Virology 445 (2013) 21–34

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Diseases associated with human papillomavirus infection

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ARTICLE INFO

Available online 9 August 2013

Keywords:
Warts
Condylomata
Intraepithelial neoplasia
Cancer

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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http://dx.doi.org/10.1016/j.virol.2013.06.007

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

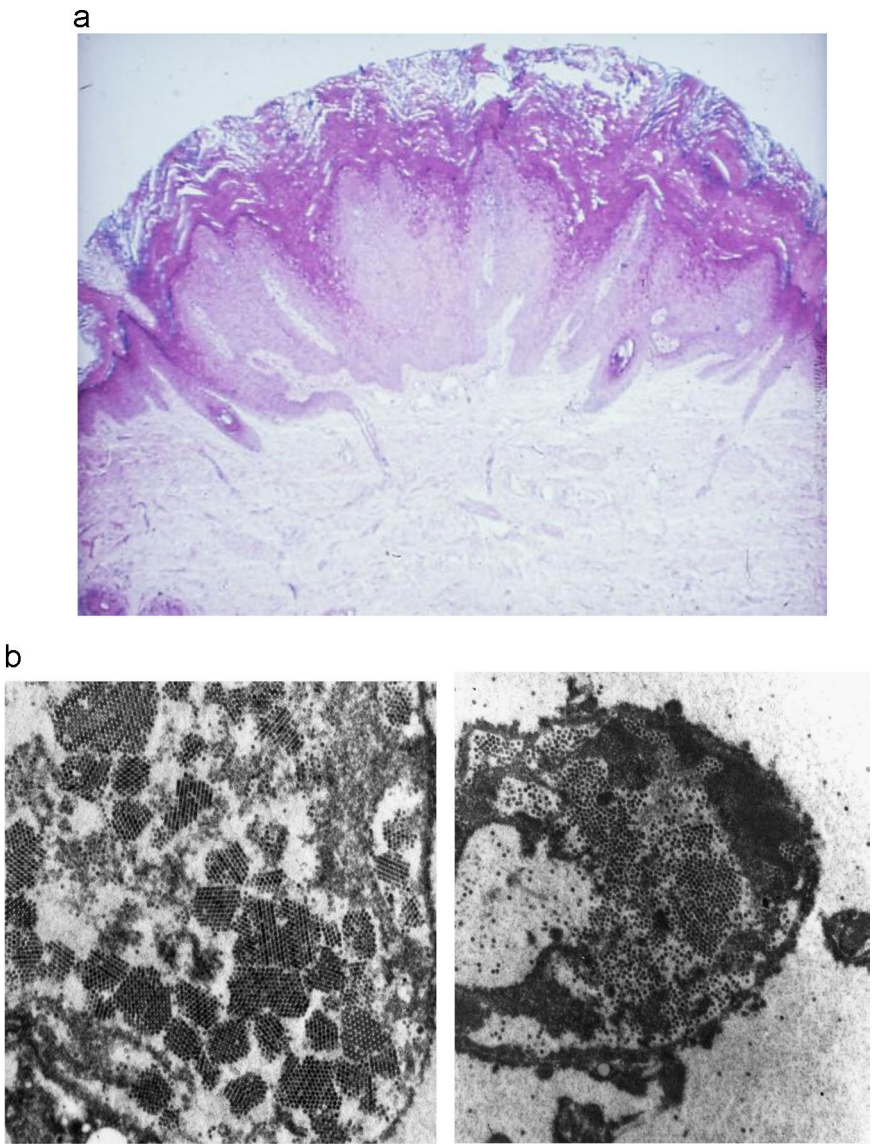

Fig. 1. Histology of an exophytic wart. (a) Section of exophytic wart showing hyperkeratosis of upper layers of epidermis and hypertrophy of basal layers. (b) Electron micrograph of virus particles in crystalline array in nuclei of granulocytic and superfical layers of HPV1 associarted plantar wart.

in Sweden (Larsson and Liden, 1980). It is not known if the prevalence has truly fallen or whether home and primary care treatment options have simply reduced the workload of dermatology clinics from the high peaks seen in earlier decades. More detail on the natural history and epidemiology of cutaneous warts can be found in recent reviews by Benton (2005) and Cardoso and Calonje (2011).

Histologically, warts are benign lesions, with hypertrophy of all layers of the dermis (Fig. 1a), resulting in acanthosis (thickening), papillomatisis (folding) and hyperkeratosis (increase in the horny layer) often with abnormal keratohyaline granules. Vacuolation of cells occurs in the upper layers and inclusion bodies are sometimes observed. Different types of cutaneous warts can show characteristic changes and for the interested reader, the histological illustrations in Croissant et al. (1985) remain useful. Resolution using the electron microscope reveals densely packed virus particles in crystalline array in the upper stratum granulosum and stratum corneum (Fig. 1b). Warts usually disappear spontaneously but occasionally may be resistant to treatment. Regrowth of lesions after treatment is frequently due to persistence of the virus in the skin surrounding the original wart.

Common warts of hands and face

Common warts are usually exophytic, multiple, irregular, rough nodules which show a variety of clinical patterns at different sites of trauma particularly on fingers (Fig. 2), but also on other frequently rubbed and abraded skin surfaces such as hands, elbows and knees. They range from small papules to large, hyperkeratotic, fissured cauliflower-like lesions. Common warts are most frequently caused by HPV 2 while the smaller, endophytic, punctate lesions most often seen on the palms of the hands are associated with HPV 4 (Jablonska et al., 1985). Histologically, common warts show prominent papillomatosis, acanthosis, hypergranulosis and hyperkeratosis of the horny layer. There is a marked clearing of the cytoplasm in granular cells ('koilocytosis') and numerous keratohyalin granules are present. HPV 4 lesions have more pronounced crescentic nuclei. HPV 2 warts are notoriously persistent, especially when present as more superficial 'mosaic' warts. Florid and persistent warts, usually associated with HPV 7, are common in fishmongers and meat handlers where the skin is chronically macerated due to moisture and cold (Fig. 3).

Plane warts (HPV 3, 10 or 28) are small and less rough, presenting as flat-topped papules, flesh coloured or lightly pigmented, especially on light-exposed areas of the face and back of the hands, usually in multiple crops (Fig. 4). HPV 3 lesions show little hyperkeratosis, while HPV 10 and 28 lesions are more hyperkeratotic and can resemble early common warts. Plane warts exhibit an unusual phenomenon in that they often show spontaneous regression of all present, observed as superficial swelling and rash. This is associated histologically with marked by T-cell infiltrate and activated Langerhans cells (Oguchi et al., 1981). In adults plane warts are more frequent in women but are rarely seen in men except

