Primary immunoglobulin A nephropathy through the 'retrospectroscope'

FMM Lai, KF To, PCL Choi, PKT Li

Objective. To review pathological approaches to the diagnosis and prognosis of primary immunoglobulin A nephropathy.
Data sources. *Medline* and non-*Medline* literature search (1966-1999) and personal experience.
Study selection. The following key words were used: IgA nephropathy, pathology, grading.
Data extraction. Data were extracted and analysed independently by the authors.
Data synthesis. Primary immunoglobulin A nephropathy is the most common glomerular disease worldwide and this also holds true in Hong Kong, where it represents the most common condition encountered in diagnostic renal biopsy examinations. This type of chronic nephropathy currently has no effective curable therapy, and in a significant proportion of patients, it progress to end-stage renal disease. Supportive treatment is very important, because it may alter the natural course and slow down the progression of this nephritis.
Conclusion. Pathological grading of immunoglobulin A nephropathy currently represents the most useful method to appraise the renal outcome.

Introduction

Primary immunoglobulin (Ig) A nephropathy was first described as a distinct entity by Berger[1] in 1968, when renal biopsy samples were first examined by immunofluorescence microscopy. Immunglobulin A nephropathy—also referred to as Berger's disease—was initially underdiagnosed because cases of the disease were dismissed as being a benign haematuric syndrome and biopsies were not performed. The condition was subsequently recognised not only as the most common glomerulonephritis worldwide, but also as a cause of end-stage renal failure in up to 30% of patients.[2,3] The prevalence of IgA nephropathy, as diagnosed from 2200 biopsy specimens at the Prince of Wales Hospital (PWH) in 1999 was 29% (unpublished data, 1999), and such a high prevalence may be similar in other parts of China.[4-6]

The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong:
Department of Anatomical and Cellular Pathology
FMM Lai, FRCPA, FHKAM (Pathology)
KF To, FRCPA, FHKAM (Pathology)
PCL Choi, FRCPA, FHKAM (Pathology)
Department of Medicine and Therapeutics
PKT Li, FRCP, FHKAM (Medicine)

Correspondence to: Dr FMM Lai

This article reviews the problems and pitfalls that can be encountered during biopsy examinations, and stresses the importance of performing a renal biopsy in helping to determine the prognosis and long-term treatment of patients.

Disease definition and classification

Immunoglobulin A nephropathy is characterised by the predominant presence of IgA-containing immune complexes that are distributed in the glomerular mesangium. Based on such a definition, the morphology of the disease can be considered as being uniform (although the light microscopic features may vary), whereas the clinical manifestations and associated conditions can be diverse.[3,7]

Primary immunoglobulin A nephropathy
In the absence of extrarenal manifestations, IgA nephropathy is also referred to as Berger's disease. An association with purpuric skin rash, arthralgia, and gastro-intestinal symptoms, however, characterises Henoch-Schönlein purpura (HSP). In spite of their different clinical manifestations, Berger's disease and HSP may be regarded as variants of the same disease, because they share similar renal pathology and pathophysiological mechanisms.[1,7,8]

Secondary immunoglobulin A nephropathies

Secondary IgA nephropathies represent a heterogeneous group of conditions whose common feature is the presence of mesangial IgA-containing immune complexes that have an unclear pathogenetic association with the nephritis. Such conditions include ankylosing spondylitis, cirrhosis, coeliac disease, dermatitis herpetiformis, erythema nodosum, myasthenia gravis, and mycosis fungoides. The significance and outcome of these secondary IgA nephropathies are poorly understood, partly because they are uncommon and not well studied.[7,8]

