Prevalence and Outcome of Disseminated Varicella Zoster Infection Post Kidney Transplantation

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Objective: *Varicella zoster (VZV) is a potentially life-threatening infection after kidney transplantation (KT) but data on the incidence and outcome of late KT VZV infection is limited.*
Material and Method: *A retrospective study of disseminated VZV infection (D-VZV) in post KT patients was conducted between 2003 and 2013. Acyclovir prophylaxis was given routinely for six months after KT. Statistical analyses were performed by SPSS software version 17.0.*
Results: *Prevalence of D-VZV was 2% [22/1,032 patients]. Patients median age were 40 (21-67) years old and 12 (55%) were male. Timing of the infection was mostly (68.2%) late (>1 year) post KT. The majority of maintenance immunosuppressive drug included prednisolone (95.5%), cyclosporine (77.3%), mycophenolate (68.2%). Two (9.1%) had a recent VZV exposure and four (18%) received intensified immunosuppression before the diagnosis. Common clinical presentations were lymphopenia (54.5%), generalized vesicular rash (50%), and multi-dermatomal distribution (50%) while liver involvement was infrequent (9.1%). None had pneumonitis or neurological involvement. All cases received systemic acyclovir with the median duration of 14 (3-31) days. One had received IVIG for fulminant hepatitis. Immunosuppressive drug/s was reduced in 59%. Median duration of hospitalization was seven (3-37) days. None of patients died. The median follow-up duration was 1939 (IQR 804-2440) days. Recurrent infection was uncommon (4.5%). Secondary prophylaxis was given only in one patient with fulminant VZV hepatitis.*
Conclusion: *Incidence of D-VZV post KT was low. Treatments with intravenous acyclovir and reduction of immunosuppression without the use of VZV IgG provided favorable outcome in resource-limited settings.*

Keywords: *Incidence, Varicella zoster, Kidney transplantation*

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Varicella zoster (VZV) is a potentially life-threatening infection after kidney transplantation (KT) especially VZV pneumonia[1]. Primary VZV infection in adults is known to be progressive, causing complications of pneumonia, encephalitis, and hepatitis[1]. Post-transplantation VZV could be due to primary infection in VZV IgG negative recipients, reinfection of VZV with new strain of virus or reactivation of VZV from latency state at dorsal ganglion cells[1]. Pretransplant screening of VZV IgG and vaccination prior to transplantation is now recommended[2]. However, in most countries, most recipients are VZV IgG seropositive[3,4]. Antiviral prophylaxis is routinely recommended post-transplant, either ganciclovir (cytomegalovirus [CMV] active) or acyclovir. The incidence of VZV is increased with the preemptive strategy of CMV with monitoring CMV viral load[5]. Several reports the infectious complications of disseminated VZV infection post kidney transplant, some were lethal such as pneumonia or neurological involvement[1,6]. Duration of antiviral prophylaxis is unknown. The incidence of VZV infection in solid organ transplant recipients was reported as 8 to 11% during the first four years post-transplant. In center acyclovir prophylaxis was given routinely for six months after KT. The VZV IgG or vaccination was not part of routine care. Incidence and outcome of late KT VZV infection in resource limited settings without acyclovir prophylaxis was limited.

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Material and Method

A 10-year retrospective study of disseminated VZV infection (D-VZV) in post KT patients between 2003 and 2013 was conducted. Data collection included baseline demographic data, type of KT, induction

regimen, maintenance immunosuppressions, baseline creatinine (Cr), clinical presentation of VZV (prior VZV infection/exposure, laboratory results at time of diagnosis VZV including complete blood count, chemistries, liver function tests, drug level, treatment for VZV, management of immunosuppression, infectious complications, co-infections, outcome, and last follow-up date. Medical records were reviewed. The present study had been approved by the Institutional Ethics Committee. Data were presented as median (range), number (%). Statistical analyses were performed by SPSS software version 17.0.

