

# Pathological assessment of allograft nephrectomy: An Iranian experience

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**Background:** The aim of this study was to determine the pathologic causes of renal allograft failure in transplant nephrectomy specimens. **Materials and Methods:** In this cross-sectional study performed in the referral transplant center of Isfahan, Iran, medical files of all patients who underwent nephrectomy in 2008–2013 were studied. Age at transplantation, sex, donor's characteristics, causes of primary renal failure, duration of allograft function, and pathologic reasons of nephrectomy were extracted. Slides of nephrectomy biopsies were evaluated. Data were analyzed using SPSS. **Results:** Medical files of 39 individuals (male: 56.4%; mean age: 35.1 ± 16.0 years) were evaluated. The main disease of patients was hypertension (17.9%), and most cases (64.1%) were nephrectomized < 6 months posttransplantation. Renal vein thrombosis (RVT) (51.3%) and T-cell-mediated rejection (TCMR) (41.0%) were the most prevalent causes of transplanted nephrectomy. Cause of primary renal failure was correlated to nephrectomy result ( $P = 0.04$ ). TCMR was the only pathologic finding in all of patients nephrectomized >2 years posttransplantation. There were 14 cases in which biopsy results showed a relationship between primary disease of patients and pathologic assessment of allograft ( $P = 0.04$ ). A significant relationship between transplantation-nephrectomy interval and both the nephrectomy result and histopathologic result existed ( $P < 0.0001$ ). A relationship between primary allograft biopsy appearance and further assessment of nephrectomized specimen ( $P < 0.001$ ) existed as well. **Conclusion:** The most pathologic diagnoses of nephrectomy in a period of less than and more than 6 months posttransplantation were RVT and TCMR, respectively. Early obtained allograft protocol biopsy is suggested, which leads to better diagnosis of allograft failure.

**Key words:** Allograft nephrectomy, chronic T-cell-mediated rejection, kidney transplantation, renal vein thrombosis

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## INTRODUCTION

The increasing number of end-stage renal disease (ESRD) patients clarifies the importance of choosing the best treatment strategies, among which renal transplantation helps most of ESRD patients. Renal transplantation improves quality of life and consequently survival rate of these patients.<sup>[1]</sup>

However, transplanted kidneys do not act properly lifelong, and it should be considered that, although the outcome of the procedure has improved dramatically in the last decades, current data indicate that rate of graft failure is 10% in the 1<sup>st</sup> year, and 3%–5% each year afterwards.<sup>[2,3]</sup> Failure in allograft-transplanted kidney is associated with a high rate of morbidity and mortality, mainly due to inflammatory and infectious reactions.<sup>[4,5]</sup> The causes of graft failure include renal vein thrombosis (RVT), renal artery occlusion, acute rejection refractory to treatment, and sepsis.<sup>[6]</sup>

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A question is raised whether transplanted nephrectomy (TN) should be done in failed allografts or not. There are controversies regarding proper management of renal allograft failure. A nonfunctional kidney, i.e., the failed allograft inside the body, can present with elevated levels of c-reactive protein, malnutrition, hypoalbuminemia, and elevated erythrocyte sedimentation rate caused by chronic inflammatory reactions.<sup>[5,7,8]</sup> However, nephrectomy procedure of failed allografts would also lead to bleeding and infection among all, which may lead to high rates of morbidity and mortality.<sup>[9]</sup> There is also another approach considering the time of graft failure, meaning that TN is a more favorable approach for cases with early graft failure, but not for late graft failure cases.<sup>[6]</sup>

Knowledge about the etiology of graft failure has a potential role, not only in the prevention of the failure but also in helping the physicians to act properly against it. The etiologies of graft failure are not similar in different populations, and knowledge regarding this issue would consequently improve the outcome of renal transplantation. The aim of this study was to determine the pathologic causes of renal allograft failure divided into early and late period after transplantation in our referral transplant center.

## MATERIALS AND METHODS

This cross-sectional study was performed in the Pathology Department of Alzahra Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. The protocol of this study was reviewed by the Pathology Review Board and Ethics Committee of Isfahan University of Medical Sciences (#393364).

