IGA NEPHROPATHY — A CLINICOPATHOLOGICAL REVIEW OF 12 CASES SEEN AT THE DEPARTMENT OF NEPHROLOGY, GENERAL HOSPITAL, KUALA LUMPUR

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SYNOPSIS

From a total of 163 renal biopsies there were 12 cases (9.1%) of IgA nephropathy. All of them presented with symptomatic or asymptomatic proteinuria and/or haematuria. The pattern of disease here generally conforms to reports elsewhere. However in contrast it appears to be common in both sexes and the clinical course tends to be more severe in males. The absence of IgG in the glomeruli on immunoflourescence was an unexpected finding. The presence of hypertension, renal insufficiency and glomerulo-interstitial scarring seem to indicate poorer prognosis. There is no known effective treatment.

INTRODUCTION

IgA nephropathy is a form of idiopathic glomerulonephritis first described in France by Berger in 1969(1). Since then, this form of glomerular disease has been reported to occur in North America, United Kingdom, Australia, Japan, Hong Kong and Sinagpore (2, 3, 4, 5, 6, 7). This well defined pathological entity is characterised by deposits by IgA and C_3 in the mesangium of every glomerulus accompanied by a focal segmental proliferative glomerulonephritis on light microscope.

The disease is commoner in males and runs a chronic course. Patinets characteristically present with recurrent macroscopic or microscopic haematuria and slight proteinuria, offten occuring 24 — 48 hours after an upper respiratory or gastrointestinal infection. This glomerulopathy was initially called "Benign recurrent haematuria" because progression of the disease, if at all, is usually slow. However present evidence suggests that it is far from benign and chronic renal failure requiring dialysis and renal transplantation may eventually develop in up to 25% of cases (8). The purpose of this present report, is to document the existence of these disease in our local community and to evaluate clinical and pathological features which would indicate poorer prognosis.

MATERIALS AND METHOD

Between January 1980 to March 1981, 132 patients presenting with various forms of glomerular disease at the Department of Nephrology, General Hospital, Kuala Lumpur were successfully subjected to a renal biopsy. All the biopsies were done under local anaesthesia using a Trucut biopsy needle and the tissue specimens were subjected to light microsocopy examination and direct immunofluorescence. The sections for light microscopy examination were routinely stained with haematoxylin and eosin, PAS, Silver methamine and Masson's trichrome. The frozen sections for immunfluorescence microscopy were sectioned at 4-5 micron and then stained with fluorescein isothiocyanate-conjugated antibody reagents reactive to human.

