True, true unrelated? Coexistence of Waldenström macroglobulinemia and cardiac transthyretin amyloidosis

Waldenström's macroglobulinemia (WM) is an indolent disorder that may not always require treatment. Among the indications for treatment is the co-existence of light chain (AL) amyloidosis,[1] reported to affect nearly 3% of patients.[2] In a multicenter study of 72 individuals with IgM-related amyloidosis (in whom criteria for WM were met in 75%), 69 individuals were classified as AL amyloid and 3 as reactive (AA) amyloidosis. None were diagnosed as having transthyretin amyloidosis (ATTR).[3] This publication, and other published series, was comprised of patients in whom amyloid typing was done prior to the widespread use of mass spectrometry (MS), and thus was subject to inaccuracy.

Wild-type transthyretin amyloidosis (ATTRwt) was previously considered a rare form of amyloidosis.[4] However, over the last decade, concordant with advances in imaging modalities, such as ^{99}technetium-labeled scintigraphy (Tc-PYP), it is now recognized as far more common than previously described.[5] As WM tends to occur in an older population in which ATTR is prevalent, it might be expected that some WM patients with evidence of cardiac amyloidosis, could have unrelated ATTRwt amyloidosis. In this report, we describe our single-center experience with WM-associated cardiac amyloidosis highlighting 4 cases of WM with co-existent ATTR cardiomyopathy.

Consecutive cases of WM with suspected cardiac amyloidosis referred for evaluation to the Brigham and Women's Hospital Cardiac Amyloidosis Program between 2012 and 2016 were reviewed. All patients had been evaluated by an expert in WM (JJC). The diagnosis of WM was based on the findings of an IgM monoclonal gammopathy and features of lymphoplasmacytic lymphoma in the bone marrow.[6] Cardiac AL amyloidosis was diagnosed based on endomyocardial biopsy (EMB) with positive Congo red or sulfated Alcian blue staining followed by immunohistochemistry, or cardiac imaging features of amyloidosis with known extra-cardiac amyloidosis. ATTR amyloidosis was diagnosed based on EMB or on a typical echocardiogram and a strongly positive (Tc-PYP) scan, per recent guidelines.[7] Genetic testing was performed to detect TTR variants in ATTR patients.

Fourteen patients with WM and cardiac amyloidosis were identified, of whom 10 were diagnosed as AL and 4 as ATTR amyloidosis. Baseline characteristics of the two groups are provided in Table 1. The patients with ATTR (Table 2) are the focus of this report, and are described in detail:

Patient 1. A 75-year-old Caucasian male presented with symptoms of congestive heart failure. He was diagnosed with WM (IgM-kappa) 4 years prior to presentation and IgM levels had remained stable after an initial course of rituximab. Echocardiography showed severe left ventricular (LV) thickening, and EMB revealed amyloid deposits, which stained positive by immunohistochemistry for kappa light chains and negative for TTR; an initial diagnosis of AL amyloidosis was made. Due to his age, marked LV thickening and isolated cardiac involvement (no proteinuria, organomegaly or capillary fragility), the clinical suspicion for ATTRwt remained high. Tc-PYP imaging demonstrated an intense uptake, strongly suggestive of ATTR. MS of the EMB confirmed ATTR amyloidosis and genetic testing did not reveal a TTR mutation. Over 14 months of follow up, he has had gradually progressive dyspnea, managed by up-titration of diuretics.

Patient 2. An 80-year-old Caucasian male with IgM-lambda WM presented with fatigue and shortness of breath. An ejection systolic murmur and a ruptured biceps tendon[8] were noted. Echocardiography revealed mild aortic stenosis with a disproportionate LV thickening, raising the possibility of amyloidosis. EMB confirmed amyloidosis, but immunohistochemistry was indeterminate. MS confirmed ATTRwt, and genetic testing did not reveal any TTR mutation. He has remained clinically stable over 7 months of follow up.

Patient 3. A 73-year-old Caucasian male with IgM-lambda WM developed syncope and angina. An echocardiogram revealed severe LV thickening. EMB showed amyloid deposits, but immunohistochemistry was equivocal, staining positive for both lambda light chains and TTR. He had no signs of systemic involvement – namely, no proteinuria, macroglossia, organomegaly or bruising. Tc-PYP scan of the heart was strongly positive, highly suggestive of TTR. Genetic testing did not reveal any TTR mutation. Over 17 months of follow up, he has remained well without any therapy directed against WM, consistent with the expected natural history of ATTRwt.

Patient 4. A 78-year-old Caucasian male with history of extensive atherosclerosis presented with facial numbness suggestive of a transient ischemic attack. An echocardiogram revealed moderate LV thickening, suspicious for cardiac amyloidosis. Lab work revealed an IgM-lambda monoclonal gammopathy and normal serum viscosity. Bone marrow biopsy revealed lymphoplasmacytic lymphoma. Tc-PYP scan revealed intense uptake, but the patient refused EMB. The constellation of his symptoms and age made ATTRwt the most likely possibility. He has remained clinically stable, over 3 years of follow up.

In this case series, we report, to our knowledge, the first description of ATTR amyloidosis among patients

Table 1. Baseline characteristics stratified by sub-type of amyloidosis.

