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Renal Amyloidosis: clinicopathologic and evolutive characteristics of Morrocan series

Sara FASSIL*, Lahoucine ALTIT, Wafaa FADILI, Inass LAOUAD.

Department of Nephrology,CHU Mohammed VI. Marrakech. Morroco

ABSTRACT

Background and objectives : *Systemicamyloidosis is a disease resulting from extracellular deposition of fibrillar protein in different organs. The kidney is the organ most commonly involved in systemicamyloidosis. The aim of this study is to evaluate the clinicopathologic and evolutive characteristic of a renalamyloidosis series including 21 patients.* ***Results:*** *The average age at diagnosis was 53+/- 11.9 years, with a sex ratio H/F of 2.5. The clinical picture was dominated by nephrotic syndrome, noted in 66% cases; a renal failure is noted in 28.5% patients. The diagnosis of amyloidosis is carried on renal biopsy in 20 cases, in most of cases. AL amyloidosis was noted in 4 patients (19%), all cases were secondary to multiple myeloma. AA amyloidosis was noted in 17 patients (80.9%), mainly caused by chronic infections in 42 %, pulmonary tuberculosis was noted in 8 patients, a digestive tuberculosis was found in one patient. Chronic inflammatory rheumatisms were noted in 3 patients (14%), one case of rheumatoid polyarthritis, one case of psoriatic arthritis, and one case of systemic lupus eryhtematosus. An association of pulmonary tuberculosis and rheumatoid polyarthritis was noted in two patients (9.5%). Solid cancer was found in one case. Bronchiectasies, without tuberculosis history, were noted in 2 patients (9.5%). Evolution was marked by the setting of end stage renal disease in 5 patients, with an average of 9mois. Death occurred in 3 patients. 8 patients were progressing to chronic renal kidney disease; 5 patients were lost of view.* ***Conclusion:*** *Amyloidosis is a progressive and fatal disease. Complications of end-stage renal disease are the main causes of death. The treatment is the one of the causal disease. In our context, predominance of AA amyloidosis is noted; so we have to improve the infectious diseases care, in order to reduce the prevalence of this affection.*

Keywords : *amyloidosis ; renal biopsy; etiologies ; evolution.*

INTRODUCTION

Amyloidosis is a rare clinical disorder caused by the extra cellular tissue deposition of insoluble abnormal amyloid fibrils that alter the normal function of tissues.The global incidence of amyloidosis is estimated at 5 to 9 cases per million patient-years(1).The main types of systemic amyloidosis are primary light-chain (AL) amyloidosis, amyloid A (AA) amyloidosis, familial amyloidosis, hereditary or senile transthyretin amyloidosis and beta2-microglobulin-related amyloidosis in patients with endstage renal disease. AA amyloidosis is frequent in developing countries and some European regions, and AL amyloidosis is prevalent in developed countries

(1.2).Amyloidosis can be localized or systemic. The diagnosis of this condition is based on histological study of tissues biopsies.Renal involvement is frequent in most types of systemic amyloidosis. Cardiac and neuropathic involvement may be seen rarely. The overall renal biopsy incidence of amyloidosis ranges from 1.3% to 4%(3,4,5). It has been reported that 50% to 80% of patients with AL have kidney involvement (6), whereas in patients with AA, the kidney shows variable involvement.

RESULTS AND DISCUSSION

Patients and methods:

This retrospective observational study, included 21 cases of renal amyloidosis, collected inour department between January 2015 and September 2017. Data on detailed history, clinical features (age, gender, weight, height, blood pressure, organ involvement, indication of biopsy, biopsy reports, underlying disease and cause of death) and laboratory results at diagnosis were obtained from the medical records. In addition, serum creatinine, albumin, eGFR and 24h UPE values at the end of follow-up were obtained. Follow-up period included the duration from diagnosis to the last clinical control or to death of the patient.

This study included15 men and 6 women (figure 1). The average age at diagnosis was 53+/- 11.9 years with extremes of 27 and 68 years. The majority of patients were from the regions of southern and central Morocco (94.6%).

