

# VIRAL INFECTIONS

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# INTRODUCTION

01	What are some viruses infecting the skin?
02	What are the disease manifestations of viral infections?
03	Do viral infections cause cutaneous tumors? Malignancies? Rashes? Exanthems?
04	What are their histopathologic features?
05	Does one need ancillary testing for the virally induced cutaneous diseases?

# WHAT IS A VIRAL EXANTHEM?

- A cutaneous eruption that develops because of a viral illness
- Examples: measles, rubella, fifth disease, roseola, varicella, hand, foot, and mouth disease, HIV infection

*McKee's Pathology of the Skin*

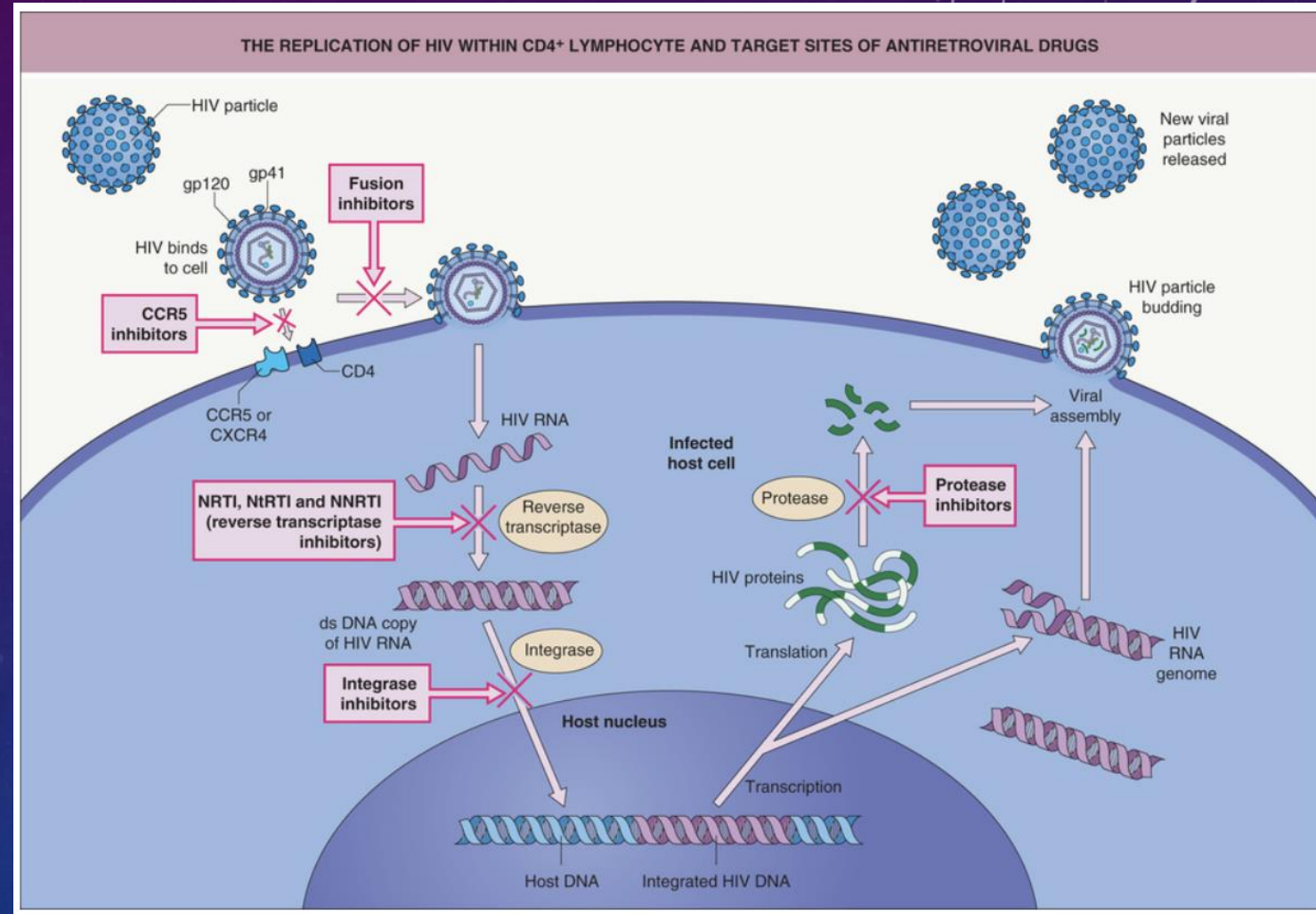


Hand, foot, mouth disease  
Small vesicles with surrounding erythema.



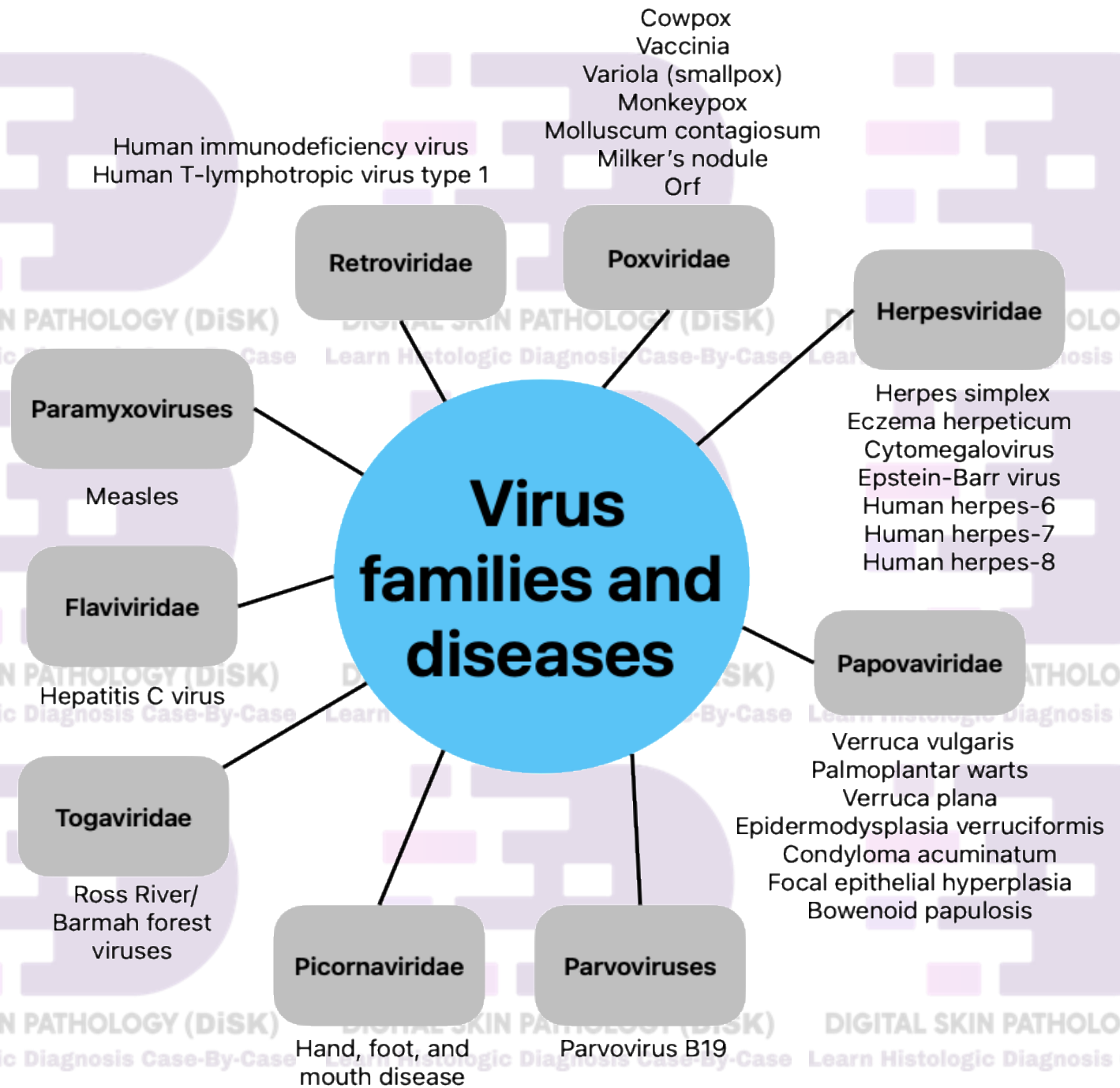
# WHAT ARE THE GENERAL PRINCIPLES OF VIRAL SKIN INFECTIONS?

- Viral Characteristics:
  - Obligate intracellular parasites (20–300 nm) with DNA or RNA cores.
  - Classified by nucleic acid type, capsid shape (spherical/cylindrical), and tropism (e.g., HPV for epithelial cells).
- Infection Mechanism:
  - Entry via pinocytosis/phagocytosis → capsid removal → viral nucleic acid release.
  - Outcomes: Acute replication (cell lysis) or latency (integration into host DNA).
- Host Response:
  - Antibodies (limit systemic spread) and cell-mediated immunity (CD8+ T-cells resolve infection).
  - Immunocompromised hosts risk uncontrolled infection (e.g., severe herpesvirus reactivation).

