

8.5.19 Papillomaviruses and polyomaviruses 877

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8.5.19 Papillomaviruses and polyomaviruses 877 Prognosis The case fatality of filovirus infections is extremely high and possibly dependent on the infecting species, with up to 90% for Ebola virus Zaire and Marburg virus disease Angola. Among 27 patients with Ebola virus disease who were cared for in the United States or Europe, close monitoring and aggressive supportive care that included intravenous fluid hydration, correction of electrolyte abnormalities, nutritional support, and critical care management for respiratory and renal failure were needed; 81.5% of these patients who received this care survived (Uyeki et al., 2016). Common denominators of survival in filovirus-infected macaques are maintenance of D-dimer levels, maintenance of protein C activity (>50%), maintenance of levels of proinflammatory/procoagulant cytokines, and low viral load. Areas of uncertainty/controversy None of the trials conducted with antiviral drugs during the 2014 Ebola virus epidemic produced results sufficient for licensure, so their future development and availability during the next filovirus outbreak is uncertain. Likely developments over the next 5–10 years The licensing of a recombinant, vesicular stomatitis virus-based Ebola virus vaccine is to be expected in the United States of America within 1–2 years. FURTHER READING Cardile AP, et al. (2017). Will there be a cure for ebola? *Annu Rev Pharmacol Toxicol*, 57, 329–48. Cross RW, et al. (2018). Post-exposure treatments for Ebola and Marburg virus infections. *Nat Rev Drug Discov*, 17, 413–31. Lamontagne F (2018). Evidence-based guidelines for supportive care of patients with Ebola virus disease. *Lancet*, 391, 700–08. 8.5.19 Papillomaviruses and polyomaviruses Raphael P. Viscidi, Chen Sabrina Tan, and Carole Fakhry ESSENTIALS Papillomaviruses and polyomaviruses are small, nonenveloped, double-stranded DNA viruses. Human papillomavirus There are nearly 200 human papillomavirus types that infect epithelia of skin and mucous membranes. They infect only humans, and cause conditions including the following: Skin warts and verrucas—caused by types 1 and 2; infection initiated when, after minor skin abrasions, for example, the basal cells of the epithelium come in contact with infectious virus. Anogenital warts—caused by types 6 and 11; transmitted by direct sexual contact, these are the most common sexually transmitted infection; present clinically as multiple exophytic lesions or as subclinical flat lesions. Can be treated topically with podophyllin or imiquimod, or by ablative surgical methods. Recurrences are common. A highly efficacious prophylactic vaccine is available. Cervical cancer—the second most common

tumour in women worldwide; most often caused by types 16 and 18, whose DNA can be recovered from nearly all cases of invasive disease and squamous intraepithelial lesions of the cervix, which precede invasive cancer. Prevention is by cervical screening and vaccination (two highly effective vaccines are available). Other cancers—human papillomaviruses can cause cancers at other lower anogenital tract sites and in the oropharynx. Human papillomavirus DNA is often detected in nonmelanoma skin cancers, but it is not known whether this is pathogenic. Respiratory papillomatosis—caused by types 6 and 11; usually involves the vocal cords, leading to presentation with hoarseness or voice change; may rarely cause life-threatening airway obstruction; mainstay of treatment is surgical removal of papillomas, which commonly recur. Human polyomaviruses Exposure to polyomaviruses is nearly universal: primary infection is most likely asymptomatic and occurs in childhood and then persist as latent infections, primarily in the kidney epithelial cells, producing disease in the context of immunosuppression. BK virus—can cause (1) nephropathy and renal failure in renal transplant patients; management is by gradual reduction in immunosuppression, but more than 50% of patients lose their allograft, and (2) ureteral stenosis; (3) haemorrhagic cystitis in bone marrow transplant patients. JC virus—causes progressive multifocal leukoencephalopathy, a demyelinating disease of the central nervous system that is usually relentlessly progressive and fatal. Progressive multifocal leukoencephalopathy is most often seen in patients with HIV/AIDS, but recently reported as a rare complication of treatment with many immunoregulatory monoclonal antibodies, but most commonly with natalizumab given to patients with multiple sclerosis or Crohn's disease. Merkel cell polyomavirus has recently been implicated as the aetiological agent of Merkel cell cancer, a rare aggressive skin tumour. Trichodysplasia spinulosa-associated polyomavirus causes a skin disease, trichodysplasia spinulosa, in paediatric heart transplant patients. Other polyomaviruses include Washington University polyomavirus, Karolinska Institute polyomavirus, Malawi polyomavirus, and St Louis polyomavirus, named for the geographic location where the viruses were isolated; and human polyomavirus 6, 7, 9, 12, and 13, named in order of their discovery. These have been isolated from both sterile sites such as blood (human polyomavirus 9) and nonsterile sites, including nasopharynx (Washington University polyomavirus and Karolinska Institute polyomavirus) and stool (Malawi and St. Louis polyomaviruses). It is currently unclear if these polyomaviruses cause specific human disease.

