CLINICAL VIGNETTE

Adeno-Where: A Case of Disseminated Adenovirus in a Transplant Patient

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Introduction

Adenovirus is a ubiquitous viral pathogen responsible for a wide range of mild disease including upper respiratory infections, conjunctivitis, and diarrheal illness.[1-3] Infection is typically mild and most common in pediatric patients.[2,3] However, adenovirus infections in immunocompromised patients, specifically in stem-cell and solid organ transplant recipients, can cause significant morbidity and may present as disseminated disease in both adults and children.[2,3] In transplant patients, disease ranges from asymptomatic to severe and can cause significant graft dysfunction.[2,3] In this case, we present an adult renal transplant recipient with hemorrhagic cystitis, renal failure, and diarrhea, found to have disseminated adenovirus infection.

Case

A 30-year-old female with end-stage renal disease due to IgA nephropathy, had a deceased-donor renal transplant ten months prior and presented to the emergency department with 2 weeks of fevers and hematuria. In the weeks leading up to her presentation, she noticed dysuria, increased urinary urgency and hematuria and was seen by her transplant nephrologist. Urinalysis showed 1+ protein, 3+ blood, no nitrites or leukocyte esterase, >210 RBC per HPF, 17 WBC per HPF, and bacteria were present. She was prescribed a 10-day course of oral ciprofloxacin 500mg twice daily, for a presumed urinary tract infection (UTI). After starting antibiotics, her dysuria improved but hematuria persisted. Her urine culture result showed no bacterial growth, and after speaking with her nephrologist she stopped taking the ciprofloxacin after 7 days of treatment.

Her symptoms subsequently worsened, and she developed fevers, chills, myalgias, and night sweats prompting ED evaluation.

She also developed watery diarrhea, with about 3 bowel movements per day. There were no recent sick contacts, though had traveled recently and returned from Texas. She had been taking all her immunosuppressive and prophylactic medications as prescribed, including tacrolimus 8mg every morning and 7mg nightly, mycophenolate 500mg twice daily, prednisone 5mg daily and trimethoprim-sulfamethoxazole 80-400mg daily.

She presented to the emergency department, with temperature of 37.9˚C, heart rate of 127 beats per minute, respiratory rate of 38 breaths per minute, blood pressure of 113/73 mmHg, and oxygen saturation of 100% on room air. Initial physical exam was unremarkable, with no abdominal tenderness including over her graft site in the right lower quadrant, and no costovertebral angle tenderness. Urinalysis again showed 3+ blood, 1+ protein, no nitrites or leukocyte esterase, >210 RBC per HPF, 14 WBC per HPF, and bacteria were present, along with hyaline casts. Labs were notable for a creatinine of 2.44 mg/dL, up from her stable post-transplant baseline of approximately 0.7 mg/dL. BUN was also elevated at 29 mg/dL. WBC and lactate were normal at 6.88 $x10^3$/uL and 5 mg/dL, respectively. Her sodium was 127 mmol/L and bicarbonate was 15 mmol/L. Venous blood gas showed a pH of 7.36 with pCO2 of 33 mmHg. Renal ultrasound and CT Kidneys, Ureters and Bladder (CT KUB) on admission showed mild hydroureteronephrosis and diffuse urothelial thickening of the bladder and renal allograft. She was admitted to the hospital with concern for urosepsis and pyelonephritis of her graft. In the emergency department she received fluid resuscitation and empirical ertapenem 1 gram intravenously.

Admission, a broad infectious evaluation was sent, including *C. difficile* polymerase chain reaction testing (PCR), blood cultures, urine culture, stool cultures, urine ureaplasma, urine AFB and STI testing. Given ongoing tachycardia and fevers despite empiric treatment with ertapenem, antibiotics were broadened to meropenem and vancomycin, which were renally dosed. The renal transplant and transplant infectious disease teams were consulted. For the next 2 days she continued to have fevers despite broad spectrum antibiotics, and per discussion with transplant infectious disease the decision was made to monitor off antibiotics. Bacterial blood cultures and bacterial stool cultures were negative, along with a negative urine culture, but on hospital day 4 her stool and serum studies returned positive for adenovirus, with high viral load of 6,140,000 copies/mL. Cidofovir antiviral therapy, was initiated with pre- and post-therapy probenecid and IV hydration. She received cidofovir on hospital days 4, 6, 8, 11, and 13, for a total of 5 doses. Her adenovirus viral load improved to 17,800 copies/mL after 3 doses of cidofovir, and her creatinine decreased to 1 mg/dL by hospital day 13. At her post-discharge follow-up appointment,

adenovirus viral load was undetectable, and her creatinine was stable at 0.95 mg/dL.

