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Case Report

Herpes Zoster in Kidney Transplant Recipients: A Series of Three Cases

Ramy M. Hanna[a, b] Farid Abd-El-Malak[c] Ammar Alnaser[a] Rumi Cader[c] Julie M. Yabu[a]

[a]Division of Nephrology, Department of Medicine, David Geffen School of Medicine, Los Angeles, CA, USA; [b]Division of Nephrology, Department of Medicine, University of California Irvine School of Medicine, Orange, CA, USA; [c]Department of Medicine, David Geffen School of Medicine, Los Angeles, CA, USA

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Abstract
Kidney transplant recipients require lifelong immunosuppression to prevent organ rejection. The need for this intervention, however, leads to decreased cellular immunity and, in turn, increased risk of developing herpes zoster (HZ) from reactivation of latent varicella zoster virus. HZ commonly presents as a painful rash in a dermatome presentation followed by post-herpetic neuralgia. In immunosuppressed individuals, the presentation can be atypical and vary in severity depending on degree of immunosuppression and host immune response. We present the clinical course of 3 kidney transplant recipients who developed HZ after transplantation at different times post-transplant with varying clinical manifestations. The balance between maintaining immunosuppression and preventing or subsequently treating disseminated disease is discussed.

KARGER

Ramy M. Hanna
UC Irvine Medical Center, Department of Medicine Division of Nephrology
333 The City Dr. Suite 400
Orange, CA 92868 (USA)
rhannamd81@yahoo.com, ramyh1@hs.uci.edu

Introduction

Kidney transplant recipients require lifelong immunosuppression to prevent acute or chronic allograft injury but are also at risk for opportunistic infections due to decreased immune cell function [1]. However, the infectious risk posed by immunosuppression need not only be due to uncommon infections. More common infections and more severe presentations of common diseases are also a threat to transplant recipients [2]. This is why prior to transplant, many common immunizations are given to prevent infection [3]. Now with the development of the herpes zoster (HZ) subunit vaccine (Shingrix©) non-live vaccine, there is an opportunity for varicella vaccination as well [4, 5]. Herpes simplex and HZ (varicella) infections post-transplant can occur, and the presentation can range from a painful condition to life-threatening disseminated zoster [5, 6]. There are other special considerations concerning patients who develop auricular involvement (Ramsay Hunt syndrome) [7] or herpes ophthalmicus that may result in permanent ocular damage [8–10]. These cases must be treated very promptly in an inpatient setting with close monitoring.

The overall mortality rate of disseminated HZ in kidney transplant recipients can be very high up to 30% [11]. Early detection can be accomplished via serological means with DNA PCR being positive in some cases before a rash appears [12]. Any rash or prodromal symptoms, such as pain or numbness, in a transplant recipient should be suspect, even if it does not display the classical dermatomal pattern. This is because transplant recipients often have atypical presentations of varicella zoster [13].

We present 3 cases of HZ in kidney transplant recipients of varying severity (Table 1); one case was in the cranial nerve V (V1) distribution near the eye. The second case involved multiple thoracic dermatomes (T2–T5) with accompanying septic shock and acute kidney injury likely due to acute tubular necrosis. The third case was a non-dermatomal varicella zoster skin infection involving the head, trunk, arms, and legs. Management of disease, concomitant infections, and special considerations for herpes ophthalmicus are discussed. We also highlight the need for the delicate balance in the management of immunosuppression management in conjunction with the appropriate transplant and infectious disease specialists.

Case Reports

Case 1

A 53-year-old man with end-stage renal disease secondary to IgA nephropathy underwent living unrelated renal transplant about 7 years prior to presentation with baseline serum creatinine 1.5–1.7 mg/dL post-transplant (Table 1). The patient was not sensitized and received basiliximab for induction immunosuppression. Post-transplant, he was maintained on tacrolimus (trough level 4–6 ng/mL) and mycophenolate acid 360 mg twice daily. He received anti-microbial prophylaxis with acyclovir for 3 months, nystatin for 1 month, and trimethoprim and sulfamethoxazole single strength for 12 months. His transplant course was complicated by squamous cell carcinoma of the lower lip 6 years post-transplant, which was excised with flap closure. Biopsy of the lesion showed well-differentiated squamous cell carcinoma with free peripheral and deep margins.