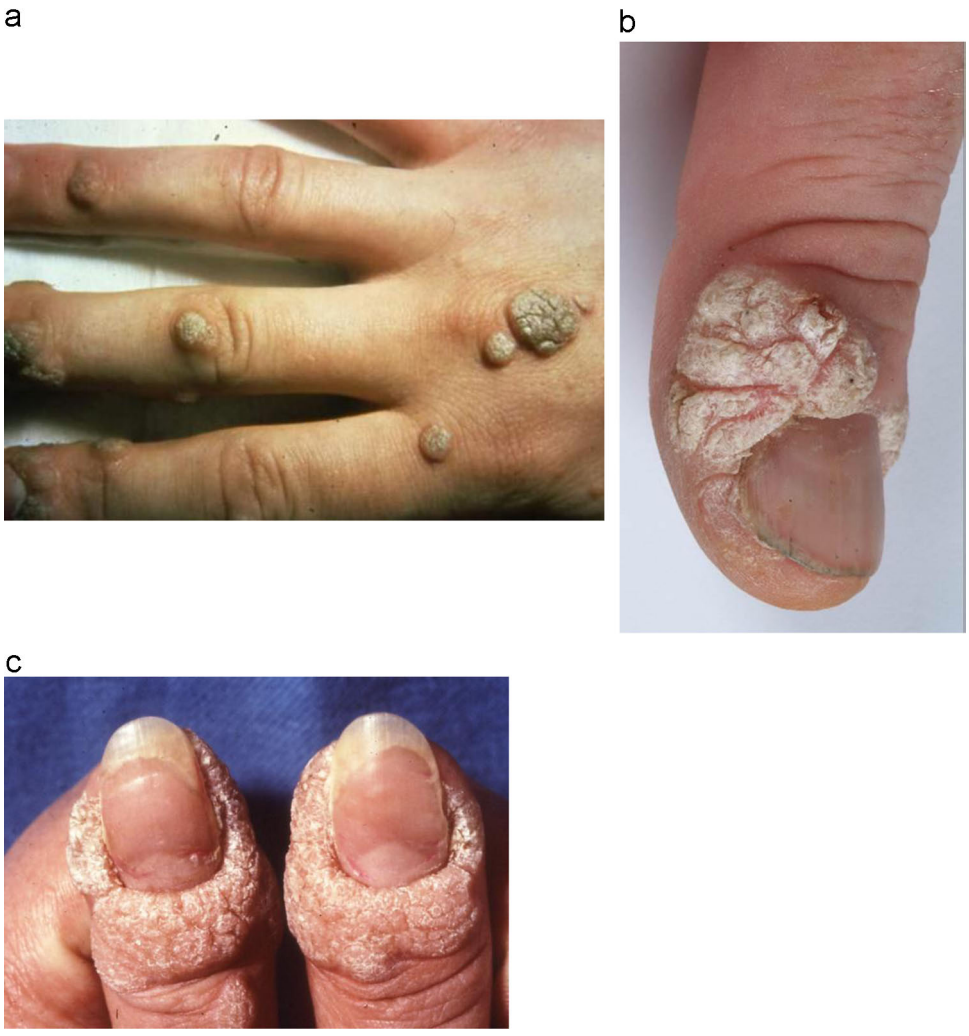

Fig. 2. Common warts on hands (HPV 2 associated). (a) Multiple common warts across back of hand. (b) Periungual warts. (c) Florid hand warts in patient with some immunosuppression.

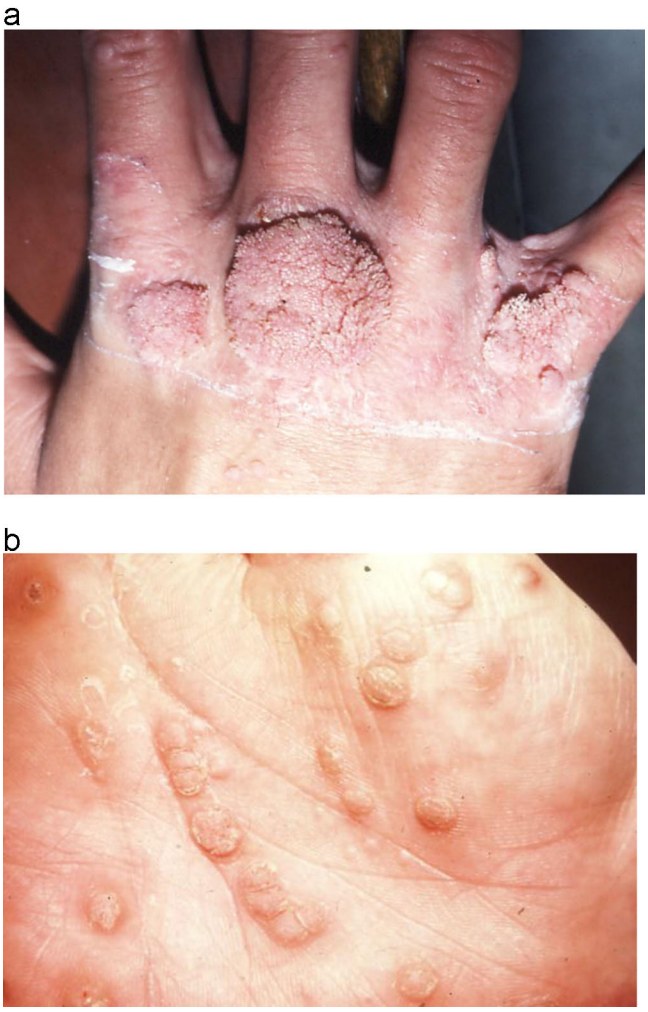

Fig. 3. Florid persistent hand warts associated with occupation. (a) From a fish handler (HPV7 detected). (b) From a chicken factory worker.

those who are immunosuppressed especially by HIV (Cardoso and Calonje, 2011).

For most children, cutaneous HPV infections are simply an inconvenience with spontaneous resolution occurring in almost 80% within 2 years (Sterling et al., 2001). Topical salicylic acid solutions used at home are effective for most cutaneous warts and should generally be the first line therapy, reserving the application of cryotherapy with dry ice or liquid nitrogen for recalcitrant warts.

Plantar warts

Plantar warts (often called verruca from the Latin meaning 'little hill') rarely occur before the age of 5 years and have a peak distribution at 10–14 years (Fig. 5). They arise most frequently through barefoot activities and more often in girls exposed to barefoot dancing and gymnastics. Activities which cause maceration of the skin such as swimming provide an additional risk of transmission. Infected keratinocytes are shed on to abrasive surfaces such as diving boards or swimming pool surrounds, thus spreading virus to the feet of other swimmers.

Deep plantar warts (myrmecia; caused by HPV 1 (Fig. 5a, b); also by HPV 63) occur most frequently on weight-bearing areas or pressure points of the feet. Clinical observation shows a rim of keratin surrounding a softer keratotic plug, with scattered capillary points which bleed on paring down. Histologically, the granular layer is disorganised due to the endophytic growth, with prominent koilocytic cells and parakeratotic cells with nuclear inclusions in the upper layers. Deep plantar warts are painful, often tender when lateral pressure is applied, but their response to treatment is generally good. However, pain together with local haemorrhage and thrombosis causing myrmecia to turn black (Fig. 5d) is often associated with regression. In contrast, warts due to HPV 2 and HPV 4, which have a superficial mosaic pattern and lack prominent keratohyalin granules, tend to be less painful, but are more persistent and respond poorly to treatment (Fig. 5c). Rarer types associated with plantar lesions such as epidermoid cysts include HPV 57 and 60, the latter sometimes pigmented due to melanin granules in the keratinocytes (Cardoso and Calonje, 2011). HPV 57 is phylogenetically closely related to HPV 2.

Epidermodysplasia verruciformis

Epidermodysplasia verruciformis (EV) was first described almost a century ago by Lewandowsky and Lutz (Orth, 1987; Leiding and Holland, 2012). EV is a rare autosomal recessive condition linked to mutation in one of two genes (EVER1 and EVER2) on the long arm of chromosome 17 (Ramoz et al., 2002), in which selective depletion of specific T cell clones is associated with extensive infection restricted to a sub-set of about 20 β-HPV types. The EVER genes encode transmembrane proteins which are important regulators of zinc homoeostasis, loss of which enhances expression of viral E6 and E7 genes (Lazarczyk et al., 2009).

There are two presenting conditions in EV:

i. Disseminated benign plane warts, associated with HPV 3 and 10 which develop in early childhood and persist throughout life (Fig. 6). These occur mainly on the trunk, neck and extremities as flat, hypo- or hyperpigmented papules which can coalesce into scaly patches resembling those of *pityriasis versicolor* in which a high level of viral replication occurs in differentiating keratinocytes. Histologically, EV lesions show hyperkeratosis, acanthosis and hypergranulosis. Enlarged keratinocytes with granular and often vacuolated cytoplasm are characteristic (Fig. 6d).
ii. Verrucous lesions which occur on light-exposed areas and have greater malignant potential. These lesions are associated with HPV 5 and 8, often with more than one HPV type being detected, and they contain high copy numbers of HPV genomes and abundant E6 and E7 transcripts.

The β-HPV genus now comprises more than 40 types (Pfister, 2011). They are ubiquitous in the general population (Astori et al., 1998) and acquired in early infancy (Antonsson et al., 2003), with hair follicles regarded as the natural reservoir (Boxman et al., 1997). Their detection in normal skin in healthy adults with no immune defects suggests that visible lesions are prevented by immune control. EV-like conditions develop in HIV infected individuals including children born with HIV in Africa (Cardoso and Calonje, 2011) and those with other immunodeficiencies. EV-HPV types have also been found in a high proportion of lesions associated with epithelial hyperproliferation such as psoriasis (Favre et al., 1998). Current thinking is that EV represents a primary deficiency of innate immunity, or specifically restricted to deficiency against B-HPVs or both (Orth, 2008).

