Renal Amyloidosis

Nasreen Mohamed, MD, FRCPA[a], Samih H. Nasr, MD[b,*]

KEYWORDS

• Amyloidosis • AL amyloidosis • AA amyloidosis • Amyloid types
• Laser microdissection and mass spectrometry • Renal biopsy

ABSTRACT

Amyloidosis is an uncommon group of diseases in which soluble proteins aggregate and deposit extracellularly in tissue as insoluble fibrils, leading to tissue destruction and progressive organ dysfunction. More than 25 proteins have been identified as amyloid precursor proteins. Amyloid fibrils have a characteristic appearance on ultrastructural examination and generate anomalous colors under polarized light. Amyloidosis can be systemic or localized. The kidney is a prime site for amyloid deposition. Immunofluorescence, immunoperoxidase, and more recently laser microdissection and mass spectrometry are important tools used in the typing of renal amyloidosis.

OVERVIEW

Amyloidosis constitutes a large group of uncommon diseases that share a common trait characterized by distinctive extracellular deposition of pathologic insoluble fibrillar proteins in which protein misfolding has an essential role in the pathogenesis.[1] The term was first adopted by Virchow in the nineteenth century to describe an abnormal extracellular material in autopsy cases, and later it was discovered to stain for Congo red and exhibit anomalous colors under polarized light. Its unique β-pleated sheet configuration confers on the amyloid the typical staining properties and stability under physiologic conditions.

Amyloid is characterized by deposition of homogenous and amorphous pale eosinophilic material, which ultimately leads to destruction of tissues and progressive disease. Besides its peculiar staining pattern, it is characterized by the presence of rigid, nonbranching, randomly oriented fibrils ranging in diameter from 7 to 14 nm on ultrastructural examination.[1]

In the United States and Europe, amyloidosis derived from immunoglobulin (Ig) light chain (AL) is the most prevalent form, followed by AA amyloidosis (AA). The incidence of AL is 6 to 10 cases per million population.[2] In a series of 1315 patients with amyloidosis seen at the Mayo Clinic (Rochester, Minnesota) between 1981 and 1992, 70% had AL, 19% localized amyloidosis, 4% familial amyloidosis, 4% senile amyloidosis, and 3% AA.[3] In developing countries, however, AA is more common than AL.[4]

Renal involvement is frequent in most types of systemic amyloidosis with AL, previously called primary amyloidosis, being the most common type involving the kidney. It has been reported that 50% to 80% of patients with AL have kidney involvement,[3] whereas in patients with AA, the kidney shows variable involvement. The overall renal biopsy incidence of amyloidosis ranges from 1.3% to 4%.[5–8]

AMYLOIDOSIS TYPES THAT AFFECT THE KIDNEY

There are more than 25 precursor proteins identified leading to amyloid deposition. The types of systemic amyloidosis that may be associated

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[a] Department of Pathology and Laboratory Medicine, King Fahad Specialist Hospital-Dammam, Omar Bin Thabit Street, Dammam, Kingdom of Saudi Arabia; [b] Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA
* Corresponding author. Division of Anatomic Pathology, Mayo Clinic, 200 First Street Southwest, Hilton 10-20, Rochester, MN 55905.
E-mail address: nasr.samih@mayo.edu

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with clinically significant kidney involvement are listed in **Table 1**. **Fig. 1** depicts the origin of renal amyloidosis in 474 cases diagnosed by renal biopsy at the Mayo Clinic Renal Biopsy Laboratory between 2007 and 2011. Ig-related amyloidosis (AIg) is by far the most common form affecting the kidney.[6–9] AIg is associated with B-cell lymphoproliferative disorders encompassing multiple myeloma–plasma cell dyscrasia, malignant lymphoma, and macroglobulinemia. AIg in most cases is derived from fragments of monoclonal light chains (AL) but rarely is derived from fragments of the Ig-heavy chain and light chain (AHL) or Ig heavy chain only (AH).[10–12]

