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Case report

Everolimus and papillomavirus lesions in female renal transplant recipient: A case report

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ABSTRACT

We describe the case of a transplanted patient with high-risk HPV infection that manifested as multiple genital condylomas and abnormal Papanicolaou (Pap) smear. Her immunosuppressants were corticosteroids, cyclosporine, and azathioprine. Since gynecologic treatments to eradicate condylomas were completely unsuccessful, cyclosporine was replaced by everolimus. Soon after, condylomas disappeared, HPV status became negative, and Pap smear returned to normal and has remained normal since.

1. Introduction

Human papillomavirus (HPV) infection affects hundreds of millions of people worldwide and is associated with benign and malignant neoplasms of the anogenital region in men and women. HPV is a DNA virus, classified into high-risk and low-risk types based on the virus's tendency to cause cancer. Besides cancer, low-risk and high-risk HPV (hrHPV) can cause anogenital warts (condyloma acuminata). Clearance of HPV infection depends on adequate immunity, and it happens in more than 90% of cases of immunocompetent individuals (Plummer et al., 2007). Renal transplant recipients (RTRs) due to lifelong immunosuppressive (IS) therapy are at high risk of developing persistent infection, treatment-refractory anogenital condylomas, and HPV-related cancer (Reusser et al., 2015). Among female RTRs, cervical cancer is one of the biggest concerns since it is one of the most common types of cancer in women worldwide. In the majority of cases, it is caused by hrHPV (Munoz et al., 2006). It has even been shown that spontaneous regression rate of HPV-related diseases in female RTRs, if left untreated, was 0% (Tanaka et al., 2016). If actively treated, HPV-related diseases still persisted in 43% of cases (Tanaka et al., 2016). In contrast, the condition of the majority of immunocompetent patients regressed spontaneously (Tanaka et al., 2016).

There is evidence that most patients in the pretransplant period with normal cervical cytology change to abnormal cytology in the post-transplant period due to either reactivation of a latent or new HPV infection (Wang et al., 2012). Also, progression in abnormal cervical cytology happens significantly faster in transplant patients than in the general population (Tanaka et al., 2016).

IS therapy decreases the ability to eradicate new HPV infection and permits HPV replication in latently infected cells. The aim of IS therapy is to prevent graft rejection, while altering as little as possible the immunity unrelated to the graft, such as viral reactivation. Some of the IS protocols include mammalian target of rapamycin inhibitors (mTORi), such as everolimus.

2. Case presentation

A 16-year-old girl came to Croatia in 1992 as a refugee due to war. According to the available medical chart and her knowledge, she had no serious illnesses in childhood. During 1992, she began taking antihypertensive therapy. The same year, she underwent an urgent abdominal surgery with resection of 80 cm of ileum due to gangrenous changes of the intestine. Right after the surgery she became oliguric and underwent dialysis for the first time. Abdominal ultrasound revealed very small kidneys with chronic alterations. For that reason, kidney biopsy had never been done. Soon after, she had arteriovenous fistula constructed and had begun hemodialysis sessions three times a week.

In December 1998, she underwent cadaveric kidney transplant, and in 1999 she underwent bilateral native kidney nephrectomy due to unregulated hypertension. During the first two years after transplant she had three episodes of acute graft rejection and was successfully treated with boluses of corticosteroids. Afterward, kidney graft function was stable with creatinine 140 to 150 μmol/L (1.6 mg/dL). Her regular therapy were corticosteroids, cyclosporine, azathioprine, and

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antihypertensive therapy, with well-regulated blood pressure.

Until 2008, the patient did not experience any medical crisis. But in 2008, a Papanicolaou (PAP) test for the first time showed cervical intraepithelial neoplasia stage I (CIN I) and hrHPV infection. Ever since, she has had regular gynecologic checkups every 6 months. Colposcopy and Schillers iodine test were positive several times, along with CIN I and hrHPV. Since 2010, the patient had begun having problems with multiple genital condylomas (condylomata accuminata vaginae et vulvae). Therefore, over the next 2 years she underwent several gynecologic treatments: electrocauterization, electroexcision, and podophyllin therapy. Since that therapy proved completely unsuccessful, cyclosporine was replaced by everolimus in May 2012. Since 2013, she had no more genital condylomas, although PAP smear was still CIN I and hrHPV positive. In the meantime, she became HPV negative, with completely normal PAP test. Gynecologic findings have been within normal range for 3 years now. Graft function is maintained, with slowly "creeping" creatinine, at current levels around 280–300 umol/L (3.16–3.39 mg/dL). Currently, her regular therapy consists of everolimus 2 × 1 mg, azathioprine 50 mg, prednisone 5 mg every other day, antihypertensive therapy (perindopril/amlodipine 4/5 mg), folacin acid, and calcitriol. Plasma concentration of everolimus has been maintained at a range 1–2 μg/L, as she was intended to reach a lower level of overall IS due to her chronic infection and premalignant history.

3. Discussion

Besides IS characteristics, mTORi also have positive immunomodulatory effects. Compared with other IS drugs after renal transplantation, mTORi have been proven to cause a lower rate of de novo malignancy, less nephrotoxicity, and a lower rate of cytomegalovirus disease (Nashan et al., 2012; Brennan et al., 2011). They are also a choice for BK virus nephropathy (Polanco et al., 2015). This class of ISs also leads to an increase in number and quality of antigen-specific CD8+ memory T-cells (Araki et al., 2009). They stimulate innate immunity (Saemann et al., 2009) and reverse some of the negative effects of glucocorticosteroids on innate immunity (Weichhart et al., 2011).

Everolimus, as an mTORi, is currently recommended for various conditions, including preventing organ rejection after renal transplant. It is also known for its antiviral and anticancer effects.

It is well known that mTOR signaling pathway is activated in both HPV-positive and HPV-negative cervical carcinoma (Molinolo et al., 2012). It also has been shown that mTORi activation occurs in at least 60% of the HPV-caused cancers (Feng et al., 2009). At the same time, female solid organ transplant recipients with HPV infection are at a 20- to 100-fold increased risk of CIN (Avery and Michaels, 2008). They have faster progression of HPV-related lesions and a higher risk of cervical cancer (Hinten et al., 2012). Cell-mediated immunity is important for successful eradication of HPV infection. However, transplant recipients have impaired cell-mediated immunity due to IS therapy. Besides, no specific treatment for HPV infection currently exists.

Our patient underwent transplantation at age 22. Only 10 years after, her gynecologic tests showed CIN I and hrHPV for the first time. We presume she had a new HPV infection rather than reactivation of latent infection. At the time of her transplant, HPV vaccine was not available.

Discontinuation of cyclosporine itself might has had a positive impact in normalizing our patients gynecological findings. But, given the fact that mTOR inhibitors are known for their antiproliferative effects and the fact that mTOR signaling pathway is activated in cervical carcinoma we believe switching to everolimus, as an mTOR inhibitor, has in major part helped normalize and maintain our patient's gynecologic findings within normal range. We also believe that screening for HPV in the pre- and post-transplant periods and vaccination before transplantation should become usual practice.

In the end, we can say that graft recipients diagnosed with hrHPV infection require close monitoring because IS therapy may cause inadequate immune response in case of primary infection or reactivation of the latent infection. Close monitoring also includes possible changes in IS therapy with emphasis on mTORi.

Conflict of interest statement

Authors have no conflict of interest to declare.

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