Persistence and malignant conversion of cutaneous warts

HPV infections are normally controlled by intact cell-mediated and humoral immune systems. Regression was shown to be largely driven by cytotoxic T cells and NK cells many years ago, while protection from subsequent infection with the same HPV type

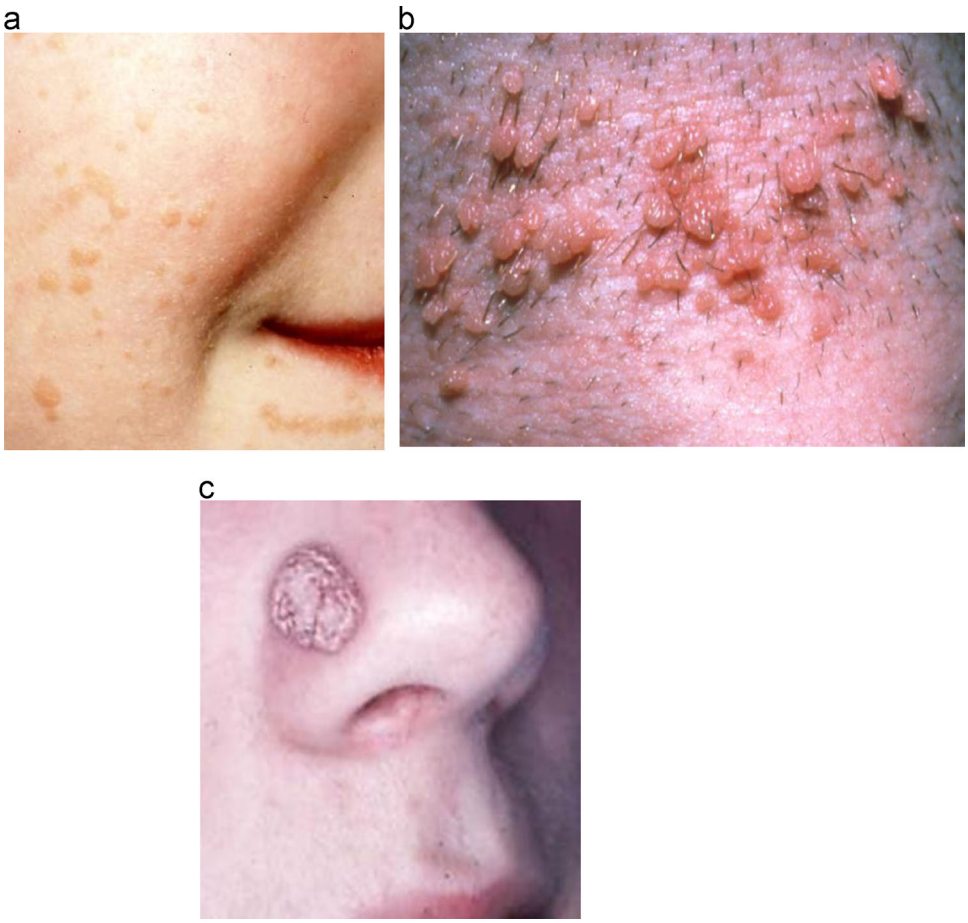

Fig. 4. Warts on the face. (a) Plane warts on face and in linear arrangement below lip arising from a scratch (Koebner phenomenon). (b) Filiform common beard warts. (c) Common wart arising at site of nose piercing.

results from stimulation of the adaptive response and production of antibodies. However, sequestration of HPV in epithelial cells provides protection for the virus, resulting in inefficient activation of innate immunity, poor priming of the adaptive response and persistence of infection (Stanley, 2010).

Patients with cell-mediated immunodeficiencies, whether primary (as in or familial CD4 lymphopaenia), secondary (as in haematological malignancies HIV positivity) or iatrogenic (as a result of immunosuppressive therapy) are all therefore at increased risk of developing extensive, persistent and recurrent warts. Examples are shown in Fig. 7. Persistence of HPV lesions is a major issue for effective clinical management of immunosuppressed patients and can affect their quality of life significantly. Up to 40% of renal allograft recipients in Edinburgh when treatment was more immunosuppressive than current regimes, were shown to develop cutaneous warts within a year of receiving the graft, rising to more than 90% in those with graft survival for longer than 15 years (Benton and Arends, 1996).

While β-HPV are ubiquitous and most cause in-apparent infections in the general population, a few types are associated with squamous cell carcinomas (SCC) in EV patients. HPV 5 and 8 account for 90% of the tumours with HPV 14, 17, 20 and 47 accounting for the remainder (Sterling, 2005). Most EV patients will develop SCC before the age of 40 on sun-exposed sites and the tumours are locally destructive. Usually they are low grade carcinomas *in situ* with some features in common with Bowen's disease, but others are aggressive and likely to metastasize. Bowen's disease is an early *in situ* SCC with 3–5% risk of invasion, which appears as a red scaly patch often on sun-exposed sites in the elderly, particularly women with fair skin.

Cutaneous EV-associated HPV DNA is also frequently found in SCC in transplant patients, other immunosuppressed people and sometimes in non-melanoma skin cancers in immunocompetent individuals. However, cutaneous HPV types are only weakly transforming *in vitro* and evidence to link HPVs causally to skin carcinogenesis is limited by the frequency of infection with β-HPV types in the general population and by common risk factors for activation (UV exposure, immunosuppression and hyperproliferation) (Pfister, 2003). Fig. 8 shows an *in situ* squamous cell carcinoma, progressing to invasive disease.

On rare occasions, persistent plantar lesions are associated with the development of verrucous carcinoma (McKee et al., 1981).

HPV in mucosal and anogenital skin

Mucosal infections associated with α-HPV types are more common than cutaneous HPV (Winer et al., 2005) and the majority are asymptomatic. Around 10% of young women in Scandinavia developed external genital warts (EGW) before the age of 45 (Kjær et al., 2007) and while the prevalence of HPV in women with normal cytology is also estimated at 10% (De Sanjosé et al., 2007), the incidence of infection may be many times that which is reported. HPV DNA testing suggests a presence of HPV in 50–80% of sexually active young men and women (Stanley, 2006). EGW are the most common sexually transmitted infection with a

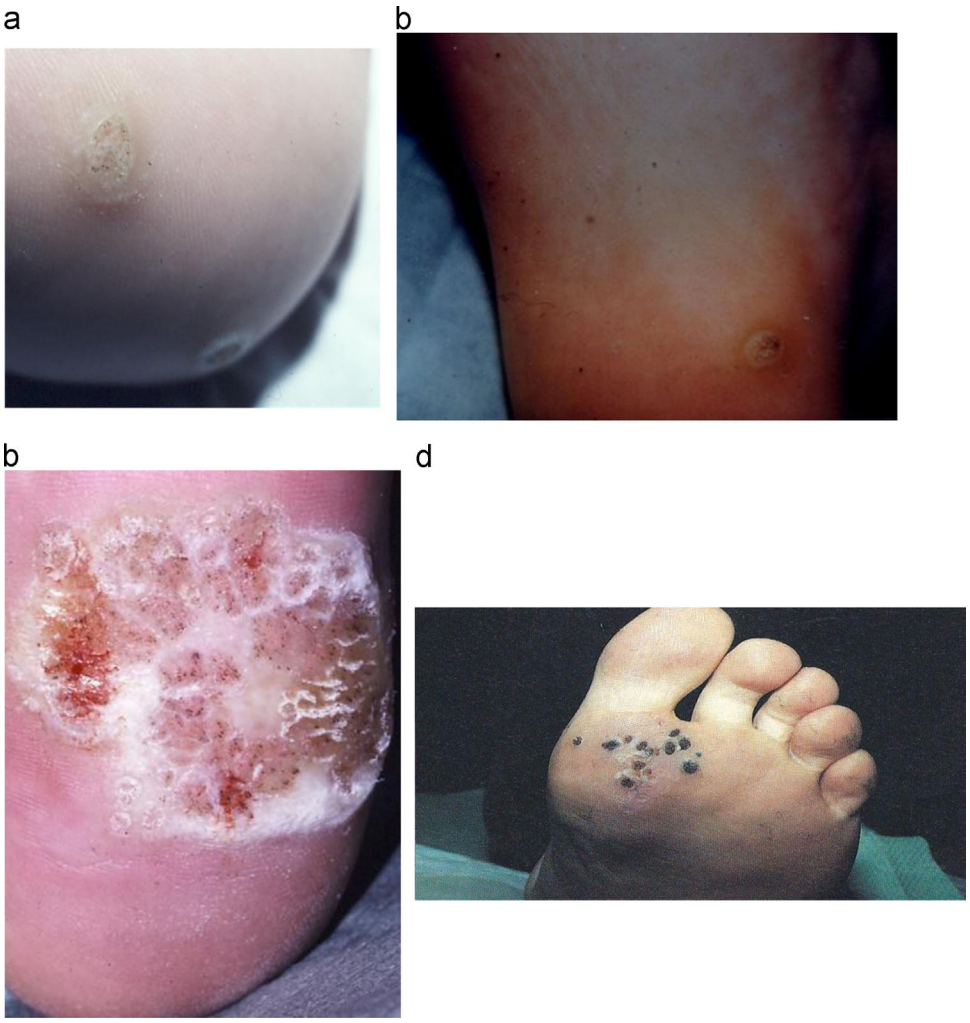

Fig. 5. Plantar warts on feet. (a) Deep plantar warts caused by HPV1. (b) Deep plantar wart caused by HPV1. (c) Mosaic plantar wart caused by HPV2. (d) Thrombosed capillaries in plantar wart due to spontaneous resolution. (Image (d) previously published in Bunney, M.H., Benton, C., Cubie, H.A. (Eds.). 1992. 'Viral warts' – Biology and Treatment, 2nd edition. Oxford University Press. ISBN0-19-262062-2. *With permission from surviving authors (Drs. Benton and Cubie*).)

