Clinical features of patients with immunoglobulin light chain amyloidosis (AL) with vascular-limited deposition in the kidney

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Abstract
In the kidney, immunoglobulin light chain amyloidosis (AL) can be deposited in vascular-limited AL (V-AL) or diffuse (D-AL) pattern. These patterns are associated with different clinical presentations. A nested case study was performed to describe these differences. V-AL was defined by the vascular-limited deposits. Cases were matched for age, sex and date of renal biopsy. There were 12 cases of V-AL (mean age 61 ± 11 years) and 24 cases of D-AL. Median follow-up was 26 months for V-AL and 38 months for D-AL, P = 0.14. Lambda was more common in D-AL (83.3%) than V-AL (50%, P = 0.04). Cardiac function was similar between the two groups. V-AL patients presented with lower renal function (serum creatinine = 2.1 versus 1.3 mg/dL, P = 0.02; estimated glomerular filtration rate 31 versus 59 mL/min/1.73m², P = 0.01 and creatinine clearance 38.5 versus 64 mL/min/1.73m², P = 0.02, respectively). Proteinuria was low grade in V-AL [0.4 (0.09–0.98) g/day] compared to nephrotic range in D-AL patients [8.0 (0.2–22) g/day, P < 0.001]. Stem cell transplantation was performed on 62.5% of the D-AL but on only 25% of the V-AL, P = 0.08. Median survival was longer in patients with D-AL (77.2 months) versus V-AL (40.6 months, log-rank P = 0.02). Our study found that V-AL patients presented with more severe renal insufficiency and less proteinuria than D-AL. There was a preference for λ light chain in the D-AL that was not noted in the V-AL. Patients with D-AL in this study had a longer median survival but most of them were stem cell transplantation candidates.

Keywords: AL; amyloidosis; proteinuria; renal insufficiency; vascular

Introduction
Amyloidosis represents a group of diseases characterized by protein misfolding and the extracellular deposition of the resultant β-sheet fibrils [1]. These fibrils have the unique ability to absorb Congo red dye and give off an apple-green birefringence when viewed under polarized light. In industrialized countries, monoclonal immunoglobulin light chain amyloidosis (AL) is the most common form, which is the sequela of a plasma cell dyscrasia [2]. The kidney is the most frequently affected organ. In a study...
of 474 patients, 73% presented with proteinuria and nearly half with renal insufficiency [3]. In a separate study of 145 patients, end-stage renal disease (ESRD) was much more common in those who presented with renal manifestations than those without (42 versus 5%) [4]. A recent Italian study of biopsy-proven renal AL patients showed a similar rate (39%) of ESRD and median survival on dialysis [5]. Life expectancy after initiation of dialysis was short with a median survival of 10.4 months with 20% dying within the first month of initiating dialysis.

Since renal manifestations are so common in AL, the diagnosis is often made by renal biopsy [6]. On light microscopy, amyloid is identified as an amorphous eosinophilic material that is weakly positive to negative on periodic acid Schiff stain and typically negative on silver methenamine stain. All types of amyloid demonstrate apple-green birefringence when viewed under polarized light after Congo red staining and the fibrils have an average diameter of 8–12 nm. In most cases, the mesangium is the first place where amyloid deposition occurs. In more advanced cases, amyloid deposits can be seen throughout the glomeruli, interstitium and vascular compartments. AL amyloidosis is diagnosed by demonstrating light chain restriction by immunofluorescence staining or immunohistochemistry in the amyloid deposits. In rare cases, the deposits may be vascular limited [7]. The vascular-limited deposition has been described in AA (serum amyloid A) but little has been reported about this pattern in AL [8, 9]. The aim of this study is to compare the clinical features of patients with vascular-limited AL (V-AL) versus those with diffuse renal involvement (D-AL).

Materials and methods

This study was approved by the Institutional Review Board at the Mayo Foundation in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act guidelines. The Renal Biopsy Database at Mayo Clinic from July 1994 to November 2009 was queried for diagnosis of amyloidosis. Of the 316 renal biopsies with amyloidosis, 234 were found to be AL. Amyloidosis was diagnosed by Congo red staining and the fibrils have an average diameter of 8–12 nm. In most cases, the mesangium is the first place where amyloid deposition occurs. In more advanced cases, amyloid deposits can be seen throughout the glomeruli, interstitium and vascular compartments. AL amyloidosis is diagnosed by demonstrating light chain restriction by immunofluorescence staining or immunohistochemistry in the amyloid deposits. In rare cases, the deposits may be vascular limited [7]. The vascular-limited deposition has been described in AA (serum amyloid A) but little has been reported about this pattern in AL [8, 9]. The aim of this study is to compare the clinical features of patients with vascular-limited AL (V-AL) versus those with diffuse renal involvement (D-AL).

