RESEARCH PAPER | Medical Science | Volume : 6 | Issue : 4 | April 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Recurrent IgA nephropathy following kidney transplantation in Chinese: not a benign prognosis

KEYWORDS: Kidney transplantation, Biopsy, Recurrent Ig A nephropathy, Latent IgA deposition, Prognosis

Ji Shu-Ming
National Clinical Research Center of Kidney Diseases, Jinling Hospital（210002）, Nanjing University School of Medicine, Nanjing, China, 210016

Chen Jin-Song
National Clinical Research Center of Kidney Diseases, Jinling Hospital（210002）, Nanjing University School of Medicine, Nanjing, China, 210016

Wen Ji-Qiu
National Clinical Research Center of Kidney Diseases, Jinling Hospital（210002）, Nanjing University School of Medicine, Nanjing, China, 210016

Cheng Dong-Rui
National Clinical Research Center of Kidney Diseases, Jinling Hospital（210002）, Nanjing University School of Medicine, Nanjing, China, 210016

ABSTRACT

Objective: The aims of this study were to determine the incidence of immunoglobin A nephropathy(IgAN) recurrence assessed by protocol biopsies and to identify predictive factors including pathological and clinical characteristics following kidney transplantation in China. Methods: Of the 148 recipients of allografts for end-stage renal disease caused by primary IgA nephropathy between January 1996 and April 2009 at our institution. Reccurent IgAN was found in 46 patients out of 148 renal biopsy from allogaft kidneys. Biopsies were taken at a median time of 9.3 ±3.6 months after transplantation. Results: 46 patients (31.1%) had biopsy-confirmed recurrent IgAN. The urinary red blood cell sediment（U-RBC） and proteinuria at 5 yr after transplantation differed significantly between recurrent IgAN group and non-recurrent IgAN group, respectively,180±27 vs. 10±5 M/ml and 2.6±0.51 vs. 0.4±0.2 g/d. Serum creatinine(SCr) levels at 5 yr after transplantation was significantly higher in the recurrent IgAN group than in the non-recurrent IgAN group(4.52±1.61 vs. 1.19±0.20 mg/dl). Glomerular filtration rate was significantly lower in the recurrent IgAN group than in the non-recurrent IgAN group at 5 yr after transplantation: 30.24±9.04 vs. 68.58 ml/min. The prevalence of cellular crescents, glomeruli with adhesions, mesangial cell proliferation, mesangial matrix increase, global sclerosis and glomeruli with segmental sclerosis was significantly greater in the reccurent IgAN group than in the non-reccurent IgAN group(P<0.001), The rate of global obsolescence and the average score of interstitial fibrosis in the reccurent IgAN group were significantly greater than in the non-reccurent IgAN group(P<0.001). Ten recipients(21.7%) among the 46 patients with recurrent IgAN progressed to graft loss within 5 yr after transplantation. Graft survival both groups was no significant, respectively 93.8% and 95.6% in 1 year and 86.7% and 88.3% in 3 years. 5 years graft survival rate was lower in the reccurent IgAN group than in the non-reccurent IgAN group (51.4% vs. 83.8%, p< 0.001). The grade of chronic rejection was tended to be higher in the graft loss group than in the graft survival group. Interestingly, incidences of latent IgA deposition from the donor kidney was higher in the graft loss group than in the graft survival group. Conclusion: Recurrent IgA nephropathy following renal transplantation is not a benign prognosis in Chinese. Our data suggest that 31.1% out of patients with primary IgAN will develop recurrence, 21.7% among the 46 patients with recurrent IgAN progressed to graft loss within 5 yr after transplantation. Latent IgA deposition from the donor kidney was one of the risk factors of recurrent IgAN progressed to graft loss.

