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Amyloidosis and the Kidney

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Abstract

Amyloidosis results from deposition of fibrillar proteinaceous material in the extracellular space in organs and tissues. Diagnosis is made microscopically on biopsy by visualizing apple-green birefringence in Congo red-stained sections under polarized light. Renal amyloidosis most often leads to glomerular deposits, resulting in proteinuria. If untreated, progressive decline in renal function can culminate in end stage renal disease. The type of protein that forms the fibrils can vary, but the result is disruption of structure and function. Renal impairment is seen most often in reactive secondary amyloidosis from serum amyloid A, monoclonal immunoglobulin light chain amyloidosis and amyloidogenic leukocyte chemotactic factor 2 (ALECT2) amyloidosis a recently described amyloid-forming protein. When possible, decreasing production of the amyloidogenic precursor or removing the amyloid protein may regress amyloid deposits and stabilize or improve renal function. Kidney transplantation may be indicated for carefully selected patients with amyloid-induced end stage renal disease.

Keywords

Amyloid, Kidney, Inflammation, Glomerulus, Management

Introduction

The amyloidoses are a group of diseases characterized by protein misfolding and subsequent deposition of insoluble amyloid fibrils with an anti-parallel, beta-pleated sheet tertiary structure [1]. These fibrils can deposit in a variety of locations including the heart and kidneys, leading to organ failure. Early detection of amyloidosis is difficult because the disease can present with diffuse non-specific symptoms and when a diagnosis is finally made, severe, irreversible organ damage may already be present. The kidney is especially susceptible to impairment in the presence of amyloid fibrils and this review will focus mainly on the types of amyloidoses that are most likely to impact renal function.

An Overview of Amyloidosis

Amyloidosis refers to a group of rare diseases characterized by abnormal extracellular tissue deposition of misfolded low molecular weight protein subunits in the form of fibrils [2]. Fibrils can form from a diverse group of unrelated normally soluble proteins. Each type of amyloidosis is characterized by one specific protein or polypeptide that has failed to fold correctly, leading to aggregation and filament formation (Table 1). The events are stepwise from formation of nuclei to small protofibrils that elongate to protofilaments which intertwine as mature fibrils. Under the electron microscope, amyloid usually appears as a straight, unbranched particle with a diameter of 10-15 nm. The polypeptide chains within amyloid deposits exhibit polymorphism such that the components are of varying shapes and sizes [3].

Virchow was the first to use the term amyloid meaning "starch like" to describe tissue deposits that stained pale blue when treated with iodine solutions [4]. Histologically, when stained with Congo red and viewed under polarized light, amyloid deposits emit a characteristic apple green birefringence. With conventional light microscopy, Congo red stained amyloids appears mahogany brown. On H&E stain, amyloid appears as ho-

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Table 1: Summary of proteins responsible for amyloidosis, the corresponding abbreviations and the key characteristics associated with each.

Amyloidogenic protein	Abbreviation	Characteristics
Immunoglobulin light chain	AL	Primary amyloidosis, plasma cell dyscrasias. Cardiomyopathy, hepatomegaly, nephrotic syndrome.
Immunoglobulin heavy chain	AH	Plasma cell dyscrasias, renal involvement.
Transthyretin	ATTR	Familial amyloidosis, systemic, associated with peripheral neuropathy and cardiomyopathy.
Leukocyte chemotactic factor 2	ALECT 2	Renal dysfunction, lack of cardiac or nerve involvement.
Serum amyloid A	AA	Acquired, reactive, systemic, linked to inflammatory disorders or chronic infection. Proteinuria, loss of renal function.
Apolipoprotein A-I	AApoAI	Autosomal dominant systemic, organ involvement related to specific mutations.
Apolipoprotein A-II	AApoAII	Autosomal dominant systemic, renal failure.
Lysozyme	ALys	Autosomal dominant, GI and renal dysfunction.
Fibrinogen	AFib	Autosomal dominant, deposition in kidney, heart, liver, and spleen; prominent renal involvement.
Gelsolin	AGel	Autosomal dominant, polyneuropathy, corneal lattice dystrophy.
β2-microglobulin	Aβ2M	Hemodialysis-related amyloidosis with musculoskeletal manifestations.

mogeneous amorphous eosinophilic (pink) material and it is weakly positive on periodic acid-Schiff (PAS) stain [5,6]. On X-ray diffraction, deposits of amyloid exhibit a β-pleated sheet ultrastructure. This sheet conformation makes it stable, insoluble and resistant to proteolytic enzymes so that clearance is prevented.

