Diagnostic Challenges of Amyloidosis in Waldenström Macroglobulinemia

Giovanni Palladini, Giampaolo Merlini

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 2, 244-6 © 2013 Elsevier Inc. All rights reserved.

Abstract

Amyloidosis associated with immunoglobulin M clones is a distinct clinical entity that poses specific challenges to clinicians. Although there is substantial overlap, the pattern of organ involvement is peculiar, with higher frequencies of lung, lymph nodes, and peripheral nervous system involvement. Early diagnosis is vital to start effective therapy before irreversible organ damage has occurred and should be based on markers of initial, asymptomatic organ dysfunction, such as natriuretic peptides for heart involvement and albuminuria for renal amyloidosis. Immunoglobulin M clones can give rise to both light chain (AL) and reactive (AA) amyloidosis, and once the diagnosis of amyloidosis is made, correct amyloid typing is necessary to design appropriate therapy and follow-up. Prognostic stratification should include serum albumin concentration, which is an independent prognostic factor.

Introduction

Waldenström macroglobulinemia (WM) is a heterogeneous disease, and treatment can be required for a variety of reasons. Although most subjects present with symptoms related to tumor burden, such as anemia or lymphadenopathy, approximately 3% develop immunoglobulin (Ig) M–related disorders, including immunoglobulin light chain (AL) amyloidosis. Conditions related to the monoclonal (M) protein are difficult to diagnose because they can occur independently from the concentration of the M protein and the extent of bone marrow infiltration. These diseases are caused by the so-called dangerous small clones. One of the most dangerous disorders related to the M protein is AL amyloidosis. This disease can deceptively give rise to fatal organ damage. However, if therapy is initiated before irreversible organ impairment has occurred, then AL amyloidosis can be effectively treated and organ function can be restored, which prolongs survival. The diagnosis of organ damage related to the M protein in patients with non-IgM monoclonal gammopathy of undetermined significance (MGUS) has recently been reviewed. In this article, we discuss the diagnosis of AL amyloidosis in patients with WM.

IgM-related AL Amyloidosis

In AL amyloidosis, a monoclonal light chain (LC) misfolds, aggregates, and deposits in tissues, which causes organ dysfunction and ultimately death if left untreated. An IgM clone is responsible for the disease in approximately 4% to 7% of cases. Patients with IgM–AL amyloidosis share many of the major characteristics of other patients with this disease. The frequency of heart involvement ranges from 33% to 53%, and the kidney is involved in 32% to 70% of cases, with no statistically significant differences compared with patients with AL amyloidosis and without IgM. However, subjects with IgM are more likely to have amyloid deposits in the lungs (3%-22%) and lymph nodes (21%-31%) as well as peripheral or autonomic neuropathy (10%-38%). Lymphadenopathy is caused by replacement with amyloid rather than involvement by lymphoma. It has been reported that patients with polyneuropathy and IgM–AL amyloidosis frequently have anti-myelin-associated glycoprotein antibodies; however, they do not appear to affect the occurrence or expression of polyneuropathy. Moreover, patients with IgM–AL amyloidosis have a lower concentration of circulating amyloidogenic free LCs (F.LC). Also, the concentration of the cardiac biomarkers N-terminal prohormone type-B (NT-proBNP) and troponins are significantly lower in IgM–AL amyloidosis, which indicates less-severe cardiac dysfunction. Bone marrow studies are normal or nondiagnostic in 26% to 33% of cases. In the other patients, the bone marrow infiltrate is most commonly lymphoid or lymphoplasmacytoid, with predominant plasma cell infiltration in 13% to 21% of subjects.

In recent series, the median survival of patients with AL amyloidosis and an underlying IgM clone ranged from 49 to 78 months, with no significant differences compared with patients without IgM. Not surprisingly, survival was independently affected by heart involvement, assessed according to conventional criteria or NT-proBNP. Interestingly, however, serum albumin concentration, which is not recognized as a strong prognostic marker in the overall population of patients with AL amyloidosis, was found to be an additional prognostic factor, independent of the presence and severity of cardiac involvement, in patients with IgM. Importantly, as it is established in non–IgM–AL amyloidosis, also in patients with
IgM hematologic response translates into a significant survival advantage, which is independent of known adverse prognostic factors.6

**Diagnosing IgM–AL Amyloidosis**

The diagnostic workup of AL amyloidosis requires (1) early recognition of amyloid-related organ damage, (2) identification of amyloid deposits in tissues, (3) accurate and unequivocal amyloid typing, (4) identification and measurement of the amyloidogenic precursor, and (5) risk stratification. The identification of the IgM monoclonal component precedes the diagnosis of AL amyloidosis in 34% of patients, and amyloidosis is diagnosed after patients have been followed up for an IgM MGUS for more than 2 or 5 years in 14% and 8% of cases, respectively.5 This observation suggests that, at least in one-third of cases, an asymptomatic phase of IgM-MGUS precedes the onset of amyloidosis. Indeed, the Mayo Clinic Group reported that approximately 7% of patients who progress from IgM-MGUS, and 2% of those who progress from smoldering WM develop AL amyloidosis.12,13 Thus, it seems reasonable to include tests for the early detection of amyloid-related organ damage in the follow-up of patients with IgM monoclonal gammopathies. The organs most frequently involved in IgM–AL amyloidosis are the heart, the kidney, and the peripheral nerves. However, when cardiac and renal involvement becomes clinically evident, irreversible organ damage has often already occurred, and physicians should rely on markers of early organ dysfunction. Increased concentrations of natriuretic peptides, NT-proBNP, and BNP have a very high sensitivity in detecting cardiac amyloidosis and are found before heart failure and echocardiographic signs of the disease become manifest.14,15 Kidney involvement manifests with proteinuria and, before an overt nephrotic syndrome and subsequent renal failure become evident, albumin can be detected in the patient’s urine. Early signs of peripheral and autonomic neuropathy are loss of sensitivity to pain and temperature, and development of hypotension or resolution of hypertension. The differential diagnosis of peripheral neuropathy is particularly challenging in patients with IgM monoclonal components because amyloidosis can be confused with neuropathy caused by antimielylin-associated glycoprotein and chronic inflammatory demyelinating polyneuropathy. Clues to the diagnosis of amyloidosis are the λ isotype of the monoclonal component, the presence of axonal damage, and the association with autonomic dysfunction.16 Based on these considerations, the workup of patients with IgM MGUS, particularly those with an abnormal FLC ratio, at baseline and at each follow-up evaluation should include measurements of NT-proBNP or BNP and albuminuria. Moreover, the patients should be specifically questioned about symptoms of neuropathy, and the physical examination should include a neurologic assessment. These tests should be repeated annually.

