IgA Nephropathy with Minimal Change Disease

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Abstract

Background and objectives Patients with IgA nephropathy typically present with hematuria and subnephrotic proteinuria. Nephrotic syndrome is uncommon in IgA nephropathy, and when present, it is usually associated with severe histologic features, such as endocapillary proliferation, segmental sclerosis, and crescent formation. Rarely, patients with IgA nephropathy present with nephrotic syndrome and only mild mesangial disease. This study sought to better characterize these patients.

Design, setting, participants, & measurements A retrospective review of cases of IgA nephropathy diagnosed from 2004 to 2011 identified patients with nephrotic range proteinuria and histologically mild IgA nephropathy. Specifically, using the Oxford Classification of IgA Nephropathy, we identified cases that lacked endocapillary proliferation or segmental sclerosis.

Results The cohort consisted of 17 patients, including 10 men and 15 adults. The median serum creatinine was 0.9 mg/dl (range=0.7–3.1), median 24-hour urine protein was 8.0 g/d (3.0–18.0 g), and 14 patients were fully nephrotic, whereas the remaining 3 patients fulfilled two of three criteria for nephrotic syndrome. Biopsies revealed IgA-dominant or codominant deposits accompanied by mesangial proliferation in 14 patients (82.4%). Electron microscopy showed mesangial deposits and extensive foot process effacement (median=90%). Initial treatment consisted of corticosteroids, although many patients required additional agents to maintain remission status. Over a median follow-up of 20 months (2.2–82 months), 14 patients experienced a complete response, and 3 patients showed a partial response, with a median response time of 2 months (0.5–27 months). At least one relapse of nephrotic syndrome occurred in nine patients (53%). All patients exhibited stable or improved renal function over the follow-up period.

Conclusions The findings in this cohort and previous studies suggest that rare cases of mild IgA nephropathy with nephrotic range proteinuria exhibit a clinical presentation, biopsy findings, treatment response, and outcome more typical of IgA nephropathy with superimposed minimal change disease. This study favors the view that such cases represent a dual glomerulopathy.


Introduction

IgA nephropathy (IgAN) is the most common GN worldwide (1). IgAN is typically an indolent disease with a slow progression to end stage kidney disease in approximately 30% of patients over 20 years (2). Clinical risk factors for progression of IgAN include proteinuria>1.0 g/d, hypertension, and persistent microscopic hematuria (1). Clinical presentations of IgAN vary widely, but the most common presentation is that of hematuria with subnephrotic proteinuria. Nephrotic syndrome (NS) is an unusual presentation occurring in approximately 5% of cases (3). Heavy proteinuria and/or NS in patients with IgAN are often accompanied by renal insufficiency and biopsy findings of more aggressive disease, with endocapillary proliferative and sclerosing glomerular lesions typically associated with subendothelial IgA deposits.

A subset of patients with IgAN presents with NS and has histologic findings of only mild mesangial proliferative IgAN. In these patients, electron microscopy typically reveals diffuse foot process effacement without peripheral capillary wall immune deposits, reminiscent of minimal change disease (MCD). Many of the patients are rapidly responsive to treatment with corticosteroids. Such cases are uncommon but have been presented as case reports and in small series over the last 30 years (4–17). Some of these reports have suggested that the clinical and pathologic findings in these unusual cases of IgAN (4–17), as well as the clinical outcomes (4–17), are more typical of mild IgAN with superimposed MCD.

The literature on treating MCD and IgAN as separate entities is abundant. In recent years, first-line treatment of MCD (i.e., corticosteroids) (18) also has been established as a standard therapy for patients with IgAN with significant proteinuria (19–21), generally considered to be >1 g/d despite effective use of renin angiotensin system-blocking drugs. Thus, the patient who presents with NS and is found to have findings...
suggestive of both MCD and mild IgAN should be a straightforward treatment decision. Still, the prognosis for these patients remain uncertain (specifically, whether they will have the often benign long-term course of mild IgAN or the frequently relapse-ridden course of MCD).

We present a series of 17 patients from the United States who developed nephrotic range proteinuria (NRP) and, in most cases, full NS and were found to have mild mesangial proliferative IgAN with diffuse podocyte foot process effacement. The mild degree of immune complex deposition and mesangial proliferation, in the absence of endocapillary proliferation or subendothelial deposits, seemed insufficient to explain the severe foot process effacement. We believe that these cases represent mild IgAN with superimposed podocyte pathotopy, which is most consistent with MCD. Clinical presentation, biopsy findings, treatment, and prolonged follow-up are presented to better characterize these unusual cases of mild IgAN with severe proteinuria.

