

# Clinicopathologic Correlation in IgA Nephropathy

David Philibert, MD, FRCPC,\* Daniel Cattran, MD, FRCPC,\* and Terence Cook, FRCPath†

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**Summary:** IgA nephropathy is the most common biopsy-proven pattern of glomerulonephritis in the world. Many factors, both clinical and histologic, have been suggested to impact on prognosis. We review the wide variations in how patients with immunoglobulin A nephropathy can present and the important differences derived from the clinical pathologic setting through the description of 4 cases. These include the clinical scenarios of modest proteinuria, acute kidney injury, and the nephrotic syndrome.

Semin Nephrol 28:10-17 © 2008 Elsevier Inc. All rights reserved.

**Keywords:** IgAN, histology, clinicopathologic correlation, prognosis

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IgA nephropathy (IgAN) is the most common biopsy-proven pattern of glomerulonephritis in the world.<sup>1,2</sup> Despite the initial reports that it was benign, its annual incidence rate as a cause for end-stage renal disease has increased steadily over the past 2 decades. Many different factors have been implicated in influencing prognosis in IgAN including age, geographic origin, male sex, and the clinical features of hypertension and proteinuria. Part of the issue in determining the importance of these factors in prognosis is the wide variation in the natural history of both the presentation and progression of IgAN. We introduce the topic by illustrating the major clinical variations that can be seen, each with their distinct pathology in IgAN.

## PATIENTS WITH MODEST PROTEINURIA

A modest level of proteinuria with or without renal impairment is the most common presentation of clinical significance seen in IgAN. Isolated microhematuria is the most common ini-

tial event overall of the disease but is rarely, if ever, associated with progressive renal failure. The frequency of the combination of hematuria and proteinuria at the time of biopsy is very dependent on geography, detection/screening methods, and biopsy policy of the country and/or individual nephrologist.<sup>3</sup>

## Case 1

A 32-year-old man, known to have biopsy-proven IgAN for the past 7 years, was noted to have a slowly increasing creatinine level over the previous 2 years, from a baseline of 110  $\mu\text{mol/L}$  to 140  $\mu\text{mol/L}$ . Proteinuria also had increased over this period from 0.6 g/d to 1.4 g/d despite angiotensin receptor blockade. The patient was totally asymptomatic. He had no history of macroscopic hematuria. His blood pressure (BP) had been reasonably well controlled, and generally was less than 130/80 mm Hg on the angiotensin receptor blocker, losartan 100 mg once a day. On physical examination, he appeared well. His BP was 136/82 mm Hg. There was no peripheral edema.

A repeat renal biopsy was performed and is shown in **Figure 1**. There was a moderate increase in mesangial cells and mesangial expansion with moderate tubulointerstitial scarring and no significant vascular changes. Glomerulosclerosis was minimal. On immunofluorescence, mesangial staining was seen for IgA (3+) and C3 component of complement. This was

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\*University Health Network, Toronto General Research Institute, Toronto, Canada.

†Department of Histopathology, Imperial College, Hammersmith Hospital, London, United Kingdom.