878 section 8 Infectious diseases Introduction Papillomaviruses and polyomaviruses are small, spherical, non-enveloped, double-stranded DNA viruses that multiply in the cell nucleus. The two virus groups are unrelated. Papillomaviruses infect surface epithelia and produce disease at these sites. Polyomaviruses cause viraemia and spread, after initial multiplication at the site of entry, to affect internal organs such as the kidney, the brain, or skin. Viruses of both families produce experimental tumours in laboratory animals and both viruses are responsible for some cancers in humans, although only papillomavirus-associated cancers are common. Within each family the viruses are immunologically related and share nucleotide similarity. Nearly 200 human papillomaviruses have been recognized, about 35 of which infect mucous membranes (genital and respiratory tracts, and the oral cavity) and the remainder infect skin. Human papillomaviruses cause skin warts, genital warts, respiratory papillomas, and papillomas at other mucosal sites (e.g. mouth, eye). In addition, infection with some genital tract human papillomaviruses causes cervical cancer, one of the most common female malignancies in the world, as well as a proportion of cancers at other genital tract sites and the oropharynx. JC virus is the aetiological agent of progressive multifocal leukoencephalopathy, a fatal demyelinating disease occurring in

immunodeficient people. BK virus is associated with haemorrhagic cystitis in bone marrow transplant recipients, and with nephropathy and renal failure in renal transplant recipients. Merkel cell polyomavirus is implicated as the aetiological agent of Merkel cell cancer, a rare aggressive skin tumour. Trichodysplasia spinulosa-associated polyomavirus is found in the rare skin disease of the same name and may play a role in the development of the disease. It is not known if the other human polyomaviruses cause disease. Human papillomaviruses (HPVs) Human papillomaviruses cannot be propagated in tissue culture and require nucleic acid hybridization assays for their identification. Their double-stranded circular genome contains about 8000 bp, divided into an early region, necessary for transformation, a late region, encoding for capsid proteins, and a regulatory region, containing control elements (Fig. 8.5.19.1). Open reading frames of the viral genome are located on one strand: E1 to E8 in the early region and L1 and L2 in the late region. The functions assigned to the different open reading frames are listed in Table 8.5.19.1. Human papillomaviruses infect only humans. They show a marked degree of cellular tropism. Mucosal human papillomaviruses do not readily infect cutaneous epithelia and cutaneous human papillomaviruses are rarely present on mucous membranes. Infection is initiated when, after minor trauma (e.g. during sexual intercourse or after minor skin abrasions), the basal cells of the epithelium come in contact with infectious virus. The virus stimulates the proliferation of basal cells. The early region open reading frames are expressed in all layers of the infected epithelium, but expression of the late region open reading frames and synthesis of viral particles occur only in the upper differentiating and keratinizing layers. Important disease associations and characteristics of mucosal HPVs are listed in Table 8.5.19.2. The burden of human cancers attributable to HPVs is shown in Table 8.5.19.3. The genital tract is the reservoir for all but a few mucosal human papillomaviruses, and genital human papillomavirus infections constitute the most common viral sexually transmitted infections. Genital human papillomaviruses may sometimes infect nonanogenital mucosal sites (e.g. the respiratory tract, the mouth, and the conjunctiva). Transmission of genital tract HPV types 6 and 11 from an infected mother to the baby at birth results in juvenile-onset recurrent respiratory papillomatosis. Infection with two types, HPV-13 and HPV-32, appears to be confined to the oral cavity. Table 8.5.19.4 lists disease associations of cutaneous HPVs, which are transmitted by direct contact with infected tissue or by contact with a contaminated object. Anogenital warts Anogenital warts (condylomas) are the most commonly recognized clinical manifestations of genital HPV infections. More than 90% of condylomas result from infections with HPV-6 and HPV-11. In the LCR E6 E7 E1 E2 E5 E4 L2 L1 HPV-16 P97 AE 1000 2000 3000 4000 5000 6000 7000 7904/1 AL Fig. 8.5.19.1 Genomic map of HPV-16. On the inner circle, P97 represents the transcriptional promoter and AE and AL designate early and late polyadenylation sites. The location of the early region open reading frames (E1-E8), the late region open reading frames (L1, L2), and of the long control or regulatory region (LCR) are shown. Reproduced from Shah KV, Howley PM (1996). Papillomaviruses. In: Fields BN, et al. (eds) Fields virology, vol. 2, pp. 2077-109. Lippincott-Raven, Philadelphia, with permission. Table 8.5.19.1 Functions of human papillomavirus open reading frames

Function	ORF
Major capsid protein and neutralizing epitopes	L1
Minor capsid protein	L2
Replication of viral DNA	E1, E2
Regulation of transcription	E2
Coding for late cytoplasmic protein	E4
Cellular proliferation	E5
Transformation	E6, E7
Not known	E3, E8
ORF, open reading frame	

Modified from Shah KV, Howley PM (1996). Papillomaviruses. In: Fields BN, et al. (eds) Fields virology, vol. 2, pp. 2077-109. Lippincott-Raven, Philadelphia.

