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IgM-Related Immunoglobulin Light Chain (AL) Amyloidosis

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Abstract: Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic disorder characterized by an IgM paraprotein. The clinical presentation of WM varies and can include common manifestations such as anemia and hyperviscosity, in addition to less common features such as cryoglobulinemia, IgM-related neuropathy, and immunoglobulin light chain (AL) amyloidosis. Amyloidosis is a protein-folding disorder in which vital organ damage occurs due to the accumulation of misfolded protein aggregates. The most common type of amyloidosis in patients with an IgM paraprotein is AL amyloidosis, although other types of amyloidosis may occur. IgM-related amyloidosis has distinct clinical features when compared with other subtypes of AL amyloidosis. This review highlights the diagnostic criteria of IgM-related AL amyloidosis, as well as the clinical characteristics and treatment options for this disorder.

Keywords: amyloidosis; IgM monoclonal gammopathy; light chain; lymphoplasmacytic lymphoma; plasma cell disorder; Waldenström macroglobulinemia

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1. Introduction

Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma characterized by an IgM paraprotein [1]. The clinical presentation of WM varies widely and can include common manifestations such as anemia, hyperviscosity, and IgM-related neuropathy, in addition to less common features such as cryoglobulinemia and immunoglobulin light chain (AL) amyloidosis [2]. Amyloidosis is a disorder characterized by the deposition and accumulation of a misfolded protein [3]. The underlying protein misfolds, aggregates, and forms fibrils that deposit in organs resulting in organ dysfunction and life-threatening consequences in the absence of effective therapy. There are multiple types of amyloidosis, each defined by the specific precursor protein, the most common of which are immunoglobulin light chain (AL), transthyretin (TTR), and serum amyloid A (AA) amyloidosis [4]. AL amyloidosis is typically associated with an underlying clonal hematologic disorder, such as monoclonal gammopathy of undetermined significance, multiple myeloma, or WM. In most cases of AL amyloidosis, the misfolded protein is a lambda free light chain, although approximately 5–7% of AL amyloidosis has an associated IgM monoclonal paraprotein [5–8]. In this review, we will focus on the diagnosis, clinical presentation and treatment of IgM-related AL amyloidosis.

2. Detection and Typing of Amyloidosis

In all suspected cases of IgM-related amyloidosis, it is critical to confirm the presence of amyloid fibrils and accurately type the precursor protein. Although amyloid fibrils can be detected in a bone marrow biopsy [9,10], in most cases, the diagnosis will require an additional tissue biopsy for accurate typing. Abdominal fat biopsy and salivary gland biopsy are low-risk and high-yield procedures that are often adequate for an accurate diagnosis [11,12]. Although these are sufficient in most cases, some patients may require

an organ biopsy if initial work-up is negative and the suspicion of amyloidosis remains high [13].

In most patients with a concurrent monoclonal paraprotein, the biopsy will confirm a diagnosis of AL amyloidosis, although it is known that patients may have coexistent ATTR amyloidosis with a monoclonal gammopathy [14,15] or IgM-related lymphoproliferative disorder [16], so tissue typing is critical. Biopsy material should be thoroughly evaluated for the presence of amyloid fibrils with tissue typing performed at an experienced center either with immunofluorescence, immunohistochemistry with or without electron microscopy with gold labeling, or by using the gold standard of liquid chromatography–tandem mass spectrometry (LC-MS/MS) [17]. These methodologies can determine the precursor protein, and consequently the type of amyloidosis. In most cases of immunoglobulin-related amyloidosis, the unstable protein is a free light chain [13], although there are cases of immunoglobulin heavy chain (AH) as well as immunoglobulin light and heavy chain (AHL) amyloidosis that have been reported [18,19]. The sensitivity of the fat pad biopsy and bone marrow for the detection of amyloid is low in AH and AHL amyloidosis, so additional organ biopsies are often required in these cases [18].

