Clinical Presentation, Natural History, and Treatment of Crescentic Proliferative IgA Nephropathy

By James A. Tumlin and R. A. Hennigar

IgA nephropathy is one of the most common causes of glomerulonephritis in the world and is characterized histologically by the deposition of polymeric forms of IgA within the mesangium and in some cases along the glomerular capillary wall.[1] Proliferative and crescenteric forms of IgA are associated with nephrotic range proteinuria, accelerated hypertension, and a more rapid decline toward end-stage renal disease. Previous attempts to categorize the incidence and clinical significance of proliferative IgA nephropathy have given conflicting results. This is in part the result of the lack of a uniform nomenclature and the failure of clinical therapies to prolong renal survival in specific subgroups. In the present study, we performed a prospective open-label trial of pulse solumedrol and intravenous cyclophosphamide in 20 patients with IgA nephropathy and at least 10% cellular crescents or endocapillary proliferation on renal biopsy. Seventeen patients underwent repeat kidney biopsies after 6 months of therapy, and the morphologic response to treatment was assessed using a modified systemic lupus erythematosis (SLE) histologic activity and chronicity index score. To determine the long-term efficacy of intravenous cyclophosphamide on renal survival, the results of the treated patients were compared with 12 untreated historical controls. Pulse solumedrol and intravenous cyclophosphamide effectively reduced peak serum creatinine, degree of proteinuria, the rate of decline in renal function, and the incidence of end-stage renal disease at 36 months.

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IgA NEPHROPATHY IS a complex disorder with disease manifestations ranging from mild mesangial matrix expansion and hematuria to fulminate rapidly progressive glomerulonephritis with endocapillary proliferation and crescent formation.[2] The binding of IgA to putative Fc receptors on the surface of mesangial cells leads to mesangial hypercellularity and production of proinflammatory cytokines. In addition, IgA complexes can indirectly stimulate cell proliferation and mesangial matrix deposition through the activation of compliment through the mannan-binding lectin and/or alternative pathway.[3] An increasing body of literature suggests that this broad array of histologic and clinical manifestations results in specific subgroups with different risks for end-stage renal disease (ESRD) and disease progression.[4-6] Although mesangial cell hypercellularity and matrix expansion are common in IgA nephropathy, additional glomerular pathology can include endocapillary proliferation, karryhorexis, and cellular crescents.[2,7-9] The incidence and clinical significance of these lesions are unknown. In the present study, we prospectively treated 20 patients with IgA nephropathy and at least 10% cellular crescents or endocapillary proliferation with pulse solumedrol, oral steroids, and intravenous cyclophosphamide. A repeat biopsy was performed in 17 of 20 patients after 6 months of therapy, and the morphologic response to treatment was assessed using a modified National Institutes of Health (NIH) Systemic Lupus Erythematosis (SLE) disease activity and chronicity index score. When the long-term outcomes of the treated patients were compared with 12 untreated historical controls, we found that steroids and intravenous cyclophosphamide reduced peak serum creatinine, level of proteinuria, and the incidence of ESRD at 36 months.

METHODS

Study Criteria and Patient Population

Twenty consecutive patients with IgA nephropathy and at least 10% crescents or endocapillary proliferation referred to Emory University Hospital were enrolled in a prospective, open-label study of pulse solumedrol, oral prednisone, and monthly intravenous cyclophosphamide after signing informed consent. Histologic criteria for study enrollment included the presence of incipient-to-fulminate cellular crescents with or without segmental endocapillary proliferation in 10% or more of glomeruli. Clinical entry criteria included the presence of hypertension (>140/90 mm Hg) and greater than 1.0 g of proteinuria per 24 hours. Patients were also considered eligible for enrollment if IgA nephropathy was associated with clinical signs of Henoch-Schönlein purpura (HSP). All

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drugs, including antihypertensive medications, were allowed to continue throughout the study except for alternative immunosuppressives (e.g., azathioprine, mycophenolate, or cyclosporin A). Patients were excluded from the study if IgA nephropathy was present in a transplanted kidney or associated with cirrhosis and other secondary etiologies. Patients were also considered ineligible if the initial biopsy demonstrated greater than 50% cortical scarring or if the patient was pregnant or lactating. A repeat biopsy was performed in all patients after the completion of 6 months of intravenous cyclophosphamide. A histologic activity and chronicity scoring system was used to compare scores in the initial biopsies with those obtained after 6 months of therapy.

Study Protocol

Patients enrolled in the study received intravenous methylprednisolone (15 mg/kg per day) for 3 days in conjunction with oral prednisone (1 mg/kg per day) for 60 days. Patients were then tapered to 0.6 mg/kg per day for 60 days followed by 0.3 mg/kg per day prednisone for 60 days and 0.15 mg/kg per day for an additional 60 days. At the time of repeat biopsy, all patients were maintained on 10 mg prednisone per day. Intravenous cyclophosphamide was given at 0.5 to 0.75 g per square meter body surface area (m^2 BSA) monthly for 6 months. Cyclophosphamide dosages were titrated to achieve a nadir white blood cell count between 2500 and 3000 cells/mL^3. All patients enrolled in the study underwent a repeat kidney biopsy 1 month after completion of six courses of cyclophosphamide. Omega-3 fatty acid fish oil supplementation was then initiated at 12.0 g per day. During the follow-up period, oral prednisone was maintained at 0.15 mg/kg per day and systolic and diastolic blood pressure was maintained between 120 and 130 and 60 and 70 mm Hg, respectively. Unless clinically contraindicated, all patients received angiotensin-converting enzyme inhibitors as part of their antihypertensive regimen.

Historical Controls

To determine the long-term clinical response to therapy, changes in the slope of the reciprocal of the serum creatinine (1/serum Cr), 24-hour proteinuria, and incidence of ESRD in the treated patients were compared with 12 untreated patients with similar degrees of histologic activity. The surgical tissue archives of The Department of Pathology and Laboratory Medicine, Emory University Hospital, Atlanta, Georgia, were searched by computerized SnoMed codes for a diagnosis of IgA nephropathy. Approximately 4500 biopsies dating from 1992 through mid-2001 were screened. A total of 331 cases were found in which the diagnosis of IgA nephropathy was confirmed or considered. Of the 331 cases of IgA nephropathy, 28 were identified with histologically active disease as defined by the presence of incipient-to-fulminate cellular crescents with or without endocapillary proliferation in 10% or more of glomeruli. The incidence of crescentic/proliferative IgA nephropathy at Emory University Hospital was approximately 8.5%. Of the 28 patients with crescentic proliferative IgA nephropathy, 12 patients matched for age, baseline creatinine, proteinuria, and incidence of hypertension but managed without immunosuppressive therapy were analyzed and compared with the treatment group. Biopsies from renal allografts were excluded.