Results

Prevalence of D-VZV was 2% [22/1,032 patients]. Patient's median age was 40 (21-67) years old, and 12 (55%) were male, median of baseline Cr was 1.45 (0.8-6.4) mg/dL, GFR (calculated) was 44 (9-87) ml/minute. Demographic data, type of KT, maintenance immunosuppressive regimen at diagnosis, laboratory results, and treatment were shown in Table 1. Most [15 (68.2%)] patients developed VZV infection after one year post KT, five (23%) patients developed VZV infection more than four years after KT. Timing of the infection was mostly (68.2%) late (>1 year) post KT, median time of 588 (range 67-5,886) days, data shown in Fig. 1. Only one patient developed VZV within six months while acyclovir prophylaxis was withheld. None of the patients who received acyclovir prophylaxis had breakthrough infection. Two (9.1%) had a recent VZV exposure, 3 (13.6%) had previous history of chicken pox. The maintenance immunosuppression at the time of VZV diagnosis included prednisolone (95.5%), cyclosporine (77.3%), mycophenolate (68.2%), and azathioprine (22.7%), tacrolimus (18.2%), sirolimus (9.1%), everolimus (13.6%), dosage (range) data shown in Table 1. The most common combination regimen used was cyclosporine, mycofenolate, and prednisolone in 10 (45%) patients. Median level of cyclosporine, tacrolimus, sirolimus, everolimus was 97 (24-276), 1.25 (3.3-10.2), 7.55 (5.4-5.6), and 5.91 (5-12.2) ng/mL, respectively.

Four patients (18.2%) received intensified immunosuppression before the diagnosis due to allograft rejection in three (13.6%) and one patient with antibody mediated hemolytic anemia.

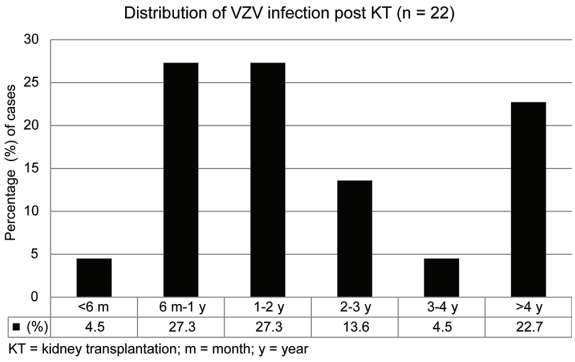

Fig. 1 Distribution of VZV infection post kidney transplantation.

Table 1. Baseline characteristics of 22 patients with disseminated VZV infection

Data	Number (%)	Median (range)
Demographic data		
Age (years)		40 (21-67)
Gender, male	12 (54.5)	
Weight (kg)		61 (50-89)
Onset of VZV infection		
Days after KT		588 (67-5,886)
Years after KT		1.6 (0.51-16.13)
Type of KT, living related	14 (63.6)	
Immunosuppressive agents [dose (mg/day)]		
Azathioprine	5 (22.7)	100 (50-100)
Cyclosporine	17 (77.3)	100 (50-200)
Mycofenolate	15 (68.2)	1,500 (1,000-2,250)
Tacrolimus	4 (18.2)	1.25 (1-2.5)
Sirolimus	2 (9.1)	2.5 (2-3)
Everolimus	3 (13.6)	2 (0.75-2.5)
Prednisolone	21 (95.4)	5 (5-45)
Laboratory results		
WBC (cells/mm^3)		6,120 (3,390-21,000)
Lymphopenia	12 (54.5)	
ALC (cells/mm^3)		880 (485-1,600)
AST (u/L)		27 (9-1,962)
ALT (u/L)		48 (21-2,329)
Cr (mg/dL)		1.71 (0.8-6.87)
GFR (ml/minute)		44 (9-87)
IgG level (g/L)	3 (13.6)	8.65 (7.5-10.7)
Treatment		
Acyclovir	22 (100)	
- iv (mg/kg/dose)	20 (90.9)	8.9 (3.4-10.6)
- iv (mg/kg/day)		20 (4.4-30.8)
- po	2 (9.0)	14 (3-31)
Duration (days)		7 (0-24)
- iv		7 (0-14)
- po		
Duration of hospitalization (days)		7 (3-37)