3. Diagnostic Evaluation of IgM-Related Amyloidosis

All patients with a new diagnosis of IgM-related AL amyloidosis should have a thorough work-up to evaluate for the presence of an associated hematologic disorder, as well as a complete organ evaluation to establish the extent of organ involvement (Table 1) [13]. The hematologic work-up should include serum immunofixation electrophoresis, serum protein electrophoresis, serum free light chain levels, quantitative immunoglobulin levels, urine immunofixation electrophoresis, urine protein electrophoresis, and complete blood counts. In most cases of AL amyloidosis, the unstable immunoglobulin is a lambda rather than a kappa free light chain with a ratio of 4:1 [20]. As in most subtypes of AL amyloidosis, a lambda free light chain (FLC) clone is often found in IgM-related amyloidosis, although the proportion of kappa clonality is significantly higher in IgM-related disease, and some cases of biclonal disease have also been reported [5,7]. Despite the presence of a clonal free light chain on serum immunofixation, approximately half of the patients with IgM-related amyloidosis have low FLC levels, which render patients unevaluable by the traditional AL amyloidosis response criteria [21]. In these cases, the IgM paraprotein may be a more reliable disease marker and the quantitative IgM level should be followed closely [22]. Therefore, hematologic responses should be measured by free light chains, using the traditional AL amyloidosis free light chain response criteria or the low difference in free light chains (dFLC) response criteria [22–24], in addition to the measurement of IgM levels, as performed in WM [25]. The accurate determination of hematologic response is important and should be followed closely, as prognosis is improved in patients who achieve a free light chain or M-protein response [26].

Initial diagnostic work-up in these patients should also include a bone marrow biopsy and aspirate to delineate the source of the amyloidogenic immunoglobulin and evaluate for a concurrent plasmacytic or lymphoplasmacytic disorder. The diagnosis of an IgM monoclonal gammopathy may occur simultaneously with the initial diagnosis of AL amyloidosis or may occur prior to the diagnosis of amyloidosis in a third of the patients [6,27]. In a 75-patient case series from the Mayo Clinic, the related hematologic disorders present at the time of diagnosis of IgM-related amyloidosis were 70% monoclonal gammopathy of undetermined significance, 9% smoldering lymphoplasmacytic lymphoma, and 22% previously treated lymphoplasmacytic lymphoma. Waldenström macroglobulinemia is the most common underlying lymphoplasmacytic lymphoma associated with IgM amyloidosis, and approximately 7.5% of patients with WM have coexisting AL amyloidosis [28]. Other lymphoproliferative disorders, such as follicular lymphoma, chronic lymphocytic leukemia, and mantle cell lymphoma, have also been reported as pre-existing or concurrent disorders with IgM-related amyloidosis [8,29,30]. In cases with pre-existing WM or other

IgM disorders, the median time from diagnosis of the antecedent IgM-related disorder to the diagnosis of amyloidosis was reported with a range of 32 to 65 months.

Table 1. Recommended initial hematologic and organ assessment in IgM-related amyloidosis.

Hematologic Assessment	Organ Assessment
Immunofixation electrophoresis and protein electrophoresis for serum and urine	Renal: creatinine, 24 h urine testing with urine immunofixation and protein electrophoresis with quantification of albuminuria
Serum free light chain levels	Liver: AST, ALT, alkaline phosphatase, bilirubin, albumin
Quantitative immunoglobulins	Neurologic: thorough physical exam and history with electromyography/nerve conduction study, anti-MAG antibody testing, and autonomic testing as needed
Complete blood counts	Cardiac: electrocardiogram, echocardiogram (including global longitudinal strain), troponin, and NT-proBNP with cardiac MRI and DPD/PYP scan as needed
Bone marrow biopsy and aspirate, including immunohistochemistry, cytogenetics, multiple myeloma FISH panel, and MYD88 testing	Pulmonary: CT scan and/or pulmonary function tests as needed