Histology

To determine whether intravenous cyclophosphamide improves glomerular histopathology, patients underwent repeat renal biopsies and the level of cellular proliferation and cortical scarring was determined using a modified SLE disease activity/chronicity scoring system. Tissue for light microscopic examination was prepared in the conventional manner. A portion of each biopsy was snap-frozen for immunofluorescence studies. Frozen sections were stained with fluorescein isothiocyanate (FITC)-labeled antisera against human IgG, IgA, IgM, C3, C4, C1q, and, sometimes, kappa/lambda light chains. The portions of each specimen separated for electron microscopic examination were fixed in glutaraldehyde, postfixed in osmium tetroxide, and embedded in epoxy resin. Thin sections were stained with uranyl acetate and lead citrate. Each biopsy contained at least 13 glomeruli. An experienced renal pathologist (RAH) reviewed the glass slides and electron photomicrographs in blinded fashion. Each biopsy was graded in terms of histologic activity and chronicity (Table 1). Basic grading criteria for histologic activity included degree of (1) mesangial proliferation, (2) glomerular endocapillary proliferation, (3) extracapillary proliferation in the form of cellular crescents, (4) karyorrhexis with or without fibrinoid necrosis of glomeruli, (5) subendothelial "immune-type" dense deposits, and (6) interstitial inflamma-

Table 1. Histologic Grading Criteria Used for Determining Activity and Chronicity Indices in Patients With IgA Nephropathy

Histologic Activity	Chronicity
Mesangial proliferation (0-3 points)	Glomerular obsolescence (0-5 pts)
0 = minimal	0 = none
1 = mild to moderate focal (<50%) segmental	1 = between 1-20% of glomeruli
2 = marked segmental accentuation in one or more glomeruli	2 = between 21-40%
3 = diffuse (>50%) global	3 = between 41-60%
Endocapillary proliferation (0-4 pts)	4 = between 61-80%
0 = none	5 = >80%
1 = mild focal segmental	Partial glomerular sclerosis and/or collapse (0-5 pts)
2 = moderate focal segmental	0 = none
3 = marked focal segmental	1 = between 1-20% of glomeruli
4 = global diffuse	2 = between 21-40%
Cellular crescents (0-5 pts)	3 = between 41-60%
0 = none	4 = between 61-80%
1 = between 1-10% of all glomeruli	5 = >80%
2 = between 11-20%	Fibrous crescents (0-5 pts)
3 = between 21-30%	0 = none
4 = between 31-40%	1 = between 1-20 of glomeruli
5 = >40%	2 = between 21-40%
Karyorrhexis/fibrinoid necrosis (0-5 pts)	3 = between 41-60%
0 = none	4 = between 61-80%
1 = between 1-10% of all glomeruli	5 = >80%
2 = between 11-20%	Tubular atrophy (0-5 pts)
3 = between 21-30%	0 = none
4 = between 31-40%	1 = between 1-20% of glomeruli
5 = >40%	2 = between 21-40%
Subendothelial “immune-type” dense deposits (0, 2, 3, 5 pts)	3 = between 41-60%
0 = none	4 = between 61-80%
2 = rare	5 = >80%
3 = scattered/occasional	Interstitial fibrosis (0-5 pts)
5 = many	0 = none
Interstitial inflammation (0-5 pts)	1 = 1-20% scaring of renal cortex
0 = none	2 = 21-40%
1 = involving 1-20% of renal parenchyma	3 = 41-60%
2 = 21-40%	4 = 61-80%
3 = 41-60%	5 = >80%
4 = 61-80%	_____Total pts (chronicity score)
5 = >80%	_____Chronicity index (out of a possible 25 pts)
_____Total pts (activity score)	
_____Activity index (out of a possible 27 pts)	

tion. Grading criteria for chronicity included extent of (1) global glomerular sclerosis (i.e., obsolescence), (2) partial glomerular sclerosis and/or collapse, (3) fibrous crescents, (4) tubular atrophy, and (5) interstitial fibrosis. Activity and chronicity indices were then calculated for each biopsy.

Clinical Data and Statistical Analyses

A detailed chart review for patients in the control and treatment groups was performed and the following clinical data determined: (1) time of kidney biopsy, (2) age, (3) sex, (4) race, (5) basal and peak serum creatinine, (6) basal and nadir albumin, (7) systolic and diastolic blood pressures, (8) presence of microscopic or gross hematuria, (9) 24 hour proteinuria, and (10) and time to renal replacement therapy. Data was obtained on all 32 patients included in the study. Data of aggregate basal and peak serum creatinines (Cr), slope of 1/serum Cr, proteinuria, and pre- and postactivity/chronicity scores were included in the statistical analyses for the study group and historical controls. Data are expressed as mean ± standard error of mean for continuous variable or number (percentage) for dichotomous variable unless otherwise stated. Differences within the treatment group

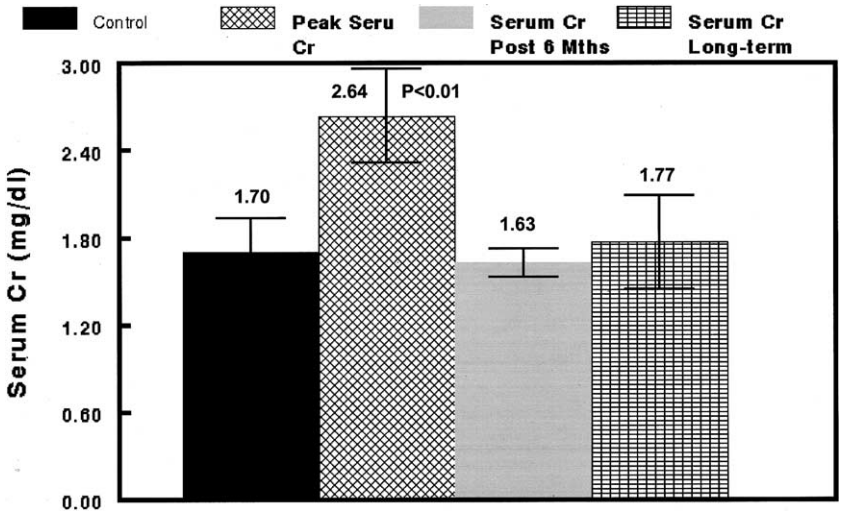

Fig 1. Steroids and cyclophosphamide stabilizes renal function in patients with crescentic/proliferative IgA nephropathy. Serum creatinine was averaged for all 20 patients at study entry, at peak levels, and after mean of 28 months of follow up (6–60 months). Serum Cr significantly ($P < 0.01$) increased during the course of therapy from a baseline of 1.70 mg/dL to 2.64 mg/dL and returning to baseline levels by 6 months. After a mean of 28 months of follow up, serum Cr was not significantly different than baseline levels.

were calculated using a Student *t* test and a two-sample paired analysis. Differences between the treatment group and historical controls were calculated using a Student *t* test and a two-sample separate variance analysis. The incidence of ESRD at 36 months was calculated using a 2×2 contingency table and chi-squared analysis. Statistical calculations were conducted using GB Stat for Windows, version 5.0 (Dynamic Microsystems, Inc, Silver Spring, MD). A P value of <0.05 was considered to be statistically significant.

