Journal of Clinical Virology 32S (2005) S67–S71

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Review

Human papillomaviruses and skin cancer

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Received 24 August 2004; accepted 5 November 2004

Abstract

Cutaneous epidermodysplasia verruciformis (EV)-associated human papillomaviruses (HPVs) are found frequently in skin cancers especially in immunosuppressed people. They are also detectable in the normal skin and hair follicles of a proportion of individuals who have no immune defect. The available evidence to link HPVs causally with skin carcinogenesis is not conclusive, but includes epidemiological, molecular and immunological studies.

Keywords: HPV; Epidermodysplasia verruciformis; Immunosuppression; Squamous cell carcinoma; Ultraviolet radiation

Contents

Abbreviations: BCC, basal cell carcinoma; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbant assay; EV, epidermodysplasia verruciformis; HIV, human immunodeficiency virus; HPV, human papillomavirus; Ig, immunoglobulin; PCR, polymerase chain reaction; PUVA, psoralen and ultraviolet A; SCC, squamous cell carcinoma; SLE, systemic lupus erythematosus; URR, upstream regulatory region; UV, ultraviolet; VLP, virus-like particles

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doi:10.1016/j.jcv.2004.11.018

1. Introduction

The association between human papillomavirus (HPV) infection and squamous cell neoplasia of the lower genital tract is now well established with many lines of good evidence supporting a causative relationship. The role of HPVs in the development of cutaneous malignancy is not as definite, but nevertheless, there is emerging evidence to suggest that they have a potentially important part to play in the process of skin carcinogenesis.

2. Epidermodysplasia verruciformis

Cancer-associated skin HPV types were first discovered in patients with the rare condition of epidermodysplasia verruciformis. Those affected have a mild but demonstrable defect of cell-mediated immune responses and develop warty and scaly areas of skin, especially on sun-exposed sites, in their childhood and early adult life (Majewski and Jablonska, 2001). Most will also have squamous cell carcinomas (SCCs) of the skin appearing before the age of 40 and in many cases, the skin malignancies can be aggressive and likely to metastasise. Analysis in the 1980s of the tumours and later the benign or pre-malignant areas of skin in people with epidermodysplasia verruciformis (EV) revealed the DNA of a large number of HPV types which had not previously been found in either warts of the skin or genitalia or cancers (Orth, 1987).

The HPVs found in the SCCs are most commonly types 5 or 8 (in about 90% of the cases) and less commonly types 14, 17, 20 and 47, whilst non-cancerous warty or flaky lesions contain these or other HPVs (types 9, 12, 15, 19, 21–25, 36–39, 49). It initially seemed as if these were EV-specific HPVs that contributed to the development of skin cancer. However, as time and the techniques of polymerase chain reaction (PCR) progressed, these HPVs and phylogenetically closely related types were detected not only in the patients with EV but also in patients with profound immunosuppression following organ transplantation and even in immunocompetent individuals. In addition, the viral DNA could be found in normal as well as abnormal skin.

3. Epidemiological association between HPV and skin cancer

3.1. Molecular

Many studies have examined the skin lesions in immunosuppressed individuals and also immunocompetent people for the presence and type of HPV DNA. Early work with renal transplant patients using DNA extraction and restriction enzyme analysis has been superceded by the application of sensitive PCR DNA amplification using degenerate primer sets to increase the detection of many different types (reviewed in Harwood and Proby, 2002). Cutaneous HPVs of the EV or EV-related and putative new EV-related types are detected very frequently in a variety of individuals and skin lesions (Table 1). The results vary according to the specific sensitivity of the primers used and the amplification protocol.

Table 1
Frequency of detection by PCR of cutaneous HPV DNA in skin and skin lesions

Skin lesion	Immunosuppressed (%)	Immunocompetent (%)
SCCs	54–81	27–33
Bowen's disease	33–40	67–100
Actinic keratoses	33–93	55–70
BCCs	33–83	21–44
Normal skin	60–73	35–70
Plucked hairs	45–92	16–76

References: Antonsson et al., 2003; Astori et al., 1998; Boxman et al., 1997; de Jong-Tieben et al., 1995; Forslund et al., 2003; Harwood and Proby, 2002; Harwood et al., 2000; Shamanin et al., 1996; Struijk et al., 2003.

In a third of the cases, a mixture of more than one HPV type is found in non-melanoma skin cancers. The viral DNA is more readily detectable in SCCs than pre-malignant lesions, but not as abundant as in EV SCCs (Berkhout et al., 2000). In the SCCs of EV, the virus is transcriptionally active and there is some recent evidence that in transplant recipients, a single virus type may be expressed in lesions which harbour more than one type (Purdie et al., in press).

Some groups have also tested for the presence of genital HPV types in the skin lesions of immunosuppressed patients and have found high-risk genital types in over 60% of the lesions (Iftner et al., 2003; Soler et al., 1993). In addition, two particular skin lesions stand out as harbouring genital types: verrucous carcinoma or carcinoma cuniculatum and periungual squamous cell lesions.

Verrucous carcinoma, often called carcinoma cuniculatum when extra-genital or giant condlyoma of Büschke and Löwenstein in the genital area, is a slowly growing well-differentiated squamous cell tumour which enlarges with a 'pushing' edge rather than the infiltrative pattern usually seen in the SCC. These tumours can harbour the HPVs more commonly found in genital warts, especially HPV 11 (Garven et al., 1991; Knobler et al., 1989) or the high-risk types.

The second specific finding of genital HPV types in skin lesions is in hand and in particular, periungual carcinoma. A number of anecdotal cases and small series have all reported genital HPVs, usually high-risk types, in periungual warts, Bowen's disease and cancers. In a review of 51 published cases of HPV-positive digital SCC, Alam et al. (2003) reported that HPV 16 was found in 94% of the cases and there was associated genital disease in 10%. Other genital types occasionally found in such lesions include HPV 31, 54, 58, 61 and 73 (Mituishi et al., 1997).