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Original Paper

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Dose CMV infection increase the incidence of infective endocarditis following kidney transplantation?

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Summary

Background: Infective endocarditis (IE) is a rare but life threatening infection after renal transplantation. In addition, coinfection of CMV and IE has not been reported. Therefore, the current study was initiated to determine whether CMV infection is a risk factor for developing of IE after kidney transplantation.

Material/Methods: In a retrospectively study, we analyzed the medical records of 3700 kidney recipients at two transplant centers in Iran, between January 2000 and June 2008 for infective endocarditis.

Results: During the study, 15 patients with IE hospitalized in our centers were included. The predominant causative microorganisms (60%) were group D non-enterococcal streptococci and enterococci. Patient survival rate in all recipients was 66% at 6 months. Data analysis showed no significant differences in 6 months patient survival from hospitalization between both groups with and without CMV infection (P=0.2). The presentation time of infective endocarditis in recipients with CMV coinfection was more likely to be early when compared to CMV negative coinfection patients (P=0.03).

Conclusions: The present study indicates that CMV infection may lead to predispose to infective endocarditis after kidney transplantation. Rapid diagnosis, effective treatment, and prompt recognition of complications in kidney transplant recipients are essential to good patient outcome.

Key words kidney transplantation • infective endocarditis • CMV infection

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Background

Although advances in immunosuppressive therapy have led to increased survival of renal transplant recipients, suppression of immune system after transplantation renders the transplant recipient susceptible to developing infectious complications [1]. Cytomegalovirus (CMV) infection remains an important complication following kidney transplantation worldwide [1]. In addition, infective endocarditis (IE) is a rare but serious infection after renal transplantation which can be deadly [2]. Importantly, coinfection of CMV and SBE has not been reported. Because of its rarity, coinfection with CMV and IE may be missed, especially in its early stages. Unfortunately, CMV disease remains a significant cause of morbidity and mortality in kidney transplantation [3]. Moreover, infective endocarditis can be life threatening and carries a high risk of morbidity and mortality [4]. On the other hand, limited data are available on the patient survival of kidney allograft recipients with bacterial endocarditis. Therefore, the current study was initiated to determine the outcome of kidney transplant patients hospitalized for bacterial endocarditis and to determine whether CMV infection is associated with infective endocarditis following kidney transplantation in two major transplant centers in Iran.

Material and Methods

We retrospectively analyzed the medical records of 3700 kidney transplant recipients at Baqiyatallah and Labbafi-Nejad hospitals, leading transplant centers in Iran, between January 2000 and June 2008 for infective endocarditis. During the study, 15 patients with IE hospitalized in our centers, were included if they met the modified Duke's criteria for definite IE [5]. Data were gathered for patient age and sex, the source of the donated kidneys (deceased versus living donor), immunosuppressive regimen, clinical presentation of infective endocarditis, time presentation since transplantation, comorbid conditions, treatment modalities, the patient's response to treatment, and the effect of IE on graft and patient survival. In-hospital mortality was also determined. Survival time was calculated from the date of hospital admission for bacterial endocarditis. Echocardiography examinations in all patients were done. The great majority (67%) underwent transoesophageal echocardiography (TEE), and 33% had only a transthoracical echocardiography. Measurements of vegetation length were carried out in various planes. In the presence of more than one vegetation (n=6), the largest length was used for analysis. Indications for surgery were severe valvular dysfunction with heart failure, severe valvular dysfunction without heart failure, abscess or perivalvular extension, failure of conservative medical treatment, or large vegetations with high risk of embolization.

The diagnosis of CMV infection was documented by direct detection of CMV pp65 antigen in blood and polymerase chain reaction (PCR) assay.

Repeated transthoracic echocardiography and outpatient visit were scheduled during the follow up period. Mean follow-up for these patients was 14±19 (SD) months.

Statistical analysis

Data were analyzed using the Statistical Packages for Social Sciences [SPSS] version 13.0 for windows. Qualitative variables were expressed as number and percentage, while quantitative variables were expressed as mean ±standard deviation (SD). The paired-t test was used to determine the significance of differences between mean values of two paired continuous variables. Pearson chi-square and Fisher exact test were used to find the association between two independent variables. Wilcoxon ranks test was used for comparison of qualitative variables, and Mann-Whitney test was used for comparison of continuous variables where appropriate. The Spearman's rank correlation coefficient (r) was used to evaluate the strength of association between two continuous variables. Kaplan-Meier method was used for survival analysis [6]. Differences were considered to be significant if probability value was less than 0.05.

Results

Of 3700 kidney transplant recipients, 15 (0.4%) had infective endocarditis. Eight patients had also CMV coinfection. Table 1 summarizes the demographic characteristics of the recipients who were included in the study. Fever was seen in almost all patients and followed by anemia (86.6%), weakness (46.6%), dyspnea (40%), weight loss (13.3%) and subconjunctival hemorrhage (6.6%).

