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Scoring, Grading and Typing the Patients Diagnosed with Renal Amyloidosis by Renal Needle Biopsy

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Abstract

Objective: Amyloidosis is a common diagnosis of a group of diseases with extracellular accumulation of amyloid fibrils. Histopathological diagnosis of amyloidosis is made by Congo Red (CR) staining as routine histochemical method. The clinical and histopathological features of amyloid deposition vary according to the type of precursor protein. Renal amyloidosis is one of the causes of chronic renal failure. In this study, we aimed to describe the typing, classifying and grading of renal amyloidosis, evaluation of clinical prognosis, and to identify the parameters to standardise the reports and to determine the relationship between these parameters and their subtypes with clinical prognosis.

Materials and Methods: This study was approved by the Erciyes University Clinical Research Ethics Committee with the number 2013-163 In our study, 160 of the cases who were diagnosed with renal amyloidosis between 1998 and 2012 were included. Extracellular deposition of eosinophilic amorphous amyloid was seen in the sections stained with hematoxylin-eosin. In order to identify the amyloid deposits, sections were stained with CR. Green reflection under polarised light was considered as positive. Amyloid deposition sites and distribution were scored and AA amyloid, CD95, Ig kappa, Ig lambda, β2 microglobulin were used as immunohistochemical markers. The results were analysed using chi-square, multivariate analysis tests. P value of <0.05 was considered significant.

Results: In 75 of the cases diagnosed with renal amyloidosis were identified as advanced stage of amyloidosis. As the amount of amyloid deposition in the glomeruli increased, a statistically significant relationship was found between the renal prognostic amyloid score and vascular amyloid accumulation. There was a significant relationship between amount of proteinuria and stage of the disease. There was a significant relationship between serum creatinine levels and interstitial fibrosis as well as interstitial inflammation. Immunohistochemical markers were used in 89 cases. AA amyloid was detected in 76 cases (85%), positive staining for Igλ detected in 1 case, CD95 in 1 case and there was no positive staining in 11 of the cases.

Discussion: Histopathologic differentiation of renal amyloidosis from similar lesions is needed. The importance of detection and typing of amyloid proteins is increasing, and in cases diagnosed with amyloidosis, reports need to be standardized. The diagnostic approach should be multidisciplinary and clinical and pathological evaluation should be performed carefully.

Keywords: Amyloidosis; Congo red; Immunohistochemistry; Kidney; Standardisation

Introduction

Amyloid is a proteinous substance that accumulates between cells and causes dysfunction of many tissues and organs. The diagnosis of amyloidosis is made by chemical analysis, macroscopic and microscopic examination, application of immunohistochemical methods and electron microscopy. Eosinophilic amorphous extracellular material accumulation is important in the examination of frozen or paraffin sections of surgical specimens or needle biopsies after H&E staining [1-5]. In the sections stained with Congo Red (CR), brick red stained amorphous material accumulation and presence of green birefringence as result under polarized light in light microscope is the gold standard in diagnosis. Sirius red, Thioflavin-T fluorescence methods, crystal violet, Thioflavin-T methods are some of the other methods other than CR that can be used to demonstrate amyloid deposition [6-9]. Renal involvement of amyloidosis is the most common and the most serious involvement of amyloidosis. Renal amyloidosis is seen in 1-5% of patients who presents findings of nephrotic syndrome. Its prevalence increases with age. The development is initially manifested without proteinuria and it is followed by microalbuminuria and eventually presents the findings of nephrotic syndrome. Proteinuria is moderate and nonselective (5-7 g/dl). Amyloidosis, independent of whether it is primary and secondary, accounts for 90% of the kidneys. In our country, in chronic tuberculosis, spondyloarthritis and especially in FMF, secondary nephropathy associated with amyloidosis is observed [10-12].

Macroscopically, there may be no change in the kidney, and in the case of long-term disease the size of the kidney may be small [13,14]. Amyloid deposits settle mainly on the glomeruli in the kidney but can be found in interstitial, peritubular tissue, blood vessel walls. In glomeruli, accumulations can be seen at first as focal deposition in the mesengial matrix and diffuse or nodular thickening in basal membrane of the bundles of capillary. Storage progresses over time to the capillary lumen and eventually causes total obliteration of the vascular bundle [10,15,16]. Correlation of amyloidosis type with clinical findings is important in the treatment of renal involvement of systemic amyloidosis, in terms of treatment selection, and determining the prognosis [17]. Amyloid deposition in vascular and interstitial deposits has a better prognosis. Although there is no clear classification in determining treatment options, in recent years, a classification based on the appearance of glomerular deposits in light microscope was performed in similarly to the classification of glomerulonephritis in systemic lupus erythematosus [16].

