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Renal Amyloidosis- An Eight Year Experience In A Tertiary Care Center In North India.

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ABSTRACT

Renal manifestation of systemic amyloidosis carries a significant morbidity and mortality. Primary amyloidosis(AL) is more prevalent in developed countries, whilst Secondary amyloidosis(AA) is more common in the developing world. Aim of present study was to know the patterns of amyloidosis and to correlate with clinic-pathological findings in patients. The retrospective study was conducted on renal biopsies in PGIMS, Rohtak over a period of eight years (January 2017 to December 2024). All the biopsies were subjected to hematoxylin and eosin staining and special histochemical stains, immunofluorescence and immunohistochemical staining (SAA, B-Amyloid). A total of 716 renal biopsies were received [adequate 576 (80.4%), inadequate 140 (19.6%)] out of which 37 cases were diagnosed with amyloidosis. Male: Female ratio was 1.4:1. Age ranged from 14 to 72 years. Two cases were of primary amyloid. Thirty five cases were of secondary amyloidosis out of which many correlated with tuberculosis and Rheumatoid Arthritis etc. Almost all cases presented as nephrotic syndrome as renal manifestations, few of them presented as nephritic syndrome. Amyloidosis is a rare cause of kidney disease with poor outcome. Primary amyloidosis is rare under the age of 40 years. There is usually an interval of some years between the preceding infectious or inflammatory disease and the diagnosis of amyloidosis. Whereas secondary amyloidosis can occur as early as the first or second decade of life with tuberculosis, rheumatoid arthritis etc. being some of common causes.

Keywords: Renal Amyloidosis, immunofluorescence, immunohistochemistry, Congo Red, Nephrotic syndrome

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INTRODUCTION

Renal manifestation of systemic amyloidosis carries a significant morbidity and mortality and is most frequently seen either in the setting of chronic inflammation (AA amyloidosis), or plasma cell dyscrasias (AL amyloidosis) [1-5]. Primary amyloidosis (AL) is rare under the age of 40 years [6]. It is observed that AL amyloidosis is more prevalent in developed countries, whilst AA amyloidosis is more common in the developing world [7]. AA amyloidosis is secondary amyloidosis which occurs when Serum Amyloid A protein is deposited in various organs and causes clinical manifestations later in life. It occurs as a result of chronic infection such as Tuberculosis or chronic inflammation (Rheumatoid arthritis). Incidence of amyloidosis in India is 8.4% of renal biopsies from patients who present with clinical evidence of glomerular diseases [8]. There is paucity of Indian literature related to reported incidence of amyloidosis. Our research highlights the incidence and importance of diagnosing renal amyloidosis. We carried out the present study with an aim to know the patterns of amyloidosis and to correlate with clinic-pathological findings.

MATERIAL AND METHODS

The retrospective study was carried out on renal biopsies in Pt B. D. Sharma PGIMS, Rohtak over a period of eight years (January 2017 to December 2024). Ultrasound guided percutaneous renal biopsy was performed under local anaesthesia. Renal biopsy tissue was preserved in 10% formalin for routine paraffin blocks to carry out histopathological examination. Biopsy was processed further to prepare paraffin wax blocks. Sections of approximately 3 to 4 micrometre thickness were cut and stained with routine haematoxylin and eosin stain. Special stains such as Periodic Acid Schiff (PAS), Masson's Trichrome, Jones Methenamine Silver (JMS) stain were also used in all renal biopsies as a routine procedure. Biopsies were categorised as adequate or inadequate. Congo red stain was applied to renal biopsies to confirm amyloidosis which showed apple green birefringence under polarising microscope. Immunohistochemical stains for Amyloid A (AA) and Beta 2 Amyloid for amyloid deposit were performed to differentiate between primary and secondary amyloidosis. Patients were archived from the records of Pathology department of Pt. B D Sharma PGIMS, Rohtak to identify the cases of renal amyloidosis. The research was approved by the Ethics committee of the institute as there was no conflict of interest. The biopsies which were sent to department of pathology as a part of routine diagnostic intervention were only reviewed for the research. Also there was no revelation of patient name or information in the retrospective study. Confirmed cases of renal amyloidosis were included in the study. The record of renal amyloidosis patient were screened in the department of pathology for relevant findings like clinical history, physical examination findings, presence of amyloidosis and urine examination. Electron microscopy is not available in our institute.