Materials and Methods

All native renal biopsies received and processed at Columbia University Medical Center from 2004 to 2011 were reviewed retrospectively (Columbia University Institutional Review Board AAAI3051) for the diagnosis of IgAN occurring in the setting of NS or NRP with edema or hypoalbuminemia. IgAN was defined by the presence of dominant or codominant glomerular staining for IgA in the absence of systemic lupus. Biopsies were graded according to the Oxford Classification of IgAN (22,23). Specifically, the degree of mesangial hypercellularity (M), the presence of endocapillary proliferation (E) and segmental glomerulosclerosis (S), and the degree of tubulointerstitial scarring (T) were assessed, producing an Oxford-MEST score. Cases with endocapillary proliferation, necrosis, or cellular crescents were excluded, and an Oxford-MEST score of either M1E0 or M0E0 was required. We identified a total of 17 cases, which originated from multiple nephrology centers in the northeastern United States. All cases were processed for light microscopy, immunofluorescence, and electron microscopy according to standard techniques. For immunofluorescence, 3-μm cryostat sections were stained with FITC-conjugated rabbit anti-human IgG, IgM, IgA, C3, C1q, κ-light chain, and λ-light chain (Dako Corporation, Carpinteria, CA). The intensity of immunofluorescence positivity was graded on a scale of 0, trace, or 1–3+. Electron microscopy was performed with a JEOL 1011 electron microscope. For each case, a percentage estimate of the degree of podocyte foot process effacement was performed by an experienced renal pathologist examining at least 10 distinct fields.

Patient charts were reviewed retrospectively for presenting symptoms, laboratory findings, treatment, and follow-up. For the purpose of establishing clinical definitions, patients ≥18 years of age were considered adults (n=15) and those patients <18 years of age were considered children (n=2). For adults, the following definitions were used: NRP: 24-hour urine protein ≥3 g/d; hypoalbuminemia: serum albumin ≤3.5 g/dl; renal insufficiency: serum creatinine (SCr) ≥1.2 mg/dl; and hematuria: more than five red blood cells per high-power field on microscopic examination of the urinary sediment. NS was defined as NRP, hypoalbuminemia, and peripheral edema. Hypertension was defined as systolic BP >140 mmHg, diastolic BP >90 mmHg, or use of antihypertension medication. For children, NRP was defined as ≥40 mg/m2 per hour (24), hypoalbuminemia was defined as serum albumin <2.5 g/dl (24), renal insufficiency was defined as calculated creatinine clearance <90 ml/min normalized for body surface area (25), and hypertension was based on the clinical assessment of the referring nephrologist.

For the purpose of outcomes analysis, the following definitions were applied. Stable renal function was defined as a change in SCr of ≤25% of the initial value. Complete remission (CR) was 24-hour urine protein of ≤500 mg/d at last follow-up. Partial remission (PR) was 24-hour urine protein of ≤3 g/d and a reduction in proteinuria of at least 50%. CRs were further subdivided into patients who achieved remission but were still on therapy at the last follow-up (CR on therapy) and patients in remission who were no longer on therapy (CR off therapy). If a patient achieved remission for 6 months or longer while off therapy, subsequent episodes of NS were considered to be relapses. If remission status was lost within 6 months of therapy withdrawal, the return of proteinuria was considered to be evidence of therapy dependence and not categorized as a relapse. Data are presented descriptively, because the small number of subjects precludes formal statistical analysis.

Results

The cohort of 17 patients included 10 men and 7 women: 15 adults between the ages of 22 and 72 years and 2 children (ages 5 and 6 years). Eleven patients were Caucasian, three patients were Hispanic, two patients were Asian, and one patient was African American (Table 1). Past medical history was significant for obesity in four patients, diabetes in two patients, and coronary artery disease and chronic obstructive pulmonary disease in one patient each. No secondary causes of IgAN were identified (e.g., chronic liver disease, HIV infection, and inflammatory bowel disease).

Laboratory findings at the time of biopsy are summarized in Table 1. Fourteen patients (82.4%) had preserved renal function (SCr ≤1.2) at the time of biopsy. The median 24-hour urine protein was 8.0 g/d (range 3.0–18.0 g), and median serum albumin was 2.1 mg/dl (range 0.7–4.0 mg/dl), with all but one patient having evidence of hypoalbuminemia. Peripherial edema was present in 15 patients. Fourteen patients fulfilled criteria for full NS, and the remaining three patients had NRP. Of the three patients not qualifying as fully nephrotic, two patients lacked only edema, and one patient had edema but a serum albumin of 4.0 mg/dl. Serologic testing revealed positive anti-nuclear antibody in two patients, neither of whom had other clinical or laboratory features of systemic lupus. Complement levels (C3, C4, and CH50) were normal in all patients.