In amyloidosis patients, the prognosis varies according to the type of amyloid and the underlying cause. The mean survival in AL amyloidosis is 1-2 years, while it is in the ATTR amyloidosis higher as it is 15 years.-The prognosis is worse in cases with light chain cast nephropathy [18]. Renal amyloidosis can be defined as glomerular, interstitial or vascular amyloid deposition according to the distribution of amyloid deposits in the renal parenchyma [10,15,16,19]. Amyloid A protein quantity evaluated also in adipose tissue of patients with AA amyloidosis. In this study, we aimed to determine the clinical correlation by applying the suggested classification and in addition by dividing the patients into subtypes in 160 patients whom diagnosis is established by renal needle biopsy as renal amyloidosis.

Materials and Methods

This study was supported by Clinical Research Ethical Committee of Erciyes University with number 2013-163. In this study, 160 patients with amyloidosis that obtained by renal biopsy in Erciyes University Faculty of Medicine Department of Pathology between the years 1998-2012 were retrospectively examined. Specified blocks and hematoxylin and eosin stained preparations of the patients with amyloidosis as their pathology reports pointed founded in the archive re-evaluated. Amorphous material accumulation that observed pink with H&E staining was stained with CR. 5-micron cross sections were made from formalin-fixed paraffin-embedded tissue. Sections were kept in CR for 5 minutes and then differentiated in alcoholic potassium hydroxide solution for 3-10 seconds and washed in water. 2-3 minutes after had stained with H&E, washed with and passed through a series of increasing concentrations of alcohol and was closed with the shutdown solution.

In sections which showed positive staining, the ones that cause green birefringence under polarised light were considered as positive. It was classified and scored according to the location, quantity and characteristics of this substance which accumulated in cases. Scoring was made according to the scoring system which supported by Şen S, et al. [16] (Table 1).

Classification of glomerular amyloid accumulation	GAP None: 0	Minimal: 1	Minimal mesengial: 2	Focal Mesengial: 3	Mesengio Capillary: 4	Membranous: 5	globally sclerotic: 6
% of glomerular amyloid deposition	GA% 0, :0	1-10%: 1	11-25%: 2	26-50%: 3	51-75%: 4	76-100%: 5	
Accumulation of vascular amyloid	VA None: 0	Minimal: 1	Focal: 2	Middle: 3	Severe: 4		
Interstitial amyloid accumulation	No IA: 0	Minimal: 1	Focal: 2	Middle: 3	Severe: 4		
Interstitial fibrosis and tubular atrophy Ifib	0	1-10%:1	11-25%: 2	26-50% :3	51-100%: 4		
Interstitial inflammatory infiltration Iinf	0	1-10%: 1	11-25%: 2	26-50%: 3	51-100%: 4		
Glomerular sclerosis; GS	0	1-10%: 1	11-25%: 2	26-50%: 3	51-100%: 4		

Table 1: Grade and Renal Amyloidosis Prognostic Score.

