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ORIGINAL ARTICLE

Detection of Human Papillomavirus in Nonmelanoma Skin Cancer Lesions and Healthy Perilesional Skin in Kidney Transplant Recipients and Immunocompetent Patients☆

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Abstract

Background: The influence of human papillomavirus (HPV) on the development of nonmelanoma skin cancer (NMSC) is a topic of debate. HPV types from the beta genus (HPV-β) have been most frequently associated with the development of skin cancer.

Objectives: To analyze the prevalence and range of HPV types in NMSC lesions and healthy perilesional skin in immunodepressed and immunocompetent patients and to evaluate the influence of various clinical factors on the prevalence of HPV in skin cancer.

Methods: Nested polymerase chain reaction and sequencing were used to detect HPV in 120 NMSC samples obtained by biopsy from 30 kidney transplant recipients and 30 immunocompetent patients. In all cases, a sample was taken from the tumor site and the surrounding healthy skin. Potential confounders were assessed and the data analyzed by multivariate logistic regression.

Results: HPV DNA was detected in 44 (73.3%) of the 60 samples from immunodepressed patients and in 32 (53.3%) of the 60 samples from immunocompetent patients (adjusted odds ratio, 3.4; 95% CI, 1.2-9.6). In both groups of patients, HPV was more common in healthy perilesional skin than in lesional skin. HPV-β was the most common type isolated.

Conclusion: We found a wide range of HPV types (mostly HPV-β) in the skin of kidney transplant recipients and immunocompetent patients with skin cancer.

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PALABRAS CLAVE
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Detección del virus del papiloma humano en muestras de cáncer cutáneo no melanoma y piel sana perilesional en pacientes trasplantados renales y pacientes inmunocompetentes

Resumen

Antecedentes: La influencia del virus del papiloma humano (VPH) en el desarrollo de carcinoma cutáneo no melanoma es un tema controvertido. VPH-β es el género más frecuente relacionado con el desarrollo de cáncer de piel.

Objetivos: Analizar la prevalencia y espectro de los tipos de VPH presentes en piel tumoral y piel sana perilesional en pacientes inmunodeprimidos y pacientes inmunocompetentes, así como evaluar la influencia de diferentes factores clínicos en la prevalencia del VPH en cáncer de piel.

Métodos: Se determinó la presencia de VPH en 120 muestras mediante PCR *nested* y posterior secuenciación. Se tomó biopsia de piel de 30 pacientes trasplantados renales y de 30 pacientes inmunocompetentes con cáncer cutáneo tanto de zona tumoral como de piel sana perilesional. Se registraron las variables potenciales de confusión. Los datos fueron analizados utilizando análisis de regresión logística multivariado.

Resultados: ADN del VPH fue detectado en 44/60 (73,3%) de las muestras de pacientes inmunodeprimidos y en 32/60 (53,3%) de las muestras de pacientes inmunocompetentes (OR ajustada 3,4 [1,2-9,6]). Al comparar la presencia de VPH en los 2 grupos entre piel tumoral y piel sana perilesional la presencia de VPH en piel sana perilesional fue mayor que en piel tumoral. El género más frecuente aislado fue el VPH-β.

Conclusión: Un amplio espectro de tipos de VPH, la mayoría del género β, se encuentran en la piel de pacientes trasplantados e inmunocompetentes con cáncer cutáneo.

Introduction

The human papillomavirus (HPV) is a known risk factor for developing cervical cancer.[1,2] It is also implicated in the pathogenesis of squamous cell carcinoma of the mucous membranes (vulva, penis, anus) and of the head and neck (pharynx).[3] However, its role in the development of nonmelanoma skin cancer (NMSC) is more controversial. Studies of the role of HPV in cutaneous oncogenesis vary widely, in part because of differences in the types of sample analyzed and the methods used for the detection and typing of HPV. Moreover, many studies fail to account for potential confounders that influence the risk of developing skin cancer, particularly factors related to sun exposure.

According to current taxonomic classification[4] the Papillomaviridae family contains 16 genera, which are identified by Greek letters (α, β, γ, *etc.*). Each genus contains one or more species, which are numbered, and each species in turn contains types, subtypes, and variants. The classification of the β-papillomavirus (β-PV) genus is shown in Table 1. The relationship between HPV and skin cancer is based on several observations, including the epidemiological association between warts and cutaneous squamous cell carcinoma (SCC) in patients with epidermodysplasia verruciformis,[5] the coexistence of epithelial dysplasia and histological signs of viral infection in biopsy,[6,7] and the identification of HPV DNA in many NMSCs.[8,9] Initially, the mechanisms identified in mucosal oncogenic HPVs were extrapolated in an attempt to identify the molecular strategies or mechanisms by which the β and γ genera induce skin cancer. However, distinct and much more complex mechanisms of action were identified for cutaneous HPV types, possibly involving other cofactors such as ultraviolet (UV) radiation and immunosuppression. Molecular studies performed in cell culture indicate that β-PVs mainly target antiapoptotic mechanisms and block pathways that maintain genomic integrity by repairing damage caused by UV radiation. HPV-8 and HPV-20 of the β genus block the action of the proapoptotic proteins BAK and BAX,[10] whose action is similar to but independent of p53. XRCC1, another protein that repairs thymidine dimers induced by UV radiation, can also be intercepted by some forms of HPV, such as HPV-8.[11] The HPV proteins E6 and E7 are oncoproteins encoded by the virus. Recent studies have investigated the role of these proteins in the transformation to SCC in transplant patients. E6/E7 transcripts of HPV-8, HPV-9, and HPV-15 have been found in actinic keratoses and SCC, suggesting an active role of HPV in the pathogenesis of these conditions.[12] Furthermore, HPV-8 and HPV-5 exert an inhibitory effect on interleukin-8, which is involved in the stimulation of an immune response that targets cells damaged by UV radiation.[13]

However, given the lack of consistent results demonstrating the presence of HPV DNA in skin cancer, the frequent detection of HPV in normal skin, and the failure to identify a group of skin cancer patients at high risk of developing HPV, the role of HPV in the development of NMSC is unclear.

In the present study we sought to determine the prevalence and spectrum of HPV types in skin tumors and healthy perilesional skin from renal transplant recipients and immunocompetent patients, and to evaluate the influence of different clinical factors on the prevalence of HPV in skin cancer.