huge increase in incidence reported in recent years and an estimated transmission rate between partners of 60% (Woodhall et al., 2008). Incidence and prevalence peaks in late teens/early 20s as a result of both behavioural and biological factors. Prevalence declines until around age 50–55, when there is a secondary peak in many countries, associated either with reactivation of latent virus or incident new infection due to new sexual partners.

EGW (also known as *condylomata acuminata*) are found predominantly at sites traumatised during sexual intercourse. This includes the glans penis, coronal sulcus and inner aspect of the foreskin in uncircumscribed men, while infection in circumcised men is less common and generally restricted to the penile shaft (Cook et al.,1993). In women, the labia, clitoris, vulva, vagina and ectocervix can all be infected, with vulvar and vaginal warts usually plainly visible. In both sexes, HPV can be detected in the pubis, perineum, urethra and peri-anal area. Intra-anal warts are most commonly, but not always, a consequence of receptive anal intercourse.

EGW may occur as discrete, small, papular or large cauliflower-like lesions on moist surfaces, or as keratotic lesions resembling skin warts on dry surfaces such as the labia (Fig. 9). They vary in colour from white, through pink and red to brown and pigmented. Many EGW are so small that they need a magnifying glass to be seen. Subclinical lesions may increase in size and number in pregnancy, resulting in increased shedding of HPV from the genital tract, followed by spontaneous regression after delivery. Vaginal warts may occasionally grow so large that the birth canal is obstructed.

Symptoms of EGW include itching, bleeding, fissuring and painful intercourse. Histologically, condylomata show epithelial thickening due to severe acanthosis and papillomatosis, but without the hyperkeratosis of external cutaneous warts. A chronic inflammatory infiltrate is usually observed. The majority of EGW are associated with HPV 6 and 11, although other LR-HPV types such as HPV 42 and 81 are common (Clifford et al., 2005; Petry et al., 2012). HR-HPV may also be detected and about 10–15% may contain multiple HPV types. Productive virus replication is less efficient than in cutaneous warts and fewer virus particles are produced. EGW cause significant psychosocial stress and impact on quality of life, whether by the creation of feelings of guilt and anxiety, loss of self-esteem or the embarrassment of, and delays in, seeking treatment (Woodhall et al., 2008). Topical treatment at home and/or removal by ablation in the clinic setting are often effective, but only surgical interventions have clearance rates approaching 100% (Lacey et al., 2011).

Transmission requires close contact, but not necessarily penetrative sex (Moscicki et al., 2006). Indeed indirect transmission can also occur by innocent contact such as sharing baths or towels. HPV DNA has been isolated from underwear and towels of infected

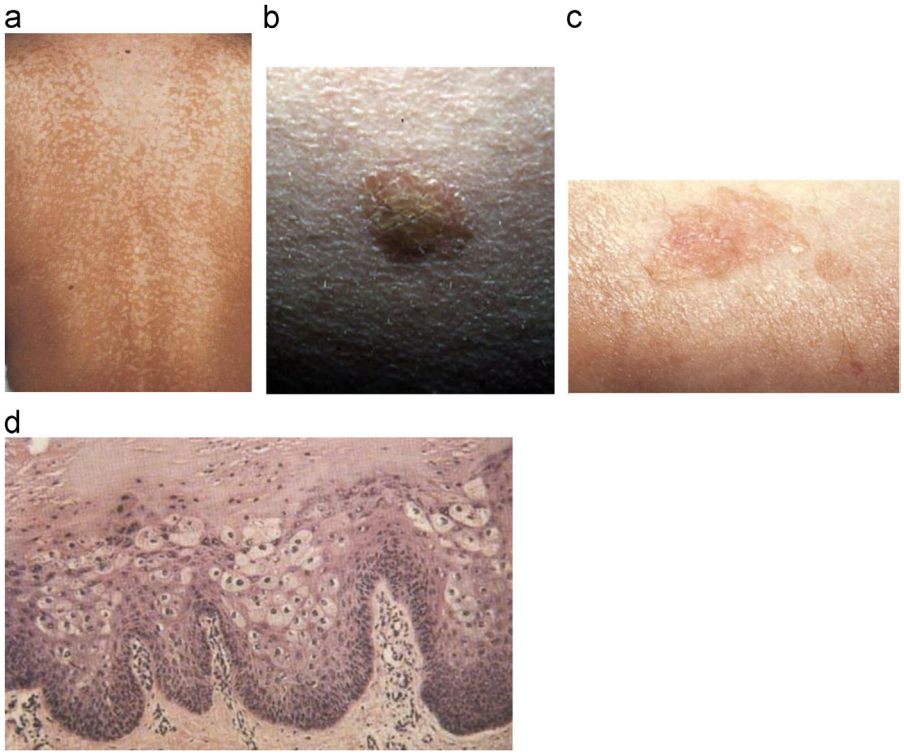

Fig. 6. Epidermodysplasia verruciformis. (a) Extensive atypical plane warts. (b) EV-like plaque in renal allograft recipient (associated with HPV 5/8). (c) EV-like plaque in renal allograft recipient (associated with HPV 5/8). (d) Histology of an EV-like lesion showing characteristic large clear cells in spinous and granular layers.

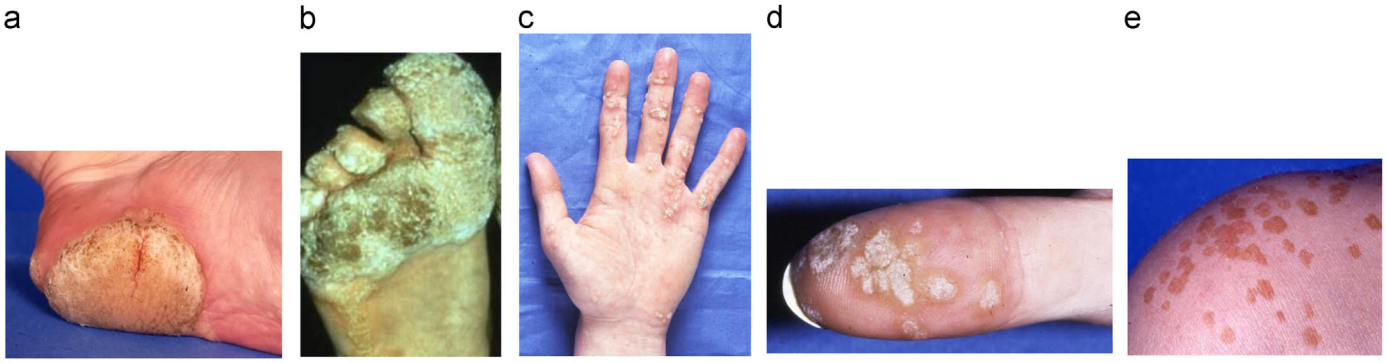

Fig. 7. Recalcitrant warts in immunosuppressed patients. (a) Mosaic plantar wart in liver transplant recipient. (b) Renal allograft recipient 1960s treated with high dose steroids+azathioprine. (c) Extensive persistent warts from childhood with severe familial CD4 lymphopaenia. (d) Recalcitrant mosaic warts on thumb of young woman after chemotherapy for Hodgkin's disease. (e) Extensive flat warts on shoulder of HIV infected patient.

individuals (Bergeron et al., 1990) and virus can be spread through the use of inadequately sterilised instruments and from laser plumes when inadequate extraction facilities exist (Lacey et al., 2011). Condoms can protect against acquisition of EGW (Manhart and Koutsky, 2002).

