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# Clinical and pathological characteristics of patients with glomerular diseases at a university teaching hospital: 5-year prospective review

KW Chan, TM Chan, IKP Cheng

**Objective.** To examine the prevalence of glomerular disease in Hong Kong.

**Design.** Prospective review.

**Setting.** University teaching hospital, Hong Kong.

**Patients.** All patients who presented with suspected glomerular disease from 1993 through 1997.

**Main outcome measures.** Histopathological diagnosis from biopsy examination and clinical features of presentation.

**Results.** A total of 1629 consecutive percutaneous renal biopsies of native kidneys showed glomerular disease in 1413 cases. The most common clinical indication for renal biopsy was persistent proteinuria (n=735; 52.0%), while the most frequently found glomerular lesion was immunoglobulin A nephropathy (n=338; 23.9%). Minimal-change nephrotic syndrome (n=125; 8.8%) and immunoglobulin M nephropathy (n=11; 0.8%), were the most common glomerular diseases that presented with nephrotic syndrome. The male to female ratio for lupus nephritis was 1:14 (n=290), whereas for minimal-change nephrotic syndrome, the ratio was 1.8:1 (n=125). Immunoglobulin A nephropathy and membranous glomerulonephritis (n=117) affected approximately equal numbers of male and female patients. Familial fibrillary glomerulonephritis, a disease hitherto unknown in Hong Kong, was diagnosed in two siblings.

**Conclusion.** Immunoglobulin A nephropathy was the most common glomerular disease in this survey and represents an important cause of end-stage renal failure in the Hong Kong population.

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*Key words: Biopsy; Glomerulonephritis; Kidney diseases/pathology*

## Introduction

Percutaneous renal biopsies have been performed routinely at the Queen Mary Hospital (QMH) since the early 1960s. Such biopsies are done mainly to study suspected cases of glomerular disease and, much less frequently, tubulo-interstitial and vascular diseases. Owing to an increasing number of patients who have undergone an allograft kidney transplantation, more biopsies are being performed in cases of suspected rejection of or glomerular disease in the grafted kidney. We have recently reviewed the pathology of

the glomerular diseases that occurred in kidney allografts of patients who attended the QMH.<sup>1</sup> In this study, we present clinical data and histological findings that were prospectively collected at the QMH from 1993 through 1997 to determine the prevalence of glomerular disease in Hong Kong.

## Materials and methods

From 1993 through 1997, renal tissue from percutaneous biopsies that had been performed in cases of suspected glomerular disease were routinely divided into three portions and studied under the light, fluorescent, and electron microscopes. Standard procedures<sup>2</sup> were used with the following modifications: the use of formalin instead of Bouin solution for tissue fixation before paraffin embedding; and the routine immunofluorescent staining for immunoglobulins (Ig) A, M, and G, and complement components C3b and C1q only. Staining renal biopsy

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Table 1. Histopathological diagnosis of 1413 consecutive native kidney biopsies

