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– CASE REPORT –

When the Eyes Speak: A Multisystem Challenge with CNS and Orbital Spread Light Chain Myeloma

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Abstract

Introduction. *Multiple myeloma (MM) is a type of cancer that affects plasma cells and makes up about 10% of blood cancer. It's characterized by uncontrolled growth of plasma cells in the bone marrow, which often leads to excess monoclonal immunoglobulins or free light chains. Lambda light chain multiple myeloma (MM) is a specific type of light chain MM, accounting for roughly 15–20% of all MM cases, and it tends to exhibit more aggressive clinical features and organ involvement.[1,2] Involvement in multiple myeloma is exceptionally rare, accounting for less than 1% of extramedullary presentations, and is typically associated with aggressive disease biology.[3]*

Several cytogenetic abnormalities—most consistently gain(1q21), del(17p), and t(4;14)- are well-established adverse prognostic markers associated with inferior progression-free and overall survival. The impact of some additional risk features may vary by treatment era and regimen intensity, emphasizing the need to interpret prognostic markers alongside contemporary induction, transplant, and maintenance strategies [4]. Extramedullary disease (EMD) is heterogeneous (e.g., soft-tissue plasmacytomas vs bone-associated lesions) and lacks standardized treatment protocols. While EMD may respond less reliably to conventional approaches, the evidence base remains limited, and responses can vary with newer agents, including anti-CD38 antibodies and evolving cellular therapies.[5]

This report details a particularly complex case of lambda light-chain MM presenting with rare orbital involvement and intracranial extension, features that underscore the clinical rarity and high-risk nature of extramedullary spread and highlight the need for multimodal therapy, including early radiotherapy. The case highlights the diagnostic challenges posed by unusual presentations and highlights the growing importance of new treatment options in high-risk MM.

Keywords: *Multiple myeloma, lambda light chain, orbital mass, 1q21 gain, extramedullary involvement, stem cell transplant, bortezomib, daratumumab, Revlimid*

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Case presentation

In November 2024, a 57-year-old Hispanic man with a background of hypertension and high cholesterol presented with progressive left orbital pain, proptosis, and visual disturbance. Neurologic examination revealed intact cranial nerves II–XII, with mild limitation of left

extraocular movements and reduced visual acuity in the affected eye. No focal motor or sensory deficits were noted at presentation. A CT scan of the orbit showed a mildly enhancing mass in the left superolateral extraconal space with associated bony erosion, suggesting an aggressive infiltrative process, raising concern for plasmacytoma, lymphoma, or metastatic disease. The extraconal location was clinically relevant, as it increased the risk of mass effect on adjacent neurovascular structures. At this stage, the differential diagnosis for an extraconal orbital mass with bony erosion included plasmacytoma, lymphoma, metastatic disease, granulomatous inflammation, and infectious processes. Early recognition of potential neurologic or optic nerve compromise was critical, given the risk of irreversible visual loss associated with aggressive orbital disease**.** An MRI of the thoracic and lumbar spine was obtained for systemic staging and evaluation of back pain, revealing an L1 lesion with a mild pathologic fracture and additional involvement at T7, findings consistent with disseminated disease rather than isolated orbital involvement, with potential risk for early spinal instability or neurologic compromise. Given the destructive extraconal orbital lesion with bony erosion, the differential diagnosis included plasmacytoma, lymphoma, metastatic disease, granulomatous/inflammatory disease, and infection, warranting urgent tissue diagnosis and systemic evaluation. The cerebrospinal fluid did not demonstrate leptomeningeal involvement or any malignant cells. Thus, the results correlated with orbit extramedullary disease of the skull base and intracranial extension, rather than with primary central nervous system multiple myeloma.

He was then referred to hematology/oncology for further evaluation and had a biopsy done.