The renal biopsy findings are presented in Table 2. Glomerular findings by light microscopy were predominantly mild (Figure 1A). There was mesangial proliferation (Oxford M1) in 14 biopsies (82.4%), whereas the remaining 3 biopsies (17.6%) had no significant mesangial proliferation (Oxford M0). Based on inclusion criteria, none of the biopsies exhibited endocapillary proliferation (Oxford E0), necrosis, or cellular crescents. One biopsy had a single segmental scar
associated with a small overlying fibrous crescent, suggestive of an old proliferative lesion of IgAN. This patient had a 10-year history of steroid-dependent NS with stable creatinine. No other biopsy exhibited segmental sclerosis lesions. Tubulointerstitial scarring was mild in all cases (Oxford T0). Using the Oxford classification for IgAN, patients fell into one of three MEST scores: M1, E0, S0, and T0 in 13 patients (76.4%); M0, E0, S0, and T0 in 3 patients (17.6%); and M1, E0, S1, and T0 in 1 patient (5.9%) with a 10-year history of steroid-dependent NS.

Immunofluorescence showed dominant or codominant IgA staining in all cases (Figure 1B), with a median intensity of 1.85, and a range of 1–3+ (scale 0–3+). Staining was confined to the mesangium in all cases. Electron microscopy (Figure 1, C and D) showed mesangial immune-type electron dense deposits in all 17 cases, rare segmental subepithelial deposits in 1 case, and no subendothelial deposits in any case. No biopsy exhibited glomerular basement membrane thinning or lamellation. Podocyte foot process effacement ranged from 50% to 100%, with median effacement of 90%. Three cases showed podocyte effacement of <70%. Two of these patients were biopsied during a relapse of NS and had already commenced corticosteroid therapy before biopsy. The third patient was on low-dose prednisone (15 mg/d) for chronic obstructive pulmonary disease.

Clinical follow-up is presented in Table 3 and was available in all 17 cases, with median and mean follow-up durations of 20 and 30 months, respectively (range=2.2–82 months). All patients were treated initially with corticosteroids, and various alternative regimens were used in patients who did not achieve sustained response. Fourteen patients experienced CR, three patients achieved PR, and there were no nonresponders. The response categories were further subdivided into patients who were therapy-dependent at the time of last follow-up (CR on therapy, n=5; PR on therapy, n=3) and patients who were off therapy at last follow-up (CR off therapy, n=9). Time to achieve response averaged 4.8 months, with a median time of 2 months and a range of 0.5–27 months.

| Table 1. Clinical characteristics |
|-------------------------------|--------|
| Characteristic               | Value  |
| Age (yr), median (range)     | 46 (5–72) |
| <18, n                       | 2      |
| 18–50, n                     | 9      |
| >50, n                       | 6      |
| Sex (men/women), n (%)       | 10/7 (59/41) |

| Table 2. Pathologic findings |
|-------------------------------|--------|
| Modality/Finding              | Value  |
| Light microscopy              |        |
| Number of glomeruli, median (range) | 15 (5–38) |
| Percent of globally sclerotic glomeruli, median (range) | 5.5 (1–31) |
| Number of biopsies with no cellular proliferation (%) | 3 (17.6) |
| Number of biopsies with mesangial proliferation only (%) | 14 (82.4) |
| Number of biopsies with segmental sclerosis (%) | 1 (5.9) |
| Tubulointerstitial scarring   |        |
| Biopsies with ≤5% scarring, n (%) | 8 (47.1) |
| Biopsies with >5%–10% scarring, n (%) | 9 (52.9) |
| Oxford-MEST classification of IgAN, n (%) |        |
| M1, E0, S0, and T0            | 13 (76.4) |
| M0, E0, S0, and T0            | 3 (17.6) |
| M1, E0, S1, and T0            | 1 (5.9) |

| Immunofluorescence            |        |
| Percent IgA-dominant or codominant IgA intensity, scale 0–3+, median (range) | 100 |
| Electron microscopy           |        |
| Percent podocyte foot process effacement, median (range) | 90 (50–100) |
| Mesangial deposits, n (%)     | 17 (100) |
| Subendothelial deposits, n (%) | 0 (0) |
| Subepithelial deposits, n (%) | 1 (5.9) |

*Of three patients not meeting criteria for full nephrotic syndrome, two patients lacked only edema. One patient had nephrotic range proteinuria and edema but normal serum albumin of 4 g/dl.

