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REVIEW ARTICLE

New Insights into the Pathogenesis and Treatment of Patients with Immunoglobulin A Nephropathy

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Immunoglobulin A (IgA) nephropathy (also called Berger's disease) is the most common primary chronic glomerulonephritis worldwide, and was first described by J. Berger et al in 1968. Histopathologically, IgA nephropathy is characterized by expansion of glomerular mesangial matrix with mesangial cell proliferation and/or mononuclear cell infiltration. Glomeruli typically contain generalized-diffuse granular mesangial deposits of IgA (mainly IgA1), IgG and C3. Electron-dense deposits are observed in the glomerular mesangial areas and partially in the glomerular basement membrane. Thus, this disease is considered to be an immune-complex-mediated glomerulonephritis. Clinically, patients with IgA nephropathy show microscopic and macroscopic hematuria and/or proteinuria. Advanced patients (almost 40% of patients) progress to end-stage kidney disease during 20 years of observation. However, the pathogenesis and radical treatment of IgA nephropathy have still not been established.

1. Introduction

Immunoglobulin A (IgA) nephropathy is considered to be an immune-complex-mediated glomerulonephritis, although the antigenic substances are still obscure.[1] Clinically, patients with IgA nephropathy show microscopic and macroscopic hematuria and/or proteinuria. Advanced patients progress to renal hypertension, renal anemia and end-stage kidney disease (ESKD). Progression to ESKD in patients with this disease is not as rare as originally thought. Thus, it is important to determine the mechanism of onset and progression in patients with IgA nephropathy. The objectives of this review are to introduce clinicopathological features of IgA nephropathy, and to summarize new insights into the pathogenesis and treatment of patients with IgA nephropathy.

2. Clinicopathological manifestations

2.1. Clinical findings

Patients with IgA nephropathy show microscopic and macroscopic hematuria and/or proteinuria. Macroscopic hematuria is occasionally observed after upper respiratory infections including acute tonsillitis and/or pharyngitis. IgA nephropathy is frequently preceded by episodes of upper respiratory or gastrointestinal infections, which are presumed to have a viral or bacterial etiology. Many dysmorphic red blood cells, various cellular casts and activated platelets in the urinary sediments are frequently observed in the advanced stage of this disease.[2] Serum IgA >350 mg/dL has frequently been observed in adult patients with IgA nephropathy. We have already reported the importance of four clinical markers in the diagnosis of patients with IgA nephropathy, or in the differential diagnosis from other types of chronic glomerulonephritis as follows: (1) more than five red blood cells in urinary sediments; (2) persistent proteinuria (>0.3 g/day); (3) serum IgA level >315 mg/dL; and (4) serum IgA/C3 ratio >3.01. Patients with three or four clinical markers have been diagnosed with IgA nephropathy in previous studies.[2,3]

A Joint Committee of the Special Study Group on Progressive Glomerular Disease, Ministry of Health, Labor and Welfare of Japan found in 1995 that it required >3 years on average from estimated onset to the first consultation and subsequent diagnosis of IgA nephropathy by renal biopsy.[4] About 30% and 5–10% of IgA nephropathy patients develop ESKD within 15–20 years and 5 years, respectively. Conversely, about 60% can avoid ESKD. Notably, some of them spontaneously achieve natural remission or maintain a clinically stable condition without any treatment.

Clinical markers for poor prognosis of this disease are as follows: (1) renal (glomerular and tubulointerstitial) histopathological changes; (2) heavy proteinuria; (3) renal dysfunction at the time of

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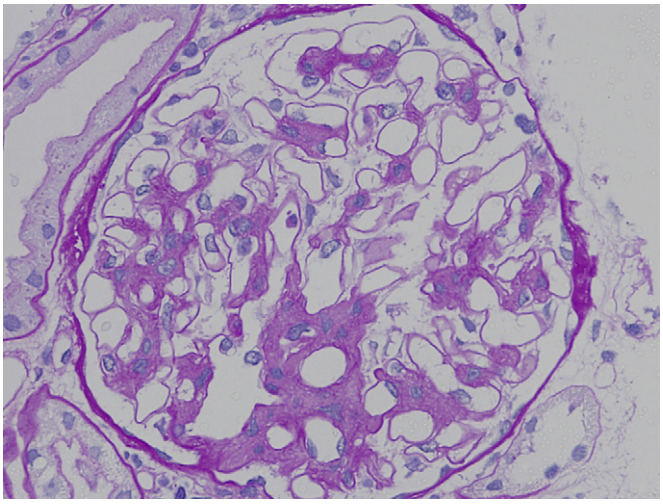

Figure 1 Paramesangial deposits in a glomerulus of an IgA nephropathy patient viewed by light microscopy (periodic acid–Schiff staining).

biopsy; (4) hypertension; (5) male sex; and (6) age <30 years.[5] The significance of gene polymorphisms of the renin angiotensin system in prognosis is still controversial in patients with IgA nephropathy.

