Documenta Haematologica -
Revista Romana de Hematologie | 2026, Vol. 4, Nr. 1

https://doi.org/10.59854/dhrrh.2026.4.1.11

– CASE REPORT –

Early Orbital Relapse in Mantle Cell Lymphoma: Rarity, Risk, and Transplant Strategy

Georgiana ENE[1*], Ana-Maria ILINESCU[1], Luminita OCROTEALA[2], Gabriela Diana CANTOR[1,2]

Abstract

Introduction: *Mantle cell lymphoma (MCL) is a rare, subtype of B-cell non-Hodgkin lymphoma (NHL), characterized by the chromosomal translocation t(11;14)(q13;q32) and cyclin D1 overexpression. MCL accounts for approximately 6–8% of all NHLs, typically affecting older adults with a male predominance. Although the clinical course can vary, the prognosis has been poor compared to other indolent lymphomas due to frequent relapses and resistance to therapy. Involvement of extranodal sites such as the gastrointestinal tract, bone marrow, and peripheral blood is well documented. Orbital involvement, however, is exceedingly uncommon, and early relapse (within months of first remission) poses significant therapeutic challenges.*

Methods: *Our aim is to present a 51-year-old male who was diagnosed with classic mantle cell lymphoma (MCL) following lymph node biopsy. The Ki-67 proliferation index was 43%. Baseline PET-CT staging revealed Ann Arbor stage IVB disease with bone marrow involvement and an intermediate-risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score. The patient received six cycles of alternating R-CHOP and R-DHAP, achieving complete metabolic remission per Lugano criteria. Less than 12 months later, he experienced nodal relapse and was treated with salvage therapy, again achieving complete metabolic response. During admission for planned autologous stem cell transplantation, he developed acute unilateral orbital symptoms. Orbital imaging demonstrated a soft tissue mass without optic nerve compression or intracranial extension, consistent with early extranodal relapse.*

Results: *Given the early relapse with extranodal orbital involvement, the multidisciplinary team proceeded directly to high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). Peripheral blood stem cells were successfully mobilized. The patient underwent ASCT after myeloablative conditioning with Tepadine. Neutrophil engraftment was achieved on day +10 and platelet recovery on day +15. The post-transplant course was notable primarily for hematologic toxicities, all of which resolved with standard supportive care. Consolidative orbital radiotherapy was subsequently performed. Response assessment at day +100 demonstrated a complete metabolic response on PET-CT, with no residual orbital or systemic disease. Maintenance therapy with a Bruton tyrosine kinase inhibitor was initiated thereafter.*

Conclusion: *This case emphasizes the need for heightened clinical vigilance for atypical relapse patterns in MCL. New focal symptoms, particularly involving extranodal sites, should prompt thorough evaluation even in the setting of recent systemic remission. Early identification of relapse allows timely initiation of salvage therapy and consideration of consolidative strategies such as ASCT, which may meaningfully impact long-term outcomes.*

Keywords: *Mantle Cell Lymphoma, Orbital Relapse, ASCT*

[1] Bone Marrow Transplantation Ward, University Emergency Hospital Bucharest, Bucharest, Romania

[2] Filantropia Municipal Hospital Craiova, Craiova, Romania

Corresponding author:
* **Georgiana ENE,** Bone Marrow Transplantation Ward, University Emergency Hospital Bucharest, Bucharest, Romania
Email: georgi_dap@yahoo.com

