ISSN: 2091-2331 (PRINT) 2091-234X (ONLINE)

Journal of Nobel Medical College

Available Online: www.nepjol.info, www.nobelmedicalcollege.com.np

Volume 6, Number 1, Issue 10, January-June 2017, 6-11

Original Article

Immunoglobulin A (IgA) Nephropathy in Protocol Graft Kidney Biopsy done at six months Post Transplantation in a Tertiary Care Center Hospital of Nepal

Midhan Shrestha* and Dibya Singh Shah

Department of Nephrology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Received: 10th July, 2016; Revised after peer-review: 12th August, 2016; Accepted: 27th September, 2016

Abstract

Background

Renal transplantation is the treatment of choice for end stage renal disease. The focus of interest has been to increase the life of the transplanted graft. Recurrence of native kidney disease or occurrence of denovo glomerulonephritis has adverse effects in graft survival. Protocol graft biopsy done at fixed time interval after transplantation aids in early identification of post-transplant glomerulonephritis before development of clinical signs and symptoms. This study describes the incidence of post-transplant IgA Nephropathy in protocol renal graft biopsies done at six months post- transplantation.

Materials and Methods

This is a hospital based observational descriptive study, done in Tribhuvan University Teaching Hospital, Kathmandu, Nepal, a tertiary medical referral center in the capital. Protocol biopsy of the graft kidney was performed at six months post-transplantation in all recipients who underwent kidney transplantation in this hospital between 2071 Kartik and 2072 Ashwin.

Results

Protocol biopsy was performed in total 47 recipients. Mean age of the recipients was 33.7 years ±10.83 years. The study population consisted of 33 (70.2%) male and 14 (29.8%) female recipients. IgA Nephropathy was present in 6 (12.8%) recipients.

Conclusion

Our study demonstrates that IgA Nephropathy does occur in patients with stable GFR and without any clinical or laboratory abnormalities. Protocol biopsy is valuable in detection of early histologic abnormalities before onset of clinical manifestations, thus helping in prompt management with aim to prolong the graft survival.

Key words

IgA nephropathy, Post-transplant glomerulonephritis, Protocol biopsy, Recurrent disease

Introduction

Protocol biopsy is the biopsy that is performed at pre-determined time points after renal transplantation in patients with stable allograft function.

It aims to detect subclinical insults to the allograft so that the appropriate early intervention can be done to prolong allograft survival.

Recurrence of native disease is common after transplantation. IgA Nephropathy also recurs, with reportedly great variation in the incidence. The variation may be because of difference in duration of follow

Corresponding Author: **Dr. Midhan Shrestha, Assistant Professor /E-mail: drmidhan@hotmail.com*

up and biopsy policy of different transplant centers. Most centers perform biopsy only when patients present proteinuria, hematuria or decline in renal function. This may potentially underestimate the true rate of recurrence. The patients who are clinically asymptomatic but have histological changes in the graft kidneys would remain undiagnosed. For centers which perform routine protocol biopsies, histological recurrence with mesangial IgA deposits and mesangial hypercellularity have been reported in 50–60% of patients. [1,2] In the presence of clinical symptoms, the recurrence rate has been reported from 13–50%. [3,4]

Graft loss from histologic recurrence have been reported between 1.3% and 16% when there were features of diffuse mesangial proliferative expansion and glomerular sclerosis[5]. One of the latest registry report containing possibly the largest number of IgAN patients has shown the estimated 10-year incidence of graft loss due to recurrence to be 9.7% (CI = 4.7–19.5 %). [5]

We performed protocol graft biopsy in all transplant recipients to find out the histological occurrence of IgA nephropathy in asymptomatic patients with normal urine findings and stable graft function.

Materials and Methods

Recipients Selection

This study was done in settings of TU Teaching Hospital. All patients who underwent kidney transplantation between 2071 Kartik and 2072 Ashwin were eligible for enrollment in the study.

Immunosuppressive Protocol

All renal transplant recipients received triple immunosuppressive regimens. They were started on tacrolimus and mycofenolate mofetil two days prior to surgery. Intravenous methylprednisolone was given on the day of surgery, followed by oral prednisolone on subsequent days.

All recipients received induction with rATG on Day 0 and Day 1 post-operatively. The usual dose of rATG was 1mg/kg on each day. However, patients who were highly sensitized received up to 2mg/kg of rATG on each day. Patients with two haplo-identical HLA at A, B, DRB1 loci were not prescribed induction with ATG.