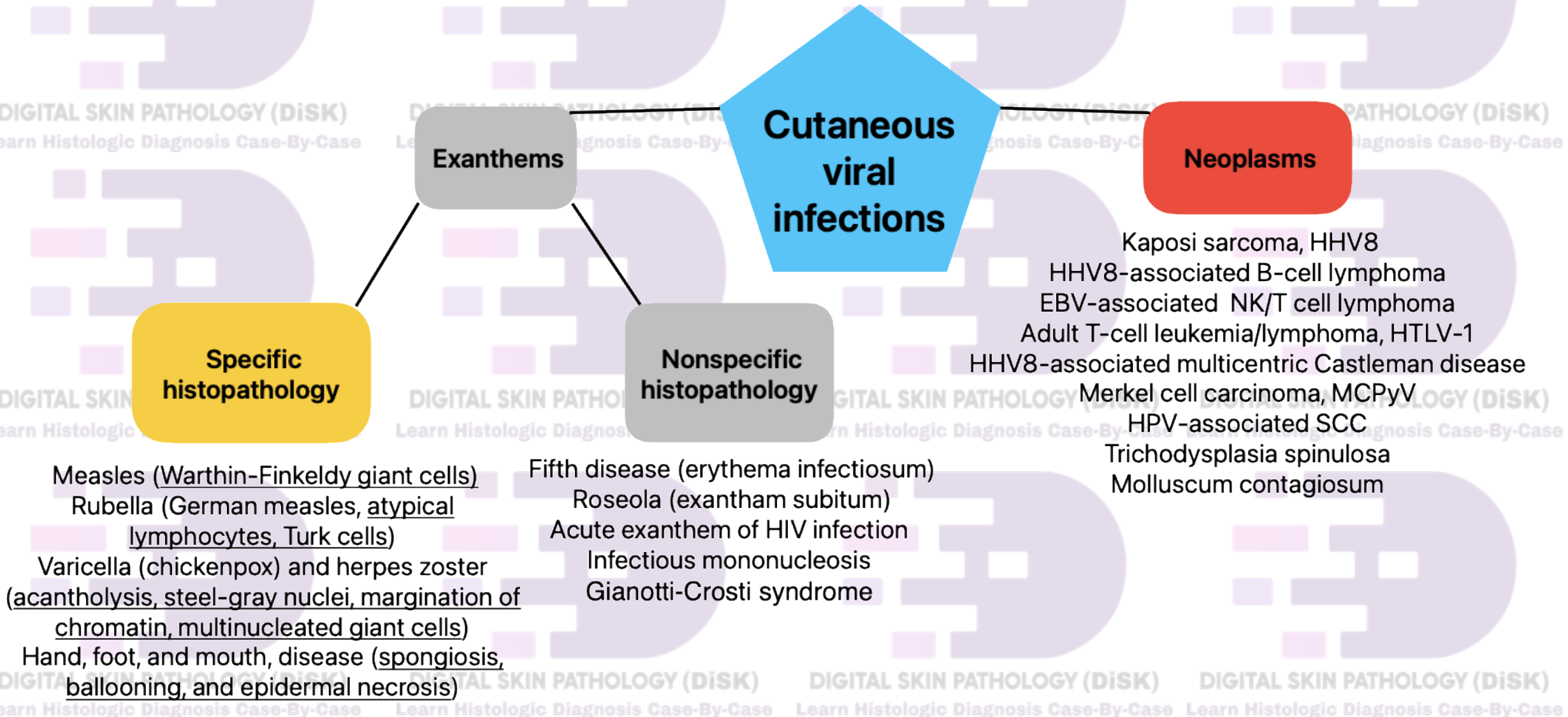


*Dermatology: Replication of HIV within CD4<sup>+</sup> Lymphocytes*

# VIRUS FAMILIES AND THEIR DISEASES



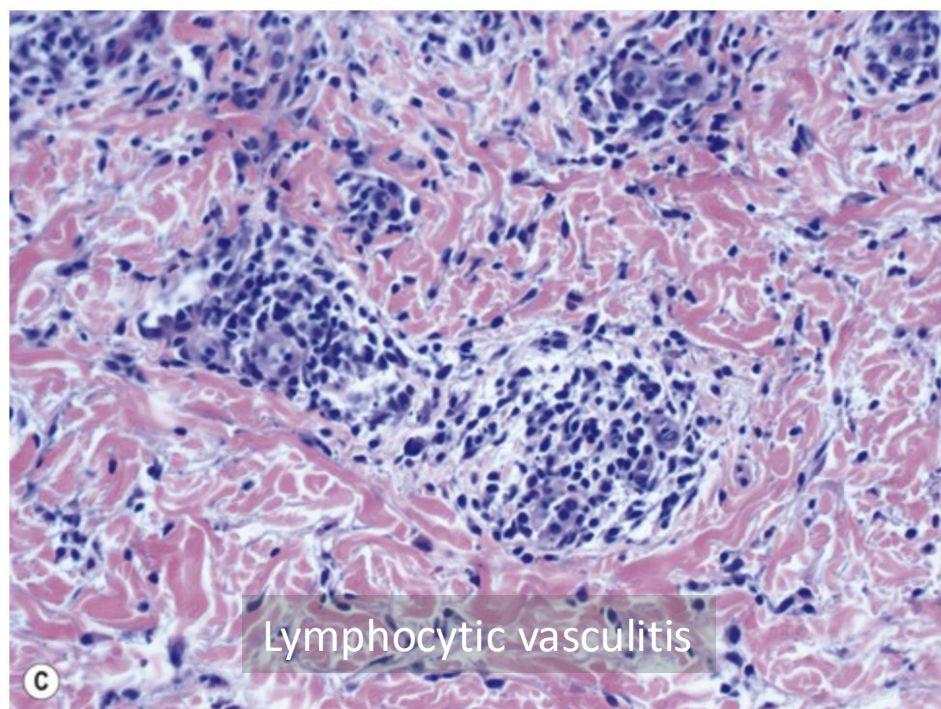
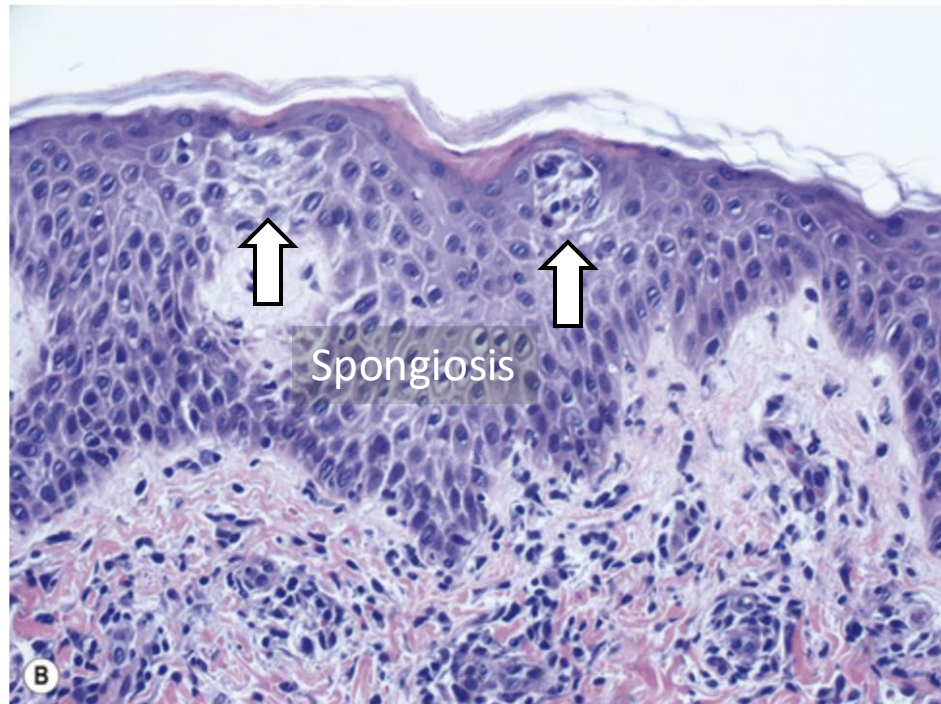
# DISEASE MANIFESTATIONS OF VIRAL INFECTIONS



# WHAT ARE THE VIRALLY INDUCED CUTANEOUS REACTIONS?

- Spongiosis with perivascular lymphocytes (Gianotti-Crosti syndrome)
- Reticular degeneration and dyskeratosis (Hand, foot, and mouth disease)
- Vesicular reaction with nuclear chromatin change (Herpes)
- Nuclear or cytoplasmic inclusions (Cytomegalovirus)
- Koilocytosis (Condyloma)





# WHAT IS GIANOTTI-CROSTI SYNDROME?

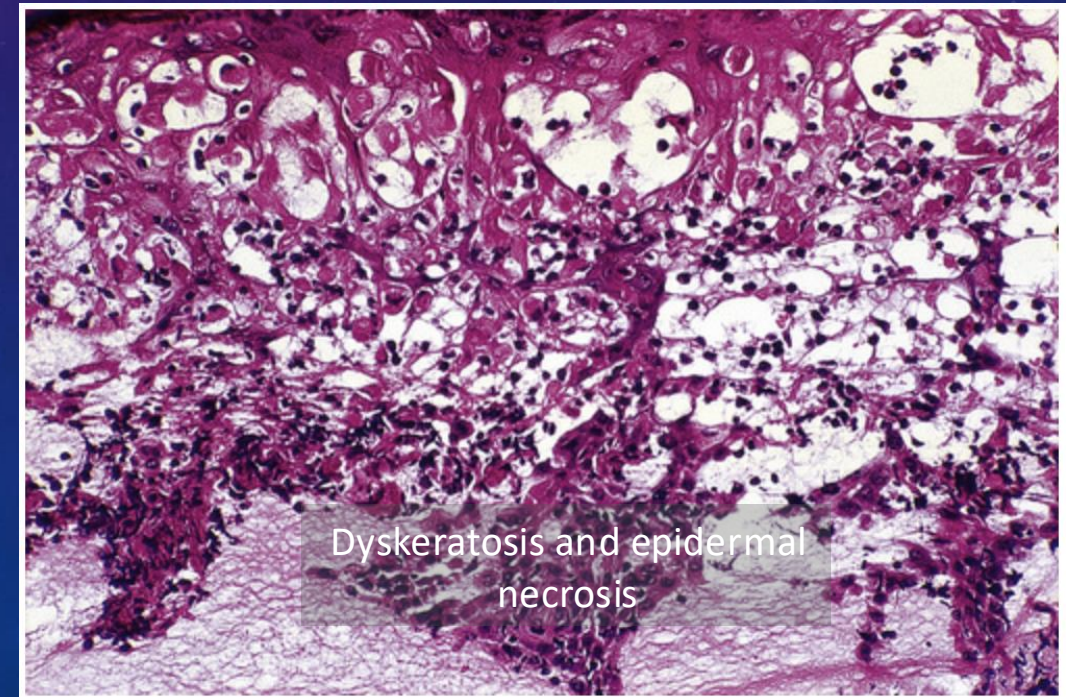
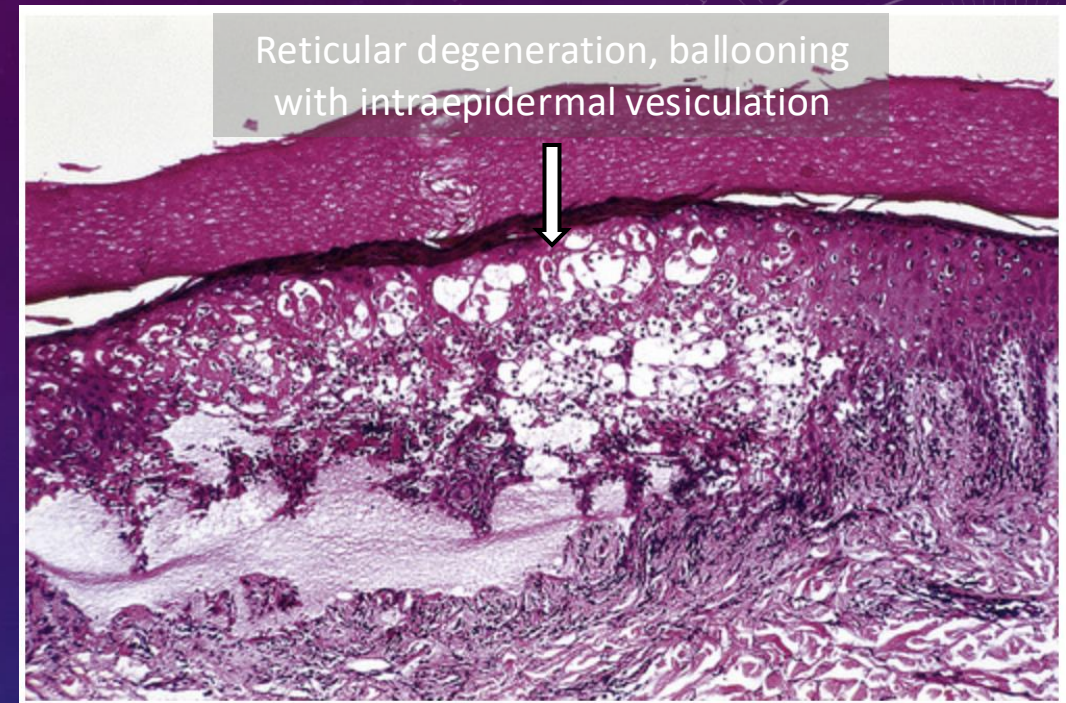
- Viruses (and nonviral triggers): Hepatitis B (classic association), hepatitis A, EBV, CMV, HHV-6 (and others)
- Rash:
  - Children aged 2–6 years.
  - Symmetrical, maculopapular (monomorphic) eruption
  - Distribution: Primarily face, limbs (extensor surfaces), occasionally trunk.
  - Duration: ~3 weeks (non-relapsing).
- Systemic Associations:
  - Lymphadenopathy (cervical/axillary).
  - Acute hepatitis (usually anicteric, linked to hepatitis B).