8.5.19 Papillomaviruses and polyomaviruses 879 United States of America, there are more than a million annual consultations for anogenital warts. Epidemiology Genital and anal warts are most common between the ages of 16 and 24 years. They are transmitted by direct sexual contact. Anogenital warts in children can also be due to close but nonsexual contact within a family but, in many cases, sexual abuse by an infected adult is responsible. Clinical features The incubation period is between 3 weeks and 8 months (mean = 2.8 months). In men, condylomata acuminata (exophytic condylomas) most often appear on areas exposed to coital trauma, the glans penis, coronal sulcus, prepuce, and terminal urethra. The soft fleshy vascular tumours are usually multiple and may coalesce into large masses (Fig. 8.5.19.2). Sessile or papular warts are more likely to occur on dry areas such as the shaft of the penis (Fig. 8.5.19.3). The raised pink or grey lesions, 0.5–3 mm in diameter, may occur alone or with exophytic condylomas. Subclinical HPV lesions (flat condylomas) are identified by examining the genitalia with magnification after the application of 5% aqueous acetic acid solution. The affected areas are slightly raised and shiny white (acetowhite), with a rough surface. Flat condylomas affect the same areas as exophytic condylomas. Perianal warts are usually exophytic and in moist conditions around the anus may reach a large size. In 50% of cases, condylomas also appear in the anal canal. Areas of acetowhite epithelium indicative of subclinical HPV infection may be associated with perianal warts or occur alone. In women, exophytic condylomas (Fig. 8.5.19.4) appear at the fourchette and adjacent areas, and may spread to the rest of the vulva, the perineum, anus, vagina, and cervix. Multiple sessile warts may affect the labia and perineum. Subclinical HPV infection presents as slightly raised acetowhite lesions: the fissuring of these may cause dyspareunia. About 15% of women with vulval warts have exophytic condylomas on the cervix. Subclinical infection is more common, and consists of acetowhite lesions with punctation due to capillary loops, which can be identified by colposcopy. Large, exophytic vulval condylomas may develop during pregnancy and can become so large that they compromise delivery. Most regress post-partum. Even with therapy (see next), recurrence of genital warts occurs within 3 months in 25–67% of cases. Recurrences are often at sites of previous genital warts and are attributed to persistent infection that then reactivates.

Diagnosis and management Genital warts must be distinguished from Fordyce's spots, fibroepithelial polyps, molluscum contagiosum, and the papillar lesions of secondary syphilis. Lesions that appear atypical or respond poorly to treatment must be biopsied early. Associated sexually transmitted infections must be excluded. Sexual partners should be examined. Intraepithelial neoplasia must also be excluded. Cervical cytological examination should always be done on women with vulval warts and on female partners of men with penile warts. Treatments for genital warts can be classified as topical, immunomodulatory, or surgical. Podophyllin and podophyllotoxin, which are derived from the root of the mayapple plant, are antimitotic agents that disrupt viral activity by inducing local tissue necrosis. Patient-applied topical podophyllotoxin, 0.5%, has a clinical cure rate of 56%; however, recurrence rates range from 23 to 65%. Disadvantages of podophyllin compounds include local

Table 8.5.19.2 Mucosal human papillomaviruses: chief clinical associations

Clinical association	Viral type(s)
Exophytic condyloma; respiratory papillomas; oral and conjunctival papillomas	HPV-6, -11
Cervical cancer: High-risk infections	HPV-16, -18, -31, -45, -33, -35, -39, -51, -52, -56, -58, -59
Low-risk infections	HPV-6, -11, -40, -42, -43, -44, -54, -61, -70, -72, -81
Vulval, vaginal, penile, anal, and oropharyngeal cancers	HPV-16
Focal epithelial hyperplasia of the oral cavity	HPV-13, -32

Modified from Shah KV, Howley PM (1996). Papillomaviruses. In: Fields BN, et al. (eds) Fields virology, vol. 2, pp. 2077–109. Lippincott-Raven, Philadelphia. Includes material from The Oxford textbook of medicine, 3rd edition, pp. 3366–9.

Table 8.5.19.3 Cancers attributable to HPV infection in 2002

Site	Attributable
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to HPV (%) Total cancers Attributable to HPV % of all cancers Cervix 100 492 800 492 800 4.54
 Penis 40 26 300 10 500 0.10 Vulva, vagina 40 40 000 16 000 0.15 Anus 90 30 400 27 300 0.25
 Oropharynx 50 52 100 26 500 0.25 All sites c.5 10 862 500 Modified from Parkin DM and Bray F
 (2006). The burden of HPV-related cancers. Vaccine, 24, Suppl 3, S11–S25.

