CLINICAL VIGNETTE

Individualized Treatment of IgM-Associated AL Amyloidosis

Maxwell J. Kroloff, MD and Tasha L. Lin, MD

Introduction

Amyloid light-chain (AL) amyloidosis is a rare clinical entity characterized by the deposition of misfolded immunoglobulin light chains throughout various organs, particularly the kidneys, peripheral nerves and heart.[1] Symptoms are directly related to organ involvement. For instance, amyloid deposition into the kidney may often cause nephrotic-range proteinuria. Deposition in the heart may result in restrictive cardiomyopathy. The pathophysiology is distinct from transthyretin (TTR) and serum amyloid A (AA) amyloidosis, as the amyloid protein is being generated by an underlying plasma cell disorder, and thus, requires plasma cell-directed therapy. In comparison to AA amyloid or TTR amyloid, treatment involves systemic therapy aimed at reduction of the monoclonal protein and free light chains. Both hematologic and organ response to treatment are generally correlated with a better prognosis including improved survival and preserved organ function.[2]

AL amyloid with immunoglobulin M (IgM) as opposed to immunoglobulin G (IgG) or immunoglobulin A (IgA) is even more rare, representing 5-7% of AL amyloidosis cases.[3] Given its rarity, treatment strategies have been extrapolated from both non-IgM amyloidosis and IgM gammopathies, such as lymphoplasmacytic lymphoma, which further complicates the approach. Current strategies are aimed at treatments directed towards the B-cell lymphoproliferative process and/or the plasma-cell clone. These include: fixed-duration chemoimmunotherapy (bendamustine/rituximab), incorporation of proteasome inhibitors (e.g. bortezomib), Bruton's tyrosine kinase (BTK) inhibitors, and combination quadruple therapy (rituximab, cyclophosphamide, bortezomib, dexamethasone) followed by autologous stem cell transplant. We present such a case in an otherwise healthy patient who presented with nephrotic-range proteinuria and was found to have an IgM-associated AL amyloidosis requiring initiation of systemic therapy with rituximab and zanubrutinib.

Case

A 60-year-old female developed bilateral lower extremity edema, which lasted a month with spontaneous resolution. The bilateral lower extremity edema recurred five months later, and urinalysis revealed 3+ proteinuria. 24-hour urine collection confirmed nephrotic-range proteinuria with 3.3g of protein. She was started on low-dose hydrochlorothiazide with improvement in her symptoms without additional clinical complaints including fatigue, pain or neuropathy.

Her initial evaluation found a low-level serum monoclonal protein of 0.2 g/dL with mild serum kappa elevation of 149.28 mg/L. This compared to lambda 32.24 mg/L with a serum free light chain ratio of 4.63, prompting hematologic evaluation. At that time, IgM was 529 mg/dL with a confirmed IgM kappa monoclonal protein on serum immunofixation. Bone marrow biopsy demonstrated a small B-cell lymphoma with plasmacytic differentiation. This involved 15-20% of the cellularity with loose lymphoplasmacytic aggregates in the background. Congo red staining was positive for focal amyloid deposition. Fluorescence in situ hybridization (FISH) studies demonstrated monosomy 13 and molecular testing confirmed MYD88 mutation without presence of a CXCR4 mutation. Kidney biopsy two weeks later also confirmed amyloidosis with mass spectrometry demonstrating AL-type amyloid. Baseline PET/CT was without lytic lesions, hepatosplenomegaly or lymphadenopathy but did show trace bilateral pleural effusions and mild volume overload. Baseline transthoracic echocardiogram demonstrated mild concentric left ventricular hypertrophy but was otherwise unremarkable with normal left ventricular size and an ejection fraction of approximately 60 to 65%. Cardiac magnetic resonance imaging did not show clear radiographic evidence of amyloid deposition.

