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Prevalence of Monoclonal Gammopathy in Wild-Type Transthyretin Amyloidosis

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Abstract

Objective: To evaluate the prevalence of monoclonal gammopathy (MG) in patients with wild-type transthyretin amyloidosis (ATTRwt) (formerly known as senile amyloidosis).

Patients and Methods: We retrospectively analyzed the serum protein electrophoresis and serum immunofixation results, free light chain (FLC) levels, and renal function of 113 consecutive patients with ATTRwt seen at the Brigham and Women's Hospital's Cardiac Amyloidosis Program between February 21, 2006, and November 9, 2016. Monoclonal gammopathy was defined as a monoclonal protein present in the serum. Light chain MG was defined as an abnormal serum FLC κ/λ ratio with an elevated FLC level in the absence of a monoclonal protein. In patients with renal dysfunction, the renal FLC reference range was used.

Results: The mean age of the population was 75 years, 3 of the 113 patients (3%) were female, and 110 (97%) were white. Monoclonal gammopathy was present in 26 patients (23%), 24 of whom had monoclonal protein present and 2 others who met criteria for light chain MG. Most clones (12 of 20 [60%]) were λ restricted. Another 7 patients had an abnormal FLC κ/λ ratio in the setting of renal dysfunction.

Conclusion: In this study, MG was present in 23% of patients with ATTRwt. The finding of MG or an abnormal FLC κ/λ ratio in an elderly man may cause diagnostic confusion during subtyping of amyloidosis. A high degree of clinical suspicion for ATTRwt and precise tissue typing using mass spectrometry may overcome such diagnostic challenges.

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Monoclonal gammopathy (MG) of undetermined significance (MGUS) is a well-recognized hematologic abnormality characterized by overproduction of specific immunoglobulin proteins by a clonal population of plasma cells. Monoclonal gammopathy of undetermined significance can progress to multiple myeloma or related plasma cell disorders including light chain (AL) amyloidosis, although risk of progression is low, with 1% of patients per year experiencing progression to multiple myeloma and even fewer to AL amyloidosis.[1,2] Monoclonal gammopathy of undetermined significance demonstrated increasing prevalence with age in the Olmsted County, Minnesota, population, an almost exclusively white cohort; 3% of patients between the ages of 50 and 69 years, 5% between the ages of 70 and 84 years, and 7.5% of patients aged 85 years and older had MGUS (detected by electrophoresis and subsequent immunofixation).[3] If the definition of MGUS is expanded to include individuals with an elevated free light chain (FLC) level and abnormal FLC κ/λ ratio in the absence of a monoclonal protein, defined as light chain MGUS, the total MGUS population increases by approximately one-fifth.[4]

The hallmark of AL amyloidosis is the finding of an MG, present in greater than 90% of patients and usually associated with an abnormal FLC κ/λ ratio. The importance of not relying solely on the finding of an MG to establish a diagnosis of AL amyloidosis, in a patient with biopsy-proven amyloidosis is underscored by results of proteomic analyses, which have demonstrated that individuals with an MG and abnormal FLC κ/λ ratio may, on occasion, have unrelated wild-type transthyretin amyloidosis (ATTRwt) (formerly known as senile amyloidosis), even when immunochemical staining suggests otherwise.[5]

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Several reports have noted a higher than expected prevalence of MG in the ATTRwt population, but this finding has not been precisely defined. Among 102 patients with ATTRwt (mean age, 73 years) studied at the National Amyloidosis Centre in London, United Kingdom, 15% had a monoclonal protein in the serum or urine, and an additional 9% had an abnormal serum FLC κ/λ ratio suggestive of light chain MG (LC-MG).[6] In contrast, a lower prevalence of 10% based on only serum protein electrophoresis (SPEP) was reported by Connors et al[7] in a group of 121 patients seen over a period of 20 years. In a retrospective study of endomyocardial biopsy–proven cardiac amyloidosis, an MG was present in 20 of 81 patients with ATTRwt (25%), and an additional 5 patients (6%) had an abnormal serum FLC κ/λ ratio suggestive of LC-MG; all cases were confirmed with mass spectrometry.[8] In a multicenter study with data pooled from several centers (including the National Amyloidosis Centre, London; Boston University, Boston, Massachusetts; and Mayo Clinic, Rochester, Minnesota), an MG was found in 19% of patients with transthyretin amyloidosis.[9] The patients in this study potentially overlap with those reported by the individual centers referenced previously.[6-8] None of these studies reported details of the predominant abnormal FLC in those defined as having a gammopathy.