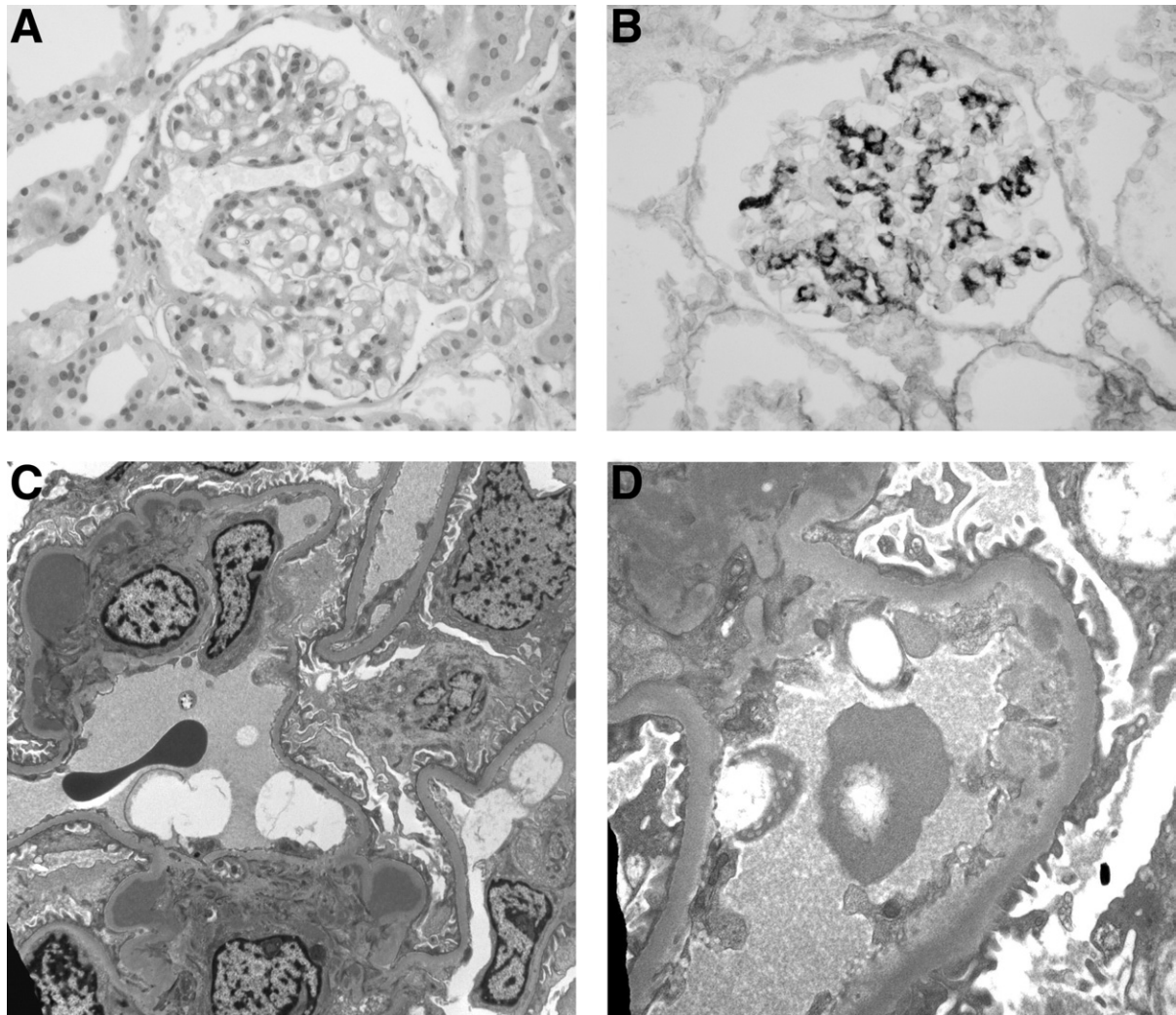
Supported in part by La Faculté de Médecine de l'Université Laval à Québec (D.P.).

Address reprint requests to Dr. Daniel Cattran, Toronto General Hospital, 585 University Ave, NCSB 11C-1256, Toronto, Ontario M5G 2N2, Canada.

E-mail: daniel.cattran@uhn.on.ca

0270-9295/08/\$ - see front matter

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**Figure 1.** (A) Glomeruli show a mild to moderate increase in mesangial cells and matrix. (B) On immunoperoxidase staining there is prominent mesangial IgA deposition. Electron microscopy shows (C) mesangial expansion with large mesangial electron-dense deposits, and (D) occasional small subendothelial deposits.

confirmed by immunoperoxidase. On electron microscopy, a large number of mesangial deposits as well as a few scattered subendothelial ones were seen.