VZV = varicella zoster; WBC = white blood cells; ALC = absolute lymphocyte count; AST = aspartate transaminase; ALT = alanine transaminase; Cr = creatinine; GFR = glomerular fultration rate; IgG = immunoglobulin G; iv = intravenous; po = per oral

Common clinical presentations were generalized vesicular rash (50%) and multi-dermatomal distribution (50%) while liver involvement was infrequent (9.1%). None had pneumonitis or neurological involvement. Laboratory confirmation included findings of multinucleated giant cell from Tzanck smear, five (22.7%) had positive VZV polymerase chain reaction (PCR) from skin lesions and one had (fulminant hepatitis) with positive plasma VZV PCR. Lymphopenia was found in 54.5% of the cases, and hypogammaglobulinemia was found in two out of three patients.

Treatment with acyclovir was given intravenously in 20 (90.9%) patients, with median dose of 8.9 (range 3.4-10.6) mg/kg/dose, 20 (4.4-30.8) mg/kg/day with median duration of intravenous treatment was seven (0-24) days, oral treatment was seven (0-14) days, total median duration of treatment was 14 (3-31) days. One patient received intravenous immunoglobulin (IVIG) for fulminant hepatitis. Immunosuppressive drug/s was reduced in 59%, mainly mycofenolate. Median duration of hospitalization was seven (3-37) days. No patient died. The median follow-up duration was 1,939 (IQR 804-2,440) days. Recurrent infection was uncommon (4.5%), occurring in one patient with an interval of five years. Secondary prophylaxis was given only in one patient with fulminant VZV hepatitis. Only one patient who did not receive prophylaxis had relapse VZV. None of the patients died, median follow-up was 1,939 (IQR 804-2,440) days.

Discussion

To our knowledge, the present study is the first to evaluate the prevalence and outcome of disseminated VZV infection post kidney transplantation in resource limited settings in the absence of antiviral prophylaxis. Prevalence of late onset post-transplantation VZV infection was low 2% similar to incidence report from Spain of 1% (1/812 patients in 9 years, 1995-2004) and Croatia of 3.8% (40/1,139 patients in 38 years, 1972-2010)[7,8]. The incidence of VZV infection in solid organ transplant recipients was reported as 8 to 11% during the first four years post-transplant[9]. A Korean cohort of patients (2008-2010) reported the incidence rate of VZV was 80 vs. 13 per 1,000 person-years compare between in preemptive therapy for CMV group (without acyclovir prophylaxis) vs. universal CMV prophylaxis for more three months. Of the 812 adult renal transplant recipients from a single institution in Spain (1995 and 2004), eight (1%) had disseminated VZV infection with the median time from transplantation to infection was 32 months (range 2 to 92), similar immunosuppressive regimen consisted of prednisone, cyclosporine, mycophenolate, prednisolone[7]. Interestingly, mostly 68% VZV infection occurred more than one year later post-transplantation, and even up to 16 years post KT after cessation of acyclovir prophylaxis. A similar study from Croatia reported that median onset of VZV was 2.13 years and could be as late as 19 years post KT[8]. Late onset VZV infection post kidney transplantation within 5 and 10 years was 70% and 89%[10]. It is important to note that long-term antiviral prophylaxis is not feasible since the risk of reactivation and reinfection remained while patients were on immuno-suppressive medications. Among seronegative recipients, varicella zoster vaccination is recommended. Most of our recipient were VZV seropositive (personal communication).