*One patient, whose clinical history was marked by 10 years of steroid-dependent NS, had already commenced corticosteroid therapy before biopsy. The third patient was on low-dose prednisone (15 mg/d) for chronic obstructive pulmonary disease.
Nine patients (53%) showed a CR and were off therapy at the time of the last follow-up. Three of these patients had experienced at least one episode of relapsing proteinuria during the follow-up period and were subsequently successfully treated with cyclophosphamide (CTX) in one patient, cyclosporine (CSA) followed by CTX in one patient, and FK506 (which caused AKI) followed by CTX and 1 year of maintenance therapy with mycophenolate mofetil (MMF) in one patient. Renal function in the group of complete responders off therapy at last follow-up was stable in seven patients and showed improvement in two patients.

Five patients achieved a CR but were still dependent on therapy at the time of last follow-up. Each of these five patients had experienced at least one relapse when therapy had been withdrawn. One patient was treated solely with steroids and remained steroid-dependent at last follow-up, whereas another patient briefly received azathioprine, which produced leucopenia, and was switched back to steroids. The remaining three patients were treated with alternative regimens after steroids had failed, and they continued to be treated at the time of last follow-up. One patient was treated with CTX followed by MMF and then CSA, one patient received MMF only, and one patient received CSA followed by FK506. Renal function was stable in four patients and improved in one patient at last follow-up.

Three patients achieved only a PR and were being actively treated at the time of the last follow-up. Two patients have never been off therapy since initial diagnosis, including one patient with a PR who remains steroid-dependent after 5 months of treatment and one patient who was treated with steroids followed by MMF and has been on MMF for 10 months. The third patient has experienced a relapsing course and been sequentially treated with prednisone, CSA, rituximab, MMF, and most recently, adrenocorticotropic hormone. Despite the limited response to therapy, all three patients had stable renal function at last follow-up.

Discussion

In patients with IgAN, there is typically a reasonable degree of correlation between clinical and pathologic findings. When solely mesangial proliferation is present, patients most commonly exhibit subnephrotic proteinuria, hematuria, and normal renal function. In contrast, findings of endocapillary proliferation, segmental sclerosis, crescent...
formation, and tubulointerstitial scarring are associated with more severe disease that is characterized clinically by more severe proteinuria, in some cases full NS, and renal dysfunction.

We report a series of 17 patients with IgAN who presented with NRP or, in most cases, full NS and discordant findings of only mild histologic disease. All patients met criteria for IgAN, including mesangial deposits that stained dominantly or codominantly for IgA by immunofluorescence, with corresponding mesangial electron dense deposits on ultrastructural evaluation. By light microscopy, 14 biopsies showed mesangial proliferation (82.4%), and glomeruli appeared histologically unremarkable in the remaining 3 cases (17.6%). We only included cases without endocapillary proliferation (E0), necrosis, or cellular crescents. One biopsy exhibited a segmental glomerular scar (which was associated with an old fibrous crescent). The single pathologic finding that correlated with the presentation of full NS was extensive (median=90%) foot process effacement. The clinical and biopsy findings in these 17 patients, as well as similar cases that have been previously reported (4–17), are most consistent with mild IgAN with superimposed MCD.

The combined diagnosis of MCD and IgAN is supported by the discrepancy between the purely mesangial distribution of the immune deposits and the diffuse nature of the podocyte effacement and severity of proteinuria. Mesangial cells may respond to immune deposits and release inflammatory cytokines that cause mild alterations of the glomerular filtration barrier, but this typically results in only mild, subnephrotic proteinuria (26). Hill and colleagues (27, 28) have suggested that aberrantly glycosylated IgA1 can cause mesangial cells to release cytokines that cause podocyte injury, resulting in some of the segmental sclerosis often seen in IgAN (although predominantly absent in this series). In the analogous example of lupus nephritis (LN), patients with mesangial proliferative LN (class II) who present with full NS and extensive foot process effacement in the absence of endocapillary involvement are interpreted as having LN II with superimposed MCD (29) or lupus podocytopathy (30, 31). Similarly, we believe that the cases reported herein represent MCD superimposed on mild underlying IgAN. This interpretation is further supported by the outcomes in this cohort, where despite the presence of NRP or NS, many patients had a rapid response to steroid therapy, all patients had a complete or partial response, and no patient developed worsening renal function over a median follow-up of 20 months.