Amyloidosis can be acquired or inherited, localized or systemic and may affect any organ, leading to tissue destruction, disruption of structure and function and ultimate progression to organ failure [7]. Vital organs compromised by amyloidosis include kidney, liver and heart. Although amyloid can involve peripheral nerves, central nervous system involvement is extremely rare [8,9].

The most common form of amyloidosis is immunoglobulin (Ig)-amyloid light chain (AL), which is associated with underlying plasma cell dyscrasias and comprises about 85% of systemic amyloidosis [10]. AL amyloidosis most often occurs in isolation, but can also be associated with multiple myeloma or Waldenström macroglobulinemia [7,11,12]. A majority (over 60%) of AL amyloidosis patients have less than 10% plasma cells in the bone marrow [13].

Ig-amyloid heavy chain (AH) is much more rare, but also associated with plasma cell dyscrasias [14,15]. Elevated N-terminal pro-brain natriuretic peptide and high-sensitivity cardiac troponin T (> 0.025 ng/ml), and greater difference between involved and uninvolved free light chains (dFLC) indicate poor prognosis because they reflect the major impact of cardiac amyloidosis and persistence of amyloid generation on mortality [16,17]. The most common familial form of amyloidosis is transthyretin (ATTR) amyloidosis, in which the amyloid is derived from transthyretin (TTR), a plasma protein produced in abundance by the liver. Hereditary ATTR is an autosomal dominant disease caused by single amino acid substitution mutation in TTR with high mortality unless treated [18]. The acute-phase reactant serum amyloid A (SAA), a protein synthesized by the liver that circulates in association with high density lipoprotein causes a secondary amyloidosis (AA amyloidosis) that most often affects the kidneys, spleen and liver. In secondary AA amyloidosis, SAA is overproduced as the result of chronic infection or inflammation due to disorders such as rheumatoid arthritis, Crohn's disease and osteomyelitis [19]. The main treatment strategy for secondary amyloidosis is control of underlying disease. Leukocyte chemotactic factor 2 is the source of amyloid in a newly described form, leukocyte chemotactic factor (ALECT 2) amyloidosis [20]. In a recent series ALECT2, seen in 10% of cases, was the second most common type of amyloid after AL amyloidosis [21]. Renal involvement is most common in AL, AA, and ALECT2 amyloidosis.

Diagnosis of renal amyloid is established by biopsy of the kidney [22]. Bleeding is a significant complication of biopsy due to amyloid involvement of the vasculature and abnormalities of hemostasis related to amyloidosis. Diagnosis of amyloidosis may be confirmed by fine needle aspiration of subcutaneous abdominal fat for amyloid deposits [23,24].

As a general observation, primary or immunocyte-derived (AL) amyloidosis more often involves the kidney, heart, gastrointestinal tract, carpal tissue (carpal tunnel syndrome may be an early symptom), peripheral nerves, tongue and skin [25], whereas secondary amyloidosis (AA) is most likely to involve kidneys, spleen, liver, gastrointestinal (GI) tract, adrenal, thyroid and lymph nodes with rare cardiac involvement and no tongue involvement. Familial transthyretin-associated (ATTR) amyloid predominantly affects the peripheral and autonomic nervous systems and carpal tunnel. β(2)-microglobulin amyloid, seen in patients on hemodialysis for prolonged periods, deposits in the

musculoskeletal system causing pain and compromising function [26].

The Kidney in AL

About two-thirds of AL amyloidosis involves the kidney. Presenting symptoms of AL are generally vague and non-specific, with fatigue and weight loss the primary initial signs of illness [27]. Enlarged tongue can be noted once the disease has progressed. The definitive diagnosis of AL amyloidosis is often established late in the disease process when symptoms reflect the involvement of a particular organ. Deposition of immunoglobulin light chains in the kidney leads to nephrotic syndrome while in the heart it manifests as restrictive cardiomyopathy [28]. AL is highly toxic to the renal and cardiovascular system and prognosis is poor overall, with cardiac or renal failure the predominant causes of early death [29]. The liver may be enlarged because of engorgement due to right heart failure or because of amyloid load. Diagnosis is confirmed by biopsy. If AL amyloidosis is suspected, serum and urine protein electrophoresis are indicated [30].

AL-amyloid protein and light chains deposit in glomeruli disrupting architecture so that progression to renal failure occurs. Probability of renal survival decreases with increased proteinuria, and lower eGFR and serum albumin [31]. Amyloid generally accumulates throughout all renal compartments. It is not known exactly how amyloid fibrils amass in the kidney, but mesangial cells are critically involved [32]. Mesangial areas in the glomeruli and blood vessel walls are early sites of amyloid deposition within the renal parenchyma. The fibrils are nonbranching and randomly arranged.