# WHAT IS HAND, FOOT, AND MOUTH DISEASE?

- Cause: Primarily coxsackievirus A16, but other enteroviruses (e.g., enterovirus 71) can cause severe outbreaks.
- Symptoms:
  - Febrile illness with vesicular rash on:
    - Oral mucosa (painful ulcers, usually anterior).
    - Palms, soles, and sometimes buttocks/genitals.
  - Atypical presentations:
    - Cases without oral lesions reported.
    - Onychomadesis (proximal nail shedding) linked to severe HFMD.
- Complications:
  - Enterovirus 71 can cause neurologic (meningoencephalitis) or cardiopulmonary complications.

*McKee's Pathology of the Skin*



# HERPESVIRIDAE: RELATED FAMILY MEMBERS CAUSING WIDELY DIFFERENT HISTOPATHOLOGY



## Alpha-herpesviruses

- HSV1, HSV2
- VZV

## Gamma-herpesviruses

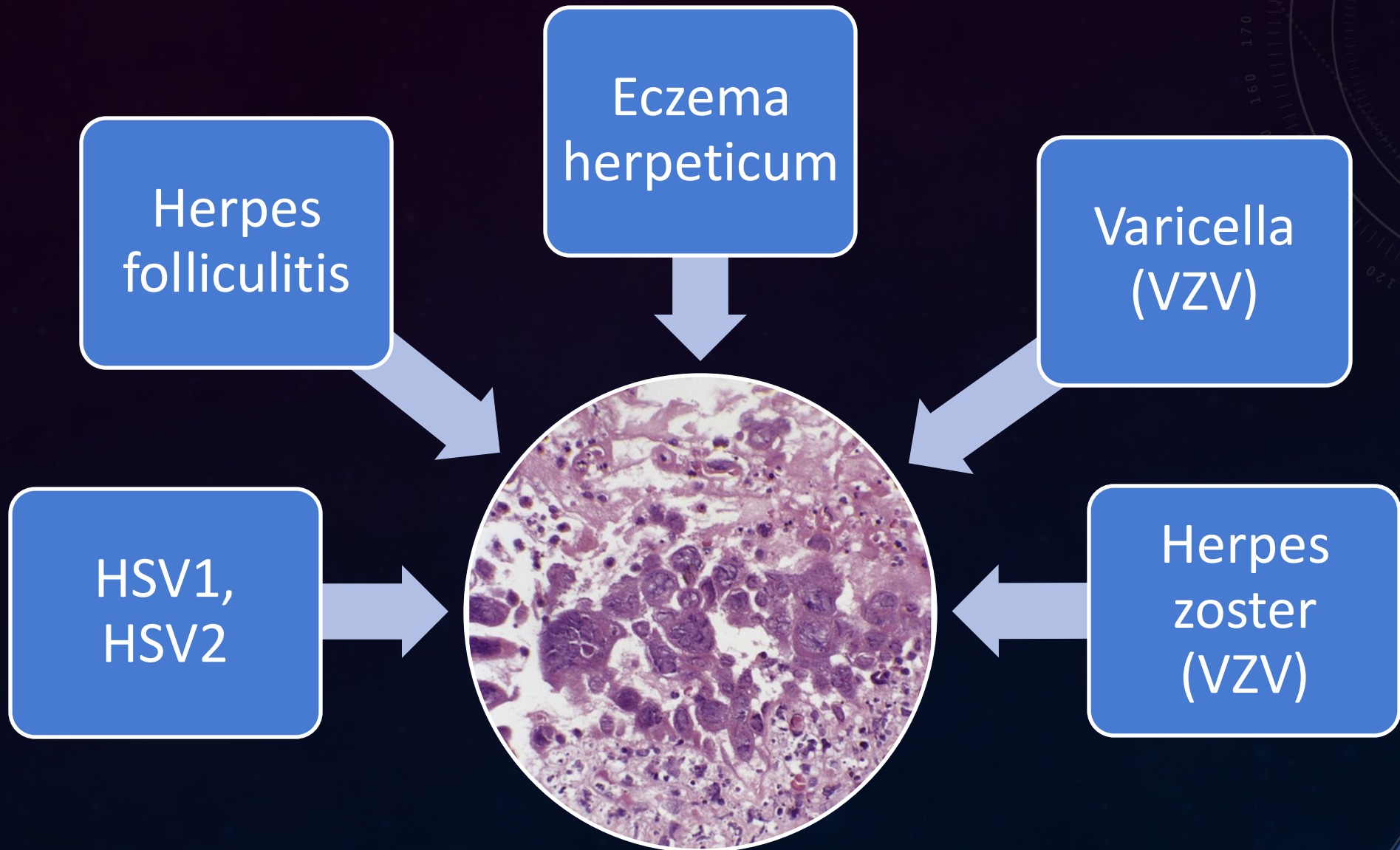
- EBV
- HHV-8

## Beta-herpesviruses

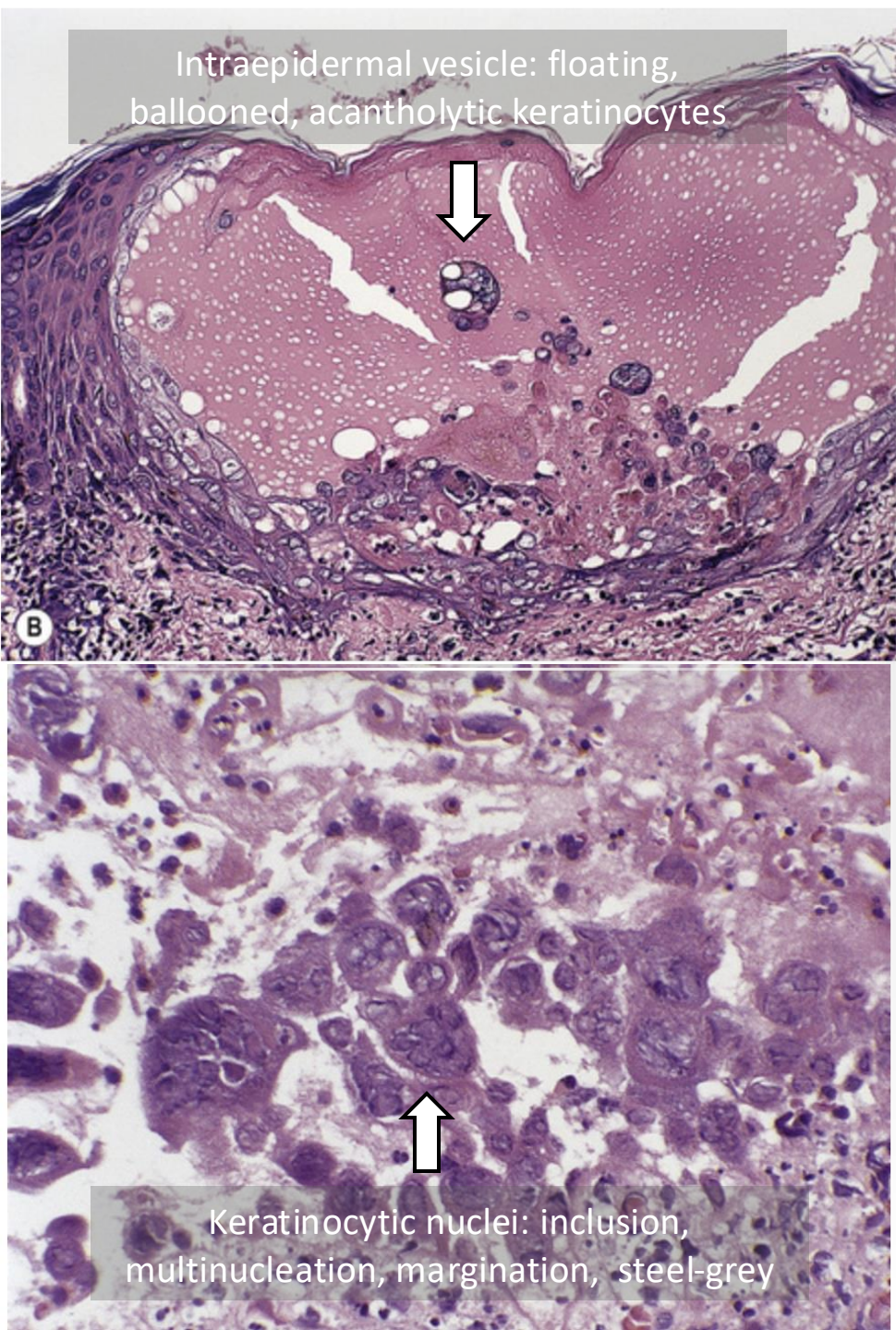
- CMV
- HHV-6, HHV-7



# IDENTICAL HISTOPATHOLOGY





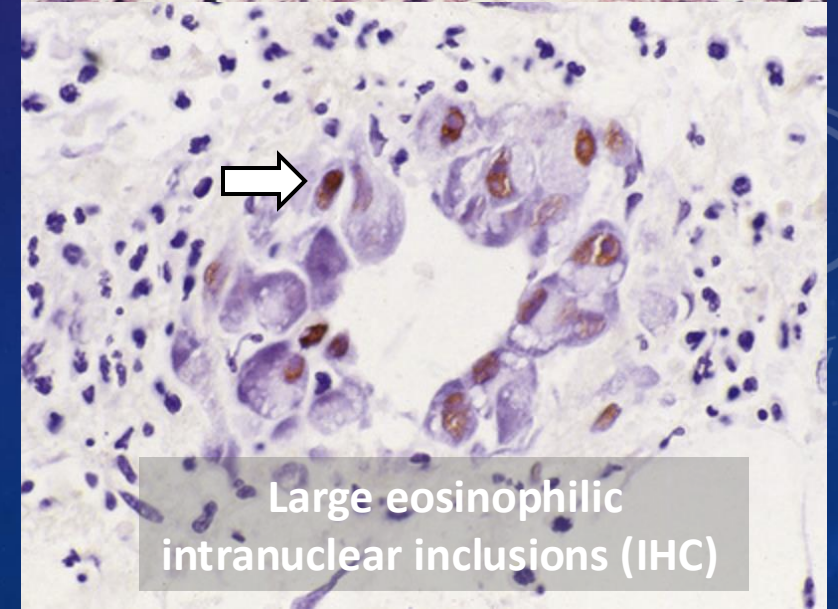


- Oral Herpes (HSV-1):
  - Gingivostomatitis (in children): Painful oral ulcers, fever, lymphadenopathy, drooling.
  - Herpetic Whitlow (finger infection): Vesicles, pain, erythema (common in healthcare workers).
  - Keratoconjunctivitis: Eye pain, photophobia, dendritic corneal ulcers.
- Genital Herpes (HSV-2):
  - Painful vesicles/ulcers on genitals, dysuria, inguinal lymphadenopathy.
