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THE HISTOPATHOLOGICAL PATTERN OF PRIMARY IGA NEPHROPATHY IN A MALAYSIAN PATIENT POPULATION

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Summary

In the 10-year period from October 1977 to July 1987, 149 cases of primary IgA nephropathy were histologically confirmed through renal biopsies in the Department of Pathology, University Hospital, Kuala Lumpur. The ages of these patients ranged from 5 to 72 years, with the majority in the 20—30 year age group. There was no sex preponderance. The ethnic distribution showed a significant predominance of Chinese with 107 (71.8%) Chinese, 24 (16.1%) Malays, 15 (10.1%) Indians and 3 others. A wide range of renal glomerular pathology was seen, the commonest being diffuse mesangioproliferative glomerulonephritis (59.1%). Focal proliferative glomerulonephritis (14.1%) followed by minimal change glomerulonephritis (10.7%) were next in order of frequency. Immunofluorescence studies consistently demonstrated heavy and predominant IgA deposition in the mesangium. Weak deposition of C3, IgG and IgM were also observed in various combinations.

Keywords: Berger's disease, glomerulonephritis.

INTRODUCTION

Primary IgA nephropathy, also known as Berger's disease, was first documented by Jean Berger in Paris in 1968.[1] This disease, one of the most frequent forms of nephritis in young adults with asymptomatic haematuria and/or mild proteinuria, was initially thought to be prevalent only in France. Primary IgA nephropathy is now known to have a wide geographical distribution,[2,3] having been reported to be common in Europe, Asia and Australia. High prevalences of 50% and 35—40% have been reported in patient populations in Singapore[4] and Japan[5,6] respectively. It is felt that a study of the situation in Malaysia would provide useful information for further understanding of the disease, in view of her multiracial society and her close geographical relationship to Singapore, a high incidence area.

MATERIALS AND METHODS

In the 10-year period from October 1977 to July 1987, a total of 149 cases of primary IgA nephropathy were diagnosed by renal biopsy in the Department of Pathology, University Hospital, Kuala Lumpur. The standard diagnostic criterion of positive mesangial immunofluorescence on renal biopsy, with IgA as the predominant immunoglobulin, was used. Patients in whom the IgA deposition may be secondary to overt systemic diseases such as liver cirrhosis or systemic lupus erythematosus were excluded from this study. The histopathology of renal biopsies was reviewed and the demographic data of the patients obtained from case records. Where a patient had more than 1 biopsy, only the first diagnostic biopsy was included in this study.

Renal biopsy tissue was fixed in 10% buffered formalin, embedded in paraffin and sections cut at 2um thickness. These sections were stained with haematoxylin and eosin, periodic acid Schiff, Masson's trichrome, Lendrum's Martius-Scarlet-blue and periodic acid silver methanamine (PASM).

In addition, fresh biopsy tissue was snap frozen by immersion in isopentane cooled to —160°C with liquid nitrogen. 4um cryostat sections were cut and overlaid with fluorescein conjugated antisera to human IgG, IgA, IgM, IgD, IgE, C3 and fibrinogen. All the antisera were commercial preparations (Hoechst, Behringwerke AG, West Germany). The stained sections were examined by fluorescence microscopy.

A portion of the biopsy was also processed for electron microscopy. After fixation in 4% glutaraldehyde, the tissue was post-fixed in 1% osmium tetroxide prior to embedding in epon. Ultrathin sections were stained with uranyl acetate and examined under a Hitachi HS8 electron microscope operating at 50kV.

