Leukocyte chemotactic factor 2 (LECT2) amyloidosis presenting as pulmonary-renal syndrome: a case report and review of the literature

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Abstract
Leukocyte chemotactic factor-2 (LECT2) amyloidosis has been described as being associated with kidney disease; however, no clinical manifestations outside of the kidney have been previously reported. We describe a patient presenting with pulmonary-renal syndrome found to have deposition of amyloidogenic LECT2 (ALECT2) within both the lung and the kidney. This case is unique in regard to both the patient’s clinical presentation of pulmonary-renal syndrome in the setting of amyloidosis and the biopsy finding of ALECT2 deposition within the lung. It also emphasizes the importance of tissue diagnosis in such cases, given that amyloidosis was not initially considered in the differential diagnosis.

Keywords: amyloid; lect2; pulmonary-renal syndrome

Background
Amyloidosis represents an uncommon group of disorders which results from abnormal deposition of protein fibrils arranged in cross-β sheet quaternary structures [1]. An expanding list of native proteins has been implicated, with amyloidogenic leukocyte chemotactic factor 2 (ALECT2) being a recent addition [2]. Deposition of ALECT2 within the kidney is a known cause of kidney dysfunction; however, extra-renal manifestations and pulmonary ALECT2 deposition have not been reported. Herein, we report a patient presenting with pulmonary-renal syndrome found to have ALECT2 deposition within both the lung and the kidney.

Clinical report
An 84-year-old Mexican-American man with diabetes mellitus, hypertension, hyperlipidemia and prostatic adenocarcinoma, status-post prostatectomy presented with shortness of breath and fatigue, which had progressed over 2 weeks. Three days prior to presentation, he experienced an acute worsening of his respiratory status, prompting him to seek emergency care. The patient did not report any neurologic symptoms, rash, recent fever or infection. At presentation, he was hypoxic with oxygen saturations of 80% on room air. An arterial blood gas showed a pH 7.43 (reference range 7.35–7.45), partial carbon dioxide of 28 mm Hg (reference range 35–45 mm Hg) and partial oxygen of 61 mm Hg (reference range 80–100 mm Hg) on inspired oxygen of 60%.

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episode of hemoptysis. Shortly after the initiation of hemo-
dialysis, the patient was weaned from positive airway
pressure ventilation. Pulse intravenous methylprednisolone
was initiated and plasmapheresis was started as empiric
therapy for a presumed diagnosis of microscopic polyangii-
tis with diffuse alveolar hemorrhage. Kidney and lung biop-
sies were performed for tissue diagnosis. A bone marrow
biopsy was also obtained which showed no plasma cell
dyscrasia.

The kidney biopsy showed renal cortex containing up to
eight glomeruli per level, of which two were globally scler-
osed. The non-sclerotic glomeruli showed segmental me-
sangial expansion by extracellular amorphous material
which did not stain with Jones methenamine silver stain,
stained weakly on periodic acid Schiff stain, and demon-
strated a gray hue on the trichrome stain. Glomerular cap-
pillaries were patent without hypercellularity and no
fibrinoid necrosis or crescents were identified. The intersti-
tium and walls of arteries and arterioles demonstrated
diffuse infiltration by the same amorphous material. There
were no lesions of vasculitis. A Congo red stain was per-
formed and showed strong staining of the mesangial, in-
terstitial and vascular deposits (Figure 2A). Apple-green
birefringence was demonstrated upon polarization of the
Congo red stain, confirming the presence of amyloid
(Figure 2B).

Immunofluorescence microscopy was performed using
antisera to human immunoglobulin G (IgG), IgA, IgM, C1q,
C3, albumin, fibrinogen and kappa/lambda light chains
(DAKO Corporation - Carpinteria, CA) and graded on a scale
of 0–4+. Weak and smudgy staining (1–2+) was seen in the
interstitium and vessel walls for IgG, IgA, IgM and both
kappa and lambda light chains. There was no significant
staining for C3, C1q, fibrinogen or albumin or evidence of
immunoglobulin restriction. Ultrastructural examination re-
vealed extensive haphazard deposition of fibrils ranging in
thickness from 6–10 nm within the interstitium and focally
within mesangial areas (Figure 2C). The size and distribution
of the fibrils were consistent with amyloid. An immunohis-
tochemical workup was initiated to better classify the
amyloid subtype, which included stains for kappa and
lambda light chains, amyloid A and prealbumin (transthre-
tin), all of which were negative (DAKO Corporation). Further
immunohistochemical evaluation with anti-LECT2 anti-
bodies (performed at Nephropath Laboratories—Little
Rock, AR) demonstrated diffuse positive staining within the
amyloid deposits (Figure 2D).

Due to uncertainty in the lung pathology, wedge biopsies
of the upper, middle and lower lobes of the right lung were
performed. Biopsies showed multifocal, small deposits of
the same extracellular amorphous material within the al-
veolar septa and walls of small and large vessels. These de-
posits were strongly positive on the Congo red stain
(Figure 2E) and demonstrated apple-green birefringence
upon polarization, consistent with amyloid. There were no
lesions of vasculitis. Immunohistochemical staining with
anti-LECT2 antibodies was positive within the amyloid de-
posits (Sigma Life Sciences—St. Louis, MO) (Figure 2F).

