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VIRAL INFECTIONS

HUMAN PAPILLOMAVIRUS (HPV) (INCLUDING CONDYLOMA ACUMINATUM)

Clinical and gross features (Fig. 1.1)

- Sexually transmitted HPV (usually low-risk types, especially HPV 6 and 11) is the cause of condyloma acuminatum (venereal wart), the incidence of which in the USA increased 4- to 5-fold between 1966 and 1981.
- Condylomas, which are considered LSIL/VIN1, most commonly involve the vestibule and the medial aspects of the labia majora and vary from only colposcopically visible lesions to small excrescences to large, sessile or pedunculated, white to red, cauliflower-like masses that may be multiple or confluent.
- Synchronous or metachronous condylomas, precancerous changes, or invasive squamous cell carcinoma (ISqCC) may occur locally, including the perineal and perianal skin and the mucosa of the anus, urethra, vagina, and cervix.
- The clinical course is typically protracted unless the lesions are ablated or removed. They may enlarge and increase in number during pregnancy but can regress postpartum.
- Srodon et al. found that condylomas harbored a low-risk HPV in 67% of cases, but 42% contained a high-risk HPV that may account for the progression of some condylomas to high-grade VIN or ISqCC.

Histologic features (Figs. 1.2–1.5)

- Fully developed condylomas are characterized by simple to complex branching papillae of acanthotic squamous epithelium and fibrovascular cores. Flat condylomas occur but are less common in the vulva than in the cervix (see Chapter 5).
- The pathognomonic koilocytes (HPV-infected keratinocytes) in the superficial layers are usually prominent but may be focal or even absent. 'Condyloma without cytopathic effect' has been applied in the latter situation, but 'squamous papilloma, possibly condyloma' may be preferable given the implications of a condyloma diagnosis.
- The variably sized koilocytes have a perinuclear halo of clear cytoplasm typically surrounded by a peripheral zone of condensed amphophilic cytoplasm. Their hyperchromatic, granular or smudgy, enlarged to shrunken nuclei have an irregular contour ('koilocytotic atypia'); binucleated or multinucleated cells are common. Occasional mitoses, usually confined to the lower third of the epithelium, may be seen.
- Ki67 expression is present in the upper two-thirds of the epithelium and correlates with the presence of HPV.
- p16 staining is typically focal, cytoplasmic, and often in the upper layers (consistent with LSIL), although rare condylomas harbor foci of HSIL (as noted above) with typical diffuse (block) p16 staining (Sulaiman et al.) necessitating thorough sampling. Lewis et al. found focal block p16 staining in 4% of lesions they considered flat vulvar LSILs, although most investigators equate block staining with HSIL.
- Nonspecific features include para/orthokeratosis, hypergranulosis, parabasilar hyperplasia, and underlying superficial chronic inflammation.
- Variant condyloma phenotypes:
  - Seborrheic keratosis (SK)-like condyloma. HPV+ SK-like lesions have also been referred to as 'condyloma with features of SK' (see Seborrheic Keratosis).
  - Condyloma with pseudobowenoid change. Apoptosis in the superficial keratinocytes with chromatin dispersal or clumping and cytoplasmic condensation and retraction results in a dense hyaline globule (the residue of a dead cell). The appearance may suggest

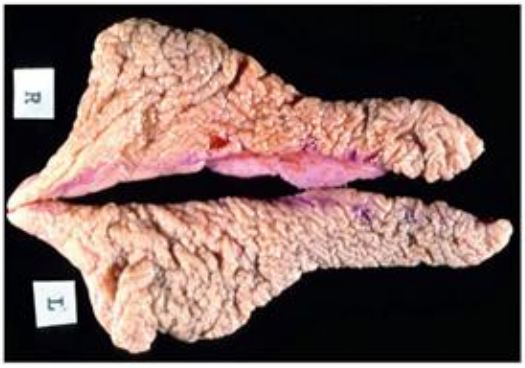

Fig. 1.1 Condylomata acuminata. The vulva is involved by confluent condylomas.