In our study, primary infection (chicken pox) developed in one recipient with fulminant hepatitis. The VZV IgG was negative at time of admission and turn positive at week 3 of treatment. Interestingly, reinfection was also noted in one patient who developed generalized vesicular rash, five years apart and another one with previous history of chicken pox infection presented with generalized vesicular rash after being exposed to VZV. These cases were consistent with the previous report of VZV pneumonia in KT recipients with history of VZV infection after being exposed to a child with chicken pox[1]. In terms of infection control, we would like to emphasize that these populations remain at risk despite VZV seropositive. Among patient who had reactivation in the present study had multidermatomal rash. Visceral organ involvement was rarely seen in our study. The VZV infection in the past decade at our institution had favorable outcome, similar to recent studies (2008-2010)[5]. Notably, none of our patients had lung or neurological involvement, which could reflect the early diagnosis, treatment, and hence better survival. Literature review data from 1985 to 2011, show mortality rate of disseminated VZV infection in 56 kidney transplant was 47% in the era before 1995 to 17% after 1995, including cases with disseminated intravascular coagulation occurred in two thirds of patients, pneumonitis 29%, and neurological involvement in 12%[10]. However, from the most recent study cohort of patient (2008-2010), no death was reported relating to VZV infection[5].

Known risk factors for mortality included visceral involvement, use of azathioprine as

immunosuppressant, and longer time between transplantation and VZV infection[10]. From our study, we postulated that profound lymphopenia that was seen in more than half of the patients is the risk factor, as consequences of cumulative state of immunosuppression.

Treatment modalities of disseminated VZV infection in eight patients from Spain were treated with antiviral drugs (acyclovir or gancyclovir), reduction immunosuppression, and 75% received varicella-zoster immunoglobulin: two pneumonitis, one hepatitis and thrombotic microangiopathy, and one developed multiorgan failure and died[7]. In contrast to our study, who received varicella-zoster immunoglobulin, only one with fulminant hepatitis received immunoglobulin. In resource limited settings, the use of varicella specific immunoglobulin (VZIG) was not feasible due to the cost and the availability. Therefore, reduction of immunosuppression may prevent further progression of the disease in the lack of use of varicella-zoster immunoglobulin. Long-term follow-up outcome revealed that none of our patients had post-herpetic neuralgia, in contrast to previous study report of rate of 23%[5]. Relapse rate in our study was low 4.5% compared to 12.5% from previous report[8].

Limitations of the present study were that it was retrospective in nature, small sample size, only included D-VZV in hospitalized patients at our institution, which could underestimate prevalence of VZV infection post kidney transplantation.

Conclusion

Our study is the first study to demonstrate that antiviral prophylaxis was not needed in resource limited settings due to the low prevalence rate, the nature of late onset disease, the low relapse rate 4.5%, and favorable outcome in all patients.

What is already known on this topic?

Treatment modalities of disseminated VZV infection consist of antiviral drug, reduction immunosuppression, and the use of varicella-zoster immunoglobulin.

What this study adds?

Our study is the first to report the favorable outcome of treatment D-VZV without the use of varicella-zoster immunoglobulin in KT recipient who mainly had disseminated cutaneous disease or no lung or neurological involvement. Our study proposed the approach of management of disseminated VZV in resource limited settings without the use of varicella-zoster immunoglobulin by means to reduce the immunosuppression.

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Potential conflicts of interest

None.

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ความชุกและผลของการติดเชื้องูสวัดแบบแพร่กระจายตามหลังการปลูกถ่ายไต

มาเรีย นิน่า จิตะสมบัติ, สิริอร วัชรานานันท์

วัตถุประสงค์: *การติดเชื้องูสวัดแบบแพร่กระจายตามหลังการปลูกถ่ายไตเป็นภาวะที่ทำให้มีโอกาสเสียชีวิตได้แต่ข้อมูลด้านอุบัติการณ์และผลของการติดเชื้องูสวัดแบบแพร่กระจายตามหลังการปลูกถ่ายไตยังมีจำกัดอยู่*