section 8 Infectious diseases 880 adverse reactions, risk of systemic absorption, and teratogenicity. Imiquimod, a topical treatment for genital warts, induces macrophages to secrete cytokines, principally interferon- α , and is thought to work by stimulation of a cell-mediated immune response against HPV. Imiquimod is as effective as podophyllin for initial clearance of genital warts and results in a lower recurrence rate. The side effect profile of imiquimod is benign. Warts can be destroyed by cryotherapy with liquid nitrogen, electrocautery, electrodesiccation, scissor excision, or carbon dioxide laser therapy. Although these ablative therapies are successful in initially removing genital warts, recurrences are common. In a comparative trial, imiquimod 5% cream alone or in combination with ablative treatments was superior to ablation alone in reducing the recurrence rate of successfully treated anogenital warts. A prophylactic vaccine that prevents 100% of genital warts due to HPV-6 and HPV-11, if administered prior to exposure to HPV, is now available (see next). Respiratory papillomatosis This rare disease may have onset in childhood or in adult life. It is most common in children under the age of 5 years. It may become life-threatening if it obstructs the airways. Papillomatosis usually involves the vocal cords and the patient presents with hoarseness or voice change. Papillomas might recur despite surgical removal. HPV-6 and HPV-11, genital tract HPVs that are responsible for most of the exophytic genital warts, also cause respiratory papillomatosis. Patients with juvenile-onset disease are infected at birth during passage through an infected birth canal. In adult-onset disease, transmission may occur by sexual contact. Respiratory papillomas rarely progress to invasive cancer. Irradiation of papillomas with X-rays (a practice now discontinued) increased the risk of malignancy. Caesarean delivery for mothers who are found to have genital warts or are infected with HPV-6 or HPV-11 would reduce the risk of juvenile-onset respiratory papillomatosis, but it is not generally recommended because of the small risk of disease following perinatal infection. The mainstay of treatment is surgical removal of papillomas; however, recurrence of lesions is common. Various adjunct therapies have been tried, including interferon- α , indole-3-carbinol, cidofovir, and photodynamic treatment. These therapies

Table 8.5.19.4 Cutaneous human papillomaviruses: chief clinical associations

Viral type	Clinical association
Deep plantar wart	HPV-1
Common wart	HPV-2, -4
Mosaic wart (superficial spreading wart)	HPV-2
Flat warts	HPV-3, -10, -28, -41
Macular plaques of epidermodysplasia verruciformis	HPV-5, -8, -9, -12, -14, -15, -17, -19, -20, -21, -22, -23, -24, -25, -36, -47, -50
Squamous cell carcinoma	HPV-5, -8, -20, -36, -38

Modified from Shah KV, Howley PM (1996). Papillomaviruses. In: Fields BN, et al. (eds) Fields virology, vol. 2, pp. 2077–109. Lippincott-Raven, Philadelphia.

Fig. 8.5.19.2 Condylomata acuminata (exophytic condylomas) of the penis. Fig. 8.5.19.3 Sessile (papular) warts of the penis.

8.5.19 Papillomaviruses and polyomaviruses 881 have had only modest success in reducing the need for surgery or recurrence. It is anticipated that a child born to a mother who has received the HPV Gardasil vaccine, will have a markedly reduced risk of developing respiratory papillomatosis. Cervical cancer (See Chapter 5.1.) Human papillomavirus DNA is recovered from nearly 100% of cases of invasive cervical cancer and squamous intraepithelial lesions of the cervix, which precede invasive cancer. The viral genome is present in the tumour cells of primary as well as metastatic cervical cancer. The progression from low grade squamous intraepithelial lesions to invasive cancer

may take more than 10 years; human papillomaviruses are found throughout this disease process. The viruses are recovered much less frequently from cytologically normal women of comparable age. In prospective studies of women with normal cervical cytology, the presence of HPV is a strong risk factor for the subsequent development of squamous intraepithelial lesions. Certain HPV types are preferentially associated with invasive cancers. From their distribution in normal individuals and in preinvasive and invasive cervical disease, genital tract HPVs have been categorized as high-risk, or low-risk types (Fig. 8.5.19.5; Table 8.5.19.2). HPV-16 and HPV-18 are the predominant viruses in invasive cancers and account for 40–60% and 5–20%, respectively, of HPV-positive cancers in different studies. About a dozen additional types of HPV are found in small proportions of invasive cancers. The low-risk HPVs are almost never detected in invasive cervical cancers. Comparisons of different HPV types for their ability to transform human keratinocytes in vitro show that HPV-16 and HPV-18, types most clearly associated with naturally occurring cervical cancers, also have the greatest oncogenic potential in laboratory studies. The transforming functions of HPVs are localized to open reading frames E6 and E7; these are the viral genes consistently expressed in naturally occurring HPV-positive cancers. The viral genome is integrated into the cellular DNA in most cervical cancers. The break in the circular viral genome that is required for integration occurs most frequently in the E1/E2 region and results in an enhanced expression of the transforming E6 and E7 open reading frames. The transforming HPV proteins E6 and E7 interact with cellular tumour suppressor proteins p53 and Rb, respectively. The oncogenic effect of HPVs is mediated largely by their ability to inactivate the tumour suppressor proteins which normally regulate the cell cycle. Epidemiology Human papillomavirus infections of the genital tract are extremely common in sexually active populations. A history of multiple sexual partners, and having a male sexual partner who has many sexual partners, are the main risk factors for a woman for the acquisition of HPVs. In young sexually active women, point prevalence (single sampling) of HPV infection as measured by the detection of HPV DNA in genital tract specimens by the sensitive polymerase chain reaction (PCR) may be as high as 40%, and the cumulative prevalence (multiple sampling of women over time) may be as high as 80–90%. The prevalence decreases with increasing age. Most of these infections are found in women with normal cervical cytology and undoubtedly resolve without leaving a trace. Only a small proportion of infections persists and progresses to squamous intraepithelial lesions and then to invasive cancer. The cofactors that might be associated with progression to cancer include smoking, use of oral contraceptives, parity, and presence of other sexually transmitted infections. Human immunodeficiency virus (HIV) infection and associated immunosuppression, leads to a much higher prevalence, and longer persistence, of HPV infections, and to greater incidence of squamous intraepithelial lesions. Prevention and control Screening for cervical cytological abnormalities by cervical smear and treatment of preinvasive and invasive cancers identified by Fig. 8.5.19.4

