

Update in vulvar pathology

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WHO 5th Edition

HSIL/uVIN (HPV related) comprises 80% of VIN but less than 50% SCC

- Typically warty-basaloid **BLUE**

dVIN (HPV independent)

- Typically keratinising and background LS **PINK**

DEVIL and VAAD

HPV associated VIN/SCC

HPV independent VIN/SCC

Younger

Multifocal/centric

More radio/chemosensitive

Less nodal mets

Fewer local recurrences

Better PFS

Favorable 5-year OS

uVIN (slower progression)

P16 block/p53 wt

uVIN colonises adnexal structures

Older

Unifocal

Less sensitive

Higher frequency of nodal mets

More local recurrences

Less

Less

dVIN likely to progress/shorter interval

P16 non-block/ p53 mutant

dVIN does not

3rd category of VIN/VSCC

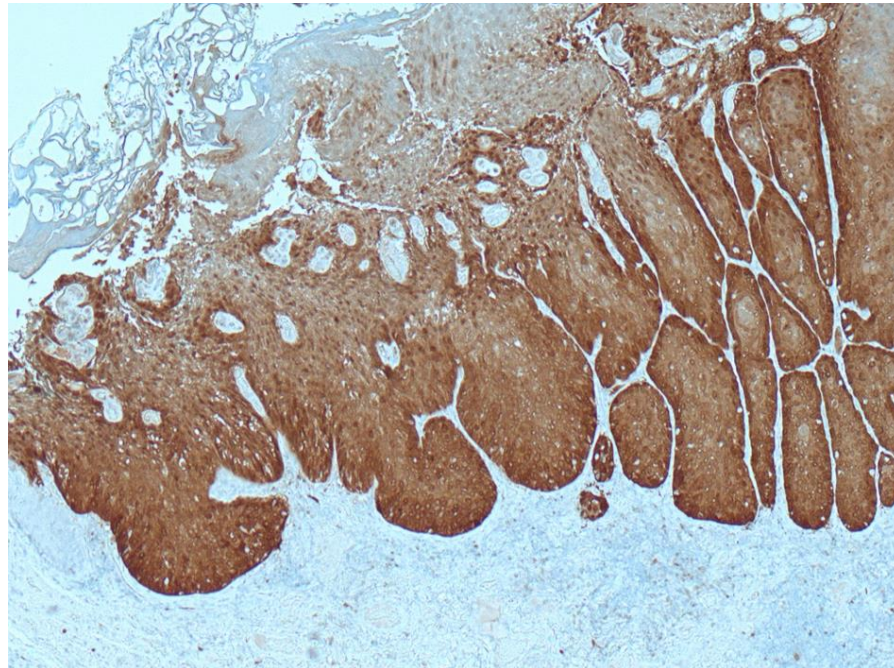
p16 non-block and p53 wt

- VaVIN
- DEVIL
- VAAD
- vLSC

Use of p16 and p53

Defining p16 staining (LAST project)

p16 overexpression is defined as “block” strong nuclear and cytoplasmic staining involving at least the basal third of the epithelium.