Vertical transmission of HPV from mother to infant, either *in utero* or during delivery, is an important mode of spread of the virus and is associated with a 1:400 risk of development of laryngeal papillomatosis or anogenital warts (Lacey et al., 2011), which may only become clinically apparent months or years later. Children who present with warts at birth or in the first two years are most likely to have acquired infection through vertical transmission, However, perinatal acquisition of HPV can also occur and the Finnish family studies show this is often a different HPV type from that found in either parent (Rintala et al., 2005). While children over the age of 3 years with ano-genital warts may need paediatric assessment if sexual abuse is suspected, HPV typing rarely adds information of value for management and is not recommended (Lacey et al., 2011). Acquisition of HPV in genital lesions in children can come from many sources, including direct inoculation of HPV 2, 27 or 57 from hand warts and transmission from oral mucosa to genital area by fingers (Jayasinghe and Garland, 2006).

Additional lesions associated with anogenital HPV infection include

- Urethral warts which are rare; complications include reduced urinary flow and infertility due to obstruction of urethral and ejaculatory ducts.
- Bowenoid papulosis, which was originally described in 1977 by Kopf and Bart as reddish-brown verrucous papules on the penis. Bowenoid papulosis is now known to occur in

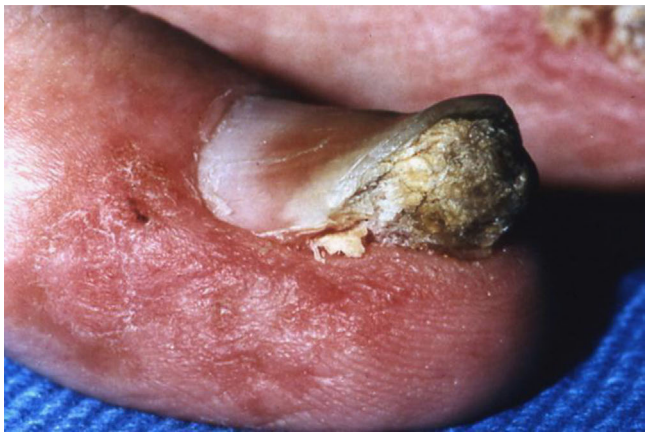

Fig. 8. *In situ* squamous cell carcinoma, progressing to invasive disease – such lesions can be associated with HPV16.

sexually active people of both sexes, is now usually referred to as a low grade carcinoma *in situ* and can be treated by locally destructive methods. While usually benign, they are associated with HR-HPV types, dysplasia is full thickness, recurrences are a potential problem and transformation to malignancy occurs in 2–3%. Bleeding, unusual pigmentation, ulceration and palpable dermal infiltration should be treated with suspicion and appropriate specialist referral (Lacey et al., 2011).

- Giant condyloma acuminatum (Bushcke-Löwenstein tumours), which is a large exophytic lesions with a verrucous, fungating surface, frequently found on the penis or in the perianal area and usually associated with HPV 6 and11. It too is characterised by local invasion and its distinctive histological appearance, in which koilocytes and cellular atypia are largely absent, suggest it is a well-differentiated variant of verrucous carcinoma. Chemoradiotherapy treatment is associated with good outcomes (Armstrong et al., 2009).

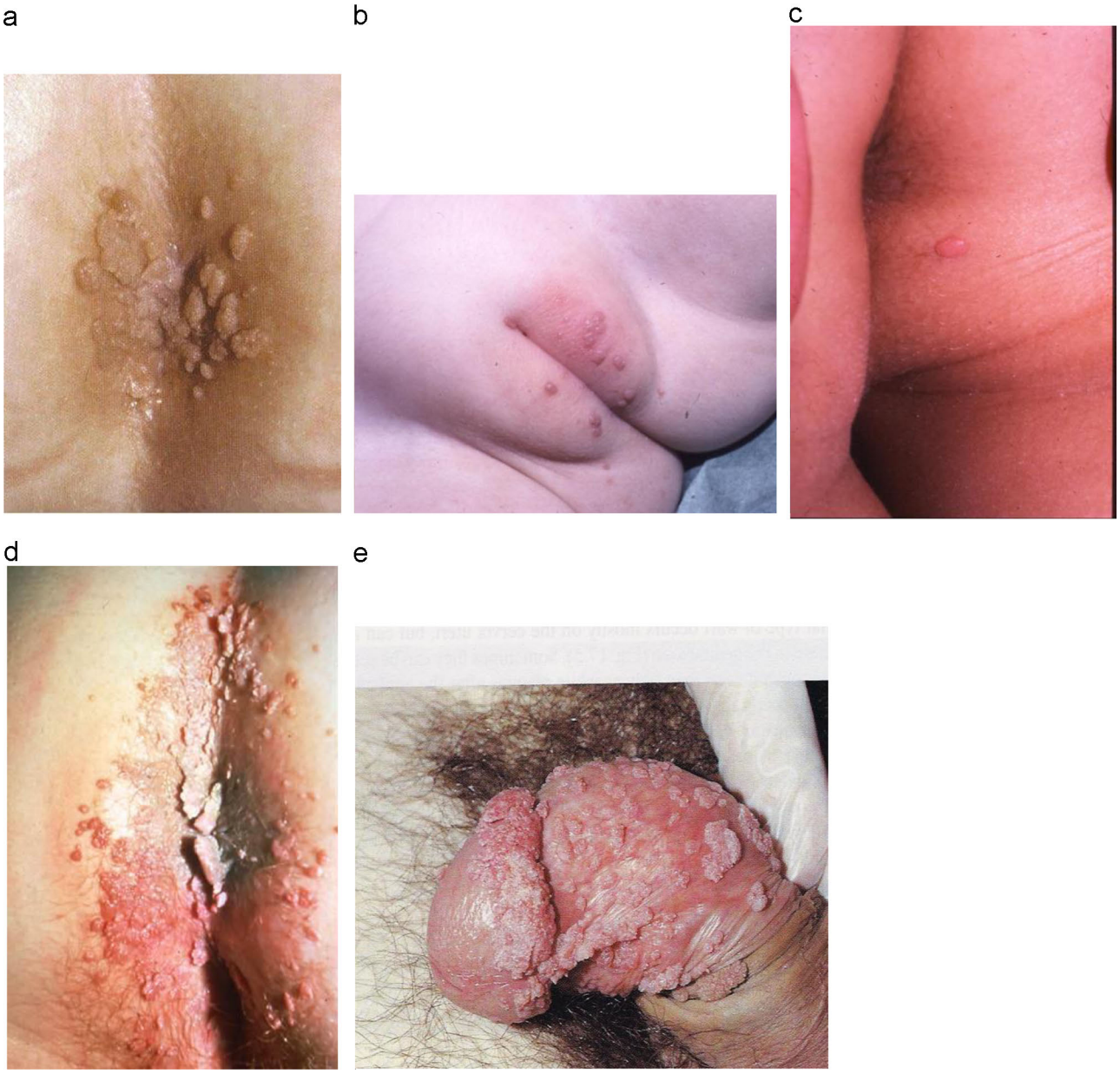

Fig. 9. Anogenital warts. (a) Anogenital warts in adult. (b) Anogenital warts on labia of child. (c) Single genital wart on buttock of child. (d) Extensive perianal warts in renal allograft recipient. (e) Condylomata acuminate on gland penis a d foreskin (courtesy of Dr. A. McMillan). (Image (e) previously published in Bunney, M.H., Benton, C., Cubie, H.A. (Eds.). 1992. 'Viral warts' – Biology and Treatment, 2nd edition. Oxford University Press. ISBN0-19-262062-2. *With permission from surviving authors (Drs. Benton and Cubie).*)

HPV associated anogenital pre-cancers and cancers

HPV associated pre-cancers present as intraepithelial neoplasia and are named after the site: cervical intraepithelial neoplasia (CIN) for the most commonly recognised and extensively studied consequence of persistent HPV infection, together with VIN and VAIN (vulval and vaginal intraepithelial neoplasia respectively), PIN (penile intraepithelial neoplasia) and AIN (anal intraepithelial neoplasia). Appropriate intervention can usually prevent progression to invasive cancer, but there is considerable morbidity associated with treatment of the precancerous stages. In the case of CIN, this can include pre-term births, increased requirement for caesarian section, low birth weight and increased deaths (Arbyn et al., 2008).