Clinical considerations

Renal manifestations

Berger's disease affects mainly young adults (mean age, 30 years), but it is also well documented in the paediatric population. In contrast, HSP affects mainly children. A male predominance is observed in Caucasians, while the sex ratio is reversed among the Chinese population—for example, the male to female ratio for the disease was shown to be 5:7 (n=637) at the PWH in 1999 (unpublished data, 1999).[5,7,9] The typical renal manifestations are haematuria, which is usually microscopic, painless, and incidentally detected, or gross haematuria associated with an upper respiratory tract infection (synpharyngitic haematuria).[3,7] Haematurias or other renal manifestations are episodic and characterised by periods of clinical quiescence and recurrence. Loin or back pain is a common associated symptom. Other symptoms may be hypertension, proteinuria, nephrotic-range proteinuria, impairment of renal function, pre-eclampsia, or the post-partum persistence of hypertension or proteinuria.[3,7,8] Patients rarely present with rapidly progressive glomerulonephritis or acute renal failure.[8,10] Occasional presentations, however, are advanced renal failure or end-stage renal disease after a relatively indolent course.[3,7,8] There is no serological marker for the disease; serum IgA levels are elevated in approximately 45% of patients, and only a few patients may show a low titre of anti–neutrophil cytoplasmic antibodies.

Extrarenal manifestations

Although primary IgA nephropathy is limited to the kidney, the condition has been regarded as a systemic disease. Apart from HSP, primary IgA nephropathy rarely has extrarenal symptoms. Abdominal pain has been observed in some patients and was related to vasculitic lesions and the deposition of IgA in small blood vessels.[11] Pulmonary haemorrhage is rare but has been reported and attributed to capillaritis in the alveolar septa.[12]

Pathological features of immunoglobulin A nephropathy

Immunofluorescence microscopy

The diagnosis of IgA nephropathy is based on the presence of dominant mesangial immune complexes of IgA and complement component C3. These deposits can be demonstrated by immunofluorescence or immunoelectron microscopy (Figs 1 and 2), with the use of appropriate controls. The global and mesangial distribution of immune complexes gives a characteristic fluorescent pattern, described as the 'branches of a tree in winter, devoid of leaves' (Fig 1). Such a distinctive pattern may be less evident in cases where scanty immune deposits are also seen in capillary walls. The predominance of IgA-C3 complexes is important, because in nearly half of the cases, mesangial IgG and IgM deposits are also present and their staining intensity is weaker than or equal to that of IgA. In this situation, IgA-C3 complexes are said to be codominant with IgG or IgM. Immune complexes can also
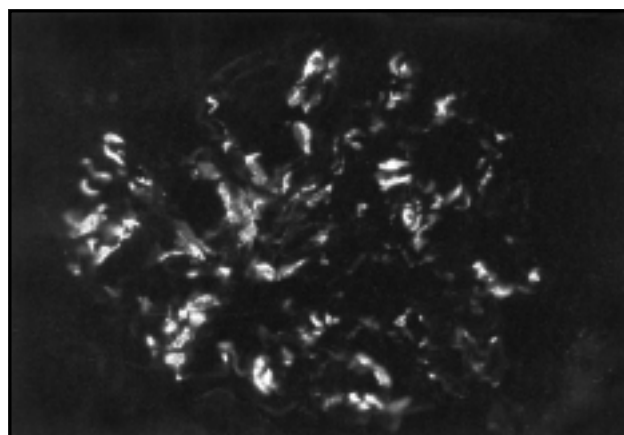

Fig 1. The mesangial distribution of IgA-containing immune complexes has a distinctive pattern, resembling branches of a tree (FITC-conjugated rabbit anti-human IgA antibodies, x265.7)
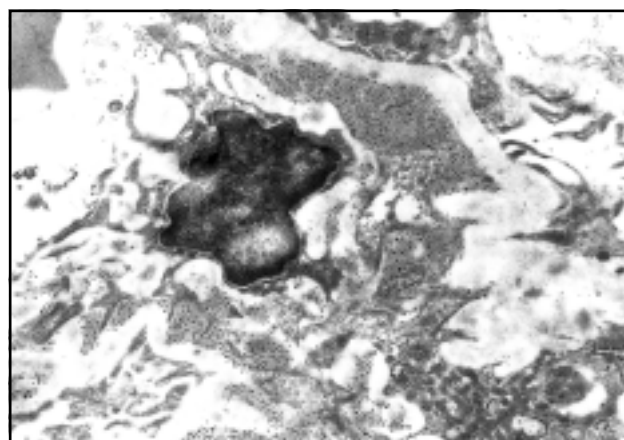