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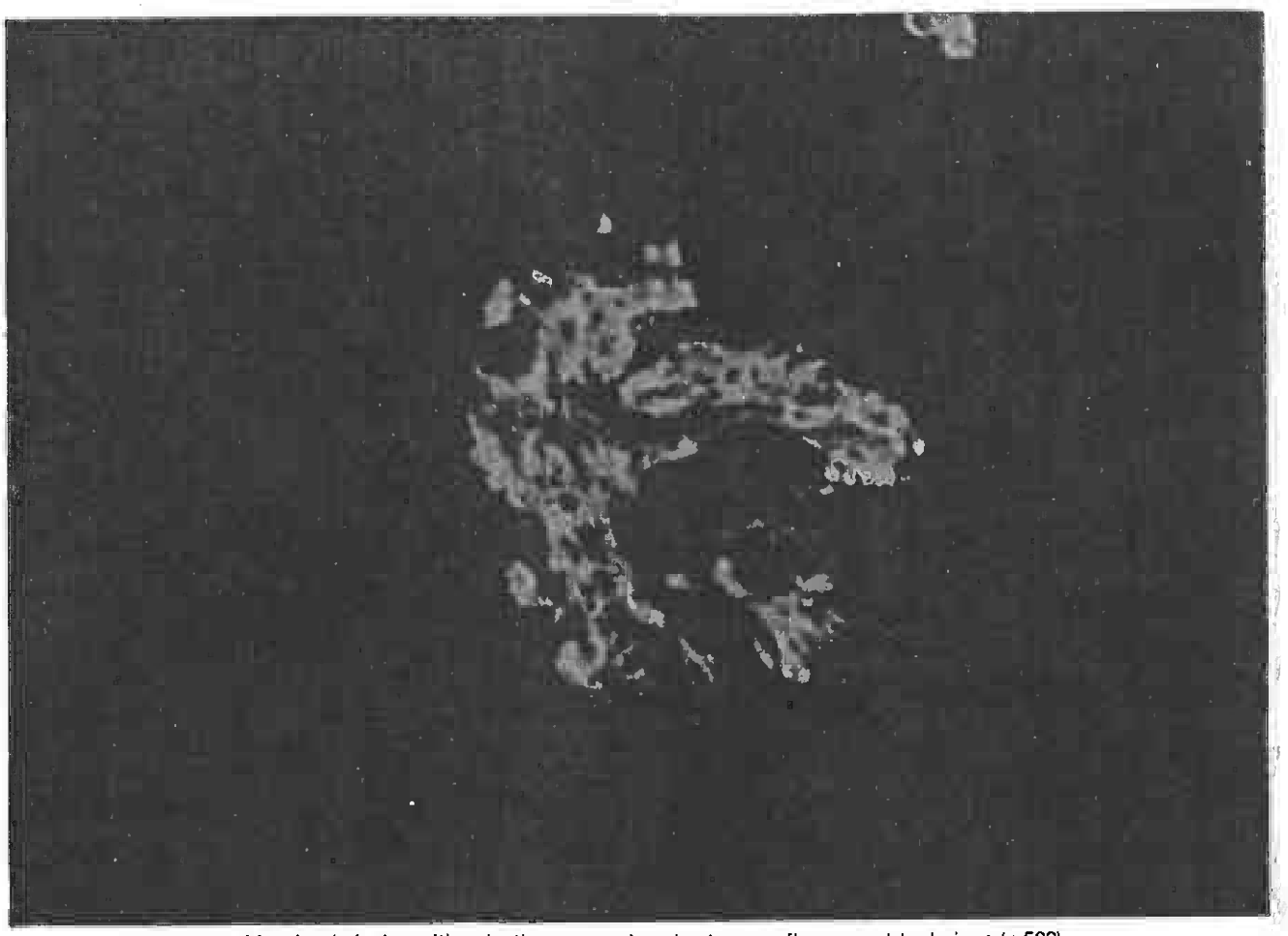

Figure 1: Massive IgA deposition in the mesangium by immunofluorescent technique (x 500)

IgG, IgM, IgA, C3 and C4.

The following criteria were taken for the diagnosis of IgA nephropathy:

1) Demonstration of predominantly IgA in the glomerulus on immunofluorescence microscopy (Figure 1).
2) Typical mesangial and paramesangial deposits on light microscopy (Figure 2).
3) Absence of clinical and laboratory evidence of systemic diseases like systemic lupus erythematosus, chronic liver disease, recent streptococcal infection and anaphylactoid purpura.

RESULTS

(a) Clinical

12 out of the 132 cases biopsied (9.1%) met the above criteria for the diagnosis of IgA nephropathy. There were 7 females and 5 males and they were between the ages of 18 — 34 years (mean 24.7 years). Of these, 6 were Malays, 5 were Chinese and 1 Indian. The mode of clinical presentation is as follows: 5 patients presented with microscopic hamaturia and proteinuria, 3 patients with microscopic haematuria and proteinuria and 4 patients with asymptomatic proteinuria. Of these 12 patients 3 were detected to have urinary abnormalities while undergoing routine medical examination.

Hypertension (defined as blood pressure equal/greater than 130/90 mm Hg) was detected in 3 patients and 5 patients had renal insufficiency (defined as serum creatinine equal/greater than 125 umol/1) at the time of presentation. 2 patients gave a history of colicky loin pain and 1 patient had recurrent tonsillitis. However none of them gave a history of upper respiratory or gastrointestinal infection preceeding the urinary symptoms. HBsAg using radioimmunoassay (RIA) method was not detected in any of the patients. Serum protein ranged from 60 — 83 g/1 (mean 70.7 g/1) with serum albumin from 29 — 44 g/l (mean 39.8 g/1). 24 hour urinary protein excretion ranged from 0.21 — 3.88 g/l (mean 1.38 g/1).

Serum complement levels were available in 9 patients with C_3 varying from 64 — 114 mg/100 ml (mean 87.0 mg/100 ml) and C_4 from 21.5 — 54.4 mg/100 ml (mean 33.6 mg/100 ml). The result indicates that only one patient had marginally raised C_4 level whereas the rests were within normal limits.