Results

Twelve or 5.1% of the total cases had only vascular-limited renal amyloidosis. Twenty-four controls were selected for age, sex and date of biopsy match. Their mean age at baseline was 57 (range 46–79) years. Males outnumbered females 2:1. The median follow-up was 26 (0–63) months for V-AL and 38 (0–110) months for D-AL, P = 0.14. Of the 36 patients, 3 patients (8.3%) had diabetes, 2 patients had hypothyroidism, 2 patients had solid tumors. Seven patients (20.6%) had multiple myeloma. No significant differences were found in the comorbidities between the two groups.

Hematologic parameters

In the V-AL patients, the distribution of κ and λ was 50:50. However, in patients with D-AL, there was a preference toward λ light chain with 83.3% having a λ monoclonal light chain, P = 0.04. In patients with V-AL, one had a monoclonal IgAL, two—IgGk and five—IgGl. In the D-AL group, three had monoclonal IgAl, one—IgDk, three—IgGk, eight—IgGl and three monoclonal λ. Serum monoclonal protein studies (serum protein electrophoresis and immunofixation) were negative in one V-AL and six of the D-AL patients. One patient in each group had a negative urine monoclonal protein study by urine protein electrophoresis and immunofixation. The median bone marrow plasma cell percentage was 8% (1.8–31%) in V-AL and 5% (1–30%) in D-AL, P = 0.06. Plasma cell labeling index was 0% for both groups, P = 0.5. There was a trend toward higher FLC levels in the D-AL but this was not statistically significant. In the κ patients, the median κ FLC was 16.4 (1.3–146) mg/dL in V-AL patients and 37.7 (3.1–270) mg/dL in the D-AL, P = 0.48. In the λ patients, the median λ FLC was 45.1 (1.8–20.3) mg/dL in the V-AL and 11.0 (3.1–58.7) mg/dL in the D-AL, P = 0.37. The reference range for κ FLC was 0.33–1.94 mg/dL, λ FLC was 0.57–2.63 mg/dL and κ:λ ratio was 0.26:1.65.

Fat aspirate was positive in 60% of V-AL and 59% of D-AL patients who had the procedure performed, P = 0.96. In addition, five V-AL patients underwent other tissue biopsies. Amyloid deposits were found in the heart (2 of 3 cases), colon (2 of 3 cases), duodenum (1 of 2 cases), esophagus (0 of 1 case), gastric antrum (1 of 1 case), liver (0 of 1 case), infraorbital tissue (0 of 1 case) and thyroid (1 of 1 case). An autopsy report was available for one V-AL patient. Amyloid deposits were found in the heart (four chambers, valves, intramural vessels, epicardium and endocardium), lungs (vascular and alveolar deposits), spleen (sinusoidal deposits), liver (arterial and portal deposits), pancreas (vascular and mild interstitial deposits), GI tract (mucosal and vascular deposits) and kidneys (vascular deposits).

Cardiac parameters

Echocardiographic findings (EF) were similar between the two groups. The median EF% for V-AL patients was 63
(40–75)% compared with 65 (42–73)% in patients with D-AL, \( P = 0.38 \). Median septal thickness in V-AL patients 13 (8–18) mm compared to 13 (9–18) mm in patients with D-AL, \( P = 0.90 \). No differences were found in the baseline levels of c-TnT between V-AL patients [0.02 (0.01–0.17) ng/mL] and D-AL patients [0.015 (0.01–0.14) ng/mL], \( P = 0.87 \). Similarly, no differences were noted between NT-pro-BNP in these patients. Median NT-pro-BNP was 154 (105–1970) pg/mL in V-AL group and 906 (85–6158) pg/mL, \( P = 0.19 \).

**Renal parameters**

No differences were noted in baseline blood pressure between the two groups. V-AL patients showed a mean baseline SBP of 115.5 ± 24.3, while D-AL patients had a mean baseline SBP of 125.70 ± 24.3 (\( P = 0.26 \)) and a mean baseline DBP of 69.6 ± 13.5 in V-AL and 76.5 ± 15.1 in D-AL (\( P = 0.21 \)). However, baseline Scr was significantly higher in V-AL patients. Their median Scr was 2.1 (0.7–3.7) mg/dL, while median Scr was 1.3 (0.8–3.2) mg/dL in the D-AL patients (Figure 1, \( P = 0.02 \)). This corresponded to a higher baseline eGFR in the D-AL patients. Baseline eGFR was 31 (13–105) mL/min/1.73m² compared to 58.5 (20–84) mL/min/1.73m² in D-AL patients, \( P = 0.008 \). This was corroborated by CrCl data where V-AL patients had a baseline CrCl of 38.5 (13–98) mL/min/1.73m² compared to 63.5 (25–118) mL/min/1.73m² in D-AL patients (\( P = 0.02 \)). The biggest difference between the two groups was in the proteinuria. Patients with V-AL had low-grade proteinuria [0.4 (0.09–0.98) g/day], while D-AL patients had massive proteinuria [8.0 (0.2–22) g/day] (Figure 2, \( P < 0.001 \)). By urine protein electrophoresis, median albumin percentage was 40.0 (22.0–64.0)% in V-AL versus 73.0 (43.0–82.0)% in D-AL patients (\( P < 0.001 \)).