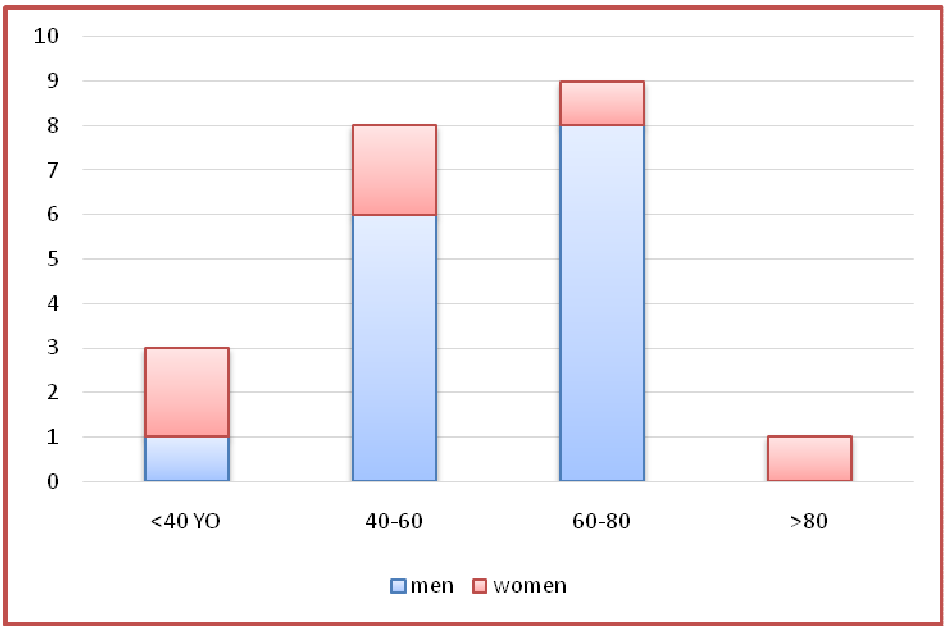

Figure 1: Distribution of renal amyloidosis according to the age of patients.

The clinical picture was dominated by the edematous syndrome (94.4%), microscopic hematuria was noted in 2patients (10.5%) and hypertension in 2cases (10.5%). Laboratory tests showed an average proteinuria of 4,65+/- 1.7 g/24h with a range of 2 and 6.5g/24h. Nephrotic syndrome is noted in 14 patients (66%); a renal failure is noted in 6 cases (28.5%), with anuria in 2 patients, 83% of them had low GFR values (<50 mL/min/m2). A glomerular proteinuria is found in 1 case.

