l, zero points; LDH=691 U/l, 1 point) with an expected 2-year survival of 47% according to this model. However, she unexpectedly exceeded these prognostic indications.

Previous exposure to nucleoside analogs has also been investigated as a risk factor for HT. Our patient received the DRC regimen for WM, including the alkylating agent cyclophosphamide. Some studies have found that there is an association between transformation following the administration of nucleoside analogs. Leleu *et al*. concluded that there were high rates of transformation events among patients pretreated with NA (12). Interestingly, Castillo *et al*. observed that HT occurred not only in patients with WM who were pretreated with nucleoside analogs, but also in those who were treatment-naïve. This suggested an inherent propensity for transformation (5). Similarly, in another study, prior use of purine analogues or alkylating agents was not statistically significant associated with the risk of HT (11). Hence, there is debate as to whether previous chemotherapy initiates or precipitates the genomic events leading to WM transformation.

Conclusion

Despite the fact that WM is a low-grade lymphoma with an indolent course, the rare event of transformation into DLBCL is characterized by a poor prognosis. Herein, we presented an exceptional case with long-term remission and survival, which underlines the need for large collaborative studies in order to discriminate patient subgroups with favorable prognosis.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: MAD; data curation: ES and INS; formal analysis: ES, MG; investigation: ES, INS, EK, ET, MAD and MG; methodology: MAD, MG; Project administration: EK and ET; supervision: MAD and MG; writing – original draft: ES and INS; writing–review and editing: all Authors. All Authors approved the final version of the article.

References

1 Gertz MA: Waldenström macroglobulinemia: 2023 update on diagnosis, risk stratification, and management. Am J Hematol 98(2): 348-358, 2023. DOI: 10.1002/ajh.26796

2 Simon L, Baron M, Leblond V: How we manage patients with Waldenström macroglobulinaemia. Br J Haematol 181(6): 737-751, 2018. DOI: 10.1111/bjh.15202

3 Castillo JJ, Olszewski AJ, Kanan S, Meid K, Hunter ZR, Treon SP: Overall survival and competing risks of death in patients with Waldenström macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database. Br J Haematol 169(1): 81-89, 2015. DOI: 10.1111/bjh.13264

4 Lin P, Mansoor A, Bueso-Ramos C, Hao S, Lai R, Medeiros LJ: Diffuse large B-cell lymphoma occurring in patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinemia. Clinicopathologic features of 12 cases. Am J Clin Pathol 120(2): 246-253, 2003. DOI: 10.1309/R01V-XG46-MFCD-VNHL

5 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 91(10): 1032-1035, 2016. DOI: 10.1002/ajh.24477

6 Durot E, Tomowiak C, Michallet A, Dupuis J, Lepretre S, Toussaint E, Godet S, Merabet F, Van Den Neste EW, Ivanoff S, Zini J, Régny C, Perrot A, Kanagaratnam L, Morel P, Leblond V, Delmer A: Retrospective analysis of 56 cases of transformed Waldenström macroglobulinemia. a study on behalf of the French Innovative Leukemia Organization (FILO). Blood 128(22): 2982-2982, 2016. DOI: 10.1182/blood.V128.22.2982.2982

7 Castillo JJ, Olszewski AJ, Kanan S, Meid K, Hunter ZR, Treon SP: Survival outcomes of secondary cancers in patients with Waldenström macroglobulinemia: An analysis of the SEER