Diagnosis	Children		Adults*		Total (%)
	Male	Female	Male	Female	
Primary glomerular diseases					
Minimal-change nephrotic syndrome <sup>†</sup>	12	4	68	41	125 (8.8)
Immunoglobulin M nephropathy	1	0	6	4	11 (0.8)
Minor glomerular abnormalities	1	1	20	26	48 (3.4)
Focal segmental glomerulosclerosis	0	1	36	29	66 (4.7)
Focal glomerulonephritis	1	0	6	15	22 (1.6)
Membranous glomerulonephritis <sup>‡</sup>	1	3	59	54	117 (8.3)
Mesangial proliferative glomerulonephritis	6	0	48	45	99 (7.0)
Endocapillary proliferative glomerulonephritis	4	1	5	2	12 (0.8)
Mesangiocapillary glomerulonephritis	1	0	11	12	24 (1.7)
Crescentic glomerulonephritis	0	0	3	6	9 (0.6)
Glomerulonephritis due to systemic diseases					
Lupus nephritis	0	6	19	265	290 (20.5)
Nephritis of Henoch-Schönlein purpura	1	2	2	2	7 (0.5)
Immunoglobulin A nephropathy <sup>§</sup>	5	1	164	168	338 (23.9)
Anti-basement membrane glomerulonephritis <sup>xx</sup>	0	1	3	2	6 (0.4)
Glomerulopathy in infective endocarditis	0	0	1	0	1 (0.1)
Glomerular lesions of vascular diseases					
Benign nephrosclerosis <sup>¶</sup>	0	0	42	40	82 (5.8)
Malignant nephrosclerosis <sup>xx</sup>	0	0	6	0	6 (0.4)
Wegener's granulomatosis	0	0	0	1	1 (0.1)
Churg-Strauss syndrome	0	0	1	0	1 (0.1)
Thrombotic microangiopathy					
Haemolytic-uraemic syndrome	0	0	1	0	1 (0.1)
Thrombotic thrombocytopenic purpura	0	0	1	0	1 (0.1)
Glomerular lesions of metabolic diseases					
Diabetic glomerulosclerosis <sup>**</sup>	0	0	55	25	80 (5.7)
Amyloidosis <sup>xx</sup>	0	0	7	0	7 (0.5)
Light-chain deposition disease	0	0	0	1	1 (0.1)
Heavy-chain deposition disease	0	0	2	0	2 (0.1)
Fibrillary glomerulonephritis	0	0	1	1	2 (0.1)
Waldenström macroglobulinaemia	0	0	1	1	2 (0.1)
Hereditary nephropathies					
Alport's syndrome	1	0	3	1	5 (0.4)
Thin-basement membrane nephropathy <sup>††</sup>	0	0	19	58	77 (5.4)
Diffuse mesangial sclerosis	0	1	0	0	1 (0.1)
Miscellaneous	0	0	0	1	1 (0.1)
Unclassified	1	3	5	8	17 (1.2)

\* Biopsies of patients aged 13 years or older

<sup>†</sup> Fifteen biopsies also showed immunoglobulin (Ig) A nephropathy

<sup>‡</sup> Three biopsies also showed IgA nephropathy; one also showed diabetic glomerulosclerosis

<sup>§</sup> Fifty-five biopsies also showed glomerular diseases

<sup>xx</sup> One biopsy also showed IgA nephropathy

<sup>¶</sup> Thirty-seven biopsies also showed other glomerular diseases

<sup>\*\*</sup> Thirteen biopsies also showed IgA nephropathy and one also showed membranous glomerulonephritis

<sup>††</sup> Two biopsies also showed IgA nephropathy

samples for fibrinogen is no longer a routine procedure at the QMH.

The majority (839; 59.4%) of renal biopsy samples that were examined during the 5-year study period were taken from in-patients of the QMH. A minority (315; 22.3%) of renal biopsies were performed in private hospitals and sent to the QMH for diagnosis. Also included in this study were 259 (18.3%) renal biopsies that had been sent from other, non-private hospitals of Hong Kong for microscopic analysis. Glomerular

diseases were classified using the diagnostic criteria formulated by the World Health Organization.<sup>3,4</sup>

Clinical data of patients were prospectively collected and categorised into the following mutually exclusive groups: nephrotic syndrome, gross haematuria, persistent proteinuria with or without microscopic haematuria, persistent microscopic haematuria, chronic renal impairment, acute nephritic syndrome, and malignant hypertension. Each of these presentations was evaluated according to established criteria.<sup>3,4</sup>

## Results

A total of 1924 biopsy samples had been taken during the 5-year study period; 295 (15.3%) of them had been from allograft kidneys and were excluded from this study. Of the 1629 biopsies of native kidneys, 68 (4.2%) had insufficient tissue for a diagnosis to be made and seven (0.4%) contained only end-stage renal tissue. Glomerular diseases were diagnosed in 1413 (8.7%) samples. Six hundred (42.5%) of the 1413 biopsies had been performed in 578 male patients (mean age, 41.0 years) and 813 (57.5%) biopsies had been performed in 753 female patients (mean age, 38.7 years). Table 1 shows the frequency distribution of all types of glomerular disease diagnosed.

