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The diagnosis and characteristics of renal heavy-chain and heavy/light-chain amyloidosis and their comparison with renal light-chain amyloidosis

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Little is known about the rare entities of heavy- and light-chain amyloidosis (AHL) and heavy-chain amyloidosis (AH). Here, we report the renal and hematological characteristics, pathology, and outcome of 16 patients with renal AH/AHL (5 with AH and 11 with AHL) and compare them with 202 patients with renal light-chain amyloidosis (AL) diagnosed during the same time period. All cases were diagnosed by kidney biopsy that showed Congo red–positive deposits. Amyloid typing was done by laser microdissection and mass spectrometry (LMD/MS) on 12 patients or by immunofluorescence on four patients. All patients with renal AH/AHL were Caucasians, with a male/female ratio of 2.2 and a median age at biopsy of 63 years. Compared with patients with renal AL, those with renal AH/AHL had less frequent concurrent cardiac involvement, higher likelihood of having circulating complete monoclonal immunoglobulin, lower sensitivity of fat pad biopsy and bone marrow biopsy for detecting amyloid, higher incidence of hematuria, and better patient survival. The hematological response to chemotherapy was comparable with renal AL. In 42% of patients, AH/AHL could not have been diagnosed without LMD/MS. Thus, renal AH/AHL is an uncommon and underrecognized form of amyloidosis, and its diagnosis is greatly enhanced by the use of LMD/MS for amyloid typing. The accurate histological diagnosis of renal AH/AHL and distinction from AL may have important clinical and prognostic implications.

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Amyloidosis is an uncommon group of diseases characterized by extracellular deposition of insoluble fibrils resulting from abnormal folding of proteins. Amyloid deposits exhibit a beta sheet configuration on X-ray diffraction and are identified histologically by their diagnostic apple green birefringence when stained with Congo red and viewed under polarized light. More than 20 precursor proteins of amyloid have been identified so far. Immunoglobulin (Ig)-related amyloidosis (also referred to as 'primary amyloidosis') is the most common type of systemic amyloidosis in the developed countries with an incidence of 6.1–10.5 cases per million person-years.[1] Renal involvement, characterized by proteinuria with or without renal insufficiency, occurs in close to three-quarters of patients with Ig-related amyloidosis and is the most common presentation in this condition.[2,3] In the vast majority of cases of Ig-related amyloidosis, the amyloid fibrils consist of fragments of monoclonal light chains and hence the name 'AL amyloidosis' (AL). Prior reports found that the deposits in AL were exclusively composed of the variable domain of light chain (V_L), particularly the V_L VI variability subtype,[4,5] whereas more recent studies demonstrated that fragments of the constant domain of light chain (C_L) are constituents of AL deposits.[6–8]

Little is known about the even rarer entities of heavy- and light-chain amyloidosis (AHL), in which the amyloid fibrils are derived from fragments of the Ig heavy chain and light chain, and heavy-chain amyloidosis (AH), in which the fibrils originate from fragments of the Ig heavy chain only. To date, there have been four reported cases of AHL[9–11] and 12 cases of AH,[11–21] all of which were published in a single case report format, except for a earlier report of four patients from our group.[11] All reported cases of AH or AHL (AH/AHL), except two,[9,14] affected the kidney. The diagnosis of renal AH/AHL in these cases was based on the Congo red positivity of deposits and the detection in amyloid deposits of one Ig heavy chain only (in AH) or one Ig heavy chain and one Ig light chain (in AHL) by immunofluorescence,[10,15–17] amino-acid sequence

analysis,[12,13,19,20] immunoelectron microscopy[16] or, more recently, by laser microdissection and mass spectrometry (LMD/MS).[11,21]

Most reported cases of AH/AHL occurred in patients with dysproteinemia who had a circulating paraprotein with or without bone marrow evidence of plasma cell dyscrasia or lymphoma; therefore, one would wonder whether renal AH/AHL is any different from renal AL clinically. In this study, we report the renal characteristics, hematological characteristics, pathology, and outcome of 16 patients with renal AH/AHL and compare them with 202 patients with renal AL diagnosed by renal biopsy during the same period of time.