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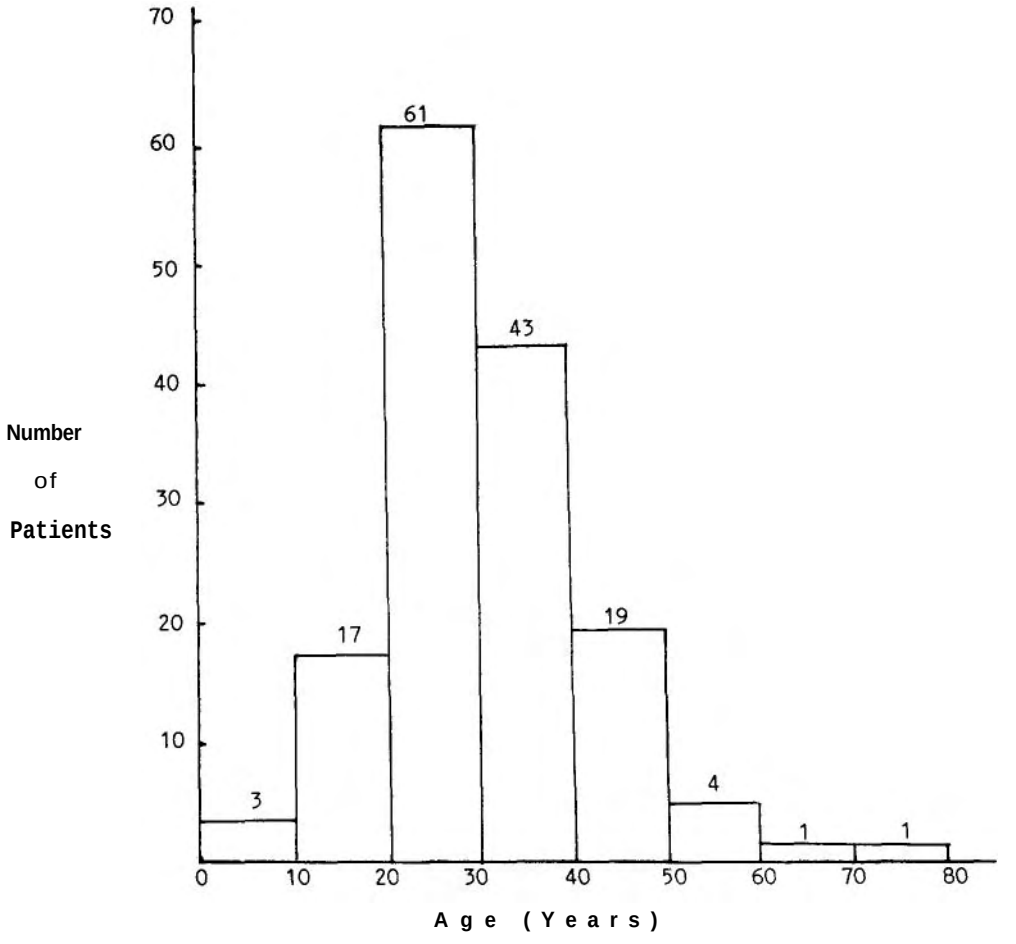

FIG. 1: Age distribution of patients with primary IgA nephropathy.

RESULTS

General

The ages of the patients ranged from 5 to 72 years. Fig. 1 shows the age distribution. The majority of patients were between 20 to 40 years of age, with a peak in the 20–30 year age group. There was no preponderance of either sex, the male:female ratio being 1:1.1. The ethnic distribution showed 107 (71.8%) Chinese, 24 (16.1%) Malays, 15 (10.1%) Indians and 3 others (Table 1). The preponderance of Chinese was found to be statistically significant ($p < 0.01$) when the ethnic distribution was compared with that of the hospital patient admission population during the same 10-year period, using the chi-squared test for goodness of fit.

TABLE 1
ETHNIC DISTRIBUTION OF PATIENTS WITH PRIMARY IGA NEPHROPATHY COMPARED WITH HOSPITAL ADMISSIONS

	IgA patients		Hospital admissions*	
Race	No.	%	No.	%
Malay	24	16.1	38484	24.3
Chinese	107	71.8	73748	46.6
Indian	15	10.1	43993	27.8
Others	3	2.0	2130	1.3
Total	149	100	158355	100

* Based on University Hospital admissions 1978–1987. Obstetrics and special care nursery admissions are excluded.

Histology

A wide range of renal glomerular pathology was encountered (Table 2). 7 biopsies were inadequate for proper histological assessment due to insufficient glomeruli but were neverthe-

TABLE 2
PRIMARY IGA NEPHROPATHY
RANGE OF GLOMERULAR PATHOLOGY

Morphology	No.	(%)
Mesangioproliferative GN	89	(62.7)
Focal proliferative GN	21	(14.8)
Minimal change GN	16	(11.3)
Diffuse proliferative GN (unspecified)	2	(1.4)
Focal glomerulosclerosis	7	(4.9)
Mesangiocapillary GN	1	(0.7)
Chronic GN	6	(4.2)
Total	142	(100)

less diagnosed as IgA nephropathy on the basis of classical immunofluorescence findings. They were, however, left out from the analysis of glomerular morphology. Of the remaining 142 cases, 89 (62.7%) biopsies showed diffuse mesangioproliferative glomerulonephritis (GN), followed by 21 (14.8%) focal proliferative GN and 16 (11.3%) minimal change GN. Other lesions included 7 (4.9%) focal glomerulosclerosis, 6 (4.2%) chronic GN and 1 (0.7%) mesangiocapillary GN. Irrespective of the type of glomerular pathology, immunofluorescence studies consistently showed heavy and predominant IgA deposition in the mesangium in all cases (Fig. 2).