The patient presented 7 years post-transplant with left facial burning pain and rash and was diagnosed with HZ with cranial nerve V (V1) distribution near the eye. Vital signs at the time of admission were as follows: blood pressure 150/90 mm Hg, heart rate 83 bpm, temperature 36.8°C, respiratory rate 18 breaths per minute, 99% oxygen saturation. Laboratory values significant for serum creatinine 1.66 g/dL, urea nitrogen 30 mg/dL, sodium 136 mmol/L, potassium 4.3 mmol/L, carbon dioxide 22 mmol/L, calcium 8.8 mg/dL, albumin 3.6 gm/dL, white blood cell count 7.1 × 10^3 (differential: 76.2% neutrophils, 16% lymphocytes, 6.6% monocytes, 0.8% eosinophils, 0.4% basophils), hemoglobin 14.3 g/dL. During his admission, he received intravenous acyclovir and supportive intravenous normal saline. During his admission, the patient's tacrolimus trough levels were in the 4–5 ng/mL range, and mycophenolic acid was discontinued. He developed acute on chronic kidney disease with serum creatinine increased to 1.95 mg/dL with 100 mg/dL (2+) proteinuria. In response, further supportive intravenous normal saline was administered until serum creatinine resolved to baseline. Despite 1 week of antiviral therapy, the patient continued to have active HZ lesions with progression of newly diagnosed conjunctivitis. At time of discharge, his ocular symptoms had resolved, and he was transitioned to oral valacyclovir 1,000 mg twice daily. He was later diagnosed with herpes ophthalmicus in outpatient follow-up, and valacyclovir was increased to 1,000 mg three times daily as his kidney function improved (creatinine 1.7 mg/dL). Mycophenolate acid was held until resolution of his HZ lesions and restarted at 360 mg twice daily (his maintenance dose) after improvement of his lesions and symptoms.

Case 2

A 58-year-old man with a history of end-stage renal disease due to unclear etiology underwent living unrelated renal transplant 17 years prior to presentation with baseline serum creatinine 3.0 mg/dL (Table 1). Post-transplant, he was maintained on cyclosporine (trough level ~75–100 ng/mL), mycophenolate mofetil 250 mg twice daily, and prednisone 5 mg daily. His post-transplant course was complicated by post-transplant lymphoproliferative disease (PTLD) 1 year prior to presentation, which was treated with ibrutinib and rituximab. In addition, mycophenolate mofetil was discontinued due to PTLD, and he was continued on cyclosporine, (trough level ~75 ng/mL) and prednisone 5 mg daily.

He presented with worsening chest and back pain with a blistering rash (Fig. 1a–f) and uncontrolled diarrhea. He received empiric intravenous vancomycin, cefepime, and acyclovir on admission. He was diagnosed with severe sepsis and neutropenia in the setting of disseminated HZ (T3-T4 dermatome), newly diagnosed clostridium difficile, and acute on chronic kidney injury. Vitals signs include blood pressure 135/71 mm Hg, heart rate 103 beats per minute, temperature 37.9°C, respiratory rate 20 breaths per minute, and 92% oxygen saturation. Laboratory values showed serum creatinine 5.7 mg/dL, urea nitrogen 88 mg/dL, carbon dioxide 15 mmol/L, potassium 3.7 mmol/L, sodium 136 mmol/L, calcium 7.0 mg/dL, albumin 2.3 g/dL, phosphorus 4.4 mg/dL, 2+ proteinuria on urinalysis, white blood cell count 2.71 × 10^3 (differential: 38.6% neutrophils, 39.9% lymphocytes, 7% monocytes, 4% eosinophils, 0.4% basophils, immature granulocytes 10%), hemoglobin 8.2 g/dL, and cyclosporine trough 54 ng/mL. His medication regimen was adjusted to intravenous acyclovir, oral vancomycin and intravenous metronidazole, and supportive intravenous normal saline was administered. During the course of his admission, cyclosporine 50 mg twice daily (no adjustment) and prednisone 5 mg daily were continued, and ibrutinib and rituximab were held. As his diarrhea

improved, his renal function improved to Cr 4.0 mg/dL. He was transitioned to oral valacyclovir 1,000 mg daily (adjusted for his renal function) and an oral vancomycin taper at time of discharge.

Case 3

A 70-year-old man with medical history of end-stage renal disease secondary to presumed hypertension status underwent post-deceased donor renal transplant 6 months prior to presentation (Table 1). The patient was not sensitized at the time of transplant and received basiliximab for induction immunosuppression. He was discharged from the hospital with admission creatinine 7.65 mg/dL, which improved to baseline serum creatinine of 1.0–1.2 mg/dL. Post-transplant, he was maintained on tacrolimus (trough level ng/mL), mycophenolate mofetil 750 mg twice daily, and prednisone 5 mg daily. He received antimicrobial prophylaxis with acyclovir for 3 months, nystatin for 1 month and trimethoprim and sulfamethoxazole single strength for 12 months.

