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Varicella zoster infection in renal transplant recipients: prevalence, complications and outcome

Z. Mustapic, P. Kes, Lj. Bubic-Filipi, [1]I. Mokos, Z. [1]Kastelan, [2]S. Zekan, N. Basic-Jukic.
Department of nephrology, arterial hypertension and dialysis, and [1]Department of urology, Clinical Hospital Centre Zagreb, and School of medicine, University of Zagreb
[2]Clinical hospital for infective diseases "Fran Mihaljevic"
Zagreb, CROATIA

Running title: VZV infection in renal transplant recipients

Corresponding author:
Nikolina Basic-Jukic, MD, PhD
Department of nephrology, arterial hypertension and dialysis, Clinical Hospital Centre Zagreb
Kispaticeva 12
10000 Zagreb
CROATIA
tel/fax: +385-1-2312-517
e-mail: nina_basic@net.hr

ABSTRACT

Varicella zoster virus (VZV) is an important pathogen after renal transplantation. In the present study we examined the prevalence, clinical presentation and outcome of VZV infections in renal transplant recipients.

Charts and medical records of adult renal allotransplant were investigated to discover patients with VZV infection.

From December 1972 until July 2010, 1139 patients received kidney allograft at our institution. VZV infection was diagnosed in 40 patients (3.51 %). Twenty eight patients (70%) had intensified immunosuppression prior to VZV infection occurrence. Median time of onset was 2.13 years after transplantation (range 9 days to 19.2 years). Thirty-five patients developed zoster during the first post transplant year (median 0.61 years). Four patients developed VZV infection more than 12 years after transplantation. Thirty-three patients (82.5%) had dermatomal distribution, five (12.5%) disseminated herpes zoster, and 2 patients (5%) who were VZV IgG negative before transplantation, developed chickenpox. Immunosuppression was reduced and patients received acyclovir. Cutaneous scarring was recorded in 7 cases (17.5%). Two patients developed postherpetic neuralgia (PHN), which was in one of them accompanied with scarring and skin depigmentation. Five patients (12.5%) experienced relapse of HZ.

Timely initiation of therapy may prevent development of complications and visceral form of disease. Based on our experience with development of chickenpox, we suggest active immunization for all seronegative patients before organ transplantation.

Key words: renal transplantation, immunosuppression, varicella-zoster, mycophenolate mofetil, infection

Introduction

An individual risk for development of infection after renal transplantation is determined by a relationship between the epidemiologic exposure of the individual and the state of immunosuppression which determines the individual's susceptibility to infection (1).
Varicella zoster virus (VZV) is an important pathogen in organ transplant recipients (2, 3).
Varicella zoster virus infection causes two clinically different forms of disease. Primary disease (varicella or chickenpox) is characterized by vesicular lesions on the trunk, head or extremities. Herpes zoster (shringles) is characterized by a painful unilateral vesicular eruption, which may rarely be disseminated.
In the present study we examined the prevalence, clinical presentation and outcome of VZV infections in renal transplant recipients.

Patients and method

Charts and medical records of adult renal allotransplant recipients transplanted between December 1972 and July 2010 were investigated to discover patients with VZV infection.
Patients received triple immunosuppressive regimen (calcineurine inhibitor, antiproliferative drug and steroids). Before 2002 we used only azathioprine (AZA) as an antiproliferative drug. Since 2005 tacrolimus was introduced beside cyclosporine (CyA). From the year 2004 patients with more than three mismatches received induction therapy with basiliximab or daclizumab, and until that time they were treated with steroid bolus (500mg).
Age, gender, time on dialysis, time of transplantation, immunosuppressive protocol, viral status before transplantation, episodes of acute graft rejection, other viral infections, and graft function were recorded. Detailed clinical characteristics of VZV infection were noted (localization, dissemination, complications and outcome).
The diagnosis was made on clinical grounds and/or VZV seroconversion.
Study was approved by the Ethics Committee of School of medicine, University of Zagreb.

Results

Patients' characteristics

From December 1972 until July 2010, 1139 patients received kidney allograft at our institution. VZV infection was diagnosed in 40 patients (3.51 %). There were 27 male patients and 13 female patients, with the mean age at diagnosis of 51.8 years (Table 1). Thirty-nine of them received renal transplant from deceased donor. Average time on dialysis was 6.8 years.

At the time of onset, 36 patients had CyA, MMF and steroids, 2 had tacrolimus, MMF and steroids, and two AZA and CyA in therapy. Mean CyA concentration was 157.5 μmol/L (range from 85 to 294 μmol/L) and mean dose of MMF was 916 mg/m^2 (range from 300 mg/m^2 to 1260 mg/m^2) at the time of VZV infection. Mycophenolic acid concentration was not determined. Two patients receiving tacrolimus had serum concentration of 12.9 and 13.6 ng/mL, and 7 patients had CyA C_0 >200 μmol/L. Eleven patients (27.5%) received induction therapy with basiliximab or daclizumab in their immunosuppressive protocol. Ten patients (25%), 2 of which received induction therapy, had acute graft rejection and were treated with 3 to 5 doses of intravenous methylprednisolone prior to VZV reactivation. Thus, 28 patients (70%) had enhanced immunosuppression prior to VZV infection.
Six patients (15%) received antiviral treatment before, due to CMV infection. Three patients had chronic hepatitis C infection.

Table 1.