AA is the second most common form of renal amyloidosis[6,8]; it is associated with chronic inflammatory diseases, such as chronic infection, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, familial Mediterranean fever, bronchiectasis, and chronic osteomyelitis.[13–15] The kidney may also be affected by several forms of familial or hereditary amyloidosis, most of which have an autosomal dominant mode of inheritance and start in midlife with a slow rate of progression. These include amyloid derived from a mutant protein of transthyretin (TTR) (ATTR),[7,8] fibrinogen A-α chain (AFib),[6,16] gelsolin (AGel),[17] lysozyme (ALys),[18] apolipoprotein A-I (AApo AI),[19] apolipoprotein A-II (AApo AII),[20] and apolipoprotein A-IV (AApo AIV).[21] In 2008, a new member was added to the amyloid family, ALECT2—amyloid derived from leukocyte chemotactic factor 2 protein (LECT2).[22] ALECT2 is now the third most common type of renal amyloidosis in the United States, accounting for 2.5% to 2.7% of cases.[6,8] It affects mainly the kidney and liver but can rarely involve other organs.[23–25]

Table 1
Systemic amyloidoses with clinically significance kidney involvement

Amyloid Precursor Protein	Name
Ig light chain	AL
Ig heavy chain	AH
Ig heavy and light chain	AHL
SAA	AA
Leukocyte chemotactic factor 2	ALECT2
Fibrinogen A-α chain	AFib
TTR	ATTR
Apolipoprotein A-I	AApo AI
Apolipoprotein A-II	AApo AII
Apolipoprotein A-IV	AApo AIV
Gelsolin	AGel
Lysozyme	ALys

CLINICAL PRESENTATION

The clinical presentation of patients with amyloidosis varies, reflecting the presence of different types of amyloidosis, with wavering predilection for organ involvement, making a diagnosis difficult.

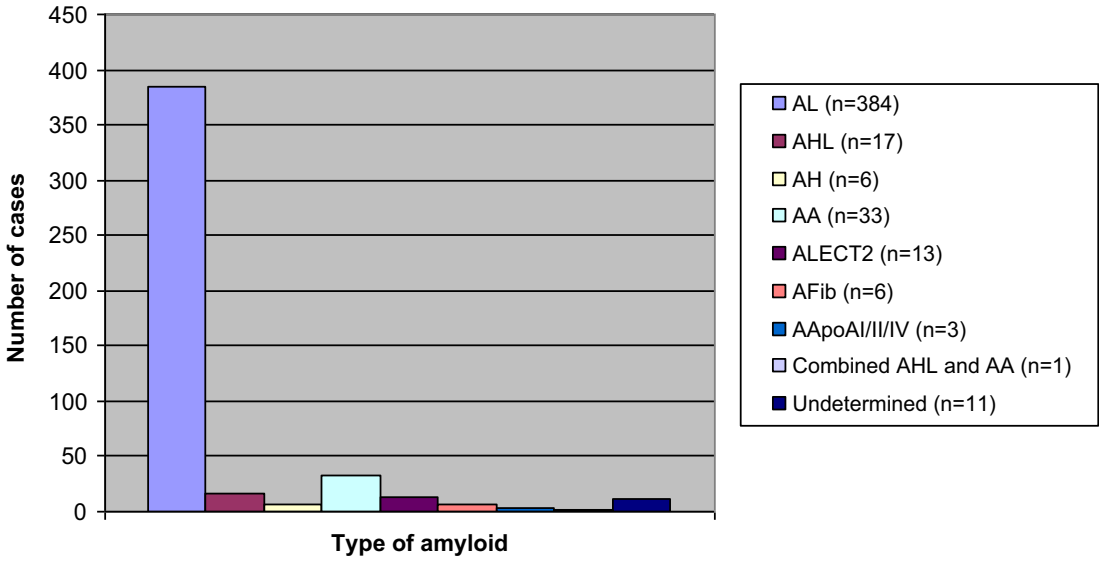

Fig. 1. The origin of renal amyloidosis in 474 cases diagnosed by renal biopsy at the Mayo Clinic Renal Biopsy Laboratory between 2007 and 2011.