Human Pathology (2007) **38**, 1798–1809

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Clinical and histological characteristics of renal AA amyloidosis: a retrospective study of 68 cases with a special interest to amyloid-associated inflammatory response

Jérôme Verine MD[a,b,c,*], Nathalie Mourad MD[a], Kristell Desseaux MS[d], Philippe Vanhille MD[e], Laure-Hélène Noël MD[f], Hélène Beaufils MD[g], Gilles Grateau MD, PhD[h], Anne Janin MD, PhD[a,b,c], Dominique Droz MD, PhD[a,c]

[a] *AP-HP, Hôpital Saint-Louis, Service d'Anatomie Pathologique, F-75010 Paris, France*
[b] *Inserm, U728, Institut Universitaire Hématologie, F-75010 Paris, France*
[c] *Université Paris 7, Institut Universitaire Hématologie, F-75010 Paris, France*
[d] *AP-HP, Hôpital Saint-Louis, Département de Biostatistiques et Informatique Médicale, F-75010 Paris, France*
[e] *Centre Hospitalier de Valenciennes, Service de Néphrologie et de Médecine Interne, F-59300 Valenciennes, France*
[f] *Inserm, U507, Hôpital Necker, F-75015 Paris, France*
[g] *AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service d'Anatomie Pathologique, F-75013 Paris, France*
[h] *AP-HP, Hôpital Tenon, Service de Médecine Interne, F-75012 Paris, France*

Received 13 December 2006; revised 13 April 2007; accepted 20 April 2007

Keywords:
AA amyloidosis;
Kidney;
Histological forms;
Inflammatory reaction;
Glomerular crescents

Summary We retrospectively reviewed the clinicopathological features of a series of 68 renal AA amyloidosis observations collected between 1990 and 2005. The amyloidogenic disease was a chronic infection (40.8%), a chronic inflammation (38%), a tumor (9.9%), a hereditary disease (9.9%), or was undetermined in 1.4% of cases. Nephrotic syndrome and renal insufficiency were noted in 63.1% and 75% of patients, respectively. The distribution pattern of glomerular amyloid deposits was mesangial segmental (14.7%), mesangial nodular (26.5%), mesangiocapillary (32.3%), and hilar (26.5%). Glomerular form was observed in 80.9% of cases and vascular form in 19.1%. AA amyloidosis-related inflammation was noted in 30 patients (44.1%) and appeared as a multinucleated giant cell reaction (27.9%) or a glomerular inflammatory infiltrate (25%), including glomerular crescents (17.6%). At the end of follow-up, 26 patients (38.2%) showed end-stage renal disease. The clinical presentation of glomerular and vascular forms was distinct with a clear predominance of proteinuria in glomerular form. Inflammatory reaction was preferentially observed in biopsies with a codeposition of immunoglobulin chains and/or complement factors in AA amyloid deposits. The distribution pattern of glomerular amyloid deposits and glomerular inflammatory reaction were independent factors influencing proteinuria

* Corresponding author. Service d'Anatomie Pathologique, Hôpital Saint-Louis, 1 Avenue Claude Vellefaux, 75010 Paris, France.
E-mail address: jerome.verine@sls.aphp.fr (J. Verine).

doi:10.1016/j.humpath.2007.04.013

level. Tubular atrophy, abundance, and distribution pattern of glomerular amyloid deposits at the time of biopsy were independent predictors of renal outcome. In conclusion, the glomerular involvement appeared as the determining histological factor for clinical manifestations and outcome of renal AA amyloidosis. AA amyloidosis-related inflammation could partly result from an immune response directed against AA fibrils and could induce amyloid resolution and crescents.