Cervical intraepithelial neoplasia and cancer

Clinically, precancerous cervical lesions can usually only be seen with the aid of a colposcope to magnify the epithelium and application of 5% acetic acid to reveal subclinical lesions which contain a high level of nuclear material, observed as areas of densely white whorls known as flat warts (Fig. 10). Microscopic examination of exfoliated cells scraped with a wooden spatula from the cervix, fixed, and stained appropriately to reveal dysplastic changes in cells of mucocutaneous epithelium was developed in the 1940s by Papanicolau (Papanicolaou, 1942). The technique was introduced for cervical screening in the 1950s/1960s and into population-based organised screening programmes in a number of developed countries from the 1990s. Peto et al. (2004) estimated that 1:80 UK women had been prevented from developing cervical cancer by accessing the national screening programme while in the US, it has been estimated that 4 out of 5 women who developed cervical cancer had not had a Pap test in the previous 5 years (Jemal et al., 2013).

The presence of vacuolated cells with enlarged, hyperchromatic nuclei described as koilocytes is pathognomonic of productive HPV infection, while the consequences of persistent infection are reflected in increasingly severe nuclear changes, mitotic figures and clumps of pyknotic cells. Observations are classified in different ways (Table 2) although the Bethesda classification is the most widely accepted, with low grade squamous intraepithelial neoplasia (LSIL) used for samples containing cells with larger, irregular and more detailed nuclei and high grade SIL (HSIL) for samples containing immature cells, small cells in sheets and syncytial groupings and with distinct cytoplasmic borders (Fig. 11). Liquid based cytology (LBC), which allows the creation of a uniform and consistent cell monolayer in the

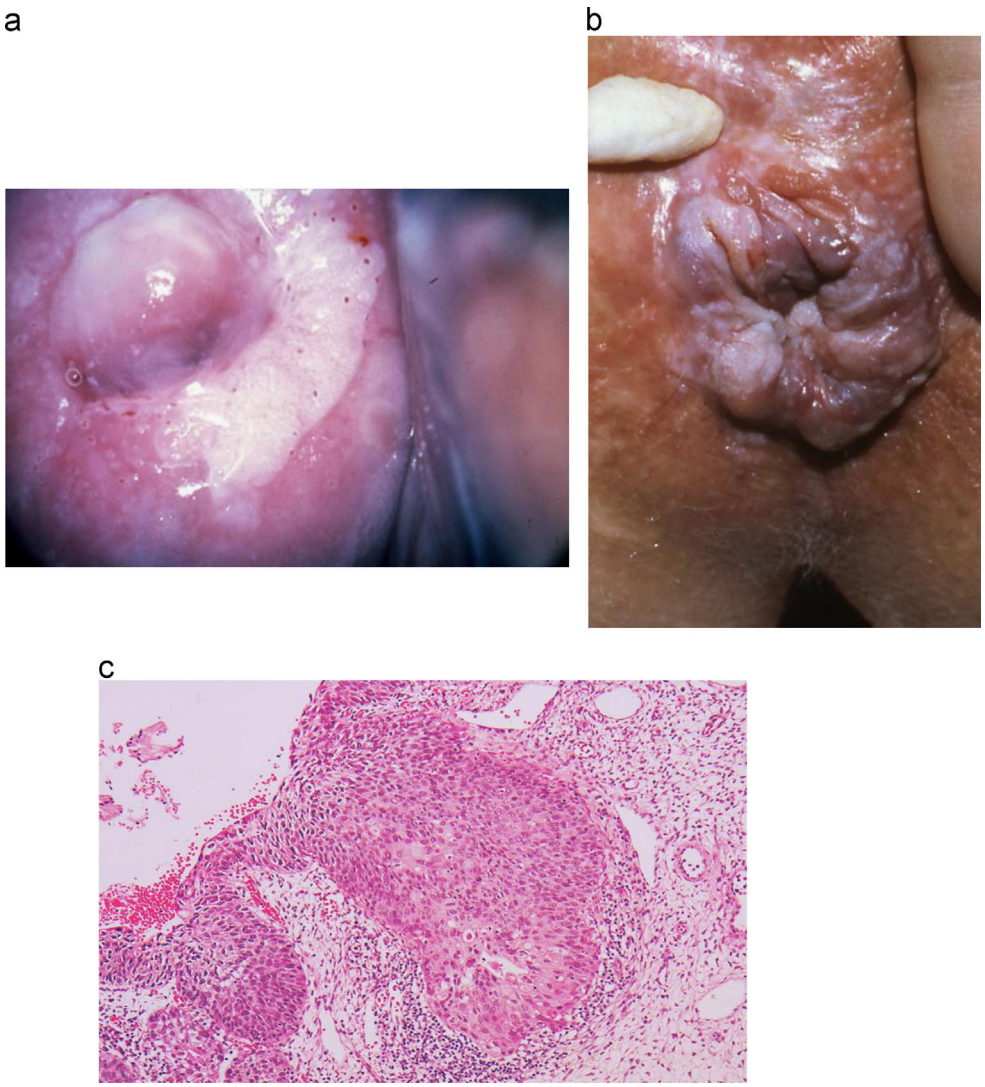

Fig. 10. Anogenital pre-cancers. (a) Colposcopic appearance of flat warts on cervix (CIN 3). (b) AIN in long-term renal allograft recipient. (c) Early invasion into stroma in CIN3.

Table 2
Classification of cytological and histological abnormalities (adapted from Solomon et al. (2002) and Schiffman et al. (2011)).

Papanicolau classification	Dysplasia classification	Bethesda classification	Histology classification
I	Negative	NILM (*Negative for intraepithelial lesion or malignancy*)	Negative
II	Squamous atypia	ASCUS (*Atypical squamous cells of unknown significance*) ASC-H (*Atypical squamous cells – cannot exclude HSIL)*	Squamous atypia
	Mild	LSIL (*Low-grade squamous intra-epithelial lesions encompassing HPV, mild dysplasia and CIN1*)	CIN1 (*Abnormal cells in 1:3 of layers; very unlikely to progress)*
III			
	Moderate	HSIL (*High-grade squamous intra-epithelial lesions, encompassing; encompassing moderate and severe dysplasia, carcinoma in situ, CIN2 and CIN3*)	CIN2 (*Abnormal cells including mitotic figures in 2:3 of layers of epithelium with loss of stratification and differentiation)*
IV	Severe CIS (*Carcinoma in situ*)		CIN3 (*Abnormal cells across all layers of epithelium; can progress to invasive cancer if untreated*)
V	Carcinoma	Carcinoma	Carcinoma

laboratory is used preferentially to improve quality and consistency and reduce the number of inadequate samples. LBC has the added advantage of providing suitable material for HPV testing, while histological examination of a lesion biopsy will show more specific features of HPV infection, such as hypertrophy of the basal layers, excess keratinisation in the surface layer and overall disorganisation of the epidermal structure (Fig. 11). CIN lesions are graded according to the proportion of epithelium affected by abnormalities (Table 2). In CIN3 there is minimal maturation, nuclear abnormalities throughout the full thickness and numerous mitotic figures. The correlation between cytology and histology is not good, particularly in the borderline/ASCUS category where ~20% will harbour CIN2+ disease (Solomon et al., 2002).

Most cervical cancers develop in the transformation zone, which is the junction between squamous cells of the ectocervix and columnar, glandular cells of the endocervical canal. Early acquisition of HR-HPV infections can disturb the metaplastic changes occurring at this time in the transformation zone and increase the risk of cervical cancer in the future. About 80–90% of cervical cancers are squamous cell carcinomas (SCC) and 10–20% are adenocarcinomas, with the percentage of the latter increasing in recent years. Occasionally cervical cancers have features of both types and are called adenosquamous or mixed carcinomas. Early stage SCC may be asymptomatic, but later stages can present with abnormal vaginal bleeding and discharge, pelvic pain, or pain during intercourse.