## Discussion

### *Clinical Risk Factors of Progression*

Slowly progressive renal dysfunction associated with proteinuria is a common and challenging presentation of IgAN. Although IgAN was once considered a benign disorder, it is now well known that a significant subset of patients eventually will progress to end-stage renal disease. In patients who develop significant proteinuria

and/or reduced glomerular filtration rate (GFR), progression to end-stage renal disease is approximately 15% to 25% at 10 years, and 20% to 30% at 20 years.<sup>4,5</sup> In contrast, the prognosis is excellent in patients with a normal creatinine level and proteinuria less than 1 g/d, with 98% of patients achieving a 15-year survival in 1 study.<sup>6</sup> If proteinuria is sustained at greater than 1 g/d, the GFR almost always decreases and renal survival worsens. In 1 report, if either proteinuria was greater than 1 g/d or the serum creatinine level was greater than 1.7 mg/dL, the 7-year renal survival rate was 87%, but this decreased to 21% if both were greater than these levels.<sup>7</sup> A change in proteinuria over time is

likely to be of more importance in determining prognosis than the absolute level at presentation. This was emphasized by the algorithm developed from a recent cohort of 298 patients with IgAN.<sup>8</sup> More recently, in a study of 542 patients with IgAN by Reich et al,<sup>9</sup> proteinuria exposure over time was found to be the strongest predictor of the rate of decline of renal function as measured by the slope of creatinine clearance. The relationship between sustained proteinuria and outcome was altered dramatically down to levels as low as 1 g/d in marked contrast to the other types of primary progressive nephropathies, such as membranous nephropathy and focal and segmental glomerulosclerosis. In this study, a semiquantitative approach was used and found that for each persistent incremental gram/day of proteinuria greater than 1, a 10- to 25-fold more rapid rate of renal function decline, and a very significant reduction in renal survival was seen.

### ***Histological Risk Factors of Progression***

Persistent proteinuria, hypertension, and an increased serum creatinine level at presentation are the strongest clinical predictors of progression. In addition, histologic classifications have been developed to aid in assessing prognosis. The majority of such classifications in IgAN have focused on the extent of mesangial cell proliferation, the presence of crescents, the severity of glomerulosclerosis, and on the severity of the interstitial infiltration  $\pm$  fibrosis and tubular atrophy. Classification systems are based on segmental scoring or global aggregates of these parameters. The aggregate systems assign a global score based on the integration of findings found in the different compartments of the tissue. The 2 best known are those of Lee et al<sup>10</sup> and Haas.<sup>11</sup> However, once important clinical data such as hypertension or proteinuria are taken into account and subsequent analyses make use of a multivariate statistical approach, the added value of these systems in determining prognosis is not always apparent.<sup>8</sup> However, even with these statistical maneuvers, there are opposing views including a recent study in which glomerular grade was found to be an independent variable that was associated significantly with progressive renal disease.<sup>12</sup>

Other classifications divide the specific lesions within different compartments seen on kidney biopsy: glomerular, tubular, interstitial, and vascular. More flexible but also more complicated than the aggregate systems, they offer the advantage of looking for specific lesions that otherwise might be missed by a more global scoring system. This approach is valuable, but it should be recognized that lesions in various compartments often are interrelated, such as tubular atrophy and interstitial fibrosis. In studies looking at the prognostic value of biopsy findings, the extent of glomerulosclerosis and of tubulointerstitial damage are usually the strongest predictors. However, these findings reflect what has happened and the irreversible damage that has occurred, and do not necessarily reflect disease activity or the potential for treatment focused on retarding progression. Instead these are generic and common end points of glomerular damage, and although it is likely that the nonsclerotic glomeruli are hyperfiltering and eventually may undergo pathologic changes, they do not in themselves indicate ongoing disease activity. The presence of diffuse mesangial hypercellularity with mesangial expansion seems logically to reflect disease activity, but it never has been found to be an independent variable to predict prognosis in multivariate analysis. Similarly, extension of IgA deposits to the subendothelial site of the capillary wall, although a significant risk factor for progression in 1 study,<sup>13</sup> has not been seen in other reports to be an independent predictor.

