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ORIGINAL ARTICLE

The Prevalence, Rainbow of Histological Features and Initial Clinical Presentation of Post-Transplant IgA Nephropathy

HANZLA MARYAM[1], MUDASSAR HUSSAIN[2], AURANGZEB AFZAL[3], USMAN HASSAN[4], SHEEBA ISHTIAQ[5]
[1,2,4]*Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan*
[3]*Department of Nephrology, Services Hospital, Lahore, Pakistan*
[5]*Department of Pathology, Gulab Devi Chest Hospital, Lahore, Pakistan*
Correspondence: Dr. Hanzla Maryam, Email: hanzlamaryam786@gmail.com Cell: 0300-5013232

ABSTRACT

Background: IgA nephropathy is the most common primary glomerulopathy which is characterized by the presence of prominent IgA deposits in the mesangial regions.
Aim: To compare the clinical and histological features of pre and post- transplant IgA nephropathy patients.
Methods: A descriptive retrospective study. Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, between 1st January 2016 and 30th September 2022. Forty eight cases of pre-transplant and 20 cases of post-transplant IgA nephropathy were enrolled. The biopsies included at least one core submitted in 10% buffered formalin and one core in normal saline. The formalin-fixed tissue was embedded in paraffin and cut at 4mm thickness, followed by staining with hematoxylin, eosin, PAS, JMS, and Trichrome stains. Immunofluorescence was performed on the tissue in normal saline. All biopsy was evaluated for the MEST-C score. Patients were also evaluated for proteinuria and hematuria; we categorized hematuria as mild (3-20 red blood cells per microliter of urine), moderate (20-50 red blood cells per microliter of urine), and severe (above 50 red blood cells per microliter of urine). Proteinuria was divided as sub-nephrotic range proteinuria and nephrotic range proteinuria.
Results: The 90% of patients were male and 10% were female, and the highest proportion of post-transplant patients (45%) were between 35 and 45 years old. 25% of patients experienced significant hematuria, and an equal percentage (25%) experienced mild to moderate hematuria. 40% of patients experienced nephrotic range proteinuria, and 20% had sub-nephrotic range proteinuria. Histological evaluation of renal biopsies of these patients demonstrated M1 lesions in 75% of patients, S1 lesions in 65% of patients, and T1 lesions in 45% of patients. Among the patients with pre-transplant IgA nephropathy, 70% were male, 27% were female, and 45% of patients were below the age of 25. 30% of patients experienced severe hematuria, while 36% experienced mild to moderate hematuria. 42% of the patients had nephrotic range proteinuria and 40% had sub-nephrotic range proteinuria. Histological evaluation of their renal biopsies demonstrated M1 lesions in 94% of the pre-transplant patients, S1 lesions in 90%, and E1 lesions in 27% of cases.
Practical Implication: The high significance in implementing the service care delivery to the kidney transplant patient as by critically assessing the urine testing predictors, biopsy results and patient gender as well as age the IgA nephropathy risk can be reduced.
Conclusion: The combination of proteinuria and hematuria assessment could provide an important insight of disease recurrence in kidney transplant patients. Moreover, the results emphasize the importance of carefully monitoring transplant patients with high M-scores and T-scores, especially those with S1 scores, to ensure early detection and management of disease recurrence.
Keywords: Prevalence, Histological features, Clinical presentation, Post-transplant IgA nephropathy

INTRODUCTION

As a pathologist, it is essential to understand the complexities of IgA nephropathy, the most common primary glomerulopathy globally. This disease is characterized by the presence of IgA deposits in the mesangial regions, and can affect individuals of any age. The disease affects people of any age, but older children and young adults are most commonly affected. Many patients present with gross hematuria after infection of the respiratory, gastrointestinal, or urinary tract. Many patients maintain normal renal functions for decades; however, slow progression to chronic renal failure can occur. Recurrence of IgA in transplanted kidneys is frequent. In primary IgAN, many clinic-pathological 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 disease. 1

When patients with IgA nephropathy present, they often have gross hematuria following an infection of the respiratory, gastrointestinal, or urinary tract. While some patients maintain normal renal function for decades, others experience slow progression to chronic renal failure. It is worth noting that the recurrence of IgA in transplanted kidneys is frequent[2].