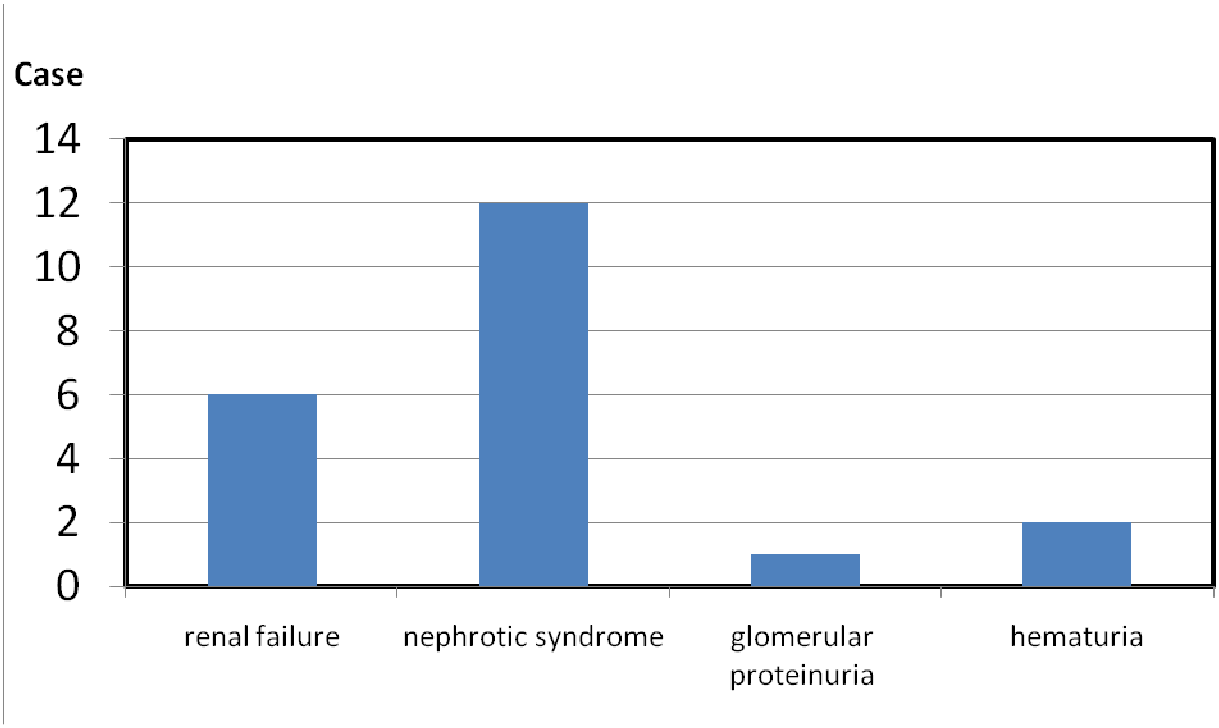

Figure 2: clinical presentation of renal amyloidosis.

At the time of diagnosis, a digestive involvement, revealed by chronic diarrhea, was noted in 4 patients. Dysautonomic involvement, including orthostatic hypotension, was noted in 17 patients (80%). No heart involvement was noted (figure 3).

The diagnosis of amyloidosis is carried on renal biopsy in 20 cases, and on one of two rectal biopsies carried out. Five accessory salivary glands biopsy realized were negatives.

AL amyloidosis was noted in 4 patients (19%), all cases were secondary to multiple myeloma. AA amyloidosis was noted in 17 patients (80.9%), mainly caused by chronic infections in 42 %, pulmonary tuberculosis was noted in 8 patients, a digestive tuberculosis was found in one patient.Chronic inflammatory rheumatisms were noted in 3 patients (14%), one case of rheumatoid polyarthritis, with an average evolution of 8 years, one case of psoriatic arthritis, with 6 years of evolution, and one case of systemic lupus eryhtematosus with 5 years of progression.

An association of pulmonary tuberculosis and rheumatoid polyarthritis was noted in two patients (9.5%). Solid cancer was found in one case. Bronchiectasies, without tuberculosis history, were noted in 2 patients (9.5%).

At the time of diagnosis, 2 patients were considered in end stage renal disease, and they were given renal replacement therapy (hemodialysis).60% of all patients received angiotensin receptor blockers or angiotensin converting enzyme inhibitors in order to reduce proteinuria.

Patients with al amyloidosis were typically treated with chemotherapy. A regimen of cyclophosphamide-bortezomib- dexamethasone. Or melphalan-dexamethasone bortezomib

The treatment of AA is directed toward the underlying condition. Two patients were treated by methotrexate but without improvement.

Evolution was marked by the setting of end stage renal disease in 5 patients, with an average of 9mois. Death occurred in 3 patients. 8 patients were progressing to chronic renal kidney disease; 5 patients were lost of view.

Organimpairement	Case	Amylose type	%
Pporgeneral state + weightloss	15	AA + AL	71.4%
Digestive involvement (chronic diarrhea)	4	AA	19%
Dysautonomicinvolvement(hypotension)	17	15 : AAamyloidoisis 2 :ALamyloidosis	80%
heart involvement	2	1 : AAamyloidoisis 1 :ALamyloidosis	9.5%
Liverinvolvement	2	1 : AAamyloidoisis 1 :ALamyloidosis	9.5%
Splenicinvolvement	1	AA	4.76%

Figure 3: the mains extra renalmanifestations

Medicalhistory	Case	Seniority (years)	%
pulmonary tuberculosis	8	16	38
digestive tuberculosis	1	7	4.7
pulmonary tuberculosis(PT)+ rheumatoid polyarthritis (RP)	2	PT 15.5 RP 8.5	9.5
rheumatoid polyarthritis	1	8	4.7
Psoriasicrheumatoid	1	6	4.7
systemic lupus eryhtematosus	1	5	4.7
Solid cancer	1	6	4.7
Bronchiectasies	2	16	9.5

Figure 4 : Etiologies of amyloidosis AA.