In this study, medical files of all patients who underwent TN in the referral transplant center of Isfahan provinces from March 2008 to March 2013 were studied. Patients with complete documents were followed, and those who were not available or did not have enough cooperation in completing the documents were excluded from the study.

Tissue slides of patients with TN were retrieved from the archives of the Department of Pathology of our center. Detailed information of each patient including age at transplantation, sex, body mass index, donor's characteristics, causes of primary renal failure, duration of allograft function, and pathologic reasons of TN was extracted from their medical files and recorded in a checklist. Slides of histopathologic and allograft biopsies were reevaluated by an expert nephropathologist, who was blinded to results by random numbering of biopsy and TN slides, which was performed by the laboratory technician.

Previous similar studies divided allograft failures into early (<1-year posttransplantation) and late (>1-year posttransplantation);<sup>[10,11]</sup> however, patients in our study were categorized in terms of transplantation-rejection interval in four subgroups as follows: 6 months and less, 6–12 months, 1–2 years, and >2 years.

## Statistical analysis

Data were analyzed using SPSS statistical software version 13.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for continuous and categorical variables. The computed statistics included mean and range for continuous variables and frequencies and relative percentages for categorical factors. To compare qualitative variables between groups, Chi-square test was performed. Considering the time interval between transplant and nephrectomy as a continuous variable, one-way ANOVA was used to evaluate its relation to nephrectomy result and pathologic TN diagnosis. Two-tailed  $P < 0.05$  was considered statistically significant.

## RESULTS

Medical files of 39 individuals aged 9–65 years old were evaluated in this study, of which 22 (56.4%) were male and 17 (43.5%) were female. Mean age and body mass index of participants were  $35.1 \pm 16.0$  years and  $23.5 \pm 8.9$  kg/m<sup>2</sup>, respectively. General characteristics of patients are illustrated in Table 1. As illustrated in Table 1, the main primary disease of patients that lead to ESRD was hypertension (7 cases; 17.9%) and most of the patients (25 cases; 64.1%) were nephrectomized in a time interval of < 6 months posttransplantation.

Regardless of posttransplantation time of TN, vascular complications (RVT) (51.3%) were the most prevalent pathologic cause of TN [Table 2]. Chronic T-cell-mediated rejection (TCMR) as the second pathologic cause of TN was diagnosed in 16 patients (41.0%). Although pathologic assessment of allograft nephrectomized specimen extracted from the body < 6 months posttransplantation showed RVT in most cases, chronic TCMR was the only pathologic report for all of patients nephrectomized > 2 years posttransplantation.

As shown in Table 3, after evaluating the 39 cases, nephrectomy result was not correlated to age, sex, or type of donor; however, cause of primary renal failure was correlated to nephrectomy result ( $P = 0.04$ ). There were 14 out of 39 cases in which biopsy was done before TN. Pearson's correlation test showed that there is no relationship between sex ( $P = 0.1$ ), age ( $P = 0.8$ ), and type of donor ( $P = 0.06$ ) and pathologic diagnosis of allograft dysfunction which led to nephrectomy; however, there was a relationship between primary disease of patients and pathologic assessment of

**Table 1: Characteristics of patients with renal allograft failure who underwent transplant nephrectomy**

Patient characteristics	n (%)
Age group (years old)	
≤21	9 (23.1)
22-50	20 (51.3)
≥50	10 (25.6)
Sex	
Female	17 (43.6)
Male	22 (56.4)
Cause of primary renal failure	
Hypertension	7 (17.9)
Nephrocalcinosis	6 (15.4)
Glomerulonephritis	5 (12.8)
Diabetes mellitus	5 (12.8)
Infectious disease	2 (5.1)
Congenital malformation	2 (5.1)
Vesicoureteral reflux	2 (5.1)
Alport syndrome	2 (5.1)
Urinary tract infection	1 (2.6)
Cystinuria	1 (2.6)
Systemic lupus erythematosus	1 (2.6)
Unknown	5 (12.8)
Type of donor	
Living unrelated donor	18 (46.2)
Living related donor	15 (38.5)
Donation after brain death	6 (15.4)
Duration of allograft function	
≤6 months	25 (64.1)
6-12 months	1 (2.6)
1-2 years	3 (7.7)
>2 years	10 (25.6)

