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Pathologic Spectrum of Kidney Diseases Within Very Elderly Patients who Underwent Kidney Biopsy

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INTRODUCTION

The population is aging with an increase in life expectances worldwide. According to the United States Census Bureau, the international population of the "very elderly" (individuals ≥80 years) will triple between 2015 and 2050. The prevalence of kidney disease increases with age; therefore, more very elderly patients are living with kidney disease than ever before. Elderly patients with kidney disease are at risk of poor outcomes. In a study of >30,000 adults with chronic kidney disease, patients ≥85 years had 25-fold increased mortality.[1] The gold standard to diagnose kidney disease is a biopsy and multiple studies have demonstrated that kidney biopsy in elderly individuals is safe[2-5] and without poorer diagnostic yield.[6,7] Therefore, kidney biopsy within this age group has increased.[8]

Etiologies of kidney disease vary within the very elderly compared to the general population. To further understand the spectrum of kidney diseases within the very elderly, we examined 2 cohorts, 1 from the United States (US) and 1 from India. These represent the largest to date.

RESULTS

Kidney Diseases Within Very Elderly Patients From the US

Of 130,774 kidney biopsies evaluated at Arkana, 6343 were from patients ≥80 years (4.85%; Supplementary Methods and Supplementary Table S1). The majority were male (53%). Of patients of known race, 80% were White, 13% Black, 4% Hispanic, and 3% Asian. The median age was 83 (80–97) years. The majority had hypertension (83%) and 38.3% had diabetes. The mean creatinine at presentation was 3.6±2.4 mg/dl, 78.1% had significant proteinuria (>1 g/day), and 71.2% had hematuria. Acute kidney injury and nephritic syndrome were common presentations (58.7% and 35.0%), and chronic kidney disease was seen in 58.7%. Of the kidney biopsies, 95% were adequate. The majority had 1 diagnosis (90.4%) with ≥2 diseases in 9.6%. Less than one-third (27.6%) demonstrated only chronic diseases, including arterionephrosclerosis and diabetic nephropathy (DN). Patients with DN often had advanced disease (73.6%) and was the most common concurrent diagnosis in patients with >1 disease (58.5%).

Of the remaining 60.8%, there was a large spectrum of diagnoses, the majority important and extending beyond only chronic disease states (Table 1). Acute tubular injury (ATI) was the most common overall (16.6%) and a second diagnosis in 12.0%. Crescentic glomerulonephritis (GN) was the next most common disease, primarily pauci-immune. The most common proteinuric kidney diseases included DN, primary podocytopathies (minimal change disease [MCD] more common than primary focal segmental glomerulosclerosis), followed by membranous nephropathy (MN). Of MN cases typed (n = 304), 44.4% were PLA2R-positive. In addition, 21 MN cases were a secondary diagnosis in patients with crescentic GN and anti-myeloperoxidase antibodies.[9,S1,S2]

Paraprotein-mediated kidney diseases were identified in 5.2%, the majority being light chain cast nephropathy. Of 262 patients with amyloidosis, most were of AL type (87.0%). Nineteen had amyloidosis as a second diagnosis, most often transthyretin amyloid

Table 1. Distribution of biopsy-proven kidney diseases in the United States (Arkana Laboratories cohort)