The patients receiving kidney transplants are prone to various complications, including the risk of kidney failure due to IgA nephropathy, The IgA deposits can be presented in the transplanted kidney. The IgA nephropathy can be recurring in carious cases due to different reasons, including mild hematuria/ proteinuria as well as rapidly decreasing kidney function. Various reaches have elaborated the recurrence rate of IgA nephropathy between 9% and 61%. The diversity within the recurrence rate is mainly due to various biopsy protocols applying as well as differences in the follow-up time[2,3].

The IgA nephropathy usually establishes over years post transplantation. Literature has elaborated on the fact that longer follow-up studies present reduced survival rates, such as after 5–10 years[4]. Studies have also detailed that in many cases the graft is lost as a consequence of recurrent IgA nephropathy. The incidence has been reported in 2% to 14% of the patients.3 In younger cases, the IgA nephropathy has been considered a high-risk post transplantation. Transplants without induction agents as well as increased HLA-mismatch and withdrawal of steroids at an early time are also considered risk factors initiating IgA nephropathy[5-12].

Research has shown that in primary IgAN, diffuse mesangial proliferation or severe sclerotic changes such as segmental/global glomerulosclerosis, interstitial fibrosis, and tubular atrophy are associated with a poor prognosis for the disease. However, little has been reported in post-transplant IgAN regarding the relationship between histopathological features and the clinical course of the allograft kidneys[13].

Therefore, the purpose was to explore and report the histological characteristics of post-transplant IgAN. Through this research, we hope to understand better the disease and its impact on patients who have received a kidney transplant[14].

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MATERIALS AND METHODS

This descriptive retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, between 1st January 2016 and 30th September 2022. The research was ethically approved by the intuitional review board. A total of 68 cases were enrolled, wherein the first group had 48 cases of pre-transplant and the second group had 20 cases of post-transplant IgA nephropathy were enrolled. The sample size was calculated using a web-based sample size calculator with a 95% CI, 80% power of test, and 5% margin of error. The kidney biopsy from 20 patients was collected by experienced post-transplant IgA5 nephropathy; however, the results of the initial renal biopsy from these patients were not recovered due to various reasons, which include lack of patients' education, loss of previous records, and demise of patients. This, in turn, limits our evaluation of whether these patients are experiencing a recurrence or this is a case of de-novo IgA nephropathy. The biopsy results of 48 pre-transplant IgA nephropathy patients to better understand the variances between two groups were also collected. The biopsies included at least one core submitted in 10% buffered formalin and one core in normal saline. The formalin-fixed tissue was embedded in paraffin and cut at 4mm thickness, followed by staining with hematoxylin, eosin, PAS, JMS, and Trichrome stains. Immunofluorescence was performed on the tissue in normal saline. All biopsies were evaluated for the MEST-C score, which involves scoring four histopathological features: Mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), and tubular atrophy-interstitial fibrosis (T). Mesangial hypercellularity (M) was defined as an increased number of mesangial cells per unit of mesangium and was scored M0 if less than 50% of glomerulus was involved and M1 if more than 50% of glomerulus was involved. Endocapillary hypercellularity (E) was defined as the proliferation of cells within the glomerular capillaries sufficient enough to cause luminal narrowing. Cases without endocapillary proliferation were scored E0, and those with endocapillary proliferation were scored E1. Segmental Sclerosis (S) was defined as the obliteration of lumina by fibrosis, involving less than 50% of the glomeruli. Cases without segmental sclerosis were scored S0, and those with segmental sclerosis were scored S1. Tubular Atrophy-Interstitial Fibrosis (T) was defined as the presence of atrophic tubules characterized by simplification of the cuboidal lining, flattening of lining cells, loss of lining cells, and/or thyroidization of tubules in a matrix increased by fibrosis. This parameter was scored according to the percentage of the cortex involved: T0 (less than or equal to 25%), T1 (26 to 50%), and T2 (more than 50%). The C score was assigned as follows: C0 (no crescents), C1 (crescents in >0% to <25% glomeruli), C2 (>25% of glomeruli). The data was analyzed through SPSS-25 by using mean and standard deviation for quantitative variables and frequency and percentage for the qualitative variables. Chi square was used for the analysis of the comparative variable, with a p value of <0.001 as significant.