IgAN is a primary glomerulonephritis, and it is reasonable to believe that the more acute the changes are on histology, the more severe its clinical presentation. Specific findings on kidney biopsy, namely crescents, are useful in identifying patients at risk of rapid progression. However, they are uncommon (see later) and because the evolution of IgAN usually is slow, caution should be exercised when looking for histologic changes that will reflect a prognosis that may take up to 20 years to evolve from the time of the biopsy to the eventual outcome. This is the most likely reason that outcome can be predicted more accurately by serial measurements of the clinical parameters such as proteinuria and hypertension. Even their value is



limited and a recent study suggested that even changes in proteinuria and hypertension can explain only 30% to 40% of the variation in progression rates in IgAN.<sup>8</sup> Certainly, the prognostic values of our current combined clinical and histologic parameters are limited. Other currently evolving techniques, such as genetic analysis and specific serum and/or urinary biomarkers, are expected to improve our understanding as well as our predictive capacity in this disorder in the near future.

## ACUTE KIDNEY INJURY

The patient with acute deterioration in renal function is another distinct clinicopathologic presentation seen in IgAN. It is relatively uncommon but is seen over the course of the disease in about 10% to 25% of all cases.

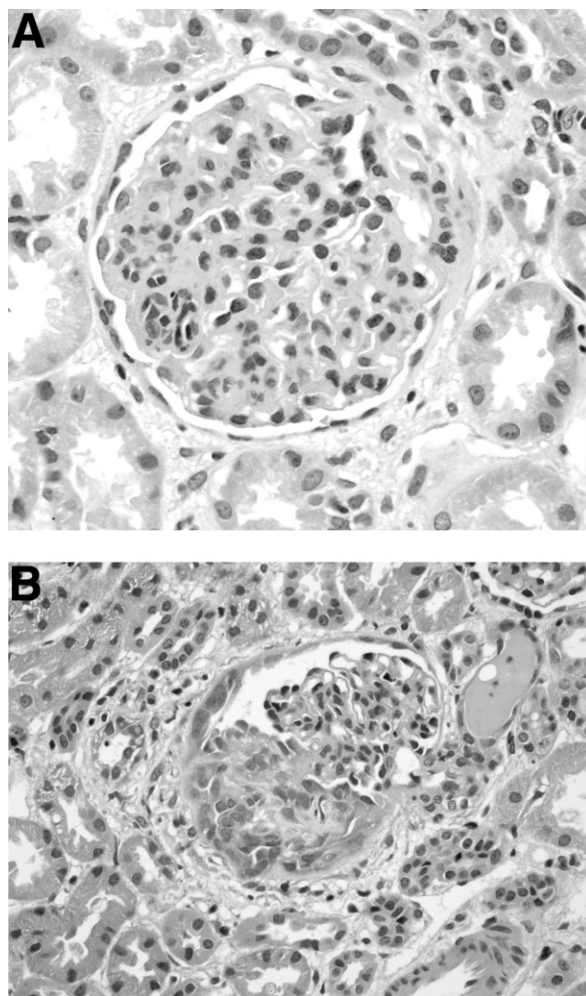
### Case 2

A 25-year-old man had IgAN diagnosed on biopsy 3 years previously in the setting of synpharyngitic macroscopic hematuria. The renal biopsy at that time had shown mesangial hypercellularity with no tubulointerstitial scarring and only mesangial IgA staining on immunofluorescence and electron-dense mesangial deposits on electron microscopy. At presentation his BP was borderline at 130/85 mm Hg, his serum creatinine level was 97  $\mu\text{mol/L}$ , and proteinuria was 2.2 g/d. He was started on the angiotensin-converting enzyme inhibitor trandolapril and his BP was controlled at less than 120/80 mm Hg, the creatinine level remained stable, and proteinuria ranged between 0.5 and 1.0 g/d during the next 3 years. He then developed bilateral mild flank ache associated with the onset of gross hematuria. In the emergency room on further questioning the patient indicated that his urine output had decreased over the previous 24 hours. The remainder of the clinical history was unremarkable. On physical examination he appeared well. His BP was 150/90 mm Hg. His lungs were clear, with only minor costovertebral angle tenderness on examination. There was no skin rash and no arthritis. Mild bilateral ankle edema was noted.

