



Is renal amyloidosis uncommon in Egypt? A-25-year study

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 8 March 2018
Accepted: 1 August 2018
Published online: 11 August 2018

Keywords:
AA amyloidosis
AL amyloidosis
Familial Mediterranean fever
Renal amyloidosis

ABSTRACT

Background: Renal amyloidosis is a well-known disease. The forms of amyloidosis that are frequently associated with renal involvement are AL and AA amyloidosis. In Theodor Bilharz Institute, in Egypt, 2.5% of the total number of renal biopsies examined showed amyloidosis including secondary type in 80% and primary type in 20% of cases.

Objectives: To investigate the prevalence of amyloidosis among Egyptian renal patients within 25 years and to screen the amyloid type whether AA or AL.

Materials and Methods: Demographic and pathological data of archived renal biopsies presented to Ain Shams University hospitals in 25 years (1990-2015) were the material of this study. The diagnosis of all renal biopsies included in the study was confirmed by electron microscopy (EM). Immunohistochemical (IHC) staining of paraffin blocks for amyloid typing was carried out on archived material from (2010-2015).

Results: Of a total number of 3962 biopsies examined; 118 were renal amyloidosis (2.97%). IHC typing of the screened samples revealed positive staining for amyloid A protein in 14 cases (73.68%). Light chain AL amyloidosis was found in 5 cases (26.3%).

Conclusions: Renal amyloidosis is not uncommon in Egypt. AA amyloidosis represents the commonest type of renal amyloidosis in this study. The most common underlying disease was systemic inflammatory diseases, on top of familial Mediterranean fever (FMF).

Implication for health policy/practice/research/medical education:

Prevalence of renal amyloidosis in Egypt is not uncommon representing 2.97% of all renal biopsies presented within 25 years to Ain Shams University Hospitals. The screened sample for amyloid typing proved that secondary amyloidosis is more common than primary amyloidosis.

Please cite this paper as: Labib A, Shakweer MM, Salman MI, Seif EI. Is renal amyloidosis uncommon in Egypt? A-25-year study. J Nephrologist. 2019;8(1):e05. DOI: 10.15171/jnp.2019.05.

1. Background

Amyloidosis is characterized by deposition of insoluble misfolded fibrils mainly in extracellular space of organs and tissues. To date, 31 known extracellular fibril proteins in humans were detected (1).

Amyloidosis may be either localized or systemic and may affect any organ. The kidney is the organ, most commonly involved by amyloid deposits (2). Clinically evident renal involvement is presented as proteinuria, nephrotic syndrome or renal failure (3).

The two most common types of renal amyloidosis are immunoglobulin-derived amyloidosis secondary to

plasma cell dyscrasia (light chain amyloidosis; AL) and reactive AA amyloidosis derived from serum amyloid A (SAA), which is typically associated with chronic inflammatory conditions (4).

Congo red staining and birefringence detection are considered the gold standard techniques for the demonstration of amyloid deposits (5). Ultrastructural analysis is particularly useful in early amyloid deposition. In these cases, amyloidosis might not be evident by light microscope (LM) because fibril deposition is minimal and Congo red staining is negative (6).

The immunohistochemical (IHC) procedure identifies

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amyloidogenic proteins under the microscope by evaluating the antibody binding pattern obtained using amyloid type specific antibodies (7). IHC procedure is considered as a fast, applicable, sensitive and reliable method by many authors (7,8). As a first step, using antibodies against SAA, lambda light chain and kappa light chain on formalin fixed paraffin embedded tissue is sufficient to type the majority of cases (9).