Discussion:

Amyloidosis 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, no branching, randomly oriented fibrils ranging in diameter from 7 to 14 nm on ultrastructuralexamination. In Turkian study, AA amyloidosis was found in 81 patients (15.2%) from an overall number of531 renal biopsies(7). The Italian Registry of Renal Biopsies reported a frequency of 2.5% of renal amyloidosis among14,777 renal biopsies in a 7-year period(8). In our study, amyloidosis was found in 9.6% from an overall number of renal biopsies.

In the United States and Europe, AL amyloidosis is the most prevalent form, followed by AA amyloidosis (AA). The incidence of AL is 6 to 10 cases per million population(6). 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(6). In developing countries such as Morocco, however, AA is more common than AL(9), as our study shows.

Renal involvement is a frequent manifestation ofamyloidosis, mainly AL, AA, and hereditaryamyloidosis(10), and it is a major source ofmorbidity in these patients.

Patients typically present with asymptomaticproteinuria, nephrotic syndrome, progressive renal decline orend-stage renal disease (11). But, in patients who have amyloid deposition limited in blood vessels or kidney tubules, renal failure may be observed with lower amounts of protein leakageor without proteinuria(12). Tsai et al(13) reported 80% of patients with amyloidosis had nephrotic syndrome and 40% of them had low GFR values (<50 mL/min/m2). In another study from Spain, 69.5% of patients with amyloidosis had nephritic syndrome and GFR values were lower than 60 mL/min/m2in 70% of AA amyloidosis group(14). In our study, UPE 4,65+/- 1.7 g/24h, and GFR was less than 50 mL/min/m2in 83%.

The diagnosis of amyloidosis can be made with certainty in a majority of cases using a combined approach including light microscopy, immunofluorescence, and ultrastructural analysis (6). Amyloid has a characteristic Congo red–positive staining (salmon pink) and fluorescence with thioflavin T or S. The Congo red–positive material must polarize and produce anomalous colors (yellow/orange/green) under polarized light to be considered diagnostic of amyloidosis (6). Amyloid can involve any compartment within the kidney, but glomerular involvement predominates in the majority of cases(15). Glomerular involvement is present in 97% of cases and vascular involvement is identified in 85% of the cases, whereas the interstitium is affected in 58% of cases(4).

In developed countries, rheumatoid arthritis is the most common cause of AA amyloidosis with renal involvement, while in developing countries patients with untreated FMF and chronic suppurative infections constitute a large proportion of AA amyloidosis cases(7). In various studies, FMF appears tobe the leading cause of AA amyloidosis in Turkey, followed bytuberculosis (7). In our study, the most frequent underlying cause of AA amyloidosis was chronic infections, followed by chronic rheumatic diseases and this observationwas consistent with previously reported findings from ourcountry(16).

The treatment of AA is directed toward the underlying condition, including anti-inflammatory therapy, antibiotics, or surgery. Patients with hereditary amyloidosis, including those with AFib, ATTR, and AApo AI, in whom the liver is the source of precursor protein, are treated with liver transplantation.

Patients with AL amyloidosis are typically treated with chemotherapy. A regimen of melphalan-dexamethasone bortezomibis used for patients with stage I and II cardiac involvement (17). Patients with stage III cardiac involvement or advanced CKD are generally treated with cyclophosphamide-bortezomib dexamethasone (17) High-dose melphalan–autologous stem cell transplant is generally offered to patients with stage I or II cardiac involvement who have a GFR greater than or equal to 30 mL/min in the absence of advanced other organ failure (17).

The natural history of AA amyloidosis is typically progressive and lead to organ failure and death, especially, in patients with active underlying inflammatory diseases(7).

Heart involvement, higher serum creatinine, lower albumin, dialysis requirement and short time to dialysis were predictors of mortality in this population. The level of SAA is a powerful predictor of both survival and renal outcome inpatients with AA amyloidosis (7).

CONCLUSION

Amyloidosis is a multisystem, progressive and fatal disease.Complications of end-stage renal disease are the main causes of death. It should be considered in the differential diagnosis of patients presenting with nephrotic syndrome or unexplained renal failure, and histological study should be performed. In our context, we have to improve the infectious diseases care, in order to reduce amyloidosis prevalence.

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