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CASE REPORT

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Kidney-limited AL amyloidosis: a case report and review of the literature

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ABSTRACT

Amyloidosis involves the deposition of abnormal proteins in various tissues and results in progressive organ dysfunction, commonly affecting multiple organs. Two types of systemic amyloidosis are AA and AL; the former is associated with acute phase reactions and the latter is composed of light chain immunoglobulins. This disease commonly affects the kidneys and is evidenced by massive proteinuria. A biopsy is the gold standard of diagnosis, with Congo Red staining revealing an apple-green birefringence under polarized light. Although the kidneys are frequently affected in this disease, it is rare that amyloidosis is limited to the kidneys without involvement of other organs. We present an 83-year-old female with bilateral lower extremity swelling for several months who was found to have 12.374 grams of protein in a 24-hour urine sample and a large amount of free lambda chains. A renal biopsy demonstrated renal amyloidosis of the AL type. Serum immunofixation and flow cytometry were unremarkable for any plasma dyscrasia; a bone marrow biopsy did not reveal systemic amyloidosis and imaging with PET/CT scan did not show evidence of other organ involvement. She was diagnosed with renal-limited amyloidosis and started on bortezomib, melphalan, and steroids. Clinicians should be aware of the signs and symptoms of amyloidosis, specifically its ability to present with unusual involvement of individual organs.

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1. Introduction

Amyloidosis is a disease of abnormal protein deposition outside of tissues which damages cell function over time. The term 'amyloid' was coined in 1853 by Rudolf Virchow when he discovered that the depositions, when stained with iodine, looked similar to starch [1]. There is a growing list of more than thirty-two different proteins thought to be involved in the pathogenesis of amyloidosis; among them, the most common is immunoglobulin light chain (AL) amyloidosis [2]. Amyloidosis can be categorized into localized and systemic disease, depending on the source and origin of the protein as well as if there is spread of the disease; classification is now determined by the type of protein deposits. Systemic disease is more common and consists of primary (AL) and secondary (AA) types. AL, also known as primary amyloidosis, is a monoclonal product of bone marrow plasma cells producing immunoglobulin light chains (LC) and involves the subtypes Kappa (κ) or Lambda (λ). Amyloidosis can affect many organs, including the heart, lungs, nervous system, skin, and visceral organs. Kidney involvement is typical in systemic AL; however, other organs are almost always affected as well, and it is rare for the kidney to be the only organ in which amyloid is deposited. Kidney involvement in amyloidosis is associated with an increase in morbidity and mortality [1–4]. We report a patient who initially presented with significant bilateral lower extremity edema and proteinuria and was subsequently diagnosed with renal-limited amyloidosis. Renal-limited amyloidosis is a rare entity, and the risk of morbidity and mortality in the condition highlights the importance of appropriate diagnosis and treatment.

2. Case presentation

An 83-year-old Caucasian female with a past medical history of hypothyroidism, hypertension, asthma, and osteoporosis presented to the emergency department complaining of bilateral lower extremity swelling for the past four months. She denied chest pain, shortness of breath, orthopnea, palpitations, fatigue, night sweats, and unintentional weight loss. She also denied dysphagia, tongue swelling, changes in bowel habits, headache, numbness, tingling in the extremities, changes in vision, skin changes, or easy bruising. She had no known history of diabetes, heart failure, or renal disease. On physical examination, vitals revealed temperature 96.8° Fahrenheit, blood

