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Hemorrhagic Herpes Simplex Virus Type 1 (HSV-1) nephritis: An unusual cause of acute allograft dysfunction

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Running title:

Allograft dysfunction due to HSV nephritis

Abbreviations:

CMV - Cytomegalovirus

CT - Computed tomography

EM - Electron Microscopy

HSV - Herpes Simplex Virus

i.v. - Intravenous

IVIG - Intravenous immunoglobulins

MMF - Mycophenolate mofetil

PCR - polymerase chain reaction

Scr - Serum creatinine

SOT - Solid organ transplantation

Abstract:

Interstitial nephritis due to viruses is well-described post solid organ transplantation (SOT). Viruses implicated include cytomegalovirus, BK polyomavirus, Epstein-Barr virus, and less commonly adenovirus. We describe a rare case of hemorrhagic allograft nephritis due to Herpes Simplex Virus type 1 (HSV-1) ten days post living donor kidney transplantation. The patient had a favorable outcome with intravenous acyclovir and reduction of immunosuppression.

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Introduction:

Viral infections are a common cause of morbidity and mortality following SOT (1). Although screening, preventive measures and laboratory monitoring have improved outcomes (2), the prevalence of viral infections after transplantation remains high. HSV-associated disease following SOT can be due to reactivation, acquisition of a new infection at or just before the time of transplant, or transmission from the donor organ (3). Only a handful of cases of HSV nephritis following kidney transplantation have been described in the English literature (3-5). We describe a case of HSV-1 nephritis in a living-related kidney transplant recipient with negative HSV serologies in both donor and recipient prior to transplant.

Case:

A 63 year-old Caucasian male with end stage renal disease attributed to hypertension underwent a one-haplotype match living-related donor kidney transplant from his daughter after being on hemodialysis for one year. Cold ischemia time was 1 hour 20 minutes. The patient had a negative panel reactive antibody and did not receive induction immunosuppressive therapy. He was started on triple immunosuppressive therapy with tacrolimus, mycophenolate mofetil (MMF) and a tapering dose of prednisone. The donor was negative, and the recipient was positive for CMV antibodies. Based on intermediate risk for CMV, the recipient was scheduled for pre-emptive monitoring for CMV viremia. Both donor and recipient were negative for antibodies to HSV serotypes 1 and 2. The patient had immediate graft function with an uncomplicated hospital course and was discharged on post-transplant day 4 with a serum creatinine (SCr) of 2 mg/dl that had improved from 12.3 mg/dl pre-transplant. Due to the nature of the surgical anastomosis (short donor ureter requiring ureteroureterostomy) the patient required a ureteral stent and was discharged with an indwelling Foley catheter. For a complete timeline of events please refer to figure 1.

The patient presented 6 days after hospital discharge (post-transplant day 10) reporting pain over his surgical wound, and mild pain and swelling in his scrotum. He denied a change in his urine output and reported clear urine from his Foley catheter. Review of systems was otherwise negative. He was noted to have low grade fever (99.1F) with normal heart rate (87 beats per minute) and blood pressure (145/67 mmHg). Physical exam was notable for rigors, mild tenderness around the surgical wound which was without erythema or drainage and mild scrotal swelling without genital lesions. He was admitted to the hospital for further evaluation. Laboratory blood testing showed a normal white blood cell count, a SCr of 1.9 mg/dL, and an FK trough of 8.5 ng/ml. A urinalysis showed a specific gravity of 1.020, 1+ protein, 3+ blood (81 red blood cells/hpf), and 2+ leukocytes (23 white blood cells/hpf). It was negative for glucose, ketones, and nitrites. A computed tomography (CT) of his abdomen and pelvis showed two ~4 cm x 3 cm fluid collections near the transplanted allograft thought to be related to the recent surgery, and a hydronephrosis of his atrophic native kidney. He was started on intravenous (i.v.) vancomycin and piperacillin/tazobactam for suspected pyelonephritis; however, urine and blood

cultures showed no bacterial growth. The day after hospital admission (post-transplant day 11), his renal function worsened with a rise in SCr to 2.4 mg/dl. Due to concerns for rejection, a graft biopsy was performed, and pulse-dose i.v. steroids were started empirically. On post-transplant day 13, the biopsy showed intense zonal inflammation with viral cytopathic effect and evidence of nuclear inclusions. The lympho-histiocytic infiltrate and overall appearance were suggestive of a viral interstitial nephritis, possibly due to adenovirus infection, rather than rejection. The patient received his last dose of pulse steroids and antibiotics on post-transplant day 13. By post-transplant day 14, urine electron microscopy (EM) sent the day prior showed non-enveloped icosahedral particles, suggestive of adenovirus. On post-transplant day 15, the patient was given 1 g/kg of intravenous i.v. immunoglobulins (IVIG) for presumed adenoviral nephritis. In addition, his MMF dose was reduced by half, and tacrolimus was re-dosed for a trough of 6-8 ng/ml. Despite these interventions, his renal function continued to worsen, and he developed gross hematuria with clots by post-transplant day 16. Immunohistochemical stains for adenovirus on the transplant biopsy specimen were read as equivocal.