Introduction

Mantle cell lymphoma (MCL) is a rare, aggressive subtype of B-cell non-Hodgkin lymphoma (NHL), characterized by the chromosomal translocation t(11;14)(q13;q32) and cyclin D1 overexpression. MCL accounts for approximately 6–8% of all NHLs, typically affecting older adults with a male predominance. Although the clinical course can vary, the prognosis has been poor compared to other indolent lymphomas due to frequent relapses and resistance to therapy. Involvement of extranodal sites such as the gastrointestinal tract, bone marrow, and peripheral blood is well documented. Orbital involvement, however, is exceedingly uncommon, and early relapse (within months of first remission) poses significant therapeutic challenges. MCL arises from naïve pregerminal center B-cells in the mantle zone of lymphoid follicles. The hallmark translocation t(11;14) results in overexpression of cyclin D1, driving cell cycle progression and oncogenesis. Clinically, MCL often presents at advanced stages (III/IV), with frequent bone marrow involvement. Orbital and ocular adnexal lymphomas consist predominantly of marginal zone lymphomas. MCL comprises a very small fraction of orbital lymphomas—data suggest less than 5% of orbital lymphoma cases. It is characterized by aggressive clinical behavior, genetic instability, and a high propensity for relapse. Despite advances in immunochemotherapy and targeted agents, MCL remains largely incurable with conventional therapy, particularly in younger, transplant-eligible patients, for whom long-term disease control remains a central therapeutic challenge (7),(4) Standard frontline treatment for fit patients typically consists of rituximab-based immunochemotherapy regimens, including R-CHOP, cytarabine-containing protocols, or intensified approaches such as R-hyperCVAD. These regimens achieve high initial response rates; however, remissions are frequently transient, and relapse is common, often occurring within the first few years following induction therapy (7). This relapse pattern reflects the underlying biology of MCL, which is marked by clonal heterogeneity, early dissemination, and resistance to cytotoxic therapy.In this context, consolidation with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has emerged as a critical component of first-line therapy for transplant-eligible patients. Prospective randomized data from the European Mantle Cell Lymphoma Network demonstrated that ASCT consolidation in first remission significantly prolongs progression-free survival compared with interferon-based maintenance strategies, establishing ASCT as a standard of care in this population (7). Subsequent long-term follow-up studies have confirmed the durability of these responses, with a subset of patients achieving prolonged remissions extending beyond a decade, particularly when ASCT is combined with rituximab maintenance. (4). The role of ASCT becomes particularly salient in patients with high-risk disease features, including early relapse, aggressive histology, or extranodal involvement. Extranodal manifestations—especially at rare sites such as the orbit—are increasingly recognized as markers of biologically aggressive disease and poor prognosis (9), (15). In such settings, early relapse following conventional immunochemotherapy underscores the need for treatment intensification and supports consideration of ASCT as part of a multimodal therapeutic strategy. Although specific prospective data addressing ASCT in the context of orbital relapse are lacking due to the rarity of this presentation, extrapolation from broader MCL cohorts suggests that consolidation with ASCT after achieving disease control may mitigate the adverse prognostic impact of early extranodal relapse. This approach is further supported by case series and retrospective analyses demonstrating improved disease control when aggressive systemic therapy is combined with transplant consolidation in high-risk MCL (9),(4).

Case Presentation

A 51-year-old male presented with generalized lymphadenopathy and B symptoms in 2022. Excisional lymph node biopsy confirmed classic MCL. Immunophenotyping demonstrated CD20+, CD5+, cyclin D1+, CD10−, and BCL6− expression. Fluorescence in situ hybridization confirmed t(11;14)(q13;q32). The Ki-67 index was 43%. PET-CT staging revealed Ann Arbor stage IVB disease with bone marrow involvement. The Mantle Cell Lymphoma International Prognostic Index (MIPI) indicated intermediate risk (Hoster et al., 2008). The patient received six cycles of alternating R-CHOP and R-DHAP. End-of-treatment PET-CT demonstrated complete metabolic remission per Lugano criteria (Cheson et al., 2014). ASCT consolidation was planned. Within 12 months, nodal relapse occurred. Salvage therapy with HyperCVAD achieved a second complete metabolic remission. During admission for ASCT, the patient developed acute unilateral exophthalmos. Orbital CT (figure 1) demonstrated a unilateral soft tissue mass without intracranial extension. Biopsy confirmed relapsed

MCL without histologic transformation. Ki-67 at relapse was 47%.