Serum immunoglobulin levels were measured in only 2 patients of which one patient had marginally raised IgA and IgG levels.

(b) Renal biopsy

All the 12 patients underwent successful renal biopsies. Focal segmental proliferative glomerulonephritis was seen in 4 patients: focal segmental proliferative glomerulonephritis with sclerosis in another 4; diffuse mesangial proliferative glomerulonephritis in 3 (Figure 3) and minimal change in 1. In addition a few segmental epithelial crescents were seen in 2 of the patients with focal segmental proliferative glomerulonephritis.

Significant tubulointerstitial scarring was seen in 4 biopsies. Of these, all 4 cases also had glomerulosclerosis

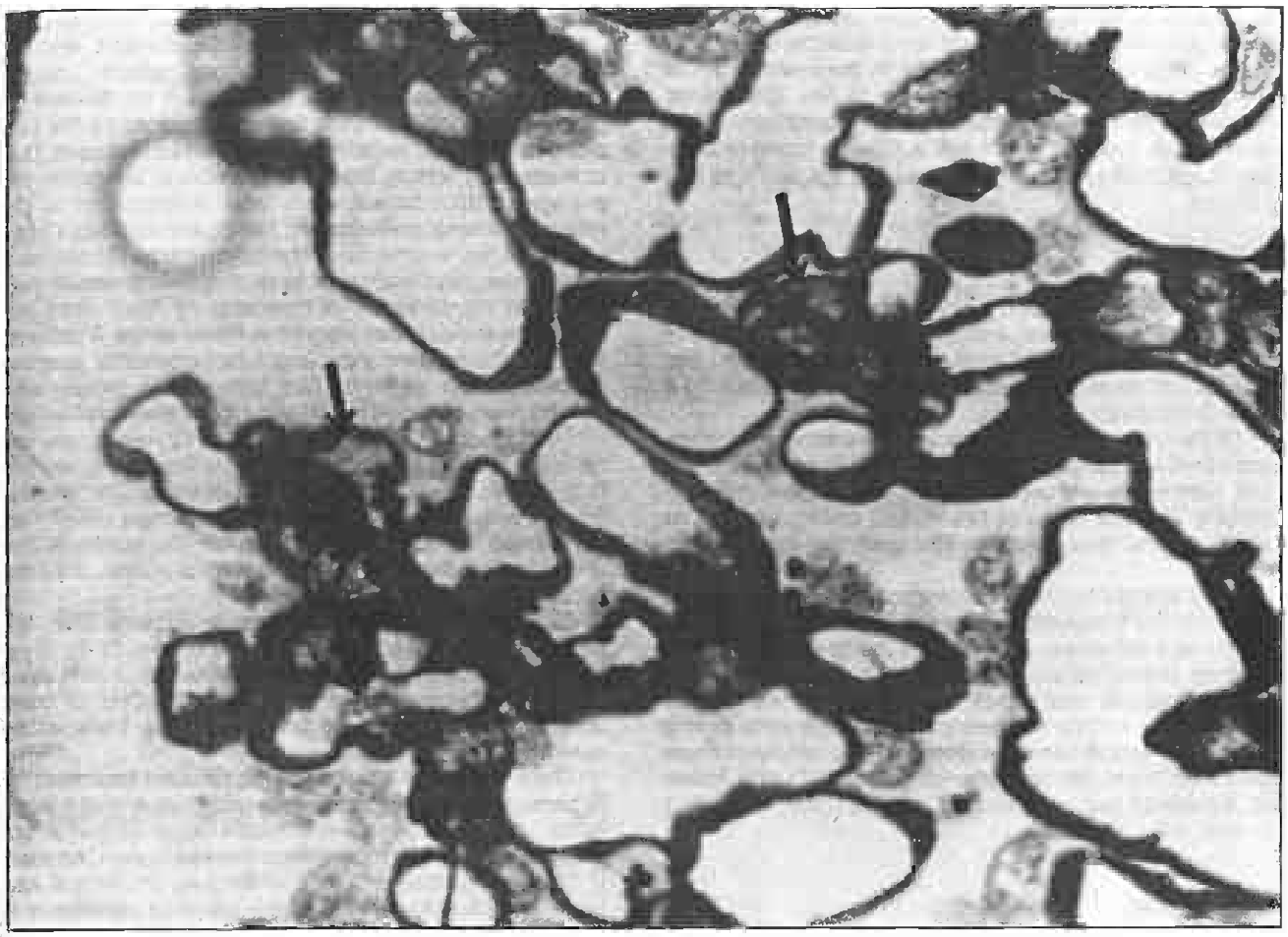

Figure 2: Large mesangial and paramesangial (arrows) deposits. (Silver methamine x 1200)