**Table 2: Distribution of pathologic diagnoses of allograft nephrectomy**

Duration of allograft function	Pathologic diagnosis of allograft dysfunction	n (%)	Total (%)
6 months and less	Renal vein thrombosis	19 (76)	25 (100)
	TCMR	3 (12)	
	Primary hyperoxaluria	3 (12)	
6-12 months	TCMR	1 (100)	1 (100)
1-2 years	Renal vein thrombosis	1 (50)	2 (100)
	TCMR	1 (50)	
>2 years	TCMR	11 (100)	11 (100)
Total	Renal vein thrombosis	20 (51.3)	39 (100)
	TCMR	16 (15.4)	
	Primary hyperoxaluria	3 (7.7)	

TCMR=Chronic T-cell-mediated rejection

nephrectomized allograft ( $P = 0.04$ ). Statistical analysis showed a significant relationship between mean time after transplantation to nephrectomy and both the nephrectomy result and histopathologic appearance of the nephrectomy specimen ( $P < 0.0001$ ) [Table 3].

A comparison between pathologic reports of allograft biopsies (performed on 14 cases) and allograft nephrectomy

is reported in Table 4 and revealed six biopsy-proven cases of infarcted renal cortical tissue that showed RVT in allograft nephrectomy specimen. Cases of TCMR had a similar pathologic diagnosis in TN specimen. Two cases showing acute tubular necrosis (ATN) regarding pathologic assessment of allograft biopsy further showed RVT, while another biopsy-proven case of ATN showed severe necrosis in background of TCMR in nephrectomy specimen. Pearson's Chi-square test revealed a relationship between primary allograft biopsy pathologic appearance and further assessment of nephrectomized specimen ( $P < 0.001$ ).

## DISCUSSION

Diagnosis of histopathologic changes damaging the allograft kidney is important, especially in diseases with recurrent features such as glomerulonephritis;<sup>[12]</sup> however, the biopsy is not necessarily obtained in all cases of allograft failure.<sup>[11]</sup> This issue would limit our information about the majority of pathologic processes of graft failure. Assessment of pathologic causes leading the allograft kidney to be nephrectomized was the major purpose of this study.

Regarding evaluation of histological changes in kidney transplant failure, a study on 1365 allograft indication biopsies showed that acute TCMR and acute antibody-mediated rejection had an independent association with graft survival; however, transplant glomerulopathy was considered as a main risk of allograft failure.<sup>[13]</sup> A study on a large number of failed kidney grafts showed the clinical and histological causes of failure as the following: glomerular disease, fibrosis and atrophy (which was not only limited to calcineurin inhibitor toxicity), and medical or surgical conditions.<sup>[14]</sup>

A previous study in our country comparing the clinical and pathologic causes of kidney allograft failure revealed necrosis concomitant with RVT as the most prevalent pathologic cause of graft failure in 2-week post-transplant nephrectomized allografts; however, necrosis was suggested as the main pathologic feature in 1–2-year post-transplant nephrectomized allografts.<sup>[15]</sup> Most of our patients were nephrectomized in a time period of < 6 months posttransplantation. In contrast to our data, in the aforementioned study, most of the graft nephrectomies were operated after 2 years posttransplant. Despite our findings, another retrospective study of sixty cases of TN also revealed that most nephrectomies were performed > 6 months posttransplantation, and chronic rejection was the most common pathologic finding of allograft failure.<sup>[16]</sup>

Commonly occurring during the 1<sup>st</sup>-week posttransplantation,<sup>[17]</sup> RVT is not considered as a common complication of kidney transplantation, but when occurs

**Table 3: Distribution of clinical and pathologic diagnoses of allograft nephrectomy across different patient characteristics**