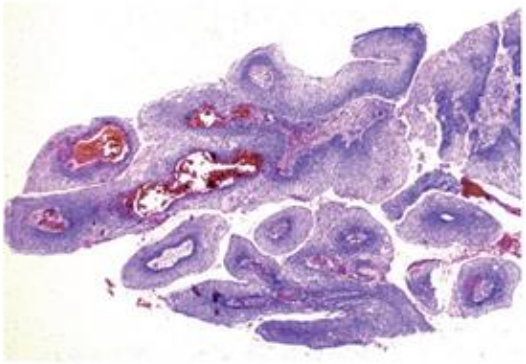

Fig. 1.2 Condyloma acuminatum. Low-power view shows typical papillary configuration.

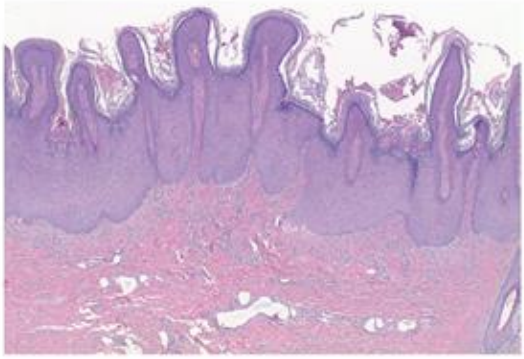

Fig. 1.3 Condyloma acuminatum. Multiple papillary projections with hyperkeratosis range from rounded to spired.

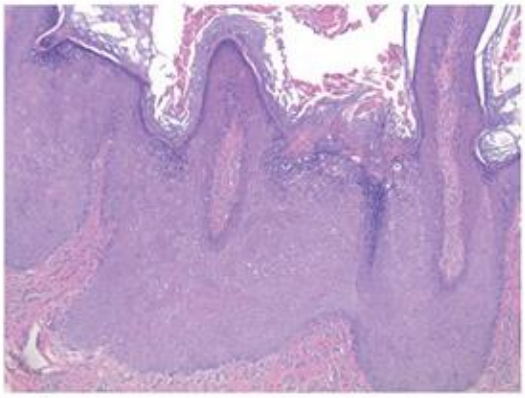

Fig. 1.4 Condyloma acuminatum. Epithelial hyperplasia with focal koilocytes, hypergranulosis, and surface papillary projections are seen.

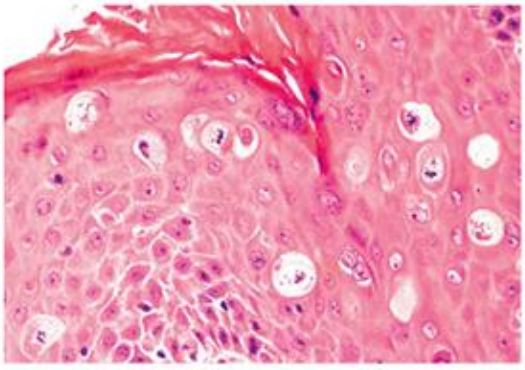

Fig. 1.5 Pseudobowenoid change in a condyloma (see text).

VIN, but nuclear atypia and mitotic activity in the lower layers are absent.
  - Epidermodysplasia verruciformis-like condylomas. Pohthipornthawat et al. described this flat condyloma variant in immunosuppressed women (with β papilloma virus type 5 infection) that exhibited acanthosis, variable hyperkeratosis, and enlarged cells with blue-gray cytoplasm, and occasional perinuclear halos. Atypical nuclei are found only superficially or extending through the full epidermal thickness.
- Podophyllin treatment results in mitotic arrest in the lower epidermis, karyorrhexis, and cellular swelling. In contrast to VIN, nuclear atypia is mild and confined to the upper layers. A history of recent treatment is obviously helpful.