  - Systemic symptoms (fever, malaise).
- Recurrent Infection
  - Cold sores (herpes labialis): Tingling prodrome → grouped vesicles → crusting.
  - Recurrent genital herpes: Milder than primary infection, shorter duration.
- Other Manifestations
  - Eczema herpeticum: Widespread HSV in atopic dermatitis patients (Kaposi varicelliform eruption).

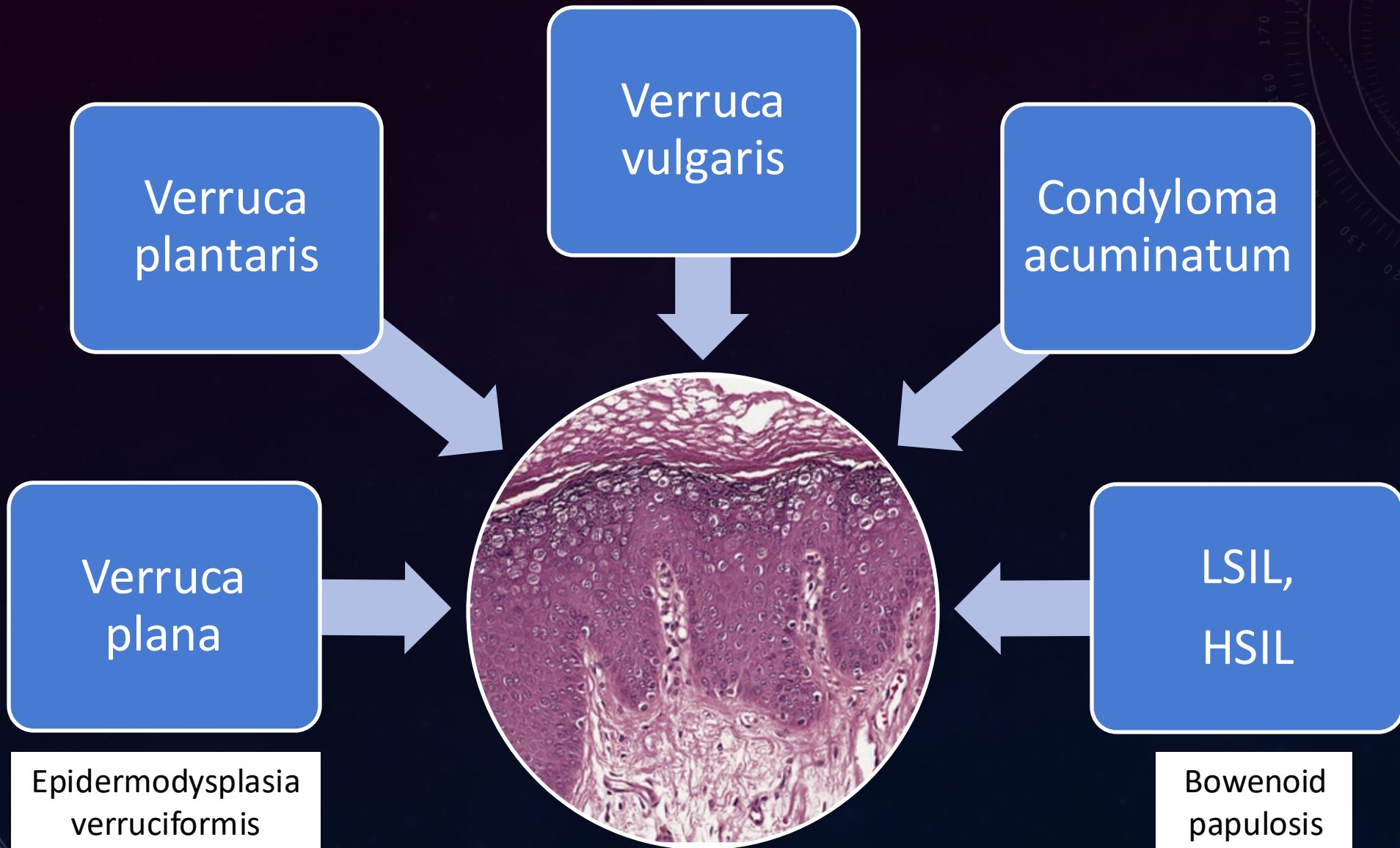


# CYTOMEGALOVIRUS

- Cutaneous involvement rare:
  - Ulcerative or verruciform lesions
  - Maculopapular rash (most common, often in ampicillin-treated patients, similar to EBV mononucleosis)
  - Other rare presentations: Urticaria, vesiculobullous lesions, pustules, genital ulcers, keratotic lesions, diaper dermatitis, epidermolysis, vasculopathy, or sclerodermoid changes.
- Immunocompromised hosts (e.g., HIV, transplant recipients, chemotherapy-induced lymphopenia) are most affected; mixed infections (e.g., HSV) may occur.
- Congenital CMV:
  - "Blueberry muffin" lesions (dermal erythropoiesis, also seen in rubella).
  - Petechiae, perineal ulcers, neurological abnormalities.
  - **Histopathology: Dermal erythropoiesis** (extramedullary hematopoiesis).



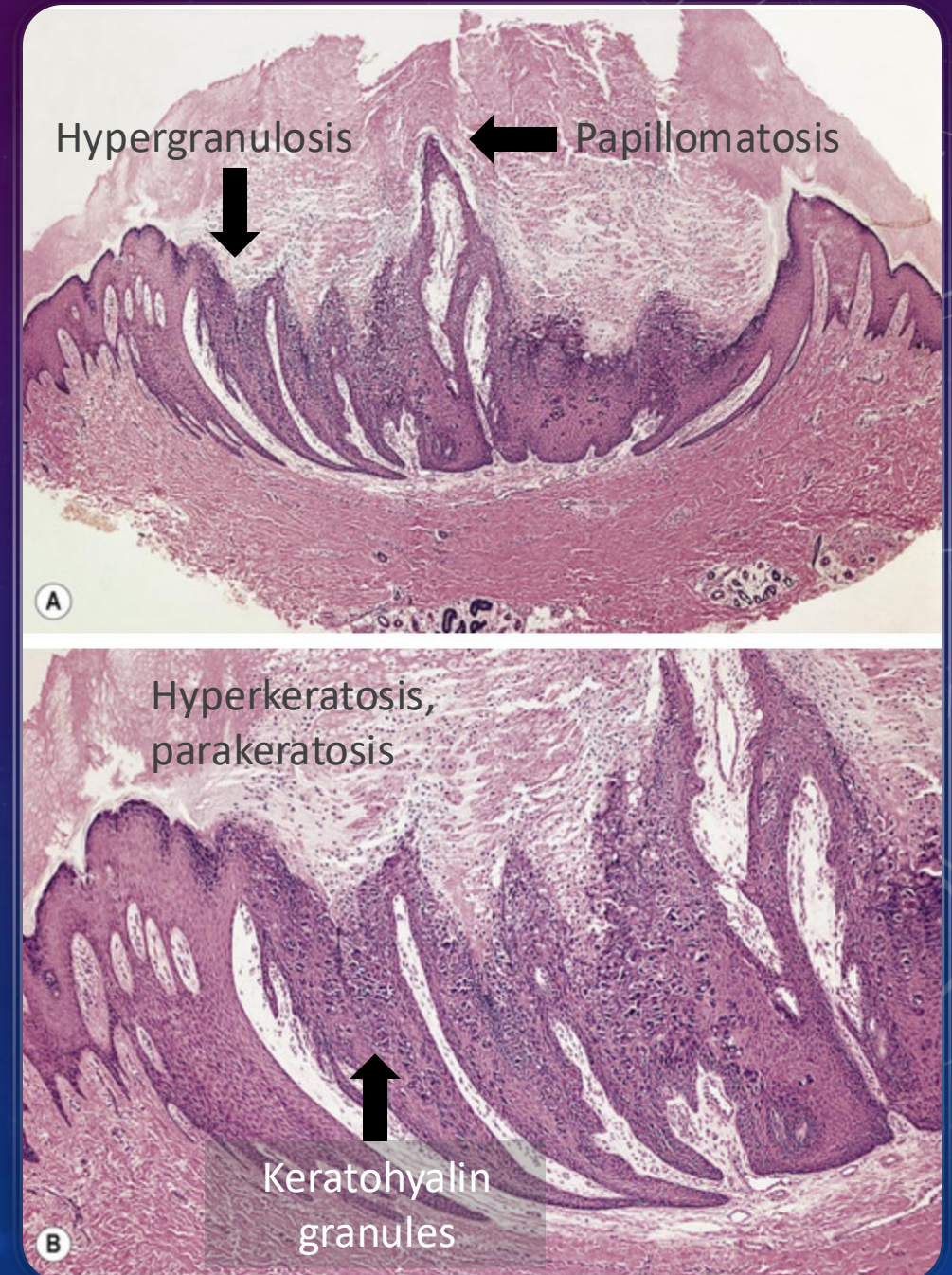
# PAPOVAVIRIDAE FAMILY: PRODUCING SIMILAR HISTOPATHOLOGY WITH VARYING DEGREE OF KOILOCYTOSIS





