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Waldenström macroglobulinemia: a challenging case treated with anti-CD19 CAR-T cell therapy

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Waldenström macroglobulinemia (WM) is characterized by lymphoplasmacytic lymphoma associated with large amounts of monoclonal immunoglobulin M (IgM) protein (Owen et al., 2003). Common signs and symptoms include fatigue due to anemia, lymph node enlargement, hepatosplenomegaly, thrombocytopenia, symptoms related to high viscosity, and peripheral neuropathy, among others. Despite significant advances in WM treatment, this type of indolent lymphoma remains incurable, with a wide array of patient outcomes (Ruan et al., 2020). In recent years, chimeric antigen receptor T (CAR-T) cell therapy targeting cluster of differentiation 19 (CD19) has shown unprecedented response rates and durability in the treatment of B-cell malignancies. In this report, we describe a challenging case of WM that involved multiple extramedullary sites, relapsed, and was refractory to chemotherapy, immunotherapy, and targeted therapy. After anti-CD19 CAR-T cell therapy, the tumor burden significantly decreased and the patient's condition remained stable at the writing of this report.

In August 2018, a 66-year-old female presented with headache and fever and was diagnosed with cryptococcal meningitis. Anemia was noted, but no further workup was performed. In December 2019, the patient developed generalized pruritus, followed by dizziness, fatigue, and low-grade fever. Laboratory tests revealed severe normocytic anemia (hemoglobin (Hb) 5.9 g/dL), elevated globulin (52.5 g/L) and IgM (4784 mg/dL) levels, and increased serum levels of β-2 microglobulin and lactic dehydrogenase, as well as lymphadenopathy. Immunohistochemical studies of lymph node biopsy showed monoclonal B-cells with the expression of CD20, CD19, and κ light chain restriction, and negative staining for CD5, CD10, and CD23. Bone marrow biopsy revealed 80% diffuse infiltration of small lymphocytic cells with *MYD88*^{L265P} mutation (the leucine to proline exchange at position 265 (L265P) in the myeloid differentiation primary response gene 88 (*MYD88*)), consistent with lymph node biopsy. Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) scan detected enlarged lymph nodes and increased FDG uptake in the paravertebral soft tissue (standardized uptake value (SUV)=3.5). The patient was diagnosed with WM, and the revised International Prognostic Staging System (rIPSS) score was 4 (very high risk) (Kastritis et al., 2019). The patient received four cycles of chemoradiotherapy with rituximab, cyclophosphamide, and dexamethasone (RCD). Subsequently, blood tests showed that Hb increased to 7.8 g/dL and IgM decreased to 2864 mg/dL. However, the patient developed multiple body rashes and back pain. Magnetic resonance imaging (MRI) suggested infiltration of lymphoma in the vertebrae and surrounding tissues. L5 vertebral body biopsy revealed an increase in small B lymphocytes. Since the patient's condition continued to deteriorate, she was enrolled in a single-arm, multicenter, phase IV clinical trial and began taking ibrutinib. Three months later, she developed dyspnea and bloody pleural effusion. Flow cytometry of the pleural fluid showed abnormal B lymphocytes.

