Clinical and histopathologic profile of patients with primary IgA nephropathy seen in a tertiary hospital in India

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ABSTRACT

Background IgA nephropathy (IgAN) is known to have an aggressive course in Asians. There is a paucity of data regarding the Oxford classification pattern of Indian patients with IgAN. This study aims to characterize the clinical and histopathologic profile of these patients.

Methods All patients diagnosed to have primary IgAN by kidney biopsy in the nephrology department from July 2009 to July 2014 were included in this study. All kidney biopsies were reviewed and the MEST score was assigned as per the Oxford classification. The clinical features and Oxford classification score of patients were characterized.

Results Nephrotic range proteinuria (NRP) (65/103, 63.1%) with or without edema was the commonest presentation. 67.0% patients had eGFR ≥ 60 mL/min and 16.5% patients had eGFR < 30 mL/min. Of the 103 patients, 80 (77.7%) had M1, 10 (9.7%) had E1, 45 (43.7%) had S1 and 41 (39.8%) had T1/T2 lesions by the Oxford criteria and 11 (10.7%) patients had crescents. 62 patients had eGFR < 30 mL/min and follow up for at least 6 months (median 17.7 (6-65.1) months) of whom 52 (83.9%) had received ACEi/ARBs and 38 (61.3%) had received immunosuppression. 11/62 (17.7%) patients developed renal worsening in this period of which 7 (11.3%) developed end stage kidney disease (ESKD).

Conclusion Indian patients with primary IgA nephropathy have a unique profile. They commonly present with nephrotic range proteinuria. A significant proportion of these patients have normal renal function despite heavy proteinuria. Mesangial proliferative lesions are predominant with a paucity of endocapillary proliferation and crescents compared to other Asian populations. Immunosuppressive use is more common in Indian patients.

Introduction

IgA nephropathy (IgAN) is the most commonly reported primary glomerular disease worldwide.1

Up to 30-40% of patients with IgAN progress to End Stage Kidney Disease (ESKD) at the end of 20 years. IgAN typically presents with either macroscopic hematuria (more common in children) or a combination of urinary abnormalities like microscopic hematuria and subnephrotic proteinuria, hypertension, and renal insufficiency.1

The prevalence as well as the prognosis of IgAN shows geographic and ethnic variation. It is reported to be significantly more common in Asians especially in Japan, Singapore, and China3–6 and Chinese patients have been shown to have poorer prognosis compared to their Western counterparts.6 The prevalence of IgAN in India7–10 is reported to be 4.5–16% of all patients with biopsy verified glomerular disease, and it is considered to be a severe disease with poor outcome.7 Nephrotic range proteinuria (NRP) is uncommon with IgAN in Whites as well as Asians with an incidence of 5-30%.11–15

The Oxford classification of IgAN developed in 2009 provides a histo-pathological grading system based on four variables: (1) mesangial hypercellularity (M); (2) endocapillary hypercellularity (E); (3) segmental glomerulosclerosis (S); (4) tubular atrophy/interstitial fibrosis (T). Crescents were not included in this classification. It has been evaluated in multiple population cohorts including a meta-analysis, but there is a
paucity of data in Indians. The original Oxford cohort also did not include Indian patients.16

The present study was conducted in a tertiary care teaching hospital in Northern India to characterize the clinical presentation and Oxford classification profile in Indian patients with biopsy verified IgAN.

Materials and methods

Medical records of all patients diagnosed to have primary IgAN on native kidney biopsy in our nephrology department from July 2009 to July 2014 were retrospectively reviewed. We excluded patients who had one of the following: secondary causes of IgAN like chronic liver disease, Henoch-Schönlein purpura, patients with a second coexisting disease on kidney biopsy, like diabetic nephropathy, inadequate/missing clinical records, unavailable pathologic material for interpretation, and inadequate kidney biopsy.

All kidney biopsies in the study period reported as IgAN based on immunofluorescence criteria of dominant/codominant IgA staining of intensity more than 1+ (on a scale of 0–3+) were reviewed by the renal pathologists independently. The MEST score was assigned as per the Oxford classification. In addition, presence or absence of crescents was recorded.

Data collected included age, gender, edema, presence of hypertension (arterial BP > 140/90 mmHg or taking anti-hypertensive drugs), baseline investigations including serum creatinine, serum uric acid (hyperuricemia was defined as serum uric acid ≥ 398.5 μmol/L based on the ROC curve), presence of hematuria (≥ 5 red blood cells/high power field) and the 24-hour urinary protein (g/day) at baseline and subsequent clinical visits. Nephrotic range proteinuria (NRP) was defined as a 24-hour urinary protein ≥ 3 g/day. Hypoalbuminemia was defined as serum albumin ≤ 35 g/L. Estimated glomerular filtration rate (eGFR) was calculated using the modified 4 variable MDRD formula for patients ≥ 18 years of age and the Schwartz formula for patients < 18 years of age. Renal deterioration was defined as ≥ 50% decline in estimated GFR or ESKD. Use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and details of immunosuppression given were also recorded.