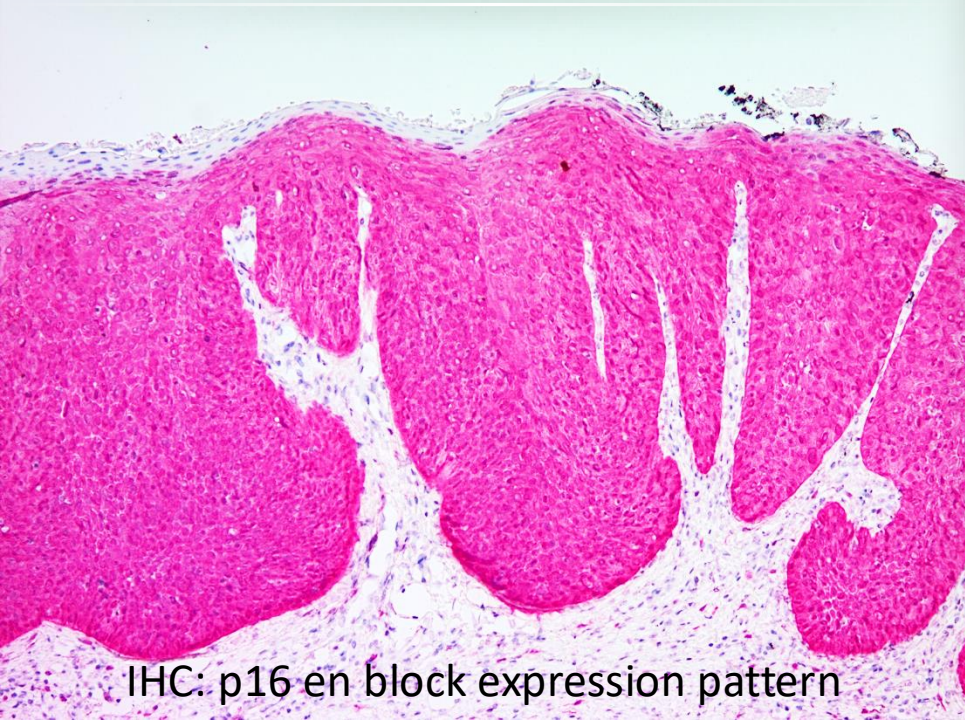
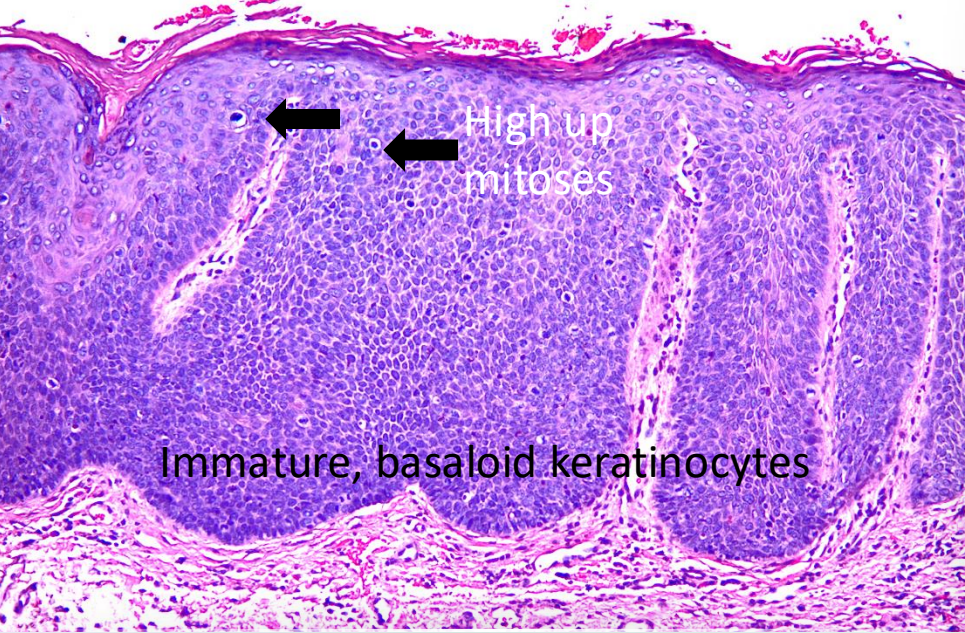
# VERRUCA VULGARIS

- Prevalence: Common in children/adolescents but also affects adults.
- Appearance: Hard, rough-surfaced papules (0.2–2 cm), often on fingers; less common in covered areas (axillae, groin, genitals).
- HPV Types: Mainly HPV-2, but also HPV-1, -4, -27, -7, -57 (recalcitrant cases). Immunosuppressed patients may have HPV-75, -76, -77.
- Special Cases:
  - Immunodeficiency (e.g., HIV, transplant recipients) can lead to extensive/recalcitrant warts.





Near full-thickness atypia



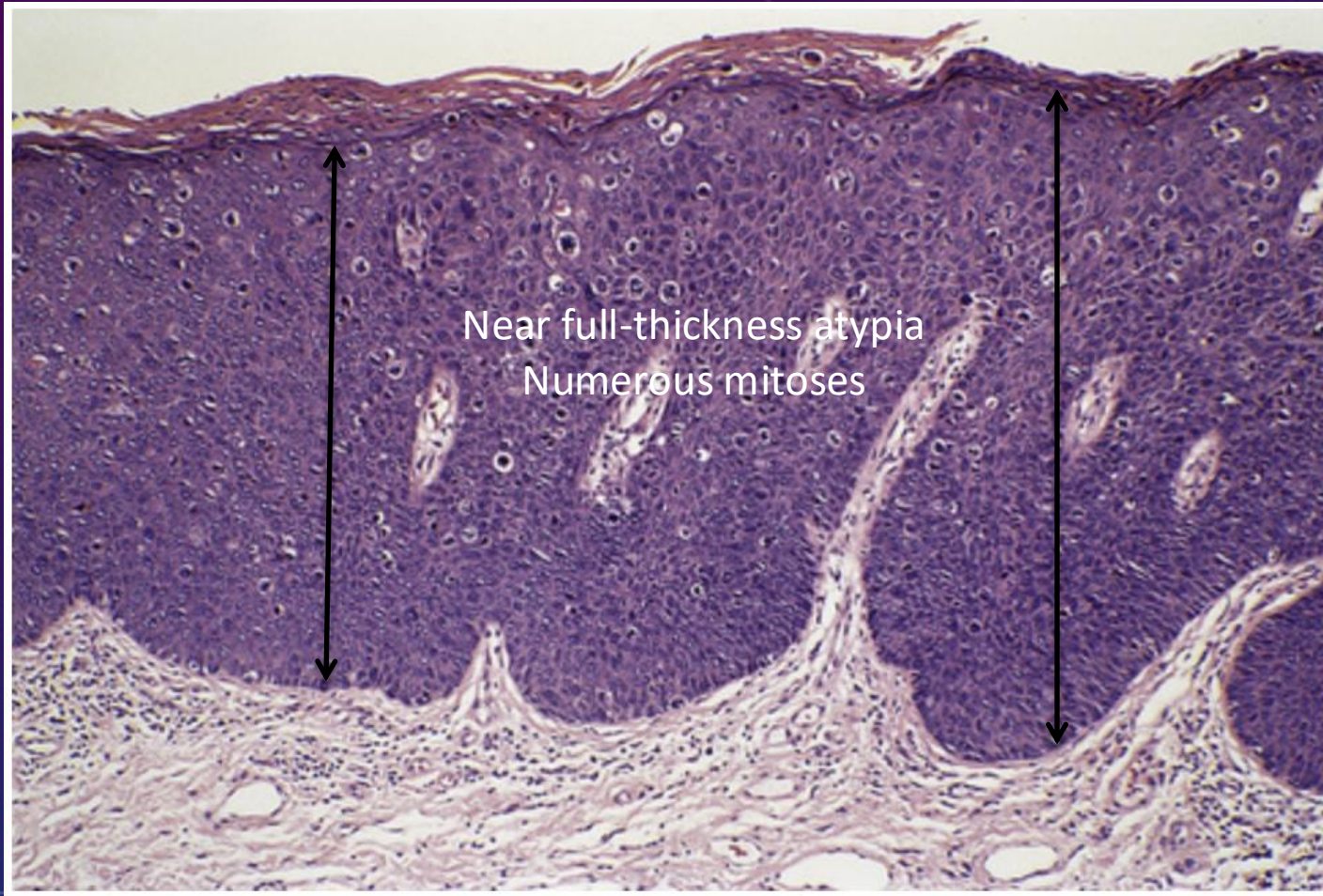
IHC: p16 en block expression pattern

# HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL)

- Definition:
  - HSIL is a premalignant squamous epithelial lesion with a high risk of progression to invasive squamous cell carcinoma if untreated.
  - Includes CIN 2/3 (cervical intraepithelial neoplasia), VIN 2/3 (vulvar), VaIN 2/3 (vaginal), and AIN 2/3 (anal).
- Common Sites:
  - Cervix (most common).
  - Anogenital regions (vulva, vagina, anus, penis).
  - Oropharynx (HPV-related).
- Etiology & Risk Factors:
  - HPV Types: Mainly HPV-16, -18 (high-risk types).
  - Other risk factors: Immunosuppression (HIV, transplant), smoking, multiple sexual partners, early sexual activity.
- Differential diagnosis:
  - Bowenoid papulosis



# BOWENOID PAPULOSIS



- Definition: Solitary or multiple verruca-like papules/plaques on genitalia
- Histology: Bowen's disease (SCC in situ).
- Demographics:
  - Sexually active young adults
  - Males: Glans penis, foreskin.
  - Females: Bilateral, often pigmented vulvar lesions.
- Etiology:
  - HPV-driven (mainly HPV-16, but also -18, -31, -33, -35, -39, -53, mixed infections).
- Behavior:
  - Often persistent, especially in immunosuppressed individuals.
  - Risk of progression to invasive carcinoma (higher in women >40, but men also at risk).



The background is a high-magnification histological image of tissue, likely skin, stained with hematoxylin and eosin (H&E). It shows a dense population of cells with prominent, dark purple nuclei and pinkish cytoplasm and extracellular matrix. A large, semi-transparent circular overlay is positioned on the right side of the image, containing the title and a list of neoplasms. The text is in a clean, white, sans-serif font.