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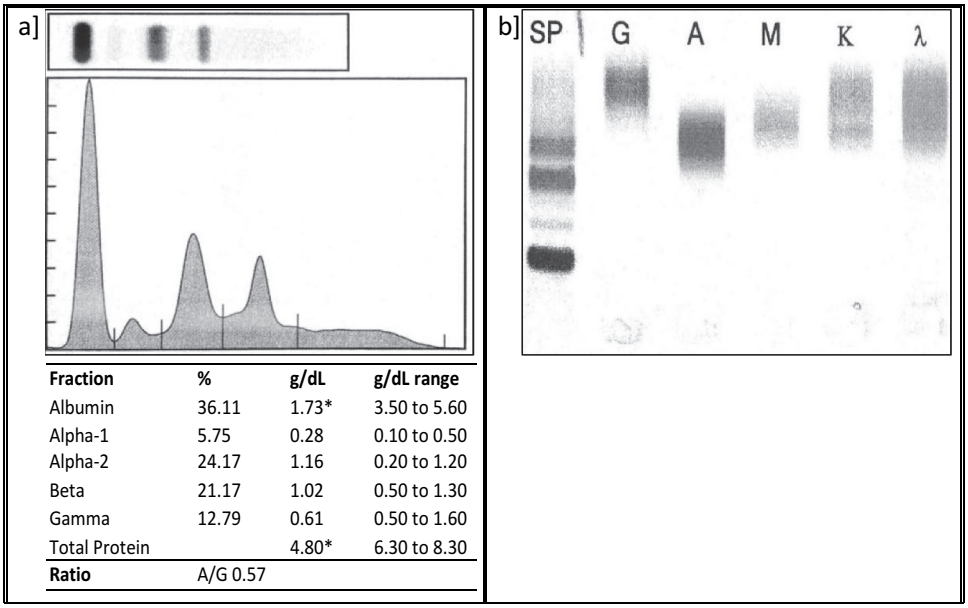
pressure 125/77 mmHg, heart rate 71 beats per minute, respiratory rate 12 breaths per minute, and oxygen saturation 98% on room air. The remainder of the exam demonstrated 3+ leg edema bilaterally up to the knees. She was awake, alert, and oriented to person, place, and time. Cardiac exam revealed a regular rhythm with no murmurs while the lungs were clear to auscultation bilaterally and the abdomen was benign. In addition to a lack of neurological deficits, she had no macroglossia, lymphadenopathy, or jugular venous distension. Evaluation of the skin revealed no thinning, thickening, rashes, or ecchymosis. Initial laboratory studies revealed BUN 18.1 mg/dL, creatinine 0.84 mg/dL, total protein 4.8 g/dL, albumin 2.3 g/dL, TSH 3.92 uIU/mL, free T4 6.6 µg/dL, and NT-proBNP 401 pg/mL. AST, ALT, and a complete blood count did not show any abnormal values. An electrocardiogram revealed a normal sinus rhythm without low voltage complexes or dysrhythmia and normal chest X-ray. A subsequent echocardiogram found normal left and right ventricular function with no valvular abnormalities. Urine studies found a total urine protein of 257.8 mg/dl, with a 24-hour urine study revealing 12,374 mg of protein. Subsequent urine and serum protein electrophoresis noted high free lambda light chains of 26.84 mg/dL and 47.7 mg/dL, respectively, and a low Kappa/Lambda urine ratio of 0.77 (Figure 1A). A renal biopsy was performed and demonstrated renal amyloidosis of the AL type with monoclonal IgG lambda involving the glomeruli and arteriolar vessels (Figure 2). Further work-up including serum immunofixation and flow cytometry were not consistent with multiple myeloma (Figure 1B). A 24-hour urine collection was negative for Bence Jones protein. Bone marrow biopsy did not reveal evidence of amyloidosis or plasma cell dyscrasia and was negative for Congo red stain. A fluorodeoxyglucose PET/CT scan showed nonspecific findings for multiple myeloma. A diagnosis of renal-limited amyloidosis was made and the patient initiated treatment with bortezomib, melphalan, and steroids. Shared decision making was employed to refer the patient to a well-known amyloid program for further management; however, the patient declined the referral.

3. Discussion

AL systemic amyloidosis occurs as a result of abnormal light chain protein deposition, of which 80% are associated with the Lambda (λ) chain and involve almost all vital organs. The heart and kidneys, with 82% and 68% of cases reported, respectively, are the most common sites of deposition. Additionally, the liver, nervous system, and gastrointestinal tract are often involved, and multiple organ systems are frequently affected [5]. Localized amyloidosis is rare but has been reported in the upper airways, orbits, urinary tracts, skin, and nails; this almost never progresses to systemic disease. Amyloidosis can also be accompanied by other plasma cell dyscrasias such as multiple myeloma (MM) or monoclonal gammopathy of undetermined significance (MGUS); these



Fraction	%	g/dL	g/dL range
Albumin	36.11	1.73*	3.50 to 5.60
Alpha-1	5.75	0.28	0.10 to 0.50
Alpha-2	24.17	1.16	0.20 to 1.20
Beta	21.17	1.02	0.50 to 1.30
Gamma	12.79	0.61	0.50 to 1.60
Total Protein		4.80*	6.30 to 8.30
Ratio	A/G 0.57		

Figure 1. (a) Serum protein immunofixation electrophoresis shows decrease in albumin due to renal loss. (b) Serum immunofixation (IFE) shows no monoclonal protein detected.