More than 99% of cervical cancers contain HPV DNA, although the proportion associated with specific high-risk HPV types (HR-HPV) is different in different countries and shows demographic, ethnic and socio-economic variation. The IARC study of over 30,000 cervical cancers showed HPV 16, 18, 58, 33, 45, 31, 52, 35, 59, 39, 51, 56, to be the most common types associated with invasive cervical cancer with HPV 16 accounting for over 50% and HPV 16 and 18 for >70% worldwide (Li et al., 2010). Due to the uneven distribution of HPV DNA in tumour biopsies, the cancers are thought to be polyclonal in origin. In the US, there are around 10,000 new cases of cervical cancer per year, with higher incidence in black and Hispanic women and also in those with low educational levels and heightened poverty (Jemal et al., 2013). Furthermore, cervical cancer is the second most common cancer of women worldwide with a mean incidence of 35 per 100,000. As cervical cancer affects women in their child-bearing and economically active years, the burden of cervical cancer in developing countries is colossal. Infection with multiple HPV types is common but is not associated with an increased risk of progression. HPV18 and 45 are more frequently detected in adenocarcinomas which can be more aggressive lesions.

Intraepithelial neoplasia and cancer at other anogenital sites

Recent data shows that asymptomatic anal and perianal carriage of HPV is common (Nyitray et al., 2008) with a prevalence of 42% reported in HIV− women with high risk behaviours (Palefsky et al., 2001). A similar squamous columnar junction exists between the anus and rectum and approximately 10% of AIN will progress to cancer within 5–10 years, comparable to the progression of CIN3 in the same time frame. As with CIN, HPV DNA can be demonstrated in all grades of premalignant anal lesions. In low grade AIN, multiple types are found in over 50% with roughly one-third containing HPV 16 and one-third containing HPV 6, and HPV 18, 33, 58 and 45 making up the remainder (De Vuyst, 2011). While anal cancer is numerically relatively uncommon, there are many reports of significant increases in recent years, particularly in men who have sex with men (MSM) and in HIV positive groups (Palefsky and Rubin 2009). HIV positive MSM have anal cancer incidences about three times that of the highest worldwide reported cervical cancer incidences (Stanley et al., 2012). Nevertheless, despite the higher risk in MSM and bisexual men, more women develop anal cancer, particularly those over 50 (Jemal et al., 2013). In Scotland, the incidence of anal SCC doubled to 0.37 per 100,000 in men and 0.55 in women between 1975 and 2002 (Brewster and Bhatti, 2006). HPV16 is detectable in an even higher proportion of SCC of the anus compared with the cervix, with HPV 16 in over 70%, HPV 18 in around 5%, followed by HPV 33,6 and 31 (de Vuyst, 2011).

The co-factors associated with anogenital malignancies are similar to those for HPV infection in general, with smoking the most significant. Other risk factors include receptive anal intercourse, age of first exposure to HPV and number of sexual partners, immune status and genetic background, long-term use of oral contraceptives and history of EGW. In women, the anatomic proximity of the vagina to the anus may facilitate non-sexual and auto-inoculation in women (Moscicki et al., 1999).

Vaginal, vulval and penile cancers are all rare. This is thought to be because these sites lack a cellular transformation zone in contrast to both the cervix and anus.

Most penile cancers occur in men over aged 50 and about 50% are HPV associated. Most are SCC, but a few are verrucous carcinomas of the Buschke–Lowenstein type. Symptoms and signs may include the painless appearance of flat blue-brown growths, red rash or warty papules under the foreskin, or on the glans or shaft of the penis; discharge or bleeding may be present. Penile cancer is less common in males circumcised at birth. While subclinical HPV infection on the penis can be detected using a colposcope and acetic acid, it is rarely undertaken and penile cancers present difficult diagnostic and therapeutic issues. Diagnosis is often delayed because patients disregard early asymptomatic lesions and there is

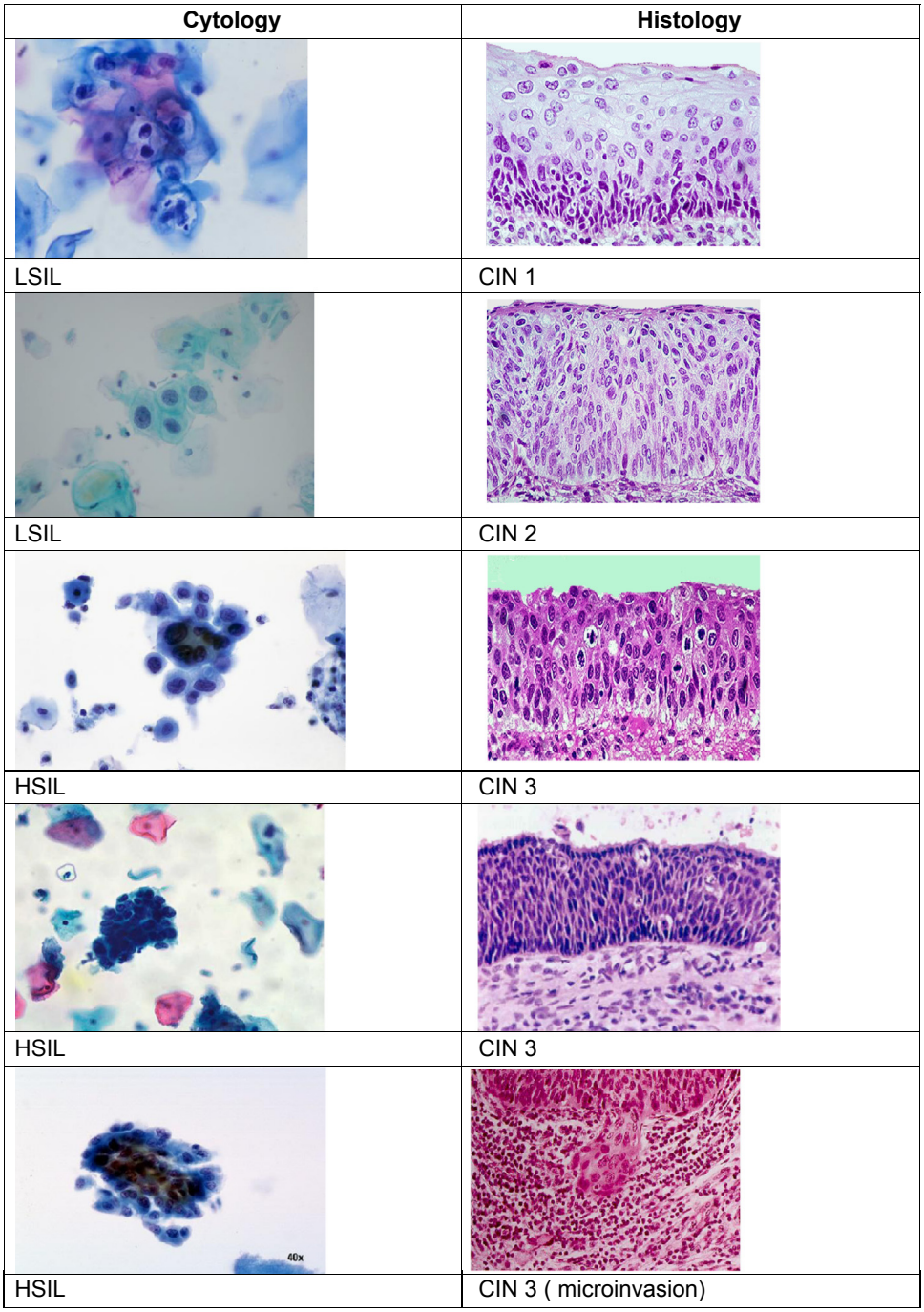

Fig. 11. Cytological and histological images of HPV associated pre-cancers.

considerable controversy as to the best form of treatment. According to recent US data (Jemal et al., 2013) the causes, racial and geographic distribution of penile cancers are similar to those of cervical cancers.

Vulvar cancer represents only 3% of gynaecological cancers worldwide (Rumbold et al., 2012). Over the last two decades however, there has been an increase in vulvar cancer in young women, usually arising in areas of basaloid or warty VIN. The peak of vulvar cancer incidence has now shifted from women over 50 to women under 20, with two different aetiological entities being recognised. Vulvar cancer in young women is associated with persistent HR-HPV, usually HPV 16 as in cervical cancer. In post-menopausal women, cancer can arise in vulvar skin following squamous hyperplasia or lichen sclerosus. Interestingly, white women in the US are more often affected by vulvar cancer, while blacks and Hispanics present with more vaginal cancers (Jemal et al., 2013).