Ten patients (67%) responded to treatment, medical therapy with or without surgical treatment; 5 recipients died from IE and its complication. Full recovery (ie, normal graft function)

Table 1. Demographic characteristics of the recipients who had infective endocarditis.

Patient outcome	Graft function	Immuno-suppression regimen	Treatment modalities: IS decreased or stoped/Abi therapy/ Surgery	Concomitant conditions	CMV coin-fection	Valve invol-vement	Blood culture	Times of Tx	Donor source	Sex/ age (years)	Case no.
Alive	Good	Cy+MMF+Pre	+/+/+	None	Yes	Aorta	group D Streptococcus	1st	LURD	M/19	1
Alive	Good	Cy+MMF+Pre	+/+/+	None	Yes	Aorta	Enterococcus	1st	LURD	M/22	2
Died	Allograft failure	Cy+MMF+Pre	+/+/+	ITP & Cardiomyopathy	No	Aorta	group D Streptococcus	1st	LURD	F/24	3
Alive	Allograft failure	Cy+MMF+Pre	+/+/-	UTI	Yes	Mitral	Enterococcus	1st	LURD	M/24	4
Alive	Good	Cy+MMF+Pre	+/+/+	UTI	Yes	Mitral and Aorta	Enterococcus	1st	LURD	F/28	5
Died	Good	Cy+MMF+Pre	+/+/-	None	No	Mitral and Aorta	group D Streptococcus	1st	LURD	M/33	6
Alive	Good	Cy+AZA+Pre	+/+/+	UTI & Brain abscess	No	Aorta	Negative	2nd	LURD	M/33	7
Alive	Good	Cy+MMF+Pre	+/+/–	None	No	Mitral	Klebsiella	1st	LURD	F/48	8
Alive	Good	Cy+MMF+Pre	+/+/–	Endophthalmitis, UTI & PTDM	Yes	Mitral	group D Streptococcus	1st	LURD	F/51	9
Died	Loss	Cy+MMF+Pre	+/+/–	Meningitis & ARDS	Yes	Mitral	Negative	1st	Deceased	F/53	10
Died	Loss	Cy+MMF+Pre	+/+/–	UTI & PTDM	Yes	Aorta	group D Streptococcus	1st	LURD	F/55	11
Died	Allograft failure	Cy+MMF+Pre	+/+/–	CHF	No	Mitral	Staphylococcus aureus	1st	LURD	F/58	12
Alive	Good	Cy+MMF+Pre	+/+/–	UTI	Yes	Mitral and aorta	Klebsiella	1st	Deceased	M/59	13
Alive	Good	Cy+MMF+Pre	+/+/–	Liver abscess	No	tricuspid	Enterococcus	1st	LURD	M/70	14
Died	Good	Cy+AZA+Pre	+/+/–	DM	No	Mitral	Negative	1st	LURD	M/74	15

No – Number; Tx – Transplantation; CMV – Cytomegalovirus; IS – Immunosuppressive drugs; Abi – Antibiotic; M – Male; F – Female; LURD – Living Unrelated Renal Donor; Cy – Cyclosporine; MMF – Mycophenolate Mofetil; Pre – Prednisone; ITP – idiopathic thrombocytopenic purpura; UTI – Urinary Tract Infection; PTDM – Post Transplant Diabetes Mellitus; DM – Diabetes Mellitus; CHF – Congestive Heart Failure.

was observed in 8 patients (54%), while one patient (7.7%) survived invasive IE and CMV infection but impaired his graft function and developed chronic allograft nephropathy. Two (25%) of 8 patients with CMV coinfection and IE died (Table 1). In-hospital and 6-month mortality rate were 33.3% (n=5) and 40% (n=6), respectively. Mortality rate was higher in older patients compared to younger cases (26.6% versus 13.3%, P=0.6). Patient survival rate in all recipients was 66% at 6 months. Data analysis showed no significant differences in 6 months patient survival from hospitalization between both groups with and without CMV infection (P=0.2).

Table 2 gives the descriptive statistic characteristics of the patients who had IE with or without CMV coinfection. The clinical presentation time of infective endocarditis since transplantation in recipients with CMV coinfection was more likely to be early when compared to CMV negative coinfection patients (P=0.03). No statistically significant difference in other parameters was noted between these two groups (Table 2).

Table 2. Descriptive statistic characteristics of the renal transplant patients who had IE with or without CMV coinfection.

	With CMV infection (n = 8)	Without CMV infection (n = 7)	P value
Gender – M/F	4/4	4/3	0.5
Age in years - mean (±SD)	38.9±17.0	48.6±19.5	0.3
Time of clinical presentation since transplantation in months – mean (±SD)	3.8±1.2	42.0±43.6	0.03
Donor source: Deceased LURD	 2 6	 0 7	0.4
Size of vegetation in mm- mean (±SD)	1.1±0.3	1.2±0.7	0.8
Time of Surgery from Diagnosis in days – mean (±SD)	28±3	26±5	0.7
Number of vegetation – n Single Two Multiple	 3 2 3	 6 0 1	0.1
Allograft function – Good/failure/loss	5/1/2	5/2/0	0.3
Patient outcome – Died/Alive	2/6	4/3	0.3

CMV – Cytomegalovirus; M – Male; F – Female; n – number; LURD – Living Unrelated Renal Donor.

