Tr. J. of Medical Sciences
29 (1999) 665-672

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The Report of 59 Patients with Renal Amyloidosis

Received: January 12.1998

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Abstract: We studied a group of 59 cases with renal amyloidosis. Mean age (45 male, 14 female) was 33.05±13.04 years. All of the cases had secondary amyloidosis. The causes of secondary amyloidosis were as follows: familial mediterranean fever (FMF) 18(30.5%), pulmonary tuberculosis 12(20.33%), chronic osteomyelitis 8(13.55), bronchiectasia 9(15.25%) rheumatic diseases 4(6.4%), Castleman's disease 1(1.6%), unknown etiology 7(11.86%) Hypertension was detected in 15.3% of the cases. In patients with less than 20 ml/min creatinine clearance (Ccr) hypertension was 20%. Hypotension was detected in 6 patients, all of these cases had severe hypoalbuminemia (<2.1 g/dl). Nephrotic range proteinuria (>3.5 g/day) was found in 75% of cases. Daily proteinuria was correlated with serum levels of albumin, total lipid and cholesterol, hematocrit and duration of disease. The mean Ccr was 51.03±40.60 ml/min. Twentynine percent of patients had Ccr less than 20 ml/min. Renal, subcutaneous fat and rectal biopsies demonstrated amyloid in 100%, 20% and 57.6% respectively of patients tested. Patients with secondary amyloidosis were treated with colchicine in addition to the therapy of primary disease (in 6 patients). Nine patients died, and end stage renal disease developed in 12 patients during four years follow up. Proteinuria disappeared or decreased in patients with secondary amyloidosis except secondary to collagen tissue disease, without advanced renal failure. Coclhicine did not affect amyloid deposotion in 2 patients with normal renal function and negative proteinuria, which rebiopsied. We can suggest that cohchicine may have effect (s) for decrement on proteinuria other than reducing the production of these amyloid precursor proteins, can be use in secondary amyloidosis.

Key Words: Amyloidosis, proteinuria, renal function

Introduction

Amyloid is a substance that appears to be homogeneous and amorphous under the light microscope. It is stained pink with haemotxylin-eosin and metachromatically with methyl violet or crystal violet (1).

The spectrum of renal symptoms and signs in amyloidosis is variable such as isolated proteinuria, nephrotic syndrome, hypertension, hypotension, renal insufficiency. The kidneys are affected in almost all patients with AA amyloidosis but less frequently in AL amyloidosis (2, 3).

The therapeutic possibilities in the treatment of amyloidosis are restricted. As amyloidosis is caused by extracellular deposotion of nonphagocytosable insoluble proteins therapy should be aimed at reducing the production of these amyloid precursor proteins.

We presented here clinical manifestations, biochemical features, clinical course of 59 cases with renal amyloidosis and discussed the colchicine's effect.

Patients and Methods

Fiftynine cases with renal amyloidosis biopsy proven were taken to this study but chronically dialyzed patients were excluded. Detailed history, physical exam and laboratory tests (including hematocrit (hct), white blood cell (WBC), erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), creatinine (Cr), Sodium (Na), potassium (K), chloride (Cl), cholesterol, total lipid, total protein, albumin, protein electrophoresis, creatinine clearance (Ccr), daily proteniuria) and urinary sediment were evaluated. The diet of the paients was low protein (0.6-0.8 g/kg/day) with salt restricted (3-4 g/day) and phosphorus restricted (800-1000 mg/day) if they had

creatinine clearance less than 40 ml/min. Calcium carbonate and calcitriol were given to patients according to their serum levels. Primary disease was the causes of the renal amyloidosis. Duration of disease was period related with nephrotic syndrome. Patients were divided into 3 groups; group I was included patients with FMF, group II patients who have infectious diseases (osteomyelitis, bronchiectasia, tuberculosus) and group III others (Behçet's Disease, rheumatic heart disease, ankylosan spondlitis, Castleman's Disease and unknown etiology). Electrocardiogram, telecardiogram, abdominal ultrasonography were used for further evaluation of the patients. Biopsies of kidney and rectum and subcutaneous fat aspiration were performed in all patients except 3 cases. Biopsy samples were stained with Congo red, Crystal Violet in addition to routine histopathologic stains. Potassium permanganate (KMnO4) test for bleaching was performed to all amyloid positive materials. Potassium permanganate sensitive samples were evaluated as AA amyloid. Additionally, the deposition of IgG, A, M, C_3 were evaluated with immunoflourescent method and immunoperoxidase method. Antinuclear antibody, rheumatiod factor, Bence Jones proteinuria and bone marrow aspiration were evaluated to determine the etiology of amyloidosis. Bone radiographs, computerised tomographies and cultures were added in some patients if necessary.