Condylomata acuminata of the vulva. 16 0 10 20 30 40 50 60 70 Contribution to cervical cancer (%)

18 45 31 33 52 58 35 59 HPV Type 56 39 51 73 68 66 X Unk Fig. 8.5.19.5 Percentages of cervical cancer cases attributed to the most frequent HPV types in all world regions combined. X includes the rare types 40, 42, 53, 54, 55, 83, and 84. 'Unk' includes specimens that were positive for HPV DNA but could not be genotyped by current methods. Data from Munoz N, et al. (2004). Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer, 111, 278–85.

882 section 8 Infectious diseases screening, have been credited with the decrease in incidence of cervical cancer and mortality due to the disease that has been observed in many developed

countries over the last 40–50 years. Cervical cancer screening by detection of DNAs of high-risk HPV types has been shown to have greater sensitivity than Pap smear for the detection of preinvasive lesions and invasive cancer. Primary screening with HPV testing or HPV cotesting with cytology is replacing cytology screening in many developed countries. Some screening algorithms include testing HPV-positive women for HPV16/18 genotypes with immediate referral of HPV 16/18 positive women to colposcopy and a 1-year follow-up for other high-risk HPV-positive women. Because the infrastructure required for the screening programme is costly, the World Health Organization has recommended that screening and treatment be performed at a single visit ('screen and treat approach') using HPV tests where available and affordable or visual inspection with acetic acid, a low-cost test that has shown sensitivity comparable to Pap testing.

Prophylactic vaccines The discovery that the L1 coat protein of papillomaviruses could assemble into a virus-like particle, when expressed as a recombinant protein, and the demonstration that immunization of rabbits, cattle, and dogs with virus-like particles of their respective papillomaviruses protected against papillomavirus-induced disease, stimulated the development of vaccines for human papillomaviruses. L1 virus-like particles appear to induce very limited cross-neutralization against other genotypes necessitating a multicomponent vaccine to provide coverage against disease caused by more than one type. Two HPV L1 virus-like particle vaccines have been developed commercially; Cervarix is a bivalent HPV-16/18 L1 virus-like particle vaccine and Gardasil is a quadrivalent HPV16/18/6/11 L1 virus-like particle vaccine. Both vaccines are generally safe and well tolerated and are highly immunogenic. Both vaccines have demonstrated truly remarkable efficacy, preventing nearly 100% of incident infections and preinvasive cervical cancers due to the HPV types in the vaccines. However, protection from incident infection or disease from non-vaccine types is restricted and the vaccines have no effect on prevalent infection and disease. Gardasil is also 100% effective in women and men in preventing genital warts associated with HPV 6/11. No clinical trials have been conducted of HPV vaccines for prevention of oropharyngeal cancers. Since genital HPV infection is sexually transmitted, the vaccines ideally should target prepubertal girls and boys, aged 11–12. Gardasil is approved for use in boys and girls, whereas Cervarix is only approved for use in girls. The vaccines are also recommended for young women 13–26 years of age and young men up to age 21, because many of them may not yet have been exposed to the HPV types in the vaccines. To extend coverage to other high-risk HPV types, a nonavalent vaccine (Gardasil 9) has been developed, which contains VLPs for types 31, 33, 45, 52, and 58, in addition to the four types in Gardasil. The durability of the immune response engendered by HPV vaccines and thus the possible need for a booster in vaccinated individuals is unknown. Because protection may wane over time and because vaccination does not protect against the HPV types not included in the vaccines, screening programmes will need to be maintained, but the strategy may change with longer intervals between screening and a greater emphasis on HPV DNA testing as a screening method.

Therapeutic vaccines Human papillomavirus-associated cancers express HPV E6 and E7 proteins in their tumour cells. Candidate therapeutic vaccines targeted to these proteins are being developed for the treatment of high grade squamous intraepithelial lesions, invasive cervical cancer, and HPV-associated oropharyngeal cancers.