RESULTS

A total of 716 patients with clinical evidence of renal manifestations underwent renal biopsy at our tertiary care centre. Out of these biopsies, 576 (80.4%) were adequate and 140 (19.6%) were inadequate. Thirty seven cases (5.2%) were diagnosed as amyloidosis. On histopathological examination, mesangial deposits of extracellular, eosinophilic, homogenous amyloidosis material were identified (Figure 1). Periodic Acid Schiff (PAS) stain was weakly positive for amyloidosis (Figure 2). Congo red staining showed positivity for amyloidosis (Figure 3) which further revealed apple green birefringence when viewed under a polarising microscope (Figure 4). All cases for secondary amyloidosis showed positivity for Serum Amyloid A (SAA) on immunohistochemistry (Figure 5).

Out of total patients which were diagnosed as amyloidosis, male patients were 22 (59.5%) while 15 were females (40.5%). Male: Female ratio was 1.4:1. Majority of patients belonged to 25 to 50 years of age followed by 13 patients in age group of 51-75 years. (Table 1 & Figure 6.) Thirty patients presented as nephrotic syndrome while 7 patients presented as nephritic syndrome. As elaborated in table 2, two patients of amyloidosis were associated with Multiple Myeloma while 35 patients were of secondary amyloidosis. Seventeen patients were associated with history of Tuberculosis, three patients each of Rheumatoid Arthritis and Chronic osteomyelitis, two patients each of chronic bronchitis and hepatitis B infection and one patient was of Reactive Arthritis. (Table 2.)

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Table 1: Age wise distribution of patients with renal amyloidosis in present study

Age group	Male	Female	Total cases	Percentage
0 to 25 years	4	3	7	18.9%
26to 50 years	11	6	17	45.9%
51 to 75 years	7	6	13	35.1%

Table 2: Clinical presentation and aetiology of all biopsy proven cases of amyloidosis.

S. No.	Age	Sex	Clinical Diagnosis	Clinical Presentation
1.	25	M	Tuberculosis	Nephrotic Syndrome
2.	48	M	Chronic Bronchitis	Nephrotic Syndrome
3.	25	M	Tuberculosis	Nephrotic Syndrome
4.	19	F	Storage disorder with CKD	Nephrotic Syndrome
5.	24	M	Autoimmune Disorder	Nephrotic Syndrome
6.	50	F	Multiple Myeloma	Nephritic Syndrome
7.	58	F	Rheumatoid Arthritis	Nephrotic Syndrome
8.	64	M	Multiple Myeloma	Nephrotic Syndrome
9.	30	M	SLE	Nephrotic Syndrome
10.	65	M	Tuberculosis	Nephrotic Syndrome
11.	27	M	Tuberculosis Spine	Nephrotic Syndrome
12.	62	F	Chronic Osteomyelitis	Nephrotic Syndrome
13.	71	F	Tuberculosis	Nephrotic Syndrome
14.	14	F	Tuberculosis	Nephrotic Syndrome
15.	27	M	Hepatitis B infection	Nephritic Syndrome
16.	17	F	Tuberculosis	Nephritic Syndrome
17.	40	M	Rheumatoid Arthritis	Nephrotic Syndrome
18.	15	M	Chronic Osteomyelitis	Nephrotic Syndrome
19.	46	M	Tuberculosis	Nephritic Syndrome
20.	65	M	Reactive Arthritis	Nephrotic Syndrome
21.	68	M	Tuberculosis	Nephrotic Syndrome
22.	28	M	Tuberculosis	Nephrotic Syndrome
23.	72	M	Tuberculosis	Nephritic Syndrome
24.	28	F	Hepatitis B Infection	Nephrotic Syndrome
25.	46	M	Tuberculosis	Nephrotic Syndrome
26.	53	F	Rheumatoid arthritis	Nephrotic Syndrome
27.	64	F	Tuberculosis	Nephrotic Syndrome
28.	30	F	Tuberculosis	Nephrotic Syndrome
29.	44	M	Chronic Osteomyelitis	Nephrotic Syndrome
30.	40	M	Chronic Bronchitis	Nephrotic Syndrome
31.	45	M	Acute Glomerulonephritis	Nephrotic Syndrome
32.	31	F	? Amyloidosis	Nephrotic Syndrome
33.	53	F	Tuberculosis	Nephrotic Syndrome
34.	44	F	Tuberculosis	Nephrotic Syndrome
35.	57	M	Unknown etiology ?	Nephritic Syndrome
36.	54	M	AKI with Gastroenteritis	Nephritic Syndrome
37.	35	F	Tuberculosis	Nephrotic Syndrome