Unless a physician is aware of this overlap of MG between both types of amyloid, there is a risk of misdiagnosis of the amyloid subtype. In light of the lack of precise details about the MG in transthyretin amyloidosis in previous studies, we sought to examine this issue by evaluating the prevalence of MG in a consecutive series of patients with ATTRwt amyloidosis, characterizing their FLC levels and investigating the influence of renal dysfunction.

TABLE 1. Baseline Characteristics of the 113 Study Patients[a,b,c]

Variable	No MGUS (n=87)	MGUS (n=26)	*P* value
Age (y)	74.0 (70.0-81.0)	78.0 (73.0-80.0)	.16
Female	2 (2)	1 (4)	.56
BUN (mg/dL)	26.0 (20.0-35.0)	23.0 (17.0-32.0)	.30
Creatinine (mg/dL)	1.2 (1.0-1.6)	1.1 (1.0-1.6)	.47
κ FLC (mg/L)	21.6 (16.7-29.0)	24.5 (16.1-51.3)	.16
λ FLC (mg/L)	19.4 (14.0-23.7)	20.2 (14.0-26.3)	.96
FLC κ/λ ratio	1.2 (1.0-1.4)	1.6 (1.0-1.9)	.015
Type of MGUS			NA
Monoclonal protein	NA	24 (92)	
Light chain	NA	2 (8)	
eGFR (mL/min/1.73 m^2)	57.5 (41.6, 73.0)	61.7 (43.9, 70.6)	.54
Severity of renal dysfunction (eGFR, mL/min/1.73 m^2)			.34
15-30	5/85 (6)	0 (0)	
30-60	43/85 (51)	11 (42)	
>60	37/85 (44)	15 (58)	
Elevated FLC	22.9 (17.5-29.1)	31.1 (18.8-68.2)	.03
Immunoglobulin type			NA
A	NA	2/20 (10)	
G	NA	14/20 (70)	
M	NA	4/20 (20)	
Immunoglobulin light chain isotype			NA
κ	NA	8/20 (40)	
λ	NA	12/20 (60)	

[a]BUN = serum urea nitrogen; eGFR = estimated glomerular filtration rate; FLC = free light chain; MGUS = monoclonal gammopathy of undetermined significance; NA = not applicable.
[b]Data are presented as median (interquartile range) or No. (percentage) of patients.
[c]SI conversion factors: To convert BUN value to mmol/L, multiply by 0.357; to convert creatinine value to μmol/L, multiply by 88.4.

PATIENTS AND METHODS

This retrospective study included 113 consecutive patients with ATTRwt seen at Brigham and Women's Hospital's Cardiac Amyloidosis Program between February 21, 2006, and November 9, 2016. Wild-type transthyretin amyloidosis was diagnosed on the basis of positive findings on biopsy and/or technetium Tc 99m pyrophosphate scan in the presence of typical echocardiographic or cardiac magnetic resonance imaging appearance.[9]

Monoclonal gammopathy was detected using SPEP and immunofixation and serum FLC assay. Urinary protein electrophoresis/immunofixation was not routinely performed, and it is possible that a small number of individuals with a monoclonal protein only in the urine were missed. Because the FLC κ/λ ratio may be affected by renal function, we defined the entity of LC-MG as an abnormal serum FLC κ/λ ratio with elevated FLC level in the absence of a monoclonal protein. In patients with renal dysfunction, those with FLC κ/λ ratios outside the renal reference range were considered to have LC-MG.[10]

Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation.[11] The normal range of FLC was defined as: κ, 3.3 to 19.4 mg/L; λ, 5.7 to 26.3 mg/L; and FLC κ/λ ratio, 0.26 to 1.65 (renal