Grade of definition: RAPS

RAPS=GAP+GA%+VA+IA+Ifib+Iinf+GS

Grades of renal amyloidosis: 0-31

No amyloidosis: Grade 0: 0

Early renal amyloidosis: Grade 1: 1-7

Late renal amyloidosis: Grade 2: 8-15

Advanced renal amyloidosis: Grade 3: ≥ 16

The cases that are classified according to this system in the second phase of this study are tried to subtyped by using β2 microglobulin, A amyloid, CD95, Ig κ and Ig λ markers. 5-micron sections were made from eighty-nine formalin-fixed paraffin-embedded tissues and were taken into Poly-L-lysine-coated slides to prevent tissue lost. Sections after waiting in 60° c drying oven for an hour was embedded into paraffin with xylene for 15 minutes. Hydrated by passing through a series of decreasing concentrations of alcohol and washed with distilled water. Sections were boiled in a microwave oven with 1 mM citrate and allowed to cool in room temperature. Tissues were washed with phosphate Buffered Saline (PBS) for 10 minutes. Endogenous peroxidase activity was bloked with hydrogen peroxide to reduce the non-specific background. Washed with PBS for 10 minutes. An Amyloid (AA), (Abcam mcl prediluted), CD 95 (Abcam rabbit polyclonal), Beta2 (β2) microglobulin (Santa Cruz (BBM 1)) Ig κ (Santa Cruz MH19-1) and Ig λ (Santa Cruz 48) were used as the primary antibodies. Avidin biotin peroxidase method was applied by using treptavidin-biotin kit in immunohystochemical staining. Washed with PBS for 10 minutes. Streptavidin peroxidase conjugate were applied for 10 minutes. Washed with PBS for 10 minutes. DAB chromogen was applied for 10 minutes. Washed with PBS for 5 min. Washed with deionized water for 5 minutes. Mayer's hematoxylin was applied as counter staining for 2 minutes. Washed in tap water for 10 minutes.

Had passed through increasing concentrations of alcohol and allowed in xylene for 15 minutes. Closed with shutdown solution. The processes were applied at room temperature and in a humid environment to allow the tissues not to dry. As a positive control, kidney tissue was used for AA, Langerhans cell islet in pancreatic tissue for β2 microglubulin, endometrial stroma for Ig κ, germinal center cells for Ig λ, and small intestinal epithelial cells for CD95. Prepared sections were examined under light microscope. Immunohistochemical evaluation revealed positive staining of amyloid deposition for AA, membranous positive staining for CD95, cytoplasmic positive staining for β2 microglobulin, cytoplasmic positive staining for Ig için, and membranous positive staining for Ig λ. In this study, positive or negative outcomes were evaluated by using Olympus brand microscope in 200 magnifications. Evaluations done by two pathologists. Statistical analysis of the findings was performed by using the SPSS (Scientific Package for Social Sciences) 15.00 program. Chi-square test, T-test, Kolmogorov-Smirnov test, variance analysis was used at comparisons. P value of <0.05 were considered as significant.

Results

160 cases were included in this study. 101 of the cases were male and 59 were female. Since two of the patients had no hospital

registration information, their ages are unknown. The mean age of the rest of the cases was 48 [3-5,9-84] One of cases (0.7%) was being followed up for presenting clinic features of nephritic syndrome. Rest of the cases were being followed up with the pre-diagnosis of nephrotic syndrome (99.3%). One of the cases was diagnosed following nephroctomy that was due to chronic renal failure and all other cases were diagnosed by renal needle biopsy. 26 (16.3%) of the cases were evaluated with RAPS grade 1, 59 (36.9%) with RAPS grade 2, 75 with RAPS grade 3 (46.9%) (Figures 1-6). The GAP and GA values increased significantly in correlation with the grade of RAPS ($p < 0.05$). Ifib, Ifib, and VA were also increased significantly in correlation with the grade of RAPS ($p < 0.05$). As GA increases, VA increases statistically significantly. ($p = 0.05$). When compared with the GA and grade of RAPS, the results are not significant in contrast to some other studies ($p > 0.05$). As the age of the patients increased, the GS value and the RAPS grade increased ($p < 0.05$). There is no significant difference between gender distribution and grades.

GA of the cases, Iinf, GS and RAPS grade were increased significantly as the proteinuria becomes more severe ($p < 0.05$) (Table 2).

Grade Proteinuria Amount Cases
RAPS Grade 1 5,010 (0.31-5.30) 18
RAPS Grade 2 5,285 (0.07-48.14) 34
RAPS Grade 3 7,865 (0.39-69.8) 54

Table 2: Proteinuria Amount According to RAPS Grade.

Biochemical serum creatinine levels were significantly increased in correlation with the increase of GAP, GA, Ifib, Inf, GS and grade of RAPS ($p < 0.05$).

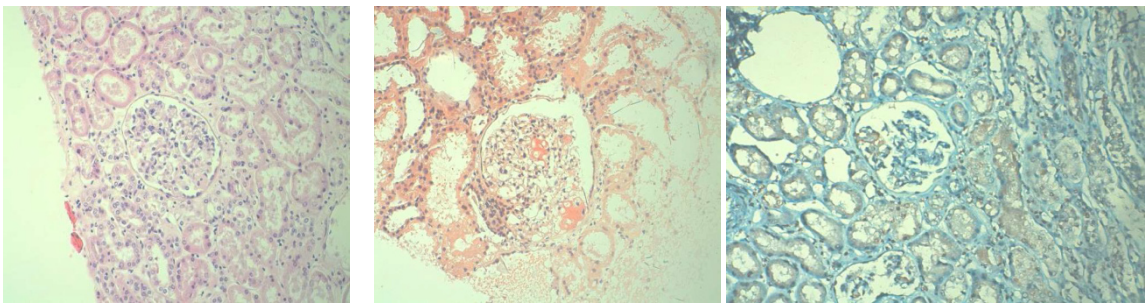

Figure 1: H & E, Histochemical and Immunohistochemical staining of GA-I.