	Biopsy result (n=14)				P	Nephrectomy result (n=39)			P
	TCMR	Hyperoxaluria	Infarcted	ATN		RVT	Hyperoxaluria	TCMR	
Age group (years)									
≤21	1	1	1	1	0.8	3	1	5	0.5
22-50	2	1	3	1		10	2	8	
≥50	0	0	2	1		7	0	3	
Sex									
Male	0	2	3	2	0.1	12	3	7	0.2
Female	3	0	3	1		8	0	9	
Cause of primary renal failure									
Hypertension	2	0	0	1	0.04	3	0	4	0.04
Nephrocalcinosis	0	2	1	0		2	3	1	
Glomerulonephritis	0	0	0	0		5	0	0	
Diabetes mellitus	0	0	2	0		4	0	1	
Infectious disease	0	0	0	0		0	0	2	
Congenital malformation	0	0	0	0		1	0	1	
Vesicoureteral reflux	0	0	0	0		0	0	2	
Alport syndrome	0	0	0	1		1	0	1	
UTI	0	0	0	0		0	0	1	
Cystinuria	0	0	0	0		0	0	1	
Systemic lupus erythematosus	1	0	0	1		0	0	1	
Unknown	0	0	3	0		4	0	1	
Type of donor									
Living-U	1	1	5	0	0.5	8	1	9	0.06
Living-R	1	1	1	0		9	2	4	
Cadaveric	1	0	0	3		3	0	3	
Transplantation-nephrectomy interval (days), mean±SD	3163.3±759.8	75.0±21.2	17.7±9.6	26.3±9.3	<000.1	67.9±160.5	57.0±34.6	2169.6±1767.7	<000.1

All data reported in numbers, unless expressed otherwise. TCMR=Chronic T-cell mediated rejection; RVT=Renal vein thrombosis; Infarcted: Infarcted renal cortical tissue; UTI=Urinary tract infection; Living-U=Living unrelated donor; Living-R=Living related donor; Cadaveric=Donation after brain death; ATN=Acute tubular necrosis; SD=Standard deviation

**Table 4: Comparison between biopsy and nephrectomy pathologic results**

Sex	Age (years)	Donor type	Primary disease	Transplantation-biopsy interval	Biopsy result	Transplantation-nephrectomy interval	Nephrectomy result
Male	32	Living-U	Unknown	3 days	Infarcted*	9 days	RVT
Male	22	Living-R	Nephrocalcinosis	22 days	ATN-oxalate	2 months	1° hyperoxaluria
Female	9	Living-U	Unknown	7 days	Infarcted	20 days	RVT
Male	46	Living-U	DM	3 days	Infarcted	10 days	RVT
Male	51	Cadaveric	HTN	3 days	Severe ATN	20 days	RVT
Female	52	Living-R	DM	29 days	Infarcted	32 days	RVT
Male	62	Living-U	Nephrocalcinosis	9 days	Infarcted	25 days	RVT
Female	44	Living-U	Unknown	6 days	Infarcted	10 days	RVT
Male	31	Cadaveric	Alport syndrome	7 days	ATN	37 days	RVT
Female	20	Cadaveric	SLE	14 days	ATN	22 days	Severe necrosis + TCMR
Male	16	Living-U	Nephrocalcinosis	10 days	ATN-oxalate	90 days	1° hyperoxaluria
Female	49	Cadaveric	HTN	9 years	TCMR	11 years	TCMR
Female	14	Living-R	Vesicoureteral reflux	6 years	TCMR	7 years	TCMR
Female	25	Living-U	HTN	7 years	TCMR	8 years	TCMR