Bone marrow biopsies and aspirates in these cases can also provide valuable information regarding the type of clonal cells and associated molecular characteristics. The biopsy and aspirate should be sent for immunohistochemical evaluation, in addition to flow cytometry, FISH testing, and molecular analysis, including evaluation for MYD88 ^{L265P}. Although other subtypes of AL amyloidosis are typically characterized by a pure plasma cell clone, in patients with IgM-related AL amyloidosis, a pure plasma cell neoplasm occurs in only 23% of patients and a lymphoplasmacytic lymphoma is diagnosed in 63% of patients. The remaining small proportion of patients may have other B-cell lymphomas, too few clonal cells to classify, or other diagnoses. In contrast to other AL amyloidosis cases in which approximately 50% of patients have t (11;14), only about a quarter of the patients with IgM-related amyloidosis have a t (11;14), and in these cases all were detected in patients with a pure plasma cell neoplasm [31]. Although this translocation has therapeutic and prognostic implications in other subtypes of AL amyloidosis; the prognostic significance of t (11;14) in IgM-related amyloidosis is not known at this time. Additionally, MYD88^{L265P} mutations which are not usually seen in AL amyloidosis have been observed in approximately half of the cases of IgM-related amyloidosis, all of which were associated with an underlying lymphoplasmacytic clone [32]. CXCR4 mutations have been reported in approximately 17% of these cases, and the traditional karyotype is typically unremarkable.

4. Clinical Features

Patients with IgM-related amyloidosis tend to present at an older age and with a distinct pattern of organ involvement compared with most AL amyloidosis patients [5,7]. To determine the extent of organ involvement and to help prognosticate, it is important to complete a thorough organ work-up including evaluation of the kidneys, heart, lungs, nervous system, lymph nodes, liver, and gastrointestinal tract. IgM-related amyloidosis more commonly presents with renal involvement and neurologic involvement compared with non-IgM AL amyloidosis [5]. Renal involvement is frequent in IgM-related amyloidosis and occurs in 32–70% of cases [5–8,33–35]. The evaluation of the kidneys should include a serum creatinine level, a 24 h urine total protein including urine immunofixation electrophoresis and urine protein electrophoresis to determine the quantity of albumin and monoclonal protein in the urine, and an assessment for signs or symptoms associated with nephrotic syndrome, such as peripheral edema or hypoalbuminemia. Rare cases of

IgM-related AL amyloidosis with renal involvement have clinical and pathological features that are not consistent with nephrotic syndrome [19]. In these cases, or others with atypical presentation or inadequate response to treatment, a renal biopsy may be warranted. Attention should be paid to the presence of hematuria, which occurs commonly in IgM-related AH or AHL amyloidosis [18].

Nerve involvement in IgM-related amyloidosis, occurring in 10–38% of patients, is higher than in most patients with AL amyloidosis [5–8,34,35]; therefore, a thorough neurologic evaluation of the peripheral and autonomic nervous systems should be performed, in addition to an assessment for carpal tunnel syndrome. The evaluation should include a physical exam and detailed patient history to assess for symptoms such as pain, numbness, tingling, or change in sensation. An assessment for orthostasis, erectile dysfunction, and gastrointestinal symptoms related to autonomic dysfunction should also be performed. Electromyography and nerve conduction studies (EMG/NCS) are needed to verify the extent and presence of neuropathy. This evaluation should be performed even in patients with known anti-myelin-associated glycoprotein (MAG), as additional evaluation may discover an axonal, rather than demyelinating, neuropathy which would be more consistent with amyloidosis [36]. A prior series reported a positive anti-MAG antibody in 20 of 46 patients with IgM-related amyloidosis [37].

All patients should be closely evaluated for cardiac involvement, although cardiac involvement is less common in IgM-related AL amyloidosis and occurs in 33 to 56% of patients with the highest level of involvement in those with an associated lymphoplasmacytic lymphoma, rather than a pure plasma cell neoplasm [5–8,32–35]. Specifically, in cases of IgM-related AH or AHL amyloidosis, there is less cardiac involvement. [18] The evaluation should begin with troponin level and brain natriuretic peptide (BNP) or NT-proBNP level, although these levels tend to be lower in IgM-related amyloidosis and translate to a significantly lower proportion of patients with IgM amyloidosis that have Mayo 2012 stage 3 or 4 disease [5,32]. Additionally, an electrocardiogram and echocardiogram to measure global longitudinal strain should be performed. Cardiac MRI may also be needed in cases where the suspicion of cardiac involvement remains elevated despite a lack of evidence on initial cardiac evaluation. DPD or PYP scans should be considered to rule out TTR amyloidosis.