Laboratory tests showed that his serum creatinine level had increased to 160  $\mu\text{mol/L}$ , and

proteinuria was greater than 3 g/L on dipstick. Urine sediment contained many red cell casts and acanthocytes, but this was unchanged from previous urine analysis. Antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and serology for hepatitis B and C were negative. Complement levels were normal. The patient was followed up closely, but 5 days later the serum creatinine level had increased further to 240  $\mu\text{mol/L}$ .

A kidney biopsy was performed and is shown in Figure 2. There was marked mesangial hypercellularity with areas of endocapillary proliferation and necrosis with cellular crescents in 20% of the glomeruli. There was a significant cellular



**Figure 2.** (A) Glomeruli show marked mesangial hypercellularity with segmental endocapillary hypercellularity. (B) Twenty percent of the glomeruli contained cellular crescents.

infiltrate and interstitial edema with minimal tubulointerstitial fibrosis.

## Discussion

Rapid and unexplained decline in GFR may occur in patients with IgAN, with or without macroscopic hematuria. This clinical presentation requires that a kidney biopsy be undertaken if the renal function does not recover within days despite supportive treatment including correction of hypovolemia and cessation of potential nephrotoxins, such as nonsteroidal anti-inflammatory drugs and certain antibiotics. Two distinctly different histologic patterns may be found in this setting: either a pattern of acute tubular necrosis with minimal glomerular injury or a crescentic glomerulonephritis. Because the natural history and management is so very different for these 2 possibilities and because the prediction, which has occurred on clinical grounds alone, is poor the need for biopsy at an early stage is evident.

Acute tubular necrosis can occur in patients with IgAN, most commonly in conjunction with episodes of macroscopic hematuria and often within a few days of an upper respiratory tract infection. This may be accompanied by an acute deterioration in GFR, thought to be caused by either tubular obstruction by red cell casts or hemoglobin toxicity.<sup>14-16</sup> Usually, these episodes are self-limited and resolve spontaneously. Macroscopic hematuria has been reported in some studies to be a marker of a better prognosis. It sometimes can take up to 70 days before complete recovery from the acute tubular necrosis (ATN), although the average usually is much shorter and in the range of 5 to 7 days. Severity can range from minor transient increases of the serum creatinine level to oliguric acute renal failure. The latter is seen more commonly in elderly patients with IgAN with histologic evidence of chronic vascular disease from hypertension and the effects of aging. Patients with acute tubular necrosis require only supportive treatment, including, rarely, dialysis treatment for their renal failure. Although it is common to give angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy to patients with IgAN, these often are held temporarily because they may

hinder or obscure renal recovery in this setting. If immunosuppression was initiated as a result of speculation of a crescentic transformation before the histology was available, it should be discontinued.