Cancers at other lower anogenital tract sites Human papillomavirus infections are very common on the vulva, vagina, penis, perineum, and anus. Synchronous neoplasia at multiple sites in the female lower genital tract is almost always associated with HPVs, especially HPV-16. Carcinoma of the vulva is aetiologically heterogeneous. Vulval cancers occurring in younger women are associated with HPVs, but the typical squamous cell carcinoma of the vulva in older women is not. Neoplasia of the anal canal, seen frequently in HIV-seropositive homosexual men, is strongly

associated with HPVs. Cancer of the oropharynx A subset of head and neck cancers is aetiologically linked to high-risk HPVs, most often HPV-16. HPV-positive head and neck cancers are distinct from HPV-negative head and neck cancers. HPV-positive cancers tend to arise in the oropharynx, specifically the tonsil and base of tongue. Patients with HPV-positive head and neck cancers tend to be younger and have less tobacco and alcohol exposure, the traditional risk factors of HPV-negative head and neck cancers. Additionally, a greater proportion of HPV-positive head and neck cancers tend to occur in men. As compared to HPV-negative cancers, the HPV-positive cancers are characterized by basaloid, non-keratinizing well differentiated pathology, less frequent p53 and Rb mutations, and better prognosis. Demonstration of HPV genome in tumour cells, presence of HPV transcripts, and immunostaining for cellular p16 characterize HPV-caused cancers. These cancers are increasing in incidence in the United States, as well as in other developed countries around the world. It is estimated that the number of HPV-caused oropharyngeal cancers in men and women will exceed the number of cervical cancers in the United States of America by 2020.

Skin warts (See Chapter 23.10.) Skin warts and verrucas may occur anywhere on the skin and are morphologically diverse. They are most common in older children and young adults. Except in the rare condition known as epidermodysplasia verruciformis (see next), they almost never become malignant. Most regress within 2 years. Specific HPV types are strongly associated with specific types of warts (Table 8.5.19.4). Epidermodysplasia verruciformis This is a rare, lifelong disease in which a patient has extensive warty involvement of the skin that cannot be resolved. It generally begins in infancy or childhood with multiple, disseminated polymorphic wart-like lesions on the face, trunk, and extremities that tend to become confluent. The warts are either flat or reddish-brown macular plaques that resemble pityriasis versicolor. In about a third of the cases, foci of malignant transformation occur in macular plaques in areas of the skin exposed to sunlight. The tumours are slow growing and rarely metastasize.

8.5.19 Papillomaviruses and polyomaviruses 883 Epidermodysplasia verruciformis (EV) is often a familial disease. Patients sometimes have a history of parental consanguinity. A susceptibility locus has been mapped to chromosome 17q25.3 and truncating mutations in either of two novel adjacent genes, EVER1 and EVER2, are associated with the disease in different pedigrees. The function of the gene products of EVER1 and EVER2 and how they confer increased risk for EV are unknown. Recent studies suggest the EVER proteins may be involved in zinc homeostasis. A second putative susceptibility locus is located on chromosome 2p21-p24. The flat warts yield the same HPV types as those of normal individuals, but a very large number of HPVs that are seldom encountered in normal individuals are recovered from the macular plaques (Table 8.5.19.3). It is unclear how patients with epidermodysplasia verruciformis become infected with these particular papillomaviruses. The factors that contribute to the occurrence of carcinoma in these patients therefore include a genetic defect, infection with specific HPVs (e.g. HPV-5 and HPV-8), and exposure of the affected area to sunlight. Nonmelanoma skin cancers HPV DNA has been detected in 30–50% of nonmelanoma skin cancers in immunocompetent populations and in up to 90% of nonmelanoma skin cancers from immunocompromised populations, in particular organ transplant recipients. The HPV prevalence is generally higher in squamous cell carcinoma than in basal cell carcinoma. The sequences represent cutaneous HPV types, EV-associated HPVs, and many novel HPV sequences. No single HPV type predominates and there is no evidence of high-risk types analogous to those seen in cervical cancer. The amount of HPV DNA in skin tumours is very low, indicating that not every tumour cell harbours an HPV genome. Because HPV DNA is frequently detected in normal skin samples, it is not clear to what extent HPVs contribute to the

development of nonmelanoma skin cancers. Ultraviolet (UV) light is considered the most significant risk factor for nonmelanoma skin cancers. Cutaneous HPVs, through the anti-apoptotic activity of their E6 gene, may act as cocarcinogens by preventing elimination of cells with UV-induced DNA damage. Human polyomaviruses

In 1971, BK virus was isolated from the urine of a renal transplant recipient with the initials 'BK', who developed ureteral fibrosis and obstruction, and JC virus was recovered from the brain of a patient ('JC') with progressive multifocal leukoencephalopathy. Human polyomaviruses, KI virus and WU virus, were detected in respiratory tract secretions of children by using molecular techniques. The viruses were detected in upper respiratory tract specimens in the presence of other recognized respiratory tract pathogens and thus their role in disease is unclear. In 2008, another human polyomavirus, Merkel cell virus, was identified in tumour cells from patients with Merkel cell carcinoma, a rare aggressive skin cancer.