In vitro studies in which human mesangial cells were incubated with light chains from persons with AL amyloidosis showed that the light chains enter via cell surface receptors, are processed in the lysosome to become fibrils and are then secreted into the extracellular space where they damage the mesangium [33]. As the mesangial cells become overloaded with light chains, they lose contractility and transform phenotypically into a more macrophage-like cell. Ultimately, the mesangial matrix is obliterated and replaced by amyloid. The process is also thought to involve matrix metalloproteinases which degrade glycoproteins and proteoglycans of the extracellular matrix, are elevated in the kidney in AL amyloidosis and participate in matrix destruction [34].

Progression to renal failure can be predicted by estimated glomerular filtration rate (eGFR) and proteinuria [35]. Median survival once on dialysis is short, 3 years or less [36,37].

Suppression of the plasma cells that produce amyloidogenic light chains is the goal of treatment. Strategies include chemotherapy, mostly melphalan, in combination with steroids and possibly the proteasome inhibitor bortezomib [38]. High-dose melphalan followed by autologous hematopoietic stem cell transplantation has been shown to improve organ function and extend median overall survival to over 5 years, but high transplant-related mortality is of great concern [39,40].

AA and Renal Function

AA amyloidosis targets the kidney, spleen and liver. Inflammatory mediators that can stimulate SAA synthesis by the liver is induced by cytokines (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]), lipopolysaccharides, and transcription factors [41]. The earliest clinical manifestation is proteinuria [19]. It may progress from proteinuria and nephrotic syndrome to renal failure. Almost all cases of AA amyloidosis affect the glomeruli with deposits in the mesangium and glomerular capillary walls [42,43]. In patients with suspected AA amyloidosis, a rectal or gingival biopsy may be helpful [44].

In addition to rheumatoid arthritis, inflammatory bowel disease and osteomyelitis, AA can arise as a complication of familial Mediterranean fever and infectious diseases such as tuberculosis. The kidneys are affected in over 90% of cases [19,45]. Biopsy gives the definitive diagnosis and pattern of amyloid distribution. In rheumatoid arthritis patients, glomerular deposition of N-terminal fragments of SAA in the form of insoluble amyloid fibrils has a poorer prognosis than deposition around blood vessels with sparing of the glomerulus [46]. Due to improved treatments for autoimmune rheumatic diseases, incidence of AA amyloidosis with this etiology has decreased [47].

Treatment of AA amyloidosis is centered on the underlying inflammatory disorder. In familial Mediterranean fever, an autosomal recessive inherited disorder characterized by repeated bouts of fever and painful inflammation of the peritoneum, synovium or pleura, colchicines decreases the frequency of episodes and can prevent renal amyloidosis by preventing SAA secretion [48,49]. In cases where the familial Mediterranean fever is colchicines resistant, blocking IL-1 activity with the human anti-IL-1 monoclonal antibody canakinumab may be effective [50]. If AA amyloidosis is untreated or if treatment is unsuccessful, end stage renal disease will ensue [51]. Patients who progress to end stage renal disease can be treated with either dialysis or renal transplant, but high risk of complications and recurrence or progression of the underlying inflammatory disorder make transplant less likely [52]. Blockade of TNF or IL-6 with a biological agent may improve renal function in AA-type renal amyloidosis associated with rheumatic diseases, while suppressing the inflammatory reactions that leads to amyloid production [53].

ALECT2-A New Type of Amyloidosis Affecting the Kidney

Although most recently discovered in 2008, ALECT2 amyloidosis is one of the more frequently occurring forms, and has been the second or third most common type in the kidney in several studies [10,54]. Persons of Hispanic ethnicity are particularly susceptible [55]. It also affects the liver, but rarely the heart. The lack of cardiac involvement may explain the superior survival rate compared to AL and AA. Proteinuria may or may not be present and nephrotic syndrome is detected in only about 10% of cases [56]. It must be diagnosed by biopsy since biomarkers have not been validated at this time. Optimally, diagnosis is made by laser microdissection and mass spectrometry-based proteomic analysis [57]. The usual presentation is chronic renal insufficiency with creatinine around 2.3 mg/dl [56].