RESULTS

To determine the efficacy of corticosteroid and cyclophosphamide therapy on the progression of crescentic/proliferative IgA nephropathy, 20 treated patients were compared with 12 historical controls matched for age, gender, baseline Cr, proteinuria, and histologic severity. The clinical characteristics of the patients in both groups are listed in Table 2. There were no statistically significant differences between the two groups in age, serum creatinine, or serum albumin. Male patients were more frequent in the control group, but this trend did not reach statistical significance. Although 5 of 12 patients in the control group had systolic and diastolic blood pressures greater than 140/90 mm Hg, all patients (20 of 20) in the treatment group were hypertensive. This difference was not statistically significant. Clinically significant proteinuria (>1.0 g/24 hour) was present in 100% of the treatment group, whereas nephrotic range proteinuria (>3.0 g/24 hours) was observed in 50% of patients. Serum complement levels were depressed in patient no. 5 and normal in the remaining 19 patients. All patients were tested for C-ANCA and P-ANCA positivity at the time of enrollment. A single patient tested positive for P-ANCA antibodies, but none of the 20 patients were positive for C-ANCA.

The mean serum creatinine before treatment was 1.70 ± 0.24 mg/dL, rising significantly during the course of induction therapy to a peak value of 2.64 ± 0.32 mg/dL ($P < 0.01$ vs. baseline) (Fig. 1). After 6 months of treatment with solumedrol and intravenous cyclophosphamide, the mean serum creatinine fell from a peak of 2.64 ± 0.32 to 1.63 ± 0.10 mg/dL. After a mean of 28 months of follow up, the mean serum creatinine rose to 1.77 ± 0.32 mg/dL. At the time of the initial biopsy, the mean proteinuria was in the nephrotic range (3.78 ± 0.54 g/24 hours) and reached a maximum value of 4.93 ± 0.71 g/24 hours during the first 6 months of therapy. At the end of 6 months, proteinuria decreased significantly from a peak of 4.93 ± 0.71 g/ 24 hours ($P < 0.01$ vs. baseline) to 1.38 ± 0.37 g/24 hours. After 28 months follow up, proteinuria was further reduced to 1.15 ± 0.43 g/24 hours (Fig. 2).

All patients in the treatment group underwent a repeat biopsy at 6 months to determine (1) the effectiveness of combined corticosteroids and cyclophosphamide in reducing histologic activity, and (2) to delay the progression of chronicity. We found that pulse solumedrol and intravenous cyclophosphamide significantly reduced the number of crescents and degree of endocapillary proliferation without significantly increasing chronicity.

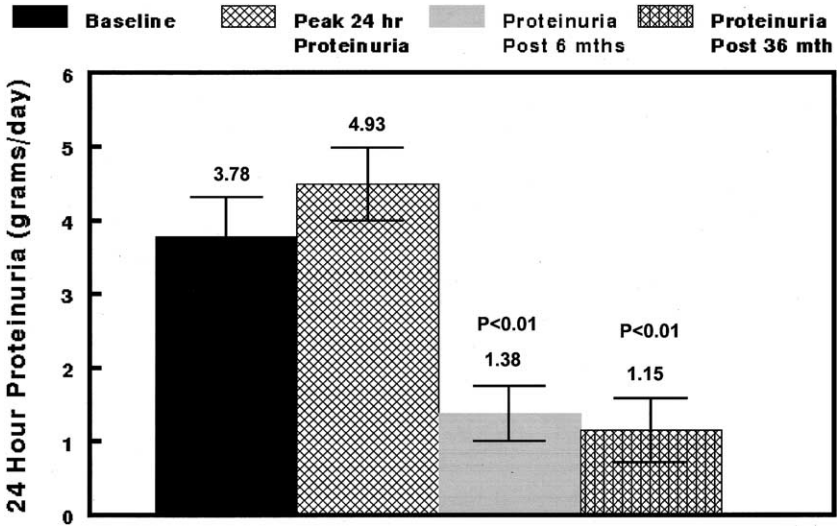

Fig 2. Steroids and cyclophosphamide reduces proteinuria in patients with crescentic/proliferative IgA nephropathy. At study entry, 50% of treated patients had nephrotic-range proteinuria with a mean proteinuria of 3.78 g/24 hours. Proteinuria significantly ($P < 0.01$) increased from 3.78 to 4.93 g/24 hours but was significantly ($P < 0.01$) lower than baseline levels after 6 months of therapy. After a mean of 28 months of follow up, proteinuria was reduced further to a mean of 1.15 g/24 hours ($P < 0.01$ vs. baseline).

Statistical analysis revealed a significant drop in histologic activity in the post- versus pretreatment group ($P < 0.004$) and not significant difference in chronicity (Fig. 3). The level of histologic activity and chronicity in the initial biopsies of treatment group and historical controls were significantly different (Fig 3). Activity in follow-up biopsies were decreased in all of the treated patients except one (patient no. 5) and fell to one-half or more of its original value in 50% of patients. To determine the efficacy of corticosteroids and intravenous cyclophosphamide on the incidence of ESRD, a Kaplan-Meier survival plot was calculated for both the treatment group and historical controls. Figure

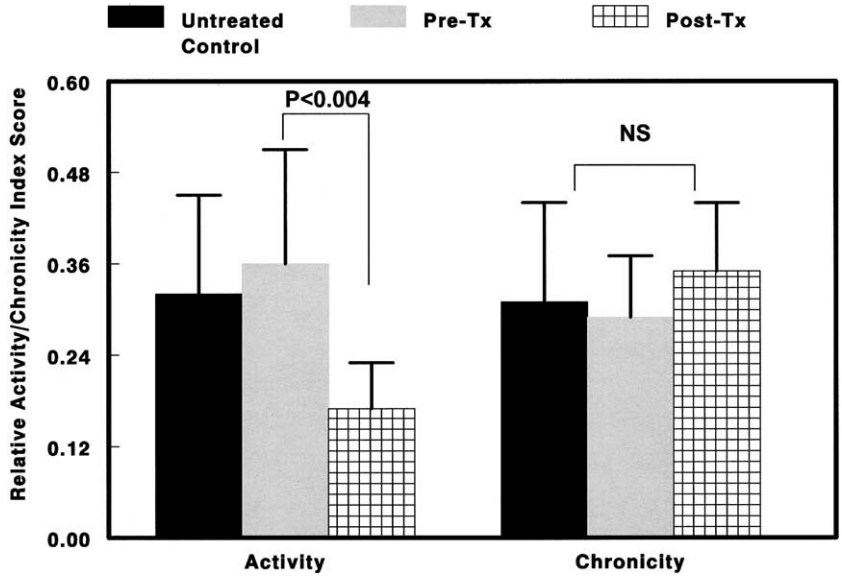

Fig 3. Steroids and cyclophosphamide reduces glomerular activity and minimizes cortical scarring. A modified NIH SLE histologic activity/chronicity index was applied to baseline renal biopsies in the treatment group and historical controls. There were no significant differences in the initial average activity and chronicity scores between the two groups. After 6 months of cyclophosphamide, the mean activity score in the treatment group was significantly lower than pretreatment levels ($P < 0.004$). Mean chronicity scores were not significantly different between baseline levels in the treatment group or baseline levels among the historical controls, and in the treatment group, it did not change significantly after the 6 months of therapy. Values are reported as means + standard error of means.