By post-transplant day 15 and 16, urine and blood polymerase chain reaction (PCR) tests returned negative for adenovirus, as did testing for serum CMV, BK polyomavirus, and parvovirus B19. On post-transplant day 17, urine EM was repeated and showed nucleocapsids measuring approximately 100 nm in diameter with some enveloped particles (complete virions measuring between 150-200 nm), features documenting a herpesvirus, as opposed to the naked icosahedral adenovirus (Figure 2). On the same hospital day, the patient developed new shallow-based ulcers on his penis, clinically consistent with the appearance of genital herpes. IVIG was discontinued, and the patient was immediately started on high dose i.v. acyclovir, adjusted to his renal function (the equivalent of 10 mg/kg/dose every 8 hours). On post-transplant day 18, a plasma HSV PCR returned with 68,500 HSV type 1 DNA copies/ml. HSV-2 was not detected. DNA PCR of a swab from the penile ulcer also was positive for HSV type 1. An HSV IgM antibody screen was positive as well. Concomitant immunohistochemical stains for HSV on the allograft biopsy were strongly positive within the foci of inflammation (Figure 3). A polyomavirus stain was performed and was negative. The final diagnosis was confirmed as acute hemorrhagic nephritis due to HSV-1.

Renal function started to improve with i.v. acyclovir. SCr peaked at 4.1 mg/dl on post-transplant day 18 and improved to 2.5 mg/dL at discharge on post-transplant day 23. He was continued on intravenous acyclovir for a total of 2 weeks and then transitioned to treatment doses of oral valacyclovir (1g twice a day) for a total of 6 weeks. By post-transplant day 50, his plasma HSV PCR and urine EM tests were negative. He was then transitioned to valacyclovir (1g daily) for another month. Renal function remained stable with a SCr of 1.6 mg/dL off antiviral therapy at his 3 month visit (post-transplant day 93). He remains on triple immunosuppression therapy, tacrolimus (goal trough ~6-8 ng/ml), half dose of MMF and 5 mg of prednisone.

Discussion:

HSV infection is rare following SOT. The overall incidence of HSV in the era of CMV prophylaxis is much reduced in comparison to the 1990's, as antiviral prophylaxis for CMV with ganciclovir or valganciclovir also protects against HSV (6). As per the CDC, in the United States, by 40 years of age over half of adults have been infected with CMV. According to Bradley et al, in 2005–2010, the seroprevalence of HSV-1 was 53.9%, and the seroprevalence of HSV-2 was 15.7% (7). These numbers might be even higher as the epidemiological use of type-specific HSV serology can be hampered by false negative results, especially if based on a single test, and the antibodies formed against either virus are highly cross-reactive (7,8).

One recent single center retrospective analysis in kidney-pancreas transplant recipients showed an incidence of HSV infection around 10% (9) with most patients having mild disease. HSV reactivation is usually seen in the first 3 months after transplantation in the absence of antiviral prophylaxis (2). The most common source for HSV disease is reactivation of latent infection in the immunosuppressed SOT recipient. Although much rarer, primary HSV infection acquired in the peri-transplant period or transmission from the donor have also been suggested (3-5).

Our case is unique, as both the recipient and donor HSV serologies were negative prior to transplant, implying low risk for HSV in the recipient, especially in a low risk donor such as a first degree living related donor. The recipient denied a history of cold sores or genital ulcers. There was no history of sexual exposure following the transplant.

The donor denied a history of genital ulcers but did give a history of recurrent cold sores, and had recently had an episode prior to organ donation. However, donor HSV serology remained negative on post-donation day 25.

Unfortunately, the source of infection in this case remains unproven. A donor derived infection might have been possible, but it also could have been an HSV reactivation or, less likely, a primary infection of the recipient. It is not uncommon to have a false negative result as low level HSV antibodies can be below the level of detection of the HSV serologic assays, thus the recipient's pre-transplant serology could have been a false negative result. False negative test results can be as high as 30%, depending on the assay in use (8).