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The patient then received two cycles of ibrutinib and rituximab (IR) treatment; however, the pleural effusion did not improve, and therefore, the patient received six cycles of bendamustine and rituximab (BR) treatment. The pleural effusion gradually subsided, resulting in a partial response. Five months after therapy, a follow-up examination showed Hb level of 11.6 g/dL and IgM level of 987 mg/dL, but a new lump was found on the right chest, accompanied by multiple pleural-based masses detected by CT, indicating disease progression. Biopsy of the lump confirmed lymphoplasmacytic lymphoma with *MYD88*^{L265P} and frameshift mutations in C-X-C chemokine receptor type 4 (*CXCR4*) by next-generation sequencing (NGS). The patient then underwent one cycle of R-CHOP regimen (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and dexamethasone) chemotherapy; however, the soft tissue lump on the right chest wall was enlarged. PET visualized multiple irregular soft masses in the right chest wall with multiple generalized lymphadenopathies, hepatosplenomegaly, and involvement of the right gluteus maximus muscle and left iliac muscle (SUV max=6.3) (Fig. 1a). The patient was subsequently enrolled in a clinical study (NCT 04532281) evaluating the safety and efficacy of anti-CD19 CAR-T therapy in relapsed/refractory (R/R) B-cell hematological malignancies. Chemotherapy was administered with fludarabine and cyclophosphamide (FC) regimen followed by infusion of second-generation CD19-directed CAR-T cells (2×10^6 cells/kg) in July 2022. These CAR-T cells containing 4-1BB co-stimulatory and CD3ζ signaling domains were manufactured by Shanghai Yake Biotechnology Company (Shanghai, China). Following CAR19 T-cell infusion, the patient experienced a low-grade fever from Days 3 to 8. Additionally, she developed grade 4 leukocytopenia (common terminology criteria for adverse events (CTCAE) version 5). To manage the grade 1 cytokine release syndrome (CRS), the patient received tocilizumab treatment. Importantly, no neurological toxicity or secondary infections could be observed. A PET/CT scan three months after treatment revealed very good partial response (VGPR) according to the 11th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-11) response criteria (Treon et al., 2023), especially due to the disappearance of the chest wall extramedullary mass (Fig. 1b), with Hb increased to 12.8 g/dL and IgM decreased to 219 mg/dL. She remained in VGPR at the 12-month follow-up.

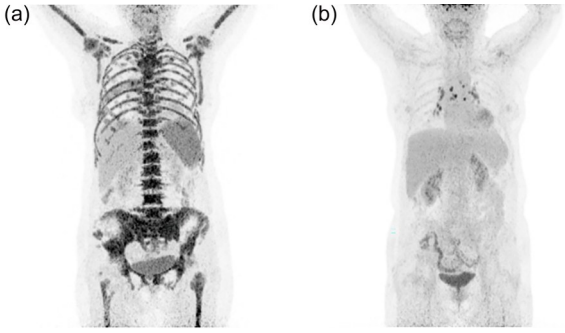

Fig. 1 Comparison of fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) before and after chimeric antigen receptor T (CAR-T) treatment. (a) PET image prior to CAR-T cell therapy. Multiple foci of hypermetabolism could be observed throughout the body. (b) FDG-PET image three months after CAR-T cell therapy. The foci of hypermetabolism were significantly reduced in number and intensity.

WM is considered an incurable disease, in which treatment decisions should take into account various factors, such as patient comorbidities, treatment goals, and risks of immunosuppression. First-line treatment options for symptomatic WM patients include CD20 monoclonal antibody combined with alkylating agents or proteasome inhibitors, and Bruton's tyrosine kinase (BTK) inhibitors. These regimens can also be used for the management of R/R patients. Drugs targeting *MYD88*, *CXCR4*, and CAR-T cell therapy have shown potential for R/R patients (Castillo et al., 2020, 2022; Gertz, 2023; Thompson and Tam, 2023).

The initial treatment chosen for this patient was the RCD regimen, which is a commonly used chemotherapeutic immunotherapy for WM patients. Comparative research on the efficacy of initial treatments in WM has been limited. Retrospective studies suggest that the BR regimen may have better efficacy than the RCD regimen, while RCD has relatively low toxicity and can control cell reduction and gastrointestinal symptoms, making it a reasonable treatment option for this patient (Abeykoon et al., 2021). Nevertheless, the patient's condition progressed with the appearance of multiple extramedullary lesions.

While ibrutinib-containing regimens are ideal for R/R WM, they may not be as effective for patients with bulky extramedullary disease, malignant pleural effusions, or severe bone marrow involvement (Treon, 2015). The examination of the chest wall mass in this

patient indicated *CXCR4* WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) in addition to *MYD88*^{L265P}, which may have affected the efficacy of ibrutinib. Thus, treatment was adjusted to BR, which resulted in a significant improvement, with the pleural effusion subsiding.