Differential diagnosis (Figs. 1.6–1.7)

- Verruca vulgaris (HPV type 2) infection:
  - Aguilera-Barrantes et al. found that 41% of vulvar warts in girls <5 years of age contained HPV 2 (likely

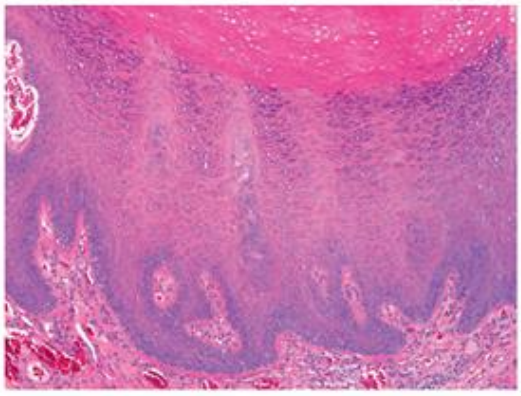

Fig. 1.6 Verruca vulgaris.

nonvenereal), the remainder HPV 6/11 (vs 3% HPV 2 and 94% HPV 6/11 in adults).
  - HPV 2-related vulvar lesions resembled typical verruca vulgaris including marked hyperkeratosis.
  - HPV testing of vulvar warts in children can be diagnostically helpful.
- Squamous papilloma (vs condyloma with loss of koilocytosis). Ki-67+ cells in the upper epithelial layers indicate condyloma.
- Vestibular papillomatosis (see corresponding heading). These squamous papillomas are typically confined to the vestibular area, are usually smaller than condylomas, and typically lack koilocytosis and hyperkeratosis.
- Condyloma lata (see Syphilis).
- Epidermolytic hyperkeratosis. This lesion exhibits acanthosis, compact papillomatous hyperkeratosis, and dissolution of the suprabasilar epithelium resulting in perinuclear clear zones. Keratohyaline clumping and dyskeratosis resulting in intracellular eosinophilic globules facilitate distinction from condyloma.
- Warty VIN and warty ISqCC. Unlike typical condylomas, these lesions (Chapter 2) have nuclear atypia and mitoses in all epithelial layers, typically strong and diffuse 'block' p16 staining, and in some, invasion.
- Verrucous carcinoma (Chapter 2). These usually large solitary highly differentiated SqCCs occur in older women and are usually HPV-negative. They lack the fine branching papillae and koilocytosis of condylomas and have a well-circumscribed deep border formed by broad bulbous pegs.
- Papillary SqCC, NOS. These lesions are rare in the vulva and are composed of obviously malignant cells that lack koilocytosis.

HERPES VIRUS (Fig. 1.8)

- Most cases of herpetic vulvitis are due to sexually transmitted herpes simplex (HSV) type 2, or less commonly, HSV-1.

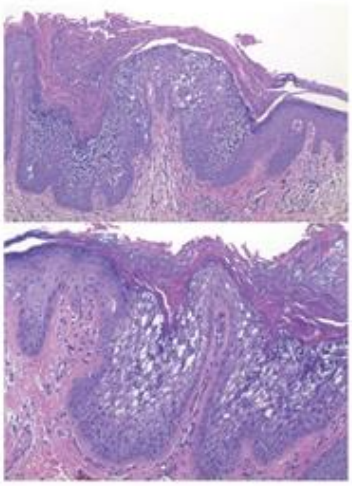

Fig. 1.7 Epidermolytic hyperkeratosis. The papillary epithelial hyperplasia and cytoplasmic clearing may lead to the consideration of a condyloma. However, viral cytopathic effect is not seen, and the prominent reticular degeneration and hypergranulosis of the stratum granulosum and spinosum with the hyperkeratosis is characteristic of epidermolytic hyperkeratosis.

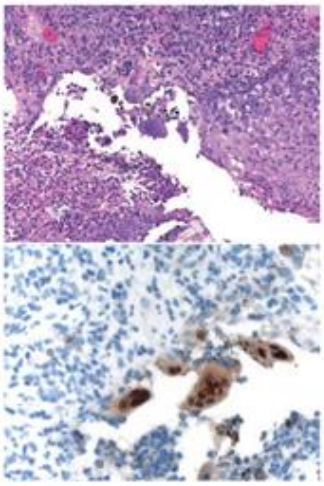

Fig. 1.8 Herpetic infection. There is marked ulceration with an inflammatory exudate and two centrally located multinucleated cells with ground glass nuclei (top). Immunohistochemical staining for HSV is positive in the multinucleated cells (bottom).

- The clinical presentation can include vulvar pain, inguinal lymphadenopathy, malaise, and fever, with sequential appearance of vesicles, pustules, and painful ulcers, often with synchronous involvement of the perineum, perianal skin, cervix, vagina, and urinary tract.