2.2. Histopathological findings

IgA nephropathy is characterized by expansion of glomerular mesangial matrix with mesangial cell proliferation and/or mononuclear cell infiltration. In light microscopy, typical periodic acid–Schiff-positive hemispherical bodies with mesangial expansion and mesangial cell proliferation are observed in the glomerular paramesangial areas (Figure 1). Tubulointerstitial fibrosis, tubular atrophy and mononuclear cell infiltration are observed in patients with advanced IgA nephropathy (Figure 2). In Japan, the Special IgA Nephropathy Study Group of the Progressive Renal Diseases Study Committee organized by the Ministry of Health, Labor and Welfare conducted a multicenter retrospective case–control study of IgA nephropathy in 2004 to develop an evidence- and lumped-system-based clinicopathological classification of IgA nephropathy for predicting long-term risk of progression to ESKD (Kawamura et al, submitted for publication). The recently published Oxford classification of this disease has identified prognostic pathological features, providing substantial evidence that histological grading systems can be used to predict renal outcome of IgA nephropathy.[6]

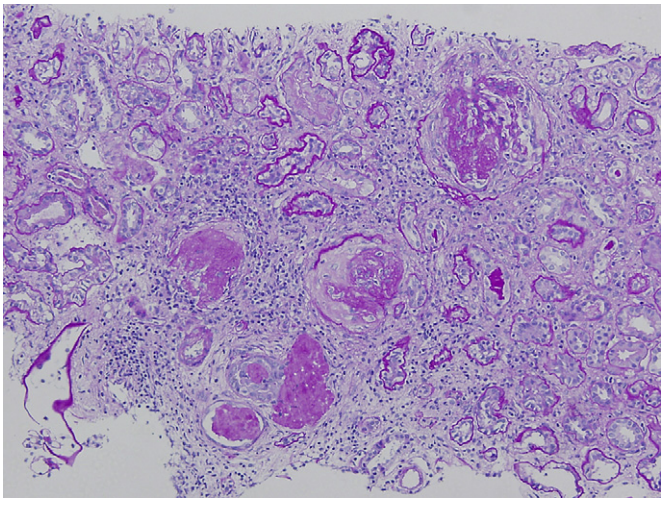

Figure 2 Tubulointerstitial injury in an advanced stage of IgA nephropathy.

3. Initiation factors

3.1. Spontaneous animal model for IgA nephropathy

In the 40 years since IgA nephropathy was first reported, the cause of this disease has never been clarified. The main reason for this appears to be that there has not been an appropriate animal model of this disease. A spontaneous animal model, the ddY mouse, is now used for investigating pathogenesis and treatment of IgA nephropathy.[7] In 1985, Imai et al[8] (Akita, Japan) first reported that the ddY strain of mouse can serve as a spontaneous animal model for human IgA nephropathy. ddY mice were imported from Germany before 1920 and have been maintained in Japan since that time. These ddY mice show mild proteinuria without hematuria and mesangioproliferative glomerulonephritis with glomerular IgA deposits. Marked deposition of IgA and C3 in the glomerular mesangial areas in association with an increase in the levels of macromolecular IgA appears in sera of these mice with aging (Figure 3). Electron-dense deposits are marked in the glomerular mesangial areas when observed by electron microscopy. These immunopathological findings appear at >40 weeks of age. Although the incidence of IgA nephropathy in ddY mice is highly variable, it appears that clinicopathological aberrations other than hematuria in ddY mice resemble those in human IgA nephropathy.

Sequential renal biopsies were performed on 361 ddY mice. IgA nephropathy occurred in about 30% of the mice by 20 weeks (early onset group) and in about 30% of the mice by 40 weeks (late onset group). It did not occur in the remaining mice (quiescent group).[9] When an “association study” on onset was performed in the early onset and quiescent groups, multiple disease receptor gene loci were observed.[9] One of the loci was found to be homologous with the gene locus reported for familial IgA nephropathy, therefore, at least some of these mice appear to be subject to the same genetic regulation as human IgA nephropathy, and ddY mice were judged to be useful as an animal model as described previously.[9] A genome-wide scan with 270 microsatellite markers has identified three chromosomal regions on chromosomes 1, 9 and 10, which are significantly associated with glomerular injuries. The peak marker *D10MIT86* on chromosome 10 is located in the region syntenic to human 6q22–23with *IgAN1*, which is the candidate gene responsible for familial IgA nephropathy.[9,10] In addition, *D1MIT16* on chromosome 1 is very close to the locus of the selectin gene, which is a known candidate for human IgA nephropathy. It appears that the three-group ddY mouse model can be a useful tool for identifying the susceptibility genes and also for examining their roles in the pathogenesis of IgA nephropathy.[7]

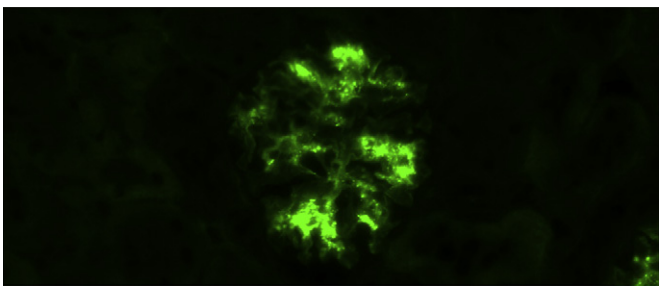

Figure 3 IgA staining of a glomerulus in ddY mouse by immunofluorescence.