Crescents found on biopsy in this clinical setting imply a significantly more ominous outlook. Studies have suggested that the prognosis in IgA with crescents is worse than in other crescentic disorders, with reported renal survival rates as low as 50% at 1 year and 20% at 5 years.<sup>17,18</sup> This is not the same as finding capsular adhesions or small noncircumferential crescents in the glomeruli of patients but without the clinical scenario of rapid deterioration in renal function. This can be more common and in 1 series this type of crescent was present in 28% of biopsy specimens.<sup>19</sup> In the setting of acute kidney injury, IgAN, unlike antiglomerular basement membrane disease, does not have exuberant or extensive extracapillary proliferation, so the exact number of crescents that should trigger alarm and more aggressive treatment is not well defined. However, even if only 10% to 20% of glomeruli show significant active crescents, in association with a decreasing GFR and/or increased proteinuria, this should be considered as indicative of an active disease process in our opinion and deserves aggressive treatment. If the crescents are fibrous or even fibrocellular, as opposed to cellular, they are less likely to reflect active disease and their response to intense immunosuppression is less likely. If either type of crescents is seen in the setting of severe glomerulosclerosis and extensive tubulointerstitial injury, a poor prognosis is almost inevitable. Serologic testing may be useful to rule out additional factors and to help identify patients with a better outlook. In one report of crescentic IgAN, for instance, a subgroup of patients with circulating ANCA responded well to immunosuppression.<sup>20</sup> Deciding which patients are likely to have the crescentic variant of IgAN and which patients also may be amenable to therapy thus requires integration of both the clinical data (acute kidney injury) and histologic findings (pattern of acute crescentic glomerulonephritis with potentially reversible damage). As always, the potential benefits of an immunosuppression regi-

men should be balanced carefully against the risk such therapy carries for the patient.

### NEPHROTIC SYNDROME

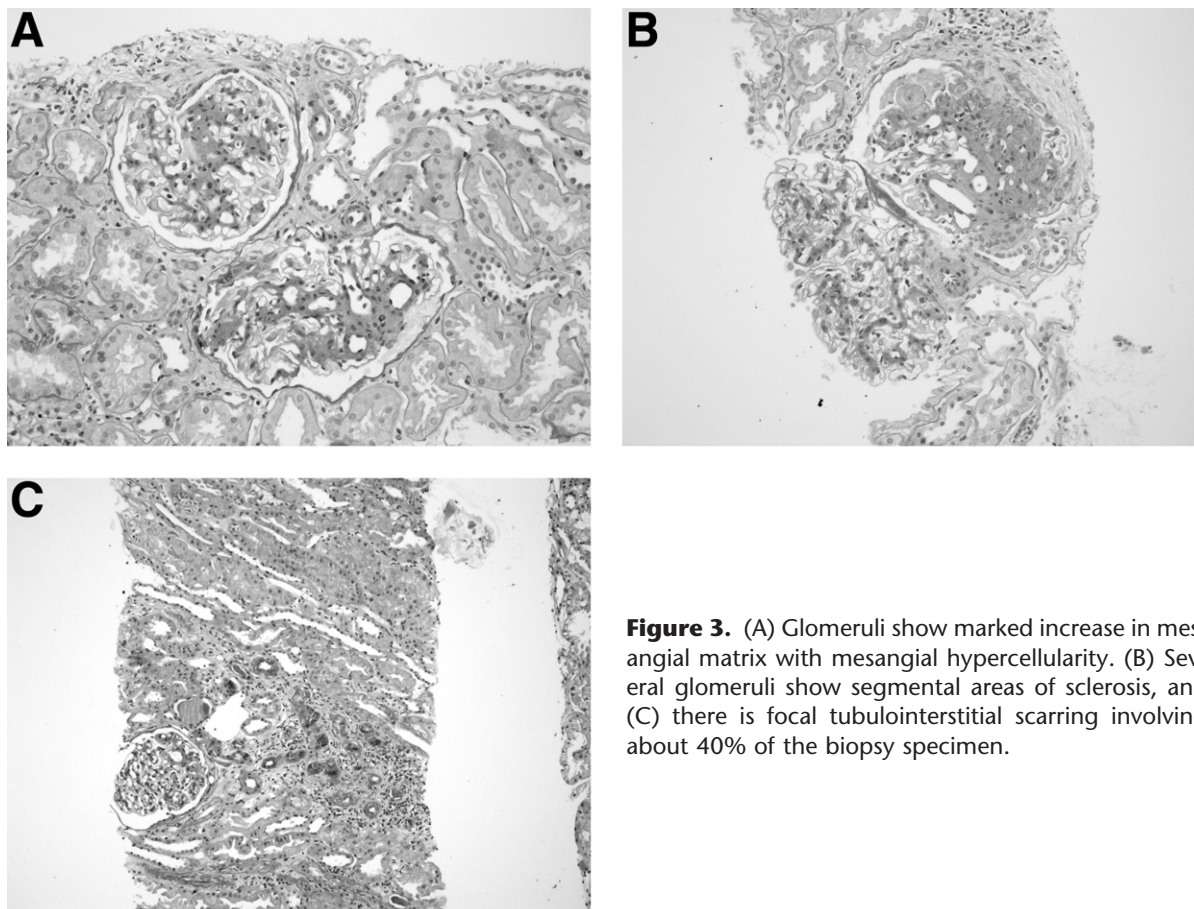
There are 2 important histologic variants of IgAN that present with nephrotic range proteinuria. Although both are uncommon, the dramatic dichotomy in treatment and outcome makes this an important and distinct clinicopathologic presentation.