INTRODUCTION

Immunoglobin A nephropathy(IgAN) is the most common form of glomerular disease in Chinese, which account for 39.9% in primary glomerulopathy[1,2]. As well known, a lot of glomerular diseases may be recurrent after kidney transplantation. However, recurrent IgA nephropathy after kidney allograft was also the most common form. It has been estimated that approximately 20% to 24.3% of Chinese[3], while 50% to 60% of western kidney transplant recipients with IgA nephropathy as the cause of their original kidney disease will develop recurrent disease[4,5]. Clinically, the manifestation of recurrent IgA nephropathy is often associated with microscopic hematuria and intermittent proteinuria, and a benign prognosis[6]. Recent data have, however, suggested that recurrent IgAN is not benign, the patients with recurrent IgA nephropathy could present as progressive glomerulonephritis and subsequent graft loss[7,8]. The recurrent IgAN in the allograft is common, factors related to IgA recurrence are unclear. The aims of this study were to determine the incidence of IgAN recurrence assessed by protocol biopsies and to identify predictive factors including pathological and clinical characteristics following kidney transplantation in China.

MATERIALS AND METHODS

Patient enrollment

Of the 148 recipients of allografts for end-stage renal disease(ESRD) caused by primary IgA nephropathy between January 1996 and April 2009 at our institution. Reccurent IgAN was found in 46 patients out of 148 renal biopsy from allogaft kidneys. Biopsies were taken at a median time of 9.3 ±3.6(6-36) months after transplantation.

Study design

Forty-six developed recurrent IgA nephropathy (recurrent IgAN group), while the remaining102 did not develop recurrent IgA nephropathy(non-recurrent IgAN group). There were no significant deference between the two groups regarding patient's gender, duration after transplantation, recipient age at transplantation, number of HLA-AB or –DR mismatches, duration of falling into ESRD and duration of hemodialysis. All recipients had all been treated with same triple-drug therapy, involving tacrolimus(FK506), mycophenolate mofetil (MMF) and steroids. There were also no significant deference in steroid dosage, FK506 serum trough level and MPA-AUC0-12h concentration. Only the number of donor kidneys with latent IgA deposition was significantly higher in the recurrent IgAN group than in the non-recurrent IgAN group(Table 1).

Volume : 6 | Issue : 4 | April 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Table 1. Comparison of demographic and clinical data between the reccurent IgAN group and the non-reccurent IgAN group

	Reccurent IgAN group (n=46)	Non- reccurent IgAN group (n=102)	*P value*
Gender (M/F)	10/36	28/74	>0.05
Duration after transplantation (years)	6.5 ± 5.5	6.8 ± 5.9	>0.05
Recipient age at transplantation(years)	46.4 ± 12.9	45.9 ± 13.8	>0.05
Donor age at transplantation (years)	44.7 ± 11.7	47.6 ± 9.48	>0.05
Number of HLA- AB mismatches	1.75 ± 0.71	1.6 ± 0.55	>0.05
Number of HLA- DR mismatches	1.00 ± 0.00	1.00 ± 0.00	>0.05
Duration of falling into ESRD (years)	8.7 ± 6.1	9.1 ± 5.2	>0.05
Duration of hemodialysis (years)	4.8 ± 1.3	4.5 ± 1.5	>0.05
Steroids (mg/day)	10.2 ± 4.3	10.1 ± 4.4	>0.05
FK506 trough level (ug/L)	6.8 ± 2.1	6.9 ± 2.0	>0.05
MMF-AUC0-12h (mg.h/L)	39.1 ± 10.4	39.4 ± 9.4	>0.05
Latent IgA deposition (%)	34.8	9.8	<0.05

Clinical observations

During the follow-up, body temperature, blood pressure, urine output, urinary red blood cell sediment (U-RBC),urinary protein and kidney graft function were monitored regularly. The incidence, degree, and outcome of acute rejection and complications, including hepatoxicity,nephrotoxicity and infection were recorded. Adverse events and survival rates of the kidney grafts and patients were calculated, and blood urea nitrogen, serum creatinine (SCr), glomerular filtration rate,blood glucose, blood lipids, peripheral hemogram, hematocrit, and urine analysis were measured each month for 2 years after surgery, and then every 3 months. The plasma concentrations of FK506 and MMF were measured regularly, and the 12 h blood concentration area under the curve (AUC0-12h) was calculated for each drug.Kidney function was assessed with the estimated glomerular filtration rate (eGFR) calculated with the modified Modification of Diet in Renal Disease formula[9].