Student "t" test, two paired student "t" test and pearson correlation tests were used for statistical analysis. Mean values were given as mean±standard deviation.

Results

Of fiftynine patients with renal amyloidosis, 45 were male and 14 were female. Mean ages were 33.05±13.04 years (range (R) 16-66 years) and duration of their diseases was between one month and 17 years (mean 25.1±35.5 mo). Disease history was 10.14±10.73 months in all patients, in group I it was 10.64±11.53, in group II patients 10.51±10.63 in group III 8.66±10.85 months. There was not any significant differences between the groups (p=0.0868). Duration of primary disease were 170.40±99.65 (R 12-480) months, 167.22±92.26 (R 72-360) months, 183.60±11.56 (12-480) months, 136.0±83.71 (60-300) months in all and groups I, II, III respectively. Disease duration correlated with the level of total protein (p=0.008) but other parameters were not correlated with disease duration. Primary diseases causing amyloidosis is shown table 1.

Table 1. The causes of renal amyloidosis

Primary Disease	No	%
FMF	18	30.5
Pulmonary tuberculosis	12	20.33
Chronic osteomyelitis	8	13.55
Bronchiectasia	9	15.25
Behcet's Disease	1	1.69
Juvenile rheumatoid arthritis	1	1.69
Rheumatic heart disease	1	1.69
Ankilosing spondylitis	1	1.69
Castleman's diseases (CD)	1	1.69
Unknown etiology	7	11.86

Physical findings: edema, ascites, hepatomegaly and splenomegaly were found to be 85.5%, 35%, 30% and 20% respectively. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 122.88±26.23 (R 80-200) mmHg and 75.96±14.78 (R 40-99) mmHg. SBP and DBP were 125.55±23.75 and 80.61±15.26, 121.03±26.60 and 74.20±14.31, 123.33±30.55 and 73.25±14.81 in groups I, II, III respectively. These values were not different each others. Hypertension (>140/90 mmHg) was found in 15.3% of the cases. The incidence of hypertension was 20% in patients with Ccr<20 ml/min and 10.2% in patients with Ccr>20 ml/min). Hypotension was detected in 6 patients and serum albumin was less than 2.1 g/dl in these 6 patients (R 1.1-2.1 g/dl). Serum level of albumin correlated with SBP (p=0.001) and DBP (p=0.02). There were no correlation between BP and Ccr, proteinuria and duration of disease.

Table 2. Daily proteinuria

Daily proteinuria (g/day)	Percent (%)
>3.5	75.8
1-3.5	17.7
<1	3.2
negative	1.6
Unknown	1.6

Proteinuria was the most frequent laboratory finding and was variable spectrum from asymptomatic proteinuria to severe nephrotic syndrome (mean 5.18±2.62 g/daily R 0.2-24.5 g/daily).

Table 2 and Figure 1 show the distribution of daily proteinuria. There was important relationship between the daily proteinuria and serum levels of albumin (p<0.036), total lipid (p<0.02), cholesterol (p<0.01), hct (p<0.05) and duration of disease (p<0.01).