Additionally, lung involvement (which occurs in 3–22% of patients) and lymph node involvement (occurring in 21–31% of patients) are more frequent in IgM-associated AL amyloidosis than in other AL amyloidosis subtypes [5–8,33–35]. For this reason, patients with pulmonary symptoms may require CT imaging or pulmonary function testing. CT scans may demonstrate adenopathy secondary to amyloid deposition, rather than involvement with a lymphoproliferative disorder [8]. In these cases, enlarged lymph nodes may appear calcified on imaging and may not decrease in size after treatment.

Alkaline phosphatase, in addition to other liver function testing and physical evaluations for hepatomegaly, is needed to evaluate potential liver involvement. A thorough history evaluating gastrointestinal symptoms should be performed, as approximately 17% of patients with IgM-related amyloidosis also have gastrointestinal involvement [33].

5. Treatment Options

The goal of treatment in AL amyloidosis is to eliminate the clonal population of cells in the bone marrow that are producing amyloidogenic light or heavy chains. Due to the rarity of IgM-related AL amyloidosis, there are no large or randomized clinical trials to guide treatment decisions. Instead, smaller published series are used as evidence of successful therapeutic regimens. The most recommended regimens are similar to those used in WM [38], while plasma cell-directed therapies may be used in those patients with IgM-related AL amyloidosis and a pure plasma cell clone.

Alkylating agents and purine analogs, although less commonly used today, have been studied with varying levels of success in IgM-related amyloidosis. In a series of 14 patients treated with melphalan and dexamethasone, the response rate was reported as 64% [7], although other series reported a hematologic response rate of 37–63% with

alkylators, including chlorambucil, melphalan, and cyclophosphamide [33,35]. Despite the overall hematologic responses, deep responses with very good partial response (VGPR) or better are reported in less than 20% of patients. Organ response rates are similarly low. Although deep hematologic and organ response rates are low with most alkylating agents, fludarabine has been used successfully for the treatment of IgM-related amyloidosis with hematologic, complete and organ response rates of 73%, 9% and 55%, respectively [35]. This agent is reserved for patients with relapsed disease and is not routinely used due to the associated immunosuppression and risk of stem cell toxicity.

Newer therapies have shown more success and safety in the treatment of IgM-related amyloidosis. Rituximab, as a cornerstone in the treatment of B-cell lymphoproliferative disorders, initially showed limited success as a single agent in IgM-related amyloidosis with a hematologic response rate of 60%, but no complete responses and no organ responses [35]. In more recent years, rituximab has been used as part of combination therapies with high success rates.

Proteasome inhibitors, such as bortezomib, carfilzomib, and ixazomib, are commonly used in multiple myeloma. These therapies have also proven to be successful for the treatment of non-IgM AL amyloidosis. Due to these successes, as well as high response rates with bortezomib-based regimens in WM [39–44], bortezomib has been used in IgM-related amyloidosis. Retrospective data showed an 82% overall response rate with 27% VGPR [33]. The combination of rituximab, bortezomib, and dexamethasone (BDR) has been studied prospectively in the treatment of IgM-associated AL amyloidosis. Ten patients were treated with a 28-day regimen of rituximab 375 mg/m^2 on day 11 and bortezomib 1.3 mg/m^2 with dexamethasone on days 1, 4, 8, and 11 [45]. Seven patients (78%) achieved a hematologic response, including three patients with a >50% reduction in the IgM paraprotein and five patients with a >50% reduction in the involved free light chain. Hematologic response was maintained at 11 months in all patients, although only two patients achieved a VGPR based on amyloidosis response criteria with a normal involved FLC and normal κ/λ ratio. No organ responses were detected. Grade $\geq$3 adverse events occurred in three patients and included pneumonia, neuropathy, and fluid retention with hypotension. In this study, all patients that achieved a response had evidence of hematologic response after cycle 2, suggesting that a lack of response at two months should prompt a change in therapy.