On January 3, 2025, Fine-needle aspiration (FNA) of the orbital mass revealed plasma cells; however, the limitations of FNA in extramedullary disease were recognized, necessitating correlation with imaging and bone marrow findings to minimize sampling error. Bone marrow biopsy demonstrated 37% clonal plasma cells, exceeding diagnostic thresholds for MM and aligning with the patient's aggressive extramedullary presentation**.** FISH revealed a gain of 1q21, a high-risk cytogenetic abnormality associated with inferior survival and early relapse**.** Serum tests showed alarmingly high levels of lambda-free light chains (23,545 mg/L), along with suppressed immunoglobulins (IgG 571, IgA 13, IgM 10), and no detectable M-spike was identified, a feature characteristic of light-chain-only MM that may delay diagnosis or lead to underestimation of disease burden if free light-chain assays are not utilized. Urine lambda light-chain excretion measured 2,359 mg/24 hours, reflecting high tumour burden and increased risk for cast nephropathy. **Figure 1** shows a clear downward trend in serum lambda light chain levels from the time of diagnosis through treatment. These levels dropped significantly from 23,545 mg/L to 3,883 mg/L, indicating a strong biochemical response to therapy despite a high-risk cytogenetic profile.

Figure 1. *Treatment Timeline and Clinical Milestones. This timeline illustrates the sequence of key therapeutic interventions, including orbital and spinal radiotherapy, initiation and modification of systemic therapy (Dara-VRd followed by Revlimid maintenance) aligned with observed changes in disease burden, biochemical markers (lambda free light-chain decline), and clinically relevant adverse events (temporary lenalidomide interruption due to rash), and the timing of significant clinical, laboratory, and imaging assessments.*

Histopathologic assessment of the orbital mass revealed (**Figure 2**) a dense population of atypical plasma cells with a plasmablast appearance on H&E stain. Immunohistochemical testing showed strong, diffuse immunostaining for CD138 and MUM1, confirming the plasma cell lineage. Staining for light chains showed marked lambda restriction and complete absence of kappa light chains, consistent with light-chain-only myeloma. Ki-67 staining revealed a high proliferative index consistent with an aggressive course of extramedullary disease.

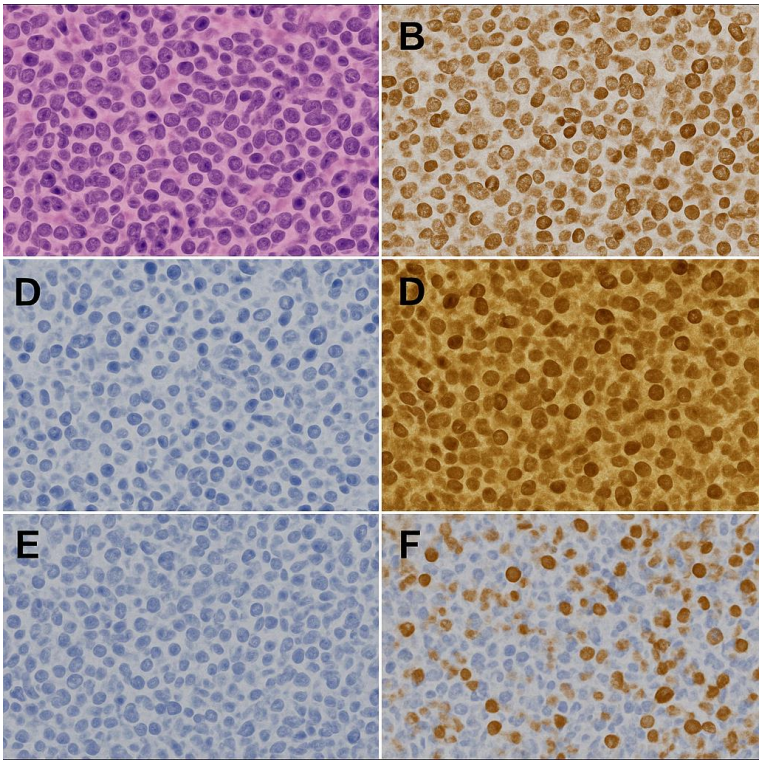

Figure 2. *Histopathologic and Immunohistochemical Correlates of Disease Activity. Representative histopathologic and immunohistochemical findings from diagnostic tissue samples demonstrate a lambda light-chain–restricted plasma cell neoplasm. These features correlate with the patient's aggressive clinical presentation and guided subsequent therapeutic decision-making.*