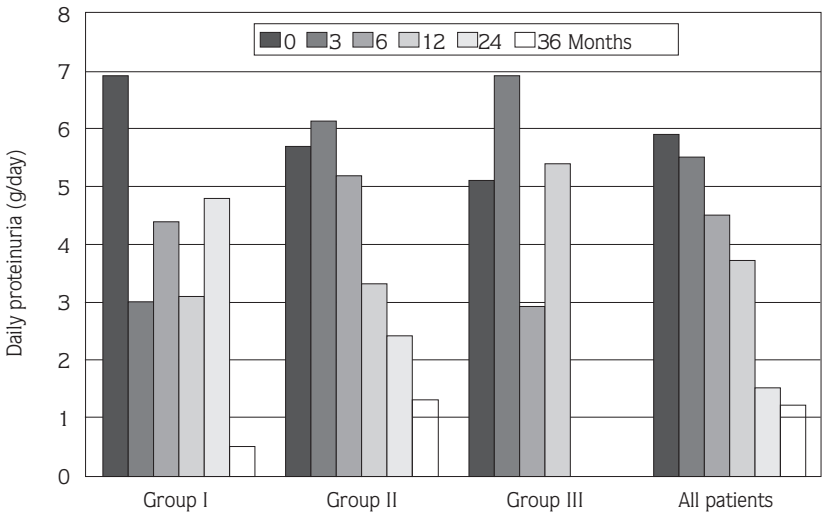

Figure 1. The mean values of daily proteinuria

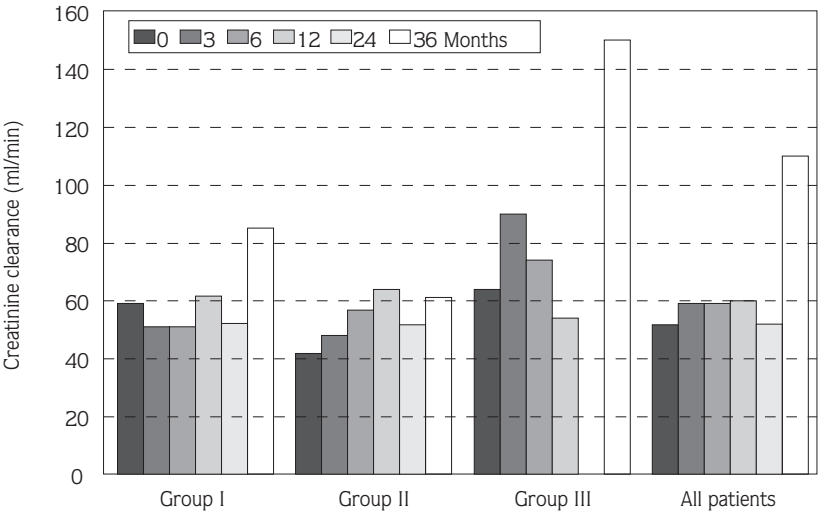

Figure 2. The mean values of creatinine clearances

Ccr values of patients (fig 2) were as follows Ccr>100 ml/min 15.25%, 50-100 ml/min 30.5%, 20-50 ml/min 25.4% 5-20 ml/min 22% and <5 ml/min 6.8%. The mean value of Ccr was 51.03±40.60 ml/min. There was positive correlation between Hct and Ccr ($p<0.001$). Mean serum albumin level was 2.3±0.9 g/dl (R 0.3-5 g/dl). Figure 3 shows the serum levels of albumin. The levels of total lipid was mean 1183±364 (R 590-2100) mg/dl (fig 4). Mean values of total protein, serum cholesterol and hematocrit are seen in figures 5, 6, 7 respectively. Figure 8 shows all these parameters in all patients. Urinary sediment was generally nonspesific. The most frequent findings were WBC and RBC and less frequently granular cast and lipiduria. Mean values of Hct, WBC and ESR were 38±8% (20-51%), 10660±4124 (2000-19800) cumm and 89±34 (12-148) mm/h respectively. In 47% of the cases, leucocytosis (>10000/cu mm) was found but leucopenia in only one patient. Mean ESR was 89±34 (R 12-148) mm/h. Bone marrow aspiration was normal except nonspesific plasmacytosis (in this study, with multipl myeloma were excluded). Positivities for amyloidosis were 100%, 57.6% and 20% in biopsies of renal, rectal and subcutaneous fat respectively. Immunoflourescent staining was disclosed IgA (%41), IgG (%58.3), IgM (50%) and C_3 (66.6%) with nonlinear pattern in glomerular, capillaries and mesangium. All cases were $KMnO_4$ sensitive. In 2 cases who were clinically and biochemically normal after therapy second renal biopsy disclosed amyloid deposotion as seen first biopsy. The