Our case illustrates the challenges in the diagnosis of HSV nephritis post-transplant owing to its rarity and the importance of early and appropriate antiviral therapy as SOT recipients might have more severe clinical manifestations and respond slower to therapy (10). In our case, the picture was initially confused with adenovirus nephritis of which there have been quite a few cases reported in the literature (11-13). Because interstitial nephritis has a wide variety of causes, providers must maintain a broad differential diagnosis and continued investigation by

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means of the clinical history and laboratory testing might be necessary. Among the viruses, BK polyomavirus is the most common cause of interstitial nephritis due to its higher seroprevalence and tropism for tubular and transitional epithelium, followed by adenovirus and CMV. For a broader differential of interstitial nephritis please refer to Table 1. Rarely, more than one etiology is present like coexistent BK polyomavirus nephritis and acute cellular rejection in renal transplant patients.

On histopathology, both adenovirus and herpesvirus cause tubular necrosis, interstitial inflammation and viral cytopathic effects. Specific immunohistochemical staining is required to confirm specific viral antigens. Urine examination by electron microscopy (EM) is a rapid diagnostic test for detection of viruses in body fluids (14); however, identification of viruses based on morphologic appearance alone requires intact virions and considerable expertise. The enveloped herpesvirus is usually larger in size compared to the non-enveloped adenovirus. Initial urine EM in our case showed incomplete virions (nucleocapsids only).

However, repeat examination, in addition to naked 100 nm nucleocapsids, also showed complete virions (nucleocapsids plus envelopes) that were approximately 150 nm in size, features demonstrating a virus from the herpesvirus family. While EM examination is a quick screening tool for the presence of viruses, in many cases, definitive identification is not possible, and direct antigen detection employing immunohistochemical staining or viral isolation with monoclonal antibody immunostaining, or molecular testing are required. Likewise, when interstitial nephritis with viral cytopathic changes are discovered on kidney biopsy, we recommend immunohistochemical staining for HSV in addition to adenovirus.

According to American Society of Transplantation management guidelines, HSV-specific prophylaxis should be considered for all seropositive organ recipients not receiving antiviral medication for CMV prophylaxis, and seronegative transplant recipients should be counseled regarding risks of HSV acquisition. The risk of early post-transplant HSV infection in an organ recipient with a negative HSV serology, and not receiving CMV prophylaxis, is not well defined (6). As our patient was at intermediate risk for CMV infection and donor and recipient had a negative HSV serology, per our institutional protocol for low risk donors, antiviral prophylaxis was not instituted and laboratory monitoring of CMV was planned post-transplant. Our case demonstrates the morbidity associated with HSV infection in the setting of a HSV seronegative organ recipient not receiving CMV prophylaxis. Given that the highest risk of severe HSV disease is in seronegative recipients at risk for primary acquisition, imperfect serologic assays, and the lack of serologic testing of donors by some organ procurement agencies, transplant centers should consider antiviral prophylaxis for HSV in seronegative, as well as seropositive recipients not receiving antiviral prophylaxis for CMV.

In summary, serologic tests for screening donors and recipients are imperfect, and solid organ transplant providers must maintain a high index of suspicion for primary and donor derived viral infections in the absence of antiviral prophylaxis. Solid organ transplant programs should

consider antiviral prophylaxis for HSV in HSV seronegative recipients when antiviral prophylaxis for CMV is not administered.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

References:

1. Smith S.R., Butterly D.W., Alexander B.D., Greenberg A. Viral infections after renal transplantation. *Am J Kidney Dis* 2001;37(4): 659-676.
2. Weikert BC, Blumberg EA. Viral Infection after Renal Transplantation: Surveillance and Management. *Clin J Am Soc Nephrol* 2008;3(Suppl 2):S76-S86.
3. Silbert P L, Matz L R, Christiansen K, Saker B M, Richardson M. Herpes simplex virus interstitial nephritis in a renal allograft. *Clin Nephrol* 1990;33:264–268.
4. Dummer JS, Armstrong A, Somers J, Kusne S, Carpenter BJ, Rosenthal JT, Ho M. Transmission of Infection with Herpes Simplex Virus by Renal Transplantation. *J Infect Dis* 1987;155(2):202-6.
5. Setyapranata S, Holt SG, Wiggins KJ, Mulley WR, Kerr PG, Landgren AJ, Eisen DP, Young A, Opdam H, Robertson A, Asadi K, Hughes PD. Renal allograft re-use and herpetic re-infection. *Nephrology (Carlton)* 2015;20 Suppl 1:17-21.
6. Wilck MB, Zuckerman RA and the AST Infectious Diseases Community of Practice. Herpes Simplex in Solid Organ Transplantation. *Am J Transplant* 2013;13:121-7.
7. Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2--United States, 1999-2010. *J Infect Dis* 2014;209(3):325-33.
8. Van Rooijen MS, Roest W, Hansen G, Kwa D, de Vries HJ. False-negative type-specific glycoprotein G antibody responses in STI clinic patients with recurrent HSV-1 or HSV-2 DNA positive genital herpes, The Netherlands. *Sex Transm Infect* 2016;92(4):257-60.
9. Netchiporouk E, Tchervenkov J, Paraskevas S, Sasseville D, Billick R. Evaluation of Herpes Simplex Virus Infection Morbidity and Mortality in Pancreas and Kidney-Pancreas Transplant Recipients. *Trans Proc* 2013;45(9):3343-3347.
10. Greenberg MS, Friedman H, Cohen SG, Oh SH, Laster L, Starr S. A comparative study of herpes simplex infections in renal transplant and leukemic patients. *J Infect Dis* 1987;156:280–287.
11. Rady K, Walters G, Brown M, Talaulikar G. Allograft adenovirus nephritis. *Clin Kidney J* 2014;7(3):289-92.
12. Lachiewicz AM1, Cianciolo R, Miller MB, Derebail VK. Adenovirus causing fever, upper respiratory infection, and allograft nephritis complicated by persistent asymptomatic viremia. *Transpl Infect Dis* 2014;16(4):648-52.

13. Asim M, Chong-Lopez A, Nickleit V. Adenovirus infection of a renal allograft. *Am J Kidney Dis* 2003;41(3):696–701.
14. Goldsmith CS, Miller SE. Modern Uses of Electron Microscopy for Detection of Viruses. *Clinical Microbiology Reviews*. 2009;22(4):552-563.

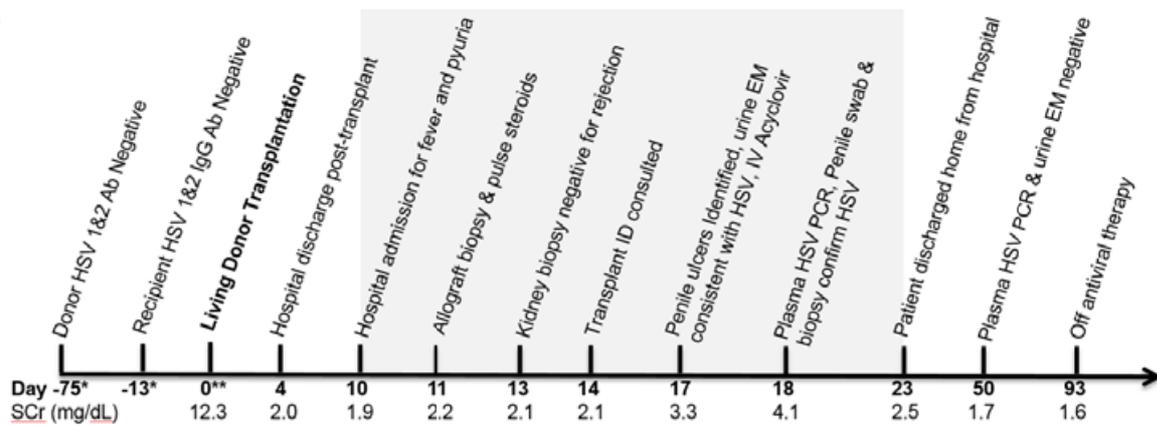


Figure 1:

Timeline of events.

* Negative days represent number of days pre-transplant.

**Day 0 represents day of transplantation.

Hospitalization of patient as referenced in the case report occurred between days 10 and 23 post transplant as highlighted in grey.

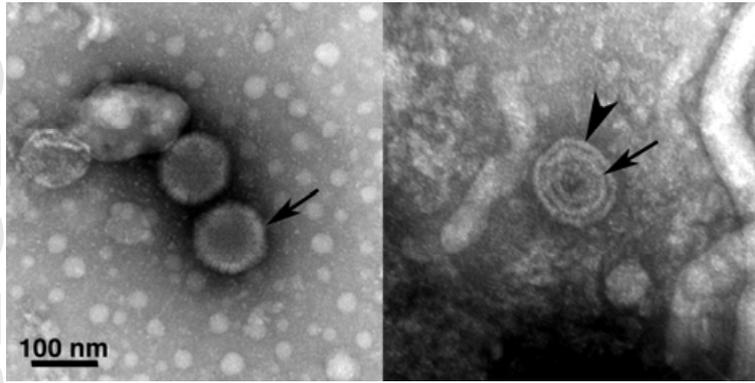


Figure 2:

Electron micrographs of negatively stained virus from urine. Left panel shows degraded virus particles, without envelopes that resemble adenovirus. After extensive reexamination, a few complete virions [particles with both an icosahedral nucleocapsid (arrow) and an envelope or membrane covering (arrowhead)] were observed (right panel). Left and right panels are shown at the same magnification with the bar representing 100 nm.