Factor	AL	ATTR
N	10	4
Age (years), median (IQR)	73.5 (66, 80)	78.5 (75, 81.5)
Male, N (%)	6 (60%)	4 (100%)
Mortality	5 (50%)	0 (0%)
IgM (mg/dL), median (IQR)	3344 (1770, 3875)	791 (745, 1853)
M protein (g/dL), median (IQR)	1.9 (0.6, 2.1)	0.6 (0.5, 0.6)
BUN (mg/dL), median (IQR)	23 (22, 34)	24.5 (22, 31.5)
Creatinine (mg/dL), median (IQR)	1 (0.9, 1.5)	1.2 (1.1, 1.2)
Free K (mg/L), median (IQR)	11.4 (7.2, 27.1)	33.1 (32, 47)
Free L (mg/L), median (IQR)	88.2 (13.5, 137)	28.9 (26.5, 43.1)
dFLC (mg/L), median (IQR)	110.8 (57.9, 144.2)	15.6 (6.4, 26.2)
K/L ratio, median (IQR)	0.1 (0.1, 2)	1.2 (0.9, 1.6)
NT-proBNP (pg/mL), median (IQR)	2956 (857, 4845)	2486 (2028, 3085)
Troponin T (ng/mL), median (IQR)	0.03 (0.02, 0.05)	0.04 (0.02, 0.06)
MYD88 L265P*	4/4	1/3
LV thickness (mm)	13 (13,15)	17 (16, 20)

IQR: Interquartile range; BUN: blood urea nitrogen; Free K: kappa free light chain; Free L: lambda free light chain; dFLC: difference between affected and unaffected free light chain; NT-proBNP: N terminal pro brain natriuretic peptide; WT: wild-type. *mutation status was missing in 7.

Table 2. Characteristics at the time of ATTR diagnosis.

Case	Age (years) / Sex	IgM (mg/dL)	M protein (g/dL)	IgM isotype	Free K (mg/L)	Free L (mg/L)	NT-pro BNP (pg/mL)	Troponin T (ng/mL)	MYD88 mutation	PYP	IVS (mm)	Mass-spectrometry	ATTR
1	76 / M	2908	0.57	Kappa	60	30.8	2581	0.07	WT	3	17	ATTR	WT
2	80 / M	784	0.6	Lambda	32.2	55.4	2392	0.01	Unknown	2	23	ATTR	WT
3	74 / M	798	0.68	Lambda	31.8	27	3590	0.03	L265P	3	17	NP	WT
4	81 / M	706	0.34	Lambda	34	26	1664	0.04	WT	2	15	NP	WT

M: Male; Free K: Kappa free light chain; Free L: Lambda free light chain; NT-proBNP: N terminal pro brain natriuretic peptide; WT: wild-type; NP: Not performed; PYP: Grade of ^{99}technetium-labeled scintigraphy; IVS: Interventricular septum thickness. Reference ranges: NT-proBNP – <1800 pg/mL for age >75 years and <900 pg/mL for age 50-75 years. Troponin-T: <0.01 ng/mL. Free K: 3.3-19.4 mg/L. Free L: 5.7-26.3 mg/L. IgM: 40-230 mg/dL.

with WM. Of the 14 WM patients with cardiac involvement referred to us, nearly one third were diagnosed with ATTR cardiomyopathy. Immunohistochemistry of cardiac biopsy was unhelpful or misleading in cases in whom it was performed. Notably, the dFLC among patients with ATTR was low compared with AL; this may serve as a potential clue raising suspicion of ATTR in patients with imaging or clinical features suggestive of amyloidosis. However, this observation will need to be validated by larger studies.

Precisely identifying the sub-type of amyloidosis in WM is critical, as a diagnosis of AL amyloidosis is an indication for initiating therapy[1] and recognition that AL amyloidosis was not present resulted in withholding of chemotherapy in some of our cases. ATTRwt is more common than previously recognized and may result not only in diastolic heart failure but may also be a cause of lumbar spinal stenosis and ruptured biceps tendon.[5,8-10] For unclear reasons, there is a higher than expected prevalence of monoclonal gammopathy among these patients, and this may confound precise diagnosis.[11] As ATTRwt is a disorder of older individuals,[12,13] it will likely coexist with WM, though unrelated in etiology. It is very possible that ATTR was unrecognized in earlier series due to reliance on immunohistochemistry which, as seen in our patients, may be inaccurate in some cases.[15-17] Radiotracers such as ^{99}Tc-PYP can detect ATTR without the need of a tissue biopsy, and have now become widely used in diagnosis. In a multi-national study, a grade 2/3 radiotracer uptake was 100% specific for ATTR in the absence of a monoclonal protein.[7] Even in the presence of a monoclonal protein, as in these patients, the specificity of a strongly positive scan for the presence of ATTR remains high, at 97%.

MS of the amyloid deposits is now considered the "gold-standard" for correct identification of amyloid subtype, and the use of this technique has highlighted the pitfalls of immunohistochemistry-related amyloid typing.[11,14,15] In our series, an incorrect diagnosis of AL amyloidosis was made by immunohistochemistry in one patient and correctly identified by MS as ATTRwt. Two additional patients with equivocal immunohistochemistry had precise diagnosis of ATTR by MS. Although none of the 10 patients with a final diagnosis of AL amyloidosis had MS, most of them had other non-cardiac major organ involvement, which is a feature of AL and not of ATTR. Nevertheless, it is possible that some may have had ATTR and these patients tended to have been seen at an earlier date, when Tc-PYP scanning was not widely used, and the high prevalence of ATTR not appreciated. There is a small possibility that AL and ATTR was co-existent in some patients, however, none of the patients with mass-spectrometry had evidence of both types of deposits, and these patients did not fit the clinical picture consistent with AL amyloidosis (no signs of other organ involvement) and have remained stable without anti-plasma cell therapy.

In summary, we report the first cases of WM and co-existent ATTR amyloidosis. It is always imperative to accurately define the sub-type of amyloidosis, as treatment pathways are vastly different. This is even more relevant for WM, as a correct diagnosis of the amyloid type can affect the decision to either initiate or withhold chemotherapy.

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