(a): The appearance of glomerular amyloid deposition under light microscope with H & E (x 40).

(b): Positive staining with Congo Red histochemical staining method (x 40).

(c): Positive staining of amyloid deposition with AA from immunohistochemical studies (x 40).

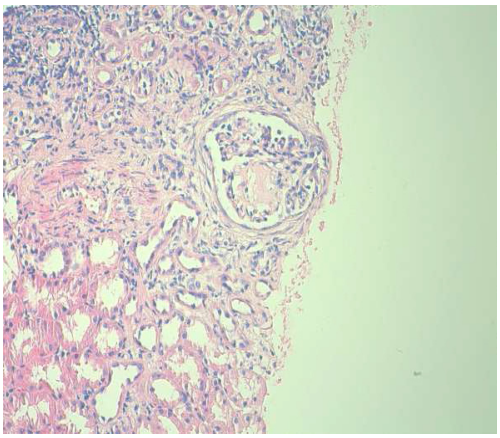

Figure 2: HE and histochemical staining of GA-II. The appearance of glomerular amyloid deposits with HE (x 40).

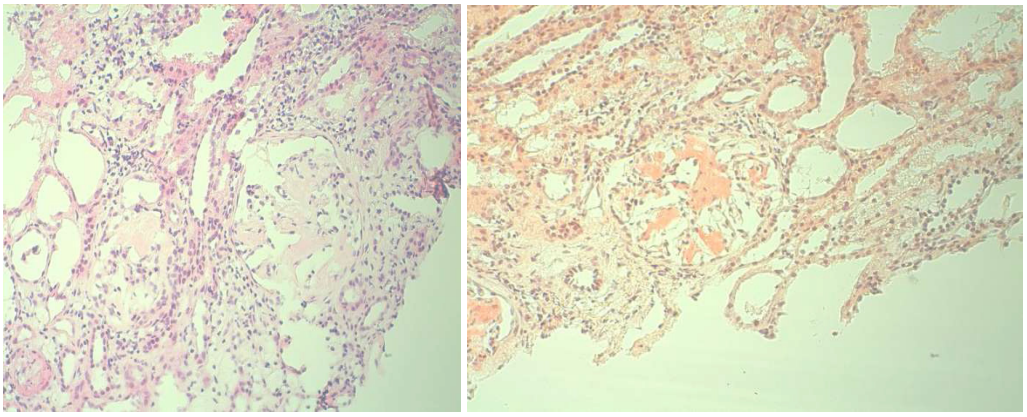

Figure 3: HE and Histochemical staining of GA-III.

(a): The appearance of glomerular amyloid deposits with HE (x 40).

(b): Positive staining with Congo Red histochemical staining method (x 40).

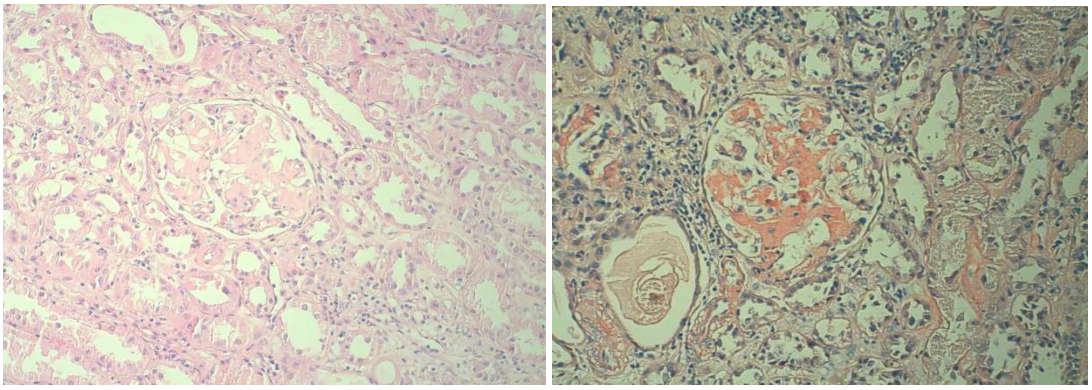

Figure 4: HE and Histochemical Staining of GA-IV.