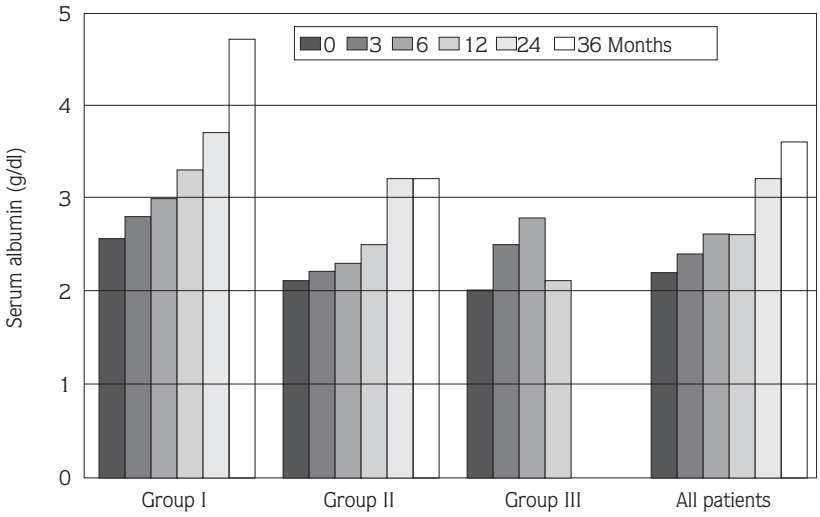

Figure 3. The mean levels of serum albumin

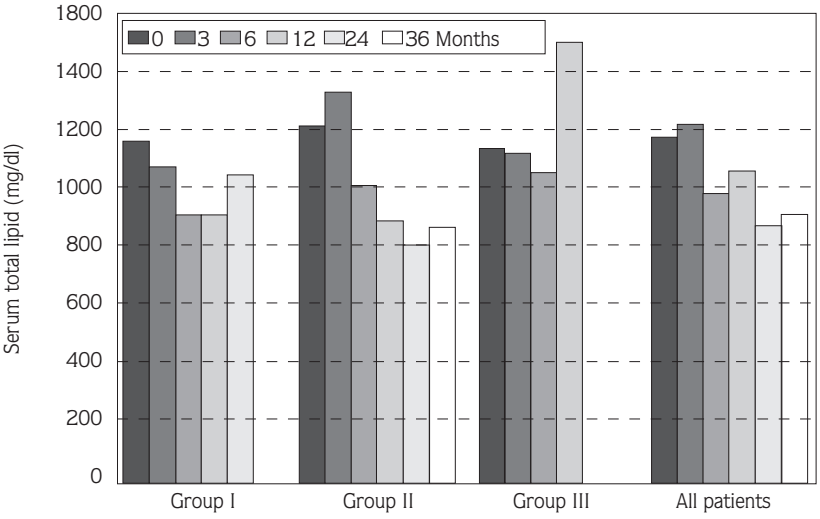

Figure 4. The mean values of serum total lipid

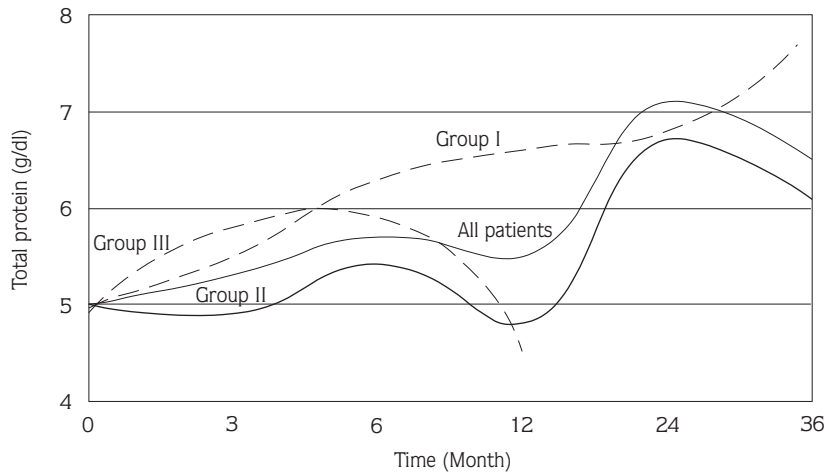

Figure 5. The mean levels of serum total protein

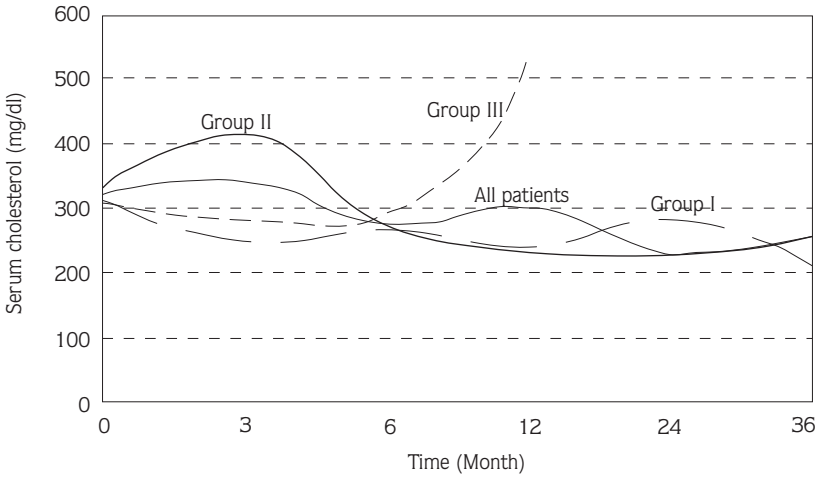

Figure 6. The mean levels of serum cholesterol

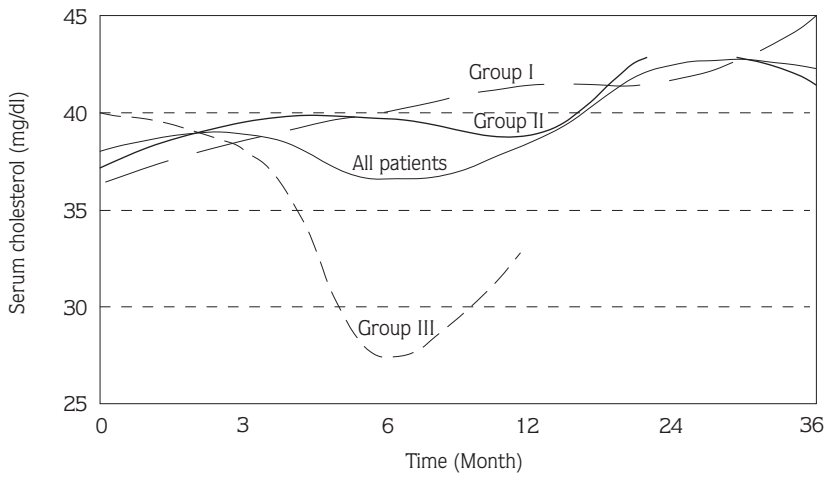

Figure 7. The mean values of hematocrit

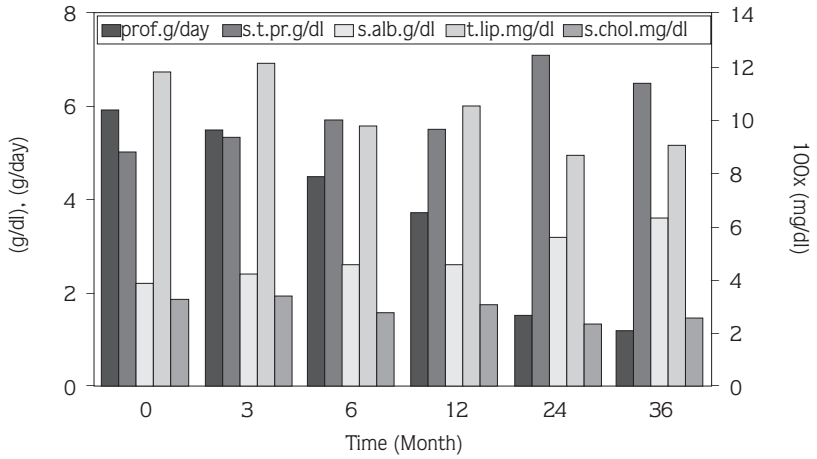

Figure 8. The mean values of daily proteinuria (prot), serum levels of total protein (s.t.pr.), albumin (s.alb.), total lipid (t.lip.) and cholesterol (s.chol.) in all patients.

patient with Castleman's disease was treated with colchicine for 6 months and second rectal biopsy was negative for amyloidosis.

Follow up and Traetment

All cases with secondary amyloidiosis were treated with colchicine 1-1.5 mg per day and other drugs according to causes of amyloidosis (eg 3 patients with osteomyelitis, 6 patients with tuberculosis). Clinical conditions of patients were classified as remission, stable and progressive. If Ccr increased ≥10 ml/min according to first values if Ccr unchanged and if Ccr decreased ≤10 ml/min according to baseline values respectively. Table 3 shows clinical outcome of patients Figure 8 summarizes some biochemical parameters in all patients.