Management differs substantially depending on the nature of the amyloid-forming protein ranging from supportive care to aggressive chemotherapy or organ transplantation (10). The amyloidogenic protein therefore needs to be identified routinely in each patient in order to get information concerning the prognosis and the design of adequate therapy (11). There is a noticeable variability regarding both overall percentage and types of amyloidosis in relation to geographic distribution. The database from pathology laboratory in Cairo, Egypt was searched for cases of amyloidosis consisted of 161 cases of renal amyloidosis (between January 2012 to May 2015). In this population, AA amyloidosis was the commonest type (48%). The newly described leukocyte chemotactic factor 2 amyloidosis (ALECT2) was the second most common type and represented nearly one-third of renal amyloid cases at 31%. AL amyloidosis accounted for only 20% of cases (12).

In a series of Turkish patients, amyloidosis was diagnosed in 8.6% in patients with familial Mediterranean fever (FMF) (13).

On the other hand, in western countries; such as a study conducted at Mayo Clinic with data collected from 1950-1990 reported an approximate of 2200 new cases of AL amyloidosis could occur annually in the United States (14, 15).

In UK National Health Service National Amyloidosis Centre, systemic AL amyloidosis was reported to be the most common type with minimum incidence of 0.3/100000 population (15,16).

2. Objectives

To investigate the relative frequency of renal amyloidosis in renal biopsies received in electron microscopy (EM) laboratory for the past 25 years.

3. Materials and Methods

3.1. Procedure

We present a retrospective study of renal amyloidosis diagnosed by kidney biopsy from January 1990 to December 2015 at Ain Shams University Specialized Hospital - Electron Microscopy laboratory (ASUSH-EM lab). The total proportion of adequate renal biopsies

received during this period was 3962.

Diagnosis of amyloidosis was made on the basis of presence of apple-green birefringence under polarized light of Congo red stained sections. The diagnosis of renal amyloidosis was confirmed by EM in all studied cases.

Nineteen cases of amyloidosis with sufficient renal tissue were subjected to IHC staining for anti-SAA, lambda and kappa light chain antibodies for typing of amyloidosis.

3.2. Clinical and laboratory data

Demographic and clinical information was recorded at the time of biopsy. Therefore archival files were subsequently evaluated together with the histopathologic findings (light microscopy, Congo red examination under polarized and immunofluorescence [IF] microscopy and also and EM).

Demographic and clinical information included age, gender, indication for renal biopsy (proteinuria, nephrotic syndrome, hypertension, edema, arthritis/arthralgia and associated diseases either chronic infection or chronic inflammation).

3.3. Histologic data

Light microscopic, immunofluorescence and electron microscopic results were retrieved from archival files at EM unit and pathology laboratory.

Available hematoxylin and eosin (H&E), Congo red, Thioflavin T, Masson's trichrome and periodic acid-Schiff (PAS) stained slides (were retrieved from pathology laboratory) as well as semi-thin plastic sections stained by toluidine blue were re-examined for evaluation of amyloid deposits (localization either glomerular, interstitial or vascular), interstitial infiltrate, tubular atrophy and associated lesions.

The glomerular amyloid deposits were sub-classified into nodular and/or diffuse patterns.

The extent of diffuse glomerular amyloid deposition (GA) was divided to three scores (mild, moderate and severe) according to the percentage of amyloid deposition to the total area of glomeruli; 1%-25%, 25%-75%, and >75%, respectively.

The extent of vascular amyloid (VA) deposition was scored (mild, moderate and severe), according to the percentage of amyloid deposition to the cross-sectional area of interlobular artery; 1%-25%, 25%-75%, and >75%, respectively.

The extent of interstitial amyloid (IA) deposition, inflammatory infiltration (Inf), interstitial fibrosis (Ifib) and tubular atrophy were divided to three scores (mild, moderate and severe) according to the percentage of

lesion involvement: 1%-25%, 25%-75%, and >75%, respectively (17).