Pathological examination in kidney allograft

Donor kidney and renal allograft biopsies were performed routinely and when considered clinically necessary. Routine renal allograft biopsy was performed during surgery (before transplantation), and at 6 months, and 1, 2, 3, and 4 years after surgery. Biopsies were also performed when there was episodes of increasing U-RBC,proteinuria and/or a rising SCr levels. All patients were given B-mode ultrasound-guided percutaneous renal biopsy. Needle renal biopsy used oblique needle puncture and negative pressure aspiration. Histological material was examined under light and immunofluorescence microscopy. Biopsies were classified according to Banff'97[10] by another pathologist. The glomerular histological changes included scoring of chronic graft injury[11]. C4d was routinely analysed with immunofluorescence.

Diagnosis of recurrence of IgAN

Based on widespread mesangial proliferation with markedly large, clump deposits of IgA and C3 in mesangial areas of glomeruli.

The diagnosis of renal allograft loss

Graft loss was defined as the loss of kidney function due to acute rejection, chronic rejection and IgAN recurrence and the need for kidney graft removal or maintenance dialysis.

Statistical analysis

SPSS (ver. 13.0) was used for statistical analysis. Continuous data with normal distributions are presented as means ± standard deviations, and discrete data are presented as counts and percentages. Variables with normal distributions were compared with the unpaired t-test, Percentages were compared using the chi-square test. All tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

RESULTS

During the follow-up period of 5 years, there were no significant deference in steroid dosage, FK506 serum trough level and MPA-AUC0-12h concentration. Renal allograft biopsies were performed in 148 kidney transplant recipients who had biopsy proven IgAN as the course of their end-stage renal failure. 46 patients (31.1%) had biopsy-confirmed recurrent IgAN .

Abnormal urine test

U-RBC increased gradually and significantly in the reccurent IgAN group (at the time of transplantation: 2± 1M/ml, at 1 yr after transplantation: 69±11M/ml, at 3 yr after transplantation: 102±19M/ml,polymorphic type,P<0.001, at 5 yr after transplantation: 180±27M/ml, p< 0.0001). The U-RBC at 5 yr after transplantation differed significantly between the groups(Figure 1.). Similarly,the proteinuria also increased gradually and significantly in the reccurent IgAN group (at the time of transplantation: 0.1 ± 0.1 g/d, at one year after transplantation: 0.36±0.14 g/d, at 3 yr after transplantation:0.98± 0.31 g/d, p < 0.01, at 5 yr after transplantation: 2.6± 0.51 g/d, p < 0.001). The proteinuria at 3 yr after transplantation and at 5 yr after transplantation was significantly different between the groups(Figure 2.).

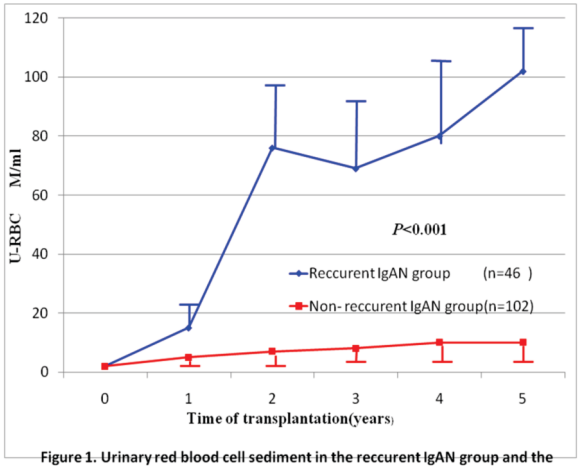

Figure 1. Urinary red blood cell sediment in the reccurent IgAN group and the non-reccurent IgAN group following renal transplantation

Volume : 6 | Issue : 4 | April 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

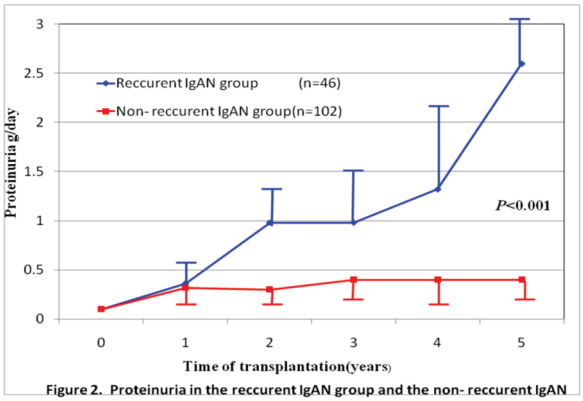

Figure 2. Proteinuria in the reccurent IgAN group and the non- reccurent IgAN group following renal transplantation