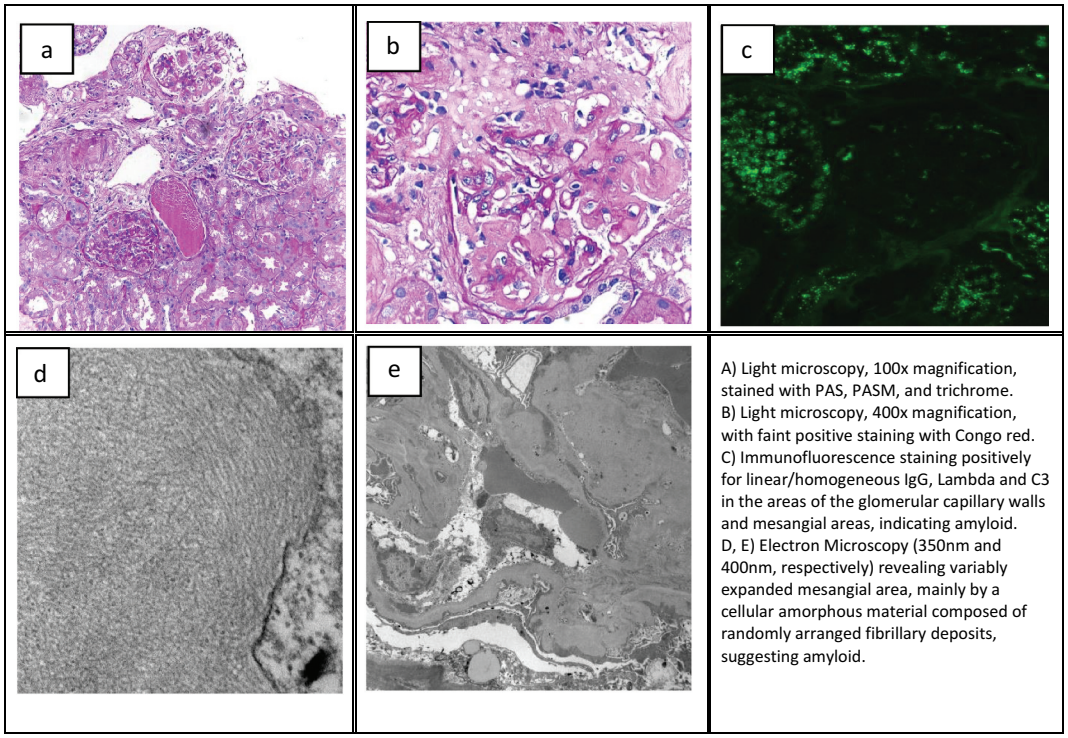


Figure 2. Histopathology and staining of kidney biopsy.

should be evaluated and excluded at the time of diagnosis. As noted, systemic disease commonly involves multiple organs, and there is a predilection for one organ to be affected more than others. The kidneys are frequently involved in systemic amyloidosis, but it is extremely rare for the kidneys to be the sole organ involved in the disease process [6].

In our review of the available literature, renal-limited immunoglobulin light chain (AL) amyloidosis was only discussed in one other case report [3]. Thus, epidemiologic and demographic data is very limited. Clinical manifestations of amyloidosis affecting the renal system are broad, and protein loss due to nephrotic syndrome may cause a variety signs and symptoms. Our patient presented with normal kidney function (evidenced by a normal creatinine) but her presenting complaint was significant leg swelling, with proteinuria found on further evaluation. She had no constitutional symptoms and no cardiac, respiratory, abdominal, or integumentary complaints. She also had no findings concerning for other system involvement, including heart failure, neuropathy, hepatic disease, or bleeding [3]. The diagnosis of AL amyloidosis, either local or systemic, is based on the clinical findings of the affected organs and positive histologic findings. Signs and symptoms may mimic other diseases, such as those limited to specific organs, especially in the elderly population. This may lead to a delay in diagnosis and treatment and will likely result in irreversible organ dysfunction [1,5]. Although amyloid protein can be detected anywhere in the kidney, it causes the most damage by depositing in the glomeruli and small vessels. Laboratory findings demonstrate proteinuria greater than 0.5 grams in 24 hours with albumin being the predominant protein lost. However, AL amyloidosis usually does not cause massive renal impairment [7].