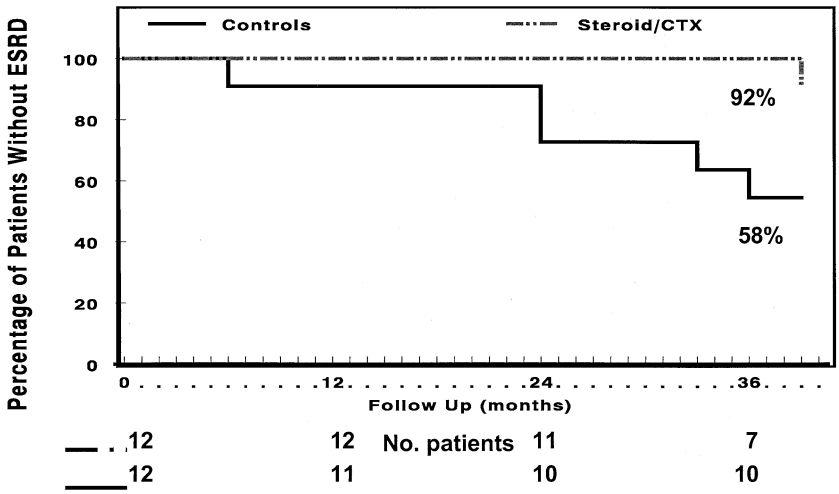

Fig 4. Steroids and cyclophosphamide prolongs renal survival in crescentic IgA nephropathy. An estimated Kaplan-Meier renal survival curve in the treatment group and historical controls is presented. After 36 months, renal survival in the treatment group was 91.5% versus 58% within the historical controls. This trend did not reach statistical significance (chi-square 0.14). The X-axis records the number of patients being followed throughout the 36-month follow up.

4 demonstrates that after 36 months of follow up, one of 12 (8.3%) of patients in the treatment group reached ESRD compared with five of 12 (42%) in the historical controls. This value did not reach statistical significance. To determine whether the reduction in proteinuria and prolonged renal survival correlated with reductions in disease activity, we compared biopsies samples taken before and after completion of cyclophosphamide therapy. Figure 5 (panels A, C, and E) are representative light microscopic biopsies of three patients with increasing histologic severity. As shown in Figure 5, endocapillary proliferation (large arrow, panel A) or circumferential crescents (large arrow, panel C) could be seen alone or in combination (panel E). To determine whether treatment with cyclophosphamide reduces cellular proliferation and histologic activity, all patients underwent repeat renal biopsies. Figure 5 (panels B, D, and F) are representative biopsies samples taken after 6 months of steroids and intravenous cyclophosphamide therapy in the same patients featured in panels A, C, and E. After 6 months of cyclophosphamide and steroids, endocapillary proliferation (panel B) and crescents (panel D) were nearly eliminated. Residual activity in follow-up biopsies was manifested primarily as ongoing mesangial proliferation and interstitial inflammation. Glomerulosclerosis was present in some biopsies despite aggressive immunosuppression (panel F). Figure 6 represents the biopsy of patient no. 6 with a clinically very aggressive course. The serum creatinine in this patient increased from 0.9 mg/dL to 6.7 mg/dL within 4 months of the onset of symptoms. Biopsy results demonstrate diffuse endocapillary proliferation and circumferential cellular crescents. After 6 months of solumedrol and intravenous cyclophosphamide therapy and 28 months of follow up, the patient's serum creatinine has reduced to 1.3 mg/dL, with resolution of the severe histologic activity on the posttreatment biopsy. To determine whether intensive immunosuppression altered the deposition of IgA immune complexes, we compared immunofluorescence and electron micrograph images before and after treatment with cyclophosphamide. In Figure 7, panels A and B demonstrate the presence of subendothelial dense deposits in one patient. Treatment with solumedrol and cyclophosphamide did not alter the degree of subendothelial or mesangial deposits. As shown in panels C and D, induction therapy did not reduce the amount of mesangial staining of IgA in the glomeruli. Recurrence of proliferative IgA disease has occurred in two patients (patient nos. 2 and 3) 20 and 26 months, respectively, after completion of initial cyclophosphamide therapy. Both patients were reinduced with cyclophosphamide therapy. Renal function stabilized in patient no. 3 after retreatment, but patient no. 2 did not respond and ultimately came to ESRD approximately 26 months after diagnosis. Therapy with steroids and cyclophosphamide was well tolerated in the majority of patients. Patient no. 1 developed compression fracture of the first lumbar vertebra 12 months after initiating therapy, whereas patient no. 2 developed severe pneumonia during a second induction for disease relapse.