Graft dysfunction

The SCr levels increased gradually and significantly in the reccurent IgAN group (at the time of transplantation: 0.91±0.32mg/dl, at 1 yr after transplantation: 1.02±0.32mg/dl, at 3 yr after transplantation: 2.53±0.50 mg/dl,at 5 yr after transplantation: 4.52±1.61mg/dl,p < 0.001). Furthermore, SCr levels at 5 yr after transplantation was significantly different between the groups (Figure 3.). Glomerular filtration rate reduced gradually and significantly in the reccurent IgAN group (at the time of transplantation: 44.81±9.88 ml/min, at 1 yr after transplantation: 55.53±10.09 ml/min, at 3 yr after transplantation: 38.19± 6.69 ml/min, at 5 yr after transplantation: 30.24±9.04 ml/min,p < 0.001). Furthermore, glomerular filtration rate at 5 yr after transplantation was significantly different between the groups (Figure 4.).

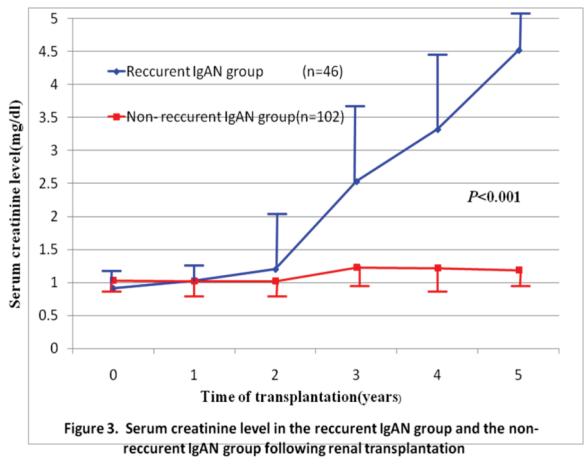

Figure 3. Serum creatinine level in the reccurent IgAN group and the non-reccurent IgAN group following renal transplantation

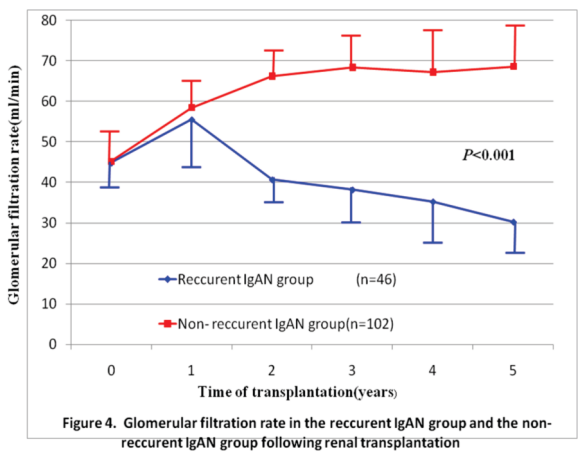

Figure 4. Glomerular filtration rate in the reccurent IgAN group and the non-reccurent IgAN group following renal transplantation

Comparision of adhesion,crescents,segmental sclerosis,global obsolescence,and interstitial fibrosis between the reccurent IgAN group and the non-reccurent IgAN group(Figure 5.). The prevalence of cellular crescents, glomeruli with adhesions(glomerular tuft adhesion to Bowman's capsule against all glomerulus), mesangial cell proliferation, mesangial matrix increase,global sclerosis and glomeruli with segmental sclerosis was significantly greater in the reccurent IgAN group than in the non-reccurent IgAN group(P<0.001), The rate of global obsolescence and the average score of interstitial fibrosis in the reccurent IgAN group were significantly greater than in the non- reccurent IgAN group(P<0.001). Chronic graft injury score was present 7.68±2.27 in the recurrent IgAN group and 4.62±1.44 in the non-recurrent group, P<0.01.