Table 1. *Summary of Initial Diagnostic Laboratory Findings*

Test	Result	Reference Range
Free Lambda Light Chain	23,545 mg/L	5.7–26.3 mg/L
Free Kappa Light Chain	6.4 mg/L	3.3–19.4 mg/L
Kappa/Lambda Ratio	0.00	0.26–1.65
IgG	571 mg/dL	700–1600 mg/dL
IgA	13 mg/dL	70–400 mg/dL
IgM	10 mg/dL	40–230 mg/dL
Urine Lambda (24 hr)	2,359 mg	<30 mg

Table 1 *Summarizes key diagnostic laboratory findings that helped confirm the diagnosis of light-chain-only multiple myeloma, even in the absence of a monoclonal spike on serum electrophoresis.*

Orbital radiotherapy was prioritized due to symptom burden and visual risk, followed by spinal RT to mitigate neurologic compromise; doses aligned with disease-directed palliative regimens. He began orbital

radiotherapy (RT) on February 5, 2025, receiving 2400 cGy in 12 fractions, followed by spine RT on February 27, 2025, with a total of 2500 cGy in 5 fractions. On March 6, 2025, he started daratumumab, bortezomib, lenalidomide, and dexamethasone (Dara-VRd), initially without lenalidomide due to financial issues. After getting dental clearance, he began taking Revlimid 25 mg on April 24, 2025, but had to pause treatment because of a rash. A 2nd degree of maculopapular rash formed shortly after starting lenalidomide oral 25mg/day without any systemic involvement or mucosal features. Given lenalidomide's well-known immunomodulatory effects and hypersensitivity profile, lenalidomide was held until supportive therapy with oral antihistamines and topical corticosteroids was established to manage the rash, which resulted in complete resolution of the symptoms. After successful management of the rash, lenalidomide was reintroduced at a reduced dosage of 20mg/day (down from 25mg/day) without recurrence of the rash, allowing continuation of therapy without compromising treatment intensity.

Serial lab tests (**Figure 3**) showed a steady decline in lambda levels: from 23,545 mg/L at the start to 7,847 mg/L by March 20, 2025, and down to 3,883 mg/L by June 12, 2025. A CT scan of the orbit on May 16, 2025 (**Figure 4**) revealed that the soft tissue mass in the left orbit remained stable in size (2.3 × 2.2 × 1.6 cm), although there were some associated bone erosion and proptosis. These results suggest a partial radiologic response following radiotherapy, despite the ongoing mass effect on nearby structures. Neuropathy symptoms from Velcade improved after reducing the dose to 2 mg, and Revlimid was resumed at 20 mg. He is scheduled for an autologous stem cell transplantation.