Within the group of ***mesangioproliferative GN,*** the large majority of glomeruli were enlarged and exhibited varying degrees of mesangial hypercellularity and an increase in the amount of mesangial matrix (Fig. **3).**

In ***focal proliferative GN,*** occasional (usually less than a third) abnormal glomeruli were present. These glomeruli exhibited mesangial or endothelial cell proliferation, often segmental in distribution. The majority of other glomeruli showed minor or no abnormality.

The glomeruli in ***minimal change GN*** appeared normal on light microscopy. Nonetheless, IgA deposits were demonstrated in the mesangium on immunofluorescence examination and electron-dense immune-complex

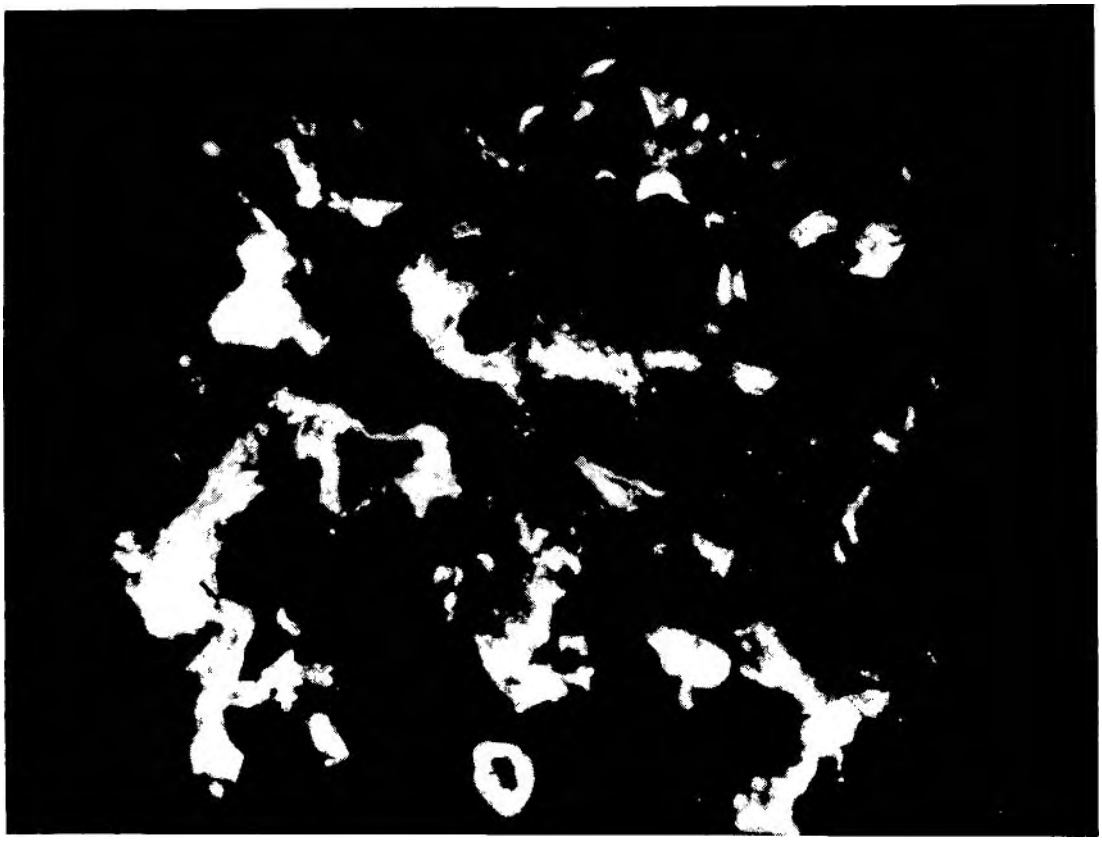

FIG. 2: Immunofluorescence microscopy showing heavy IgA deposition in the glomerular mesangium (X 800)

