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Diseases associated with human papillomavirus infection

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ABSTRACT

Human papillomaviruses (HPVs) are ubiquitous, well adapted to their host and cleverly sequestered away from immune responses. HPV infections can be productive, subclinical or latent in both skin and mucosa. The causal association of HPV with cervical cancer, and increasingly with rising numbers of squamous cell carcinomas at other sites in both men and women, is increasingly recognised, while the morbidity of cutaneous HPV lesions, particularly in the immunosuppressed population is also significant. This chapter sets out the range of infections and clinical manifestations of the consequences of infection and its persistence and describes why HPVs are both highly effective pathogens and carcinogens, challenging to eliminate.

Introduction

The papillomaviridae are ancient and ubiquitous viruses, with over 200 types of species-specific viruses classified into 16 genera. PVs preferentially infect differentiating squamous epithelium and in humans, almost every part of human skin can be infected. HPV was the first known human tumour virus, associated with benign, epithelial proliferations or papillomas and there are now 120 different HPV types officially recognised with others pending classification (Bernard et al., 2010). In recent decades, the causal association of HPV with cervical cancer, but also with an increasing number of squamous cell carcinomas at specific sites, has been recognised. This chapter sets out the range of infections and clinical manifestations of the consequences of infection and its persistence.

HPVs are divided into three main groups: cutaneous, mucocutaneous and those associated with the rare autosomal recessive disorder, *epidermodysplasia verruciformis* (EV). The cutaneous HPVs belong to the beta genus with a few members in the gamma, mu and nu genera, while the alpha genus contains all of the mucosal HPVs and a few cutaneous types (Bernard et al., 2010). They can also be grouped according to the areas of the body where infection is found – external skin, anogenital and oral regions. The mucocutaneous HPV types can be further sub-divided into low risk (LR-HPV) mainly associated with benign warts and high risk (HR-HPV) defined by their risk of progression to malignancy. While certain HPV types are associated with particular morphological characteristics, the association is not absolute and HPV infection can be productive, subclinical or latent in both skin and mucosa. Productive lesions such as warts can be seen clinically, while sub-clinical mucosal infections need additional tools such as microscopic examination with the aid of topically applied acetic acid, as in colposcopic examination of the cervix or anoscopy of the anal canal. Latent papillomaviruses are detectable only through the demonstration of HPV DNA in clinically and histologically normal skin and mucosa. Productive infections are associated with full viral gene expression and production of mature virus particles, while in persistent infections, normal cell function is abrogated and late events in the virus life cycle are disrupted. Approximately 70% of HPV infections resolve spontaneously in 1 year and 90% in 2 years, while HPV persistence develops in the remainder (Veldhuijzen et al., 2010). Clearance requires an effective cell mediated immune response, while persistent infection with HR-HPV types represents a failure of the immune response and increases the risk of progression to cancer (Stanley, 2010). Table 1 shows the HPV types most frequently associated with particular diseases.

HPV in external skin

Warts have been recognised since Greek and Roman times, since when and in many cultures, warts have been associated with magic and a multitude of folk cures, due to the sudden appearance and disappearance of warts (Bunney et al., 1992). Cutaneous warts are spread either by direct contact from person to person or indirectly by contact with contaminated surfaces or objects, transmission being facilitated by minor breaks in the epidermal barrier. Re-infection and autoinoculation, particularly in children, are important methods of spread and include transmission to the oral region by sucking and chewing of fingers, spread from one

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child to another, through contact games and from hand to face or to elbows and knees through minor abrasions. Prevalence varies across different populations and age ranges, but is highest in children and adolescents at an estimated 3–5% (Williams et al., 1993). Studies from some time ago suggested prevalence rates as high as 10% in 1955 in children aged 5–18 in UK and 20% in 1980 in children aged 12–16

Table 1
HPV types associated with particular diseases (adapted from several sources).