The study was approved by the Institute Ethics Committee-IEC/NP-625.

Statistical analysis

Statistical analysis was carried out using Stata 11.0 (College station, TX). Data were summarized as frequency (%) or mean ± SD. The categorical and continuous variables were compared between the groups using chi-square test/Fisher’s exact test and independent t-test/Willcox on rank sum test, respectively. Predictors of renal outcome were not calculated due to the small number of events.

Results

There were 103 patients who had been diagnosed to have biopsy proven primary IgAN during the study period and met our inclusion criteria. Fifty-five (53.4%) patients presented with edema and were found to have NRP with or without renal dysfunction and only 9 (8.7%) presented with gross hematuria. Thirty (28.6%) patients had incidentally detected renal dysfunction and/or urinary abnormalities (proteinuria/microhematuria). Eight (7.8%) patients presented with a rapidly progressive renal failure (diagnosed to have crescentic IgA nephropathy) and 3 (2.9%) presented with acute kidney injury (AKI). Two of the 3 patients with AKI also had concomitant gross hematuria.

Table 1 shows the baseline clinical and laboratory profile of these patients. They were predominantly males (73.8%). Mean age at the time of kidney biopsy was 28.8 ± 12.5 years. Hypertension was present in 41 (39.4%) patients. Mean proteinuria was 3.8 ± 2.2 g/day and 91 (88.4%) patients had hematuria. Mean serum uric acid was 410.4 ± 113.0 μmol/L and 50 (48.54%) patients had hyperuricemia. Mean serum creatinine was 159.3 ± 177.0 μmol/L and mean eGFR was 76 ± 42.6 mL/min/1.73 m². Sixty-nine (67.0%) patients had eGFR ≥ 60 mL/min and 17 (16.5%) patients had eGFR < 30 mL/min.

| Table 1. Baseline clinical and laboratory profile of patients at the time of biopsy. |
|---------------------------------|--------------------------|--------------------------|
| Age (yrs) (Mean ± SD) (Range) | 28.8 ± 12.5 (14–60)     | Gender (F:M) (n)        | 27:76         |
| HT (%)                          | 41 (39.4)                | SBP (mm of Hg) (Mean ± SD) | 132.0 ± 19.4 |
| DBP (mm of Hg) (Mean ± SD)     | 83.7 ± 11.7              | Serum uric acid (μmol/L) (Mean ± SD) | 410.4 ± 113.0 |
| Urinary protein (g/day) (Mean ± SD) | 3.8 ± 2.2            | Serum albumin (g/L) (Mean ± SD)   | 33 ± 10       |
| Hematuria (%)                   | 91 (88.4)                | Serum creatinine (μmol/L) (Mean ± SD) | 159.3 ± 177.0 |
| eGFR (mL/min/1.73 m²) (Mean ± SD) | 76.0 ± 42.6         | eGFR (%) ≥ 60 mL/min (CKD stage 1 and 2) | 69 (67.0)     |
| < 30 mL/min (CKD stage 4 and 5) | 17 (16.5)              | Patients with follow up (n) | 62           |
| Duration of follow up (Months) (Median, Range) | 17.7 (6–65.1)        | ACEI/ARBs (%) (n = 62) | 52 (83.9)    |
| Immunosuppression (%) (n = 62) | 38 (61.3)              | Steroids (%)             | 38 (61.3)    |
| Renal worsening (%) (n = 62)   | 11 (17.7)               | ESRD (%) (n=62)          | 7 (11.3)     |
The distribution of the MEST lesions were as follows (Figure 1): Mesangial hypercellularity (M1) was present in 80 (77.7%), endocapillary hypercellularity (E1) in 10 (9.7%), segmental glomerulosclerosis (S1) was present in 45 (43.7%) and tubular atrophy/interstitial fibrosis (T1/T2) was present in 41 (39.8%). Eleven patients (10.7%) had crescents of which 8 presented with rapidly progressive renal failure. 65/103 (63.11%) patients had NRP on evaluation at the time of kidney biopsy (Table 1). Six (9.23%) patients in this group had presented with rapidly progressive glomerulonephritis due to crescentic IgA nephropathy. Table 2 shows the characteristics of IgAN patients with NRP and sub-nephrotic proteinuria. Compared to the patients with subnephrotic proteinuria, patients with NRP had significantly higher baseline eGFR (81 ± 43.5 mL/min vs. 67.5 ± 40.2 mL/min, p = 0.023). As shown in Table 3, mesangial and endocapillary proliferation as well as segmental sclerosis were more common in patients with sub-nephrotic proteinuria, but these were also not statistically significant.