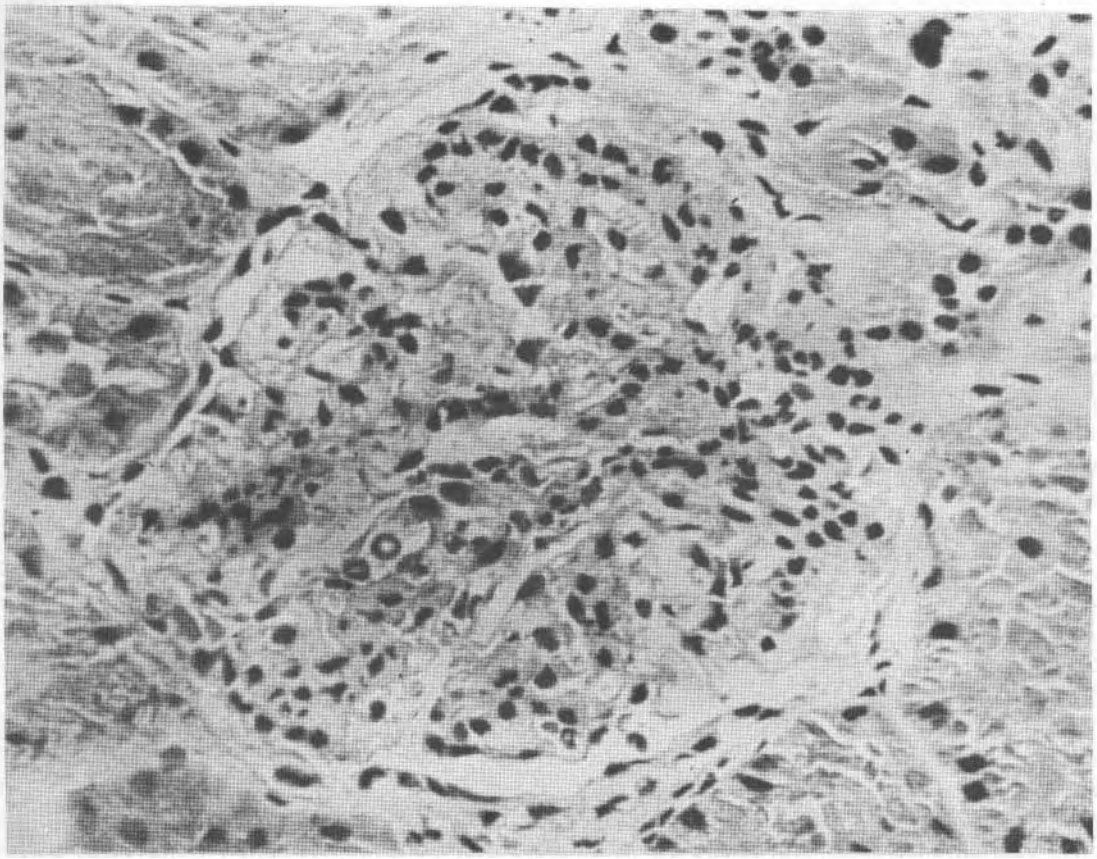

FIG. 3: Diffuse mesangioproliferative glomerulonephritis. The glomerulus shows widening of the mesangium with increased cellularity and matrix. H & E X 550.

TABLE 3
PRIMARY IGA NEPHROPATHY: HISTOLOGICAL FINDINGS

Features	% patients
Crescents	5.6
Mesangial trichrome red deposits	68.1
Hypertensive vascular changes	27.5
Interstitial inflammation	53.6
Tubular atrophy	74.6

deposition was observed in the mesangium on electron microscopy.

Further analysis showed that 68.1% of these cases exhibited trichrome-red deposits in the mesangium (Table 3). 27.5% of biopsies showed hypertensive vascular changes such as medial hypertrophy or hyaline arteriolosclerosis. 5.6% exhibited crescents and 53.6% showed significant collections of inflammatory cells in the interstitium. Tubular atrophy was a common pathological finding, being present in 74.6% of biopsies.

In addition to IgA deposits in the mesangium, complement and other immunoglobulins were sometimes detected. Table 4 shows the frequencies whereby C3, IgG and IgM were demonstrated in the mesangium of these biopsies. In some cases, deposits of complement and immunoglobulins were observed to extend into the capillary loops. C3 was present in 81.2% of cases, followed by 57.7% and 40.3% with IgG and IgM respectively. The latter 2 irnmunoglobulins were not only less frequently detected, but were usually present in smaller amounts as evidenced by weak fluorescence. Table 5 shows the various combinations of immunoglobulins and complement in the biopsies as demonstrated by immunofluorescence microscopy. Small amounts of fibrinogen were seen in 50.3% of cases.