Table 3. Changes in renal function of patients and mortality in follow up

	Renal function				Lost in	
Months	Improvement	Stable	Deterioration	Exitus	follow up	HD
3	13	22	8	4	8	4
6	12	19	8	1	11	(-)
9	8	20	9	(-)	13	(-)
12	9	18	6	3	14	4
24	9	13	4	(-)	16	1
36	7	11	1	1	21	1
48	4	10	2	(-)	22	2

Discussion

In this study we summarized the etiology, clinical presentation, clinical outcome in patients with renal amyloidosis. Duration of diseases was not correlated any chinical parameter except serum total protein (p=0.008). Duration of primary disease had wide range (12-480 months) as other studies (2, 3, 4).

In developed countries rheumatic diseases are 75% cause of secondary amyloidosis (4) however FMF and tuberculosis were the most important diseases. Our interland includes Mediterranean area. It was not suprised FMF was 30.5% of cases.

One patient had rheumatic heart disease, who had operated for mitrale stenosis 14 years ago. Amyloidosis due to rheumatic heart disease is not common but it can be seen (5). Another patients with AA amyloid was treated with colchicine for 2 years because of Behcet's disease. Behcet's disease is systemic vasculitis however renal disease in Behcet's disease is rare (6) and the incidence of amyloidosis is 2%. This case died due to pulmonary hemorrhagie with normal renal function in 2 years after diagnosis of renal amyloidosis.

Amyloidosis secondary to malign diseases except Castleman's disease was not included into this study. Our case with Castleman's disease had severe proteinuria (15 g/day) persisted removal of giant lymph node hyperplasia. After 4 months removal of abdominal mass plasmacytic type we found AA amyloidosis in rectal biopsy and started cohchicine 1.5 mg/day. Six months later proteinuria and hypoalbuminemia disappeared. She was very well clinically and biochemically. She become pregnant. At the end of pregnancy normal baby was born. Control rectal biopsy did not show amyloid deposition in 20th month.

In a renal transplant patient who had amyloidosis secondary to FMF, chronic rejection and AA amyloidosis was detected in transplant kidney. Although it was reported colchicine (1.5 mg/day) prevented amyloid deposotion in transplant kidney (7). The recurrence of amyloidosis without colchicine therapy was reported as 20% (8). Our patient came to us from another center and he had not treated with colchicine regularly.

In our study group proteinuria was the most frequent finding. Nephrotic range proteinuria was detected in 75% of patients as seen in other series (3). Daily proteinuria and serum albumin levels were correlated each other.

Serum levels of total lipid and cholesterol were correlated positively with proteninuria. Duration of disease and degree of proteinuria was found to be correlated. Indeed Cohen (9) reported that asymptomatic proteinuria continued for years. In cases of FMF, it was reported it takes 3-5 years (10).

Hypotension is an important symptom causing severe morbidity. Autonomic neuropathy, surrenal failure, hypoalbuminemia, cardiac disfunction and peripheral vascular amyloidosis can cause hypotension (11). In our group the incidence of hypotension was 10.17% and

hypotensive cases were hypoalbuminemic. Neurologic manifestation among hypotensives patients was not investigated in this study. But in 30 patients with renal amyloidosis we did not find relation between neurologic manifestations and blood pressure (12).

The incidence of hypertension was found to be 15.3% in our group. Jansen (13) found hypertension in 11 of 53 patients. In patients with advanced renal failure the incidence of hypertension was reported to be 35% (14). We also found that hypertension was 20% in patients with Ccr <20 ml/min and 10.2% in patients with Ccr>20 ml/min.

Another common finding was decreased renal function. The patients with Ccr<50 ml/min was 44% of patients and Ccr<5 ml/min 6.8%. In secondary amyloidosis renal falure is the most important causes of death. In our series baseline renal function was prognostic factor as in other studies (2, 4).

In some series focal and generalised bleeding defect were reported due to amyloid infiltration of blood vessels or isolated factor X deficiency (15, 16). We did not find an important bleeding defect in our patients. Except one case with Behcet's disease (which may be due to amyloidosis). But in this case we did not performed autopsy. This hemorragie may be due to amyloidosis, pulmonary vascular involvement of Behcet Disease or pulmanory thromboembolism or etc.