When the chest wall mass continued to enlarge after R-CHOP therapy, an unconventional treatment approach was urgently needed to address the refractory extramedullary lesion. At this point, the possibility of autologous stem cell transplantation (ASCT) was considered. However, hematopoietic stem cell transplantation (HSCT) has limited data on its effectiveness in WM patients, especially for those with chemotherapy-refractory disease (Kyriakou, 2018).

The implementation of new therapies and participation in clinical trials are crucial to improving the prognosis of WM patients. In recent years, for example, CAR-T cell therapy has shown significant effectiveness against resistant B-cell malignant tumors, particularly in large B-cell lymphoma and transformed follicular lymphoma (Locke et al., 2019). Notwithstanding, the application of CAR-T cell therapy in WM has not been systematically evaluated. Palomba et al. (2022) showed that CD19-targeted CAR-T cell therapy could effectively target WM cells and led to responses in three patients with repeatedly R/R diseases, including complete remission, partial remission, and stable disease. Although disease recurrence occurred between 3 and 26 months after initial treatment, CD19-targeted CAR-T cell therapy was effective in R/R WM patients. Successful CAR-T cell therapy was also reported in a patient with a transformed WM. The patient had poor responses to various chemotherapy regimens, and the disease progressed even after ASCT. However, CAR-T cell therapy targeting CD19 resulted in complete remission, which was maintained during the one-year follow-up period (Bansal et al., 2020). Furthermore, in a phase 1/2 clinical trial, CD20-targeted CAR-T cell therapy achieved a 100% complete remission in four WM patients (Shadman et al., 2023). The reported cases are presented in Table 1.

The patient in our case tolerated the CAR-T cell therapy well with no significant CRS or neurotoxicity events. She has been followed up for over a year and her disease remains in very good partial remission, indicating the potential of CAR-T cell therapy as an alternative for R/R WM. Larger-scale clinical studies are eagerly apticipated to evaluate the efficacy and safety of this therapy.

Data availability statement

Data sharing is not applicable to this article as all the data are already listed in this paper.

Table 1 Cases of WM treated with CAR-T treatment

Target	Age (years)	Genotype	Prior lines of therapy	Best response	PFS (months)	OS (months)	Reference
CD19	66	*MYD88* p.L265P, *CXCR4* p.S345fs	5	VGPR	NR	NR	Current report
	73	*MYD88* p.L265P, *CXCR4* p.S342fs, *TP53* p.R175H/R196Q	7	SD	6.8	12.4	Palomba et al., 2022
	75	*MYD88* p.L265P, loss of *MYB* and *ATM*	6	PR	4	4	Palomba et al., 2022
	64	*MYD88* p.L265P, *DNMT3A* p.R823K	5	VGPR	26.5	NR	Palomba et al., 2022
	71	*MYD88* p.L265P	5	CR	12	NR	Bansal et al., 2020
CD20	NA	*MYD88* p.L265P	NA	CR	1.5	NR	Shadman et al., 2023
	NA	*MYD88* p.L265P	NA	CR	3	NR	Shadman et al., 2023
	NA	*MYD88* p.L265P	NA	CR	7	7	Shadman et al., 2023
	NA	*MYD88* p.L265P	NA	CR	19	NR	Shadman et al., 2023

WM: Waldenström macroglobulinemia; CAR-T: chimeric antigen receptor T; PFS: progression-free survival; OS: overall survival; CD: cluster of differentiation; *MYD88*: myeloid differentiation primary response gene 88; L265P: leucine to proline exchange at position 265; *CXCR4*: C-X-C chemokine receptor type 4; *TP53*: tumor protein p53; *ATM*: ataxia telangiectasia mutated; *DNMT3A*: DNA (cytosine-5)-methyltransferase 3A; NA: not available; VGPR: very good partial response; SD: stable disease; PR: partial remission; CR: complete remission; NR: not reached.