Tacrolimus was given at the dose of 0.1mg/kg/day. Tacrolimus trough level (C0) level was measured on D1 and D5 after transplantation. It was then measured weekly for the first month. After the first month, it was requested on clinician's discretion. At the time of protocol biopsy, i.e. at six months of renal transplantation, the target level of 6-7ng/ml was aimed. Mycofenolate mofetil was given at the dose of 2 gm per day in divided doses. Recipients were maintained at 5 mg of prednisolone as the continuation dose. Sensitized recipients were maintained at 10 mg as the continuation dose.

They were followed up post-operatively on out-patient basis, as per institution protocol. At six months post transplantation, surveillance graft biopsy was performed in all patients who gave informed written consent.

Recipients Exclusion

Following recipients were excluded:

1. Recipients not consenting to the study
2. Recipients who had proteinuria at six months
3. Recipients who didn't have stable graft function at six months
4. Recipients with acute kidney injury, active infections or urinary tract obstruction

Biopsy Protocol

Recipients undergoing protocol graft biopsy were admitted a day prior to the procedure. All basic investigations including coagulation parameters and viral serology were sent routinely. Contraindications to biopsy were uniformly ruled out prior to the procedure.

*Corresponding Author: **Dr. Midhan Shrestha,** Assistant Professor | E-mail: drmidhan@hotmail.com

Renal biopsy was performed under real time ultrasound guidance with Bard 18 gauze automated biopsy gun. Two core of tissues were obtained from each individual and preserved in normal saline and formalin. Presence of active post-procedure bleeding was ruled out by ultrasonography. All patients underwent structured health history and physical examination. Patients' clinical and laboratory parameters were recorded. Renal biopsy reports were reviewed on follow-up.

Results

Total of 57 CKD patients underwent renal transplantation during the study period. Eight recipients refused to undergo renal biopsy at six months. Out of 49 recipients who underwent renal graft biopsy at 6 months, 2 already had significant proteinuria or renal impairment. Remaining 47 recipients underwent the defined protocol biopsy and were included in data analysis.

Characteristics of the Study Population

The mean age of enrolled renal transplant recipients was 33.7 years ± 10.83 years. The study population consisted of 33(70.2 %) male and 14(29.8 %) female. The cause of CKD was listed as Hypertension in 23 (48.9%), Undetermined in 21 (44.7%), Chronic Glomerulonephritis in 1 (2.1%) and Diabetes Mellitus in 2 (4.3%) recipients. The mean HD duration before undergoing renal transplantation was 6.47 months. ±4.4 months. Six (12.8%) recipients underwent pre-emptive kidney transplantation. Among all recipients, 27 (57.4%) received kidney from blood related donors, whereas 20 (42.6%) received kidney from non-related donors. The mean age of the donor was 44.0 years ± 11.33 years. The donor population consisted of 34 (72.34%) female and 13 (27.65%) male. The level of HLA Mismatch was 0 in 7 (14.9%) recipients, 1-3 in 22 (46.7%) recipients and 4-6 in 18 (38.3%) recipients. HLA DRB1 mismatch was 0 in 14 (29.8%), 1 in 23 (48.9%) and 2 in 10 (21.3%) recipients. Induction with rATG was given in 40 (85.1%) recipients. The mean dose of ATG was 94.47±45.28 milligrams. Maintenance immunosuppressive regimen was triple drug regimen consisting of Tacrolimus, Mycophenolate Mofetil and Prednisolone in 46 (97.8%) recipients. One patient was switched to azathioprine from MMF during the study period due to financial condition. The mean tacrolimus trough level at six months post-transplantation was 6.94 ± 1.36 ng/ml.

IgA Nephropathy

IgA Nephropathy was detected in 6 (12.8%) recipients. There was no association with age (p=0.962) or sex (p=0.452) of the recipient, or age (p=0.569) or sex (p=0.519) of the donor. There was no association with whether the donor was related or not (p=0.693). There was no association with the level of HLA DR mismatches (p=0.759). There was no association with the use of rATG as induction (p=0.273).

The recipient and donor characteristics and immunologic characteristics are demonstrated in following table.