(a): The appearance of glomerular amyloid deposits with HE (x 40).

(b): Positive staining with Congo Red histochemical staining method (x 40).

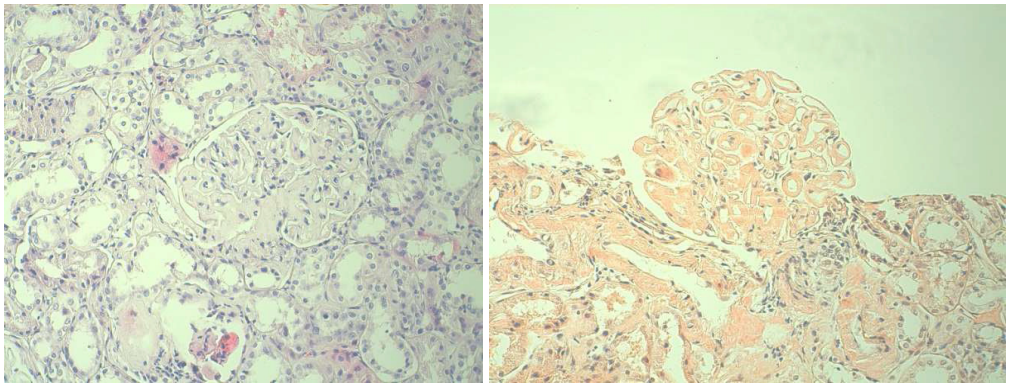

Figure 5: HE and Histochemical Staining of GA-V.

(a): The appearance of glomerular amyloid deposits with HE (x 40).

(b): Positive staining with Congo Red histochemical staining method (x 40).

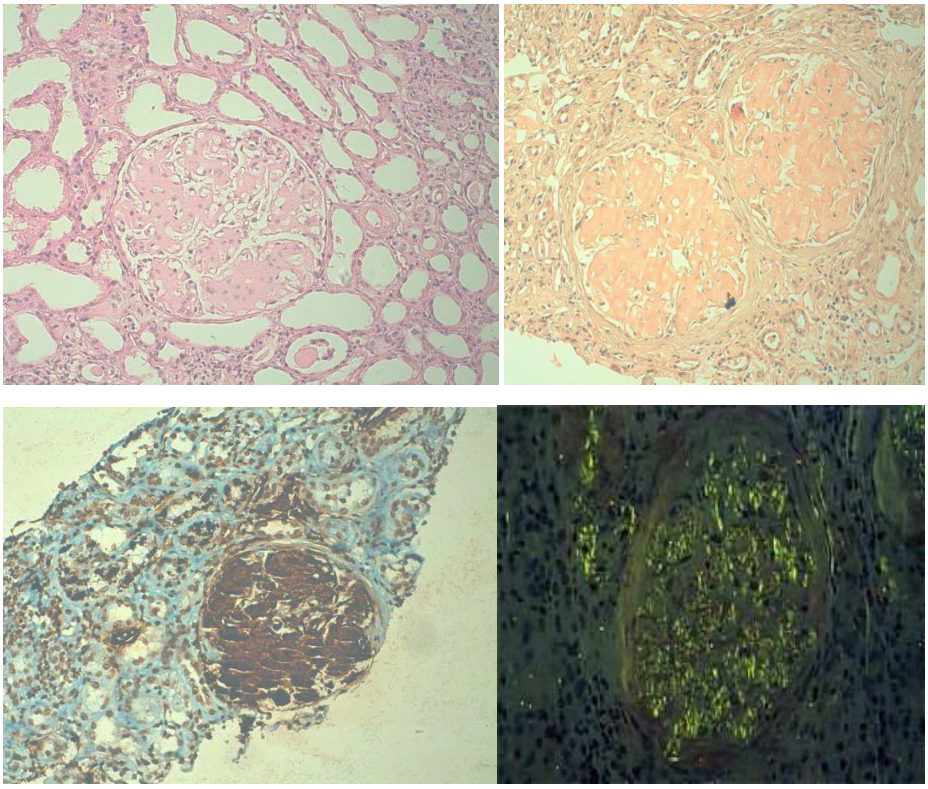

Figure 6: HE and histochemical Staining of GA-VI.