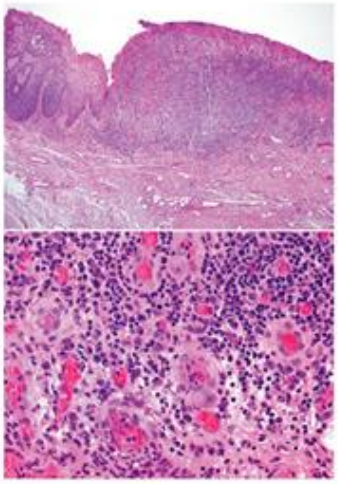

Fig. 1.9 CMV infection. Excision for carcinoma in situ (top, left) shows marked ulceration with prominent inflammation (top, right)). Enlarged endothelial cells with intranuclear inclusion which were positive with a CMV immunostain are seen on high power (bottom). (Courtesy of Dr. Judith A Ferry)

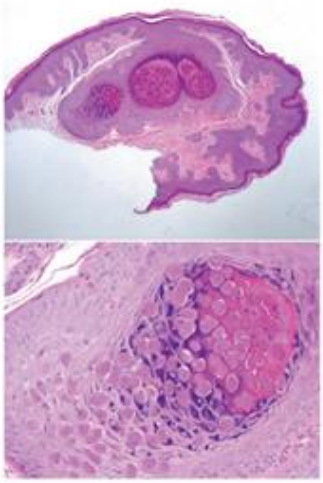

Fig. 1.10 Molluscum contagiosum. Typical low-power view showing well-delineated aggregates of eosinophilic material (top). The characteristic intracytoplasmic viral inclusions which displace the nucleus are seen on high power (bottom).

- The lesions persist for 2–6 weeks and heal without scarring. Rarely, chronic hypertrophic herpetic vulvitis clinically simulates a neoplasm or harbors carcinoma.
- Detection of HSV-2-specific antibodies is diagnostic. Antibodies in many women without a history of infection indicate that subclinical infections are common.
- A smear or biopsy of a new lesion reveals the characteristic ground-glass nuclei or eosinophilic intranuclear inclusions. Cells infected by HSV-1 or herpes zoster have a similar appearance.
- Recurrent episodes are common but are usually much milder, often inconspicuous, and become less frequent.
- Vulvitis secondary to herpes zoster (varicella) infection is rare, usually occurring in postmenopausal women who present with vulvar pain usually followed by unilateral vesicles and ulcers. Recurrent similar episodes are common.

OTHER VIRAL INFECTIONS (Figs. 1.9–1.10)

- Cytomegalovirus (CMV) causes an ulcerative vulvovaginitis resembling herpetic infection; HIV+ women are most susceptible. Characteristic CMV-inclusion bodies in epithelial and endothelial cells are detectable with routine and immunohistochemical stains, culture, or by PCR.
- Molluscum contagiosum can be venereally transmitted resulting in vulvar and perineal lesions that are often asymptomatic and overlooked by patients and physicians. The histologic features are similar to those involving extravulvar sites.
- Human immunodeficiency virus (HIV) is cultured from some genital ulcers in HIV+ women, and may cause or exacerbate genital ulcers in this population.
- Epstein–Barr virus is a rare cause of painful vulvar ulcers and may be associated with mononucleosis.

NONVIRAL INFECTIONS

SYPHILIS

- Vulvar syphilis is rare. The primary lesion or chancre forms within days or several months of initial contact. The secondary phase is evident by 6 months as a mucocutaneous rash and papules (condyloma lata). Tertiary lesions (gummas) are uncommon.
- Chancres are superficial ulcers whereas condylomata lata are nonulcerated lesions with marked acanthosis and papillomatosis, often accompanied by intraepidermal neutrophils. In both lesions, a perivascular plasmacellular infiltrate with endothelial proliferation suggests the diagnosis.
- Organisms can be confirmed by a Warthin–Starry stain. Dark-field examination or immunofluorescent staining

of lesion-derived serum and serologic studies can also facilitate the diagnosis.