Kidney biopsy diagnosis (Arkana Laboratories cohort, United States)	*n*	%
Acute tubular injury	1050	16.6%
Unknown etiology $n = 895$ (85.2%)		
Myoglobin cast nephropathy $n = 47$ (4.5%)		
Hemoglobin cast nephropathy $n = 2$ (0.2%)		
Bile cast nephropathy $n = 1$ (0.1%)		
Anti-coagulant associated $n = 8$ (0.8%)		
Lysozyme nephropathy $n = 6$ (0.6%)		
Calcium oxalate crystals $n = 91$ (8.7%)		
Arterionephrosclerosis	961	15.15%
Diabetic nephropathy	788	12.42%
Crescentic glomerulonephritis	767	12.09%
Pauci-immune type $n = 767$ (94.9%)		
Anti-GBM disease $n = 39$ (5.1%)		
Podocytopathy	404	6.37%
MCD $n = 230$ (56.9%)		
Primary FSGS-tip variant $n = 174$ (43.1%)		
Paraprotein-mediated kidney diseases, excluding amyloidosis	328	5.18%
Light chain cast nephropathy $n = 172$ (52.4%)		
Proliferative glomerulonephritis with monoclonal IgG deposits $n = 56$ (17.1%)		
Light chain proximal tubulopathy $n = 55$ (16.8%)		
Light chain deposition disease $n = 36$ (11.0%)		
Heavy chain deposition disease $n = 3$ (0.9%)		
Waldenstrom's macroglobulinemia $n = 6$ (1.8%)		
Membranous glomerulopathy	324	5.11%
Nondiagnostic	314	4.95%
Limited sample $n = 313$ (99.7%)		
No histopathologic abnormalities $n = 1$ (0.3%)		
Infection-associated glomerulonephritis	289	4.56%
IgA-dominant infection-associated $n = 113$ (39.1%)		
Immune complex type (multiple immunoreactants) $n = 110$ (38.1%)		
C3 dominant $n = 40$ (13.8%)		
Pauci-immune $n = 16$ (5.5%)		
IgG dominant $n = 10$ (3.5%)		
Amyloidosis	262	4.13%
AL lambda $n = 189$ (72.1%)		
AL kappa $n = 39$ (14.9%)		
ALECT2 $n = 18$ (6.9%)		
AA $n = 3$ (1.1%)		
ATTR $n = 2$ (0.8%)		
ApoAIV $n = 1$ (0.4%)		
AFib $n = 1$ (0.4%)		
AHL $n = 1$ (0.4%)		
Unknown type $n = 8$ (3.1%)		
Tubulointerstitial nephritis	241	3.81%
Acute interstitial nephritis $n = 157$ (65.1%)		
Chronic interstitial nephritis $n = 54$ (22.4%)		
Granulomatous interstitial nephritis $n = 20$ (8.3%)		
Tubulointerstitial nephritis with increased IgG4+ plasma cells $n = 10$ (4.1%)		
IgA nephropathy	152	2.40%
Idiopathic nodular glomerulosclerosis	84	1.32%
Renal neoplasm	59	0.93%
Thrombotic microangiopathy	57	0.90%
Cholesterol emboli	52	0.82%
Collapsing glomerulopathy	35	0.55%
Cryoglobulinemic glomerulonephritis	35	0.55%
Fibrillary glomerulopathy	31	0.49%
Renal involvement by a hematopoietic neoplasm	29	0.47%
Lymphoma $n = 24$ (82.8%)		
Myeloma $n = 3$ (10.3%)		
Myeloid sarcoma $n = 1$ (3.4%)		
Rosai-Dorfman disease $n = 1$ (3.4%)		
Acute pyelonephritis	23	0.36%
Necrosis/infarct	20	0.31%
Medullary infarct $n = 12$ (60.0%)		
Papillary necrosis $n = 6$ (30.0%)		
Cortical infarct $n = 2$ (10.0%)		
Necrotizing vasculitis	17	0.27%
Lupus nephritis	12	0.19%
Membranous glomerulopathy with masked IgG-Kappa deposits	3	0.05%
C3 glomerulonephritis	2	0.03%
Fabry disease	2	0.03%
Anti-brush border antibody disease (LRP2-associated nephropathy)	2	0.03%
Total cases	6343	100%

ATTR, transthyretin amyloid; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; MCD, minimal change disease.

(68.4%). Infection-related GN (IRGN) was seen in 4.6% patients, most often IgA dominant (39.1%). The remaining 13.3% patients had a range of biopsy diagnoses (Table 1). To explore disease etiologies, a cohort of 300 consecutive patients were examined. In this sample, 20% with MCD and 30% with MN had malignancy. In patients with crescentic GN, 77.8% were antineutrophil cytoplasmic antibodies (ANCA)-positive and 14% had infection(s).

Kidney Diseases Within Very Elderly Patients From India

Of 41,210 biopsies evaluated at the Renopath Center for Renal and Urological Pathology, 138 were the very elderly (0.33%, Supplementary Methods and Supplementary Table S1). The median age was 81.5 (80–89) years. The majority of patients (70.3%)were male. The majority (64.8%) had hypertension and 31.2% had diabetes. The mean creatinine was 3.9 ± 2.3 mg/dl, and 82.9% had significant proteinuria. Acute kidney injury and nephrotic syndrome were common biopsy indications (Supplementary Table S1). All but 1 biopsy was adequate for diagnosis. More than 1 kidney biopsy diagnosis was seen in 24.0%, with ATI most common (54.2%) followed by DN (29.2%). The majority showed more than chronic diseases, with only 10.8% having only DN or arterionephrosclerosis.

IRGN was the most common diagnosis (17.4%). The most common pattern was endocapillary proliferative (75.0%), followed by crescentic. ATI was the second most common diagnosis, the majority without a known etiology. In contrast to the US cohort, patients with crescentic

Table 2. Distribution of biopsy-proven kidney diseases in India (Renopath cohort)