Fig 2. Immunoelectron microscopy demonstrates IgA-containing immune deposits in the mesangium (gold-conjugated rabbit anti-human IgA antibodies, x4076.5)
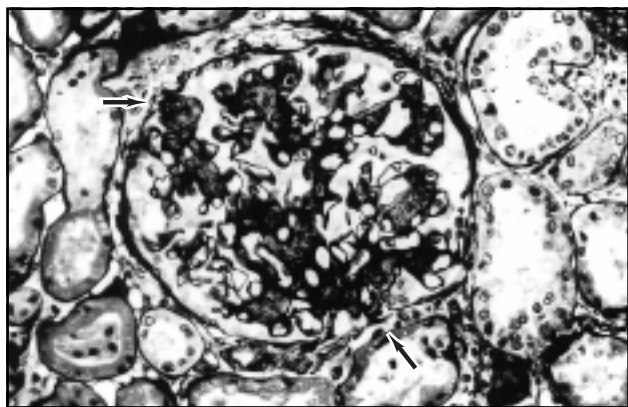
Fig 3. The lesion typically contains segmental mesangial hypercellularity and/or sclerosis, often associated with capsular adhesions (arrows) [periodic acid-silver methenamine, x221.8]

comprise C3 without the C1q subunit or C4 component. Complexes of IgA1 and IgA-associated lambda light chain can also be found, but their clinical significance is unclear, so their presence is not routinely tested for. In patients who are seropositive for hepatitis B virus (HBV), the use of antibodies to HBV surface or e antigens may demonstrate the presence of HBV antigens along with IgA-C3 complexes.

Light microscopy

In the early stages of disease, glomeruli may appear normal, but in most cases, the biopsy sample typically shows a focal segmental mesangial lesion (Fig 3). Such a mesangiopathic process consists of either hypercellularity, sclerosis, or both disorders in varying degrees of severity. Mesangial hypercellularity is defined as the presence of four or more cells in a segment, and sclerosis as the increase in mesangial matrix or accumulation of basement membrane materials. These changes can be detected histologically by using periodic acid Schiff or periodic acid-silver me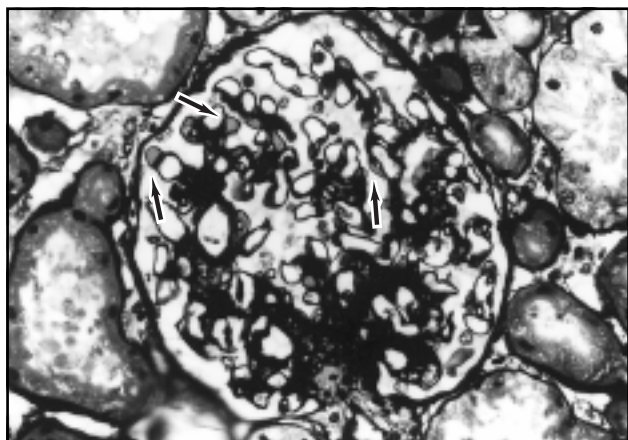thenamine stains. Mesangial immune deposits are usually inconspicuous in light microscopy, except in some cases where they appear as globular glassy structures that protrude like nipples from the mesangium; these lesions are distinctive enough to establish the diagnosis (Fig 4).

Whereas the most characteristic appearance of IgA nephropathy is segmental to global mesangial sclerosis (Fig 3), the morphology is non-specific, because it can be seen in all spectrums of renal diseases. As the disease progresses, the appearance of the glomeruli reflect the irreversible and devastative effects of the sclerosing process, with varying degrees of segmental sclerosis, capillary collapse, and capsular adhesions, which eventually lead to severe glomerular distortion and obsolescence (Fig 5). Mesangial hypercellularity is generally modest and confined, but uncommonly may give rise to the mesangiocapillary-type proliferative glomerulonephritis, in which capillary walls and subendothelial immune deposits are duplicated. Focal segmental necrotising lesions with or without crescent are occasionally observed, and the patients with this presentation are clinically nephritic. But such necrotising lesions are more commonly seen in HSP than in primary IgA nephropathy. Crescentic glomerulonephritis is a rare presentation of IgA nephropathy, in which there is either acute renal failure or a rapidly progressive glomerulonephritis.[8,10] Overall, the great majority of cases show little hypercellularity, and the extent of glomerular injury relates to the progressive sclerosing process.