(a): The appearance of glomerular amyloid deposits with HE (x 40).

(b): Positive staining with Congo Red histochemical staining method (x 40).

(c): Positive staining of amyloid deposition with AA from immunohistochemical studies (x 40).

(d): Amyloid deposition that causes green birefringence under polarised light in immunofluorescent studies (x 200).

IHC was performed on 89 paraffin blocks of the cases. Seventy of the cases were showed positive staining with immunohistochemical markers (68 of them were with AA positive, 1 CD95 positive, and 1 Ig Lambda), while 6 of cases were showed positive staining with two immunohistochemical markers (2 of them were with AA + β2, 1 AA + CD95, 2 AA + Ig Lambda, and 1 AA + Ig Kappa) and 2 of them were showed positive staining with 3 immunohistochemical markers (1 of them were AA + IgKappa + IgLambda, and 1 positive with AA + IgKappa + CD95). Positive staining with Amyloid immunohistochemical marker was observed in 76 cases. In one patient, Ig Lambda was CD95 positive, while no positive staining with any markers were observed in 11 patients. While Familial Mediterranean Fever (FMF) was the leading cause of the disease in 28 (31.4%) of the cases whom clinical information can be reached, the rate of chronic inflammatory diseases came after FMF. Collagen tissue diseases were in third place.

Discussion

Amyloidosis is an uncommon heterogeneous group of diseases that cause clinical results with extracellular accumulation of insoluble protein fibers [70]. The most commonly affected organ is the kidneys and End Stage Renal Failure (ESRF) is generally inevitable [71,72]. The diagnosis of amyloidosis is made by histopathological examination of the biopsy after clinical suspicion. In the diagnosis of systemic amyloidosis, abdominal subcutaneous fat aspiration and rectal biopsy taken by gastrointestinal endoscopy are non-invasive methods. The sensitivities of these methods are 80% and 75% respectively. In Japan, where upper gastrointestinal system screening is common, endoscopic biopsy of duodenum was reported to be highly sensitive (6,73 tar77). The sensitivity of invasive biopsies is 100% in the heart and 94% in the kidney [76-78], while this rate is about 50% in bone marrow and skin biopsy. In our study, renal biopsy was performed for diagnostic purposes

in all cases because of the complaint of edema and proteinuria as renal biopsy has a relatively high rate of positive results [79]. The risk of bleeding in renal needle biopsy is significantly higher than in non-amyloidosis cases [77]. Various methods are being used for the diagnosis of amyloidosis in biopsies.

In our study, CR histochemical staining method, which is accepted as the gold standard, was preferred for diagnosis. Amyloidosis is more common in men than in women. In our study, it is more common in men with a ratio of 1.71 in accordance with the literature.

Age distribution varies among types of amyloidosis. In developed countries where primary amyloidosis is more common, patients are older. The average age was 63 in study of Wright et al. while in the study conducted by Kyle et al. it was 61 and in their study Yılmaz M. et al. reported the mean age of 41.85 among the patients [3,81,82]. The mean age in our study was 48 years. The reason of lower mean age of the patients in our study compared to developed countries is thought to be that in our country FMF is frequently seen and infectious diseases cannot be kept under control effectively.

Bilginer et al. pointed out in their study the renal amyloidosis in children. In our study, 20 (12.5%) patients were under or equal 18 years old and FMF was found to be the underlying cause in most of this patients. In follow up of these patient's renal transplantation was performed in 4 patients and 3 patients had died due to renal failure. This shows that severe amyloidosis in childhood is also common and emphasizes the importance of early recognition. Renal amyloid deposits are well known to vary in amount and location. Early glomerular amyloid deposits are punctate and segmental; late amyloid deposits tend to be more extensive. Many investigators have attempted to describe the pattern of glomerular amyloid deposition. Watanabe and Saniter graded glomerular amyloid accumulation from 0 to 4, and vascular amyloid deposition from 0 to 3 [57]. Shiiki, et al. and Nagata et al. graded the extensity of glomerular amyloid deposition was 1 to 4, as less than 25%, between 26-50%, and between 51-75% and more than 75%.

