

Disseminated cutaneous infection by human papilloma virus in a renal transplant patient

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Abstract

Patients undergoing solid organ transplants are at risk of developing malignant and infectious diseases related to the magnitude and timing of immunosuppressive therapy. Cutaneous infections are one of the most frequent complications in these patients, viral warts being the most common clinical manifestation caused by the human papilloma virus, a DNA virus belonging to the family of the Papillomaviridae, with at least 100 serotypes, some of these with high oncogenic potential, and with a high risk of developing anogenital tract or cervical malignancies. These lesions are rarely present before the first year after transplantation and its frequency increases in direct proportion to the age of transplantation, affecting about 80% of patients after the fifth year post-transplant. In general, they are successfully treated with conventional treatments such as cryotherapy, curettage and some compounds as topical retinoids, imiquimod and cases of successful treatment with cidofovir have recently been reported. In this paper, a case which was refractory to conventional treatment is described, and new management strategies are proposed.

Key words: Human papilloma virus 6, Human papilloma virus 11, Human papilloma virus 16, Human papilloma virus 18, Kidney Transplantation, Cidofovir

Infección cutánea diseminada por el virus del papiloma humano en paciente con trasplante renal

Resumen

Los pacientes sometidos a trasplantes de órgano sólido tienen mayor riesgo de desarrollar patologías malignas e infecciosas en relación con la magnitud y el tiempo de la terapia inmunosupresora. Las infecciones cutáneas son una de las complicaciones más usuales en este tipo de pacientes, siendo las verrugas virales la presentación clínica más frecuente, causadas por el virus del papiloma humano, un virus ADN perteneciente a la familia de los *Papillomaviridae*, del cual existen cerca de 100 serotipos, algunos conocidos con alto potencial oncogénico, con un elevado riesgo de desarrollar malignidad a nivel anorrectal o cervical. Rara vez estas lesiones se manifiestan antes del primer año del trasplante y su frecuencia aumenta en relación directa a la antigüedad del trasplante, hasta afectar cerca del 80% de los pacientes tras el quinto año postrasplante. En general logran ser tratadas exitosamente con tratamientos convencionales, como crioterapia, curetaje y algunos compuestos tópicos como retinoides, imiquimod y, recientemente, se han descrito casos de tratamiento exitoso con cidofovir. Se describe un caso el cual fue refractario al tratamiento convencional y en que se plantean nuevas estrategias de manejo.

Palabras clave: Virus del papiloma humano, Trasplante renal, Cidofovir.

Introduction

The human papillomavirus (HPV) is a common virus that affects both men and women and comprises different families of viruses that cause various manifestations on the skin. The most important are the verruca vulgaris (especially in hands and feet) and the genital warts or condyloma. The latter is important because untreated infection in both women and men can lead to anogenital cancer, since these lesions initially appear as benign keratoses and frequently progress to dysplasia and subsequently invasive carcinomas^{1,2}.

Renal transplant patients are at increased risk of developing such lesions. However, extensive involvement is unusual and the development of cutaneous and anogenital cancer is more possible than for the general population. Additionally, it has been observed that in these patients the different serotypes of HPV partially lose their tissue specificity: for example, serotypes 6, 11, 16, 18, usually confined to the mucous membranes, are the cause of vulgar warts in photo-exposed areas^{1,2}. Some studies have proven the presence of oncogenic serotypes in hair follicles in 92% of transplant patients (not only renal) versus 53% of non-immunocompromised patients. This postulates that the hair follicle could be a reservoir of some HPV that would replicate due to immunosuppression^{3,4}.

The initial treatment with cryotherapy, imiquimod and podophyllin for HPV lesions in the renal transplant patient is not different from the non-immunosuppressed patient's, but it has a higher failure rate. For this reason, the systemic treatment with retinoic acid takes a greater importance, and the surgical treatment is an alternative when the lesions are susceptible to resection. Also, antivirals such as cidofovir have been proposed for the management of extensive lesions in this type of patients^{5,6}.

Methods and results

Case Description

A 33-year-old man with a history of renal transplantation due to chronic renal disease, at the final stage, secondary to rapidly progressive glomerulo-

nephritis, on immunosuppressive treatment with Tacrolimus, Mycophenolate sodium and Prednisolone, who 2 years after renal transplantation is examined because of the appearance of warty lesions suggestive of viral infection, in the perianal and testicular region, hands and feet (Figure 1-2). Histopathological diagnosis of HPV infection was performed, there were lesions that were initially treated with cryotherapy, presenting temporal improvement and subsequent reappearance and increase in both quantity, size and extension. The lesions were treated again with cryotherapy associated with imiquimod and oral isotretinoin for 3 months without favorable clinical response.