1. Introduction

Amyloidoses constitute a heterogeneous group of diseases characterized by extracellular deposition of amyloid proteins in different tissues and organs. Amyloid deposits are identified on the basis of their morphologic, structural, and tinctorial characteristics [1]. In human pathology, 25 different proteins are known to have the ability to aggregate in insoluble fibrillar deposits, including amyloid A protein responsible for AA amyloidosis [1]. The AA amyloid proteins result from a proteolytic cleavage of acute phase serum amyloid A protein (A-SAAs) usually in the C-terminal half of the 104 amino acid residues long precursor. Acquired and hereditary diseases can lead to systemic AA amyloidosis provided they are associated with chronic inflammation. Renal involvement, extremely frequent in systemic AA amyloidosis, is a major cause of morbidity and mortality. The aim of this study was to analyze the histological characteristics of a series of renal AA amyloidosis and their possible clinical implications. We were interested in the distribution pattern of amyloid deposits in renal parenchyma and more particularly in the 2 principal histological forms of renal AA amyloidosis, that is, glomerular and vascular forms [2-5]. We also studied the inflammatory reaction related to renal AA amyloidosis. Although inflammation against amyloid deposits plays an important role in Aβ and Aβ2m amyloidoses [6,7], few data are currently available on this subject in renal AA amyloidosis.

2. Materials and methods

2.1. Patients and materials

One hundred seventy-four cases of renal amyloidosis were observed between January 1990 and December 2005 in 3 departments of renal Pathology (Hôpital Necker, Hôpital Pitié-Salpêtrière, and Hôpital Saint-Louis). They included 68 cases (39.1%) of AA amyloidosis and 105 cases (60.3%) of AL amyloidosis (AA/AL amyloidosis ratio, 1:1.5). The remaining case concerned a patient with a mutation in the fibrinogen A alpha chain gene. We gathered in our series the 68 cases of renal AA amyloidosis and reviewed their medical records. The renal biopsies (n = 68) were jointly reviewed by 2 pathologists (J. V. and D. D.). The presence of amyloid was established by the appearance of an apple green birefringence from alkaline Congo red staining under polarized light. AA amyloidosis was demonstrated by positive immunohistochemical or immunofluorescence (IF) staining with mouse antihuman amyloid A monoclonal antibody (clone mc1; 1:10 dilution; DakoCytomation, Trappes, France).

Biopsy specimens for light microscopic analysis were fixed either in ethanol/formalin/acetic acid or in alcoholic Bouin solution, embedded in paraffin, and sectioned at 2 to 3 μm. The sections were stained with Masson trichrome, hematoxylin and eosin, periodic acid-Schiff, and Jones methenamine silver stains. IF specimens were studied on frozen sections with fluorescein isothiocyanate (FITC)-conjugated, monospecific, anti–heavy chains (μ, γ, α), anti–light chains (κ and λ), anticomplement factors (C3 and C1q), and antifibrinogen (1:10 dilution; DakoCytomation). An additional immunohistochemistry study with mouse anti-CD68 monoclonal antibody (clone KP1; 1:100 dilution; DakoCytomation), a marker of the monocyte/macrophage lineage, was performed in 10 cases. The present study was approved by the local institutional review board.

2.2. Clinical and laboratory findings

For each patient, the following data were gathered: age, sex, geographic origin, amyloidogenic disease(s), and main clinical manifestations of renal involvement at the time of the renal biopsy. Nephrotic syndrome was defined as massive proteinuria (>3 g/d) and hypoalbuminemia (<30 g/L). Microscopic hematuria was characterized by a urine erythrocyte count of >10,000 erythrocytes/mL in uncentrifuged urine. Renal insufficiency was defined as a creatinine clearance (CrCl) <80 mL/min (calculated using the Cockcroft-Gault formula): moderate impairment of renal function as CrCl between 30 and 50 mL/min and severe renal failure as CrCl <30 mL/min. High blood pressure was characterized according to the World Health Organization criteria. At the conclusion of the study, renal outcome was evaluated by CrCl. End-stage renal disease (ESRD) was defined as CrCl <10 mL/min or dependence on dialysis.

2.3. Pathological findings

The abundance and distribution pattern of amyloid deposits were evaluated without prior knowledge of clinical