Tubulo-interstitial injury in IgA nephropathy appears to be the passive consequence of glomerular disease, and the extent of tubular atrophy and interstitial fibrosis parallels that of glomerulosclerosis. In histological sections, each nephron is represented by

Fig 4. Heavy mesangial immune deposits may be globular and may protrude like a nipple (arrows) [periodic acid-silver methenamine, x265.7]
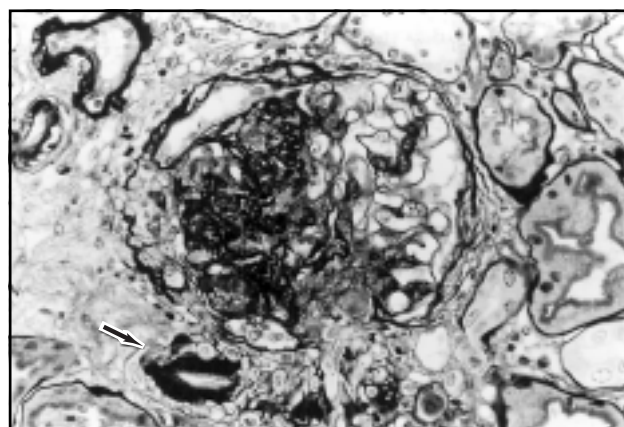

Fig 5. The progression of IgA nephropathy is characterised by increasing glomerular sclerosis, collapse of capillaries, glomerular distortion, and the appearance of hyaline arteriolosclerosis (arrow) [periodic acid-silver methenamine, x265.7]

a glomerulus and several tubular profiles, such that the obsolescence of one glomerulus is reflected by the collapse of several tubules. The observed extent of tubular damage can be used to appraise the severity of glomerular disease. Such a proposition appears to be supported by statistical analysis of the histological grading—the tubular grade is a more sensitive predictor of renal prognosis than is the glomerular grade. Hyaline arteriolosclerosis and hypertensive changes are not seen in the early stages of primary IgA nephropathy, but arteriolar lesions become more common as the disease advances.

Electron microscopy

Immunoelectron microscopy can be used to confirm the findings from the light and immunofluorescence microscope studies, and invariably shows expanded mesangial matrix with heavy electron-dense deposits, which are the IgA-C3 immune complexes (Fig 2). These immune complexes may appear as scattered islands of dense deposits or as well-circumscribed dense globular depositions, or a mixture of both. Infrequently, small subendothelial and/or subepithelial dense deposits can de detected, but the glomerular capillary basement membrane itself is relatively normal in the early stages of disease. As glomerular sclerosis worsens, various basement lesions can be observed; they have been described in the literature as thinning, splitting, disruption, garland-shape widening, and lytic attenuation.[6,8]

Histological diagnostic considerations

The diagnosis of IgA nephropathy depends on the results of the immunofluorescence studies, and is straightforward when mesangial IgA-C3 complexes are predominant, irrespective of their appearance under the light microscope. However, a differential diagnosis will need to be considered in the following situations:

Weak mesangial staining intensity

When the mesangial IgA-C3 staining intensity is weak, the diagnosis of IgA nephropathy is equivocal and clinical correlations are necessary. In a patient with haematuria, dysmorphic red cells in the urine, and detectable mesangial electron-dense depositions, the diagnosis of early IgA nephropathy is justified. The nephrologist needs to consider whether the clinical manifestations can all be explained by early IgA nephropathy, or whether they can be correlated with another condition—for example, hypertensive nephrosclerosis. When the clinical presentation does not fit, a nephritis other than IgA nephropathy must be considered. For example, the presence of nephrotic

syndrome may be due to an underlying minimal-change nephropathy, which can be confirmed by electron microscopy; otherwise, the diagnosis of hypertensive nephrosclerosis is more likely in a hypertensive patient who has impaired renal function. In some cases, a thorough clinical follow-up may be needed to clarify the diagnosis.