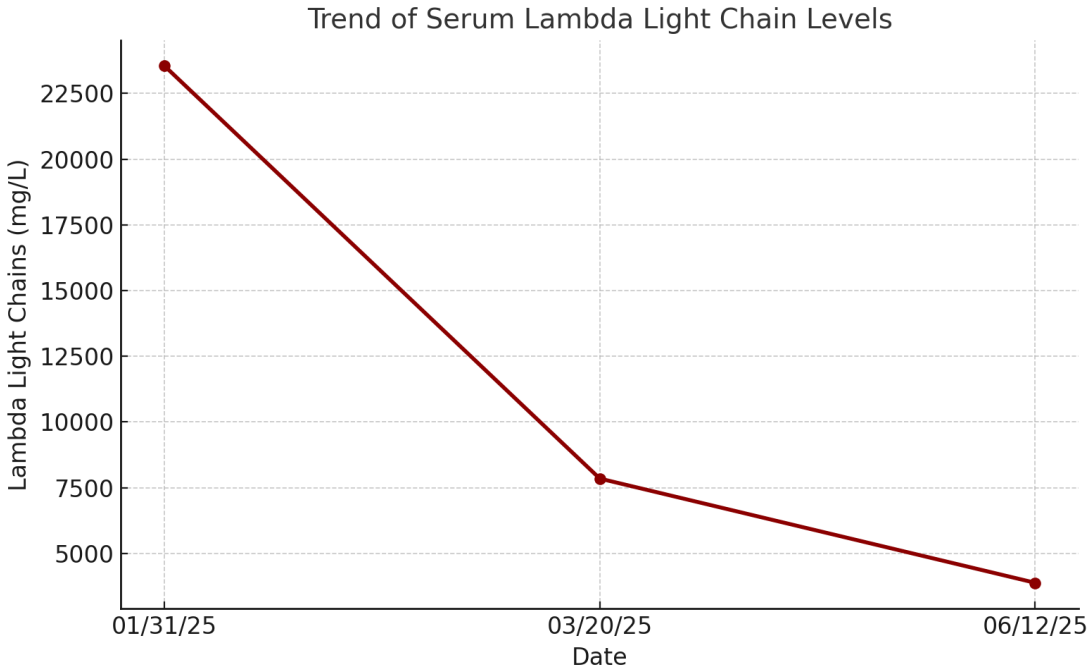

Figure 3. *Longitudinal Free Light Chain (Kappa/Lambda) Ratio in Relation to Treatment. Serial measurements of the serum free light chain ratio over time demonstrate persistent suppression of the kappa/lambda ratio, reflecting ongoing lambda-dominant monoclonal activity. Changes in laboratory values are temporally aligned with treatment initiation and adjustments, illustrating biochemical response patterns throughout the disease course. This figure was created using artificial intelligence tools to give a visual idea of disease biology.*

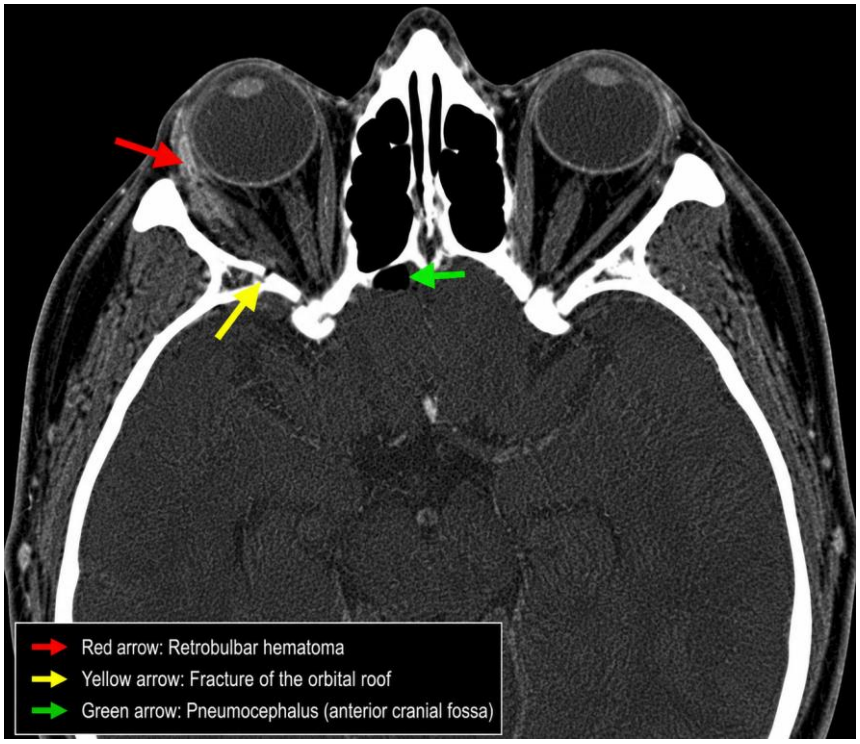

Figure 4. *Radiographic Evolution of Orbital Disease. Axial CT imaging of the orbits obtained on 5/16/2025 demonstrates a soft-tissue mass in the left superolateral orbit (arrow) causing proptosis, with associated bone erosion and extension into the anterior cranial fossa, highlighting aggressive extramedullary involvement.*