RESULTS

There was a higher number of males than females in both groups, with 90% males in the post-transplant group and 73% in the pre-transplant group. The mean age of the pre-transplant cases was as 26.7±3.5 years while of the post-transplant cases it was 39.9±3.9 years. The MESCT score and urinary testing were performed in all cases, and it was observed that mesangial hypercellularity (M-score) was M0 in 6% and 25% in 1st and 2nd groups, respectively. M1 was 94%, and 75% in both groups, respectively. The endocapillary hypercellularity (E-score) was E0 in 73% and 65% in 1st and 2nd groups, while the rest was E1. Segmental sclerosis (S-score) presented S0 was only in 10% of the pre-transplant group and 35% in the post-transplant group. Tubular atrophy-interstitial fibrosis (T-score) was greatest in the T1 group, with 44% in pre-transplant and 45% in post-transplant cases. Cres-cents (C-score) were absent (C0) in 75%, of pre transplant and 70% post transplant cases and found in severity (C2) in 6% pre-transplant and 10% post transplant cases, respectively (Table 1). The comparative age analysis within the pre- and post transplant cases showed a trend of earlier age IgA nephropathy cases in pre-transplant cases, while within the post transplant more older cases with an increased trend in age were observed (Fig. 1). Within the urinary test comparative analysis, it was observed that the majority of the cases within the pre transplant were unknown of hematuria, while within the post transplant majority (35%) were not having hematuria. The severity of hematuria was observed in 30% and 25% of pre and post transplant cases, respectively. Proteinuria was presented in 82% of the pretransplant cases while in 60% of the post transplant cases; however, there were 25% of the post-transplant cases having nil proteinuria (Table 2).

The histological slides presented M1 lesion, PAS. The lesions had a mesangial hypercellularity (>4 cells/mesangial space) in pre-transplant IgA nephropathy cases, while in S1 lesion H&E, globally sclerotic glomeruli and interstitial inflammation in pre-transplant IgA nephropathy were observed. Further the C1 lesion, PAS presented >2 layers of parietal epithelial cells within the urinary space. In the segments ofE1 lesion, H and E the capillary loops were infiltrated by inflammatory cells, while M1, T1 lesion, PAS were having mesangial hypercellularity and tubular atrophy, which was also highlighted by PAS in post-transplant IgA nephropathy. The C4d was negative in arterioles with a background non-specific staining in glomeruli and tubules. The mesangial expansion and loop adhesions on Jones silver in post-transplant IgA nephropathy were observed. The IgA antibody showed mesangial deposits in the post-transplant renal biopsy. In addition to this, the immunofluorescence pattern demonstrated positivity with the C3 antibody (Fig. 2).

Table 1: Comparison of demographics, MEST-C score, between pre and post-transplant patients

Demographics		Pre-Transplant 48 Patients	Post-transplant 20 patients	P value
Gender	Male	73%	90%	0.456
	Female	27%	10%	
Age	<=25	46%	15%	<0.001
	>25,<=35	23%	25%	
	>35,<=45	17%	45%	
	>45	15%	15%	
MEST-C Score				
M-Score	M0	6%	25%	0.004
	M1	94%	75%	
E-Score	E0	73%	65%	0.565
	E1	27%	35%	
S-Score	S0	10%	35%	<0.001
	S1	90%	65%	
T-Score	T0	33%	25%	0.453
	T1	44%	45%	
	T2	23%	30%	
C-Score	C0	75%	70%	0.675
	C1	19%	20%	
	C2	6%	10%	

Table 2: Comparison of hematuria and proteinuria between pre and post-transplant patients

