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Case report

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Conversion of calcineurin inhibitors by mTOR inhibitors contributes to the treatment of intraepithelial neoplasms in the cervix in women with renal transplantation

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Abstract

The patient is a 32-year-old woman with a history of chronic kidney disease due to interstitial nephritis. After 2 years on hemodialysis the patient received a renal transplant and was treated with standard immunosuppression: steroids, mycophenolate mofetil and tacrolimus. Three years later the patient presented a squamous intraepithelial neoplasia in the cervix and infection with human papilloma virus (HPV), with poor response to local treatment with cryotherapy and laser. Because calcineurin inhibitors have a higher risk of presenting cancer such as non-Hodgkin's lymphoma and skin cancer, and because inhibitors of the mammalian target of rapamycin (mTOR) at the intracellular level could reverse premalignant skin tumor lesions in the head and neck, tacrolimus, was suspended and changed to everolimus, an mTOR inhibitor. As a result, both cervical lesion and HPV infection disappeared 6 years later, with a fair renal function and no episodes of renal graft rejection.

Key words: Tacrolimus. Everolimus. Intraepithelial cervical neoplasia. Human papilloma virus.

Conversión de inhibidores de la calcineurina por inhibidores mTOR contribuye al tratamiento de las neoplasias intraepiteliales en cérvix en mujeres con trasplante renal

Resumen

Mujer de 32 años con antecedentes de enfermedad renal crónica debido a nefritis intersticial. Después de 2 años en hemodiálisis la paciente recibió un trasplante renal y fue tratada con inmunosupresión estándar: esteroides, micofenolato mofetilo y tacrolimus. Tres años después la paciente presentó una neoplasia intraepitelial escamosa en cérvix e infección con el virus del papiloma humano (VPH), con mala respuesta al tratamiento local con crioterapia y láser. Debido a que los inhibidores de la calcineurina tienen mayor riesgo de presentar cáncer como el linfoma no Hodgkin y el de piel, y los inhibidores de la vía mammalian target of rapamycin (mTOR) a nivel intracelular pueden revertir las lesiones premalignas de tumores de piel en cabeza y cuello, el tacrolimus, fue suspendido y cambiado por everolimus, un inhibidor mTOR. Como resultado tanto la lesión en cérvix como la infección por VPH desaparecieron 6 años después, con una buena función renal y sin episodios de rechazo del injerto renal.

Palabras clave: Tacrolimus. Everolimus. Neoplasia cervical intraepitelial. Virus del papiloma humano.

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Introduction

More than 290 million of women are infected with HPV worldwide according to the World Health Organization (WHO) report in November 2013[1]. It is the most common sexual transmitted disease STD in the United States and it is associated with condyloma, with squamous intraepithelial ano-genital lesions (Cervical, vagina, vulva, penis and anus) and with risk of skin cancer with squamous cells in head and neck[2]. The risk of presenting these lesions is higher in patients with transplant due to the immunosuppressive state[3]. As a result, the risk of developing ano-genital cancer is extremely high among these patients[4]. However, not all HPV infections associated with intraepithelial lesions progress to cancer, but they must have an accurate clinical follow-up.

HPV is a DNA virus that has multiple genotypes divided into "high risk" and "low risk". Types 16 and 18 are of high risk and have a greater association with cervical cancer[2]. The results of a cervical cytology can be described as atypical squamous cells, low grade squamous intraepithelial lesions, high grade squamous intraepithelial lesions or atypical glandular cells[2]. In the case of detecting an intraepithelial lesion and detecting HPV, in a woman older than 30 years, strict follow-up should be performed with colposcopy, cervical biopsy and local treatment for cure[5].

There is evidence that pre-malignant and malignant lesions associated with HPV and skin tumors in head and neck have a greater activation of the mTOR pathway at the intracellular level and that inhibitors of the mTOR pathway may decrease the activation of genes anomalies in the target organs[6-8]. This is due to the mutation of HPV E6 / E7 oncoproteins, which can induce cancer cells through the intracellular signaling pathway of phosphatidylinositol 3-kinase / AKT / mTOR. Therefore, in the case of patients receiving immunosuppressive medication because of renal transplantation with calcineurin inhibitors, conversion to mTOR inhibitors may be an alternative for the treatment of lesioins associated to HPV[9].