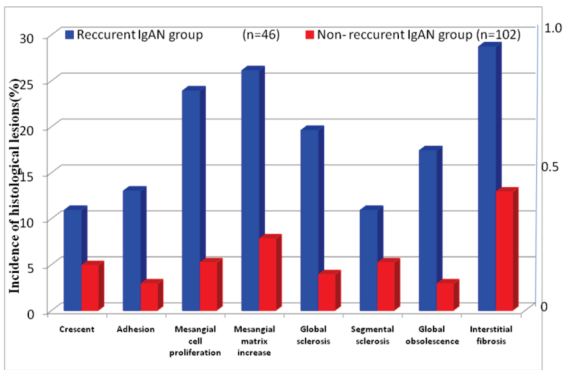

Figure 5. Comparision of histological lesions between the reccurent IgAN group and the non- reccurent IgAN group

Graft Survival by recurrence IgAN

Graft survival both groups was no significant, respectively 93.8% and 95.6% in 1 year and 86.7% and 88.3% in 3 years. But,5 years graft survival rate was lower in the reccurent IgAN group than in the non- reccurent IgAN group (51.4% vs. 83.8%, p< 0.001). However, ten recipients(21.7%) among the 46 patients with recurrent IgAN progressed to graft loss,while graft loss was observed in 9（8.8%）of the 102 recipients in the non-reccurent IgAN group. According to outcome,we divided into two groups: the graft loss group (n=19) and the graft survival group (n= 129). The risk factors that were related with graft survival, such as acute rejection, chronic rejection and tacrolimus nephrotoxicity were summarized(Table 3). The grade of chronic rejection was tended to be higher in the graft loss group than in the graft survival group. Interestingly, incidences of latent IgA deposition from the donor kidney was higher in the graft loss group than in the graft survival group(Table 3).

Table 3. Comparison of histologic features between the graft loss group and the graft survival group

	Graft loss group (n=19)	Graft survival group (n=129)	*P values*
Acute rejection(%)	10.5	11.6	>0.05
Chronic rejection (%)	21.1	22.5	>0.05
Transplant glomerulopathy (%)	10.5	10.8	<0.05
C4d-positive/tested (%)	15.8	15.5	>0.05
tacrolimus nephrotoxicity (%)	15.8	16.3	>0.05

Volume : 6 | Issue : 4 | April 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

The grade of chronic rejection	0.90±0.81	0.19 ± 0.33	<0.001
Latent IgA deposition from the donor kidney (%)	70.9	9.3	<0.001

DISCUSSION

Kidney transplantation is a successful treatment for patients with end-stage renal disease due to IgAN[12]. As for kidney transplantation, tacrolimus and mycophenolate mofetil were introduced improve renal allograft survival[13]. However, one of the largest studies on the risk of graft loss due to recurrent glomerulonephritis revealed that it comes third, after chronic rejection and patient's death[14]. Many recent studies have focused on recurrent IgA nephropathy after kidney transplantation, with rccurent IgAN rates of 24-61%, and rates of graft loos due to IgAN recurrence of 5-23%[15,16]. We found that protocol biopsies revealed an IgAN recurrence rate of 31.1 % in kidney transplant recipients with primary IgAN during the follow-up period, and rates of graft loos due to IgAN recurrence of 21.7%.

In the strict sense, the time of IgAN recurrence after kidney transplantation is different. Because the diagnosis of recurrent IgAN need to have the characteristics of the pre transplant original IgAN, and in the renal allograft and then show the same pathological type. But the above two basic elements in clinical practice, it is difficult to have. Because most of the patients have access to ESRD, there is no pathological diagnosis of the original disease; secondly, some patients with mild proteinuria or microhematuria, often refused to accept renal biopsy, so it is difficult to make accurate judgments. In this study, we have possess the above conditions, we found that the recurrence of IgAN in China was 9.3 + 3.6 months after transplantation. Therefore, it is the key to early and accurate diagnosis of recurrent IgAN in the early diagnosis of renal biopsy in the native kidney,donor kidney and renal allograft.