GRANULOMA INGUINALE

- This disorder is caused by the gram-negative bacterium *Calymmatobacterium granulomatis*. The primary lesions (vulvar, vaginal, cervical) are painless papules or ulcers that appear within a month of exposure (sexual contact or fecal contamination).
- The ulcers can persist for years and mimic a neoplasm, including ISqCC. Lymphatic spread can result in brawny vulvar edema or parametrial or retroperitoneal involvement.
- Unlike lymphogranuloma venereum, inguinal lymphadenopathy is uncommon but can be mimicked by inguinal abscesses that often ulcerate.
- Granulation tissue with neutrophils, plasma cells, and vacuolated histiocytes contain coccoid to bacillary organisms (Donovan bodies) demonstrable within the vacuoles by Giemsa or Warthin–Starry staining of tissue sections or touch imprints, or by culture.

LYMPHOGRANULOMA VENEREUM

- This venereal disease is caused by *Chlamydia trachomatis*. An initial ulcer is followed by painful inguinal lymphadenitis (buboes) that can rupture and drain through the skin. Later, chronic lymphatic obstruction can result in nonpitting vulvar edema and vaginal and rectal fibrosis (sometimes with strictures).
- The inflammatory infiltrate is nonspecific (lymphocytes, plasma cells, histiocytes including giant cells). Diagnosis rests on the characteristic clinical findings, culture, immunostaining, and complement fixation tests.

CHANCROID

- This venereal disease, which is caused by the gram-negative bacillus *Haemophilus ducreyi*, presents with painful, often purulent, vulvar ulcers and tender inguinal lymphadenopathy.
- The ulcer consists of a superficial zone, a middle zone with characteristic vascular changes, and a deep zone with a lymphocytic and plasma cell infiltrate.
- Gram stains of tissue sections or smears may reveal the organisms in the superficial zone but definite diagnosis requires culture identification.

TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIAL INFECTION

- Vulvar tuberculosis is rare and usually due to direct or lymphatic spread from other sites in the FGT that are usually due to blood-borne spread from pulmonary tuberculosis.
- The lesion begins as a nodule that later ulcerates and may drain caseous material and pus through one or more sinuses. Epidermal hyperplasia may result in a warty tumor-like mass (hypertrophic tuberculosis).
- There is typical granulomatous inflammation with caseation. Diagnosis requires acid fast stains and/or culture or molecular testing to identify the organisms (*Mycobacterium tuberculosis* or occasionally atypical mycobacteria).
- Nontuberculous mycobacterial infection can clinically mimic invasive cancer as exemplified by a cervical case in an immunocompetent woman (Ukita et al.).
- The differential includes noninfectious forms of granulomatous vulvitis (see corresponding heading).

NECROTIZING FASCIITIS AND PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE

- Vulvar involvement by these disorders, which represent mixed synergistic bacterial infections, is often associated with diabetes mellitus and/or atherosclerosis.
- Necrotizing fasciitis presents with vulvar erythema, edema, and pain, followed by rapidly progressive dark discoloration, bullae, and necrosis of the skin, subcutaneous tissue, and fascia; toxic shock syndrome is a rare complication. Fatalities can occur without prompt excision of involved tissues and antibiotic therapy.
- Progressive synergistic gangrene, unlike necrotizing fasciitis, is a slow process that can involve fascia with less severe systemic manifestations. It is more likely to develop in postoperative wounds, whereas necrotizing fasciitis is prone to develop at sites of minor injury.

OTHER BACTERIAL INFECTIONS

- Infection of Bartholin's gland (bartholinitis) is usually caused by sexual transmission of *Neisseria gonorrhoeae* or *Chlamydia trachomatis*; occasional cases follow vulvovaginal operations. Complications include Bartholin's abscess (sometimes with secondary infection by anaerobic bacteria) and, rarely, toxic shock syndrome.
- Hidradenitis suppurativa is a chronic suppurative process of the vulvar and inguinal apocrine sweat glands that often results in scarring and draining sinuses. Microscopic examination reveals acute and chronic inflammation and apocrine glands dilated with keratinaceous material. Chronic cases have been complicated by SqCC.
- Rare cases of vulvar bacillary angiomatosis occur and can result in a mass. Microscopic examination reveals a lobular epithelioid vascular proliferation and bacteria (*Bartonella henselae* or *Bartonella quintana*) that stain with the Warthin–Starry method.