In summary, kidney and lung biopsies both demon-
strated deposition of amyloid showing positive immuno-
histochemical staining for LECT2. No lesions of vasculitis
were identified in any of the biopsy specimens and cres-
cents were not seen in the kidney biopsy.

The patient was discharged 36 days after his initial pres-
etation with a creatinine of 203.3 μmol/L (2.3 mg/dL,
eGFR: 27 mL/min/1.73 m²). Steroids were gradually
tapered off at 6 months, and the patient is currently main-
tained on azathioprine. Eight months after his initial pres-
etation, his creatinine clearance improved to 20–25 mL/
min and he no longer required hemodialysis.

Discussion

Leukocyte chemotactic factor 2 (LECT2) is a recently de-
scribed amyloidogenic protein and potential cause of
kidney disease. Originally characterized in 1998, human
LECT2 is predominantly synthesized by hepatocytes. Along
with neutrophil chemotactic properties, it is also believed
that LECT2 plays a role in tissue growth and repair following
damage. The latter function has been proposed given the
similarities between human LECT2 and its bovine counter-
part: chondromodulin-II [3–5]. LECT2 amyloidosis is now a
well-described cause of kidney injury; however, extra-renal
manifestations have not been reported [2]. Since 1971,
when monoclonal light chain became the first chemically
classified amyloid protein, a growing list of amyloidoge-
nic proteins has been amassed, including, but not
limited to, monoclonal light chain (AL), amyloid A protein
(AA), transthyretin (ATTR), apolipoproteins AI (AAtI) and
AII (AAtII), lysozyme (ALys), gelsolin (AGel) and β-2 mi-
croglobulin [6, 7]. The mechanism of amyloidogenesis is
quite variable, including hereditary mutation, protein over-
production and decreased protein excretion. In the case of
ALECT2, the exact mechanism of disease has not been fully
elucidated; however, a genetic component is suspected [1].
The LECT2 gene has been mapped to chromosome 5q31.1–
32 and contains four exons and three introns. The four
exons code for a 151 amino acid protein, which is 133
amino acids in its secreted form [3]. In one published
series, four of four patients with LECT2 amyloidosis who un-
derwent LECT2 gene analysis were identified as homozy-
gous for the G allele, substituting valine at position 40 of
the mature protein for isoleucine, which is found in the A
allele [4]. This single amino acid switch may result in a pro-
Tendency to form amyloid fibrils [4]. The vast majority of re-
ported cases have occurred in patients of Mexican descent,
also supporting a genetic role [8].

Published reports and case series of clinical disease due
to LECT2 amyloidosis have thus far been limited to depo-
sition within the kidney. One report has demonstrated
incidentally discovered ALECT2 within hepatic, splenic, colonic and adrenal tissue [9]. Murphy et al. described a series of 10 patients with kidney-limited LECT2 amyloidosis, representing 2.5% of amyloid cases diagnosed by kidney biopsy over an 8.5-year period. Clinically, patients presented with varying degrees of kidney insufficiency, and the majority presented with only minimal proteinuria in contrast to AL and AA, which often present with nephrotic-range proteinuria. Histologically, ALECT2 deposition was predominantly localized within the interstitium and mesangial regions, although all compartments of the kidney parenchyma may be involved [4,10]. Other published case reports have shown similar clinical and histologic features of ALECT2 amyloidosis [10,11].

Like the kidney, the lung may be involved in systemic amyloidosis with the most frequent subtypes being AL and AA amyloid. ALECT2 has not been previously reported in the lung. Deposition of amyloid within the pulmonary parenchyma is the most common manifestation of amyloidosis within the respiratory system and may occur in a nodular or diffuse pattern [12]. In nodular pulmonary amyloidosis, deposition is typically localized and is often an incidental radiographic finding in the lung periphery [13]. Diffuse pulmonary involvement is most often seen in the setting of systemic AL amyloidosis, and although severe clinical manifestations are not common, hemoptysis and fatal pulmonary hemorrhage have been reported [14].

The case we present here is unique both in its clinical presentation and in the biopsy findings. The positive ANCA serology and the clinical picture of pulmonary-renal syndrome were highly suspicious for a systemic small vessel vasculitis. Reports of systemic amyloidosis presenting with pulmonary-renal syndrome are scant in the literature. A case of systemic AA amyloidosis in a patient with dystrophic epidermolysis bullosa resulting in recurrent
pulmonary infections and nephrotic syndrome has been reported; however, hemoptysis was not present and creatinine clearance was normal [15]. Histopathologically, this case is unique both in the extent and distribution of the amyloid deposition and the amyloid protein itself. To our knowledge, this is the first description of LECT2 amyloidosis causing clinical disease outside of the kidney and the first description of LECT2 deposition in the lung.

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References