Bendamustine with rituximab (BR) is another regimen that has shown high response rates in WM [46–48] and has now been adopted for the treatment of IgM-associated AL amyloidosis. A case series of 27 patients, including 22 treatment-naïve and 5 relapsed patients, described treatment with BR in patients with AL amyloidosis and an associated lymphoplasmacytic lymphoma (25 with IgM, and 2 with IgG M-protein) [49]. Rituximab was given at 375 mg/m^2 on day 1 and bendamustine at 90 mg/m^2 given on day 1 and day 2 of a 28-day cycle. Five patients received weekly dexamethasone in addition to BR. The overall hematologic response rate was 59% and 76% on an intention-to-treat basis and evaluable basis, respectively. Complete response (CR) rate was 17%, VGPR was 39%, PR was 17%, and no response was found in 27% of evaluable patients. With a median follow-up of 18 months (range 3–55), the median overall survival (OS) was not reached, although it was higher in those who achieved at least a VGPR (not reached vs. 9 months). Median progression-free survival (PFS) was 34 months. The most frequent grade 1–2 toxicities were constipation and fatigue and the most common grade $\geq$3 toxicity was infection without neutropenia (11%), febrile neutropenia (7%), and neutropenia (7%). Unfortunately, organ response rates remain low with approximately 18% renal and cardiac response. [49] Overall, with approximately half of patients achieving a VGPR or greater, this is an appealing treatment option and can be given even in patients with neuropathy, renal dysfunction, or cardiac disease.

High rates of disease response have also been reported with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). In a series of 38 patients from the Mayo Clinic, the overall hematologic response rate was 92% with 76% of patients achieving at least a VGPR. [50] Median PFS and OS in the series were 48 and 106 months,

respectively. The 100-day mortality in this series was 5%. Similarly, a high overall response rate of 100% was reported in another series with at least a VGPR achieved in 80% of patients. [33] These high rates of deep hematologic responses have not been reproduced with other treatment regimens for IgM-related amyloidosis, thus making this an ideal therapy for patients meeting the stringent eligibility criteria. Unfortunately, most patients do not qualify for this intense regimen because of significant co-morbidities and organ dysfunction related to amyloidosis. Patients should meet strict eligibility criteria such as left ventricular ejection fraction $\geq$40%, ECOG performance status $\leq$2, eGFR >30 mL/min/m^2, and supine systolic blood pressure $\geq$90 mmHg, which were designed to mitigate high rates of mortality initially reported in patients with AL amyloidosis undergoing treatment with ASCT [51]. This therapy should be considered as consolidation in patients not achieving a deep hematologic response with initial induction therapy.

In patients eligible for ASCT, the best conditioning regimen is not known. In the 38-patient series from the Mayo Clinic mentioned above, 32 patients (84%) received treatment with high-dose melphalan, as is traditionally used in multiple myeloma and other subtypes of AL amyloidosis [52], and 6 patients (16%) received carmustine, etoposide, cytarabine, and melphalan (BEAM), which are more frequently used for conditioning in non-Hodgkin lymphoma [53]. Other case series have also reported the use of high-dose melphalan, either 140 mg/m^2 or 200 mg/m^2, as the conditioning regimen in the majority of patients [33]. There are no clear data to guide this decision and high rates of hematologic response have been reported with both conditioning regimens, although some guidelines suggest the choice of conditioning should be based on the underlying bone marrow clone, with those having a high plasma cell burden receiving high-dose melphalan and those with a B-cell infiltrate receiving BEAM.