Table.1. Recipient and donor characteristics (N=47)

Characteristic	Value
Age of the patient (yrs.)	33.7±10.83
Sex	
Male (%)	70.2 (n=33)
Female (%)	29.8 (n=14)
Native Kidney Disease (%)	
Hypertension	48.9 (n=23)
Diabetes Mellitus	4.3 (n=2)
Chronic Glomerulonephritis	2.1 (n=1)
Undetermined	44.7 (n=21)
HD Duration (months)	6.47±4.4
Donor	
Related (%)	57.4 (n=27)
Non-related (%)	42.6 (n=20)
Donor Age (yrs.)	44.0±11.33
GFR at 6 months follow-up (ml/min)	77.03±22.6

*Corresponding Author: **Dr. Midhan Shrestha,** Assistant Professor | E-mail: drmidhan@hotmail.com

Table.2. Immunological characteristics of the recipients (N=47)

Characteristics	Value
HLA Mismatch (%)	
0	14.9 (n=7)
1-3	46.8 (n=22)
4-6	38.3 (n=18)
Pre-transplant B Cell Cross match (%)	4.3 (n=2)
Positive	95.7 (n=45)
Negative	
Second Transplantation (%)	4.3 (n=2)
Yes	95.7 (n=45)
No	
Use of induction	85.1 (n=40)
immunosuppression (%)	14.9 (n=7)
rATG	
No induction	97.9 (n=46)
Maintenance	2.1 (n=1)
immunosuppression (%)	6.94 ± 1.36
Mycofenolate Mofetil	
Azathioprine	
Tacrolimus Trough Level (ng/ml)	

Discussion

IgA Nephropathy was detected in 12.8% recipients. Unfortunately, no pre-transplant biopsies were performed in these cases. Thus, we couldn't classify them as true recurrence.

Ortiz et al reported the histological recurrence of IgAN in almost one-third of the patients after 2 years from transplantation. In a study which reviewed IgAN recurrence in 32 protocol biopsies, recurrence rate was 53%. [2] Another study including 11 biopsies had recurrence rate of 27%. [5] With regards to recurrence, the results are found to be similar in the studies including the patients using modern immunosuppression. In most centers, the suspicion of IgAN recurrence is based on the presence of hematuria, proteinuria or a decline in renal function. In those cases, the recurrence rate was between 12.5 and 50%. [6] Importantly, it was found that 52% of the IgAN recurrences diagnosed by protocol biopsies were not accompanied by proteinuria or hematuria. Thus, protocol biopsies with immunofluorescence analysis constitute an essential tool for the diagnosis of recurrence, even if it is clinically silent [7]. In our study, we were not able to rule out the possibility that IgA deposits were already present in the donors. Autopsy studies from cases without known renal disease report histologic IgANin 4–8%. [8] However, a gradual resolution of IgA deposits is expected to occur within 45 days following transplantation. In a study of 0-h renal biopsies, where 87% of transplants were from living donors, latent mesangial deposition of IgA was present in 16% of its cases. Interestingly, the co-deposition of C3 was detected in only 19%. [9] In our study, recurrent IgAN was associated with C3 deposition in all cases. This may suggest that there was already complement activation and therefore potential inflammatory response. Taking into account both the timing of protocol biopsy and the concomitant complement deposition, we do not consider that the IgA deposits were related to persistence of donor IgA deposits in the graft. Use of Mycophenolate mofetil for immunosuppression has been thought to lower incidence of recurrence as opposed to azathioprine-based therapy. However, it could not be verified in a small retrospective study and still needs to be tested in a prospective study. [10] Almost all of our patients were on MMF based therapy, except one who was switched to azathioprine. So, we were not able to make the comparison between the two groups.

Three out of six recipients with mesangial IgA deposits were treated with increased doses of prednisolone and mycofenolate mofetil. These were the ones who also exhibited glomerular or interstitial inflammation. All six recipients received cod liver oil and ARB as supportive management.

*Corresponding Author: **Dr. Midhan Shrestha,** Assistant Professor | E-mail: drmidhan@hotmail.com

The optimal regimen of immunosuppressive drugs for the treatment of primary IgAN in patients at risk of progression still remains uncertain. [11] The use of calcineurin inhibitors, either in the presence or absence of induction therapy, does not influence the risk of recurrence. When azathioprine and Mycophenolate mofetil (MMF), cyclosporine and tacrolimus, sirolimus and prednisone were compared, there was no difference in the rate of graft loss due to recurrence [12]. A study has reported development of IgAN with nephrotic range of proteinuria in two transplant recipients after conversion from a calcineurin inhibitor based immunosuppression to sirolimus [13]. Use of steroid free or rapid steroid withdrawal regimen hasn't been found to affect the risk of recurrence [14]. Recommended treatment for primary IgAN includes ACE-i or ARB [15]. There have also been case reports of fish oil having a favorable effect in recurrent IgAN, but no studies have been performed to support its routine use [16].