The distribution of amyloid in the vessels is concurrently evaluated with the degree of interstitial fibrosis as "0, none; 1, mild; 2, medium; and 3, advanced" [58,59]. A similar scoring system was used by Verine, et al. [19]. Sasatomi, et al. used a semi-quantitative assessment for amyloid deposition in the glomeruli, interstitium and vessels, which could also be applied by computer-mediated morphometry. Each lesion was scored from 1 to 3. The sum of the damage associated with amyloid deposition (0-9) indicates the numerical code of renal pathological damage [60]. Verine defined the renal amyloid load such as Sasatomi et al. Computer assisted morphometry has been used by Oguchi, et al. [61]. In their study, Hopfer et al. separated the glomerular accumulations (glomerular amyloid load) as segmentally and globally, and divided the glomerular form as mild, moderate and severe. Fibrosis was given in percent and four-grade scoring was performed for inflammation. They indicated that amyloid accumulation is a continuous process by stages I, II and III (IIIa and IIIb) which was described in the previous method. They reported that the cases were generally diagnosed in Stage III [84]. In our study, most of the cases were in advanced stages. Similarly, to the classification of glomerulonephritis in systemic lupus erythematosus which made by Şen, et al. [16], while the majority of the cases examined in the study that classified the distribution of glomerular amyloid deposits according to six different patterns were stage 2, in our study, there were signs of advanced stage amyloidosis in patients and cases with stage 3 were common. We think that this difference is due to regional and socioeconomic differences and the late referral of the patients to the hospital.

Glomerular involvement is known to be important for renal amyloidosis. They were glomerular involvement in over 80% of the patients. Hopfer, et al. has shown that in patients with diffuse global involvement of glomerulus, the amount of proteinuria increased significantly in a correlation with serum creatinine [85]. In our study, the amount of amyloid accumulation and distribution in the glomerulus increased significantly with grade and the amount of proteinuria increased as the grade increases <0,05. Watanabe, et al. reported that some renal amyloidosis cases were predominantly vascular. Hopfer, et al. Reported in their study that vascular involvement in primary amyloidosis was higher than secondary amyloidosis [85,86]. In the study conducted by Kösemehmetoğlu, et al., vascular and glomerular components affected equally [24]. In our study, it is seen that the glomerular involvement was dominant. This can be explained by the fact that AA type amyloidosis was the most common diagnosis in our study and glomerular accumulation was more frequent in our cases. Significantly, vascular involvement increases with glomerular amyloid deposition. ($p<0.05$).

There are some studies showing the relationship between prognosis and interstitial damage in renal amyloidosis. In the studies done by Manckensen S, et al. and Bohle A, et al. draws attention to the importance of tubulointerstitial injury, especially interstitial fibrosis, in determining renal function. In the study of Hopfer, et al. advanced and diffuse glomerular amyloid deposition and interstitial fibrosis increased significantly [85,87,88]. In our study, interstitial inflammation and interstitial fibrosis increases significantly as serum creatinine levels and interstitial inflammation and proteinuria amount increase similar to the other studies in literature ($p<0,05$). This is very important in terms of prognosis only in renal needle biopsies containing medulla. Interstitial amyloid deposits often occur in patients with hereditary amyloidosis. In the study conducted by Bohle A, et al. interstitial pattern has been shown to be insignificant with serum creating clearance [87]. In our study, interstitial amyloid deposits were quite a few and there was no significant relationship between the increase of grade.

Although all the amyloids share common structure and staining properties, the main protein which the fibrils consist of varies from disease to disease. Typing is necessary for the primary treatment of the disease or the treatment of the underlying disease [89]. For example, because of primary amyloidosis is associated with hematological malignancies, chemotherapy regimens are given while in FMF, which is one of the most common causes of secondary amyloidosis in our country, colchicine treatment is given primarily. In addition, primary treatment of the underlying disease in amyloidosis related to a chronic infection is essential. With appropriate methods of treatment, progression of the amyloidosis can be slowed, stopped and even eliminated. Therefore, the type of amyloid must be identified. In the first study which conducted in 1972, Romhanyl distinguished the primary and secondary amyloidosis by using the potassium permanganant method ($KMnO_4$). According to that, the double-breaking of the polarized light after $KMnO_4$ application is lost in secondary amyloidosis while continues in primary amyloidosis [90].