Sixty-two patients had eGFR >30 mL/min and follow up for at least 6 months with a median follow -up of 17.7 (6-65.1) months (Table 1 and Figure 2). Of these 62, 52 (83.9%) had received ACEi/ARBs and 38 (61.3%) had received immunosuppression. Eleven (17.7%) patients developed renal worsening with doubling of serum creatinine in this period, of which 7 (11.3%) developed ESKD.

Discussion

IgAN is a very common primary glomerulopathy conventionally described as a slowly progressive disease eventually leading to ESRD in 30–40% patients. However, it manifests more aggressively in Indian patients with a 10-year renal survival of only 35%, which is lower than what is reported in other Asian and Caucasian populations.

Hematuria and subnephrotic proteinuria are more common presentations of IgA nephropathy compared to NRP/NS. However, edema with NRP was the predominant presenting feature of patients in our study. This may be a selection bias as in the absence of a screening program in India, patients who are symptomatic due to significant proteinuria are more likely to come to the renal clinic and consent to a kidney biopsy compared to those who have isolated microscopic hematuria, episodic gross hematuria, or mild proteinuria. Typically, countries which have screening strategies like Singapore and Japan have reported not only a very high incidence of IgAN but also a very high proportion of patients with minimal or no symptoms.

There was no significant difference in the clinical and MEST characteristics of the patients presenting with NRP compared to those who had sub-nephrotic proteinuria.

Table 3. Distribution of MEST lesions in patients with nephrotic and sub-nephrotic proteinuria.

| MEST lesions (%) | Nephrotic (N=65) | Sub-nephrotic (N=38) | p  |
|------------------|-----------------|---------------------|----|
| M1               | 47 (72.3)       | 33 (86.8)           | 0.087 |
| E1               | 5 (7.7)         | 5 (13.2)            | 0.366 |
| S1               | 25 (38.5)       | 20 (52.6)           | 0.162 |
| T1               | 17 (26.2)       | 11 (29.0)           |     |
| T2               | 7 (10.8)        | 6 (15.8)            | 0.434 |
| Total (T1 + T2)  | 24 (36.9)       | 17 (44.7)           |     |
| Crescents        | 8 (12.3)        | 3 (7.9)             | 0.484 |

Table 2. Clinical profile of IgAN patients presenting with nephrotic and sub-nephrotic proteinuria.

|                          | Nephrotic range proteinuria (n=65) | Sub-nephrotic range proteinuria (n=38) | p   |
|--------------------------|-----------------------------------|----------------------------------------|-----|
| Age (yrs) (Mean ± SD) (Range) | 27.8 ± 13.0 (14–60)               | 30.4 ± 11.6 (14–59)                    | 0.304 |
| Gender (F:M) (n)          | 14:51                             | 13:25                                  | 0.158 |
| HT (n (%))                | 27 (41.5)                         | 14 (36.8)                             | 0.870 |
| SBP (Mean ± SD)           | 133.2 ± 20.1                      | 132.2 ± 8.4                           | 0.803 |
| DBP (Mean ± SD)           | 84.1 ± 11.9                       | 83.0 ± 11.6                           | 0.668 |
| Serum uric acid (mg/dL) (Mean ± SD) | 404.5 ± 107.1                     | 422.3 ± 119.0                        | 0.446 |
| Urinary protein (g/day) (Mean ± SD) | 5.1 ± 1.7                         | 1.5 ± 0.7                             | <0.001 |
| Serum albumin (g/L) (Mean ± SD) | 29 ± 7                            | 41 ± 8                                | <0.001 |
| Hematuria (%)             | 56 (86.2)                         | 35 (92.1)                             | 0.528 |
| Serum creatinine (µmol/L) (Mean ± SD) | 138.1 ± 152.2                     | 185.8 ± 203.5                        | 0.162 |
| eGFR (mL/min/1.73 m²) (Mean ± SD) | 81.0 ± 43.5                       | 67.5 ± 40.2                           | 0.023 |
in our study except that the patients with NRP had better baseline renal function (eGFR).