ALECT2 is a 16.4 kD serum protein with growth factor and neutrophil chemotactic properties that is synthesized in the liver. The gene has been mapped to chromosome 5q 31.1-32 and contains four exons and three introns [58]. No mutations have been described, but there are G and A, allelic polymorphisms and many subjects with amyloidosis carry 2 G alleles, substituting valine at position 40 of the mature protein for isoleucine. This sequence difference may result in a protein more likely to form fibrils [59].

Although all compartments of the kidney parenchyma may be involved, amyloid is predominantly localized within the cortical interstitium and mesangial regions, but minimally present in the renal medulla [54,56].

In a study by Sethi's group [56] of 72 patients with ALECT2 amyloidosis, with median follow-up of over 2 years available in 89% of the cohort, renal function remained stable in about 30%, deteriorated in 38% and reached end stage in 32%. Treatment at this time is limited to dialysis or transplantation.

Rare Forms of Amyloidosis

ATTR can result from either misfolding of the wild type transthyretin protein or from mutations in the transthyretin gene leading to production of an abnormal protein prone to misfolding. ATTR is an underdiagnosed form of amyloidosis that causes peripheral neuropathy and cardiomyopathy and, to a lesser extent, proteinuria and progressive renal failure [18]. It is one of a number of amyloidosis syndromes that can occur due to genetic mutations in specific proteins.

Mutations in the gene encoding apolipoprotein (Apo) A-I, the main protein constituent of high density lipoprotein, can cause an autosomal dominant amyloidosis that may be systemic and frequently involves the kidney, manifesting as tubulointerstitial nephritis [60]. Liver, heart and larynx can also be affected.

Similarly, a mutation in the gene encoding Apo A-II, another HDL component, causes an elongated protein that can result in amyloidosis manifesting primarily as renal failure [61]. Apo A-II amyloidosis presenting as proteinuria has also been documented by immunohistochemical staining of the renal biopsy specimen in the absence of any detectible coding sequence mutation [62].

Lysozyme amyloidosis (ALys) is an autosomal dominant hereditary disorder with high penetrance with GI symptoms and risk of GI bleeding as well as detection of amyloid in the liver, but only mild abnormalities in liver function tests [63]. Renal dysfunction is common, but progress to end stage renal disease is very variable. Transplant outcomes tend to be very good.

Another familial form of amyloidosis is fibrinogen amyloidosis (AFib) in which amyloid is deposited in kidney, heart, liver and spleen and progression to kidney failure is a near certainty once renal amyloid is detected [64,65]. Renal transplant has a high failure rate since fibrinogen production in the liver continues and the transplanted kidney is lost to recurrence of amyloid-mediated destruction. Early liver transplant may save the kidneys.

Gelsolin amyloidosis (AGel) is an autosomal dominant disorder that usually presents as a polyneuropathy, damaging the cornea and cranial and peripheral nerves. It can involve the skin as well and can, in rare cases, affect the kidney, particularly the glomeruli, leading to nephrotic syndrome [66]. There are specific gelsolin mutations that cause localized deposition in the kidney [67].

Advances in Diagnosis and Treatment

As noted previously, treatment is directed at the underlying cause of amyloidogenic protein production when possible. Proteins can be identified by immunohistochemistry, but misfolded proteins with their distorted structure may lead to failure of accurate detection. For paraffin-embedded tissues, laser microdissection and mass spectrometry increased accuracy in identifying the culprit protein to 94% versus 76% with immunohistochemistry in a study of 142 biopsy specimens [68]. Mass spectrometry coupled with proteomics is now considered the gold standard for identification of amyloid forming proteins [69]. The application of mass spectrometry in concert with bioinformatics enables protein identification without antibodies.

New treatments on the horizon for amyloidosis include the use of small interfering RNAs specific to the sequence of the amyloid-generating protein that can be used therapeutically to silence the gene and reduce the protein level. This approach is being used in clinical trials for ATTR with the small interfering RNA delivered via lipid nanoparticles [70]. Conceptually similar is the potential use of antisense oligonucleotides that bind to

and inhibit RNA translation and thereby reduce protein production [71].

Conclusions

Although amyloidosis is a group of rare disorders, the kidneys are affected in almost all patients with AA amyloidosis and ALECT2 amyloidosis and less frequently in AL amyloidosis. Kidney involvement presents as proteinuria or renal impairment. Due to the non-specific and varied manifestations, diagnosis is often made at a late stage, worsening prognosis in many cases. Over 30 different proteins exist that can cause amyloidosis and additional such proteins that impact the kidney are likely to be identified in the future. Treatment options are limited and many patients will require dialysis which is associated with high morbidity and mortality and compromises quality of life.

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