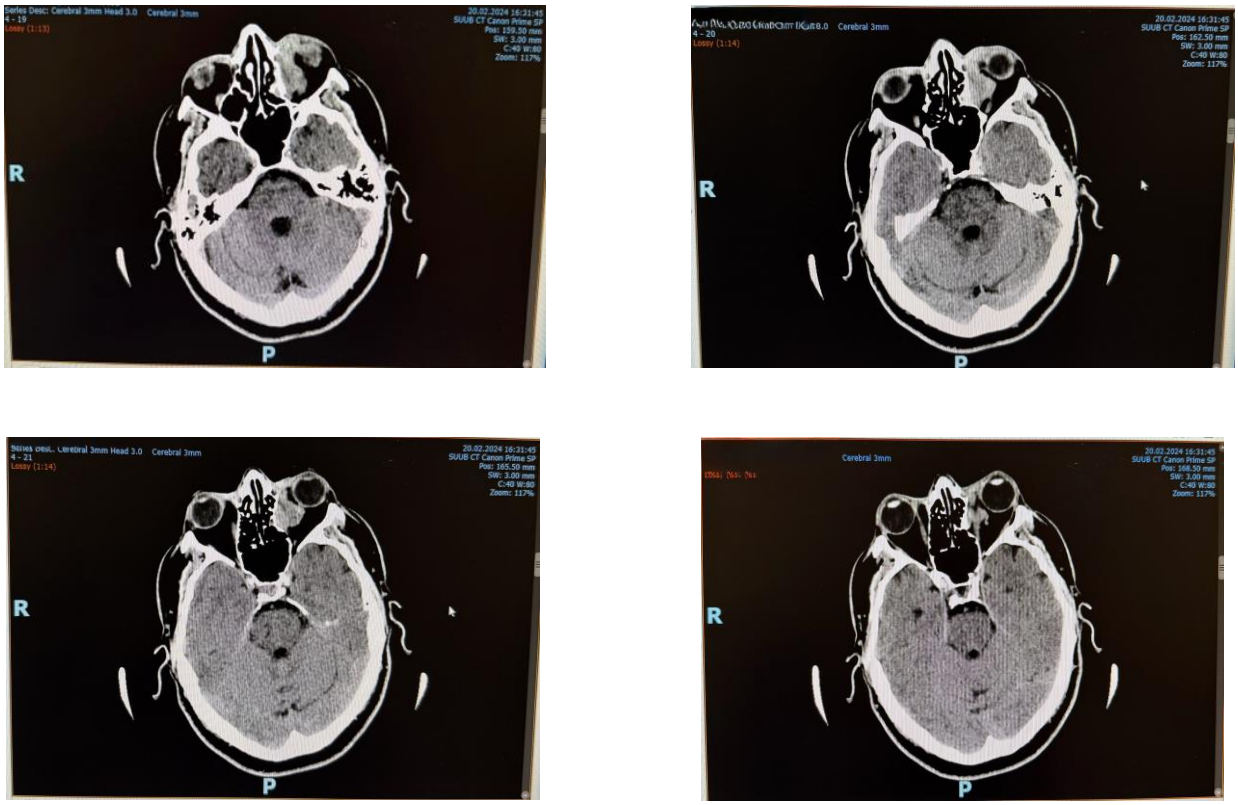

Figure 1. *Expansive iodophile process 28/24/29 mm located on the left orbit extended extrachonal in intimate contact with the inferior wall of the orbit*

Materials and Methods

Stem Cell Mobilization: Peripheral blood stem cells were mobilized and collected according to institutional standards. A total of 6.62 × 10^6 $CD34^+$ cells/kg was obtained.

Conditioning and Transplantation: High-dose conditioning was performed using the TEAM regimen (thiotepa, etoposide, cytarabine, melphalan), selected due to thiotepa's favorable tissue penetration properties (4). Autologous stem cells were reinfused following conditioning.Toxicities were graded according to CTCAE v5.0.

Post-Transplant Management: Consolidative orbital radiotherapy was administered after hematologic recovery. Maintenance therapy with ibrutinib, a Bruton tyrosine kinase inhibitor (11), was initiated following day +100 assessment.

Results

Neutrophil engraftment occurred on day +10 and platelet recovery on day +15. The transplant course was complicated by grade 3 hematologic toxicities, which resolved with supportive care. Day +100 PET-CT demonstrated complete metabolic remission. At 24 months post-ASCT, the patient remains in ongoing complete remission.

Unicenter experience with Lymphoma ASCT: At our center, autologous stem cell transplantation (ASCT) has been routinely employed as consolidation therapy for patients with relapsed or high-risk lymphoma, with conditioning regimens selected according to disease characteristics, prior therapy, and extranodal involvement. In a retrospective unicenter cohort of 38 lymphoma patients undergoing ASCT between 2020-2024, conditioning was primarily based on either thiotepa-containing regimens or lomustine-containing regimens (BEAM/LEAM). Overall, ASCT was feasible across both groups, with successful stem cell engraftment and acceptable transplant-related toxicity.