As in native IgAN, patients with recurrent IgAN can progress through asymptomatic microhaematuria, to proteinuria and a decline in allograf renal function, and then to allograft loss[17]. Rccurent IgAN after kidney transplantation, as well as performance for haematuria, proteinuria and allograft dysfunction. Our data showed that U-RBC and proteinuria increased gradually and significantly in the reccurent IgAN group, in 5 yr after transplantation was significantly different between the rccurent IgAN group and the non-rccurent IgAN. Similarly, the SCr levels increased gradually and significantly and glomerular filtration rate reduced gradually and significantly in the reccurent IgAN group. These results showed microhaematuria, proteinuria after kidney transplantation is the major cause of long-term graft loss in patients with recurrent IgAN.

In primary IgAN, many previous investigators studies revealed that diffuse mesangial proliferation, or severe sclerotic changes such as segmental/global glomerulosclerosis, interstitial fibrosis, and tubular atrophy have been shown to be associated with poor prognosis of the IgAN [18]. However, little has been reported in recurrent IgAN about the histopathologic features and its relationship to the clinical course of the renal allografts. In our investigation,the prevalence of cellular

crescents,glomeruli with adhesions, mesangial cell proliferation, mesangial matrix increase, global sclerosis and glomeruli with segmental sclerosis was significantly greater in the reccurent IgAN group than in the non-reccurent IgAN group. In patients with recurrent or posttransplant IgAN, the formation of glomerular crescents is associated with a poor outcome[19]. The rate of global obsolescence and the average score of interstitial fibrosis in the reccurent IgAN group were significantly greater than in the non-reccurent IgAN group. Global obsolescence and interstitial fibrosis in the reccurent IgAN group is a major pathologic cause of renal allograft loss.

IgAN recurrence is a risk factor for the promotion of glomerular sclerosis. Proteinuria may be associated with glomerular mesangial proliferation and IgA deposition. Proteinuria may be a risk factor for predicting recurrence of IgAN after renal transplantation.Chronic graft injury score was present 7.68±2.27 in the recurrent IgAN group and 4.62± 1.44 in the non-recurrent. The presence of chronic graft injury is a significant predictor of poor outcome[20]. Thus, there is no cure for recurrent IgAN after kidney transplantation, and even the existing immunosuppressive agents are unable to stop the development of IgAN. We noted significantly better outcomes and graft survival rates in the non-recurrent IgAN than in the recurrent IgAN group. Although graft survival both groups was no significant, respectively 93.8% and 95.6% in 1 year and 86.7% and 88.3% in 3 years, 5 years graft survival rate was lower in the reccurent IgAN group than in the non-reccurent IgAN group. Our study has shown that the rate of graft lost from recurrent Ig AN can be high. However, there were no significant deference in the prevalence of chronic rejection, transplant glomerulopathy and C4d-positive betown the graft loss group and the graft survival group. The finding that recurrent Ig AN progresses to ESRD faster than native Ig AN suggests that factors other than the Ig A deposition might be involved[21].

Mesangial IgA deposition on the donor kidney is associated with development of microscopic hematuria, proteinuria, and graft dysfunction in kidney recipients[22,23]. In these patients, the number of donor kidneys with latent IgA deposition was significantly higher in the recurrent IgAN group than in the non-recurrent IgAN group. Similarly,incidences of latent IgA deposition from the donor kidney was higher in the graft loss group than in the graft survival group. However,

latent IgA deposition from donor kidney is the major risk factor for recurrent IgA nephropathy following renal transplantation[24].

REFERENCES

1.BAO Hao, LI Leishi, LIU Zhihong,et al. Clinical and pathological features in patien ts with different subtypes of IgA nephropathy. J Nephrol Dialy Transplant 2006;15(5): 409-415

2.Chen HP, Zeng CH, Hu WX, et al. Analysis of 10594renal biopsy dara. J Nephrol Dialy Transplant 2000;(6):501-508

3.Wang AY, Lai FM, Yu AW, et al. Recurrent IgA nephropathy in renal transplant allografts. Am J Kidney Dis 2001;38:588-596

4.Ramos EL, Tisher CC. Recurrent diseases in the renal transplant. Am J Kidney Diseases 1994;24(1): 142- 154

5.Ponticelli C, Traversi L, Feliciani A, et al. Kidney transplantation in patients with IgA mesangial glomerulonephritis. Kidney Int 2001;60:1948-1954

6. Floege J,Gröne HJ. Recurrent IgA nephropathy in the renal allograft: not a benign condition. Nephrol Dial Transplant. 2013;28(5):1070-1073

7.Díaz-Tejeiro R, Maduell F, Diez J,et al. Loss of renal graft due to recurrent IgA nephropathy with rapidly progressive course: an unusual clinical evolution. Nephron. 1990;54(4):341-3.