3.4. Immunohistochemistry

Nineteen cases with available tissue in paraffin blocks were subjected for IHC staining. IHC staining was performed on 4 µm formalin-fixed and paraffin-embedded sections with a panel of antibodies, included monoclonal antibodies directed against amyloid A (1:200) and polyclonal antibodies directed against κ light chain [(Kappa Light Chain Ab-1 (Clone L1C1) Mouse Monoclonal Antibody)], λ light chains [(Lambda Light Chain Ab-1 (Clone HP6054) Mouse Monoclonal Antibody)]. The three markers above were supplied from Thermo-Scientific.

An Ultravision Plus Detection System was used. Anti polyvalent, HRP/DAB (Ready-to-use), is a labelled streptavidin-biotin immunoenzymatic antigen detection system which uses a multilink biotinylated secondary antibody, a horseradish peroxidase-conjugated streptavidin and DAB chromogen/substrate to demonstrate the antigen in cells or tissues.

3.5. Control slides

Sections from renal biopsy with positive amyloid deposit were prepared and stained. Positive staining was assigned when amyloid deposit shows extracellular staining of SAA.

Sections from human tonsillar tissue were prepared and stained. Positive staining was assigned when plasma cells show cytoplasmic staining for kappa or lambda antibody.

The diagnosis of AA was confirmed by demonstration of selective staining for SAA. The diagnosis of AL was confirmed by demonstration of selective staining for light-chain κ (AL- κ) or λ (AL- λ) in the amyloid deposition area.

3.6. Ethical issues

The research followed the tenets of the Declaration of Helsinki. The work was extracted from Master thesis of AL (first author), department of pathology, faculty of medicine, Ain Shams University and the authors acquired local ethical approval.

3.7. Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0 (IBM Corp., Chicago, USA). Descriptive statistics were done for quantitative data as minimum and maximum of the range

as well as mean \pm standard deviation (SD) for quantitative parametric data, while it was done for qualitative data as number and percentage. Inferential analysis was done for quantitative variables using independent t-test in cases of two independent groups with parametric data. In qualitative data, inferential analyses for independent variables were done using Fisher's exact test for variables with small expected numbers. The level of significance was taken at P value <0.050, otherwise is non-significant.

4. Results

Total proportion of renal biopsies received in the period from January 1990 to December 2015 was 4026 specimens. Adequate tissues for examination were found in 3962 specimens. Renal amyloidosis was diagnosed in 118 cases (2.97%). The patient's age ranged from 7 - 69 years with a mean age of 40.9 years. The proportion of male patients was 74 (62.7 %), while female patients were 44 (37.3 %) with male to female ratio of 1.7:1. Clinical presentations of the cases are illustrated in Figure 1. Suggested causes of secondary amyloidosis are shown in Table 1 where the most frequent of them was FMF as found in 13 cases (40.6%) (11% of total cases). A single

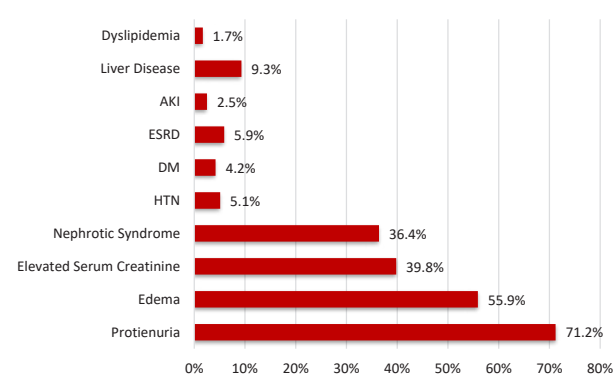


Figure 1. Clinical characteristics of the studied cases

Table 1. Proposed causes for secondary amyloidosis among the studied cases

Characteristics	No. of cases (%)
FMF	13 (34)
Bilharziasis	5 (15.6)
Rheumatoid arthritis	4 (12.5)
Ankylosing spondylitis	3 (9.3)
Psoriasis	3 (9.3)
Chronic rheumatic heart disease	1 (3.12)
SLE	1 (3.12)
Thalassemia	1 (3.12)
TB	1 (3.12)
COPD	1 (3.12)

Abbreviations: FMF, familial Mediterranean fever; SLE, systemic lupus erythematosus; TB, tuberculosis; COPD, chronic obstructive pulmonary disease;

case (0.8%) with Waldenstrom macroglobulinemia was found too.