database. Am J Hematol 90(8): 696-701, 2015. DOI: 10.1002/ajh.24052
8 Wood TA, Frenkel EP: An unusual case of macroglobulinemia. Arch Intern Med 119(6): 631, 1967. DOI: 10.1001/archinte.1967.00290240153016
9 McCallister BD, Bayrd ED, Harrison EG, McGuckin WF: Primary macroglobulinemia. Am J Med 43(3): 394-434, 1967. DOI: 10.1016/0002-9343(67)90195-7
10 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 11(1): 176-179, 2011. DOI: 10.3816/CLML.2011.n.042
11 Durot E, Tomowiak C, Michallet AS, Dupuis J, Hivert B, Leprêtre S, Toussaint E, Godet S, Merabet F, Van Den Neste E, Ivanoff S, Roussel X, Zini JM, Regny C, Lemal R, Sutton L, Perrot A, Le Dû K, Kanagaratnam L, Morel P, Leblond V, Delmer A: Transformed Waldenström macroglobulinaemia: clinical presentation and outcome. A multi-institutional retrospective study of 77 cases from the French Innovative Leukemia Organization (FILO). Br J Haematol 179(3): 439-448, 2017. DOI: 10.1111/bjh.14881
12 Leleu X, Soumerai J, Roccaro A, Hatjiharissi E, Hunter ZR, Manning R, Ciccarelli BT, Sacco A, Ioakimidis L, Adamia S, Moreau AS, Patterson CJ, Ghobrial IM, Treon SP: Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenström macroglobulinemia treated with nucleoside analogs. J Clin Oncol 27(2): 250-255, 2009. DOI: 10.1200/JCO.2007.15.1530
13 Rosales CM, Lin P, Mansoor A, Bueso-Ramos C, Medeiros LJ: Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia associated with Hodgkin disease. Am J Clin Pathol 116(1): 34-40, 2001. DOI: 10.1309/9DBY-FBUG-Y10A-AAXT
14 Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127(20): 2375-2390, 2016. DOI: 10.1182/blood-2016-01-643569
15 Elimimian EB, Bilani N, Diacovo MJ, Sirvaitis S, Fu CL: Histologic transformation in an untreated Waldenstrom's macroglobulinemia after 14 years: Case report and review of the literature. J Hematol 10(1): 25-29, 2021. DOI: 10.14740/jh767
16 Shiseki M, Masuda A, Watanabe N, Fujii M, Kimura T, Yoshinaga K, Mori N, Teramura M, Motoji T: Development of diffuse large B-cell lymphoma in a patient with Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma: clonal identity between two B-cell neoplasms. Hematol Rep 3(2): e10, 2011. DOI: 10.4081/hr.2011.e10
17 Shimizu S, Tamagawa Y, Kojima H, Mori N, Nagata M, Noguchi M, Nagasawa T: Simultaneous development of lymphoplasmacytic lymphoma and diffuse large B-cell lymphoma – analyses of the clonal relatedness by sequencing CDR3 in immunoglobulin heavy chain genes. Eur J Haematol 70(2): 119-124, 2003. DOI: 10.1034/j.1600-0609.2003.00013.x
18 Talaulikar D, Tam CS, Joshua D, Ho JP, Szer J, Quach H, Spencer A, Harrison S, Mollee P, Roberts AW, Horvath N, Lee C, Zannettino A, Brown R, Augustson B, Jaksic W, Gibson J, Kalff A, Johnston A, Trotman J, Kalro A, Grigoriadis G, Ward C, Prince HM: Treatment of patients with Waldenström macroglobulinaemia: clinical practice guidelines from the Myeloma Foundation of Australia Medical and Scientific Advisory Group. Intern Med J 47(1): 35-49, 2017. DOI: 10.1111/imj.13311
19 Jiménez C, Alonso-Álvarez S, Alcoceba M, Ordóñez GR, García-Álvarez M, Prieto-Conde MI, Chillón MC, Balanzategui A, Corral R, Marín LA, Gutiérrez NC, Puig N, Sarasquete ME, González M, García-Sanz R: From Waldenström's macroglobulinemia to aggressive diffuse large B-cell lymphoma: a whole-exome analysis of abnormalities leading to transformation. Blood Cancer J 7(8): e591, 2017. DOI: 10.1038/bcj.2017.72
20 Varghese AM, Sayala H, Evans PAS, O'connor SJM, Patmore R, Hillmen P, Owen RG: Development of EBV-associated diffuse large B-cell lymphoma in Waldenström macroglobulinemia and mantle cell lymphoma. Leuk Lymphoma 49(8): 1618-1619, 2008. DOI: 10.1080/10428190802123481
21 Durot E, Kanagaratnam L, Zanwar S, Kastritis E, D'Sa S, Garcia-Sanz R, Tomowiak C, Hivert B, Toussaint E, Protin C, Abeykoon JP, Guerrero-Garcia T, Itchaki G, Vos JM, Michallet AS, Godet S, Dupuis J, Leprêtre S, Bomsztyk J, Morel P, Leblond V, Treon SP, Dimopoulos MA, Kapoor P, Delmer A, Castillo JJ: A prognostic index predicting survival in transformed Waldenström macroglobulinemia. Haematologica 106(11): 2940-2946, 2021. DOI: 10.3324/haematol.2020.262899

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