# NEOPLASMS

HPV-ASSOCIATED SQUAMOUS CELL  
CARCINOMA

MERKEL CELL CARCINOMA

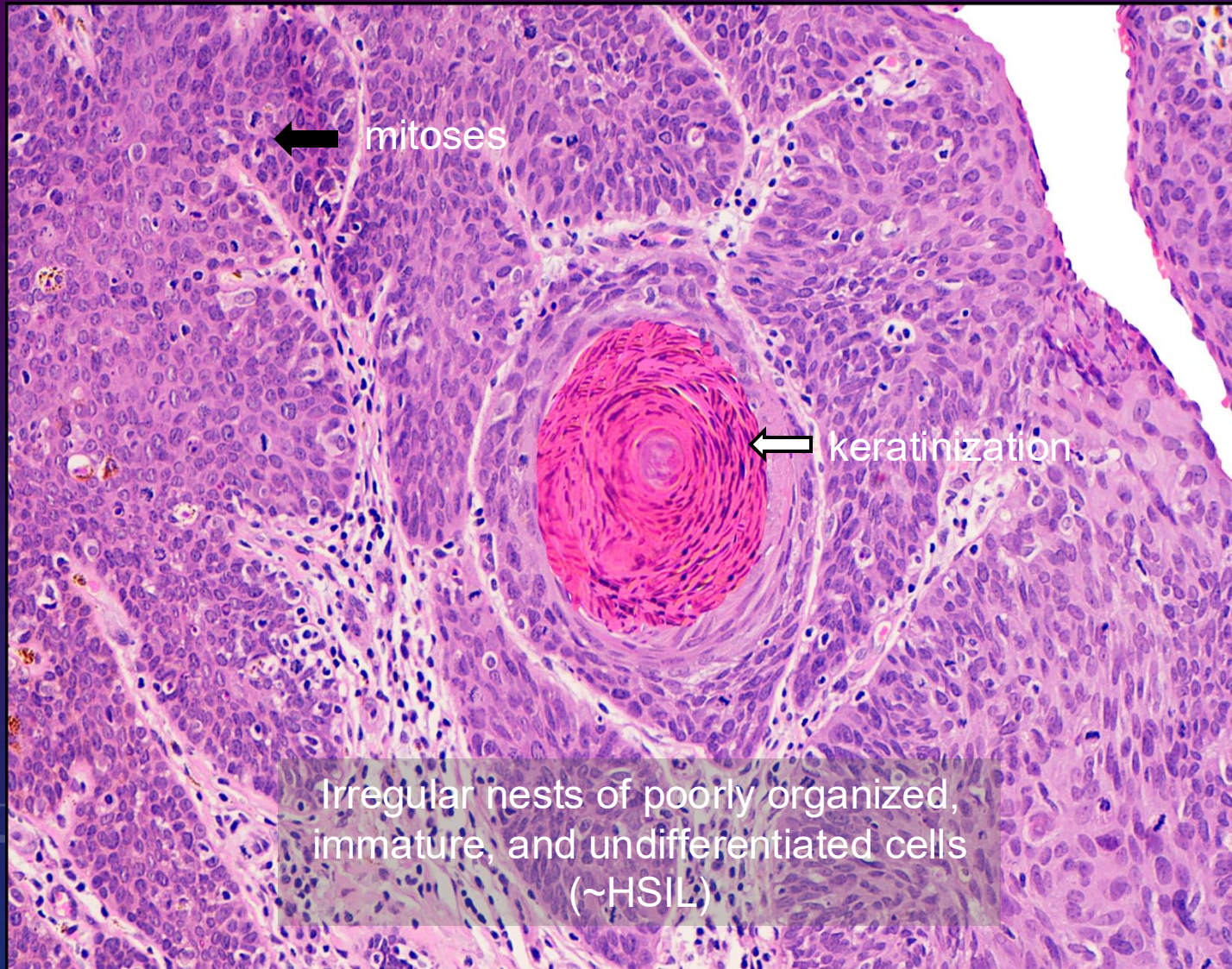
KAPOSI SARCOMA

MOLLUSCUM CONTAGIOSUM

Merkel cell carcinoma



# HPV-ASSOCIATED SQUAMOUS CELL CARCINOMA



- **Common Sites:**

- **Anogenital region** (cervix, vulva, vagina, penis, anus).
- **Oropharynx** (tonsils, base of tongue – "HPV+ oropharyngeal SCC").
- Rarely: Cutaneous SCC (fingers, periungual).

- **Risk Factors:**

- **High-risk HPV** (HPV-16, -18, -31, -33, -45, -52, -58).
- Immunosuppression (HIV, transplant recipients).

- **Precursor Lesions:**

- **HSIL (High-grade squamous intraepithelial lesion)** → Invasive SCC.
- **Bowen's disease (SCC in situ)** → Cutaneous SCC.

- **Prognosis:**

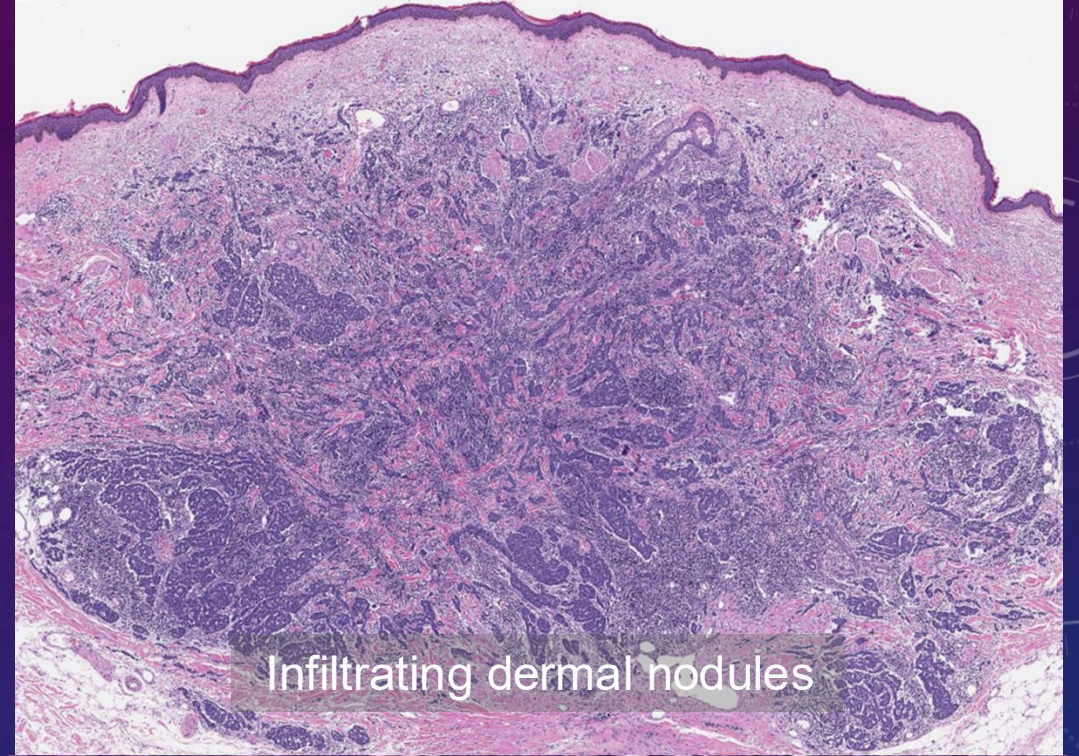
- **HPV+ oropharyngeal SCC** has better survival than HPV–.



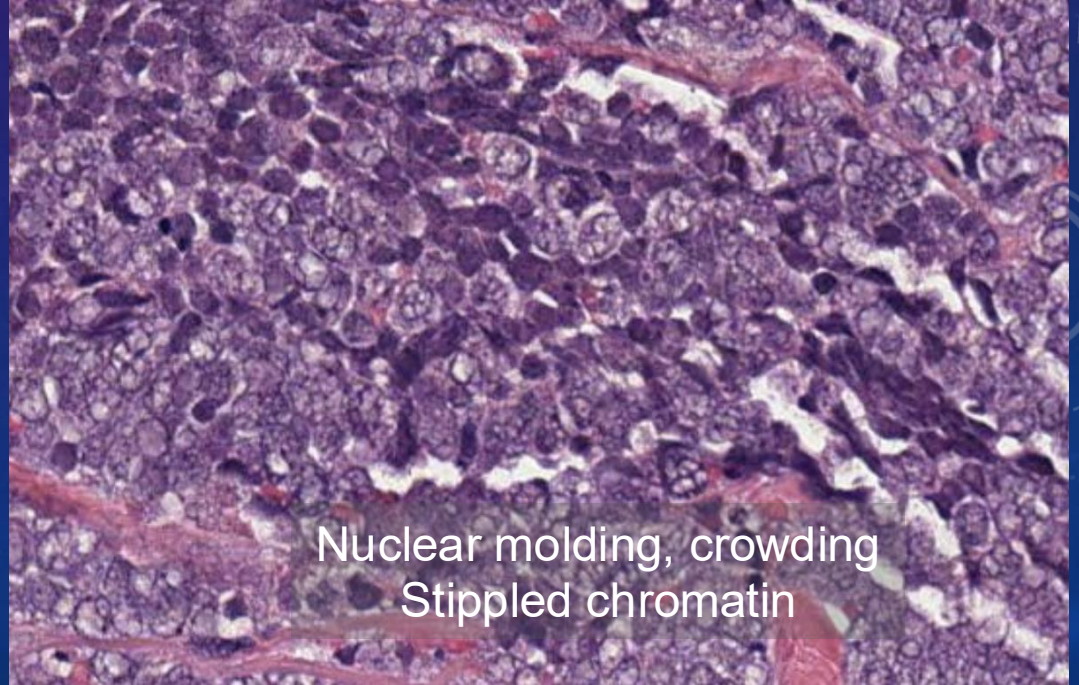
# MERKEL CELL CARCINOMA

Merkel cell polyomavirus (MCPyV)

- Sun-damaged skin: the head/neck, extremities, and trunk. Elderly Caucasians.
- Rapidly growing flesh-colored or violaceous nodule/plaque.
- Metastasis can occur without a detectable primary tumor.
- Strongly linked to immunosuppression.
- Estimated prevalence related to pathogenesis:
  - MCPyV-positive MCCs: Viral-driven tumorigenesis (80%).
  - MCPyV-negative MCCs: UV-related mutations (TP53/RB1), high mutation load (20%).
  - Combined tumors: Neuroendocrine cells derive from SCC (rare).
- CK20 (perinuclear dot-like), AE1/AE3, EMA.
- INSM1 (most sensitive), synaptophysin, chromogranin, CD56.