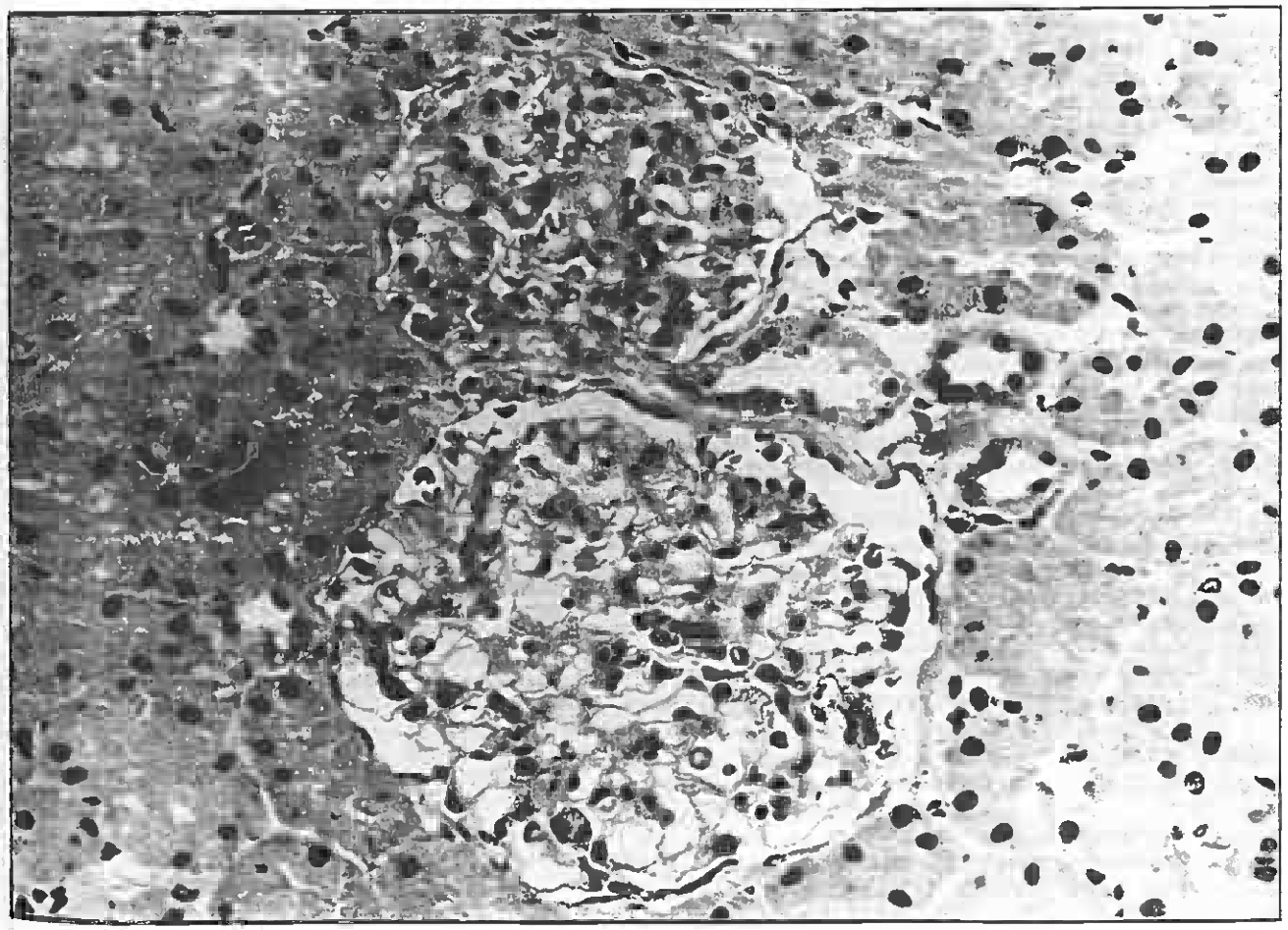

Figure 3: Diffuse mesangial proliferative glomerulonephritis in IgA nephropathy (x 600)

and 3 were hypertensive with a raised serum creatinine.