Therapeutic Course

The patient embarked on a comprehensive treatment plan, initiated with radiotherapy (RT) targeting the orbit from February 5 to 19, 2025. This was followed by another RT round focused on the L1 vertebra from February 27 to March 5, 2025. On March 6, 2025, systemic therapy with Dara-VRd began, and Revlimid was introduced on April 24. However, it had to be temporarily paused due to a rash caused by the medication. Dose adjustments were required for both Velcade (due to peripheral neuropathy) and Revlimid (due to a skin reaction). To prevent infections, the patient received prophylactic antimicrobial coverage with acyclovir and trimethoprim–sulfamethoxazole, given the immunosuppressive effects of daratumumab-based therapy and corticosteroid exposure, which increase the risk of viral reactivation and opportunistic infections.

Additionally, they started receiving planned zoledronic acid infusions every four weeks to support bone health, given the L1 pathologic fracture and overall osteolytic disease risk. Throughout the treatment, regular laboratory tests were performed, including complete blood counts and 24-hour urine light-chain quantification. Table 2 demonstrates the trend in lambda light chain levels over the course of treatment, which correlates well with imaging and clinical improvement.

Table 2. *Trend of Serum Free Lambda Light Chain Levels*

Date	Lambda Light Chain (mg/L)
1/31/2025	23,545
3/20/2025	7,847
5/15/2025	7.55
6/12/2025	3,883

Response Monitoring

The patient showed a positive biochemical response to the treatment. Lambda light chain levels dropped significantly from 23,545 mg/L to 7,847 mg/L, and then further down to 3,883 mg/L throughout the treatment period. The kappa/lambda ratio remained deeply suppressed, consistently below 0.01, indicating a strong biochemical response that met International Myeloma Working Group (IMWG) criteria for partial response, despite the presence of high-risk cytogenetics. A repeated CT scan of the orbit performed in May 2025 showed a stable residual mass measuring 2.3 × 2.2 × 1.6 cm, with a noticeable improvement in surrounding soft-tissue edema. These stable radiographic findings are a well-recognized phenomenon in extramedullary myeloma, in which biochemical responses may precede or exceed radiographic regression. Hematologic parameters, such as white blood cell count, absolute neutrophil count, and platelet count, remained within safe and stable ranges.

Adverse events:

The patient experienced a few treatment-related side effects, which were managed well. Peripheral neuropathy attributable to bortezomib improved following dose reduction and weekly subcutaneous administration, allowing treatment continuation. Lenalidomide-associated rash resolved after temporary interruption and was successfully reintroduced at a reduced dose, preserving treatment continuity. Eyelid irritation, likely related to local radiation effects or surface inflammation rather than active disease, resolved with topical tobramycin and oral cetirizine.

Follow-Up and Prognosis:

Given high-risk cytogenetics and extramedullary involvement, early autologous stem cell transplantation was pursued, consistent with current high-risk MM guidelines. The ongoing biochemical response and better imaging results are promising. However, the presence of high-risk cytogenetics and extramedullary involvement places the patient at elevated risk for early relapse, necessitating close longitudinal monitoring and consideration of intensified maintenance strategies. Although the ongoing biochemical response and partial radiologic stability are encouraging, the overall long-term prognosis remains guarded given the presence of high-risk cytogenetics and extramedullary disease.