His post-transplant course had been uncomplicated until he was presented with diffuse non-dermatomal vesicular eruption (Fig. 1a–f) and diagnosed with disseminated HZ virus infection. Vital signs include blood pressure 180/95 mm Hg, heart rate 71 beats per minute, temperature 37.1°C, respiratory rate 18 breaths per minute, and 98% oxygen saturation. Laboratory values showed serum creatinine 1.03 mg/dL, urea nitrogen 19 mg/dL, potassium 4.6 mmol/L, sodium 136 mmol/L, calcium 9.9 mg/dL, albumin 3.6 g/dL, tacrolimus trough 8.8 ng/mL. Further testing revealed PCR assay for varicella zoster virus (VZV) was positive, suggestive of acute reactivation of VZV. The patient had chickenpox at age 6 years, and he was vaccinated prior to transplant for VZV. During his admission, he received intravenous acyclovir 10 mg/kg every 8 h and supportive intravenous normal saline 250–500 mL prior to acyclovir infusion to prevent the formation of acyclovir crystals. During his admission, tacrolimus trough level was noted to be 13.8 ng/mL, and creatinine increased to 1.27 mg/dL from 1.0 mg/dL. Tacrolimus dose was decreased, and further intravenous normal saline was administered until creatinine improved to baseline.

Due to disseminated VZV infection, mycophenolate mofetil was discontinued. Eye exam by ophthalmology showed no ocular involvement with VZV infection. His active skin lesions began to crust, and he was transitioned to oral acyclovir 1,000 mg twice daily for total 14-day course.

Discussion

Kidney transplant recipients who are on lifelong immunosuppression are at higher risk for HZ infection compared to the general population. The treatment of HZ and herpes simplex whether localized or disseminated is intravenous acyclovir in combination with valacyclovir to complete at least a 14-day course. In kidney transplant recipients who have a reduced estimated glomerular filtration rate, it is important to maintain fluids to prevent the formation of acyclovir crystals in the urine. The dose should be reduced in patients with impaired kidney function [14]. We present 3 kidney transplant recipients with disseminated varicella zoster who presented at different times post-transplant with varying clinical presentations. See Table 1 for summary of patient presentations and pertinent data from case reports.

Further, it is important to monitor tacrolimus or cyclosporine levels to prevent synergistic nephrotoxicity from calcineurin inhibitors and acyclovir [15]. Hence, careful and accurate trough monitoring are vital to proper care. Further, the balance of immunosuppression can be very delicate. While holding auxiliary immunosuppressive medications is generally recommended (azathioprine, mycophenolate mofetil, mycophenolic acid) [16], it is important that the primary immunosuppressive (calcineurin based) is continued to prevent rejection. Prednisone, which is generally given in a low dose in transplant patients, can be safely continued.

The balance of immunosuppression remains crucial to prevent rejection while allowing the body the ability to fight herpes and varicella zoster infections. This is especially important in situations like herpes ophthalmicus, which can result in irreversible ocular morbidity. Disseminated zoster is even more fearsome with its potential to cause encephalitis, which results in a high mortality rate and lasting central nervous system sequalae. There are currently two types of useful vaccines for prevention of HZ; Zostavax® (zoster vaccine live) is contraindicated post-transplant but may help curb VZV infection prior to transplant [17]. Adjuvant recombinant zoster vaccine (RZV; Shingrix®) is a non-live vaccine that requires two doses and produces a potent immune response, and can be used both pre- and post-transplant to prevent development of VZV infection after transplantation [4, 18]. There is also data showing that the risk of VZV increases the longer time elapses after solid organ transplants [19]. This makes pre-transplant vaccination or in some cases post-transplant vaccination with heat killed vaccine a useful adjunct to avoid a difficult clinical dilemma like the 3 cases we discussed above.

While administering necessary vaccines prior to transplant is ideal, this is not always feasible. The best time to administer RZV after transplantation is not clear in terms of efficacy and response rate. A recent study showed immunogenicity and safety in administration of RZV in kidney transplant recipients administered vaccine 4–18 months post-transplant [18]. Therefore, most transplant centers recommend vaccinating kidney transplant recipients who are 50 years old or older and to wait at least 3–6 months after transplantation prior to administering vaccines to optimize an adequate response [20, 21]. It is also not defined whether RZV vaccination may lead to non-specific immune response of HLA antibodies and trigger rejection episodes.