Unfortunately, despite the very high response rates to BTK inhibitors seen in WM [54–56], this success has not been replicated in patients with IgM-associated AL amyloidosis. An initial case series retrospectively reviewed the response to treatment with ibrutinib [57]. In this series, eight patients with prior WM were diagnosed with AL amyloidosis. Two of seven patients tested for an MYD88 mutation had wild-type disease. Five patients had cardiac amyloidosis, four had soft tissue involvement, three had renal involvement, one had lung involvement, and one had neuropathy. Ibrutinib was administered at the standard dose of 420 mg daily and a hematologic response based on free light chains was achieved in only two patients with a median duration of therapy of 4 months (range 2–16). Five patients had no light chain or M-protein response and one patient progressed on therapy. The median OS was 9 months with a median follow-up of 6 months. The most common adverse events were peripheral edema and polyneuropathy. Two patients (25%) developed atrial fibrillation, three (38%) developed anemia, and two (25%) developed thrombocytopenia. Since this initial report, another case series of four patients with MYD88-mutated WM and associated IgM-amyloidosis was published [58]. In this series, two patients received ibrutinib and two received acalabrutinib. Three VGPRs and one CR were reported, although three of the patients also received concurrent therapy with rituximab. In this small series, one patient stopped ibrutinib due to atrial fibrillation and another patient required BTK inhibitor dose reduction due to bleeding. Future prospective studies using novel BTK inhibitors are needed, especially in patients with MYD88 mutations, and potentially in combination with another therapy such as a CD20-directed monoclonal antibody.

The BCL-2 antagonist venetoclax has preclinical data demonstrating its efficacy in AL amyloidosis [59] and deserves further exploration in the treatment of IgM-related amyloidosis. Multiple cases series have reported the success and safety of this drug in AL amyloidosis, including multiple series using venetoclax as a single agent or in combination with other therapies [60,61]. These series showed an overall response rate of 67–88%. Another multicenter retrospective review of 43 patients reported an overall response rate of 68% with higher hematologic response rates seen in patients with t(11;14) [62]. These encouraging results, along with the efficacy of single-agent venetoclax in WM, provide the rationale for future formal studies exploring the use of venetoclax in IgM amyloidosis.

In those patients with pure plasma cell clones, other plasma cell-directed therapies that are routinely used in AL amyloidosis should be employed. First-line regimens for these patients often include cyclophosphamide/bortezomib/dexamethasone with or without daratumumab, and ASCT in those who are transplant candidates. [51,63–66] In patients with relapsed or refractory disease, bortezomib-, lenalidomide-, or pomalidomide-based regimens can be employed [67–71].

6. Prognosis

The OS of patients with WM with AL or AHL amyloidosis is reportedly worse than in patients with WM alone, but median overall survival is similar to other patients with AL amyloidosis and has been reported by multiple groups as ranging between 49 and 78 months [5,7,8]. Prognosis in AL amyloidosis, including IgM-related disease, is most affected by the degree of cardiac involvement, although in IgM amyloidosis, serum albumin level has also been independently associated with OS [35]. Liver and nerve involvement are also considered to be negative prognostic factors [26].

The achievement of a hematologic response, both by free light chain response criteria or monoclonal protein response, is associated with longer overall survival [33,72]. Unfortunately, hematologic response rates and the depth of hematologic response in IgM-related amyloidosis are lower than in other subtypes of AL amyloidosis, as demonstrated in a case series including 172 patients. In this review, the hematologic response rate using a variety of therapies was only 57%, with the majority of responses being partial responses and a limited number of patients achieving a very good partial response or better [26]. Additionally, organ response rates in this series were present in <20% of patients. In IgM-related amyloidosis, organ response is known to predict better PFS and OS [50]. The highest rates of organ response have been seen with ASCT, with 65% of patients achieving a renal response at a median of 18 months (range 3–52 months), and 60% of patients having a cardiac response at a median of 12 months (range 10–35 months) in the Mayo clinic series previously mentioned [50]. This should be considered when making treatment decisions for patients who are candidates for this intensive therapy.

7. Conclusions

In conclusion, only 5–7% of AL amyloidosis is related to an IgM paraprotein. These patients may have an antecedent or concurrently diagnosed lymphoproliferative disorder, such as WM, with most patients having a lymphoplasmacytic infiltrate found in the bone marrow. In these cases, the organ involvement is distinct, with nerve, lung, and lymph node involvement seen more frequently than other subtypes of AL amyloidosis. High-quality data regarding treatment options in IgM-related amyloidosis are limited and hematologic and organ responses with known regimens remain low, except with ASCT, for which only a small number of patients qualify. Deep hematologic and organ responses are necessary to prolong survival in patients with IgM-related amyloidosis, so additional prospective treatments with novel therapies are needed.

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