### *Minimal-change nephrotic syndrome and immunoglobulin M nephropathy*

All 125 biopsy samples that had a diagnosis of minimal-change nephrotic syndrome had been taken from different patients. By definition, nephrotic syndrome was the presenting clinical feature. The mean age of the patients was 33.6 years. Immunoglobulin M nephropathy, as a variant of minimal-change nephrotic syndrome, was diagnosed in 11 patients (mean age, 32.7 years).

### *Minor glomerular abnormalities*

The 48 patients who had minor glomerular abnormalities had a mean age of 38.6 years. The clinical features at presentation were proteinuria, microscopic haematuria, and gross haematuria in 36, 10, and 2 patients, respectively.

### *Focal segmental glomerulosclerosis*

All 66 biopsies that showed focal segmental glomerulosclerosis had been performed on different patients, whose mean age was 45.4 years. Twenty-two (33.3%) of the 66 patients had presented with nephrotic syndrome. The remaining patients had persistent proteinuria.

### *Focal glomerulonephritis*

The 22 patients with focal glomerulonephritis had a mean age of 49.4 years. Cases of focal proliferative, necrotising, and sclerosing glomerulonephritis were included under this category. All modes of clinical presentation were encountered.

### *Membranous glomerulonephritis*

The mean age of the 114 patients who had membranous glomerulonephritis (excluding membranous lupus nephritis) was 49.0 years. Nephrotic syndrome was the presenting feature in 67 (58.8%) patients. The

remaining patients had persistent proteinuria. There was associated hepatitis B virus antigenemia in 12 patients, hepatitis C virus infection in one patient, and nasopharyngeal carcinoma in one patient. Two patients had positive results to the VDRL test at the time of their renal biopsy. In three patients, the membranous glomerulonephritis was associated with the use of penicillamine. The onset of nephrotic syndrome was associated with proximal muscle weakness and chronic myopathy in a 42-year-old man. A 40-year-old man died 2 months after the diagnosis of membranous glomerulonephritis, and post-mortem examination showed the cause of death to be massive pulmonary thromboembolism due to deep-vein thrombosis.

### *Mesangial proliferative glomerulonephritis*

Immunoglobulin A nephropathy and glomerulonephritis associated with other systemic diseases were excluded from the category of mesangial proliferative glomerulonephritis. There were 97 patients with this condition: 54 (55.7%) were male and 43 (44.3%) were female. The mean patient age was 36.7 years.

### *Endocapillary proliferative glomerulonephritis*

Most of the cases of endocapillary proliferative glomerulonephritis were post-streptococcal infection and were diagnosed clinically without a renal biopsy. Biopsy was performed for the 11 patients (mean age, 25.8 years) in this series because of atypical clinical features.

### *Mesangiocapillary glomerulonephritis*

The 24 biopsy samples that showed mesangiocapillary glomerulonephritis had come from 21 patients: 16 had type I disease and the remaining five had type III disease. The mean patient age was 49.8 years. Type III mesangiocapillary glomerulonephritis differs from the type I disease by the presence of frequent subepithelial immune deposits; subendothelial deposits are common to both disease types. No cases of type II mesangiocapillary glomerulonephritis—also known as dense deposit disease—were detected.

### *Crescentic glomerulonephritis*

There were nine cases of glomerular disease, the differential diagnosis of which did not include lupus nephritis, anti-basement membrane glomerulonephritis, or heavy-chain deposition disease that showed diffuse crescentic proliferation. All nine cases were diagnosed morphologically as pauci-immune crescentic glomerulonephritis and were associated with the presence of antibodies against cytoplasmic antigens from neutrophils.