Urinary Testing	Pre-Transplant 48 Patients	Post-transplant 20 patients	P value
Hematuria			
Unknown	28%	15%	0.032
Nil	6%	35%	
Mild	19%	25%	
Moderate	17%	-	
Severe	30%	25%	
Protenuria			
Unknown	17%	15%	<0.001
Nil	2%	25%	
Nephrotic	42%	40%	
Subnephrotic	40%	20%	

Fig. 1: Comparison of percentage of pre and post-transplant IgA nephropathy patients among various age groups

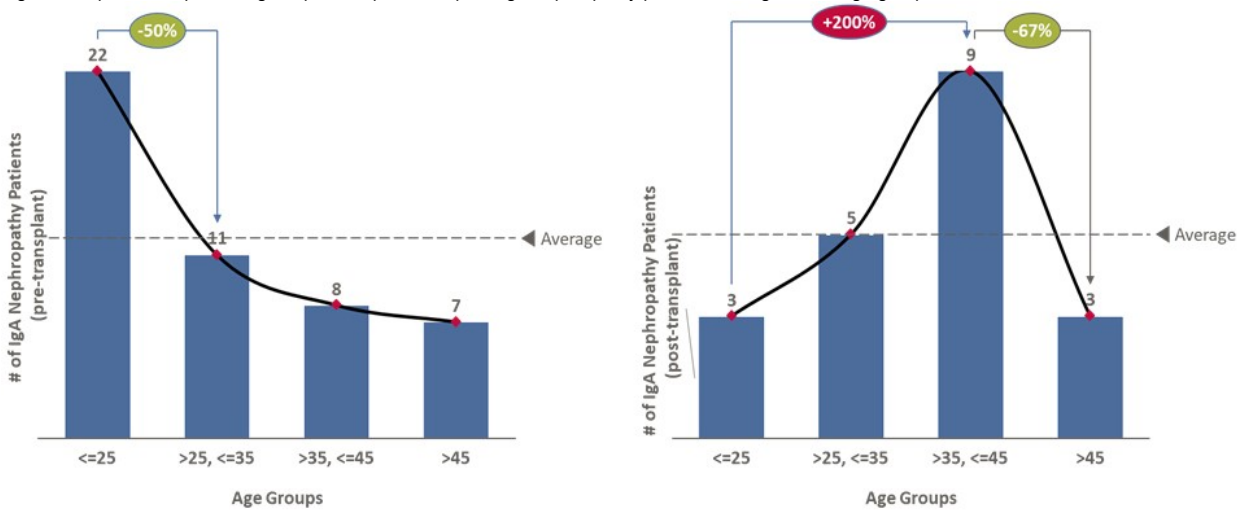
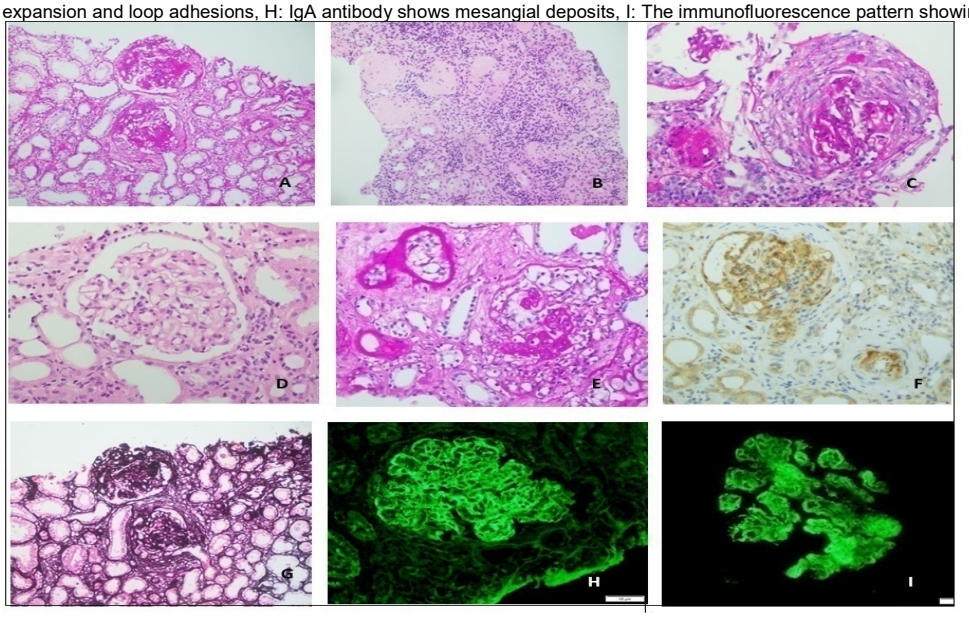


