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LETTER TO THE EDITOR

Topical cidofovir-related acute kidney injury in a kidney transplant recipient

Human papilloma virus (HPV) is mostly associated with genital warts, such as condyloma and verruca vulgaris. Recommendations for the treatment of external genital warts include the use of topical solutions such as podophyllin, imiquimod, or trichloroacetic acid, or local interventions such as cryotherapy, as well as referral to gynecology for surgical excision in cases of failed therapy.[1] Topical cidofovir has been demonstrated to be effective in the management of HPV-associated skin lesions in immunosuppressive patients.[2–4] Here we report the use of topical cidofovir in a kidney transplant recipient with verrucae vulgaris resistant to conventional treatments.

A 34-year-old female was seen in a dermatology clinic for vulvar lesions. She had received a kidney transplant from her father 12 years ago. Immunosuppressive treatment consisted of prednisolone, mycophenolate mofetil (MMF), and tacrolimus. Serum creatinine was stable ranging between 1.3 and 1.5 mg/dl. Her vulvar lesions started about a year ago for which she was treated with imiquimod, topical fluorouracil, CO_2 laser, and cryo-therapies. At initial evaluation at our hospital, diffuse papillomatous papules involving the vulva were noted and the biopsy specimen demonstrated HPV-positive verrucae vulgaris. Considering the resistance to previous topical treatments, topical cidofovir was planned. A 3% cidofovir was prepared in propylene glycol, ethanol, paraben, and water. After 5 days of twice-daily application, blood tests showed acute kidney injury. Laboratory profile revealed creatinine 2.9 mg/dl, HCO3 17 mmol/L, potassium 2.9 mEq/L, phosphorus 2.3 mg/dl, magnesium 1.5 mg/dl, and uric acid 2.1 mg/dl. While tacrolimus trough level was 5.7 ng/ml on admission. Urinalysis showed no glycosuria with mild proteinuria of 357 mg/day. Topical cidofovir was immediately stopped. Physical examination and transplant kidney Doppler ultrasound findings were unremarkable. BK virus DNA was negative. Due to the presence of hypokalemia, hypomagnesaemia and hypophosphatemia diagnosis was made as cidofovir-induced acute tubular injury. After cessation of cidofovir, intravenous hydration was started and her creatinine level decreased back to 1.4 mg/dl within 7 days. Tacrolimus trough levels ranged between 5.2 and 6.4 ng/ml during her course of stay. Following this incident, her immunosuppressive treatment was changed to everolimus replacing MMF combined with low-dose tacrolimus. After the change in immunosuppressive treatment, the lesions regressed and the creatinine level remained stable without proteinuria in the follow-up.

Cidofovir, a nucleotide analog that has antiviral activity against DNA viruses, has been used for cytomegalovirus and herpes virus infection in transplant recipients. It also inhibits viral replication of papillomaviruses. Nephrotoxicity is the major concern, especially in kidney transplant recipients. In clinical practice, optimal hydration and close follow-up of graft function are recommended during intravenous cidofovir treatment. In skin lesions, physically active substances may be preferred over systemic exposure. Topical cidofovir has been used in many transplant recipients.[2–5] Topical cidofovir can cause systemic adverse events if they are applied to damaged skin and mucous membranes. Therefore, nephrotoxicity may become a concern even with topical use. In an experimental study, it was demonstrated that the bioavailability of cidofovir was 20 times greater in abraded skin when compared to normal skin.[6] Another factor affecting the bioavailability was the compound of the topical treatment. Cidofovir prepared with propylene glycol has higher systemic bioavailability than that prepared with hydroxyethyl-cellulose.[6] Concentration of cidofovir in topical administration may also be important for bioavailability, as expected. In our patient, several factors may have aggravated graft dysfunction. Treatment-related factors are compounds of the drug, use of 3% concentration of cidofovir, and uncontrolled application in the abraded skin. There were also transplant-specific factors such as concomitant tacrolimus use, pre-existing graft dysfunction, and inadequate hydration status. In literature, acute kidney injury related to topical cidofovir use has been reported in few other case reports.[4,5]

Although we did not perform a kidney biopsy on our patient, we presumed cidofovir-related graft dysfunction due to the presence of characteristics of proximal tubular injury, lack of other causes that might be associated with graft dysfunction, and rapid improvement of kidney functions after cessation of cidofovir treatment. When we assessed Naranjo algorithm in order to determine the probability of an adverse drug reaction (ADR) being due to the administration of a drug, a score of 7, corresponding with a probable ADR was found.[7] Another limitation of this case report was lack of the cidofovir blood levels due to the unavailability of measurement in our hospital.

In our patient, everolimus was started due to its antiproliferative effects in viral infections. HPV positivity, which may cause dysplastic changes, encouraged us to this drug change. It has previously been

suggested that mTOR inhibitors can suppress viral replications and also regulate cell growth and survival; the pathways of which are often dysregulated in various types of malignancies.[8] Therefore, avoiding MMF and changing to everolimus-based treatment can be considered in cases with HPV-related conditions.

In conclusion, clinicians should be alerted regarding unintended acute kidney injury even during topical cidofovir treatment and special attention must be paid when higher concentrations of topical cidofovir are prepared. Close monitoring of creatinine is recommended, particularly in kidney transplant recipients.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated.

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