Clearly diagnostic mesangial staining

The presence of ultrastructures confirm the presence of a superimposed minimal-change nephropathy when the universal fusion of epithelial foot processes are identified, in which case the syndrome may respond to corticosteroids.[8,13] However, in the majority of patients with both IgA nephropathy and nephrotic syndrome or heavy proteinuria, there is no evidence of a superimposed minimal-change nephropathy, and proteinuria in these patients is part of the spectrum of IgA nephropathy that heralds a poor renal outcome.[2,8]

Focal necrotising glomerulonephritis

An uncommon but well-recognised condition is IgA nephropathy presenting with focal necrotising glomerulonephritis. This glomerular lesion, however, is more typical in patients with HSP; they may also show cutaneous, joint, or gastro-intestinal manifestations. When focal necrotising lesions are associated with weak and equivocal immunostains, the category of pauci-immune glomerulopathies, particularly microscopic polyarteritis and Wegener's granulomatosis, needs to be considered as a diagnosis; serological analysis to detect anti–neutrophil cytoplasmic anti-bodies is indicated.

Crescentic glomerulonephritis

Crescentic glomerulonephritis in IgA nephropathy is defined by the presence of cellular crescent in at least 50% of glomeruli, and is a rare condition, even in HSP in which occasional crescents are common. Despite the extensive glomerular destruction by crescents, immunostained IgA-C3 complexes can still be recognised in most cases.[10] When immunostainings are equivocal, however, other conditions that are more commonly associated with the presence of crescents must be considered, such as anti–glomerular basement membrane disease (in which distinctive linear staining can be overlooked because of severe glomerular damage), microscopic polyarteritis, and Wegener's granulomatosis. In these conditions, serological tests for anti–glomerular basement membrane and anti–neutrophil cytoplasmic antibodies are indicated.

Concomitant membranous nephropathy

Although rare, the coexistence of two distinct types of nephritis implies that two different pathogenetic

mechanisms can occur.[14,15] The superimposition of IgA nephropathy and membranous nephropathy was first described in chronic HBV carriers, but can also occur in non–HBV carriers. Immunostaining reveals distinctly mesangial IgA-C3 complexes and capillary wall IgG-C3 complexes, and the distribution of these immune complexes are confirmed by the presence of ultrastructures.

Immunoglobulin A nephropathy superimposed or antedating diabetic glomerulosclerosis

Diabetic patients usually develop glomerulosclerosis only 10 years after the onset of the disease. In these patients, however, IgA nephropathy may develop before or after the appearance of diabetic glomerulosclerosis.[16] The different pathogeneses leading to the IgA nephropathy and diabetic glomerulosclerosis can coexist. Thus, diabetic patients who have renal manifestations but who lack retinopathy should undergo a diagnostic renal biopsy examination. Although both conditions are mesangiopathic, the features of IgA nephropathy are distinct from those of diabetes. Well-established diabetic lesions include characteristic Kimmelstiel-Wilson nodules, a uniformly thick glomerular basement membrane, and hyaline arteriolosclerosis. The renal prognosis is poor in diabetic glomerulosclerosis, regardless of its association with IgA nephropathy.[16]

Patients with systemic lupus erythematosus

Patients with systemic lupus erythematosus (SLE) often develop lupus nephritis, and renal biopsies are performed to determine the type of lupus nephritis, its severity, activity, and chronicity indices, as well as to guide therapy. Rarely, the biopsy reveals a non-lupus nephritis; the occurrence of IgA nephropathy, HBV-related nephritis, and other nephropathies in patients with SLE has previously been reported.[17] These unusual types of glomerulonephritis in patients with SLE can be diagnosed only when lupus nephritis is absent or 'minimal'. Nevertheless, in patients in whom lupus nephritis has fully developed, the diagnosis of non-lupus nephritis would be difficult to recognise and to confirm.

Pathology grading in immunoglobulin A nephropathy

As there is no effective curative therapy, it is very important to determine risk factors that carry reliable and predictive values in assessing the renal survival. These prognostic parameters are key to determining supportive and long-term treatment of high-risk patients. Many histological grading systems have

been proposed; all are semi-quantitative and have been correlated to some extent to renal outcome.[18-20] None of the existing systems so far prevails, but all concur that grading must include both assessment of glomerular as well as tubulo-interstitial lesions, and the superiority of any one system remains to be proven. The grading system used at the PWH is based on the premise that IgA nephropathy is a chronic condition in which the irreversible process of sclerosis is directly linked to its progression or to the deterioration of renal function.[21] Thus, the grading system at the PWH does not take into account active lesions such as necrosis, cellular crescents, or mesangial hypercellularity, all of which may be reversible and may not result in permanent glomerular injury, unlike the sclerotic process.