Table 4 shows a comparison of our cohort with other study populations. Our study population was similar to the Oxford study cohort\(^{16}\) in terms of age (28.8 years vs. 30 years, respectively) and gender distribution (73.8% vs. 72% males, respectively). The mean proteinuria was higher in our study compared to the Oxford cohort (3.8 g vs. 1.7 g/24 h, respectively) and other study populations\(^{18,19,21}\). The Oxford study\(^{16}\) and Zeng et al.\(^{19}\) excluded patients with eGFR less than 30 mL/min, but our study had 16.5% patients in this category. Alamartine et al.\(^{20}\) had 13.6%, Katafuchi et al.\(^{21}\) had 4% and the VALIGA cohort\(^{22}\) had 9% patients with eGFR less than 30 mL/min. Other studies\(^{7-9}\) have shown that a large proportion of Indian patients with IgA nephropathy have significant renal dysfunction at the time of biopsy; however, renal failure has not been well defined in these studies.

The distribution of histopathologic lesions in our study cohort was uniquely different from other ethnic populations. We had a high proportion of patients with mesangial hypercellularity similar to the Oxford cohort\(^{16}\) but significantly higher than the VALIGA cohort\(^{22}\) and the studies in Japanese and Chinese populations\(^{18,19,21}\). Endocapillary hypercellularity, crescents and segmental glomerulosclerosis were less common in our patients and proportion of tubulointerstitial lesions were similar compared to other studies from Asia\(^{18}\). The other Indian study by Mittal et al.\(^{9}\), which has applied the Oxford criteria to kidney biopsies of IgAN patients has also reported a similar proportion of mesangial hypercellularity and segmental glomerulosclerosis (Table 4). However, compared to our patient cohort, their study had higher proportion of endocapillary proliferation (9.7% vs. 29.6%) and crescentic (10.7% vs. 56.6%) lesions as well as very high percentage of tubular atrophy/interstitial fibrosis (39.8% vs. 74.2%). Mittal et al.\(^{10}\) reported that majority of their patients presented with renal failure (not defined) and NRP was less common (Table 4), which could explain this difference in the MEST pattern. Chacko et al.\(^{7}\) analyzed 478 patients with IgAN and reported nephrotic syndrome in 55%, which is similar to our study and renal failure in 56% though this was defined as serum creatinine \(\geq 1.4 \text{ mg/dL}\). Their study also showed less crescentic lesions as
observed in our study. However, this study did not use the Oxford classification (published before Oxford classification was developed).

Of the 62 patients with follow up in our study, 83.9% received ACEI/ARBs which were similar in other studies (Table 4). Immunosuppression use was higher in our patients (61.3%) than other studies (Table 4). All the patients received steroids as the first-line immunosuppression, while 14 patients required second-line immunosuppressive agents. Since a majority of our patients had NRP of which 69.2% had eGFR \( \geq 60 \) mL/min, it may have necessitated the use of immunosuppression. Other studies from India have not discussed immunosuppression use.\(^7\)–\(^9\)

17.7% patients showed renal deterioration of which 11.3% developed ESKD suggesting an aggressive disease. The shorter duration of follow up in this slowly progressive disease was the main limiting factor of this study because of which we could not assess the predictors of renal outcome. To our knowledge, this is the first study which gives a comprehensive clinical profile including treatment received and histological characteristics using the Oxford classification in Indian patients. Our study population has a unique profile wherein NRP is the predominant clinical presentation, which has also been demonstrated in other Indian cohorts.\(^7\) Histologically, mesangial proliferation is predominant and endocapillary and crescentic proliferation are less common. Majority of our patients require immunosuppression. The other Indian study using Oxford criteria does report a relative higher frequency of proliferative lesions; however, it is also characterized by a very high proportion of tubulointerstitial chronicity and renal failure. This could be a center effect reflecting their practice pattern and guidelines for kidney biopsy.

At present, the KDIGO guidelines for IgAN\(^26\) suggest that patients with persistent proteinuria \( \geq 1 \) g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR \( >50 \) mL/min per 1.73 m\(^2\), receive a 6-month course of corticosteroid therapy. However, it does not clearly specify the line of treatment for patients who have IgAN with NRP without minimal change disease? With the predominance of NRP and aggressive disease in our patients we need to determine the proportion of these patients, who actually would show a significant decrease in proteinuria with conservative therapy as has been shown in other glomerular diseases like membranous nephropathy.\(^27\) Further studies are also required to ascertain whether initial conservative therapy thereby delaying immunosuppression as recommended leading to prolonged proteinuria can actually worsen renal survival especially in those with severe histopathologic disease.

**Disclosure statement**

None of the authors have declared any conflicts of interest.

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