#### Case 3

A 63 year-old woman presented with a 3-month history of gradually increasing swelling of her legs. She was known to have microscopic hematuria for 20 years and mild arterial hypertension. She had not had regular follow-up evaluations and had stopped taking her antihypertensive pills on her own volition years ago. Her only medication consisted of ibuprofen taken on a sporadic basis for ar-

thritic pain. She had no other past medical history. She had no other symptoms and, notably, no skin rash and no macroscopic hematuria. On physical examination, she appeared well. Her BP was 148/88 mm Hg. Her lungs were clear, and her cardiac examination was normal. There were no ascites. There was significant bilateral lower-limb edema. Laboratory examinations showed a serum creatinine level of 220  $\mu\text{mol/L}$  and proteinuria was 4.2 g/d. The serum albumin level was 32 g/L, total cholesterol was 7.8 mmol/L, and low-density lipoprotein cholesterol was 5.0 mmol/L. ANA and ANCA were negative and C3 and C4 complement levels were normal.

A kidney biopsy was performed and is shown in [Figure 3](#). There was significant mesangial hypercellularity. Thirty percent of the glomeruli were obsolete. Marked tubulointerstitial fibrosis and tubular atrophy were noted and were estimated to be 40% of the tubulointerstitial volume.



**Figure 3.** (A) Glomeruli show marked increase in mesangial matrix with mesangial hypercellularity. (B) Several glomeruli show segmental areas of sclerosis, and (C) there is focal tubulointerstitial scarring involving about 40% of the biopsy specimen.