Histological grading

A minimum of 5 mm of renal cortex and 10 glomeruli are required for histological grading. Sections are stained with periodic acid-silver methenamine, and counterstained with haematoxylin and eosin. Glomerular grading assesses the extent of sclerosis, which is defined as an increase in mesangial matrix or basement membrane materials, with or without luminal collapse, foam cells, and capsular adhesions. Each glomerulus is first classified, based on the percentage amount of sclerosis, into one of the following five categories: 0% sclerosis without luminal collapse (0%-5% sclerosis), and 25%, 50%, 75%, or 100% sclerosis with collapsing lumen, for 5% to <25%, 25% to <50%, 50% to <70%, and 75% to 100% sclerosis, respectively. The mean value of sclerosis per glomerulus is then calculated to determine the glomerular grades (GGs), which are classified as follows: GG 1, 0% to <25% sclerosis; GG 2, 25% to <50% sclerosis; or GG 3, ≥50% sclerosis.

Tubulo-interstitial grading assesses only the cortex. The areas of tubular atrophy and interstitial fibrosis are quantified as a percentage and given a tubulo-interstitial grade (TIG) as follows: TIG 1, 0% to <5% atrophy and fibrosis; TIG 2, 5% to <50% atrophy and fibrosis; or TIG 3, 50% atrophy and fibrosis. The extent of hyaline arteriolosclerosis is assessed by the determining the presence or absence of arteriolar hyaline, which may or may not be associated with smooth muscle hyperplasia or luminal reduction.

Significance of histological grading

Histological grading is relatively simple to perform and gives reproducible results; the inter- and intra-observer concordance rate for three pathologists carefully examining the same slides is more than 95%.

The grading system takes into consideration the GG, TIG, and extent of hyaline arteriolosclerosis. Using the Spearman's rank correlation method, the GG and TIG have both been shown to be significantly correlated with the serum creatinine concentration, proteinuria, hypertension, and the renal survival time in 126 patients, whose mean follow-up duration was 6 years.[21] Logrank univariate analysis of the Kaplan-Meier survival curve has shown that the GG, TIG, extent of hyaline arteriolosclerosis, proteinuria, and hypertension are all significantly correlated with renal survival. In addition, multivariate analysis using the Cox regression model has shown that the TIG and extent of proteinuria are independent variables that can predict the renal outcome.[21]

Pathogenetic aspects of immunoglobulin A nephropathy

Despite extensive clinical and animal investigations, the mechanisms leading to the presence of mesangial IgA-containing immune complexes remain unknown.[2,8]

Serum immunoglobulin A levels and autoimmunity
The elevated serum IgA level in many patients suggests that IgA nephropathy is a systemic disease due to an altered systemic IgA immunity. The IgA-mediated vasculitis seen in patients with HSP lends support to this concept. The hyperactivity T-helper cells and the excess production of interleukin-2 and interferon gamma during IgA nephropathy have been attributed to autoimmunity, but the underlying events or causes of such reactions are unknown.[22-24]

Presence of immunoglobulin A-containing immune complexes
Immune complexes that contain IgA are detected in only some patients, thus suggesting that mesangial immune complexes may form in situ. In patients who have detectable circulating immune complexes, reduced splenic immune clearance may be another factor that leads to the deposition of glomerular complexes.[23-25] Food antigens and respiratory viruses have been incriminated because of synpharyngitic haematuria and the association of nephritis with coeliac disease or gluten-containing diet, but these suggestions remain unconfirmed. In Hong Kong, a small subset of IgA nephropathy may be related to a chronic HBV carrier state.[13,15]

Origin of mesangial immunoglobulin A
Mesangial deposits are composed mostly of dimeric IgA1 and are often associated with the J chain. This observation supports a mucosal origin of IgA-containing immune complexes. Elutions of mesangial deposits, however, have demonstrated the lack of secretory component (which characterises mucosal IgA) and the presence in some cases of monomeric IgA, thus suggesting that mesangial complexes may originate from the bone marrow. The detection of polymeric IgA1 in some patients and monomeric IgA1 in others causes further controversy in the origin of mesangial IgA complexes.[24,26,27]