Disease		Most frequently associated HPV types
Common warts		HPV 2, 4, 7; occasionally other types in immunosuppressed (e.g. HPV 75–77)
Flat plane warts		HPV 3, 10, occasionally HPV 26–29 and 41
Plantar warts		HPV 1, 2, 4
Epidermodysplasia verruciformis	Plane warts	HPV 3, 10
	Pityriasis-like plaques	HPV 5, 8; less commonly 9,12,14,15, 17, 19,20, 21–25, 36–39, 47,49
	Squamous cell carcinomas of sun-exposed skin	HPV 5, 8, less commonly 14,17,20 and 47
Anogenital warts	External warts	HPV 6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 89
	Buschke–Lowenstein tumour	HPV 6
	Bowenoid papulosis	HPV 16, 55
Anogenital cancers and precancers	Group 1: Carcinogenic to humans	HPV 16,18, 31, 33, 45, 51, 52
	Group 2A: Probably carcinogenic to humans	HPV 68
	Group 2B: Possibly carcinogenic to humans	HPV 26, 53, 64, 65, 66, 67, 69, 70, 73, 82
Oral lesions	Oral papillomas	HPV 2,6,7,11,16,18,32,57
	Laryngeal papillomas	HPV 6,11
	Focal hyperplasia (Heck's disease)	HPV 13, 32
	Oropharyngeal carcinoma	HPV 16 predominantly,18

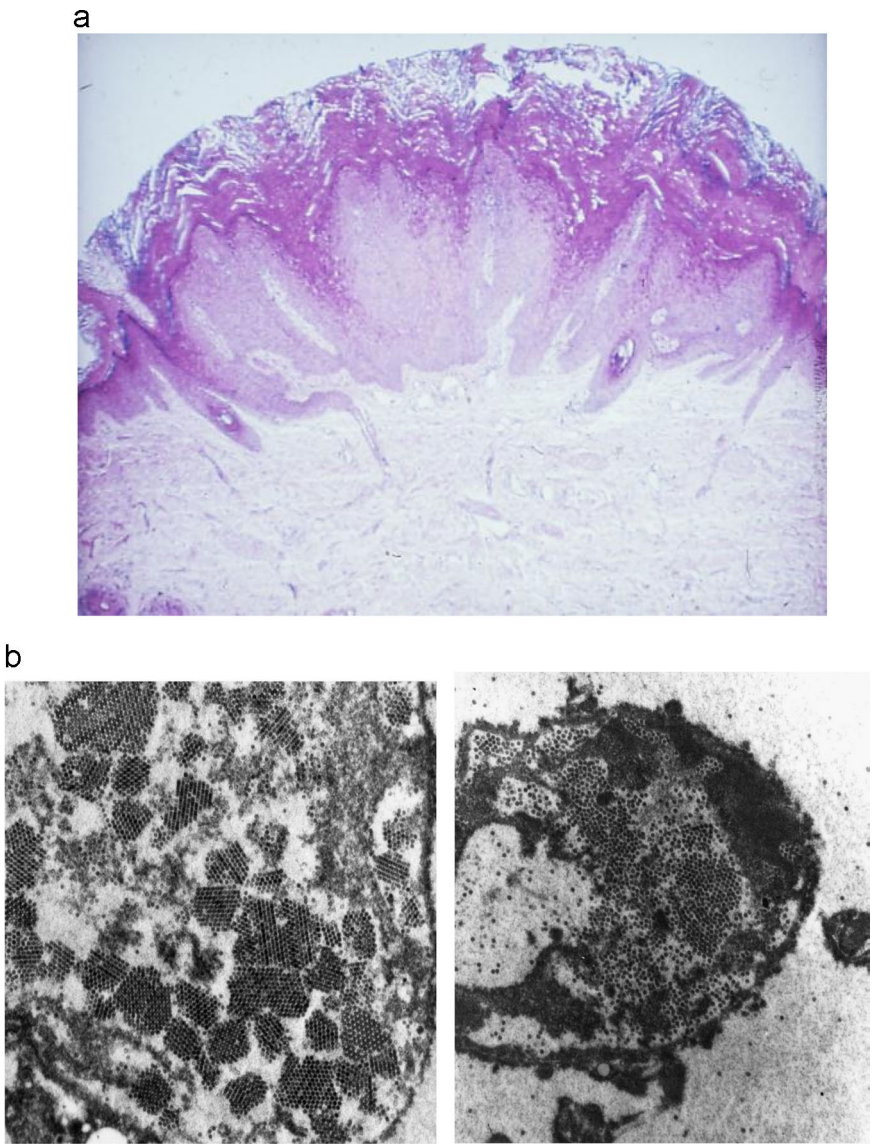

Fig. 1. Histology of an exophytic wart. (a) Section of exophytic wart showing hyperkeratosis of upper layers of epidermis and hypertrophy of basal layers. (b) Electron micrograph of virus particles in crystalline array in nuclei of granulocytic and superfical layers of HPV1 associarted plantar wart.