Currently, because of its low reliability, it has been abandoned and immunohypochemical methods, immunofluorescence methods, immunoperoxidase methods and electron microscopy are used for typing. Rainer et al. used the method of immunperoxidase, which exhibited less ground staining and longer reaction time than fluorescence in routine practice. This method is especially useful in the diagnosis of primary and β2 microglobulin Amyloidosis. In the study done by Stefan et al. indicated that immunohistochemical techniques were quite useful in the subtyping of amyloidosis [91]. It is thought to be more sensitive in comparison with immunperoxidase method in typing of secondary amyloidosis. In our study, we aimed to make this distinction by using immunohistochemical markers which are more common and easily applicable. According to the actual studies, while in developed countries, especially the United States, the most common type of Amyloidosis is AL, AA type is most common in developing countries [58]. While in Western Europe, AA/AL ratio is 2:1, this rate is 1:17 in the United States. In a study done by Mayo clinic, 74% of the amyloidosis cases were AL type, 4% was AA. In the study done by Kyle, et al., while the rate of primary amyloidosis was 55.6%, secondary amyloidosis was 8%. [92]. The rate was 91% in the study of various organ biopsies done by Ensari et al., 91% in the study of renal biopsies done by Şen S, et al., 94.4% in the study done by Kösemehmeyoğlu K. and 75.6% in the study done by Başlamışlı F. In our study, also in consistency with literature, the AA type amyloidosis was the most common as it corresponded to 85% of the cases, and each of Ig λ and CD95 corresponded to 1% of the cases and in 13% of the cases couldn't be typed. The reason of not being able to type is that the use of a limited number of immunohistochemical markers in our study. We think that there are other subtypes of amyloids in this cases. Compared to other studies, the decrease in AA ratio may be due to the fact that not all organ amyloidosis is included in the study. In addition to the geographic differences, it is thought that diseases such as FMF and Rheumatoid arthritis may be depending on ethnical differences and environmental factors.

While the most common reason of the AA in the western countries is Rheumatoid arthritis, chronical infectious processes is the primary cause in developing countries. FMF is quite common in countries with Mediterranean coast [61]. In our study, FMF was the most common cause and it was followed by the chronic obstructive pulmonary disease. In the study conducted by Nieva, et al. reported that the increase of the lipid aldehyde levels in plasma and light chain deposition disease and systemic AL amyloidosis. Also in this study, in addition to the positive history for hyperlipidemia there was plasma cell dyscrasia in Igλ positive case [93]. In our study, there was proteinuria in the cases with positive staining for CD95 and the patient died shortly after diagnosed with renal amyloidosis. In the study conducted by Altemeier W, et al. and Mulay, S. et al., has shown that the loss of Fas gene related caspase-1 activation accelerated the progression to renal failure and increased the calcium oxalate crystal structure. In the case in our study, it is observed that many procedures were made due to nephrolithiazis [94-97].

In conclusion, renal involvement is a prognostic factor in systemic amyloidosis. Therefore, a pathology report should report the amyloid distribution field, the accumulated amyloid load and the amyloid precursor protein. To determine the amyloid load, SLE-like classification has conveniences. Grade can be determined by detailed scoring. Immunohistochemical methods will be important in our country for typing of amyloid proteins, until protein analysis is done. Clinical and laboratory findings and other tissue biopsy findings should be correlated, considering the immunohistochemical evaluation problems.

More detailed histopathologic definitions and scoring systems are needed to conduct clinical-pathological or international collective and comparative studies.

Results

- Renal amyloidosis is more common in men. The mean age at the time of diagnosis is 48 years.
- While edema due to renal involvement is the most common symptom of systemic amyloidosis, proteinuria presents in almost all cases.
- When diagnosing amyloidosis, congo red staining should be used in cases suspected during routine H & E examination.
- Typing of amyloid should be made for prognostic purposes and to determine the treatment process. Immunohistochemical methods are particularly useful for the diagnosis of AA amyloidosis.

- 85% of the cases had AA amyloidosis. FMF is the most common factor of amyloidosis. Infections and inflammatory diseases are following this.
- AA amyloidosis patients who have FMF as an etiological factor admit to hospital earlier than others because of renal dysfunction.
- Differentiation of other nodular glomerulopathies should be kept in mind in the as the glomeruli may be partially normal in H&E examination of minimal amyloid cases.
- As the accumulation of glomerular amyloid increases, the rate of vascular amyloid deposition and grade of amyloidosis are increasing. The amount of proteinuria increases in severe amyloidosis. Interstitial fibrosis, interstitial inflammation and serum creatinine clearance significantly increased.
- In the report of patients with renal amyloidosis, the type and amount of glomerular amyloid deposits and renal amyloid prognostic score should be included.

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