Trichodysplasia spinulosa is a rare skin disease primarily affecting immunosuppressed patients and presenting as follicular-based papules and keratin spicules widespread on the face, along with variable degrees of alopecia and dysmorphism. In 2010, a new human polyomavirus, designated trichodysplasia spinulosa-associated polyomavirus, was identified in the trichodysplasia spinulosa lesions of a heart transplant recipient. Two new human polyomaviruses, designated type 6 and 7, were detected in the skin of healthy persons. Another new human polyomavirus, type 9, was identified in the blood and urine of a renal transplant patient. Subsequently the virus was independently identified in the skin of a Merkel cancer patient. Malawi polyomavirus was isolated from stool and wart samples, St Louis polyomavirus was isolated from stool, human polyomavirus 12 from liver tissue of a patient with colon cancer, and human polyomavirus 13 from muscle endothelial cells. No diseases have been associated with polyomavirus types 6, 7, 9, 12, 13, or the Malawi, and St Louis polyomaviruses. All the new polyomaviruses were detected by using a variety of molecular techniques that do not rely on prior knowledge of the DNA sequence of the virus.

Polyomaviruses have a double-stranded DNA genome of about 5000 bp, which is divided into an early region encoding viral large T proteins, a late region encoding viral capsid proteins VP1, 2, and 3, and a noncoding regulatory region (Fig. 8.5.19.6). The large T proteins regulate viral transcription, initiate viral DNA replication, and mediate inactivation of host cell tumour suppressor proteins, which contribute to the oncogenic potential of polyomaviruses. The viral regulatory region contains elements for viral DNA replication and promoters for transcription of early and late genes, as well as binding sites for cellular transcription factors, which determine the host and tissue tropism of polyomaviruses. The early and late regions are transcribed from different strands of the viral DNA. Although BK and JC viruses are homologous for 75% of their nucleotide sequence, the infections are readily distinguishable by both serological tests and specific PCR detection with unique primers. Infection occurs in childhood and is largely subclinical. Most children acquire antibodies to BK virus by the age of 10; infection with JC virus occurs at a later age. Infection is believed to occur by the oral route. Both viruses establish latent, often lifelong, infection in the kidney, and are often shed in the urine of immunocompetent healthy individuals. Reactivation in immunodeficient individuals is

RR Agno BKV Small t Large T 5141 bp VP1 VP2 VP3 Fig. 8.5.19.6

Genomic map of BK polyomavirus. The genome is approximately 5 kb in size. Bidirectional transcription generates proteins of the viral capsids (VP1, VP2, and VP3) in one direction, and proteins for transcriptional controls (large T and small t) in the opposite direction. The noncoding region (RR) contains binding sites for host transcription factors. The Agno region makes a small protein that may be involved in viral replication.

884 section 8 Infectious diseases responsible for most associated illnesses. The viruses are reactivated in pregnancy, but without any apparent harm to the mother or the newborn.

Polyomavirus-associated illnesses

Nephropathy in renal transplant recipients This condition is associated most often with BK virus and rarely with JC virus. It occurs in 3 to 10% of renal transplant recipients and results in a loss of the allograft in 50 to 80% of the affected patients. The recent increase in the incidence of this complication is related to the introduction of new and intensive immunosuppressive therapies. Pathologically, the disease is characterized by inclusion-bearing enlarged nuclei in renal tubular and glomerular epithelial cells which are readily detected by microscopy (Fig. 8.5.19.7). Systematic monitoring of the patients for BK virus post kidney transplant has predictive value for the risk of nephropathy and can guide decisions to reduce immunosuppression to suppress further viral reactivation. Early curtailment of BK viral replication prevents progression to nephropathy.

Haemorrhagic cystitis in bone marrow transplant recipients Haemorrhagic cystitis in bone marrow transplant recipients is associated with BK virus infection. Large amounts of BK virus are shed in urine during the haemorrhagic episodes. Haemorrhagic cystitis usually occurs after engraftment and is associated with allogeneic transplant, graft-versus-host disease, and myeloablative conditioning regimen. Patients often present with haematuria, dysuria, urgency, or suprapubic pain. Complications include severe bleeding, urinary tract obstruction, and renal failure. With use of increased immunosuppression and umbilical cord blood transplantation, BK virus is also now associated with additional renal diseases, such as nephropathy. BK virus reactivation associated diseases can affect up to 15.9% of haematopoietic stem cell transplant recipients. No antiviral therapy is available for BK virus. Patients are treated with symptom relief and decrease of immunosuppressants.