Safety of Protocol Kidney Biopsy

Use of protocol biopsies has been limited in some centers by concerns over their safety. There are a number of studies that suggest that the biopsy procedure is considerably safe [17,18]. None of the recipients in our study developed complications related to the procedure. This is in accordance with large studies which reported major complication rate between 0.4 to 1 percent. [8] It is also in accordance with the view that it is ethically justifiable to perform protocol graft kidney biopsies both in clinical trials and routine care.

Conclusion

Our study demonstrates that IgA Nephropathy does occur in patients with stable GFR and without any clinical or laboratory abnormalities. Protocol biopsy is valuable in detection of early histologic abnormalities before onset of clinical manifestations, thus helping in prompt management with aim to prolong the graft survival.

References

[1] Berger J, Noel LH, Nabarra B. Recurrence of mesangial IgA nephropathy after renal transplantation. ContribNephrol 40 (1984) 195–197.

[2] Odum J, Peh CA, Clarkson AR et al. Recurrent mesangial IgA nephritis following renal transplantation. Nephrol Dial Transplant 9 (1994) 309–312.

[3] Bachman U, Biava C, Amend W, Feduska N, Melzer J, Salvatierra O. The clinical course of IgAnephropathy and Henoch—Schonlein purpura following renal transplantation. Transplantation 42 (1986) 511–515

[4] Moriyama T, Nitta K, Suzuki K et al. Latent IgA deposition from donor kidney is the major risk factor for recurrent IgA nephropathy in renal transplantation. Clin Transplant 2005; 19 (Suppl 14): 41–48.

[5] Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 347 (2002) 103–109.

[6] Choy BY, Chan TM, Lo SK et al. Renal transplantation in patients with primary immunoglobulin A nephropathy. Nephrol Dial Transplant 18 (2003) 2399–2404.

[7] Fernanda Ortiz, Rosana Gelpi, Petri Koskinen, Anna Manonelles, Anne Räisänen-Sokolowski, Marta Carrera, EeroHonkanen, Josep M. Grinyó, and Josep M. Cruzado. IgA nephropathy recurs early in the graft when assessed by protocol biopsy. Nephrol. Dial. Transplant 27:6 (2012) 2553-2558.

[8] Jeong HJ, Park SK, Cho YM et al. Progression of renal allograft histology after renal transplantation in recurrent and non-recurrent immunoglobulin A nephropathy. Hum Pathol 39 (2008) 1511–1518.

[9] Suzuki K, Honda K, Tanabe K et al. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. Kidney Int 63 (2003) 2286–2294.

[10] Chandrakantan A, Ratanapanichkich P, Said M, Barker CV, Julian BA: Recurrent IgA nephropathy after renal transplantation despite immunosuppressive regimens with Mycophenolate mofetil. Nephrol Dial Transplant 20 (2005) 1214–1221.

[11] Floege J, Eitner F. Combined immune suppression in high-risk patients with IgA nephropathy? J Am SocNephrol 21 (2010) 1604–1606.

Corresponding Author: **Dr. Midhan Shrestha, Assistant Professor | E-mail: drmidhan@hotmail.com*

[12] Mulay AV, van Walraven C, Knoll GA. Impact of immunosuppressive medication on the risk of renal allograft failure due to recurrent glomerulonephritis. Am J Transplant 9 (2009) 804–811.

[13] Dittrich E, Schmaldienst S, Soleiman A, Hörl WH, Pohanka E. Rapamycin associated posttransplantation glomerulonephritis and its remission after reintroduction of calcine urininhibitortherapy. TransplInt 17 (2004) 215–220

[14] Ibrahim H, Rogers T, Casingal V et al. Graft loss from recurrent glomerulonephritis is not increased with arapid steroid discontinuation protocol. Transplantation 81 (2006) 214–219.

[15] Praga M, Gutierrez E, Gonzalez E et al. Treatment of IgA nephropathy with ACE inhibitors: A randomized and controlled trial. J Am SocNephrol 14 (2003) 1578–1583.

[16] Ng R. Fish oil therapy in recurrent IgA nephropathy. Ann Intern Med (2003)138:1011.

[17] Rush D: Protocol biopsies should be part of the routine management of kidney transplant recipients. Am J Kidney Dis 40 (2002) 671–673.

[18] Furness PN, Philpott CM, Chorbadjian MT, Nicholson ML, Bosmans JL, Corthouts BL, Bogers JJ, Schwarz A, Gwinner W, Haller H, Mengel M, Seron D, Moreso F, Canas C: Protocol biopsy of the stable renal transplant: A multicenter study of methods and complication rates. Transplantation 76 (2003) 969–973.

*Corresponding Author: **Dr. Midhan Shrestha,** Assistant Professor | E-mail: drmidhan@hotmail.com