Patients conditioned with thiotepa-based regimens more frequently had high-risk disease features, including early relapse, extranodal involvement, or aggressive histology, whereas lomustine-based regimens were predominantly used in patients with chemosensitive disease and standard-risk profiles. (figure.2)

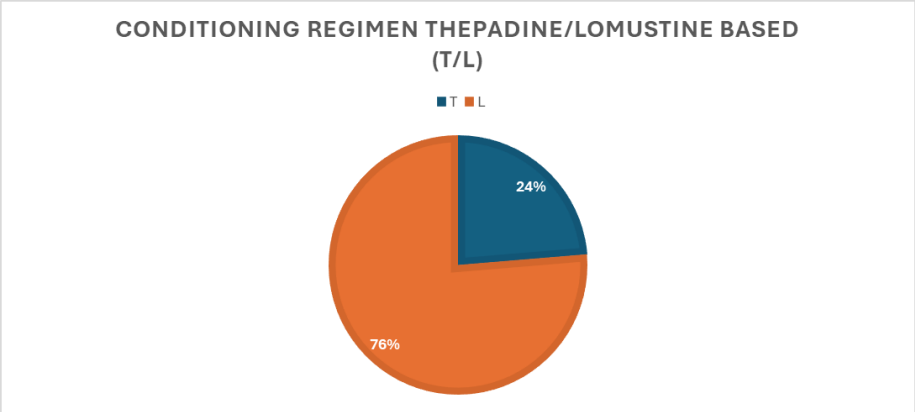

Figure 2. *Unicentre experience of Lymphoma conditioning regimens*

The patients that had late engraftment were in the lot that had undergone conidtioning treatment with lomustine and it was noticed a higher incidence of infectious complications with thepadine. (figure.3 figure.4)

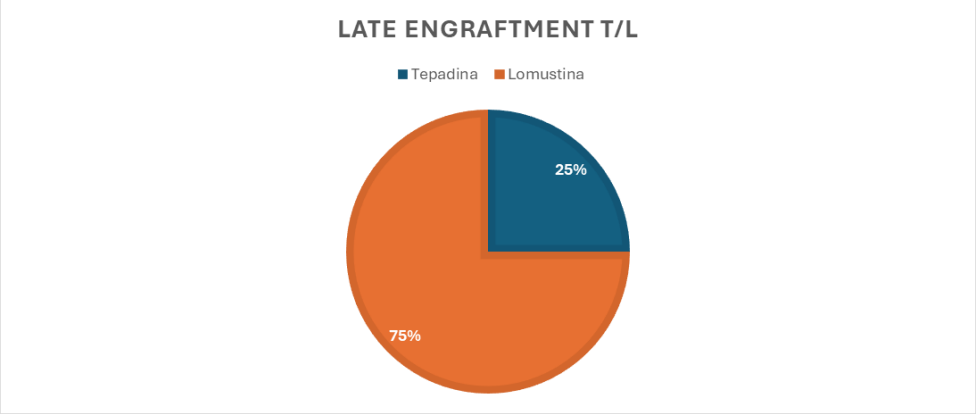

Figure 3. *Days to engraftment on regimens that contained thepadine versus lomustine*