Progressive multifocal leukoencephalopathy (See Chapters 23.5, 24.10.2, 24.11.2, and 24.11.4.) JC virus causes progressive multifocal leukoencephalopathy, a subacute demyelinating disease of the central nervous system occurring in individuals with impaired cell-mediated immunity. Until the advent of AIDS, it was a rare disease found mainly in older patients with lymphoproliferative disorders or chronic diseases. Because progressive multifocal leukoencephalopathy is a complication in 1–2% of AIDS cases, it is a more common disease and is seen much more frequently in younger patients. It has also been recognized in children who have inherited immunodeficiency diseases or have AIDS. Recently, progressive multifocal leukoencephalopathy has been recognized as a complication in patients treated with monoclonal antibodies, such as those with Crohn's disease or multiple sclerosis treated with natalizumab, which inhibits migration of cells across the blood-brain barrier. Other monoclonal antibodies and immune modulatory drugs have also been associated with rare cases of progressive multifocal leukoencephalopathy. The key pathogenetic event in progressive multifocal leukoencephalopathy is the cytotoxic JC virus infection of oligodendrocytes, which are responsible for the production and maintenance of myelin. This leads to foci of demyelination that tend to coalesce and (a) (b) Fig. 8.5.19.7 Histology of BK nephropathy. (a) Kidney tissue stained with Hematoxyline and eosin shows widespread but patchy interstitial oedema and a mixed inflammatory cell infiltrate with occasional neutrophils. Tubules show extensive viral cytopathic changes with accompanying acute tubular injury and necrosis. (b) Staining with antibody to SV40 large T antigen, which cross reacts with BK large T antigen, shows numerous cells positive for viral protein. (a) (b) Fig. 8.5.19.8 A lesion of progressive multifocal leukoencephalopathy showing oligodendrocytes with enlarged, deeply staining nuclei (arrow) and giant astrocytes (left), and a crystalloid array of JC virus particles in an infected oligodendrocyte nucleus (right). Reproduced, with permission, from Shah KV (1992). Polyomavirus, infection and immunity. In: Roitt IM (ed)

8.5.19 Papillomaviruses and polyomaviruses 885 eventually involve large areas of the brain. Infected oligodendrocytes, containing large inclusion-bearing nuclei filled with abundant virus particles, surround the foci of demyelination (Fig. 8.5.19.8). Enlarged astrocytes often show bizarre nuclear changes but are mostly virus negative. They are found within the foci of demyelination. JC virus is disseminated haematogenously to the central nervous system. Progressive multifocal leukoencephalopathy starts insidiously. Early signs and symptoms indicate the presence of multifocal asymmetrical lesions in the brain and involve impairment of vision and speech, and mental deterioration. The disease is usually relentlessly progressive and fatal within 3–6 months, but rarely may become stabilized, with survival for many years. Diagnosis is made based on images (Fig. 8.5.19.9), clinical presentations. Detection of JC virus in cerebrospinal fluid or brain biopsy also aids in the diagnosis. There are no effective antivirals against JC virus. However, viral replication can be stopped in patients who can immune reconstitute, such as HIV patients after treatment with antiretroviral therapy, and natalizumab-treated patients after plasma exchange. Other diseases caused by JC virus Although exceedingly rare, JC virus granule cell neuronopathy, where JC viruses infect and destroy cerebellar granule cell neurons, has been reported worldwide. Patients present with cerebellar-associated neurological deficits. In addition, cases of JC virus encephalopathy, meningitis, and nephropathy have all been reported. Role of polyomaviruses in human tumours The role of polyomaviruses in human tumours is the subject of debate. JC virus and BK virus are oncogenic for laboratory animals and they transform cultured cells. There are reports of finding JC virus DNA in brain and colon tumours and BK virus DNA in prostate, bladder, and brain tumours, as well as neuroblastomas and insulinomas. However, a reproducible and consistent aetiological association of either virus with any human tumour has not been demonstrated. The Merkel cell virus provides a more convincing example of a polyomavirus-induced human tumour, since the viral genome was found to be integrated into tumour cell DNA, a key event in experimental polyomavirus-induced animal tumours. Further supporting the carcinogenic potential of the virus is the observation that survival of virus-positive Merkel cancer cell lines is dependent on expression of the viral oncoprotein. The virus has been detected in approximately 80% of Merkel cell cancers worldwide. Serological studies have revealed that exposure to Merkel cell polyomavirus is very high in human populations. Thus, the precise role of the virus and modifying cofactors in the aetiology of Merkel cell carcinoma remains to be established. FURTHER READING Berger JR, et al. (1998). Progressive multifocal leukoencephalopathy in patients with HIV infection. *J Neurovirol*, 4, 59–68. Bosch FX, et al. (2002). The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol*, 55, 244–65. Chatuevedi AK, et al. (2002). Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*, 29, 4294–301. D'Souza G, et al. (2007). Epidemiological evidence that human papillomavirus is a cause of oropharyngeal squamous cell carcinomas. *N Engl J Med*, 356, 1944–56. Feng H, et al. (2008). Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science*, 319, 1096–100. Hirsch HH, Steiger J (2003). Polyomavirus BK. *Lancet Infect Dis*, 3, 611–23. Koutsky LA, et al. (2002). A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med*, 347, 1645–51. Munoz N, et al. (2004). Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer*, 111, 278–85. Randhawa P, Brennan DC. (2006). BK virus infection in transplant recipients: an overview and update. *Am J Transplant*, 6, 2000–5. Yousry TA, et al. (2006). Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med*, 354, 924–33. (a) (b) Fig. 8.5.19.9 Brain fluid attenuation inversion recovery (FLAIR) MRIs in axial (a) and sagittal

(b) planes of a 36-year-old man with AIDS and progressive multifocal leukoencephalopathy proven by detection of JC virus DNA in cerebrospinal fluid by PCR.

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