Table 2. Clinical features at presentation of patients with glomerular diseases, as diagnosed by renal biopsy examination

Clinical presentation	Biopsies, n=1413 No. (%)	
	Male patients	Female patients
Proteinuria	267 (18.9)	468 (33.1)
Nephrotic syndrome	207 (14.6)	180 (12.7)
Gross haematuria	24 (1.7)	22 (1.6)
Microscopic haematuria	62 (4.4)	93 (6.6)
Chronic renal failure	34 (2.4)	37 (2.6)
Acute nephritic syndrome	5 (0.4)	12 (0.8)
Malignant hypertension	1 (0.1)	1 (0.1)
Total	600	813

### Diabetic glomerulosclerosis

Eighty patients, whose mean age was 55.5 years, were shown to have diabetic glomerulosclerosis. Coexisting IgA nephropathy was found in 13 (16.3%) of these patients.

Table 2 shows the modes of clinical presentation of patients whose glomerular disease had been detected by renal biopsy.

## Discussion

Percutaneous renal biopsies have been routinely performed in Hong Kong for almost 40 years. They remain an essential part of investigations for the optimal management of renal parenchymal diseases. This biopsy series updates an earlier study at the QMH reported by Chan et al in 1989.<sup>5</sup>

IgA nephropathy has become the most common glomerular lesion, having been diagnosed in approximately 24% of all native kidney biopsies. As in the previous study,<sup>5</sup> Immunoglobulin A nephropathy was found to be equally prevalent in male and female patients. IgA nephropathy is an important cause of end-stage renal failure. A renal biopsy is necessary for a definitive diagnosis of this disease and to provide crucial prognostic information. It is also needed when patients are recruited for therapeutic trials, because there is still no established effective treatment for the majority of cases of IgA nephropathy.

Immunoglobulin A nephropathy was present in 15 (12.0%), 3 (2.6%), 13 (16.3%), and 2 (2.6%) biopsies that had been diagnosed to have minimal-change nephrotic syndrome (n=125), membranous glomerulonephritis (n=117), diabetic glomerulosclerosis (n=80), and thin-basement membrane nephropathy (n=77), respectively. Immunoglobulin A nephropathy was also found together with amyloidosis in one case and

with anti-basement membrane glomerulonephritis in another. The prevalence of thin-basement membrane nephropathy in patients who also had IgA nephropathy was likely to be underestimated because electron microscopy was often not performed after a diagnosis of IgA nephropathy had been established by light microscopy and immunofluorescence study.

Approximately 20% of the kidney biopsy examinations detected lupus nephritis (male to female ratio, 1:14 [n=290]). This high frequency of detection illustrates that the use of renal biopsy is an important therapeutic guide.

Minimal-change nephrotic syndrome and IgM nephropathy were diagnosed in 136 biopsy samples over the 5-year study period. In the new classification scheme of glomerular diseases of the World Health Organization, IgM nephropathy and glomerular tip lesion are described as variants of minimal-change nephrotic syndrome.<sup>4</sup> The distinction between IgM nephropathy and minimal change nephrotic syndrome or mesangial proliferative glomerulonephritis is not well defined. We require that diffuse staining for IgM and complement C3 be present in a mesangial pattern and be associated with mild or minimal mesangial cell proliferation before classifying a case as IgM nephropathy. By using these criteria, only 11 renal biopsies were diagnosed to have IgM nephropathy.