DISCUSSION

The pathogenesis of IgA nephropathy remains controversial and has been the subject of several recent reviews.[3,7,8] That IgA-containing immune complexes play a pivotal

TABLE 4
PRIMARY IGA NEPHROPATHY
RANGE OF IMMUNE DEPOSITION

Component	% patients
IgA	100
C3	81.2
IgM	57.7
IgG	40.3
Fibrinogen	50.3

TABLE 5
PRIMARY IGA NEPHROPATHY
COMBINATION OF
IG AND C3 DEPOSITION

Combination	No.	(%)
A	18	(12.1)
A, C3	26	(17.4)
A, C3, M	40	(26.8)
A, M	5	(3.4)
A, G	1	(0.7)
A, G, C3	18	(12.1)
A, G, M	4	(2.7)
A, G, M, C3	37	(24.8)
Total	149	(100)

role is generally accepted. A close association with episodes of infections of mucosal systems, particularly the upper respiratory and gastro-intestinal tracts, have been reported and support the notion that infections are important antecedant causes. Large quantities of IgA and circulating immune complexes are presumably formed in these patients resulting in trapping of these complexes within glomeruli. Several clinical studies have reported high levels of serum IgA in approximately a third to one half of patients.[2,4] An exaggerated immune response of the patient to infections and a genetic predisposition to reduced renal clearance of immune complexes are additional mechanisms under consideration. The apparent predilection for the Chinese raises the possibility that genetic factors may also play a role in the pathogenesis of this disease. Conceivably, genetic factors may also contribute to the low incidence reported in American blacks.[9]

Mesangial IgA deposition in adult idiopathic glomerular disease has been noted to be common in France where studies have indicated that IgA nephropathy constituted 20% to 25% of patients with renal biopsies.[1,10,11] Similar prevalences have been reported in other European countries such as Italy, Spain and Finland.[2] However, the British, Dutch and Americans have reported much lower prevalences.[2,3] Studies in Asian countries such as Japan and Singapore indicate a high prevalence of this disease. In a previous study of 1000 consecutive renal biopsies of Malaysian patients by the Department of Pathology, University of Malaya, IgA nephropathy constituted 5.8% of biopsies,[12] a figure much lower than that reported from Singapore. The true prevalence is almost certainly higher in view of the fact that not all the biopsies in that study had immunofluorescence examination. Hence some cases of IgA nephropathy would have been missed and categorised with the proliferative glomerulonephritides.

A wide range of pathology was observed in the renal biopsies, a finding which concurs with other studies. As observed in Singapore,[4] diffuse mesangioproliferative GN appears to be the commonest morphological entity. This is in contrast to older studies which reported focal proliferative GN as the most common morphological change encountered.[10,13] Further and more detailed investigations are required to determine whether the pattern of glomerulonephritis seen in this centre is related to the time of presentation of patients in the disease course, patient selection for biopsy or a more aggressive course of the disease among our patients.

Clinicopathological correlation would provide valuable additional information on the natural progression of the disease. Other workers have reported a closer correlation of serum creatinine levels with glomerular sclerosis than with the duration of clinical disease.[14] Severe pathological changes of the glomerular basement membrane have also been observed to be associated with marked proteinuria.[15] In general, glomerular changes correlate well with the clinical parameters of renal function.[7,16,17] Tubulo-interstitial pathology also appears to influence the clinical aspects and outcome of the disease.[1,14,17] It would be of interest, therefore, to consider in greater depth the histological findings of the renal biopsies and their relationships with the clinical

manifestations and outcome of our patients and to compare these findings with those of other centres.

Immunofluorescence examination in this study shows the presence of IgG in only approximately W0 of biopsies, unlike the consistent presence of IgG and C3 observed in the French studies.[1,11] Our finding supports the term "IgA nephropathy" as being more appropriate than "IgA-IgG nephropathy" for our patients. Categorising IgA nephropathy according to the combination of immunoglobulin deposition in the renal biopsy can be an additional approach in studying this disease. It is possible that IgA nephropathy is a heterogenous group of diseases, sharing somewhat similar clinical manifestations at first glance. Prospective and retrospective studies of patients according to the immunofluorescence findings may be helpful in substantiating or disputing this notion. It may also throw light on the aetiology as well as the pathogenesis of this disease.

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