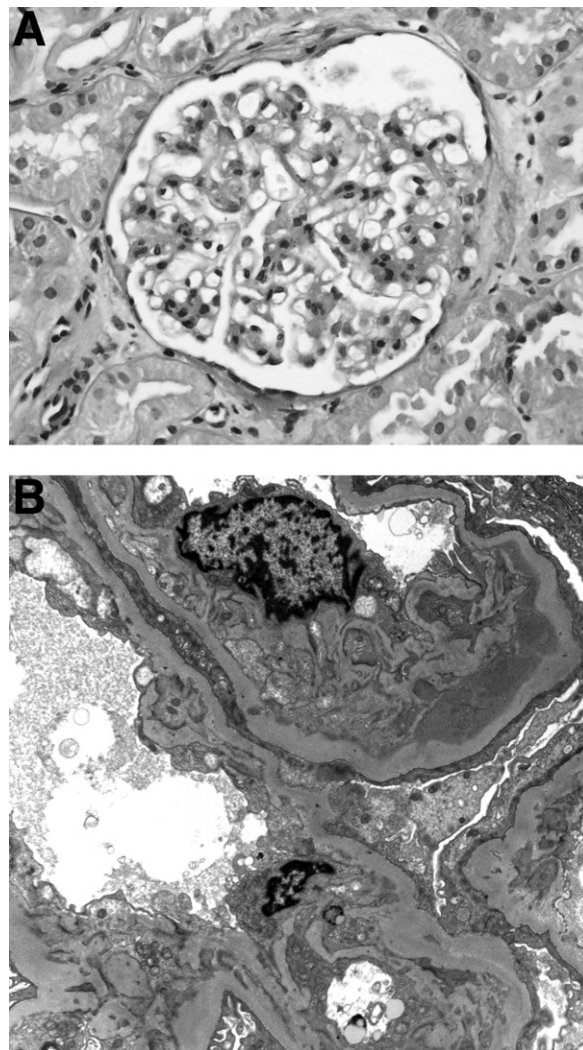
## Discussion

Although IgAN is associated more commonly with a nephritic presentation with hematuria, hypertension, and a decreased GFR, in some patients it may present with a more nephrotic picture. Microhematuria also commonly is found in these patients. Severe structural damage on renal biopsy is associated most commonly with this type of nephrotic presentation and implies a poor prognosis. The histology often shows extensive glomerulosclerosis and tubulointerstitial damage. In most studies, as reviewed by D'Amico,<sup>17</sup> proteinuria is a major risk factor for progression, both at presentation and during follow-up evaluation. This finding, and especially its persistence, is true of most glomerular diseases, and especially so in IgAN, in which even modest sustained levels of proteinuria are related to a poor outcome.

## Case 4

A 33-year-old man of Asian origin presented with increasing swelling of the ankles noted over a 2- to 3-week period. He felt well and did not have macroscopic hematuria. He had no urinary symptoms and the rest of the clinical history was unremarkable. On physical examination, his blood pressure was 150/94 mm Hg. Cardiopulmonary and abdominal examinations were normal. There were no skin rashes observed. Pedal and periorbital edema were noted. Urinalysis showed microscopic hematuria with approximately 20% acanthocytes. Laboratory examination showed a serum creatinine level of 90  $\mu\text{mol/L}$  and a serum albumin level of 16 g/L. Proteinuria was 7.5 g/d. Total cholesterol was 9 mmol/L, low-density lipoprotein cholesterol was 5.5 mmol/L. Serologic tests (ANA, ANCA, complement, and hepatitis serology) were negative.

A kidney biopsy was performed and is shown in Figure 4. There was mild mesangial matrix expansion and no endocapillary proliferation. On immunofluorescence, IgA staining was seen diffusely in the mesangial areas. On electron microscopy, in addition to electron-dense mesangial deposits, there was diffuse foot processes effacement.



**Figure 4.** (A) Glomeruli show mild mesangial hypercellularity. (B) Electron microscopy shows slight mesangial expansion with mesangial electron-dense deposits and extensive effacement of podocyte foot processes.

## Discussion

In a subgroup of IgAN patients who present with features of the nephrotic syndrome and with preserved renal function, light microscopy will show only minimal glomerular injury.<sup>21</sup> In these patients, 2 glomerular pathology patterns may be seen: minimal change morphology and an IgAN pattern. It is not clear whether this represents 2 distinct pathologies that co-exist, or whether this is a particular mode of presentation of a single disease process (ie, IgAN).<sup>22</sup> These patients most commonly respond rapidly to treatment with corticosteroids, similar to minimal change disease. In the 1 randomized con-

trolled trial of steroids in nephrotic patients with IgAN, the only patients who showed complete remission of proteinuria were those with isolated minimal glomerular changes on light microscopy.<sup>23</sup> Many of the reported cases of this association were in patients of Asian background.<sup>24</sup> Whether there truly is a racial predilection is unknown. Patients with nephrotic syndrome, IgA deposits, and minimal glomerular damage on histology constitute a small group of patients, but it is important to recognize them because their short-term response to corticosteroids is dramatic and their long-term prognosis is excellent.

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