Kidney biopsy diagnosis (Renopath cohort, India)	*n*	%
Infection-related glomerulonephritis	24	17.4%
Endocapillary proliferative $n = 18$ (75.0%)		
Crescentic $n = 4$ (16.7%)		
Mesangial proliferative $n = 2$ (8.2%)		
Acute tubular injury	18	13.0%
Myoglobin cast nephropathy $n = 2$ (11.1%)		
Calcium oxalate crystals $n = 2$ (11.1%)		
Paraprotein-mediated kidney diseases, excluding amyloidosis	14	10.1%
Light chain cast nephropathy $n = 9$ (64.2%)		
Light chain proximal tubulopathy $n = 2$ (14.3%)		
Light chain deposition disease $n = 3$ (22.2%)		
Minimal change disease	13	9.4%
Membranous glomerulopathy	13	9.4%
Diabetic nephropathy	9	6.5%
Amyloidosis	8	5.8%
AL kappa $n = 2$ (25.0%)		
AL lambda $n = 5$ (62.5%)		
AA type $n = 1$ (12.5%)		
Tubulointerstitial nephritis	8	5.8%
Acute tubulointerstitial nephritis $n = 6$ (75%)		
Chronic tubulointerstitial nephritis $n = 1$ (12.5%)		
Granulomatous tubulointerstitial nephritis $n = 1$ (12.5%)		
Acute pyelonephritis	6	4.3%
Arterionephrosclerosis	6	4.3%
Crescentic glomerulonephritis	6	4.3%
Pauci-immune type $n = 3$ (50%)		
Anti-GBM type $n = 3$ (50%)		
IgA nephropathy	5	3.6%
IgA nephropathy + membranous nephropathy $n = 1$ (20%)		
Crescentic IgA nephropathy $n = 1$ (20%)		
IgA nephropathy without activity $n = 3$ (60%)		
Focal segmental glomerulosclerosis, favor secondary	5	3.6%
Atheroembolic disease	1	0.7%
Chronic thrombotic microangiopathy	1	0.7%
Nondiagnostic - limited sample	1	0.7%
Total	138	100%

GN more often had infections than ANCA-associated disease ($n = 24$ and 3, respectively). Paraprotein-mediated kidney diseases were seen in 10.1%, most often light chain cast nephropathy. In addition, 5.8% patients had amyloidosis, primarily AL type.

MCD and MN were the leading causes of nephrotic syndrome. The majority of patients with MCD had concurrent ATI (69.2%). Of patients with MN, 36.4% were PLA2R-positive and 27.2% NELL1-positive. No patients with MCD or MN had malignancy. Of patients with MN, 15% were exposed to indigenous medicines. Eight patients had tubulointerstitial nephritis (5.8%) and 6 had pyelonephritis (4.3%). The remaining 12.9% patients had various diagnoses (Table 2).

DISCUSSION

We present the largest study of kidney disease within the very elderly from Western and Eastern cohorts. A kidney biopsy yielded an important diagnosis in the majority of patients. In addition, there was no increase in inadequate biopsies. Compared to the general population, the proportion of biopsies in the very elderly in the US cohort was higher than in India (4.85% vs. 0.33%), reflecting differences in life expectancies. In the US cohort, White patients were disproportionately overrepresented, despite Black Americans having disproportionate risk of kidney disease, reflecting disparities in life expectancies and access to care.[S3]

In the US cohort, the leading etiology of kidney disease was ATI. The most common glomerular disease was crescentic GN, primarily ANCA-associated. The frequency of crescentic GN was increased in the very elderly compared to the general biopsied population (12.1% vs. 4.5%).[S4] IRGN was the most common diagnosis in the very elderly in India, most often due to Staphylococcal infections. Unlike IRGN in children, IRGN in the very elderly has a poor renal prognosis.[S5]

Within both cohorts, the leading proteinuric kidney diseases were DN, primary podocytopathies; and MN. Patients with MN had a lower rate of PLA2R positivity compared to the general population, likely due to "secondary" triggers such as malignancies.

The distribution of kidney disease within elderly individuals was explored within multiple cohorts worldwide. Forty-four previous studies examined kidney disease in older individuals, 8 from the very elderly [S6-S13] and 36 were aged ≥60 years. Within both the elderly (≥60 years) the very elderly (≥80 years), crescentic GN is one of the 3 most common diagnoses in the US and Europe. ANCA-associated disease shows increased incidence at age 70 to 84 years.[S14] We did not see this trend in India, Africa, or South America.[S15,S16] ANCA-associated GN may be less prevalent, or there may be differences in the threshold to biopsy in low resource areas. ANCA vasculitis is unlikely of lower incidence in the Southern Hemisphere overall, because it was identified as the most common GN in older individuals in Australia.[S17] An overview of studies of kidney disease in patients aged ≥80 and ≥60 to 65 years are summarized in Supplementary Tables S2 and S3 (See Supplementary References).

Perhaps the most important observation is that there is a wide spectrum of kidney disease within the very elderly with the vast majority having diagnoses that could impact treatment decisions or prognosis. Taken together, the data from our cohort and others demonstrate usefulness of a kidney biopsy in this population which is at the highest risk of poor outcomes.

DISCLOURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplemental References.

Table S1. Clinical and laboratory data from the US (Arkana) and Indian (Renopath) cohorts.

Table S2. Frequency of various kidney diseases affecting very elderly patients reported in the literature.

Table S3. Frequency of various kidney diseases affecting older adults (≥ 60 or 65 years) reported in the literature.

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