A biopsy is the gold standard for diagnosis and it should be performed when amyloidosis is on the differential; it should be confirmed with immunofluorescent staining to evaluate the type of protein that is being deposited. The biopsy may be performed on a fat pad, bone marrow, or the organ in question. It is also important to search for other organ involvement and evaluate for any evidence of plasma cell dyscrasias. Staining with hematoxylin and eosin as well as periodic Acid-Schiff (PAS) may detect the depositions outside the cells as shapeless pink material (Figure 2A). Congo red staining with apple-green birefringence under polarized light is pathognomonic for amyloid protein deposition, as was noted in our patient (Figure 2B). A renal biopsy demonstrated renal amyloidosis composed of monoclonal IgG λ with questionable monoclonal gammopathy. Immunofluorescent microscopy revealed linear 2 + IgG, 2+ lambda, and 3+ nonspecific staining of C3 in the glomerular capillary walls and mesangial areas, with no staining for heavy chains, IgA, Kappa, or C1q, along with positive evidence in electron microscopy findings (Figure 2, C-F, respectively).

A serum-free light chain estimation assay was also performed in order to detect and quantify free light chains. The sensitivity and specificity of this test for AL amyloidosis is up to 98%. Our patient had high levels of free Lambda light chains, although the Kappa/Lambda ratio was within normal limits [3].

Bone marrow biopsy can be helpful in differentiating between systemic and localized disease, as plasma cell dyscrasias would support a systemic process. Additionally, serum and urine protein electrophoresis help differentiate systemic disease, since approximately 50% of patients have positive findings on the test. Immunofixation can further discern between systemic and localized disease; however, 20% of systemic disease cases can be falsely negative on serum and urine tests. Our patient had negative results on serum and urine electrophoresis and immunofixation, thus favoring localized kidney disease. Additionally, there were no detectable clonal plasma cells or B cell populations on peripheral blood flow cytometry analysis, and FISH analysis was negative for multiple myeloma, lymphoma, or other dyscrasias. Abdominal fat pad aspiration and salivary gland biopsies were not performed in our patient due to the lack of other physical exam and laboratory findings supporting alternate sites. The result of the completed testing supported the diagnosis of renal-limited amyloidosis [1,3,6].

Treatment of AL renal amyloidosis, as evidenced in studies as part of systemic amyloidosis therapy, is focused on elimination of the monoclonal proteins and the plasma cell clones with chemotherapeutic agents which may help to prevent organ damage. At this time, due to the scarcity of published research, it is unclear whether management of renal-limited amyloidosis should be treated similarly to systemic AL amyloidosis [3]. Per the National Comprehensive Cancer Network (NCCN) algorithm, systemic therapy based on studies of multiple myeloma previously recommended alkylating agents such as melphalan or cyclophosphamide combined with prednisolone or dexamethasone. This treatment strategy has been replaced by antineoplastic agents (such as bortezomib, carfilzomib, or ixazomib) combined with alkylating agents and corticosteroids or immunomodulatory agents such as thalidomide and lenalidomide, which are less preferred due to their organ toxicity [8,9]. In low-risk patients, high doses of melphalan along with autologous stem cell transplantation (ASCT) is still the treatment of choice [2,6,8]. The monoclonal antibody daratumumab is promising for AL amyloidosis treatment; it is being studied in different trials as both monotherapy and combined with other groups for future therapies with the aim of reabsorbing existing amyloid deposits [9,10]. Treatment response depends on baseline proteinuria and serum creatinine. Improvement in kidney function is demonstrated by a 50% reduction in the 24-hour protein excretion; conversely, a 50% increase in urinary protein loss (if total loss is greater than 3 g/24 h) or a doubling of urinary protein loss (if total loss is less than 3 g/24 h) is a poor prognostic indicator. Patients with glomerular involvement are at particular risk, as this correlates with more severe renal involvement and a higher risk of end-stage renal disease and higher mortality rate; these patients may require renal replacement therapy or kidney transplantation [6,7]. Our patient was started on a regimen of bortezomib, melphalan, and steroids and was offered a referral to a center specializing in amyloidosis; however, she declined the referral.

4. Conclusion

It is important to keep amyloidosis in the list of differential diagnoses for patients presenting with lower extremity edema. Renal failure is associated with significant morbidity and mortality; therefore, the consideration, detection, and early treatment of renal-limited amyloidosis is critical to possibly slow down this potentially deadly disease and improve life expectancy and quality of life.

Disclosure of statement

No potential conflict of interest was reported by the authors.

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