Renal amyloidosis was diagnosed first by routine H&E stain by deposition of homogenous eosinophilic material in glomeruli, tubules, wall of blood vessels and interstitial tissue (Figure 2) as well as the presence of characteristic apple green birefringence on Congo red stained sections under polarized light (Figure 3). Diagnosis was confirmed by EM through presence of randomly arranged fibrils measured 7-14 nm (Figure 4).

4.1. Light microscopic findings

4.1.2. Distribution of amyloid deposits among renal compartments

Glomeruli were the predominantly affected site in 115

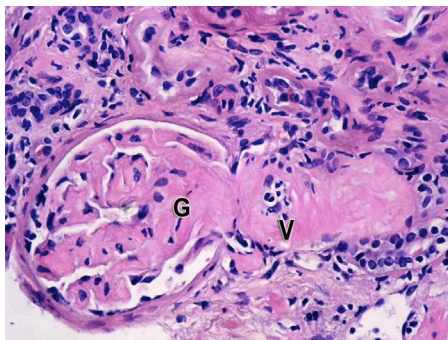


Figure 2. Glomerular & vascular amyloid deposits appears as extracellular amorphous eosinophilic material (H&E, x400).

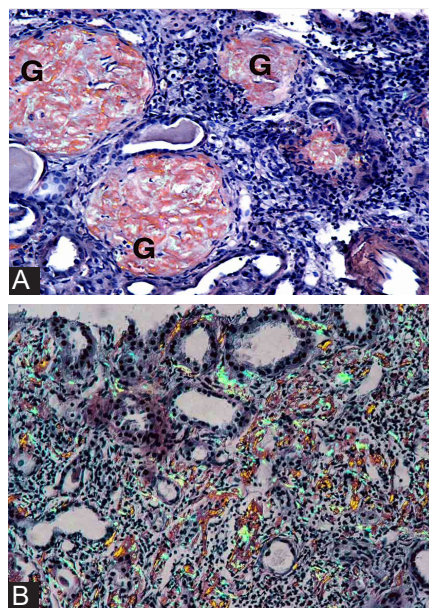


Figure 3. (A) Glomerular amyloid deposits(G) apple green birefringence (Congo red/polarized microscopy, x400). (B) amyloid deposition in interstitial tissue showing apple green birefringence under polarized light (Congo red, x400).

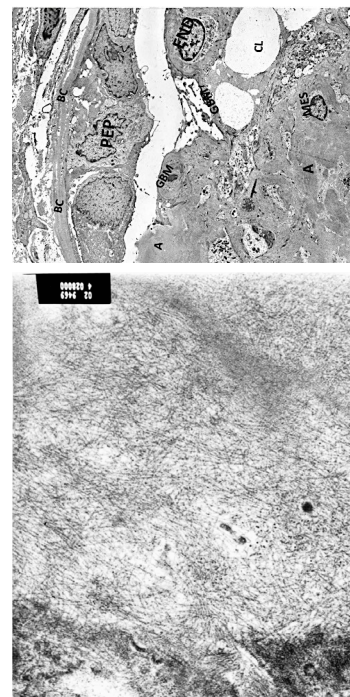


Figure 4. (A) An electron micrograph of part of glomerulus showing amyloid deposition A in relation to glomerular basement membrane (GBM) and mesangium (negative mag: 2800). (B) An electron micrograph showing Amyloid fibrils, randomly arranged non branching fibrils measured 12 nm (negative mag: 28000). BC: Bowman's Capsule; PEP: Parietal epithelial cells; END: endothelial cells; MES: mesangial cells; CL: capillary lumen.

out of 118 cases (97.5%). VA deposits were observed in 99 out of 118 cases (83.9%) followed by IA affection in 64 out of 118 cases (54.2%).