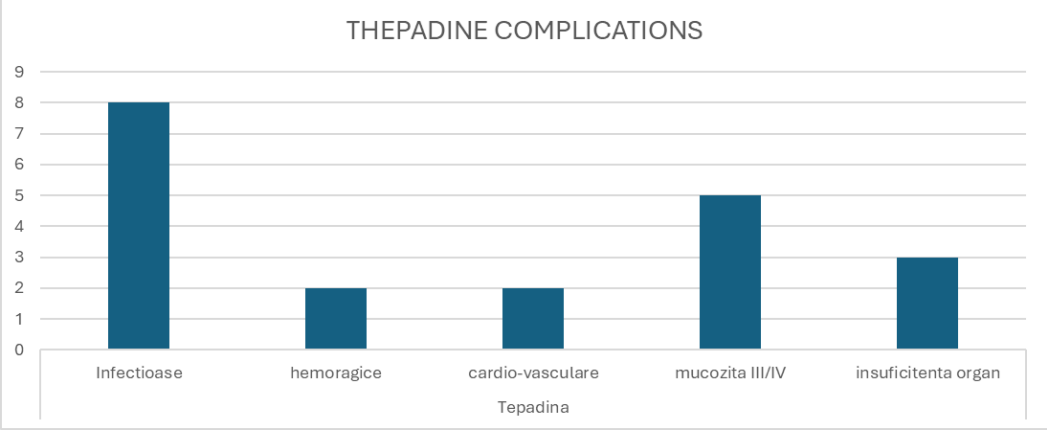

Figure 4. *Complications developed during ASCT based on regimen used*

Discussions

This case highlights the prognostic significance of early extranodal relapse in MCL. Early progression after frontline therapy has been associated with markedly inferior survival (5). Orbital involvement represents a rare but aggressive manifestation. ASCT remains a standard consolidative approach in transplant-eligible patients. The European MCL Network randomized trial demonstrated superior progression-free survival with ASCT consolidation (7). Long-term follow-up supports durable remissions (3). While BTK inhibitors have transformed relapsed MCL management (11), ASCT continues to play a role in patients achieving chemosensitive relapse who did not undergo upfront transplant (10). Thiotepa-containing regimens may offer advantages in extranodal disease due to improved tissue penetration. Retrospective analyses suggest favorable survival outcomes with acceptable toxicity (4). Multimodal therapy integrating systemic intensification and local radiotherapy appears rational in rare extranodal relapse scenarios.

Conclusion

Orbital relapse in mantle cell lymphoma is rare and signals aggressive disease biology. Early relapse warrants treatment intensification. Thiotepa-based ASCT combined with local radiotherapy and maintenance BTK inhibition may provide durable remission in selected high-risk patients.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.
Ethics Consideration:
The authors declare that all the procedures and experiments of this study respect the
ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by the participant in this study.
Conflict of interest:
No known conflict of interest correlated with this publication.
Availability of data and materials:
The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.
Competing interests:
The authors declared that they have no competing interests.
The use of generative AI and AI-assisted technologies:
AI technologies were used solely to refine English language and spelling

References

1. Campo, E., Rule, S., et al. (2011). Mantle cell lymphoma. The Lancet, 377(9769), 1211–1223. https://doi.org/10.1016/S0140-6736(10)61482-4
2. Cheson, B. D., et al. (2014). Lugano classification. Journal of Clinical Oncology, 32(27), 3059–3068. https://doi.org/10.1200/JCO.2013.54.8800
3. Dreyling, M., et al. (2017). ESMO Guidelines for MCL. Annals of Oncology, 28(suppl_4), iv62–iv71. https://doi.org/10.1093/annonc/mdx223
4. Dreyling, M., et al. (2023). EHA Clinical Practice Guidelines for MCL. HemaSphere, 7(6). https://doi.org/10.1097/HS9.0000000000000893
5. Eskelund, C. W., et al. (2016). Early progression predicts poor survival in MCL. Blood, 127(24), 2955–2963. https://doi.org/10.1182/blood-2016-01-689786
6. Ferreri, A. J. M., et al. (2012). Ocular adnexal lymphomas. Lancet Oncology, 13(11), e479–e488. https://doi.org/10.1016/S1470-2045(12)70367-8
7. Hermine, O., et al. (2005). Autologous transplantation in MCL. The New England Journal of Medicine, 352, 1587–1597. https://doi.org/10.1056/NEJMoa041020
8. Hoster, E., et al. (2008). MIPI prognostic index. Blood, 111(2), 558–565. https://doi.org/10.1182/blood-2007-06-095331
9. Knudsen, S., et al. (2017). Orbital lymphoma clinicopathologic analysis. British Journal of Haematology, 177(3), 405–415. https://doi.org/10.1111/bjh.14555
10. Le Gouill, S., et al. (2017). Rituximab maintenance post-ASCT. The Lancet, 390(10103), 2563–2573. https://doi.org/10.1016/S0140-6736(17)32284-1
11. Wang, M. L., et al. (2013). Ibrutinib in relapsed MCL. The New England Journal of Medicine, 369, 507–516. https://doi.org/10.1056/NEJMoa1306220
12. Hermine O, Hoster E, Walewski J, others. Treatment of mantle cell lymphoma with high-dose therapy and autologous stem cell transplantation after first remission: results of a European MCL Network randomized trial. Blood. 2005;105(7):2677–84.
13. Dreyling M, others. Long-term outcomes of autologous stem cell transplantation in mantle cell lymphoma. Bone Marrow Transplant. 2023;58(6):687–95.
14. Knudsen K, Rasmussen P, Coupland S, others. Mantle cell lymphoma involving the ocular adnexa: an

international multicenter cohort study. Haematologica. 2017;102(12):2097–104.

15. Shaikh H, Mewawalla P, others. Cutaneous and orbital relapse of mantle cell lymphoma: a rare extranodal presentation. Clin Case Rep. 2020;8(8):1427–31