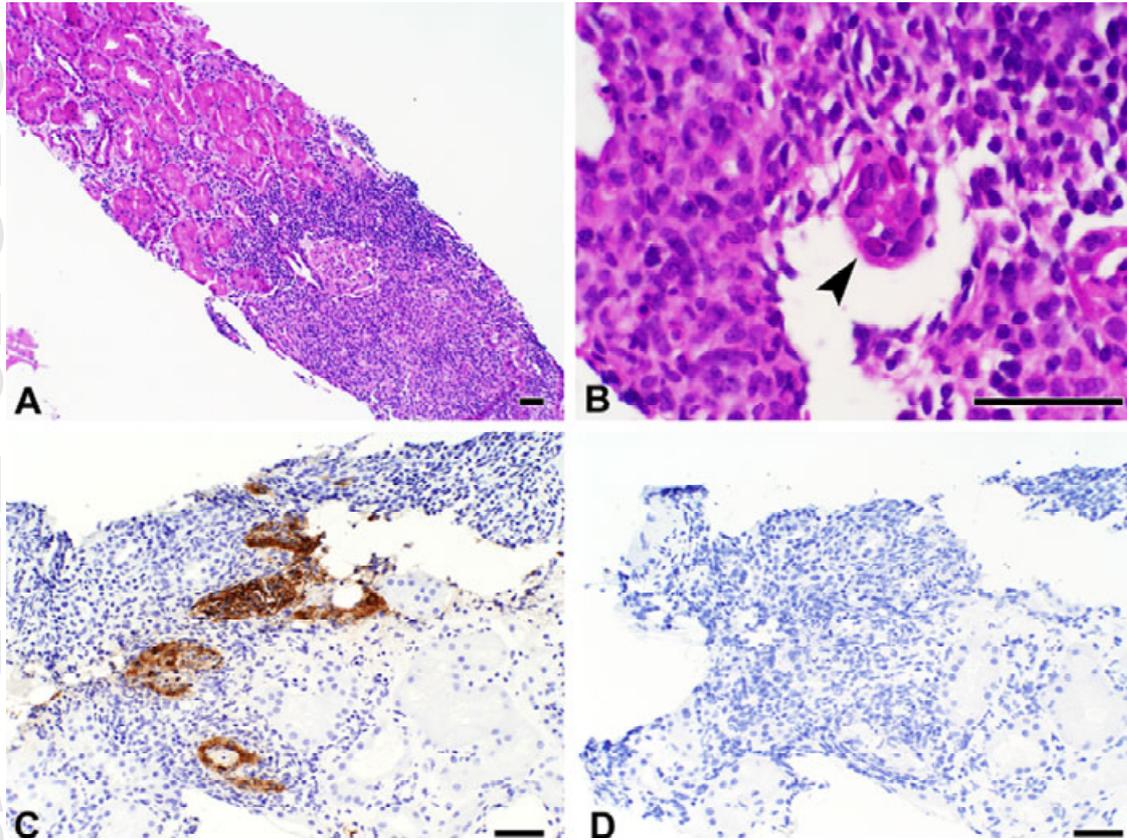


Figure 3:

Images of renal biopsy.

A. Low-magnification view of hematoxylin and eosin (H&E) stain showing dense but zonal mononuclear inflammatory infiltrate. B. High-magnification view of H&E stain showing multinucleate giant cell with "ground-glass" nucleoplasm, typical of herpesvirus infection (arrowhead). C. Immunohistochemical stain for herpes simplex virus, showing staining of several tubules. D. Serial section stained for varicella zoster virus for comparison, showing no reactivity. Bars in all panels = 50 μm.

Differential Diagnosis of Acute Nephritis	
Acute bacterial pyelonephritis	HSV nephritis
Allergic interstitial nephritis	Autoimmune disease
Acute cellular rejection of renal transplant	Lymphoproliferative disorders
Adenovirus nephritis	Plasma cell dyscrasias
BK polyomavirus interstitial nephritis	Postinfectious nephritis
CMV interstitial nephritis	Sarcoidosis
Hantavirus nephritis	Varicella Zoster virus nephritis

Table 1:

Differential diagnosis of acute nephritis in a renal transplant.