In **Table 3**, we have compiled previously reported cases of CNS and/or orbital involvement in patients with multiple myeloma to better contextualize our findings. As shown in Table 3, orbital or CNS involvement in multiple myeloma is rare, and it also frequently occurs in patients who have light chain disease and high-risk cytogenetics. In the reported cases of CNS or orbital involvement in multiple myeloma, most of the patients received multimodal therapy consisting of radiotherapy and/or proteasome inhibitor-based regimens. The heterogeneity of reported outcomes in these cases indicates that complete responses are least frequent, with most patients demonstrating only partial responses. Our findings are consistent with previously reported cases of multiple myeloma patients who had 1q21 gain and aggressive extramedullary behaviour.

Table 3. *Previously Reported Cases of Orbital/CNS Involvement in Multiple Myeloma*

Author (Year)	Age/Sex	Myeloma Type	Site of EMD	CNS Involvement	Cytogenetics	Treatment	Outcome
Chang et al. (2016)	62/M	Lambda LC MM	Orbit	Yes	Not reported	RT + Bortezomib	Partial response
Kumar et al. (2018)	55/M	IgG MM	Orbit	No	del17p	RT + VRd	Stable disease
Lee et al. (2020)	59/F	Lambda LC MM	Orbit	Yes	1q21 gain	RT + Dara-VRd	PR
Singh et al. (2021)	48/M	Light chain MM	Skull base	Yes	t(4;14)	RT + KRD	PD
Zhao et al. (2022)	64/M	IgA MM	Orbit	No	Not reported	RT + VTD	CR
Present case	57/M	Lambda LC MM	Orbit + CNS	Yes	1q21 gain	RT + Dara-VRd	PR

Discussion

This case highlights the complex challenges in diagnosing and managing high-risk lambda light-chain multiple myeloma (MM) with extramedullary and central nervous system (CNS) involvement. Gain of 1q21 involving the CKS1B locus is a well-established high-risk abnormality associated with poor survival, early relapse, and reduced responsiveness to proteasome inhibitors and immunomodulatory agents. When present alongside extramedullary disease, this cytogenetic profile suggests a biologically aggressive disease course from the outset and necessitates an intensified, closely monitored treatment strategy.[6,7]

Orbital involvement with intracranial extension in MM is exceedingly rare and typically reflects aggressive extramedullary spread. When present, it often mandates early multimodal therapy, including localized radiotherapy for symptom control and prevention of irreversible neurologic or visual compromise.[8] Orbital involvement with intracranial extension reflects aggressive extramedullary spread and is associated with a poor prognosis, not only because of adverse cytogenetics but also because of biologic barriers such as the blood–brain barrier, limited drug penetration into sanctuary sites, and clonal evolution within extramedullary compartments [9]. Therefore, for our patient, early radiotherapy targeting the orbital and spinal lesions, along with systemic therapy, was crucial in stabilizing symptoms and preventing irreversible neurological damage. The initial diagnoses considered were orbital lymphoma, metastatic carcinoma, inflammatory pseudotumor, and infectious processes. Ultimately, the diagnosis of MM was confirmed based on a combination of histopathological analyses (demonstrating CD138-positive plasma cells and lambda light chain restriction), more than 10% of the bone marrow demonstrating involvement, a sharply elevated serum free light chain level, and supportive cytogenetic findings.

The patient's light-chain-only disease added another layer of complexity to diagnosis and monitoring. Standard serum protein electrophoresis (SPEP) and immunofixation didn't show a monoclonal spike, so we had to rely on free light chain assays and 24-hour urine electrophoresis to quantify the disease. The drop in lambda light chain levels during treatment suggested a positive biological response, even in the absence of the typical serologic markers. **Figure 5** shows the unique immunopathologic profile of light-chain–only multiple myeloma, especially in high-grade extramedullary manifestations. The schematic emphasizes the critical diagnostic findings: sheets of atypical plasma cells with plasmablastic features, lack of immunoglobulin heavy-chain expression, and lambda light-chain restriction. The schematic also emphasizes two features known to be highly associated with high-risk biology—high Ki-67 proliferative index and 1q21 amplification—which provide a rationale for the aggressive clinical behaviour observed in patients with extramedullary orbital or CNS disease. This conceptual overview highlights these crucial findings: rapid progression, inherent treatment resistance, and the need for early, aggressive therapy.