When amyloidosis is suspected, amyloid deposits should be searched in a tissue biopsy to confirm the diagnosis. Subcutaneous abdominal fat aspiration is the most simple and least invasive diagnostic procedure. Its sensitivity is above 80% in AL amyloidosis.17 Labial salivary gland biopsy is also simple and yields a high diagnostic sensitivity. Congo red staining of bone marrow specimens from patients with IgM–AL amyloidosis has a 50% diagnostic sensitivity.7 Amyloid deposits are found in the labial salivary glands of almost 60% of patients with systemic amyloidosis and negative abdominal fat aspirate, and the sequential biopsy of these 2 sites has a negative predictive value of 91%, thus limiting the need for an organ biopsy to <10% of patients.18 The biopsy of the involved organs can be performed if amyloidosis is still suspected but biopsy specimens of alternative sites are negative, and the small but significant risk of hemorrhage should be taken into account.

It must be kept in mind that identifying amyloid deposits in a patient with an IgM monoclonal component is not conclusive evidence of AL amyloidosis. Indeed, although in only 4% of cases, IgM monoclonal gammopathies can be associated with reactive (AA) amyloidosis, reactive to the inflammation that often accompanies these diseases.19 In reactive amyloidosis, the amyloid deposits are formed by the acute-phase protein serum amyloid A and not by LCs, and treatment should be aimed at reducing the concentration of serum amyloid A instead of that of FLC. One more possible pitfall is the coexistence of the IgM clone and an unrelated (ie, familial or senile) systemic amyloidosis, which requires a completely different treatment. Light microscopy immunohistochemistry can consistently identify AA amyloidosis. However, conventional immunohistochemistry, as well as immunofluorescence on renal biopsy specimens, is unreliable in AL amyloidosis, when performed with commercial antibodies.19 Nevertheless, at referral centers, by using custom-made antibodies, light microscopy immunohistochemistry can also be a valuable tool for AL amyloidosis characterization.20 At our center, we routinely rely on immunoelectronmicroscopy performed on abdominal fat aspirates and organ biopsy specimens.21 Modern proteomics makes typing of amyloid a direct matter, and several proteomic approaches based on 2-dimensional electrophoresis,22,23 laser capture microdissection,24 and multidimensional protein identification technology25 have been developed by our group and by Mayo Clinic investigators. DNA analysis can be used to exclude hereditary forms.26

In AL amyloidosis, the assessment of response to therapy is based on changes in FLC concentration.11 However, in IgM–AL amyloidosis, the low FLC concentration can render this assessment unfeasible. Indeed, among 66 patients with IgM–AL diagnosed at our center, 31 (47%) had a baseline difference between involved (amyloidogenic) and uninvolved FLC < 50 mg/L, which makes them not evaluable for FLC response. In these patients, hematologic response can be assessed by changes in the concentration of the intact IgM.11

Risk stratification based on cardiac biomarkers and uninvolved FLC has become a fundamental part of the diagnostic workup of patients with AL amyloidosis.27,28 In IgM–AL amyloidosis, serum albumin is an independent prognostic factor and can be associated with NT-proBNP in a staging system. Patients with both NT-proBNP > 650 ng/L and albumin < 35 g/L have a median survival of only 6 months (Figure 1).

**Conclusion**

AL amyloidosis associated with an IgM monoclonal component is a distinct clinical entity and poses specific challenges to clinicians. The possibility that a patient with an IgM monoclonal component develops amyloidosis should be kept in mind, and appropriate testing based on markers of early organ dysfunction should be included in the follow-up. Because IgM clones can be associated with both AL and AA amyloidosis, accurate amyloid typing should be carried out.
if necessary by referring patients to specialized centers. Particular difficulties are also encountered in the application of standard criteria for prognostic stratification and response to treatment. IgM–AL amyloidosis is an extremely rare disease, and, although independent studies from referral centers have greatly contributed to the knowledge of this disease, they were hampered by small numbers. Very important questions, such as the applicability of treatment strategies developed for non–IgM–AL amyloidosis or WM and the design of a specific staging system, still need to be answered. Only international cooperation can address these issues, and the results of a multicenter European study are eagerly awaited.

Acknowledgment
Support was received from the Ministry of Health (Ricerca Finalizzata Malattie Rare), ‘Istituto Superiore di Sanità’ (526 D/63); Ministry of Research and University (2007AESFX2_003); and ‘Associazione Malattie Rare’, ‘Istituto Superiore di Sanità’ (526 D/63); Ministry of Health (Ricerca Finalizzata Malattie Rare). Support was received from the Ministry of Health (Ricerca Finalizzata Malattie Rare). Support was received from the Ministry of Health (Ricerca Finalizzata Malattie Rare).

Disclosure
The authors have stated that they have no conflicts of interest.

References