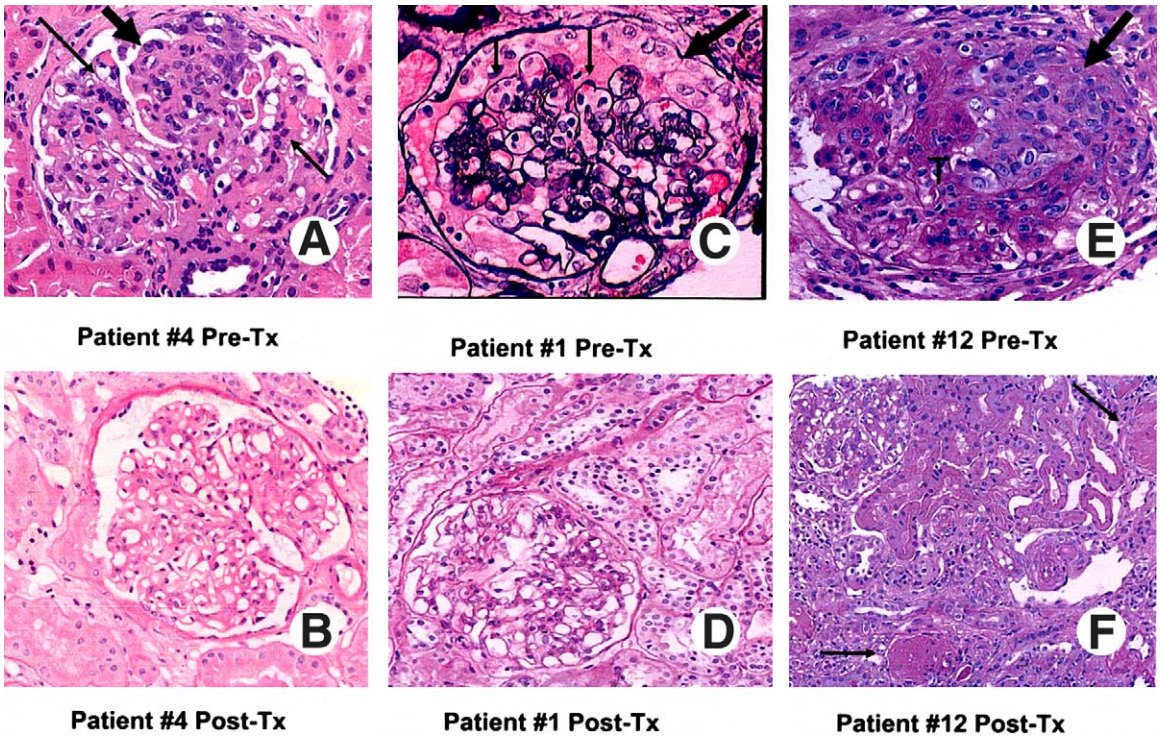

Fig 5. Histologic response to intravenous cyclophosphamide in crescentic/proliferative IgA nephropathy. Representative lesions of crescentic/proliferative IgA nephropathy before and after treatment with 6 months of steroids and intravenous cyclophosphamide are shown. (A and B) Segmental endocapillary proliferation (large arrow) is superimposed on mesangial hypercellularity and matrix expansion (small arrows) in patient no. 4 before treatment (hematoxylin and eosin [H&E] stain, ×400). The posttreatment biopsy is shown in panel B where crescents and endocapillary proliferation are absent from glomeruli (Periodic acid-Schiff [PAS], ×400). (C and D) Early extracapillary proliferation is manifested as incipient cellular crescent (large arrow) accompanied by segmental endocapillary proliferation (small arrows) in patient no. 1 (Jones' methenamine silver with PAS counterstain, ×400]. D depicts the posttreatment biopsy results in which extra- and endocapillary proliferation are absent from glomeruli (PAS, ×400). (E and F) A fulminant cellular crescent (arrow) and acute necrotizing glomerulonephritis are present in patient no. 12 before treatment (PAS, ×400). The posttreatment biopsy is shown in panel F. There is an absence of extra- and endocapillary proliferative lesions with scattered with obsolete glomeruli (PAS, ×200).

DISCUSSION

Clinical Presentation of Crescentic IgA Nephropathy

The question of whether patients with histologically aggressive forms of IgA nephropathy demonstrate clinical features consistent with a rapidly progressive glomerulonephritis is unknown. However, several investigators have reported an increased incidence of hypertension and proteinuria in patients with crescentic forms of IgA nephropathy.[4-8,10-12] For example, Wistam-Attorps et al. used 51 Cr-EDTA clearance to measure glomerular filtration rate (GFR) in 54 patients with IgA nephropathy and demonstrated that in patients with worsening proteinuria, GFR was proportionately reduced. As noted in other trials,[7,13] patients with worsening glomerulosclerosis or interstitial fibrosis presented with higher levels of proteinuria and selective loss of IgG immunoglobulins.[10] Interestingly, although mesangial matrix expansion and mesangial cell proliferation correlated with reduced GFR, these features did not correlate with proteinuria or other clinical parameters associated with disease progression.[10] In a review of 112 patients, Boyce et al. divided patients with IgA nephropathy into three different classes based on specific histopathologic criteria and attempted to correlate histologic severity with clinical presentation and the risk for ESRD. Patients whose biopsy demonstrated only IgA deposition or expansion of mesangial matrix was subdivided into class I, whereas patients with focal or diffuse mesangial hypercellularity were grouped into class II. Patients in class III had more aggressive lesions,

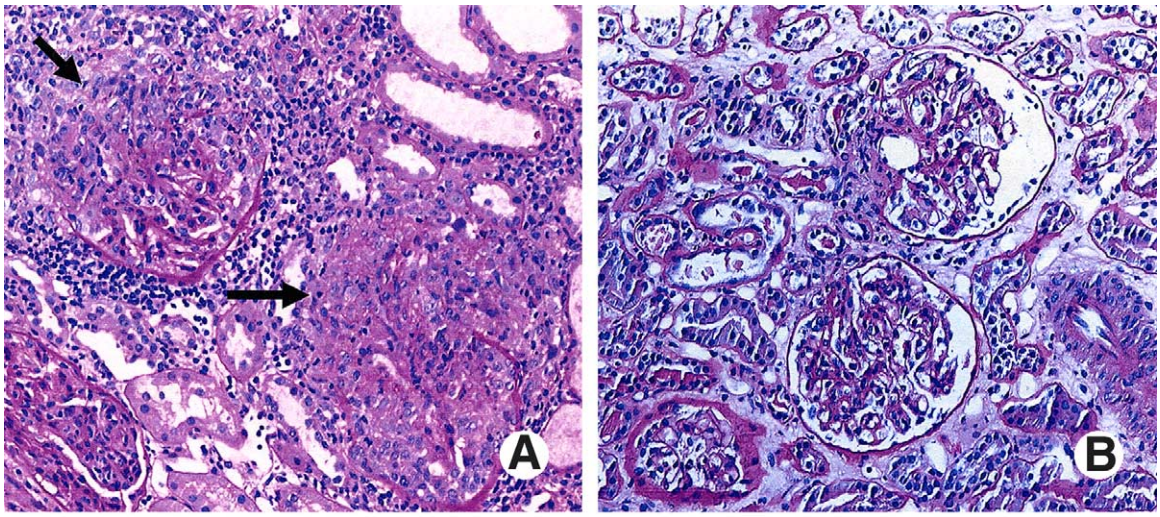

Fig 6. Histologic response to intravenous cyclophosphamide in crescentic/proliferative IgA nephropathy. (A) A representative photomicrograph of patient no. 6 with a clinical course of rapidly progressive glomerulonephritis secondary to IgA nephropathy (Serum Cr 0.9–6.7 mg/dL over 4 months). Arrows show diffuse endocapillary proliferation and circumferential cellular crescents. (B) A representative photomicrograph of patient no. 6 after 6 months of solumedrol and intravenous cyclophosphamide. Treatment resulted in complete resolution of crescents and endocapillary proliferation. Mild increase in interstitial scarring and sclerotic glomerular lesions were noted.

including focal or diffuse endocapillary proliferation with the presence of crescents.[13] In contrast to previous studies, Boyce et al. found no correlation between the presence of the nephrotic syndrome and worsening histopathology. However, patients with class III changes or the presence of crescents were more likely to be hypertensive and to progress to ESRD. Welch et al. reported that patients with proliferative IgA nephropathy were frequently hypertensive at the time of biopsy, whereas accelerated hypertension (mean arterial pressure [MAP] >150) was the presenting symptom in 20% of patients with IgA nephropathy.[5] In a similar study, Subias et al. examined 66 patients with IgA nephropathy and noted that 24 of 66 (36%) were hypertensive (MAP >114 mm Hg) at the time of initial presentation, whereas 15% had malignant or accelerated hypertension (MAP >163 mm Hg). Moreover, Subias et al. noted that crescents or endocapillary proliferation were present in 70% of the patients presenting with accelerated hypertension.[6] We studied 20 patients with 10% cellular crescents with or without the presence of endocapillary proliferation and found that hypertension (MAP >107) was present in 50% of patients at the time of biopsy. Although none of our patients had accelerated hypertension, nonnephrotic (>1.0 g/24 hours) and nephrotic (>3.0 g/24 hours) range proteinuria were present in 100% and 50% of patients, respectively. We found no correlation between the presence of nephrotic range proteinuria and the response to therapy or development of progressive renal disease.[14]

Crescentic IgA Nephropathy: Prevalence, Natural History, and Risk for End-Stage Renal Disease