The use of daratumumab (an anti-CD38 monoclonal antibody) and bortezomib (a proteasome inhibitor) is a treatment option for patients with multiple myeloma who are considered high-risk and will receive systemic therapy with these agents to induce response and improve patient survival. Dara and Bor have demonstrated activity against patients with extramedullary disease (EMD) and the ability to penetrate soft-tissue compartments in EMD-transformed/myeloma cells. By combining these agents, we hope to enhance the depth of response as a result of the inherently increased activity of Dara via the antibody-dependent cellular cytotoxicity mechanism and direct targeting of plasma cells, especially in highly aggressive, light-chain predominant diseases.[10] Our patient's response to the Dara-VRd regimen was promising, although we had to adjust doses due to neuropathy and rash.

Treatment-related toxicities required careful management and directly influenced dose intensity and treatment continuity. Peripheral neuropathy related to bortezomib necessitated dose reduction and transition to weekly subcutaneous administration, a strategy known to preserve efficacy while reducing neurotoxicity. Similarly, lenalidomide-associated rash required temporary interruption and dose reduction, after which therapy was successfully resumed. Importantly, these toxicity-driven modifications did not abrogate the patient's biochemical response, underscoring the need for individualized dose optimization to maintain therapeutic momentum in high-risk disease.

In this case, the lack of a measurable M-spike on serum protein electrophoresis (SPEP)/immunofixation made it more challenging to diagnose and monitor the patient with light-chain mm (M-component) than in patients with an M-spike. The lack of an identifiable M-spike makes it challenging to determine the extent of disease producing the light chains, evaluate the response to treatment, and may delay diagnosis. Therefore, in this patient, reliance

on serum-free light-chain (SFLC) assay and/or 24-hour urine collection was necessary; this is an essential diagnostic pitfall for the treating physician in suspected light-chain myeloma, especially in cases with atypical extramedullary presentations. Although the patient had a significant biochemical response to therapy, the radiologic studies demonstrated relative stability of the orbital lesion rather than complete regression. This discrepancy has been previously reported in patients with extramedullary myeloma; it is common for patients with extramedullary masses to continue to have soft-tissue masses despite effective systemic therapy, or for these masses to regress slowly. Recognition of this discrepancy is essential to prevent premature conclusions about treatment failure and to guide the long-term imaging approach for this patient.

In patients with light-chain-only MM and high-risk cytogenetics, autologous stem cell transplantation (ASCT) remains a key component of treatment. Patients who have extramedullary disease (EMD) tend to perform much worse than patients who do not have EMD. A number of studies confirm that patients who undergo autologous stem cell transplantation (ASCT) in this high-risk group typically have shorter progression-free survival (PFS) and overall survival (OS) due to continued resistance to therapeutic interventions and aggressive biological characteristics of their disease.[11] Unfortunately, when a patient has cytogenetic abnormalities and extramedullary disease, the duration of remission achieved with a single ASCT is often suboptimal. Earlier stem cell collection, possible tandem transplantation, and intensified post-transplant maintenance may be appropriate in this high-risk subgroup. As a result, earlier stem cell collection, the possible use of tandem stem cell collection, and increased intensity of post-transplantation treatment regimens may be appropriate for this patient group. However, no definitive "best" way to manage these patients has been established. Frequent long-term follow-up of these patients is necessary because they have a greater chance of experiencing a relapse before treatment has been completed and require ongoing care after they appear to be in remission.[12]