Discussion

Infective endocarditis has been reported as a rare complication in renal transplant recipients [2]. The incidence of bacterial endocarditis is much higher in long-term dialysis patients compared with the general population, and chronic kidney disease has been postulated as an independent host-related risk factor [7,8].

As far as gender distribution is concerned, males tend to be affected more frequently than females, although there are variations depending on age groups. Thus, in young people, the male to female ratio is 1:1; in individuals over the age of 35 years, it goes up to 2:1 and in the elderly, it is 5:1 [9]. However, the male to female ratio in our patients was 1:1: but in those lower and greater than the age 35 were 2:1 and 1:1.6, respectively.

The majority of our recipients had mitral (n=9) and aortic valve (n=8) endocarditis, but aortic valve was predominately infected in other reports [10]. Twenty percent (n=3) of IE episodes presented with two infected valvular sites. Echocardiography, especially TEE, plays an important role in the diagnosis and management of IE (Table 1). Transthoracic echocardiography (TTE) is rapid, noninvasive, and has excellent specificity for vegetations (98%) [11]. The overall sensitivity for vegetations, however, is less than 60 percent [11,12]. In our patients suspected of having IE, TTE alone can confirm 33% of all cases. TEE is safe in experienced hands and has the greatest sensitivity for detection of vegetations in IE [13]. TEE was performed in 67% of episodes in the present study; it seems to have all the qualities required for a good diagnostic test. Furthermore, TEE has a substantially higher sensitivity (76% to 100%) and specificity (94%) than TTE for perivalvular extension of infection [14,15].

The spectrum of organisms causing IE was obviously different in kidney transplant recipients than in the general population; the most common cause of IE (60% of the infections) were due to group D non-enterococcal streptococci and enterococci, but only 6.6% were due to staphylococcus aureus and approximately 20% of cases (n=3) of IE yielded negative blood culture results (i.e. culture negative IE). However, fungal infections and staphylococcus aureus predominated in the previous study [16]. Moreover, between 5 and 24% of suspected IE cases yield negative blood culture results; there are several possible explanations for this, including prior antibiotic therapy, fastidious and cell-dependent organisms or fungi [17]. Ultimately the recognition of the causative agent is the cornerstone of successful treatment of IE through appropriate antibiotic therapy and, hence, difficulties arise in the clin-

ical management of such patients; two patients with culture negative IE died.

To our knowledge, concomitant infection with CMV and IE has not been reported. We, however, found a coinfection with CMV and IE in a significant number of our patients. We thought that CMV infection may also added or enhanced immunosuppression after kidney transplantation and, hence, lead to increasing susceptibility to superinfection with other organisems. The current study revealed that IE in these patients occurred 3 to 12 months after kidney transplantation, i.e. favorable time for CMV infection happening. It seems that CMV infection acts as a risk factor for IE following kidney transplantation. Fortunately, mortality rate in this combination was not higher than those had not CMV coinfection.

Interestingly, we found some concomitant conditions with IE that have not been reported after kidney transplantation in other studies; i.e. idiopathic thrombocytopenic purpura (ITP), endophthalmitis, and post transplant diabetes mellitus (PTDM). However, diabetes is a common complication following organ transplantation that it has multiple causes, but one of important is the concurrent CMV infection and PTDM.

The overall mortality rates for both native-valve and prosthetic-valve endocarditis in patients with immune competence remain as high as 20 to 25 percent [4]. The overall mortality rate in our recipients (38.5%) was low when compared to the previously reported cases in solid organ transplant recipients [16]. Paterson et al. have been shown that the mortality rate in these patients was 57 percent [16]. On the other hand, the mortality rate in current study was still higher than in the general population [4]. In a study conducted between 1990 and 2000, the all cause-mortality rate in 513 patients was approximately 25% at the end of 6 months [18]. In comparison to kidney transplant recipients, patients receiving long term hemodialysis have much greater mortality rates from endocarditis. Spies et al. revealed that the in-hospital mortality rate for these patients was 52 percent [19].

Conclusions

Despite advances in antimicrobial therapy and the development of better diagnostic and surgical techniques have reduced the morbidity and mortality of IE, it remains a potentially life-threatening disease following organ transplantation. Although a single univariate association of CMV with earlier presentation of endocarditis is an isolated finding. This is probably not amenable to a multivariate analysis because there are only 15 endocarditis cases and 8 in which CMV was documented. We speculate CMV infection may predispose patients to infective endocarditis after kidney transplantation.

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