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Figure 1: Mesangial effacement of glomerulus by amorphous eosinophilic amyloid (Hematoxylin and eosin stain;400x)

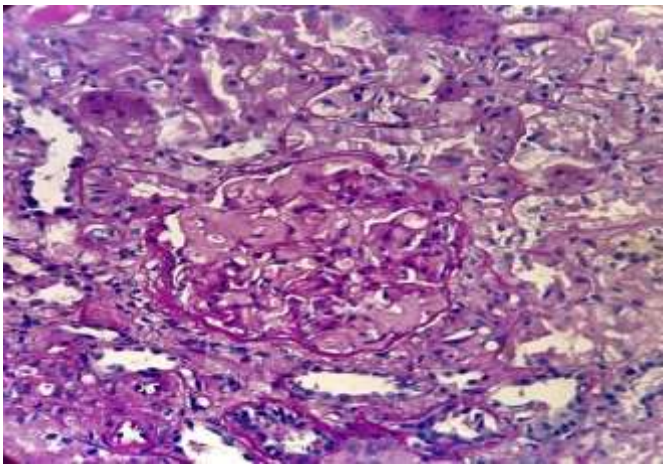

Figure 2: Pale staining mesangial regions with focal spicule formation along capillary loops, characteristic of amyloid (PAS;400x).

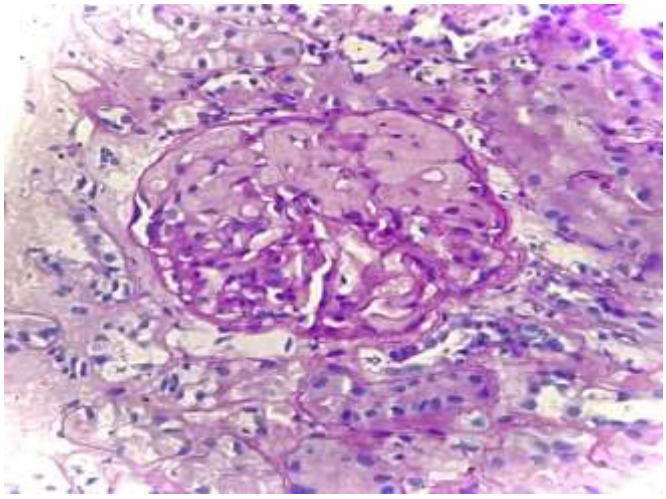

Figure 3: Strong orangeophilic staining present within glomeruli, arteriole wall and some tubular basement membranes (Congo Red;400x).

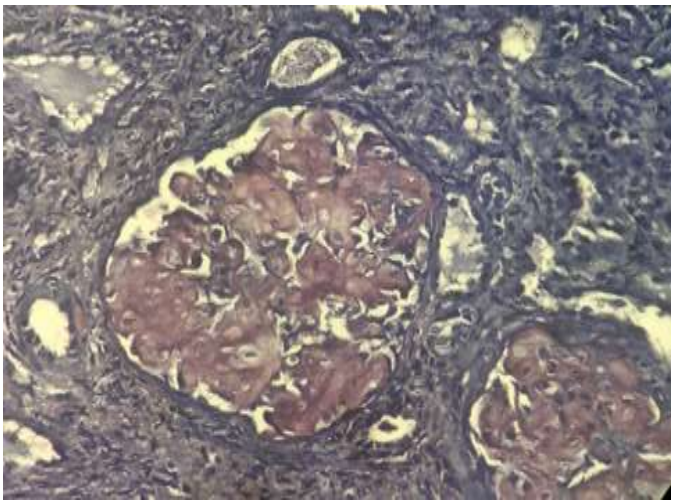

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Figure 4: Polarising microscopy: Apple green birefringence in artery (Congo Red;200x)

Figure 5: Strong staining present within mesangial regions and wall of arteries (IHC, Serum amyloid A;400x).