Fig. 2: A: M1 lesion, PAS, B: S1 lesion, H&E, C: C1 lesion, PAS, D: E1 lesion, H&E, E: M1, T1 lesion, PAS, F: C4d, negative in arterioles, G: Mesangial expansion and loop adhesions, H: IgA antibody shows mesangial deposits, I: The immunofluorescence pattern showing positivity with C3 antibody



DISCUSSION

The present study has highlighted the significance of male diversity in developing the IgA nephropathy in pre- and post transplant cases. At the same time, it must be significantly highlighted that within various cultures, the female may be underreported and treated. The current study also highlights the variance in age distribution between the two groups, wherein younger adults are prone to IgA nephropathy in pre transplantation and middle-aged men and women are at higher risk of IgA post transplant nephropathy. Similar results have been reported in researches over the globe. These findings highlight the importance of closely monitoring former kidney transplant patients in this age group, given their higher risk of disease occurrence in this limited sample size. 15-17

The hematuria formation in pre- and post transplant patients of the current study revealed that only 30% of patients experienced significant hematuria (also reported macroscopically, that is, gross hematuria) in pre-transplant cases, while only 25% of post-transplant patients experienced significant hematuria. In the present study results, the analysis of proteins in the urine samples was additionally measured and observed for better insights into the disease of kidney transplant patients. The results interpreted 42% and 40% of the pre- and post transplant patients had nephrotic range proteinuria, respectively. The combination of proteinuria and hematuria assessment could provide an even more accurate prediction of disease recurrence in kidney transplant patients. 7 Insight in hematuria and proteinuria can beneficially develop effective strategies for preventing and managing disease recurrence in these patients[15].

The M-score emerged as a powerful prognostic indicator of IgA nephropathy, with its predictive capability matched only by the T-scores. The present study results of biopsies revealed that within pre-transplant patients, 94% vs. 44% scored M1 vs. T1, and only 6% scored M0. In the post-transplant patients, 75% vs 45% scored M1 vs T1 while only 25% scored M0. Among the post-transplant patients, 30% were scored at T2, while in pre-transplant, 23% scored at T2. In addition, the S score was also found to be a

significant indicator within post-transplant patients. A majority of the pre- and post-transplant patients, such as 60% vs. 90%, scored S1, while the remaining scored S0, thereby, emerging as a strong prognostic tool for IgA nephropathy. Conversely, the E-score and C-score were found to be less reliable indicators, with 73% of pre-transplant patients scoring E0 and 75% scoring C0, while 65% of post-transplant patients were presented with E0 and 70% with C0. These findings suggest that the M-score and T-scores are strong predictors of disease recurrence, while the S-score may also provide valuable insights. The E-score and C-score, however, may have limited utility in predicting the disease[18]. The results emphasize the importance of carefully monitoring transplant patients with high M-scores and T-scores, especially those with S1 scores, to ensure early detection and management of disease recurrence. The present study results were in coordination with the previous studies conducted[18,19].

The current research elaborated that the duration of the first kidney transplant and IgA nephropathy are the most critical with disease occurrence, with a negative correlation between progression time and the risk of IgA nephropathy formation[17-22].

CONCLUSION

Middle-aged males who had their first kidney transplant within the last 4 years are at a higher risk of developing IgA nephropathy. The levels of hematuria and protein urea levels, are critical predictors of disease recurrence. Kidney biopsies need to be performed and closely reviewed for M, S, and T scores to gain a more accurate prediction.

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1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

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