Infiltrating dermal nodules



Nuclear molding, crowding  
Stippled chromatin



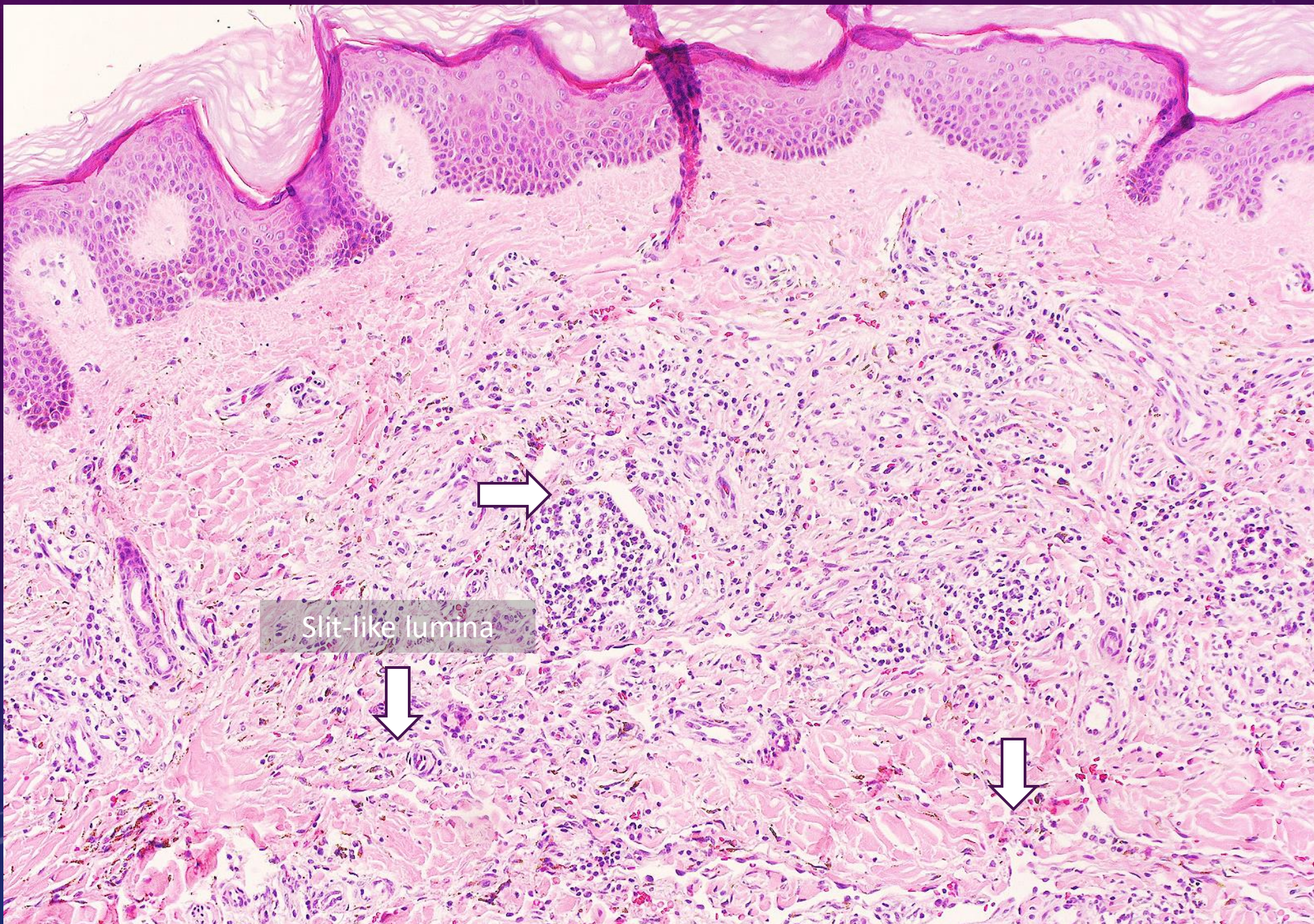
# KAPOSI SARCOMA

- Human herpesvirus (HHV-8, KS-associated herpesvirus)
- Clinical groups:
  - Classic: elderly male
  - AIDS-related: young adult males
  - Immune-associated: rare, kidney transplantation
  - African, sub-Saharan Central Africa
- Reddish-blue patch, nodule
- DDX: progressive lymphangioma, angiosarcoma, tufted angioma, KHE
- IHC: HHV8+, CD31+, CD34+, D2-40+



Bologna's *Dermatology*





Early patch stage:  
irregular dermal  
vascular spaces  
(busy dermis)