The patient was initially proposed for consideration of autologous stem cell transplant, but after further treatment discussion, proceeded with concurrent zanubrutinib/rituximab followed by rituximab maintenance. Zanubrutinib was started one month prior to prevent an "IgM flare" followed by initiation of weekly rituximab for a total of eight infusions. Treatment was initially complicated by an urticarial hand rash with diffuse pruritis. This was well controlled with PRN topical fluocinonide 0.05% and diphenhydramine 25mg every 6 hours as needed. She then developed a scattered petechial rash externally. Aspirin thromboprophylaxis was decreased from twice daily to once daily with improvement. She never developed any spontaneous bleeding.

Following completion of rituximab, repeat 24-hour urine studies still demonstrated 3.1g proteinuria. Serum monoclonal protein decreased to 0.1 g/dL with an IgM level of 266 mg/dL. Serum kappa light chains decreased to 74.09 mg/L with lambda 21.06 mg/L consistent with at least a partial response to therapy.

Discussion

AL amyloidosis associated with an IgM paraprotein is a distinct entity, which behaves differently from its more common IgG or IgA-mediated counterparts. The underlying clonal process is much more likely to be associated with lymphoplasmacytic lymphoma rather than a pure plasma cell clone with different clinical manifestations. For example. cardiac involvement is much less common with 33 to 56% involvement compared to 70% cardiac involvement in non-IgM associated disease.[4] As such, it requires unique treatment strategies targeting the underlying clonal process, which is responsible for the production of the light chains.

Currently, no standard of care exists for the treatment of IgM-associated amyloidosis. A recent large retrospective review of over 250 patients at three European amyloidosis centers reported twenty-two different, first line treatment regimens were employed.[2] Varying treatment modalities have begun to incorporate rituximab as the backbone, which targets the B-cell driven lymphomatous component. As an example, rituximab can be combined with the alkylating agent bendamustine (BR). A retrospective review of 27 patients from the UK National Amyloidosis Centre database resulted in a 59% overall hematologic response rate.[3] The median overall survival was not yet reached, with median follow-up of only 18 months, which limited the analysis. Regardless, BR remains a viable treatment option given relatively good tolerability and the ability to administer it in patients with renal, cardiac or nerve involvement.

A more aggressive, alternate approach uses high-dose chemotherapy followed by autologous stem cell transplant. This can achieve even higher response rates, though with increased risk of adverse events. A retrospective review of 38 patients at Mayo Clinic reported overall response as high as 92% with 76% achieving very good or better partial response.[1] Progression free survival and overall survival were 48 months and 106 months. Two patients died within 100 days of transplant, a 5% short-term mortality rate.[1] The impressive progression-free survival and overall survival are also limited by selection bias, as only 20-25% of patients with AL amyloidosis are candidates for autologous stem cell transplant at diagnosis.[5] Treatments are generally limited by amyloid-related organ dysfunction.

A separate approach utilizing Bruton's tyrosine kinase (BTK)-inhibitors, as in our patient, has yielded mixed results. A retrospective series of eight patients with relapsed/refractory Waldenstrom's Macroglobulinemia (WM) or marginal zone lymphoma and AL amyloidosis were treated with single-agent ibrutinib. This yielded only a partial response in 2 patients (25%) with a median overall survival of 9 months.[6] However, this was a heavily pretreated patient population. Also, only five patients demonstrated an IgM paraprotein and only four were confirmed $CXCR4^{wt}$, an indicator of susceptibility to BTK inhibition.[7] A recent series of 4 patients with IgM-associated AL amyloidosis and WM had improved outcomes of first-line treatment with BTK inhibitors (2 ibrutinib, 2 acalabrutinib). All four patients achieved at least a very good partial response, suggesting a much more promising first-line treatment.[8] Of note, all four patients' disease was MYD88 mutated. CXCR4 status was not available.