Early reports of the natural history of IgA nephropathy demonstrated an overall benign course for IgA nephropathy with only 10% of patients reaching ESRD within 10 years.[11] More recently, D'Amico et al. examined the renal survival rates in 3620 patients compiled from 18 different studies and found an average of 19% ESRD after a follow up of 10 years.[15] Previous attempts to determine the prevalence of proliferative or crescentic forms of IgA nephropathy have been slowed by the unwillingness of some clinicians to biopsy patients with suspected IgA nephropathy and the lack of a uniform system of nomenclature. As a consequence, the prevalence in previously reported series varies from 1.5% to 55%.[7,12] The explanation for the broad range in the prevalence of crescentic forms of IgA is unknown but could reflect differences in ethnic groups or deficiencies in tissue

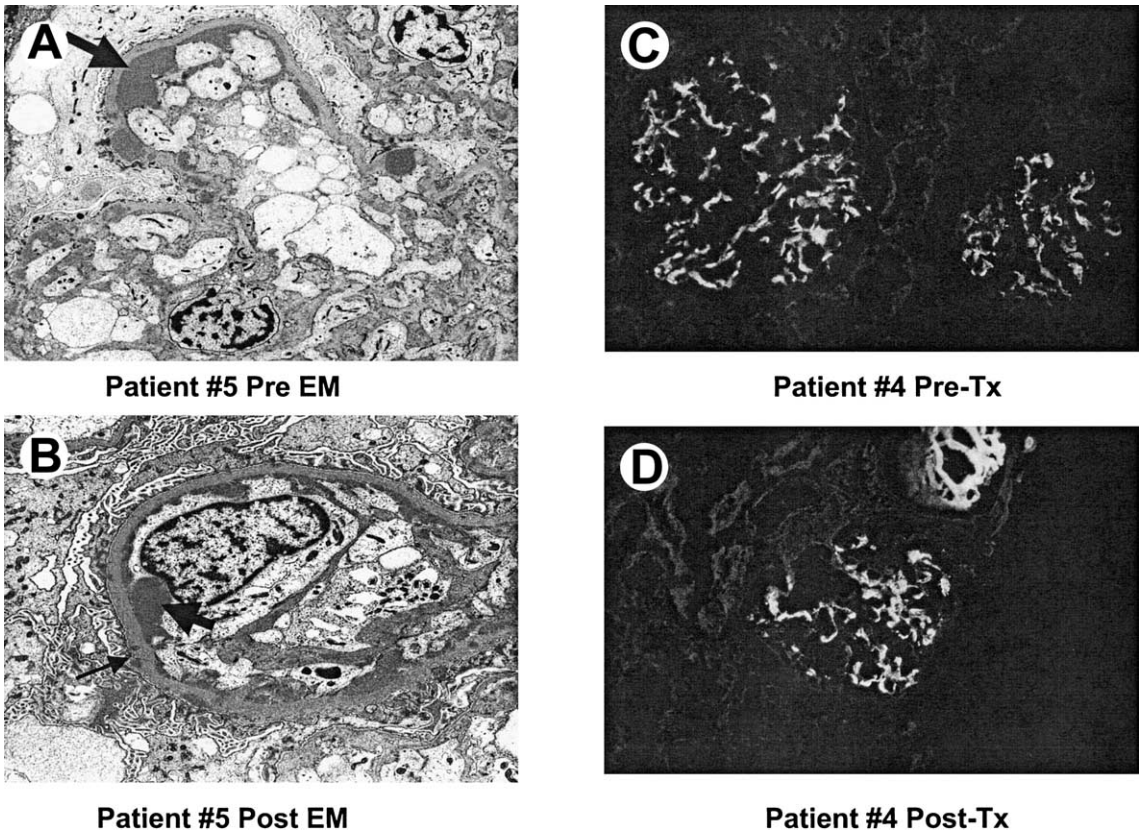

Fig 7. Electron microscopy and immunofluorescence response to intravenous cyclophosphamide. (A and B) Two representative photomicrographs of patient no. 5 demonstrating large subendothelial dense deposits before and after 6 months of intravenous cyclophosphamide. Intense treatment did not alter the presence of subendothelial dense deposits. (C and D) Two representative immunofluorescence images of patient no. 5 demonstrating intense mesangial staining with IgA. Six months of intravenous cyclophosphamide did not alter the degree of IgA deposition in patient no. 5.

processing. For example, Shouno et al. found that the presence of proliferative lesions within glomerular capillaries was underreported because of insufficient number of tissue sections. When serial biopsy sections are increased from 20 to 100, the incidence of endocapillary proliferation increased from 7% to 30%.[16] The significance of these proliferative lesions are unknown, but an increasing number of authors suggest that proliferative IgA nephropathy should be viewed as a different disease with therapies directed at the underlying histology. For example, Nicholls et al. reported a case series of three patients with an average of 22% crescents on initial biopsy (range, 4–50%) and noted that all patients reached ESRD within an average of 27 months of initial presentation.[4] In a similar prospective study of 80 children with IgA nephropathy, Hogg et al. noted that 12 of 80 patients (15%) reached ESRD within 4 years. Of the patients reaching ESRD, light microscopy demonstrated that 42% had crescents at the time of presentation, whereas 93% had evidence of focal or diffuse endocapillary proliferation.[17] Abe et al. reviewed the biopsies of 205 patients with IgA nephropathy and found that over 55% of patients were found to have 25% or more crescents.[7] When patients were stratified according to percentage of crescents and histologic severity, those with greater than 50% crescents demonstrated more rapid decline of renal function and reduced overall survival (Fig. 8).[7] D'Amico et al. found a similar reduction in renal survival among IgA patients with proliferative glomerular lesions. In a large study of 365 patients, D'Amico et al. semiquantitatively graded endocapillary proliferation from 0 to +3 severity and correlated these findings with renal survival. Among patients with diffuse (>50%) endocapillary proliferation, the rate of

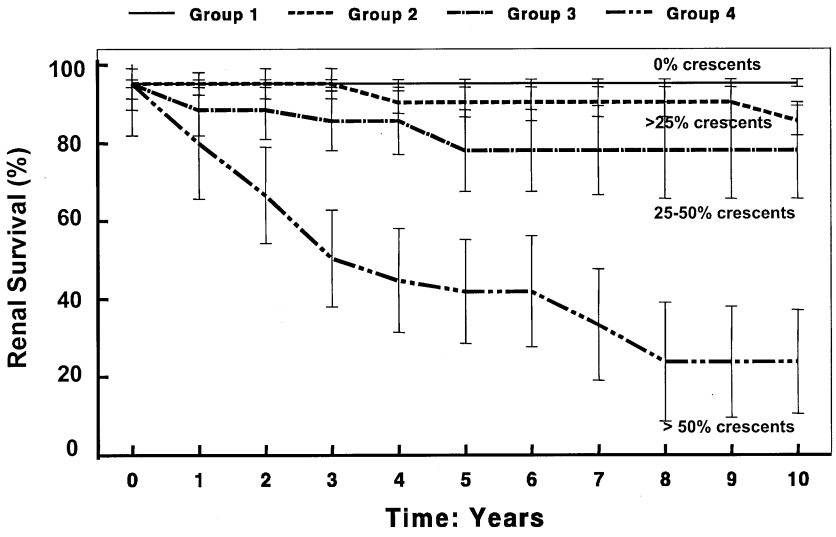

Fig 8. Crescentic IgA nephropathy is associated with decreased renal survival. Survival of renal function is plotted according to time in years. Patients in group 1 (0–25% crescentic changes) demonstrated less than 5% renal failure at 10 years. Patients in group 3 (25–50% crescents) developed end-stage renal disease (ESRD) in 20% of patients at the end of 10 years. Patients in group 4 (>50% crescents) developed ESRD in 75% of patients by 10 years follow up. Reprinted with permission from Abe T, Kida H, Yshimura H, et al: Participation of extracapillary lesions (ECL) in progression of IgA nephropathy. Clin Nephrol 25:37-41, 1986.[7]