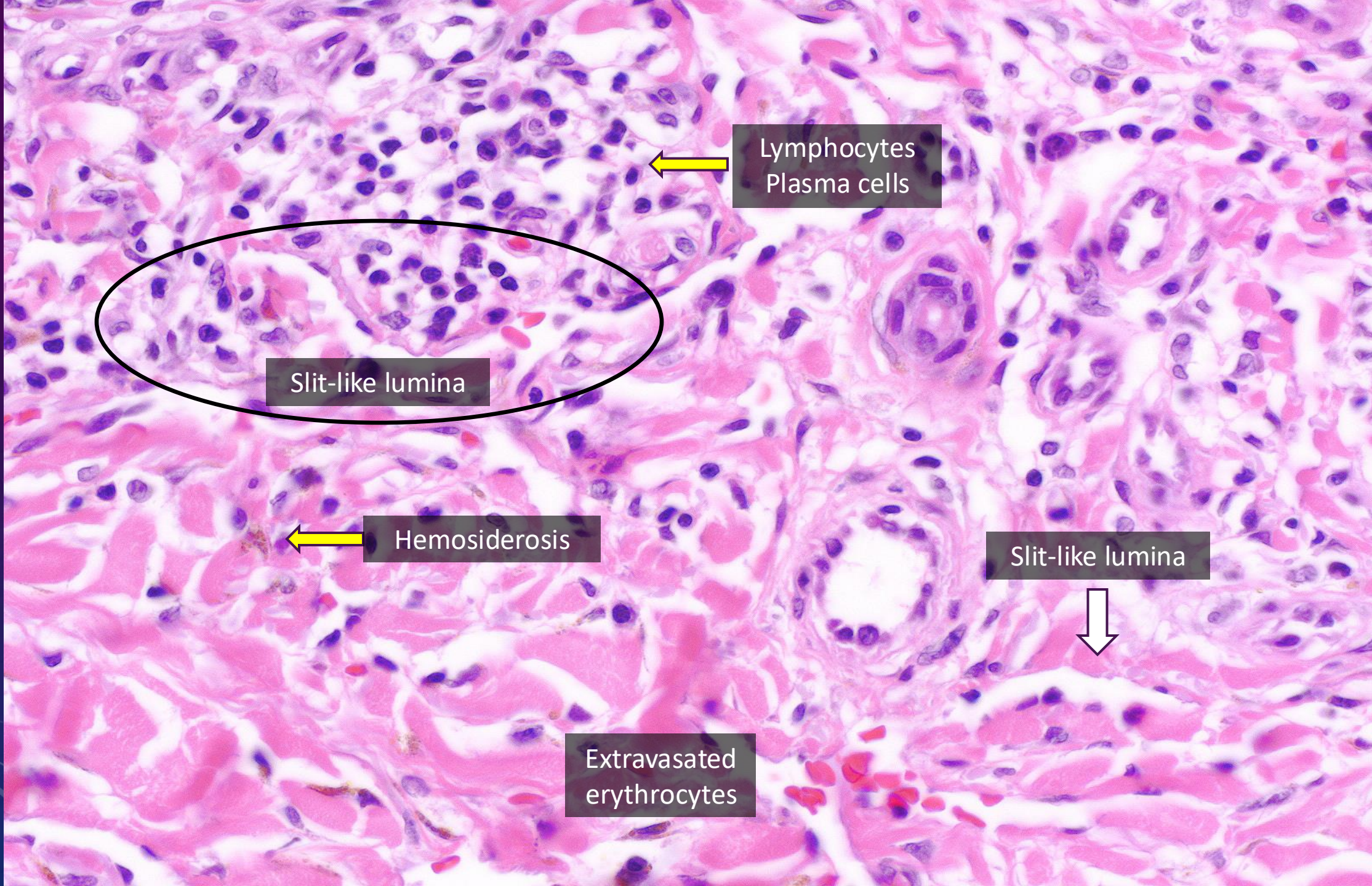
Lymphocytes  
Plasma cells

Slit-like lumina

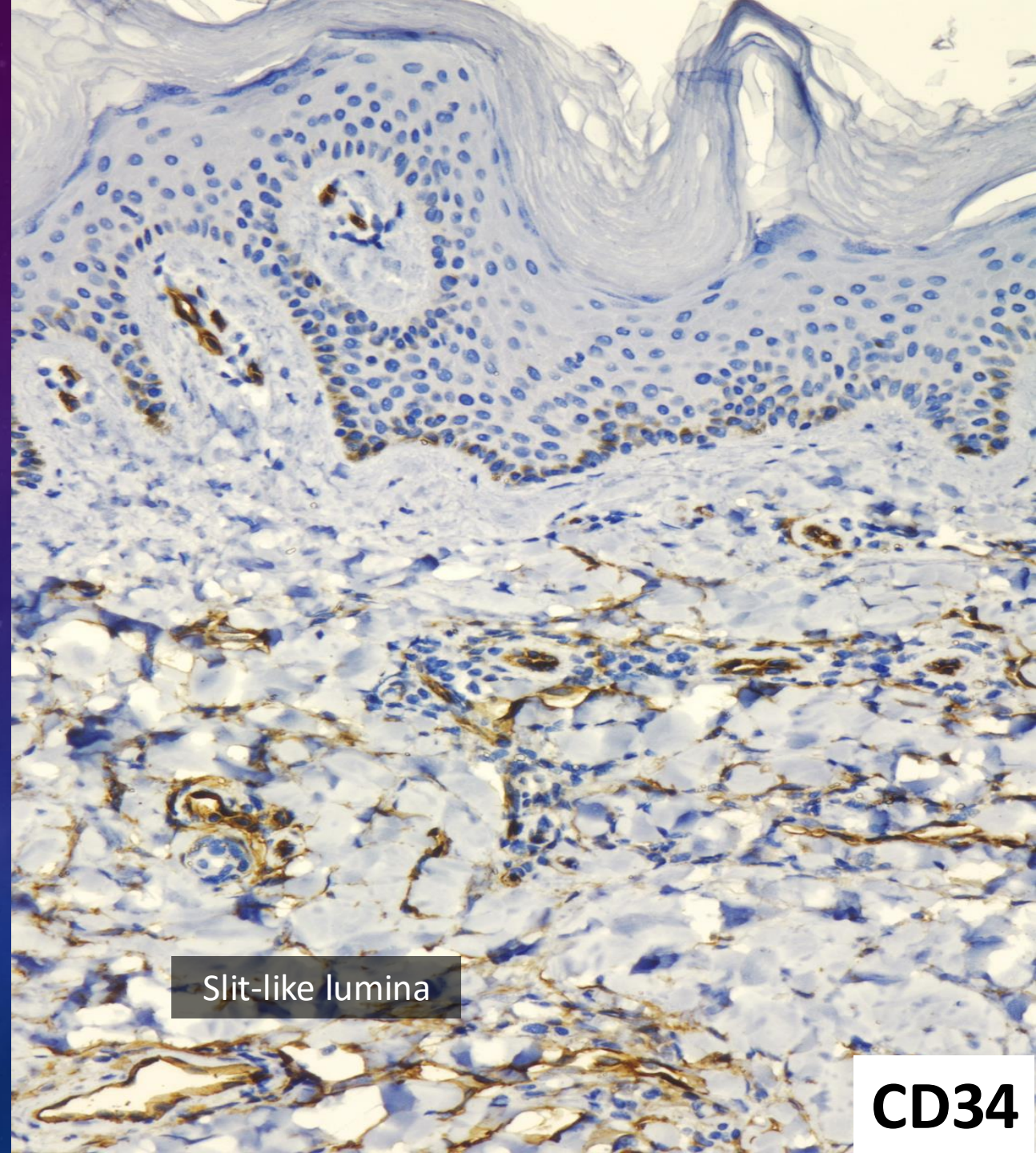
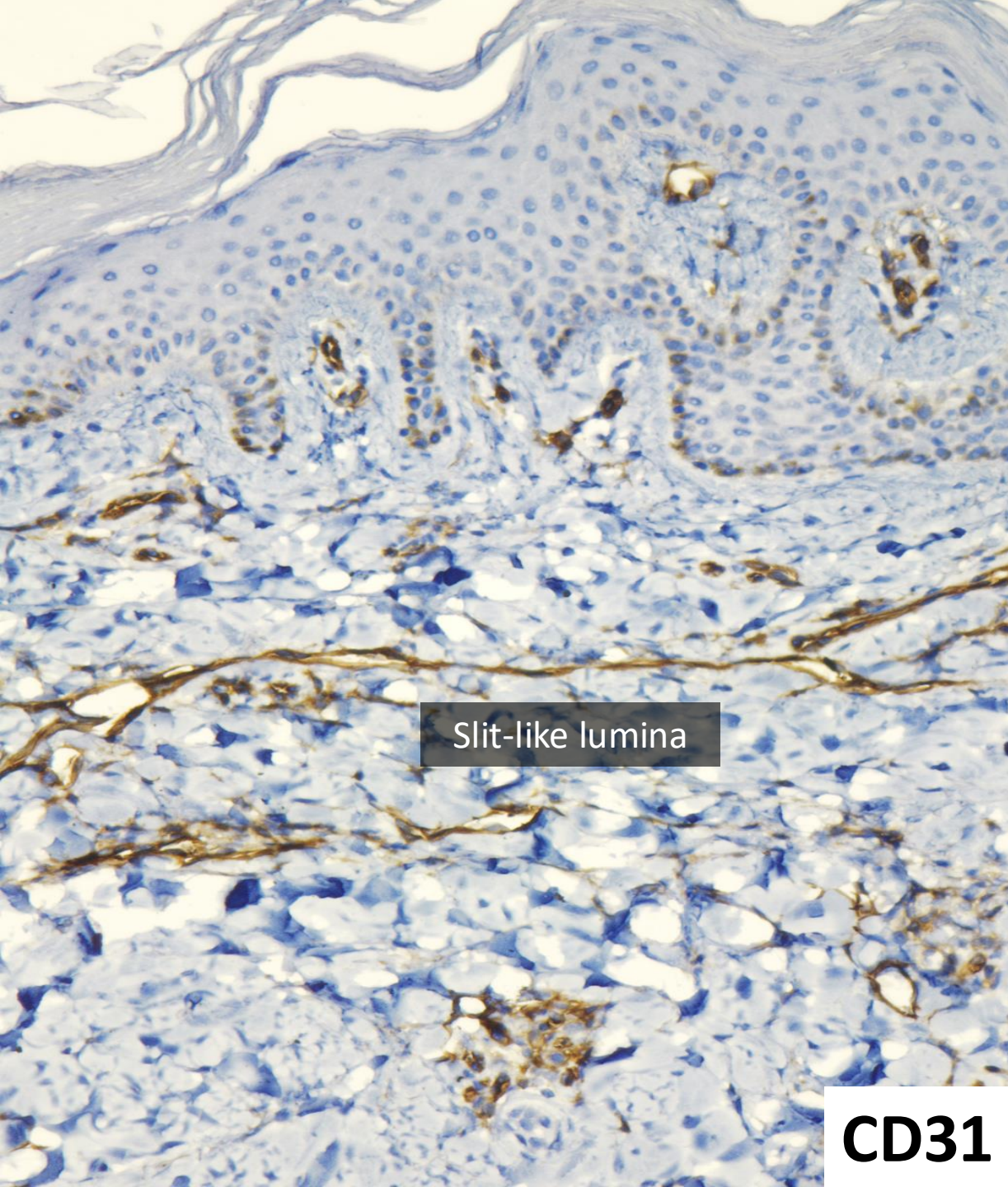
Hemosiderosis

Slit-like lumina

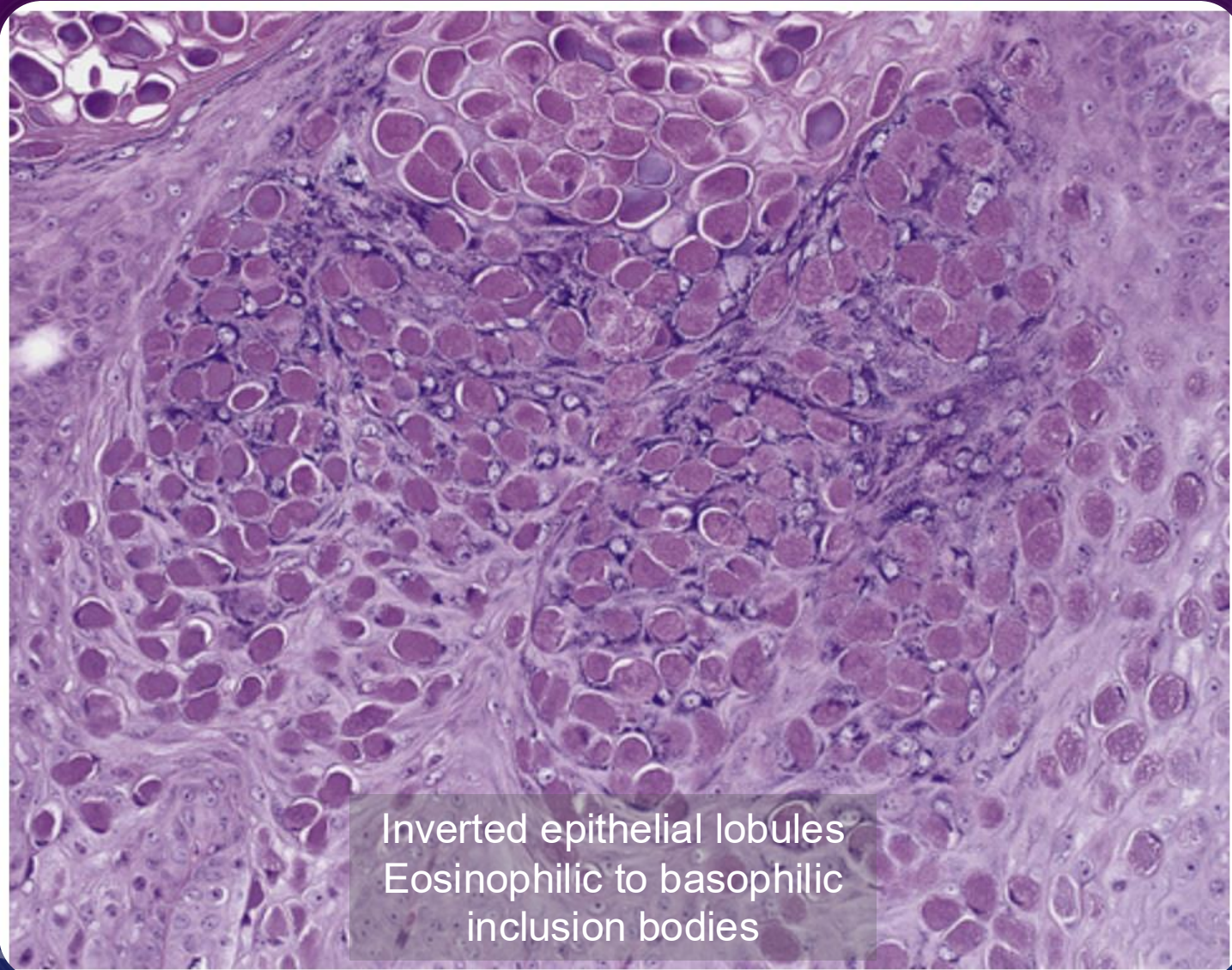
Extravasated  
erythrocytes









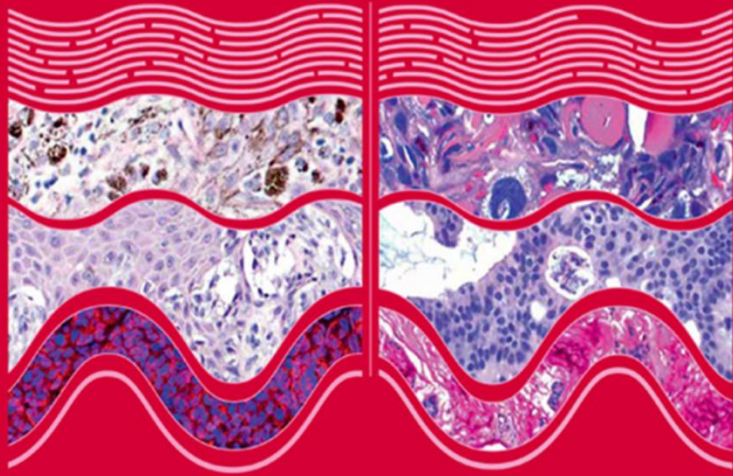


Inverted epithelial lobules  
Eosinophilic to basophilic  
inclusion bodies

# MOLLUSCUM CONTAGIOSUM

- DNA poxvirus (*Molluscipoxvirus*).
- Presentation:
  - Small (2–8 mm), dome-shaped, umbilicated, waxy papules (may be solitary or multiple).
  - Common sites: Face, trunk, flexural areas, genitals (children/adolescents).
  - Rare sites: Toes, penis, tattoos, burns, herpes scars.
- Transmission: Direct contact, fomites, sexual contact, swimming pools.
- Spontaneous regression (usually within 1 year) via cell-mediated immunity (lymphocyte response).





Diagnostic Pathology

# Neoplastic Dermatopathology

**Cassarino | Dadras**



THIRD EDITION

## REFERENCES

- Digitalskinpathology.com
  - Quiz Cases: 126-136
  - Lecture: *Viral infections*
- Dadras collection
- *Dermatology*, 4<sup>th</sup> edition
- *McKee's Pathology of the Skin*, Eduardo Calonje, 5<sup>th</sup> edition
- *Weedon's Skin Pathology*, 4<sup>th</sup> edition