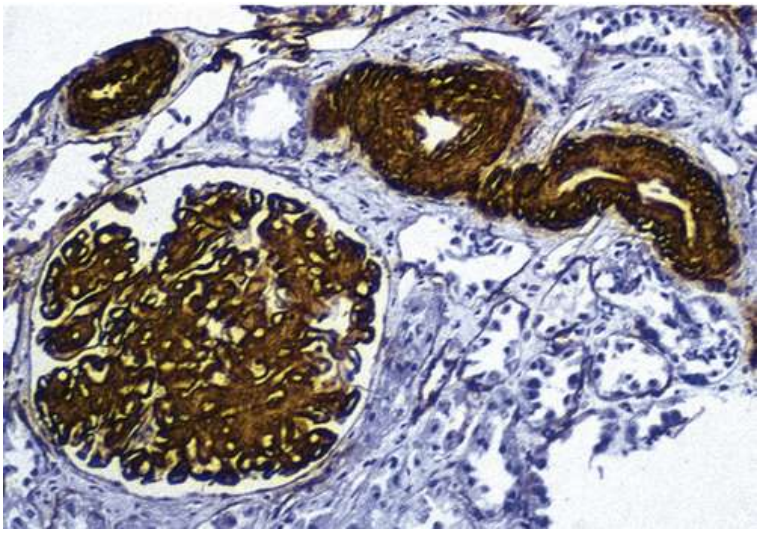
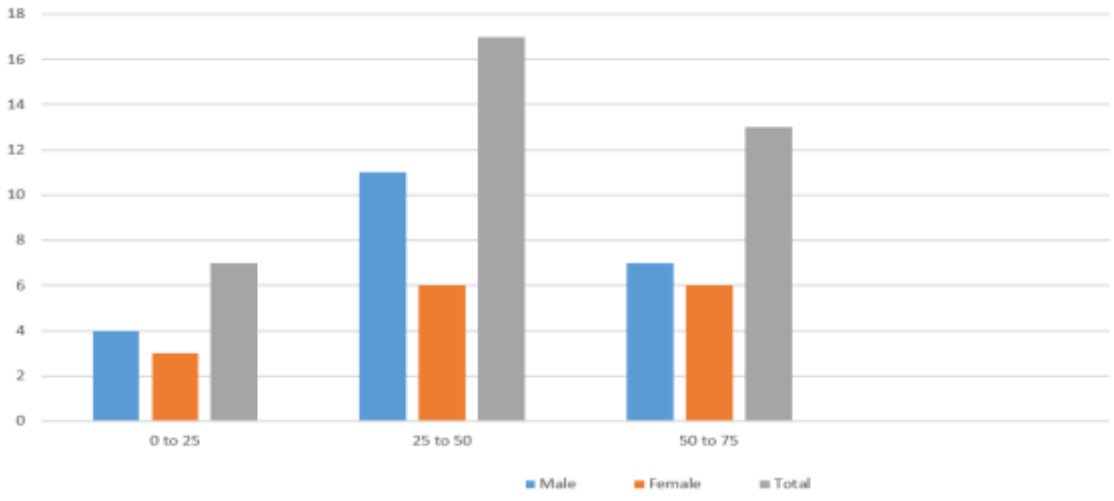


Figure 6: Age and sex distributions of patients with renal amyloidosis in present study



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DISCUSSION

Amyloidosis is a systemic condition characterised by deposition of extracellular, homogenous, eosinophilic proteinaceous material arranged in Beta pleated sheets. These proteins are typically misfolded and cannot be broken down or eliminated properly by the body, leading to their accumulation and damage to vital structures. Most commonly involved organs are kidneys, spleen, and liver. Currently, 6 amyloidogenic proteins can form amyloid. These proteins are transthyretin (ATTR), β2-microglobulin (AB2M), serum amyloid A (AA), and apolipoprotein A-IV (ApoAIV), Aβ protein (Aβ), and prion (APrP). Only the first 4 proteins are found to affect the kidney. Amyloidosis is named after the protein of origin and is often classified as wild type (acquired) or germline pathogenic variant (mutant). Primary Amyloidosis caused by AL protein is rare as it is associated with plasma cell dyscrasias when plasma cells produce large amounts of light chains which get accumulated as misfolded proteins in various organs of body including kidneys, spleen, heart, intestines, stomach etc. secreting monoclonal kappa or lambda chains. Amyloid associated (AA) protein, seen in secondary amyloidosis is caused by accumulation of serum amyloid A (SAA). It is an acute phase reactant secreted in chronic inflammation such as rheumatoid arthritis or Tuberculosis. Amyloid Beta protein secreted in Alzheimer's disease gets accumulated in brain. Transthyrein (ATTR) is liver derived transport protein for thyroxine and retinol causes amyloidosis in thyroid. Beta-2 microglobulins (AB2M) are dialysis related proteins which are normally filtered by kidneys but get deposited during prolonged dialysis. Few iatrogenic amyloids have been recently identified that appear as subcutaneous nodules at the injection sites. Kidney involvement was reported in AIL1RAP (anakinra) and 1 tumor-related amyloid calcitonin (ACal). However, the role of leukocyte cell–derived chemotaxin 2 amyloidosis (ALECT2) in causing renal amyloidosis remains incompletely understood [9].