Physical examination revealed multiple warts, irregular, pedicled of different sizes in hands and feet with distal deformity of the fingers, multiple lesions in scrotal region of different sizes and condyloma acuminata of bad smell without bleeding or secretion in the perianal region, without other alterations. The patient was considered a solid organ transplant patient who had extensive HPV infection resistant to standard first and second line treatment, an aggressive clinical manifestation difficult to manage in relation to immunosuppressive therapy. Tacrolimus was suspended and Sirolimus is included in the immunosuppressive treatment because of its antiviral effect, and topical treatment with cidofovir in hand and foot injuries is proposed.

Informed consent by the patient was made for the taking of photographs and use of information.

Discussion

HPV is a diverse group of DNA viruses belonging to the family of Papillomaviridae and represents one of the most common sexually transmitted diseases, with more than 100 viral types that, in relation to their oncological pathogenesis, are classified in high and low oncological risk, the latter being the cause of dysplasia and metaplasia that can culminate in a malignant lesion. Renal transplant patients are at increased risk of developing skin cancer, especially in areas with sun exposure following immunosuppressive therapy^{1,2}.

Figure 1.
Condylomas in right Hallux and palm of hands



Figura 2.
Condylomas in perianal and scrotal region



In renal transplant patients receiving immunosuppressive therapy, the incidence of warts and skin and genital region cancer is high and proportional to the intensity and duration of immunosuppression. At the end of the first year post transplantation, 15% of these patients have warts. At 5 years the incidence increases by 77-87%. The molecular mechanism of

oncogenesis in immunosuppressive states is not yet well known. Immunosuppression alone is not related to the onset or evolution of malignant lesions, but it is related to the appearance of early stages of dysplasia by suppressing the defense mechanisms against the virus. The risk of developing skin cancer in patients with solid organ transplants may range

from 5 to 82%, being higher in regions with a high prevalence of skin cancer. In the case of anogenital cancer the incidence ranges from 0.5 - 0.7 / 100.000 per year and specifically in these patients the incidence increases from 33 to 100 times in relation to the general population ⁷.

HPV seems to initiate a process of carcinogenesis by presenting a change in the expression of genetic material, expressing E6 and E7 proteins that are associated with tumor suppressor proteins encoded by host cells, facilitating viral replication and eliminating the apoptosis response of the host cell on viral infection ¹.

The treatment of HPV infections is currently based on the use of some available topical creams, such as imiquimod which belongs to the family of imidazole heterocyclic amines that do not act to destroy the viral lesions but induce the local synthesis of cytokines, mainly interferon alpha, thus modifying the immune response of the organism infected by HPV.

In the case of precancerous lesions produced by HPV, the most appropriate treatment when there is a small number of lesions is the removal of the affected areas by surgery with cold electrosurgical unit, electrocoagulation or cryotherapy, but this is recommended when there is a small number of injuries. Liquid nitrogen cryotherapy is currently widely used, being very effective in patients with few injuries. When it comes to numerous injuries, the use of the CO2 laser is preferred, as it allows the most precise

control of the depth of destruction and achieves very good results.

Other studies show that retinoids, derived from vitamin A, a set of compounds historically used to treat alterations of keratinization, may also be helpful in the management of these lesions. Their action is based on binding to nuclear receptors (CRBP, CRABP, RAR and RXR), thus modifying the expression of factors of growth, oncogenes, keratins and transglutamines. The main reason for the effectiveness of this treatment is that HPV produces well localized superficial lesions. However, due to the poor response of our patient and the recent publication of case reports with satisfactory resolution of lesions with cidofovir, this management is proposed by extrapolating the adequate response of this drug on lesions caused by cytomegalovirus, selectively inhibiting viral DNA synthesis. With respect to HPV infection, this drug has been proven to induce apoptosis at the level of HPV-infected cells by inducing caspases, increased protease activity, nuclear matrix disintegration and viral DNA fragmentation⁸. In the successful case reports of cidofovir use, topical administration has been performed. However, it should be considered that this drug may also induce caspase activation at the renal tubular epithelium and have a potential nephrotoxic effect. Further studies are required to determine the efficacy, safety, and cost-benefit ratio of using cidofovir in cutaneous HPV lesions in a transplanted patient ⁹⁻¹⁰.

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