8.Han SS, Huh W, Park SK,Impact of recurrent disease and chronic allograft nephropathy on the long-term allograft outcome in patients with IgA nephropathy.Transpl Int. 2010;23(2):169-175.

Volume : 6 | Issue : 4 | April 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

9.Fanny Buron, Aoumer Hadj-Aissa, Laurence Dubourg, et al. Estimating glomerular filtration rate in kidney transplant recipients: performance over time of four creatinine-based formulas. Transplantation 2011;92: 1005–1011

10.Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int 1999;55:713-23

11.Hyeon Joo Jeong,Su-Kil Park,Yong Mee Cho,et al. Progression of renal allograft histology after renal transplantation in recurrent and nonrecurrent immunoglobulin A nephropathy. Human Pathology 2008; 39:1511–1518.

12. Ji Shu-Ming, Xie Ke-Nan, Cheng Dong-Rui, et al. Long-term outcome of kidney transplantation from deceased donors with early graft dysfunction: a single-center analysis. Indian Journal of Applied Research. 2015;5(5):761-764

13.Chhabra D, Skaro AI, Leventhal JR,et al. Long-term kidney allograft function and survival in prednisone-free regimens: tacrolimus/mycophenolate mofetil versus tacrolimus/sirolimus. Clin J Am Soc Nephrol.
2012; 7(3):504-512.

14.Morozumi K, Takeda A, Otsuka Y,et al. Recurrent glomerular disease after kidney transplantation: an update of selected areas and the impact of protocol biopsy. Nephrology (Carlton). 2014;19 Suppl 3:6-10

15.Andrew Woodrffe and Anthony Clarkson. Recurrence of IgA nephropathy in renal transplants. Nephrology 2002; 7:S83–S85

16. Wang BY;Ichimaru N;Kyo M;et al.Effects of tonsillectomy for mesangial immunoglobulin A (IgA) deposition and clinical outcome in five kidney transplant patients with recurrent IgA nephropathy: case report. Transplantation Proceedings,2014;46(2):607-609

17. Von Visger JR;Gunay Y;Andreoni KA,et al.The risk of recurrent IgA nephropathy in a steroid-free protocol and other modifying immunosuppression Clinical Transplantation, 2014; 28(8):845-854

18.Andresdottir MB, Hoitsma AJ, Assmann KJ,et al. Favorable outcome of renal transplantation in patients with IgA nephropathy. Clin Nephrol. 2001;56(4):279-288

19.Tang Z, Ji SM, Chen DR,et al. Recurrent or De Nevo IgA Nephropathy with crescent formation after renal transplantation. Ren Fail. 2008;30(6):611-616

20. Koshino K, Ushigome H,Sakai K,et al. Outcome of tonsillectomy for recurrent IgA nephropathy after kidney transplantation. Clinical Transplantation,2013,27(Sup 26):22-28

21. Berthelot L,Robert T, Vuiblet V,et al.Recurrent IgA nephropathy is predicted by altered glycosylated IgA, autoantibodies and soluble CD89 complexes.Kidney International, 2015, 88(4): 815-822

22.JI Shuming,LU Min,CHEN Jinsong,et al. The fate of glomerular mesangial IgA deposition in the donated kidney after allograft transplantation. Clin Transplantation 2004;18:536-540

23.Sofue T, Inui M, Hara T, et al. Association between post-transplantation immunoglobulin A deposition and reduced allograft function.Transplant Proc. 2015;47(2):332-36

24. Sato K,Ishida H,Uchida K,at el.Risk factors for recurrence of immunoglobulin A nephropathy after
renal transplantation: single center study. Therapeutic Apheresis and Dialysis 2013; 17(2):213–220