Several case reports and small series describe findings similar to those in our series (4–17). Kim et al. (7) identified 12 patients with IgAN who presented with corticosteroid-responsive NS. Eight patients had diffuse podocyte effacement typical of MCD, and the majority of patients had histologically mild IgAN. Response to steroid therapy was prompt (median time=2 months to CR), and a total of seven relapses occurred in five patients. Kim et al. (7) favored the interpretation that their patients had IgAN and MCD rather than an unusual variant of IgAN. A series from China reported eight
cases of mild mesangial proliferative IgAN with NS, and five of six cases with available electron microscopy showed extensive podocyte foot process effacement (8). All patients were responsive to corticosteroid therapy, with responses typically occurring within 6–8 weeks. Four patients had relapses, and three patients became corticosteroid-dependent. Similar to our cohort, their patients had a high level of response to corticosteroids and a high (53.8%) relapse rate, and none of their patients progressed to ESRD during a mean follow-up of almost 5 years (16).

A recent Chinese series by Wang et al. (17) enrolled 27 patients with IgAN and minimal change-like lesions to investigate the use of corticosteroids in this population. All patients achieved a complete response (24-hour urine protein<0.4 g) after 8 weeks of treatment. Unfortunately, only 12 weeks of follow-up data are provided, limiting conclusions regarding their long-term prognosis (17).

Larger series looking at IgAN with NS encompass a heterogeneous population. Han et al. (32) reported 24 patients with NS and IgAN and later included these patients in a larger series by Kim et al. (33) that comprised 100 patients with IgAN and NS. Biopsy findings included the full spectrum of proliferative lesions, making it a mixed group. The primary end point was doubling of Scr, which occurred in 24% of patients with NS and only 7.1% of patients who did not have NS. Kim et al. (33) concluded that IgAN patients with NS have a worse prognosis, but it is notable that many of the patients had significant proliferative lesions. In fact, only four patients had the exclusively mesangial proliferative disease and diffuse podocyte foot process effacement that was characteristic of patients in our cohort (33). In the series reported herein, all 17 patients showed a response to corticosteroid therapy. Steroids induced an initial CR in 14 patients (82%) and a PR in 3 patients (18%). The response to corticosteroids was relatively rapid, with CR occurring in <2 months in 7 patients (41%) and <4 months in 11 patients (65%). This high frequency and rapidity of responsiveness are similar to the findings reported for adult patients with MCD. Across several large studies, approximately 75% of adults with MCD showed a corticosteroid response within 4 months, and 75%–93% of patients eventually responded to corticosteroid therapy (18,34–37); six of 17 patients in our cohort showed a complete and lasting response without relapse after a single course of corticosteroid therapy. Nine patients (53%) experienced a relapse of proteinuria, and seven of these patients (41%) had multiple relapses. This high level of relapse is also typical of MCD in adults. Relapse rates in several large studies of adult MCD range from 62% to 77%, and multiple relapses were reported in 21%–28% of patients (18,34–37).

Indeed, it is not just the nature of relapsing proteinuria but, also, the response to second-line therapies that clearly marks this group of patients as more typical of MCD than pure IgAN. In previous studies of adult MCD, the response rate to second-line therapies was very good (60%-70%), irrespective of which agent is used (18), and this finding is borne out here as well, with responses documented to alkylating agents, calcineurin inhibitors, and MMF. The high rate of dependency on steroids and/or calcineurin inhibitors is also quite typical of MCD (38). Of four patients treated with CTX, three patients were able to achieve long-term remission off immunosuppressive therapy. Again, this finding is fully consistent with MCD, where alkylating agents are often the only therapies that can elicit a sustained remission or produce longer intervals between relapses (39).

NS in the setting of IgAN is associated with at least two distinct patterns of histologic disease. In mild IgAN with diffuse podocyte foot process effacement, the NS correlates with the degree of effacement, a finding that suggests a primary podocytopathy and is most consistent with a diagnosis of mesangial IgAN with superimposed MCD. In contrast, in cases of more severely proliferative IgAN presenting with the NS, the prominent endocapillary proliferation and inflammation are likely responsible for the proteinuria, akin to class III or IV LN with NS. Renal biopsy is particularly important to distinguish these two groups, because patients with mild IgAN and MCD should receive treatment directed to MCD and have a more favorable prognosis, albeit one that may be associated with a relapsing course and the need for prolonged therapy. We conclude that our cohort and similar cohorts reported previously (4–17) comprise a prognostically favorable subset of mild IgAN, in which NS does not predict progressive loss of renal function. We favor the interpretation that such cases represent a dual glomerulopathy, namely mild IgAN and superimposed MCD.

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Disclosures
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References


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