Concomitant glomerular, vascular and interstitial involvement were found in 55% of cases and mixed glomerular and vascular involvement were found in 82.2% of cases.

4.1.3. Associated light microscopic lesions

Beside amyloid deposition in different renal compartments, other light microscopic findings were observed as interstitial fibrosis and interstitial inflammation. Global sclerosis was noted in 28 out of 118 cases (23.7%). Additionally, hypertensive changes were observed in one case (0.8%).

4.2. Electron microscopic findings

Ultrastructural findings were the presence of randomly arranged, non-branching fibrils, ranging in thickness between 7 to 14 nm deposited mainly in mesangium in 87.5% of cases, in glomerular basement membrane (GBM) in 32.1% of cases, in blood vessel wall in 13.4% and in tubular basement membrane (TBM) in 3.6% of

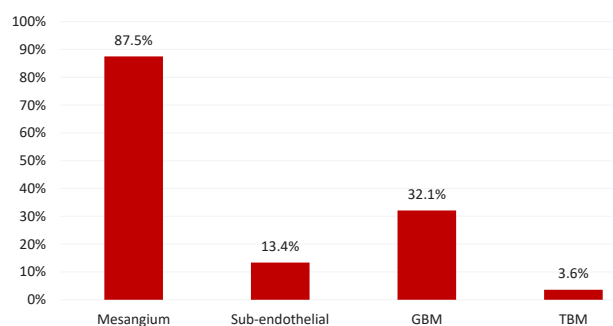


Figure 5. Fibril site demonstrated by EM among the studied samples.

cases (Figure 5).

4.3. Immunohistochemical findings

Typing of amyloidosis into amyloid associated (AA) and light chain amyloidosis (AL) types was carried out in 19 cases.

Fourteen out of 19 studied cases showed positive staining for amyloid A protein (73.68%) (Figure 6). Light chain AL amyloidosis was found in 5 cases (26.3%), while four of them showed positive staining for lambda light chain (Figure 7) and one case showed positive staining for kappa light chain (Figure 8 and Table 2).

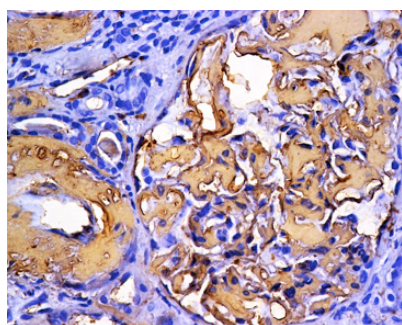


Figure 6. A case of AA amyloidosis showing glomerular and vascular amyloid deposits stained positive for anti SAA (IHC, $\times 400$).

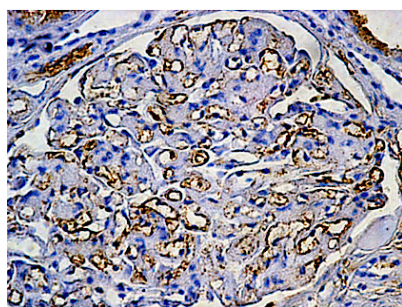


Figure 7. A glomerulus showing moderate staining of capillary walls for lambda light chain in a case of AL amyloidosis- Lambda. (IHC, $\times 400$)

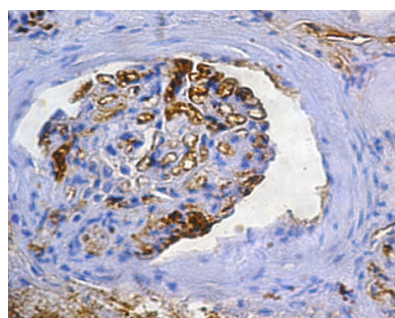


Figure 8. A glomerulus showing moderate staining of capillary walls for Kappa light chain in a case of AL amyloidosis- Kappa. (IHC, $\times 400$)

Patients with AL amyloidosis were older (mean age 57.4 years) than those with the AA type (mean age 46.4 years; $P = 0.060$). Males were more affected in both types (M: F ratio was 1.5:1 and 2.5:1 respectively (Table 3).