ESRD at 5 years approached 50% (Fig. 2), a rate that was significantly greater than patients with minimal proliferative lesions.[11] Haas examined the biopsies of 244 cases of IgA nephropathy and staged patients according to the presence or absence of specific histologic findings. Patients in subclass 1 typically expressed mild mesangial matrix expansion and did not demonstrate any sclerotic or proliferative lesions. Subclass II included those patients with mesangial deposits of IgA but histologic and clinical features of idiopathic focal segmental glomerulosclerosis. Glomeruli demonstrate focal and segmental sclerotic lesions but do not exhibit mesangial, endocapillary, or extracapillary cell proliferation. Subclass III or focal proliferative glomerulonephritis demonstrate mesangial hypercellularity in less than 50% of glomeruli, but could also demonstrate endocapillary proliferation and the presence of crescents. Hass found that subclass IV was rare (<7% of total biopsies) but clearly constituted a more aggressive form of IgA disease. Patients in subclass IV demonstrate hypercellularity in more than 50% of glomeruli, the proliferative lesions are not limited to mesangial cells, and can include endocapillary proliferation and crescents. Subclass V represents patients with advanced chronic sclerosing glomerulonephritis with at least 40% senescent glomeruli and extensive cortical fibrosis. In an attempt to determine whether different subgroups of IgA disease corresponded with worsening clinical outcomes, Haas plotted renal survival for all five subclasses. As shown in Figure 10, patients with class IV had a 45% chance of reaching ESRD within 5 years, whereas patients with mild mesangial matrix expansion and hypercellularity (classes I and II) did well overall.[2] In addition, recent observations by D'Amico et al shows that patients with persistent mesangial hypercellularity have reduced long-term renal survival (Fig 9). These results suggest that in contrast to lupus nephritis, mesangial hypercellularity is an important prognostic sign. These results are in stark contrast to the findings of Alamartine et al. who examined the biopsies of 282 patients with IgA nephropathy and attempted to identify histopathologic changes that correlate with a poor clinical outcome. Although the percentage of crescents was not reported, only 1.5% of patients demonstrated any form of crescentic IgA nephropathy. Moreover, the presence of crescents in their series did not correlate with nephrotic range proteinuria, hypertension, or other poor prognostic signs.[12] We retrospectively analyzed a series of 12 patients with IgA nephropathy and at least 10% crescents or endocapillary proliferation and found that, if untreated, the ESRD rate was 40% within 3 years.[14] Although there remains some conflicting reports in the literature, a substantial body of evidence suggests that even a small percentages of crescents in IgA nephropathy portends a poor prognosis. Moreover, these observations point to the need to have a uniform nomenclature for IgA nephropathy that will enable clinicians to conduct controlled trials in patients with specific subgroups of IgA disease.

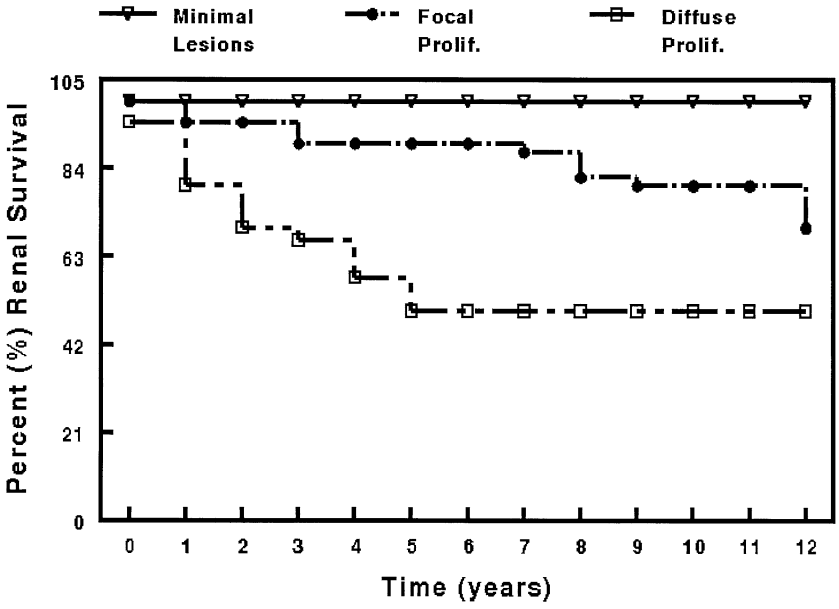

Fig 9. Differential renal survival among patients with increasing mesangial cell proliferation. Kaplan-Meier survival curves of renal survival among patients with worsening mesangial cell proliferation. Renal survival among patients with minimal mesangial cell hypercellularity was 100% after 12 years follow up. Renal survival among patients with focal mesangial hypercellularity (<50%) decreased 70%, whereas patients with diffuse (>50%) mesangial hypercellularity was reduced to 50% after 12 years follow up. Reprinted with permission from D'Amico G: The commonest glomerulonephritis in the world: IgA nephropathy. Q J Med 64:709-727,2001.[24]

Crescentic IgA Nephropathy: Role of Steroid Hormones and Cyclophosphamide

The lack of uniform definitions for specific subpopulations of IgA nephropathy has slowed the development of effective treatments for proliferative forms of IgA nephropathy. Because of the heterogeneity of IgA nephropathy, early studies using steroid hormone therapy have given conflicting results. In a prospective trial of 86 patients with IgA nephropathy and moderate to severe proteinuria, Pozzi et al. demonstrated that pulse corticosteroids for 6 months slowed the loss of renal function compared with control subjects matched for clinical severity.[18] A recent analysis of trials assessing the efficacy of glucocorticoids in the treatment of IgA nephropathy concluded that for patients with preserved renal function (CrCl >70 mL/min), prolonged therapy (>2 years) effectively slows the loss of renal function.[19] However, in the majority of these studies, patients were not classified by pathologic changes or histologic severity, thus the efficacy of glucocorticoids in patients with more severe pathologic changes was not assessed. In an attempt to address this question, Lai et al. divided 34 patients with IgA nephropathy into three groups based on the degree of mesangial proliferation, glomerulosclerosis, and percentage of crescents and prospectively studied the efficacy of short-term steroid therapy. In patients randomized to oral prednisone, 4 months of treatment stabilized renal function and reduced proteinuria but only in those patients with greater than 20% crescents on initial biopsy.[20] Recently, Hotta et al. examined the effects of pulse methylprednisolone and tonsillectomy in 35 patients with hematuria and known IgA nephropathy. Although the percentage was not recorded, over 91% of patients had evidence of crescents on initial biopsy. To assess the response to steroid hormone therapy, all 35 patients underwent repeat biopsy after 1 year of therapy. Interestingly, mesangial cell proliferation, glomerular sclerosis, and crescent formation were all significantly reduced on repeat biopsy.[21] These recent data supports the finding of Pozzi et al. and suggest that even in the face of epithelial cell proliferation, steroid therapy can have a positive clinical and histologic result.