Glomerular tip lesion was an entity first described by Howie and Brewer.<sup>6</sup> This was a very rare condition in this survey: we encountered one biopsy showing focal segmental glomerular lesions characteristic of the glomerular tip lesion. The patient was a 58-year-old man who presented with nephrotic syndrome. The biopsy specimen showed a focal segmental collection of intracapillary foam cells and evidence of capillary dilatation as well as sclerosis that was localised to the peripheral segment of the glomerular tuft. The patient showed a good response to steroid treatment. It is important to distinguish glomerular tip lesion from focal segmental glomerulosclerosis and hyalinosis, which carry a much worse prognosis.<sup>7</sup> Minimal-change nephrotic syndrome and its variants had a male preponderance, the male to female ratio being 1.8:1. We have previously shown this ratio to be 2.5:1 (n=76).<sup>5</sup>

We have also previously shown that for membranous glomerulonephritis, the male to female ratio is 2.5:1 (n=76),<sup>5</sup> which is comparable to the ratio of 2:1 that was reported by another group of investigators in Hong Kong.<sup>8</sup> In this series of patients, however,

the number of biopsies that showed membranous glomerulonephritis was similar for both male (60) and female (57) patients. The marked difference in the male to female ratios between this study and the two previously reported studies might reflect a change in the incidence of membranous glomerulonephritis in Hong Kong. We therefore sought the corresponding data from the Princess Margaret Hospital and found that the same diagnosis had been made from renal biopsy samples of 45 male and 28 female patients from January 1988 to July 1998 (Lee KC, written communication, 1998). Since the male to female ratio of 1.6:1 is more in line with the general trend, the ratio calculated in this study (1.1:1) was probably due to sampling variation.

Thin-basement membrane nephropathy is characterised by the generalised thinning of the glomerular basement membranes. The clinical manifestation of thin-basement membrane nephropathy is persistent microscopic haematuria without the impairment of renal function. Diagnosis of thin-basement membrane nephropathy depends on the electron microscopic examination of optimally processed renal tissue. Because renal biopsy samples usually originate from several different hospitals, the quality of the renal tissue might be difficult to ensure. Consequently, the diagnosis of thin-basement membrane nephropathy in many cases in this study was not firmly established. Such cases might be more appropriately classified as minor glomerular abnormalities.

The proportion of renal biopsies that showed diabetic glomerulosclerosis was relatively high (80/1413; 5.7%). Contributing to this result were the biopsies from a clinicopathological study that aimed to define the clinical indicators of non-diabetic renal disease in patients with non-insulin-dependent diabetes mellitus who had proteinuria at a rate of more than 1 g/d of protein (normal rate of protein excretion in urine, <0.15 g/d).<sup>9</sup> Of a total of 51 patients recruited in the study, 17 (33.3%) had non-diabetic renal disease, as diagnosed by renal biopsy examination. The study showed that the presence of microscopic haematuria and non-nephrotic proteinuria are features associated with non-diabetic renal disease.<sup>9</sup>

Two rare glomerular diseases that were encountered in this biopsy series were fibrillary glomerulonephritis and crescentic glomerulonephritis complicating occult IgA multiple myeloma. Within the 5-year study period, the diagnosis of fibrillary glomerulonephritis in two siblings was the first such diagnosis

in Hong Kong.<sup>10</sup> The case of occult IgA multiple myeloma presented as crescentic glomerulonephritis associated with the deposition of abnormally shortened IgA heavy chains in the kidney.<sup>11</sup> Renal biopsy examination was repeated in this 62-year-old patient 6 months after the initial diagnosis was made and chemotherapy was subsequently given. Paraprotein deposition was diffuse in the basement membranes and formed mesangial nodules that resembled diabetic Kimmelsteil-Wilson nodules. Diffuse crescentic proliferation was also present in this patient.

In summary, this survey of glomerular diseases based on the examination of 1413 native kidney biopsy samples taken from 1993 through 1997 shows that in Hong Kong IgA nephropathy was the most common glomerular disease, followed by lupus nephritis, minimal change nephrotic syndrome, membranous glomerulonephritis, and mesangial proliferative glomerulonephritis. The most common mode of clinical presentation that required renal biopsy examination was persistent proteinuria and the second most common was nephrotic syndrome.

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