Mechanisms of glomerular injury
The importance attributed to IgA-containing immune complexes in glomerular injury has been tempered. The emphasis has changed to mediators such as interleukin-2, transforming growth factor β and platelet-derived growth factor, the expression of which in glomeruli correlates with the extent of sclerosis.[8,28,29]

Genetic markers
Genes that encode complement factors, human leukocyte (HLA) antigens, and immunoglobulin heavy chains have been investigated, but none appear to be implicated in the development of IgA nephropathy. While a few familial and ethnic associations with *HLA-B35*, *HLA-DR4*, *HLA-DQ* have been reported, no putative loci have so far been linked to IgA nephropathy, HSP, or both.[8,23,30] In the Chinese population, the *HLA-DQA2 U* allele is more prevalent in patients with IgA nephropathy who have poor renal function, and the presence of the allele is associated with poor prognosis.[30]

Management of immunoglobulin A nephropathy

Effective curative therapy
Effective curative therapy for IgA nephropathy does not currently exist. Many therapeutic trials have resulted in either failure or limited success.[31-33] Therapy thus mostly comprises supportive care.

The control of hypertension has proved to be effective in retarding the deterioration of renal function or in the progression of IgA nephropathy, and angiotensin-converting enzyme inhibitors can be used reduce proteinuria. The use of antagonists to platelet-derived growth factor and transforming growth factor β to oppose the sclerosing process is logical, but such a therapeutic approach is still at the experimental stage.[8,31-33]

Pregnancy and immunoglobulin A nephropathy
Because IgA nephropathy affects women in their reproductive age, pregnancy in IgA nephropathy is an important issue. The effect of pregnancy on the

natural course of IgA nephropathy is controversial and there is currently no consensus regarding the adversity of pregnancy on the nephritis. The increased renal blood flow and hyperfiltration that occur during pregnancy may potentially aggravate the sclerosing process. The main obstetrical concerns are intrauterine growth delay, accelerated hypertension, preeclampsia (which may cause foetal growth delay), risk of prematurity, and the increased risk of stillbirth and neonatal morbidity. The obstetrical and maternal risks appear lowest in women who are normotensive before pregnancy and who have good renal function.[34] Abe[34] studied 30 women with IgA nephropathy and followed 38 pregnancies: the obstetrical risks appeared low and 74% of the pregnancies were normal. Complications such as restricted foetal growth, abruptio placentae, or post-partum haemorrhage arose in 13% of the pregnancies, and neonatal deaths occurred in 10% of the pregnancies.[34]

Transplantation

The recurrence of IgA nephropathy in renal allografts is not surprising, considering that the disease is a systemic one.[23,24,31] The rate of recurrence of IgA nephropathy in allografts is difficult to assess, because the existence of original disease in many patients is not known; the estimated rate of recurrence is 50%. The significance of mesangial IgA-containing complexes in recurrent disease is uncertain and despite giving immunosuppressive treatment, the progression of the nephritis and the sclerosing process seem to be similar. No obvious difference is detected between the pathology of nephritis in allografts and that of the non-transplant counterpart.

Conclusion

Immunoglobulin A nephropathy is a chronic progressive glomerular disease with infrequent reversal. The rate of progression of the disease is very variable. For many patients, there is an apparent absence of progression because normal renal function can be maintained for decades. For some patients, the condition is characterised by haematuria, hypertension, proteinuria, and the gradual loss of renal function over as few as 5 years. IgA nephropathy is no longer considered as a benign disease, because as many as 20% to 30% of patients will eventually have renal failure within 10 to 20 years; these patients will require life-saving dialysis and/or kidney transplantation. Thus, both clinical and histological prognostic factors are very important in identifying patients whose condition may progress to end-stage renal failure, and in planning their immediate as well as long-term management.

Pathological grading currently represents the most useful method to appraise the renal outcome in IgA nephropathy.[19-21,30] It is possible that histological grading can still be refined in the future; however, the current grading system that we have adopted and included in this report is directly beneficial to patients. While performing renal biopsy is necessary to establish the diagnosis, it is more important to thoroughly assess and extract all prognostic information, because it will complement the clinical assessment of the patients and that will contribute to treatment planning.

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