Therapeutic options might increasingly play a role for patients with high-risk extramedullary myeloma that relapses. Innovative therapies include BCMA-directed CAR T-cell therapy, bispecific T-cell engagers, and antibody-drug conjugates, all of which have shown encouraging efficacy in relapsed and refractory disease. Ongoing clinical trials are assessing the safety and efficacy of these therapies in patients with extramedullary disease. Initial referrals to consider cellular therapy may be appropriate in select patients.[13]

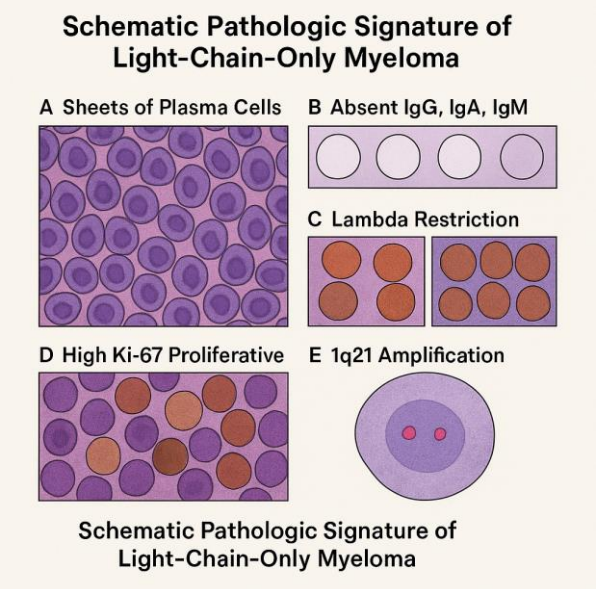

Figure 5. *Schematic Overview of High-Risk Light-Chain Myeloma Features and Clinical Implications. These schematic highlights key biologic features of aggressive light-chain multiple myeloma, including plasmablast morphology, absence of heavy-chain expression, substantial lambda light-chain restriction, high Ki-67 proliferative index, and 1q21 gain. These pathologic characteristics are linked to the patient's extramedullary involvement and high-risk clinical behaviour. This figure was created using artificial intelligence tools to give a visual idea of disease biology.*

Several limitations exist in this report; for example, because it includes only one patient, it cannot be generalized. In addition, it only has a short follow-up duration, so we cannot yet determine what the long-term outcome will be after receiving an autologous transplant, with or without maintenance treatment. There is also a great need for much larger, future-focused studies to develop suitable ways to treat this rare presentation.

Conclusion

This case highlights the diagnostic and therapeutic complexity of high-risk light-chain-only multiple myeloma with extramedullary orbital and CNS involvement. Negative SPEP/IFE results necessitated reliance on free light-chain assays, emphasizing a crucial diagnostic pitfall. The presence of 1q21 gain and EMD required early multimodal therapy, including radiotherapy, intensive systemic treatment, and planned autologous transplantation. Continued vigilance, long-term monitoring, and consideration of intensified maintenance therapy are essential in such high-risk presentations. While a positive initial reaction was observed overall, the presence of an extra-medullary component and a 1q21 gain indicates a guarded long-term prognosis and requires continued observation, intensified maintenance therapies, and new therapies to help treat patients more effectively.

Declarations

Funding: No specific funding was received for this study.

Conflicts of Interest / Competing Interests

The authors declare that they have no competing interests.

Ethics Approval: Not applicable.

Consent to Participate: Not applicable.

5. Written Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of Data and Material (Data Transparency)

All data generated or analysed during this study are included in this published article. No additional datasets were generated or analysed beyond those presented in the manuscript.

Code Availability: Not applicable.

8. Authors' Contributions

- Nasim Salimiaghdam, MD: Conceptualized the case report, led data collection and clinical interpretation, drafted the manuscript, and coordinated revisions.
- Usha Niranjan, MD: Contributed to diagnostic evaluation and interpretation, provided Hemato-Oncology expertise, and critically reviewed the manuscript.

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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