ESR was increased. Correlation was found between ESR and serum albumin level and WBC. The values total lipid, cholesterol, proteinuria, Ccr were negatively correlated with Hb levels. Increase in ESR is common finding in amyloidosis.

Renal amyloidosis was diagnosed with renal biopsy in all of the patients except 3. Amyloid deposotion was established in different degree in mesangium, wall of the capilleries tubulu, and blood vessels. Interstitiel fibrosis was prominent in patients with decreased renal function. The positivity for amyloidosis were 100%, 57.6% and 20% in biopsies of kidney and rectum and subcutaneous fat aspiration respectively. These ratios were different from literature (3). It is known that biopsy material must contain blood vessels. So that second or more biopsies may be necessary. But we didn't perform second or more biopsy.

In patients with secondary amyloidosis we used colchicine routinely. If baseline Ccr less than 20 ml/min especially <10 ml/min, colchicine did not affect renal function. Obvious improvement of creatinine clearance can be seen in Fig 2. It can be thought that reason for this improvement attributed to underlying disease was acute renal failure or some renal pathologies which can be spontaneous regression or increased tubular secretion of creatinine in advanced renal failure. In addition dietary protein restriction may be causes improvement of renal function. But in Modification of Diet in Renal Disease Study among patients with moderate renal insufficiency, the slower decline in renal function that started four months after the introduction of a low protein diet suggest a small benefit of this dietary intervention (17). As seen fig 2, the increasing creatinine clearance is very obvious in first 6 months in some patients and then showed more stable plato. Colchicine can influence the creatinine clearance level but, its effect on proteinuria is more obvious. The improvement of creatinine clearance can be due to acute renal failure but the gradually decrease in proteinuria may be attributable to colchicine. Saatçi et al found that only 2.3% of the patients who were treated with colchicine developed amyloidosis (18). Zemer et al (19) have stated that none of their patients developed amyloidosis after colchicine. Saatçi et al (20) had increased beta2 microglobulin excretion and microalbuminuria during the attacks decreases after colchicine administration, however the mechanism of its effects remains to be eluciated. They believed that persistant microalbuminuria and beta2 microglobulinuria may indeed be early markers for renal amyloidosis as in diabetic nephropathy. But in addition to colchicine effect, spontaneous regression of glomerular pathologies or vascular lesion can cause decrease in proteinuria Among the patients improved; six of them were treated with anti-tuberculosis therapy, (one of them was on therapy). The rest of patients were taking only colchicine but not any medication related primary disease. But in patients with relatively good renal function, severe proteinuria, hypoalbuminemia proteinuria improved, serum albumin level increased and edema disappeared after 6 months beginning of colchicine therapy. We also have good result with colchicine therapy in patients with secondary amyloidosis such as tuberculosis, osteomyelitis and bronchiectasia as well as FMF. However in patients with amyloidosis secondary rheumatic diseases cohchicine therapy did not affect proteinuria or renal function for example one of them died in 3 year due to end stage renal failure and septicemia.

Survival showed wide variation. Some patients died at first 3 months on the other hand some patients lived more than 10 years. Baseline renal function and primary disease were the most important prognostic factors for survival and response to therapy. Four patients died due to uremic syndrome and infection in 3 months after first

diagnosis. Totally 8 patients (13.5%) died at first year but after than one of patient with Behcet's disease died due to pulmonary hemorrhagie.

In two patients who had AA amyloidosis due to chronic osteomyelitis and FMF, second renal biopsies were performed at 3th years and 10th years of colchicine therapy during negative proteinuria and normal renal function. These biopsies revealed diffuse amyloid deposotion which was not different from the first biopsies for amyloid deposition. It can be say that colchicine did not affect amyloid deposition. As known, colchicine can cause in decreased secretion of amyloid A protein from liver, changes microtuble function or decreases amyloid enhancing factor. So that stopping of process cas cause clinically important improvement.

In spite of clinical and laboratory improvement, morphological changes can be dissolve or not. There are many reports about this matter (21, 22). Although disappearance of proteinuria even recovery of renal function morphologic findings unchanged it can be hypothesized that colchicine may have some effects on the proteinuria besides known its effect. At least it can be say that colchicine can be use with effectively in secondary amyloidosis.

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