Genital warts and mucosal papillomavirus disease

Charles JN Lacey

Abstract

Human papillomavirus (HPV) is an ancient stable DNA virus, which has evolved over millennia and causes a variety of niche-specific cutaneous and mucosal infections and diseases, including squamous carcinoma and its precursor lesions. There are numerous HPVs and these are widely distributed in the human population. Mucosal infection by HPV is very frequent, is often sexually transmitted, and is often subclinical. Prophylactic vaccines against HPV have recently been developed, and population-based vaccination programmes have already been shown to result in significant reductions in HPV disease.

Keywords Anogenital cancer; cervical cancer; condylomata acuminata; genital warts; HPV; HPV vaccine; human papillomavirus; sexually transmitted infection

What's new?

- A prophylactic quadrivalent HPV vaccine is now given routinely in the UK to girls aged 12—13 years via a school-based programme.
- Dramatic declines in the incidence of genital warts have been seen within five years of introducing an HPV-6/11/16/18 vaccine programme.
- The proportion of cases of oropharyngeal carcinoma caused by HPV is rising in many countries worldwide, and nowadays ~55% of cases in the UK are caused by HPV.

Aetiology

HPV virions are small (60 nm), non-enveloped, icosahedral capsids enclosing an 8-kb, circular double-stranded DNA genome. HPV is exclusively epitheliotropic and infects cutaneous or mucosal epithelium.

Many new cutaneous HPV types have been detected in recent years and about 300 different genotypes of HPV have been described. Some of these (Table 1) are detected almost exclusively in genital or mucosal lesions, and these HPV types can be classified phenotypically as being associated with either a low risk of cancer (LR HPV), or a higher risk of cancer (HR HPV).

Spectrum of mucosal papillomavirus disease

On anogenital mucosae (i.e. penis, vulva, vagina, cervix and anus), HPV can cause warts, intraepithelial neoplasia or cancer. Genital warts [also known as (aka) condylomata acuminata, anogenital warts] are usually caused by HPV-6 or HPV-11. However, a much wider spectrum of HPV types including many HR HPVs infect the genital mucosa, causing clinical disease (e.g. bowenoid papulosis, cervical, anal, vulval and vaginal cancer) or subclinical disease (e.g. cervical intraepithelial neoplasia [CIN] detectable by cytology or colposcopy); they can also exist in a latent form in essentially normal epithelium.

HPV is also frequently detected in the oropharyngeal mucosa. There the principal clinical diseases caused by HPV include oral papillomas (aka warts, condylomata), oral intra-epithelial lesions (aka leukoplakia), focal epithelial hyperplasia (aka Heck's disease), laryngeal papillomatosis, and oropharyngeal squamous carcinoma. HPV-associated cancers at mucosal sites are usually caused by HPV-16 or HPV-18.

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Pathology

Warts

HPV infects long-lived cells (probably stem cells) on the basement membrane, and then undergoes its life cycle in differentiation-committed cells as they migrate upwards within the epithelium. Typical features of an LR HPV-driven papilloma (wart) include elongation of the dermal papillae (papillomatosis) and hyperplasia of the stratum spinosum (acanthosis). In the stratum granulosum, large, vacuolated cells (koilocytes) are seen (Figure 1a).

Intraepithelial neoplasia

When HR HPVs infect mucosal epithelium varying degrees of intraepithelial neoplasia are frequently seen. The epithelium within such a lesion shows a failure of orderly maturation, excessive and abnormal mitotic activity, and cells will have an increased nuclear:cytoplasmic ratio. These changes of intraepithelial neoplasia were first described in cervical epithelium (CIN) and classified as:

- CIN1 (de-differentiation confined to the deepest third of the epithelium)
- CIN2 (de-differentiation in the deepest two-thirds)
- CIN3 (de-differentiation through the full thickness).

The classification was later extended to the vulval, vaginal, anal, and penile epithelia (VIN, VAIN, AIN, PIN), respectively (Figure 1b).

Cancer

HPV-16 and HPV-18 were first demonstrated in cervical cancer tissues in the early 1980s. With gradual refinement of HPV DNA detection systems it became clear that HPV could be detected in

Relative risk association of common anogenital human papillomavirus types

• Low risk	6, 11, 40, 42, 43, 44, 53, 54, 57, 66
• High risk	16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68