RESULTS

Clinical features

Table 1 shows the demographics and hematological characteristics of the group of patients with renal AH/AHL and the group of patients with renal AL. The cohort of patients with AH/AHL consisted of 11 men and 5 women, all Caucasians, with a median age of 63 years (range 50–77 years). An additional organ involved by amyloidosis (based on clinical evidence) was present in eight (50%) patients, including heart in three patients (#AH4, AH5, AHL8), liver in two patients (#AHL10, AHL11), nerves in two patients (#AH1, AHL3), and gastrointestinal tract (also biopsy-proven) in one (#AHL1), but none had two or more additional organs involved. Cardiac involvement was significantly less common in renal AH/AHL compared with renal AL ($P=0.02$). Furthermore, fat pad biopsy and bone marrow biopsy were less likely to be positive for amyloid in renal AH/AHL than in renal AL ($P<0.001$, $P=0.014$, respectively). Patients with renal AH/AHL were more likely to have $\geqslant$30% light-chain-restricted plasmacytosis in the bone marrow (i.e., having multiple myeloma) than those with renal AL ($P=0.017$). The frequency of positive serum protein electrophoresis/serum immunofixation or urine protein electrophoresis/urine immunofixation for paraprotein was not statistically different; however, AH/AHL patients were more likely to have whole monoclonal immunoglobulin on serum protein electrophoresis ($P=0.038$) or urine protein electrophoresis ($P=0.011$). The percentages of patients with abnormal or markedly abnormal serum-free light-chain ratio were not statistically different among the two groups. None of the patients with AH/AHL had biclonal gammopathy.

Table 2 shows the clinical renal characteristics at kidney biopsy of the group of patients with renal AH/AHL and the group of patients with renal AL. There was no statistical difference among the two groups with regard to the 24 h urine protein, percentage of albumin on urine protein electrophoresis, serum albumin level, percentage of patients with full nephrotic syndrome, serum creatinine level, or estimated glomerular filtration rate. Microscopic hematuria was more common in renal AH/AHL compared with renal AL ($P=0.013$).

Table 3 shows the follow-up data of the group of patients with renal AH/AHL and the group of patients with renal AL. Follow-up patient survival data were available on 15 of the 16 (94%) patients with renal AH/AHL and in 192 of the 202 (95%) patients with renal AL. The median duration of the follow-up was 22 months for the renal AH/AHL group and 20 months for the renal AL group ($P=0.22$). Patients with renal AH/AHL tended to have a better renal response to therapy than those with renal AL ($P=0.02$). End-stage renal disease was reached by 7% of the AH/AHL patients and 13% of the AL patients. Time to end-stage renal disease was similar and not reached by either group ($P=0.17$). There were no statistical differences between the two groups with regard to the type of therapy received, partial hematological response to therapy, or very good hematological response to

Table 1 | Demographics and hematological characteristics

	AH/AHL	AL	*P* value
No. of patients	16	202	
Gender: male/female	11/5 (69%/31%)	126/76 (62%/38%)	0.79
Age, median (range)	63 (50–77)	62 (36–86)	0.92
Additional organ involvement	8 (50%)	126 (62%)	0.42
Cardiac involvement	3 (19%)	100 (50%)	0.02
% Of plasma cells in bone marrow, median (IQR)	9 (5–26)	6 (5–10)	0.56
$\geqslant$30 Plasma cells	4 (25%)	11/198 (6%)	0.017
Positive SPEP/SIF for paraprotein	14 (88%)	158/200 (79%)	0.54
Presence of whole monoclonal protein on SPEP	13 (81%)	108/200 (54%)	0.038
Positive UPEP/UIF for paraprotein	12/15 (80%)	158/189 (84%)	0.72
Presence of whole monoclonal protein on UPEP	10/15 (67%)	61/189 (32%)	0.011
Abnormal serum FLC ratio (<0.26 or >1.65)	9/11 (82%)	150/188 (80%)	1.00
Markedly abnormal FLC ratio (<0.125 or >8)	5/11 (45%)	100/188 (53%)	0.76
Positive bone marrow for amyloid	6/15 (40%)	135/183 (74%)	0.014
Positive fat pad biopsy for amyloid	2/13 (15%)	105/145 (72%)	<0.001

Abbreviations: AH/AHL, heavy-chain amyloidosis/heavy- and light-chain amyloidosis; AL, light-chain amyloidosis; FLC, free light chain; IQR, interquartile range; SPEP/SIF, serum protein electrophoresis/serum immunofixation; UPEP/UIF, urine protein electrophoresis/urine immunofixation.