Cervical cytology is the standard screening test for cervical cancer and premalignant lesions, and it should be performed in immunocompromised patients, just as in the general population[2,5]. In addition, the identification of HPV has improved the detection of cervical neoplasia and it allows a stratification of the risk to present it in the future.

In referente to this, we present a clinical case of a renal transplanted woman who, after being diagnosed with a low-grade intraepithelial lesion in the cervix, the calcineurin inhibitor (tacrolimus)is changed by an inhibitor of mTOR with a total disappearance of the lesions after a few months.

Case presentation

A 32-year-old woman with a history of chronic renal failure secondary to non-affiliated interstitial tubule nephritis and nephrocalcinosis. She underwent hemodialysis in May 2003. In April 2004, she received a kidney transplant from a brain death donor with standard immunosuppressive treatment, steroids, mycophenolate mofetil (1 gc / 12h) and tacrolimus (levels 7-10 ng / ml), without induction. She did not presented delayed graft function or rejection data from the latter, with a creatinine of 1 mg / dl at the time of hospital discharge.

Since the renal transplant was performed, she is continually monitored by the Gynecology Service with a vaginal cytology every year. In June 2007, a low-grade intraepithelial cervical squamous lesion and HPV infection with genotypes 6, 16, 42, 51 and 53 were diagnosed. It was confirmed by biopsy. Local treatment with cryotherapy was decided without showing any improvement. Instead, condylomata in the cervix, vaginal fundus and left vagina wall developed. Once again, local treatment with cryotherapy and laser treatment is carried out without the disappearance of the lesions. Because of the lack of response to local treatment, tacrolimus is converted to everolimus (levels 6-8 ng / ml) and subsequently mycophenolate mofetil is discontinued in February 2011. In subsequent checks, the lesions are disappearing and since April Of 2012 the results of the

cytology, colposcopy, cervical biopsy and HPV serology are negative to date.

After the decrease in immunosuppression, conversion of tacrolimus to everolimus, and mycophenolate mofetil discontinuation (decreased immunosuppression), lesions in both the cervix and vagina have disappeared, as well as the risk of tumor progression. The current immunosuppressive treatment is prednisolone administered 5 mg daily, everolimus with target levels of 6-8 ng / ml. No renal graft rejection has been proven. The patient presents a glomerular filtration rate greater than 60 ml / min and albuminuria less than 6 mg / L, without complications associated with mTOR inhibitors.

Discussion

The most relevant finding of this case is that the conversion of calcineurin inhibitors to mTOR inhibitors has contributed to the resolution of cervical-related HPV lesions, which had persisted despite local gynecological treatment.

The risk of cervical cancer among kidney transplant patients is approximately 14 to 16 times higher and the risk of vulvar cancer is 100 times higher4,10. It has been observed that treatment with mTOR inhibitors may be effective for some types of neoplasms associated with HPV[9].

After reviewing the literature, we have not found any studies regarding the resolution of HPV-related lesions at the cervix level after conversion of calcineurin inhibitors to mTOR inhibitors. Small series and clinical cases have been published in which resolution of head and neck skin cancer lesions is shown after treatment with mTOR inhibitors. In our case, despite performing all the gynecological procedures to eradicate an intraepithelial squamous lesion in the cervix, it has only been possible with the conversion of a calcineurin inhibitor by an mTOR inhibitor and the discontinuation of mycophenolate mofetil. In squamous cell carcinoma at the head and neck level associated with HPV, the virus has shown to act by activating the mTOR pathway at the cellular level; Therefore, its inhibition causes a considerable reduction of the lesions[2,9].

Studies with adequate statistical design and larger case series are needed to understand and determine the importance of mTOR inhibitors in patients with pre-malignant or malignant lesions. Both in the complete population and in the immunocompromised population, as is the case of patients with a solid organ transplant.

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