Co-infection with HIV and HPV is well known to increase the risk of cancer at several sites. Recently HPV has also been shown to be a cofactor in HIV acquisition (Houlihan et al., 2012). In HIV+ women, the higher risk starts with increased cervical HPV detection and infection, increased persistent infection, and increased cervical abnormalities/CIN, while in HIV+ men, the increased risk is for anal HR-HPV infection, persistence and AIN (Hagensee et al., 2004). In HIV+ women, AIN/anal cancer is found more frequently in association with CIN/cervical cancer and with the same HPV types in anus and cervix, compared with HIV− women (Hessol et al., 2013). The greater risk of *in situ* cancers in HIV+ people is associated with increasing immunosuppression, but progression to

invasive disease does not appear to be associated with immune status (Frisch et al., 2000).

Head and neck HPV

Oral papillomas

Oral papillomas have been recognised since the 17th century and are the most common benign tumours of the oral mucosa. In the Finnish Family HPV study, persistent oral HPV carriage was detected in 6% of women under 30 years of age and estimates of adult carriage from other studies range from 5% to 15% (Rintala et al., 2005). Common warts can spread from the hands to lips by finger sucking and nail biting, with cutaneous HPV types identified in the lesions. They can become warty on the tongue and hard palate which has a stratum corneum (Fig. 12a). Other HPV-induced oral lesions include common warts on the oral mucosa associated with HPV 2; the multiple soft papules of Heck's disease (focal epithelial hyperplasia) found most commonly in Eskimos and North American Indians and associated with HPV 13 or 32; and oral florid papillomatosis which presents as multiple lesions on the buccal mucosa. As with EGW, typical virus particles are found only rarely and in small numbers in oral lesions due to the lack of keratinisation of the mucosal epithelium. Subclinical lesions can be detected on the oral mucosa of normal adults after the application of acetic acid and the associated HPV types are usually the same as those found in the genital tract. Despite effective antiretroviral therapy, HIV+ individuals have an increased risk of acquiring oral warts (Hagensee et al., 2004) (see Fig. 12b).

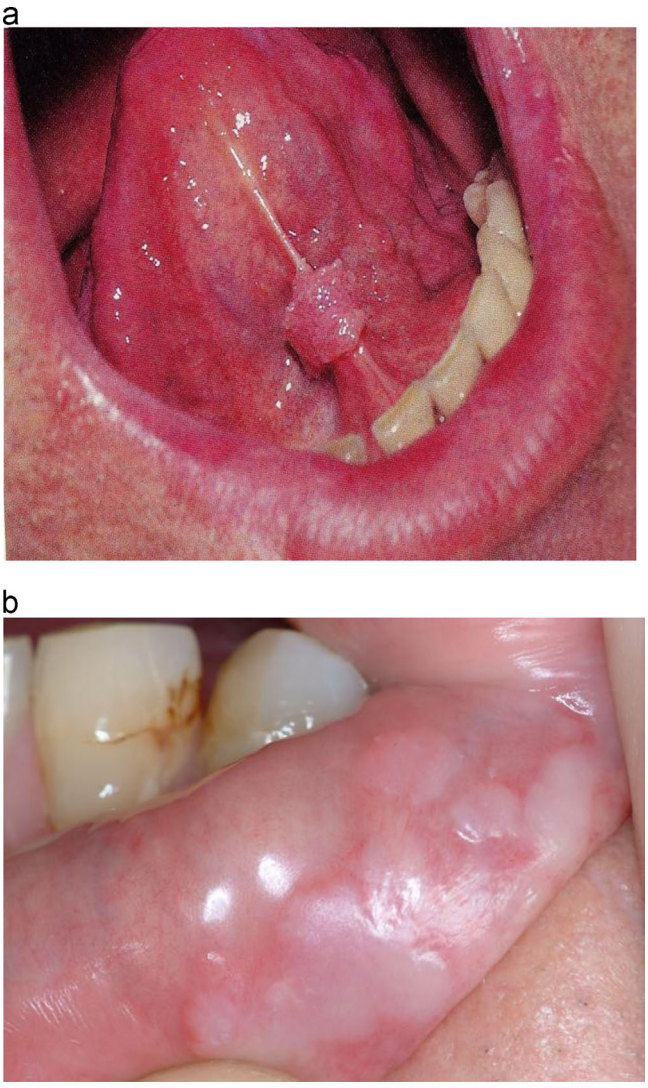

Fig. 12. Oral HPV lesions. (a) Wary lesion resembling condyloma on base of tongue. (b). Oral lesions in patient with AIDS. (Image (a) previously published in Bunney, M. H., Benton, C., Cubie, H.A. (Eds.). 1992. 'Viral warts' – Biology and Treatment, 2nd edition. Oxford University Press. ISBN0-19-262062-2. *With permission from surviving authors (Drs. Benton and Cubie*).)

Laryngeal papillomatosis occurs in both children and adults. Juvenile onset recurrent respiratory papillomatosis (JORRP) is the most common benign neoplasm of the larynx in children and occurs in 4/100,000 live births (Larson and Derkay, 2010). JORRP is acquired either during birth or *in utero* from a mother with current HPV infection in the cervix or with genital warts. It presents with an abnormal cry and/or hoarseness of voice due to pressure on vocal cords, has a peak incidence in children under 5 and is characterised by the presence of HPV 6 or 11 exophytic warty lesions. These consist of a vascular connective tissue core covered by hyperplastic stratified epithelium. JORRP can be life-threatening, as rapid growth of the lesions can easily block the small airway, making surgical intervention essential and life-saving. Some children can require surgery as often as monthly. Recurrences are frequent, morbidity is high, treatment is challenging, management is difficult for both patients and their families and the costs to healthcare are high.

The incidence of RRP in adults is lower (2/100,000) with a peak incidence around aged 20 and acquisition is thought to occur through orogenital contact with an infected partner. While the most common site of infection is the larynx, the oral cavity, trachea, bronchi, lung parenchyma and oesophagus can also be infected (Kashima et al., 1993). Recurrence of tumours of the upper respiratory tract, extension into the lower airway in approximately 17% of patients and malignant conversion in 3–4% make clinical management difficult (Steinberg et al., 1988). HPV 11 infections are more aggressive than those caused by HPV 6, are more likely to migrate further down the airway and show a higher malignant conversion rate (Katsenos and Becker, 2011). The rare pulmonary and oesophageal lesions associated with HPV are almost invariably fatal.

HPV associated oral cancers

There are about 650,000 new cases of head and neck cancer annually worldwide, the majority of which (75–80%) occur in men and are associated with alcohol and smoking in the West and chewing of tobacco and betel nuts in South East Asia. While the overall incidence is declining, the proportion of oropharyngeal cancers has increased rapidly in recent years in several countries. For example, incidence in the UK increased by 51% between 1989 and 2006 and in the USA by 22% between 1999 and 2006 (Mehanna et al., 2010). This increase has been greatest in individuals under 50 years old, is linked to the proportion of tumours which harbour HPV, without the traditional risk factors of smoking and alcohol consumption and is limited to cancers of lingual and palatine tonsils, base of tongue and back of the throat (Jemal et al., 2013). HPV 16 is even more dominant than in cervical cancers and the increase in HPV positive oral cancers is presumed to be associated with changes in sexual behaviours, including oral sex. Further details of the changing pattern of HPV-positive head and neck cancers can be found in the recent systematic review by Syrjanen et al. (2011).

Five year survival from oropharyngeal cancer is $<50\%$, largely due to lack of visible lesions and therefore often late presentation, but the prognosis for HPV positive cases is better (Goon et al., 2009), prompting a new area of clinical research concentrating on

de-escalation of treatment in this subgroup and in new diagnostics to aid patient management.

Concluding remarks

The range of infections, precancers and malignancies associated with HPV continues to grow. While much effort worldwide focusses on the potential to eradicate cervical cancer by HPV vaccination programmes targeting pre-sexually active girls, the burden of disease is increasing in other areas, particularly with the high prevalence of genital warts and of anal and oropharyngeal cancers, in both men and women. It is important also to recognise the morbidity of cutaneous HPV lesions, particularly in the immunosuppressed population. HPVs remain both highly effective pathogens and carcinogens, well adapted to their ecological niches, capable of avoiding immune responses and therefore challenging to eliminate.

Acknowledgments

I am indebted to Dr. E. Claire Benton, retired consultant dermatologist, Royal Infirmary of Edinburgh for much helpful discussion, access to her extensive library of clinical images and for editing drafts of this manuscript.

My thanks are also due to Dr. Alistair Williams, consultant pathologist, University of Edinburgh for histological images in Figs. 10 and 11.

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