**Last follow-up parameters**

No significant differences were noted in the blood pressure at last follow-up. V-AL patients showed a mean last follow-up SBP of 109.4 ± 23.3, while D-AL patients had a mean SBP of 117.8 ± 19.3, \( P = 0.30 \). Similarly, last follow-up DBP was not statistically different between V-AL patients (66.3 ± 10.2) and D-AL (69.8 ± 10.4, \( P = 0.39 \)). Differences in Scr remained borderline significant at last follow-up (Figure 1). The median Scr in V-AL patients was 2.4 (1.1–4.0) mg/dL, while D-AL patients was 1.4 (0.7–5.1) mg/dL, \( P = 0.055 \). However, eGFR at last follow-up remained significantly different with 26.5 (14–52.1) mL/min/1.73m² in V-AL versus 50 (6–90) mL/min/1.73m² in D-AL, \( P = 0.05 \).

**Treatment and outcomes**

Melphalan + prednisone was the treatment of choice in 31.3% of the patients, followed by dexamethasone alone (12.5%), melphalan + dexamethasone (6.25%), and 3.13% of patients received melphalan + thalidomide + dexamethasone, melphalan + bortezomib + dexamethasone, melphalan + lenalidomide + dexamethasone, melphalan + prednisone + bortezomib, melphalan + prednisone + lenalidomide and vincristine + carmustin + melphalan + cyclophosphamide + prednisone. No treatment was recorded for 31.3% of patients as some were treated elsewhere. No significant differences were found in the treatment plan between V-AL and D-AL patients (\( P = 0.70 \)). Fifteen patients (5 V-AL and 12 D-AL) underwent stem cell transplantation and 5 patients (1 V-AL and 4 D-AL) required dialysis. The median time from the diagnosis to the patient requiring dialysis was 24 (1–97) months. None of the patients underwent renal transplantation. No significant differences were
found in the renal outcome between both groups. There was, however, significant difference in terms of patient survival. Median survival was 77.2 months in patients with D-AL versus 40.6 months in V-AL patients (Figure 3, P = 0.02).

At the time of the study, nine patients had died from each group, P = 0.03.

Discussion

Traditionally, renal amyloidosis is associated with massive proteinuria and renal insufficiency. In a large population of AL patients, the median 24-h urine protein excretion was found to be 1.2 g/day but 36% had proteinuria and renal insufficiency. In a large population of AL patients, the median 24-h urine protein excretion was found to be 1.2 g/day but 36% had proteinuria and renal insufficiency. In a large population of AL patients, the median 24-h urine protein excretion was found to be 1.2 g/day but 36% had proteinuria and renal insufficiency.

In contrast to AA, little is known about vascular-limited renal amyloidosis in AL patients. There are similarities between V-AL and the vascular-limited AA patients. Both groups have significantly lower proteinuria than the patients with glomerular deposits in both types of amyloidosis. The highest level of proteinuria in this study was 1 g/day in contrast to 22 g/day in the D-AL group. Renal function was significantly lower at diagnosis in the V-AL as compared to the D-AL, which was similar to the AA patients with vascular-limited amyloid deposits [9, 10]. However, unlike the AA patients, the D-AL in our study did not have a worse renal prognosis as compared to the V-AL. Moreover, the overall prognosis was actually much worse for the V-AL in this study than the D-AL. The reason for this remains unclear. It is possible that the lack of proteinuria and features of nephrotic syndrome in patients with V-AL may cause delay in diagnosis resulting in more advanced disease. We had tried to avoid the influence of potential differences in treatment by matching the time of diagnosis during the nested case study. There were no significant differences in terms of treatment received between the two groups of patients. The disparity in mortality is even more interesting when one considers that cardiac involvement was similar between the two groups at the time of diagnosis as best we can tell.

To the best of our knowledge, this study represents the largest cohort of vascular-limited renal AL patients. The results of this study show that similar to AA, AL can involve the kidney without significant proteinuria with the only presenting sign being an elevated Scr and decreased eGFR. It is important to recognize this and AL should be in the differential diagnosis when seeing a patient with unexplained renal failure without proteinuria. Monoclonal protein studies from both serum and urine should be performed since neither is 100% sensitive. If either is positive, a renal biopsy should be performed even if the patient has no or little proteinuria. Early referral to an amyloid center would be beneficial as these patients may have a poorer prognosis. Further studies are warranted to better understand the difference in prognosis and to try to determine if different treatment options are needed for the vascular-limited patients.

Conflict of interest statement. None declared.

References


*Received for publication: 20.12.10; Accepted in revised form: 6.6.11*