วัสดุและวิธีการ: *การศึกษาแบบรวบรวมข้อมูลย้อนหลัง 10 ปี ตั้งแต่ พ.ศ. 2546 ถึง พ.ศ. 2556 ในผู้ป่วยที่มีการติดเชื้องูสวัดแบบแพร่กระจายตามหลังการปลูกถ่ายไตที่โรงพยาบาลรามาธิบดี โดยที่ให้ยาป้องกัน acyclovir ในช่วง 6 เดือนแรก หลังการปลูกถ่ายไต การวิเคราะห์ข้อมูลด้วยโปรแกรมทางสถิติ SPSS software version 17.0*

ผลการศึกษา: *ความชุกของการติดเชื้องูสวัดแบบแพร่กระจายตามหลังการปลูกถ่ายไตอยู่ที่ร้อยละ 2 โดยเกิดในผู้ป่วย 22 ราย จากผู้ป่วยปลูกถ่ายไตทั้งหมด 1,032 ราย ในระยะเวลา 10 ปี ค่ามัธยฐานอายุเฉลี่ย 40 ปี โดยมีค่าอยู่ระหว่าง 21 ถึง 67 ปี ส่วนมากร้อยละ 55 เป็นผู้ชาย ระยะเวลาในการเกิดโรคส่วนมากร้อยละ 68.2 มักจะเกิดมากกว่า 1 ปี ยากดภูมิต้านทานที่ผู้ป่วยได้รับ คือ ยาสเตียรอยด์ ร้อยละ 95.5, cyclosporine ร้อยละ 77.3, mycophenolate ร้อยละ 68.2, azathioprine ร้อยละ22.7 ผู้ป่วย 2 ราย มีประวัติการสัมผัสอีสุกอีใสมาก่อน และ 4 ราย ได้รับการปรับเพิ่มยากดภูมิต้านทานขนาดสูงขึ้นก่อนที่จะเกิดอาการ อาการแสดงที่พบร้อยละ 50 มีผื่นตุ่มน้ำใสกระจายทั้งตัว และที่เหลือเป็นผื่นตุ่มน้ำใสกระจายหลายตำแหน่งของร่างกายตามทางเดินเส้นประสาท โดยไม่พบการอักเสบของปอดหรือระบบประสาทร่วมด้วย แต่มี 1 ราย ที่มีการอักเสบของตับแบบรุนแรงร่วมด้วย การรักษาผู้ป่วยทั้งหมดได้รับยา acyclovir แบบฉีด ระยะเวลาโดยค่ามัธยฐานอายุเฉลี่ย 14 วัน โดยมีค่าอยู่ระหว่าง 3 ถึง 31 วัน มีผู้ป่วย 1 ราย ได้รับการรักษาด้วย IVIG เนื่องจากมีการอักเสบของตับแบบรุนแรง นอกจากนี้ร้อยละ 59 ของผู้ป่วยยังได้รับการปรับลดยากดภูมิต้านทาน ระยะเวลาในรักษานอนโรงพยาบาลของผู้ป่วยค่ามัธยฐานอายุเฉลี่ย 7 วัน โดยมีค่าอยู่ระหว่าง 3 ถึง 37 วัน โดยที่ไม่มีผู้ป่วยเสียชีวิต ผู้ป่วยได้รับการติดตามค่ามัธยฐานอายุเฉลี่ย 1,939 วัน โดยมีค่าอยู่ระหว่าง 804 ถึง 2,440 วัน พบว่ามีการติดเชื้อซ้ำร้อยละ 4.5 โดยมีผู้ป่วยจำนวน 1 ราย เท่านั้นที่ได้รับยา acyclovir ป้องกันการติดเชื้อกลับซ้ำ*

สรุป: *ความชุกของการติดเชื้องูสวัดแบบแพร่กระจายตามหลังการปลูกถ่ายไตพบได้น้อย การรักษาด้วยการให้ยา acyclovir แบบฉีดและปรับลดยากดภูมิต้านทานโดยที่ไม่ได้ให้ varicella zoster Immunoglobulin ได้ผลดีในประเทศไทย*