In sum, we present 3 kidney transplant recipients with different clinical presentations and treatment courses, focused on careful reduction of immunosuppression, anti-viral therapy, and symptomatic care. Ultimately, the administration of vaccinations against HZ is an important preventive strategy to decrease the morbidity and mortality associated with HZ.

Statement of Ethics

The patients have given documented informed consent to publish their cases (including publication of images) under condition of anonymity. The research was conducted within framework of the guidelines for human studies, and it was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. IRB permission was not applied for as it is not required for case series with fewer than 3 patients.

Conflict of Interest Statement

Despite a lack of direct link to this subject, the author declarations are as follows. Dr. Ramy Hanna is a paid speaker and consultant for Alexion pharmaceuticals for eculizumab (Soliris®) and ravulizumab (Ultomiris®).

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Author Contributions

Dr. Ramy M. Hanna led in writing of manuscript, especially Introduction and Discussion. Dr. Farid Abd-El-Malak wrote case 2 and edited text. Dr. Ammar Alnaser wrote case 3. Dr. Rumi Cader edited text and significantly contributed to its intellectual content. Dr. Julie M. Yabu had oversight of project as senior author.

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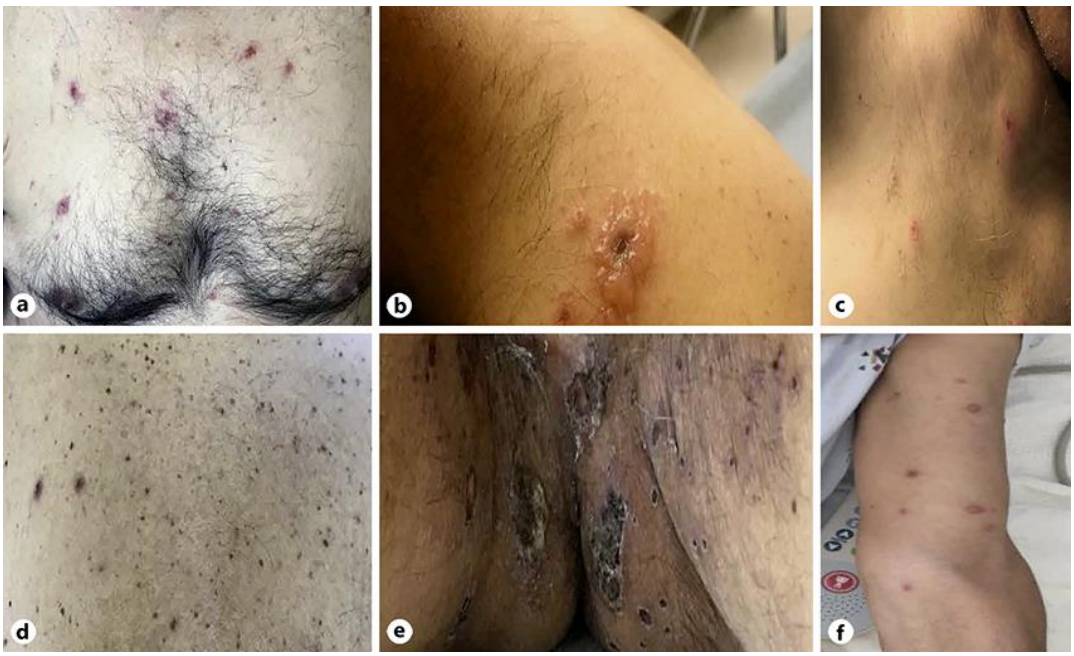

Fig. 1. Rash from disseminated varicella in patient 3, across multiple dermatomes. **a** Herpetic lesions on patient's thorax. **b** Herpetic lesions on patient's axilla. **c** Herpetic lesions on patient's abdomen. **d** Herpetic lesions on patient's back. **e** Herpetic lesions on patient's perineum. **f** Herpetic lesions on patient's leg.

Table 1. Three renal transplant patients with VZV infection

Patient	Age, years	Ethnicity	Gender	Type of renal transplant	Presentation
1	53	Caucasian	Male	LURRT	CN V-V1
2	58	Asian	Male	LURRT	T3-T4
3	70	Caucasian	Male	DDRT	Disseminated

CNV, fifth cranial nerve distribution; DDRT, deceased donor renal transplant; HSV, herpes simplex virus; LURRT, living unrelated renal transplant; T3-T4, thoracic dermatome 3 and 4; V1, first branch of fifth cranial nerve sub distribution; VZV, varicella zoster virus.