Discussion

This patient presented with a constellation of symptoms including fevers, diarrhea, and hemorrhagic cystitis, all which may be attributed to adenovirus infection.[4-6] Hemorrhagic cystitis is known to occur in immunocompetent children infected with adenovirus infection, however in adults infection seems to be more limited to immunocompromised patients, specifically bone marrow transplant and renal transplant patients.[1-4] Given the frequency of bacterial UTIs in young, female patients, a bacterial source of infection was initially suspected as the most likely diagnosis. However, because her symptoms did not improve with broad spectrum antibiotics, the differential expanded to include resistant bacterial or viral etiologies. As she continued to have minimal improvement in symptoms with appropriate inpatient broad-spectrum IV antibiotics, other causes including viral pathogens or graft rejection became more likely. Many of her findings including renal failure, proteinuria, and imaging findings could have also been attributed to graft rejection.[7]

The diagnosis of adenovirus infection was made in our patient via stool and blood PCR testing, both quantitative and qualitative. Biopsies were not performed because the presumed diagnosis of disseminated adenovirus with positive PCR testing in multiple samples explained her clinical findings and symptoms, and she showed improvement with treatment. However, a kidney biopsy is still considered the gold standard for adenovirus diagnosis in adrenal transplant patients and can help differentiate between rejection, infection, and other acute pathology.[3,4] Interestingly, histopathologic findings on kidney biopsy of acute adenovirus infection, including tubular necrosis and interstitial inflammation, can appear similar to graft rejection.[3-6] Immunohistochemical staining to identify adenovirus can help to differentiate between the two, as well as nuclear changes including basophilic nuclear inclusions.[1,3-6]

There are currently no United States Food and Drug Administration (FDA) approved antiviral treatments for adenovirus infection, regardless of patient presentation. Though there are no randomized controlled trials supporting any specific antiviral treatment for disseminated adenovirus infections, cidofovir is the current favored treatment option and recommended per guidelines from the American Society of Transplantation Infectious Diseases Community of Practice.[1-3,8] Cidofovir is a nucleotide analog that inhibits viral DNA polymerase and has been shown in case reports to be effective against adenovirus infections.[1-4,8] However, the drug has significant side effects including nephrotoxicity, which is why it is recommended to be given with probenecid and IV hydration.[3] The nephrotoxicity of cidofovir can make treatment of adenovirus infections in renal transplant patients particularly challenging as the virus often also worsens renal graft function.[2-4]

Brincidofovir is a new drug, recently FDA approved for the treatment of smallpox, that is also being studied in clinical trials for potential use in adenovirus infections.[9] It is a lipid conjugate of cidofovir and has a few potential advantages over cidofovir including improved oral bioavailability, lack of nephrotoxicity and increased potency against adenovirus.[1-4,8] It does appear to cause significant gastrointestinal side effects including nausea and vomiting.[2,3] In the future, brincidofovir may become more widely used in the treatment of disseminated adenovirus given this preliminary data.

This patient was treated with cidofovir 1mg/kg three times per week, along with pre- and post-treatment probenecid and IV hydration. This regimen was effective in both improving clinical symptoms and decreasing the viral load, while also preserving kidney function. On the first day of treatment her creatinine was 1.93 mg/dL, and improved to 0.95 mg/dL by the date of discharge.

This is an example of successful treatment of disseminated adenovirus with cidofovir, with a measurable decrease in viral load to undetectable, resolution of symptoms, and improvement of renal graft function. This case adds to the growing evidence of cidofovir's effectiveness in treating disseminated adenovirus infection in immunocompromised patients.

Conclusion

In summary, this adult renal transplant patient presented with fevers, hematuria, diarrhea, and acute renal failure in the setting of disseminated adenovirus infection with a high serum viral load. The patient was treated successfully with cidofovir, with subsequent improvement in renal function and decrease in viral load. Future areas of investigation include use of the newly approved antiviral medication brincidofovir, which may be effective and less nephrotoxic than cidofovir. Long term follow-up of renal transplant patients treated with cidofovir is needed to ensure normalization of renal function and to identify any long-term sequela of disseminated adenovirus infection and treatment.

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