Conclusion

IgM-associated amyloidosis is an extremely rare disease that is further complicated by its heterogeneous underlying clonal process and clinical course. Diagnostic awareness and clinical suspicion are needed to fully diagnose these patients and determine optimal treatment. Current treatment strategies are extrapolated from related disease subtypes and vary greatly. Further investigation is required to identify a more tailored treatment approach, as in our patient. Given her limited disease burden and favorable prognostic factors, a combination of rituximab and the BTK-inhibitor, zanubrutinib, was administered to optimize depth of response to prevent future end-organ damage, prolong overall survival, and avoid side effects associated with more intensive regimens.

REFERENCES

1. **Sidiqi MH, Buadi FK, Dispenzieri A, Warsame R, Lacy MQ, Dingli D, Leung N, Gonsalves WI, Kapoor P, Kourelis TV, Hogan WJ, Kumar SK, Gertz MA**. Autologous Stem Cell Transplant for IgM-Associated Amyloid Light-Chain Amyloidosis. *Biol Blood Marrow Transplant*. 2019 Mar;25(3):e108-e111. doi: 10.1016/j.bbmt.2018.12.003. Epub 2018 Dec 7. PMID: 30529461; PMCID: PMC6445701.
2. **Sachchithanantham S, Roussel M, Palladini G, Klersy C, Mahmood S, Venner CP, Gibbs S, Gillmore J, Lachmann H, Hawkins PN, Jaccard A, Merlini G, Wechalekar AD**. European Collaborative Study Defining Clinical Profile Outcomes and Novel Prognostic Criteria in Monoclonal Immunoglobulin M-Related Light Chain Amyloidosis. *J Clin Oncol*. 2016 Jun 10;34(17):2037-45. doi: 10.1200/JCO.2015.63.3123. Epub 2016 Apr 25. PMID: 27114592.
3. **Manwani R, Sachchithanantham S, Mahmood S, Foard D, Sharpley F, Rezk T, Lane T, Quarta C, Fontana M, Lachmann HJ, Gillmore JD, Whelan C, Hawkins PN, Wechalekar AD**. Treatment of IgM-associated immunoglobulin light-chain amyloidosis with rituximab-bendamustine. *Blood*. 2018 Aug 16;132(7):761-764. doi: 10.1182/blood-2018-04-846493. Epub 2018 Jun 20. PMID: 29925500.
4. **Sarosiek S, Branagan AR, Treon SP, Castillo JJ**. IgM-Related Immunoglobulin Light Chain (AL) Amyloidosis. *Hemato*. 2022;3(4):731-741. doi:10.3390/hemato3040049
5. **Gertz MA, Schonland S**. Stem Cell Mobilization and Autologous Transplant for Immunoglobulin Light-Chain Amyloidosis. *Hematol Oncol Clin North Am*. 2020 Dec;34(6):1133-1144. doi: 10.1016/j.hoc.2020.07.007.

Epub 2020 Sep 12. PMID: 33099429; PMCID: PMC7594100.

6. **Pika T, Hegenbart U, Flodrova P, Maier B, Kimmich C, Schönland SO**. First report of ibrutinib in IgM-related amyloidosis: few responses, poor tolerability, and short survival. *Blood*. 2018 Jan 18;131(3):368-371. doi: 10.1182/blood-2017-09-806463. Epub 2017 Nov 27. PMID: 29180400.
7. **Khan AM**. The Use of Bruton Tyrosine Kinase Inhibitors in Waldenström's Macroglobulinemia. *J Pers Med*. 2022 Apr 22;12(5):676. doi: 10.3390/jpm12050676. PMID: 35629099; PMCID: PMC9146645.
8. **Bou Zerdan M, Valent J, Diacovo MJ, Theil K, Chaulagain CP**. Utility of Bruton's Tyrosine Kinase Inhibitors in Light Chain Amyloidosis Caused by Lymphoplasmacytic Lymphoma (Waldenström's Macroglobulinemia). *Adv Hematol*. 2022 Jan 19;2022: 1182384. doi: 10.1155/2022/1182384. PMID: 35096069; PMCID: PMC8791721.