Several small trials have studied whether the addition of oral cyclophosphamide to steroid treatment improves renal survival. For example, Ballardie et al. treated 38 patients with progressive IgA nephropathy with a combination of steroids and oral cyclophosphamide for 34 months followed by 2 additional years of prednisone and azathioprine. Kaplan-Meier analysis of renal survival showed a 72% 5-year survival compared with 6% for matched controls.[22] Although histologic changes, including mesangial hypercellularity, interstitial fibrosis, and tubular atrophy were similar between groups, patients were not controlled for presence of crescents or endocapillary proliferation.[22] Ferrario et al. treated six patients with focal

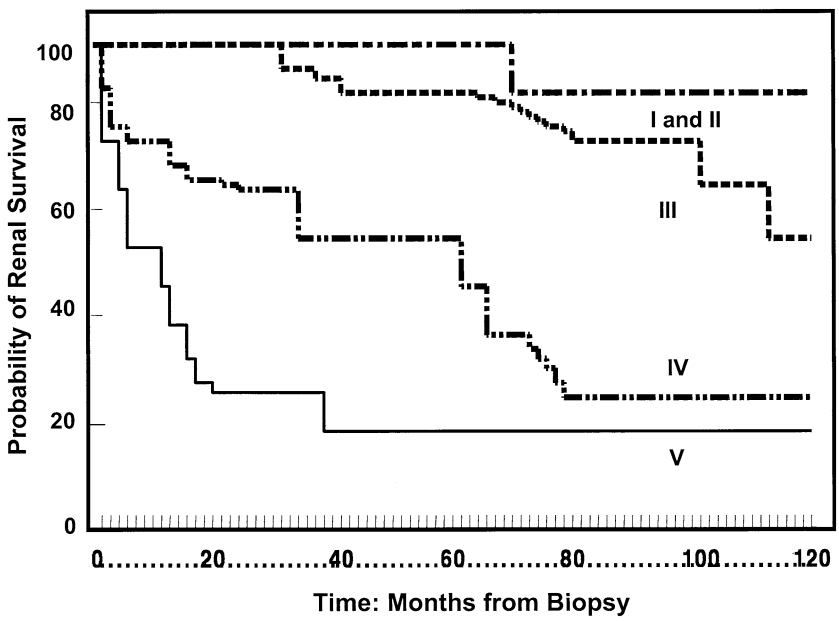

Fig 10. Renal survival as function of Haas classification of IgA nephropathy. Kaplan-Meier renal survival was plotted against time for each of the four IgA subgroups. Class I and II demonstrated excellent renal survival with less than 5% progressing to end-stage renal disease (ESRD) over 10 years. Class III demonstrated a more rapid loss of renal function with a 35% ESRD rate at 10 years. Classes IV and V demonstrate very rapid loss of renal function with over 40% patients reaching ESRD by 36 months with approximately 80% achieving ESRD by 10 years. Reprinted with permission from Haas M: Histological subclassification of IgA Nephropathy: A clinicopathologic study of 244 cases. Am J Kidney Dis 29:829-842, 1997.[2] © 1997 by National Kidney Foundation, Inc.

glomerular necrosis and 20% or more cellular crescents with steroids and oral cyclophosphamide and demonstrated that when compared with eight historical controls, 6 months of combination therapy significantly prolonged renal survival.[8]

We examined the effect of intense immunosuppression in 20 patients with progressive IgA nephropathy and histologic evidence of 10% or more cellular crescents. In our hands, prednisone and intravenous cyclophosphamide reduced proteinuria and stabilized renal function after 6 months of therapy. Both proteinuria and serum creatinine reduced to near-baseline levels within 6 months. Long-term follow up in the treatment group demonstrated that proteinuria and renal function remained stable over an average of 36 months. To investigate the response to treatment of glomerular histopathology, 17 of 20 patients underwent repeat biopsy. The percentage of crescents and endocapillary proliferation was compared between the pre- and postbiopsies after induction therapy. During the preliminary analysis of our clinical and histologic data, we determined that early nomenclature systems designed to identify specific IgA subgroups were not sensitive enough to discriminate between our treatment and control groups. Therefore, we applied a modified version of the World Health Organization SLE disease activity and chronicity indices to our population of patients. Using this system, we demonstrated that 6 months of steroids and intravenous cyclophosphamide eliminated all active cellular crescents and endocapillary proliferation. In addition, intensive immunosuppression using intravenous cyclophosph-

Table 2. Emory University Protocol: Crescentic Proliferative IgA Nephropathy

Clinical Data	Control (N = 12)	Steroids/CTX (N = 20)
Age (years)	43	44
Percent Male	64% (7/12)	40% (8/20)
Percent hypertension (>140/90 mm Hg)	41% (5/12)	85% (17/20)
Percent accelerated (>210/130 mm Hg)	40% (2/5)	0
Percent proteinuria (>1.0 gm/24 hrs)	75% (9/12)	100% (20/20)
Percent nephrotic (>3.0 g/24 hrs)	42% (5/12)	55% (11/20)
Serum creatinine (mean, mg/dL)	1.85	1.70
Serum albumin g/dL		
Mean ± standard error mean	3.5 ± 0.2	3.2 ± 0.2

amide minimized the amount of cortical scarring and tubular dropout in the majority of patients. Numerous studies have documented the poor prognosis with crescentic forms of IgA nephropathy, but few had used follow-up biopsies to prospectively assess a response to treatment. In a similar study, McIntyre et al. treated nine patients with severe crescentic IgA nephropathy (cellular crescents involving 20% to 70% of glomeruli) with prednisone and oral cyclophosphamide for up to 6 months followed by 2 years with prednisone and oral azathioprine. Long-term follow up demonstrated that steroids in conjunction with alkylating agents reduced proteinuria and improved creatinine clearance. On repeat biopsy, three of the eight patients showed an increased in glomerulosclerosis.[23] In our series, we compared the clinical and histologic response of the treated patients with 12 historical controls receiving conventional medical therapy but no immunosuppression. Five of 12 (42%) patients in this control group reached ESRD within 36 months compared with only 8.5% among the treatment group. The recent data of Hotta et al. raises the question of whether treatment of proliferative IgA nephropathy with steroid hormones alone is as effective as therapy combined with cyclophosphamide. Moreover, these observations raise the question of whether attempts should be made to create a unified histologic nomenclature for subgroups of IgA nephropathy that parallels the system in widespread use in SLE. Ultimately, an international application of such a system would allow for more precise definition of the natural history of specific subgroups and facilitate the design of clinical therapies to treat these patients.

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