We reported thirty seven cases of biopsy proven renal amyloidosis over a period of 8 years. Incidence of Renal amyloidosis is only 5.16% which is comparable with other Indian and southeast Asian studies [8, 10, 11]. Most cases belonged to 25 to 50 years of age (16 cases) followed by 13 cases in age range of 50 to 75 years. In elderly age group, males were predominant whereas there was an equal Male: Female ratio among cases below 25 years age. Similar to other Indian studies, majority cases were of secondary amyloidosis [8, 10, 11]. Tuberculosis remained the most common cause for secondary amyloidosis in all age groups as it caused amyloidosis in 27% patients. This can be attributed to a very high incidence of Tuberculosis in developing countries like India. Few patients (10%) had history of autoimmune disorders like SLE, Rheumatoid arthritis and Reactive arthritis which later developed as secondary amyloidosis in kidney. Few cases were also associated with Hepatitis B infection, chronic osteomyelitis, Focal segmental Glomerulosclerosis. Primary amyloidosis (AL) was identified only in two cases. These cases were previously diagnosed of Multiple Myeloma. These findings were coherent with the observation that AL amyloidosis is more prevalent in developed countries, whilst AA amyloidosis is more common in the developing world. Developing countries have high incidence of chronic infections or inflammatory conditions such as tuberculosis or autoimmune disorders whereas malignancies are disease of the western world [7].

In our study there were 140 (19.6%) inadequate renal biopsies. Adequacy criteria of renal biopsy is based primarily on number of glomeruli identified on light microscopy. Crushed biopsy, autolyzed or poorly fixed tissue, improper sectioning or embedding are also considered inadequate. Less than 10 glomeruli present in the specimen are considered inadequate for light microscopy. For immunofluorescence (IF) and electron microscopy (EM), at least 1–2 glomeruli are required in each portion. For renal transplant rejection more than 7 glomeruli along with at least one artery are typically needed. Inadequacy of renal biopsy was contributed to the procedure performed by radiologist and residents of medicine where on-site evaluation of biopsies were not done, delayed sample fixation, inadequate sample size. This highlights the importance of performing the procedure by experienced nephrologist under ultrasound or CT guidance. Lower pole cortex should be targeted by typically 14 - 18 G core needle and 2-3 cores must be extracted for light microscopy, electron microscopy and immunofluorescence respectively. [12].

Kidney is one of the most common organ to be affected by amyloidosis. Thus, it is the most common underlying cause of death. Glomerulus is the most common site of deposit. Kalle et al[10] scored all renal amyloidosis based on Renal amyloidosis scoring system (RAPS). Scoring of amyloid is done in kidney which includes extent of involvement of glomerular, interstitial, and vascular compartments as well as interstitial fibrosis and tubular atrophy, interstitial inflammation, and glomerular sclerosis in addition to the

glomerular class. The score is added cumulatively known as the renal amyloid prognostic score (RAPS). The renal findings are finally graded according to the RAPS into four grades from 0 to 3 [10].

CONCLUSION

Amyloidosis is a rare cause of kidney disease with poor outcome. There is usually an interval of some years between the preceding infections or inflammatory disease and the diagnosis of amyloidosis [11]. Secondary amyloidosis can occur as early as the first or second decade of life with tuberculosis, rheumatoid arthritis etc. being some of common causes. Cases which remain inconclusive should be diagnosed with broader diagnostic methodologies in higher centres for appropriate diagnosis, treatment and to prevent patient loss by avoiding potentially harmful therapies. The strength of this study lies in extended period over which data was available, use of various specialized tests to confirm the diagnosis and type of amyloidosis and various databases which were searched to obtain and confirm the data over this period.

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