Proteinuria was the main finding in both types with no statistically significant difference between two types regarding clinical characteristics ($P > 0.05$).

Among the fourteen cases with AA, only three cases (21.4%) with chronic inflammatory conditions (two patients with FMF, and one patient with ankylosing spondylitis) was detected.

There was no statistically significant correlation between the biochemical type of amyloid and amyloid distribution within the kidney, while both types followed the same pattern, mainly glomerular, vascular then interstitial. Both types showed the same associated LM finding in the same manner with no statistically significant difference ($P > 0.05$) (Table 4).

5. Discussion

In this study, 2.97% of renal specimens were diagnosed as renal amyloidosis from January 1990 to December 2015. A slightly lower percentage was previously reported in Theodor Bilharz Institute, in Egypt where renal amyloidosis cases represented 40 cases (2.5%) of total number of renal biopsies examined in the period from Feb 2003 to May 2009 (18). A possible explanation to our slightly higher frequency is that almost all cases were subjected to be confirmed by EM which is a more sensitive and specific method in detection of early cases of amyloidosis.

Variable results were reported by Bergesio et al (19) (2.9%), Da Fonseca et al (20) (2.3%), Said et al (4) (2.1%), Prakash et al (21) (1.8%) and Von Hutten et al (8) (1.7%).

Bergesio et al (19) reported a prevalence of 2.9% in an

Table 2. Amyloidosis types among the studied samples

Amyloid type	No. of cases	%
AA	14	73.7
AL	5	26.3
AL	Lambda = 4	21.1
	Kappa= 1	5.3

Table 3. Comparison between amyloidosis types regarding demographic and clinical characteristics

	AA (n=14)	AL (n=5)	P
Demographic			
Age (y)	46.4±18.1	57.4±5.5	0.060 ^a
Sex, No. (%)			
Male	10 (71.4)	3 (60.0)	1.000 ^b
Female	4 (28.6)	2 (40.0)	
Clinical, No. (%)			
Nephrotic syndrome	4 (28.6)	0 (0.0)	0.530 ^b
Edema	5 (35.7)	0 (0.0)	0.257 ^b
Elevated serum creatinine	8 (57.1)	3 (60.0)	1.000 ^b
Proteinuria	12 (85.7)	3 (60.0)	0.272 ^b

^a Independent t-test, ^b Fisher exact test.

Table 4. Comparison between amyloidosis types regarding compartmental affection and LM findings

Characteristics	AA (n=14)	AL (n=5)	P ^a
Compartmental affection, No. %			
Glomerular amyloid deposition	14 (100.0)	5 (100.0)	--
Vascular amyloid deposition	11 (78.6)	4 (80.0)	1.000
Interstitial amyloid deposition	10 (71.4)	4 (80.0)	1.000
LM findings, No. %			
Global sclerosis	3 (21.4)	1 (20.0)	1.000
Interstitial infiltrate	11 (78.6)	3 (60.0)	0.570
Interstitial fibrosis	7 (50.0)	3 (60.0)	0.570
Tubular changes	13 (92.9)	4 (80.0)	0.468
Periglomerular fibrosis	1 (7.1)	1(20)	1.000

^a Fisher exact test.

Italian retrospective nationwide study collected cases from different centers. Our results are in line with those of Italy where FMF is known in the Mediterranean basin. The largest study published to date by Said et al (4) in the United States reported a prevalence rate of 2.1%. This study provided characteristics of 474 renal amyloidosis cases out of 22330 renal biopsies evaluated at the Mayo Clinic Renal Pathology Laboratory from 2007 to 2011, which is an international referral center. In Asia, an Indian study by Prakash et al (21) reported

a prevalence rate of 1.8% of all kidney biopsies in the period from 1992 to 2010.