\*Infarcted: Infarcted renal cortical tissue. RVT=Renal vein thrombosis; TCMR=Chronic T-cell-mediated rejection; DM=Diabetes mellitus; Living-U=Living-unrelated donor; Living-R=Living-related donor; Cadaveric=Donation after brain death; ATN=Acute tubular necrosis; ATN-oxalate=ATN with extensive oxalate deposition; 1°=Primary; SLE=Systemic lupus erythematosus; HTN=Hypertension

it may deteriorate the transplanted kidney and lead to allograft failure which is especially seen in cases of

complete RVT.<sup>[18-20]</sup> Ariyarathenam *et al.* designed a recent study on 42 cases of TN that, similar to our findings,

showed 43% of cases were nephrectomized in the 1<sup>st</sup>-week posttransplantation time, and “graft thrombosis related to technical issues during transplantation surgery” was reported to be the most common indication of TN.<sup>[21]</sup> Our pathologic data are in line with their studies in terms of clinical indication of TN, which revealed RVT as the most common complication of transplantation leading to TN. RVT is mostly reported as an immediate postoperative period complication which may be caused by surgical technical matters, antiphospholipid syndrome, thrombosis of iliac axis, trauma, hypovolemia, and compression caused by perinephric fluid collection.<sup>[18,22]</sup> Thrombophilic state caused by increased plasma procoagulant factor activity in the group of peritoneal dialysis-treated patients also leads to higher risk of posttransplantation RVT occurrence.<sup>[23]</sup> After renal transplantation, both acute and chronic RVT may occur.<sup>[22]</sup> The high prevalence of cases of RVT that causes TN emphasizes the importance of technical accuracy and other aforementioned considerations to preserve the allograft inside the body.

In our study, there were several cases which had a previous indication biopsy before nephrectomy and their biopsy showed infarcted renal cortical tissue that prospectively correlated with the diagnosis of RVT in the pathological assessment of TN specimen.

Our previous study on renal allograft biopsies showed that, considering Banff classification, interstitial fibrosis and tubular atrophy and ATN were the most common histopathological pattern on obtained biopsies.<sup>[24]</sup> Necrosis of individual tubular epithelial cells and loss of brush borders in proximal tubules are two major characteristics of ATN,<sup>[25]</sup> whereas sloughing of cells into the tubular lumen and tubular casts consists of protein, tubular debris may also present.<sup>[26]</sup> It is said that ATN would be the dominant histologic pattern of RVT, and RVT should be considered as a probable diagnosis in cases of widespread and uniform ATN, especially those with extensive tubular damage.<sup>[27]</sup> There were also two cases of ATN assessed in biopsy that later read as RVT in TN specimen meaning that there are differential diagnoses between above topics which clarify the need for correlation between pathologic, clinical, and radiological aspects of any patients with deterioration of allograft kidney.

TCMR as another entity discussed in this manuscript is related to the chronic allograft damage. All of our patients who were nephrectomized after 2-year posttransplantation and most of them after 6-month posttransplantation had a pathological diagnosis of TCMR. Assessment of histologic pattern of TCMR on allograft kidney is necessary: interstitial inflammation and tubulitis are two principal lesions seen in TCMR which can also present in other injuring situations such as acute kidney injury or primary renal disease.<sup>[28]</sup>

For example, polyomavirus nephropathy can often mimic TCMR-like histologic pattern in response to a reduction in immunosuppressive regimen for the management of virus-positive cases. On the other hand, response to viral antigens in allograft tissue may reflect a TCMR-like pattern,<sup>[28,29]</sup> and this is why efforts to find molecular diagnostic ways are continued to find definite diagnostic criteria of TCMR.<sup>[28]</sup>

Protocol biopsies have a role in indicating the original pathologic process leading to chronic allograft failure and can also make points to optimize the immunosuppressive regimen.<sup>[30]</sup>

Although we tried to design a solely pathologic study, lack of clinical data and laboratory information of patients such as clinical indication of TN, immunosuppressive therapy duration, and time of tapering or serum creatinine may limit the assessment of clinicopathologic correlation.

## CONCLUSION

Most of our TN operations were performed in a period of < 6 months posttransplantation. The most pathologic diagnoses of TN in a period of < 6 months posttransplantation and > 6 months posttransplantation were RVT and TCMR, respectively. Early histopathologic assessment of allografts by protocol biopsy is suggested that lead to better prevention and management of allograft failure which may only present with nonspecific pathologic appearance as ESRD on late biopsies or TN specimens.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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