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Once AL amyloidosis: not always AL amyloidosis

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Amyloid cardiomyopathy could be related to AL amyloidosis, wild-type transthyretin amyloidosis (ATTRwt) or hereditary amyloidosis (ATTRm). It is crucial to distinguish and accurately type the precursor amyloidogenic protein in order to offer appropriate treatment, prognosis and genetic counseling. Treatment for AL amyloidosis is directed towards the plasma cell dyscrasia, whereas treatment for transthyretin amyloidosis is directed towards stabilization of misfolded TTR [1] or reduction in production of mutant TTR [2,3]. Median survival of patients with ATTRwt cardiomyopathy is 2.71 years from diagnosis compared to 0.87 years for cardiomyopathy from AL amyloidosis [4]. While ATTR amyloidosis can now be conclusively diagnosed by imaging [5] and blood testing alone, it is also important to note that the possible co-existence of AL amyloidosis and ATTRwt amyloidosis may be difficult to distinguish clinically, often requiring histologic identification of the amyloid precursor protein [6,7].

To illustrate the importance of amyloid typing when assigning the accurate cause of amyloid cardiomyopathy, we describe two such cases of patients with amyloidosis who required endomyocardial biopsy for accurate diagnosis.

Case 1

A 69-year-old man was diagnosed with AL amyloidosis with renal and cardiac involvement with an underlying IgA lambda plasma cell dyscrasia by renal biopsy. Immunofluorescence studies on renal biopsy showed 3+ staining for lambda light chains. His plasma cell dyscrasia markers showed M peak of 3.1 g/dL, serum and urine immunofixation electrophoresis (IFE) with IgA lambda monoclonal protein and elevated serum free lambda light chain levels of 120 mg/L with ratio of 0.06. A bone marrow biopsy revealed 25% lambda-restricted lymphoplasmacytic cells with areas of Congo red positivity, diagnosing lymphoplasmacytic lymphoma complicated by IgA-lambda AL amyloidosis. His end organ dysfunction was characterized by urine protein excretion of 7 g/24 h, serum albumin of 1.1 g/dL, interventricular septal diameter of 14 mm and BNP 2633 pg/mL. He underwent treatment with six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) followed by high dose melphalan (140 mg/m²) with stem cell transplantation. He achieved a complete hematologic response (CR), with elimination of his lymphoplasmacytic clone and markers of plasma cell dyscrasia and with renal and cardiac response that persisted for 6 years after treatment.

Six years after the initial diagnosis of AL amyloidosis, he developed progressive exertional dyspnoea and echocardiogram showing increasing IVSd with worsening LVEF of 25%.

He continued with haematologic complete response at this time without recurrence of lymphoma. In view of continued hematologic CR and new cardiomyopathy, an endomyocardial biopsy (age 76 years) revealed amyloid deposition by Congo red staining. Microdissection and liquid chromatography with laser capture tandem mass spectrometry identified transthyretin protein as the precursor amyloid protein. Serum isoelectric focusing and genetic testing demonstrated normal DNA sequence, confirming wild-type TTR amyloid cardiomyopathy.

The patient was enrolled in a clinical trial examining the effect of a TTR protein stabilizer, tafamidis, on ATTR amyloid cardiomyopathy (Clinicaltrials.gov identifier: NCT01994889). Progressive heart failure and conduction disease led to recurrent syncope episodes, prompting placement of a pacemaker. Shortly thereafter, the patient developed necrotizing fasciitis complicated by acute renal and respiratory failure which ultimately led to his death.

Case 2

A 63-year-old man was diagnosed with AL amyloidosis with renal and liver involvement with an underlying lambda plasma cell dyscrasia by renal biopsy. Immunofluorescence studies on renal biopsy showed 4+ staining for lambda light chains. His plasma cell dyscrasia markers showed serum and urine IFEs with lambda monoclonal protein. A bone marrow biopsy revealed 5% lambda-restricted lambda restricted plasma cells, diagnosing lambda AL amyloidosis. His end organ dysfunction was characterized by urine protein excretion of 3.7 g/24 h, serum albumin of 2.7 g/dL, alkaline phosphatase of 178 U/mL. He underwent treatment with 18 months of oral with melphalan and prednisone with a total melphalan dose of 576 mg from September 1995 to May 1997. He obtained a complete hematologic response and an organ response, with reduction in liver size, normalization of alkaline phosphatase and disappearance of his proteinuria. These responses were durable and maintained for over 20 years.

Twenty-one years after the initial diagnosis of AL amyloidosis, he endorsed a few infrequent episodes of palpitations. BNP and troponin levels were borderline elevated (159 pg/mL and 0.049 ng/mL respectively) from a normal baseline. Echocardiogram showed interventricular septal diameter of 17 mm, LVEF of 48%, and a restrictive LV-filling pattern. With progression in wall thickness in addition to new systolic and diastolic dysfunction in the absence of any significant cardiac history, he was evaluated with technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy. This showed increased myocardial uptake of the radiotracer, with a Perugini visual score of three and heart-to-contralateral

lung ratio (H/CL) of 1.6, consistent with ATTR cardiac amyloidosis. All haematologic parameters suggested a continued hematologic CR of his AL amyloidosis. He underwent right ventricular endomyocardial biopsy which demonstrated amyloidosis by Congo red staining. Liquid chromatography and tandem mass spectrometry confirmed amyloid deposition in the myocardial tissues which was transthyretin (ATTR)-type. TTR gene sequencing documented normal TTR DNA sequence, confirming ATTR wild-type cardiac amyloidosis in the setting of systemic AL amyloidosis in complete haematologic response for 20 years. Given his normal renal function and volume status, he was started on Diflunisal 250 mg twice daily as a transthyretin tetramer stabilizer, which he has been continuing to take currently without any significant progression of his cardiac amyloidosis.

This report aims to highlight the importance of accurate typing to determine the nature of the amyloidogenic protein in patients with clinical presentations that could be consistent with several types of amyloidosis. Although both of our patients had biopsy-proven AL amyloidosis, they achieved a hematologic CR after treatment with appropriate chemotherapeutic agents. Many years later, both developed symptoms of heart failure, despite continuing to be in a hematologic CR. Understanding the nature and relevance of ATTRwt enabled us to pursue additional tests. Both patients were eventually found to have endomyocardial biopsy proven cardiac ATTRwt amyloidosis and were treated with regimens that are specific for this type of amyloidosis. It is also important to note the pitfalls in the diagnostic utility of imaging with bone markers in ATTR cardiomyopathy [8].


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