Systemic inflammatory conditions and chronic infections were seen in 32 cases of our series. FMF came as the first identified cause in 13 cases (40%). Concordant results were reported by Abdallah et al (18), where FMF was reported as the most common cause of secondary amyloidosis (30% of AA cases). Akar et al (22) detected that FMF is more prevalent among non-Ashkenazi Jews, Turkish, Armenian, and Arab populations. Turkey appears to have the highest proportion of FMF patients worldwide, with a reported prevalence of FMF ranging from 1: 400 to 1: 1000. Moreover, FMF patients residing in Turkey, Armenia and Arabian countries had a three-fold increased risk of developing AA amyloidosis compared to other countries (23). This explanation might be supported by the results of the studies by Tuglular et al (24) who reported that FMF was found in 64% cases of AA amyloidosis in a large Turkish series with 287 cases of AA amyloidosis and Sen et al (6) where FMF was the most frequent cause of AA amyloidosis. In other studies, chronic inflammatory conditions other than FMF (like rheumatoid arthritis) were reported as the main cause of secondary amyloidosis (8,9,25).

Regarding the clinical features of patients in our study, proteinuria was reported in (71.4%).

Raised serum creatinine was found in 44 cases (37%) at the time of renal biopsy. Similar results were reported by Said et al (4) and Da Fonseca et al (20) who found elevated serum creatinine in 31% and 30.7%, respectively. However, Yao et al (26) noticed a raised serum creatinine in only 18.6% of their cases.

Picken et al (11) stated that the amount of proteinuria depends on the extent of glomerular involvement. In contrast, patients with extra-glomerular amyloid deposits typically present with renal failure which is not associated with significant proteinuria. Compatible with this explanation, all cases with proteinuria in the current study (100%) showed variable degrees of glomerular amyloid deposition. On the other hand, 42 out of 44 of cases (95.4%) with raised serum creatinine had interstitial fibrosis with tubular atrophy.

Nineteen of our studied cases were typed by immunohistochemistry. A positive staining for amyloid A protein was seen in (73.68%). Light chain (AL) amyloidosis was found in (26.3%). In Egyptian population, close results were reported. Around 32 out of 40 studied cases of AA type (80%) and 8 out of 40 studied cases (20%) of AL type, while the typing method wasn't done by immunohistochemistry but the old staining technique was potassium permanganate (18). In Turkey,

AA amyloidosis was detected in 91% of cases (6). On the contrary, the results of Said et al (4) in the United States showed predominance of AL amyloidosis (85.9%), AA amyloidosis in 33 (7.0%), leukocyte chemotactic factor 2 amyloidosis (2.7%).

In most published series from the Western world, AL amyloidosis comprised the majority of cases followed by AA amyloidosis. All other forms are infrequently found (8,19). Variation in these results could be explained by many factors. For example FMF is more prevalent in Egypt and Mediterranean countries than in the United States. Moreover, incidence rate of multiple myeloma is higher in developed countries (3.3%) than developing countries (0.9%) (27).

Study limitations

The use of immunohistochemistry for screening type of amyloidosis was done only on cases diagnosed from 2010 to 2015 and not all cases through the 25 years registry.

Authors' contribution

AL: Collecting and analysis of data; Scoring of amyloid deposits and interpretation of immunohistochemistry; Writing thesis. MS: Revising and adjusting the thesis work; Extraction of the manuscript from the thesis work. MIS: Revising and adjusting the thesis work; Revision, scoring and photographing of slides (H&E, Congo red, and immunohistochemistry). EIS: Presenting the main idea and study plan for the thesis work and also revising and adjusting the thesis work. All authors read and signed the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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