Immunofluorescene findings were available in all 12 patients. Deposits were mainly found in the mesangium of the glomeruli. IgA was detected in all the 12 patients. However, IgG and C4 could not be detected in any of the biopsies. A combination of IgA & C_3 was found in 8 patients, IgA, IgM and C_3 in 3 patients and IgA and IgM in 1 patients.

(c) Follow up

The 12 patients attended clinic for periods ranging from one month to 4 years and 2 months (mean 1 year 4 months). During this period one patient did not return and one patient developed end-stage renal failure requiring a renal transplant.

Of the remaining 10 patients, urinary examination at the last clinic attendance showed that 6 patients have persistant haematuria and proteinuria, 3 patients have only proteinuria whereas 1 patient has normal urinary findings. In addition, 4 patients were receiving treatment for hypertension.

In an attempt to identify poorer prognostic features, we analysed the 5 patients who presented with renal insufficiency as a sub-group. There were 4 males and 1 female. 4 patients presented with asymptomatic proteinuria and 1 with haematuria and proteinuria. 4 of them were either hypertenisve initially or developed it subsequently during follow up. In addition 4 patients had glomerulosclerosis with significant tubulointerstitial scarring. During follow up 4 patients had worsening of renal function whereas 1 patient remained stable.

DISCUSSION

IgA nephropathy has generated much interest partly because it is a relatively newly identified disease entity but more so because it is increasingly being recognised in many parts of the world. Incidence has been reported to vary from 7.9% to 31.3% (4, 5, 6, 7, 9). Prathap and Looi (10) recently reported an incidence of 5.8% in a Malaysian community. The present series of 9.1% indicates that this disease is not uncommon in our community. However, we suspect that the incidence may even be higher as there were some cases in the present series who had clinical and histopathological features highly suggestive of the disease but were not included in the report because immunofluorescence findings were not available.

Of the total 132 patients, 40 were biopsied because of haematuria and/or proteinuria. Looking at it selectively, the 12 patients who had IgA nephropathy who presented likewise thus accounted for 30.0%. This figure shows that IgA nephropathy should be considered in any patients found to have symptomatic or asymptomatic haematuria and/or proteinuria.

In general, the clinicopathological features of this disease in our community conforms with those reported elsewhere. The disease appears to affect all the 3 major racial groups. However, in contrast to other reports, it appears to be common in females too. This may not be statistically significant as the sample population was small.

The renal histopathology showed that most patients have a focal segmental proliferative glomerulonephritis with or without sclerosis.

The frequent finding of glomerulosclerosis and interstitial scarring suggests that our patients maybe presenting themselves late in the course of the disease for proper investigation. This is further supported by the fact that 5 patients had renal insufficiency when first seen. Due to inadequate history, it was not possible to determine the average duration between the onset of symptoms to the time of first renal consultation. The 2 patients whose biopsies had a few segmental epithelial crescents did not have progressive deterioration of renal function. It would suggest that the presence of crescents by itself need not necessary indicate bad prognosis. However the 4 patients with significant glomerular and tubulointerstitial scarring at presentation seem to fare worse as a group, with development of hypertension and progressive renal failure.

The absence of IgG in all the 12 cases on immunofluorescence microscopy differs from other reports (1, 2, 3). This may suggest a regional variation. The reaction for IgA was generalised and diffuse and was usually accompanied by C_3. The absence of C_4 supports the evidence that the complement system is activated via the alternate pathway in IgA nephropathy.

Contrary to literature our results indicate that IgA nephropathy is not a 'benign' glomerulopathy. Of the 5 patients who presented with renal insufficiency, 4 developed progressive worsening of renal function. One of them developed end-stage renal failure and was transplanted recently.

There were also 4 patients who required treatment for hypertension. It is interesting to note that 4 of the 5 patients with renal failure were males suggesting that IgA nephropathy may be more severe disease in man. As there is no specific treatment for this disease, proper and adequate control of hypertension appears to be paramount in the long term management.

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