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Author contributions

Yang YANG and Xiaolin GU structured and wrote the manuscript. Jingsong HE collected the clinical sample. Yongxian HU and Zhen CAI conducted the clinical trials of CAR-T. Zhen CAI reviewed the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Yang YANG, Xiaolin GU, Jingsong HE, Yongxian HU, and Zhen CAI declare that they have no conflict of interest.

Our study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (No. 20230720A). All procedures followed were in accordance with the ethical standards of the responsible committee on humanexperimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from the patient for being included in the study.

References

Abeykoon JP, Zanwar S, Ansell SM, et al., 2021. Assessment of fixed-duration therapies for treatment-naïve Waldenström macroglobulinemia. *Am J Hematol*, 96(8):945-953. https://doi.org/10.1002/ajh.26210

Bansal R, Jurcic JG, Sawas A, et al., 2020. Chimeric antigen receptor T cells for treatment of transformed Waldenström macroglobulinemia. *Leuk Lymphoma*, 61(2):465-468. https://doi.org/10.1080/10428194.2019.1665668

Castillo JJ, Meid K, Flynn CA, et al., 2020. Ixazomib, dexamethasone, and rituximab in treatment-naive patients with Waldenström macroglobulinemia: long-term follow-up. *Blood Adv*, 4(16):3952-3959. https://doi.org/10.1182/bloodadvances.2020001963

Castillo JJ, Allan JN, Siddiqi T, et al., 2022. Venetoclax in previously treated Waldenström macroglobulinemia. *J Clin Oncol*, 40(1):63-71. https://doi.org/10.1200/JCO.21.01194

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

Kastritis E, Morel P, Duhamel A, et al., 2019. A revised international prognostic score system for Waldenström's macroglobulinemia. *Leukemia*, 33(11):2654-2661. https://doi.org/10.1038/s41375-019-0431-y

Kyriakou C, 2018. High-dose therapy and hematopoietic stem cell transplantation in Waldenström macroglobulinemia. *Hematol Oncol Clin North Am*, 32(5):865-874. https://doi.org/10.1016/j.hoc.2018.05.013

Locke FL, Ghobadi A, Jacobson CA, et al., 2019. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*, 20(1):31-42. https://doi.org/10.1016/S1470-2045(18)30864-7

Owen RG, Treon SP, Al-Katib A, et al., 2003. Clinicopathological definition of Waldenstrom's macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*, 30(2):110-115. https://doi.org/10.1053/sonc.2003.50082

Palomba ML, Qualls D, Monette S, et al., 2022. CD19-directed chimeric antigen receptor T cell therapy in Waldenström macroglobulinemia: a preclinical model and initial clinical experience. *J Immunother Cancer*, 10(2):e004128. https://doi.org/10.1136/jitc-2021-004128

Ruan G, Zanwar S, Abeykoon JP, et al., 2020. Predictors of short-term survival in Waldenström macroglobulinemia. *Leuk Lymphoma*, 61(12):2975-2979. https://doi.org/10.1080/10428194.2020.1789625

Shadman M, Yeung C, Redman MW, et al., 2023. CD20 CAR-T therapy with MB-106 for BTK inhibitor-refractory Waldenström macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL) – single institution study. *HemaSphere*, 7(S3):e68877ca. https://doi.org/10.1097/01.HS9.0000971284.68877.ca

Thompson PA, Tam CS, 2023. Pirtobrutinib: a new hope for patients with BTK inhibitor-refractory lymphoproliferative disorders. *Blood*, 141(26):3137-3142. https://doi.org/10.1182/blood.2023020240

Treon SP, 2015. How I treat Waldenström macroglobulinemia. *Blood*, 126(6):721-732. https://doi.org/10.1182/blood-2015-01-553974

Treon SP, Tedeschi A, San-Miguel J, et al., 2023. Report of consensus Panel 4 from the 11th International Workshop on Waldenstrom's macroglobulinemia on diagnostic and response criteria. *Semin Hematol*, 60(2):97-106. https://doi.org/10.1053/j.seminhematol.2023.03.009