Timing of VZV infection

Median time of onset was 2.13 years after transplantation (range 9 days to 19.2 years). Thirty-five patients (85%) developed zoster during the first post transplant year (median 0.61 years). Four patients (10%) developed VZV infection long time after transplantation (2 in the year 1988, 1 in 1992 and 1 in 1998). Two of these patients had received AZA since transplantation, while in two patients AZA was replaced with MMF after acute graft rejection, 3.7 and 7.8 years prior to VZV infection. None of the patients treated with AZA developed disseminated disease.

Clinical presentation of VZV infection

Thirty-three patients (82.5%) had dermatomal distribution, five (12.5%) disseminated herpes zoster, and 2 patients (5%), who were VZV IgG negative before transplantation, developed chickenpox. Severe skin changes were recorded (Figure 1A). Two patients who received organ from the same donor developed VZV infection 29 days after transplantation. Donor was VZV IgG positive, IgM negative. One recipient was VZV IgG positive and developed disseminated vesicular rash (Figure 1B), and another was VZV IgG negative (he developed chickenpox). For other patients there was no known exposure to the virus.
Deterioration of graft function was recorded in one patient, and two had transient elevation of liver enzymes.

Treatment of VZV infection

In the treatment of VZV infection, 33 patients (82.5%) received acyclovir orally, 6 patients (15%) acyclovir intravenously and one (2.5%) had no antiviral treatment while he failed to visit doctor. Antiviral therapy was introduced 0-3 days after vesicular eruption. Seven (17.5%) patients had no changes in immunosuppressive treatment (they were treated in local hospitals). MMF was reduced in 28, and temporarily switched off in 5 patients.

Complications and outcome

All patients and grafts survived. Complications occurred in 9 patients (22.5%). Cutaneous scarring was recorded in 7 cases (17.5%). Two patients (5%) developed postherpetic neuralgia (PHN), which was in one of them accompanied with scarring and skin depigmentation.
Five patients (12.5%) experienced relapse of HZ. In two of them with 3 or more relapses, immunosuppression was changed, and AZA was introduced instead of MMF.

Discussion

Varicella zoster virus infection is rare but potentially serious complication in renal transplant recipients. Lethal outcomes of VZV infection were recorded (2, 4). Our results demonstrated relatively low prevalence of VZV infection in renal transplant recipients (3.51%), compared with other studies which recorded prevalence of 3 to 10 % (5, 6). Female gender is considered as risk factor for developing HZ (5). It is interesting that in our cohort of patients, 67.5 % of patients were male.
The frequency and intensity of VZV infection is associated with the intensity of immunosuppression (7, 8). Introduction of mycophenolate mofetil (MMF) in immunosupressive protocol improved graft survival (9, 10). However an increased incidence of different viral infections was recorded (11-16). According to our results, introduction of MMF in immunosuppressive protocol resulted in higher incidence and more severe VZV disease. All our patients with disseminated disease were in MMF era. Early therapy with acyclovir orally with reduction of MMF dose is a therapy of choice. We believe that dose adjustment and finding an upper limit of the therapeutic range of mycophenolic acid (MPA), above which the risk of different viral infection is increased, needs to be determined for MMF therapy in the following studies (17), at least in patients who received enhanced immunosupression early in the posttransplant period. Seventy percent of patients were exposed to intensive immunosuppressive treatment before VZV infection, while they received either induction or steroid bolus therapy for

treatment of acute rejection, or had high calcineurin inhibitor concentration. This is in line with the previous observations that intensive immunosuppression presents risk factor for development of VZV infection (1,8).

Majority of our patients developed VZV infection during the first posttransplant year. Only 4 patients experienced disease long time after transplantation, thus prolonging the median time of onset (2.13 years). Previous studies reported the onset of VZV infection after solid organ transplantation to be between 2 and 92 months (3, 5, 18). Switch from AZA to MMF resulted in more intensive immunosuppression and subsequently in development of VZV infection in 2 of our patients (up to 228 months after transplantation).

Five cases of disseminated HZ were recorded, what is relatively high proportion in comparison with other studies (less than 40 cases described in the literature). Mortality rate of 34 % was described in patients with disseminated HZ (2). None of our patients died, probably because of the fast recognition and initiation of antiviral therapy.

We report a low rate of PHN (5 %) in our patients, but relatively high rate of cutaneous scarring (17.5 %). Other authors reported PHN up to 42.7 % of solid organ recipients (5, 19).

High dose acyclovir therapy together with reduction of immunosuppression is a cornerstone of VZV infection treatment. Timely initiation of therapy may prevent development of complications and visceral form of disease. Based on our experience with development of chickenpox, we suggest active immunization for all seronegative patients before organ transplantation.

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Table 1. Clinical characteristics of the patients. VZV- varicella zoster, MMF- mycophenolate mofetil, Aza-azathioprine, CyA-cyclosporine A.

	Number
Patients	40
Gender (% male)	67.5
Age (mean, range)	51.8 (28-69)
Induction (%)	28.9
MMF vs. Aza	38 vs. 2
CyA vs. Tacrolimus	38 vs. 2
Onset of VZV after transplantation (years; mean (range))	2.13 (9 days to 19.2 years)
Intensified immunosuppression (%)	70
Localized vs. disseminated	33 vs. 5
Chickenpox	2
Treatment (peroral vs. intravenous)	34 vs. 6
Complications - neuropathy - cutaneous scarring	 2 7
Relapses (no of patients)	5

Figure 1. A – Severe form of localized herpes zoster with central necrosis. B – Disseminated herpes zoster.