Table 1

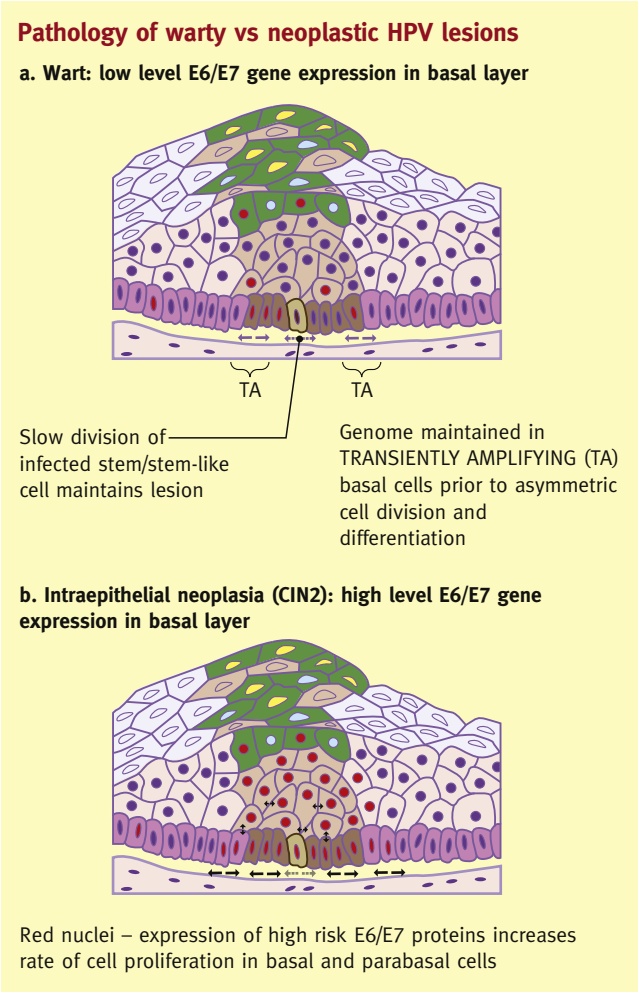

Figure 1 Adapted from Doorbar J. Latent papillomavirus infections and their regulation. *Current Opinion in Virology.* 2013, **3**:416–421.

virtually all cervix cancer tissue. The proof that HPV causes cervix cancer is based on the following observations:

- HPV DNA is detectable in almost all cases of cervical cancer[1]
- the association between HPV and cervical cancer is very strong and consistent in case–control studies
- the association is specific to high-risk oncogenic genotypes, and their transforming genes are transcriptionally active in the lesions
- persistent infection with HR HPV and increasing HPV viral load is necessary for progression to CIN3 and malignancy.[2]

HR HPV types are also found in approximately 90% of anal cancers, 70% of vaginal cancers, 40% of vulval cancers, 50% of penile cancers,[3] and 55% of oropharyngeal cancers.[4] In all these cancers the above latter three criteria are fulfilled and HPV has been defined as a definite human carcinogen.[3]

Clinical features

Genital warts

Genital warts occur in males on the frenulum, corona, glans, urinary meatus, prepuce, shaft of the penis, scrotum, groin, perineum and perianal area (Figure 2). In females, genital warts occur on the vaginal introitus, fourchette, labia minora, clitoris, vagina, cervix, perineum and perianal area (Figure 3). In both sexes, proctoscopy may reveal lesions in the anal canal as far as the dentate line (the squamocolumnar cell junction between the anal canal and the rectum).

Bowenoid papulosis

Bowenoid papulosis is an HPV-16-induced disease of male and female external genitalia. It comprises itchy, pigmented papules with high degrees of intraepithelial neoplasia (Figure 4). In women, these may be associated with multifocal genital tract pre-cancer involving the cervix, vagina, vulva or anus.

Cervix

Although macroscopic inspection of the cervix only occasionally shows white patches or papillomas, colposcopy reveals a spectrum of change, from condylomata (Figure 5) to CIN grade III (Figure 6).

Oral warts

Condyloma acuminata are occasionally seen in the oral cavity and are usually associated with orogenital contact.

Respiratory papillomatosis

Respiratory papillomatosis caused by HPV-6 or HPV-11 presents in children and young adults. In children, the infection is acquired from the mother during childbirth. The latency period and mode of transmission in adults are less clear.

Diagnosis

Thorough genital examination

Thorough genital examination is essential. In males, the prepuce must be retracted fully and the meatus must also be inspected. In subjects with anal symptoms or peri-anal lesions the anal

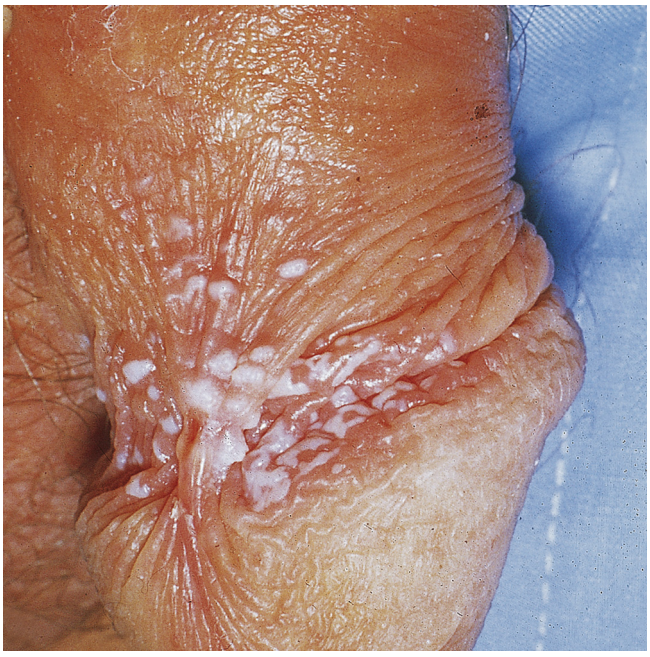

Figure 2 Small, white, papular and flat, warty lesions around the frenulum and in the coronal sulcus.