p16

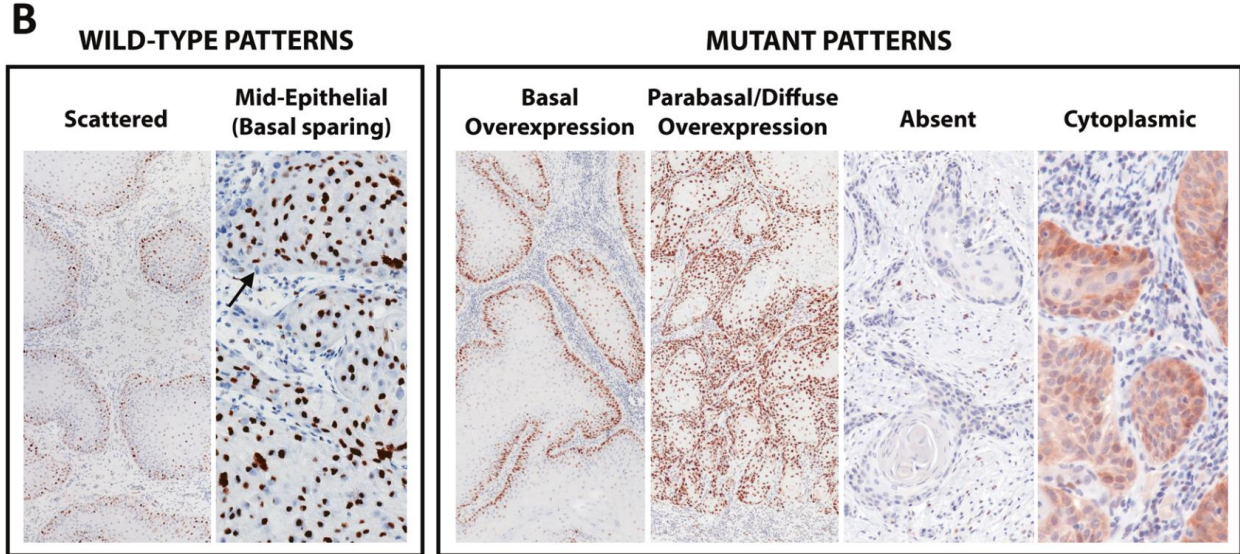
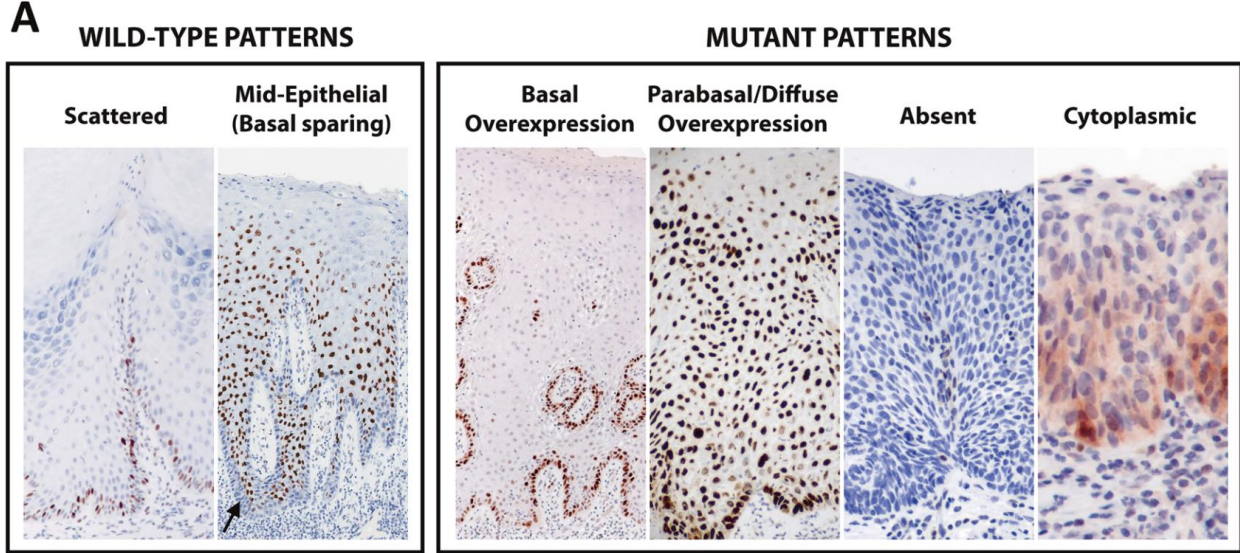
In HSIL/uVIN <5% false negative rate

Non-block or negative staining supports dVIN

Patterns of p53 staining

- Associated with TP53 mutations include
 - basal overexpression) >90% cells with intense nuclear staining
 - parabasal/diffuse overexpression)
 - absent/null
 - cytoplasmic staining
- wild-type TP53 include
 - scattered (heterogeneous basal/parabasal staining with variable intensities)
 - Basal sparing mid-epithelial (heterogeneous strong staining in mid-epithelial cells, with notable sparing of basal cells which are negative to at most weakly positive).
 - Null-like pattern in HPV associated lesions is described

P53 staining pattern *Modern Pathology (2020) 33:1595–1605*



Modern Pathology (2022) 35:1317 – 1326

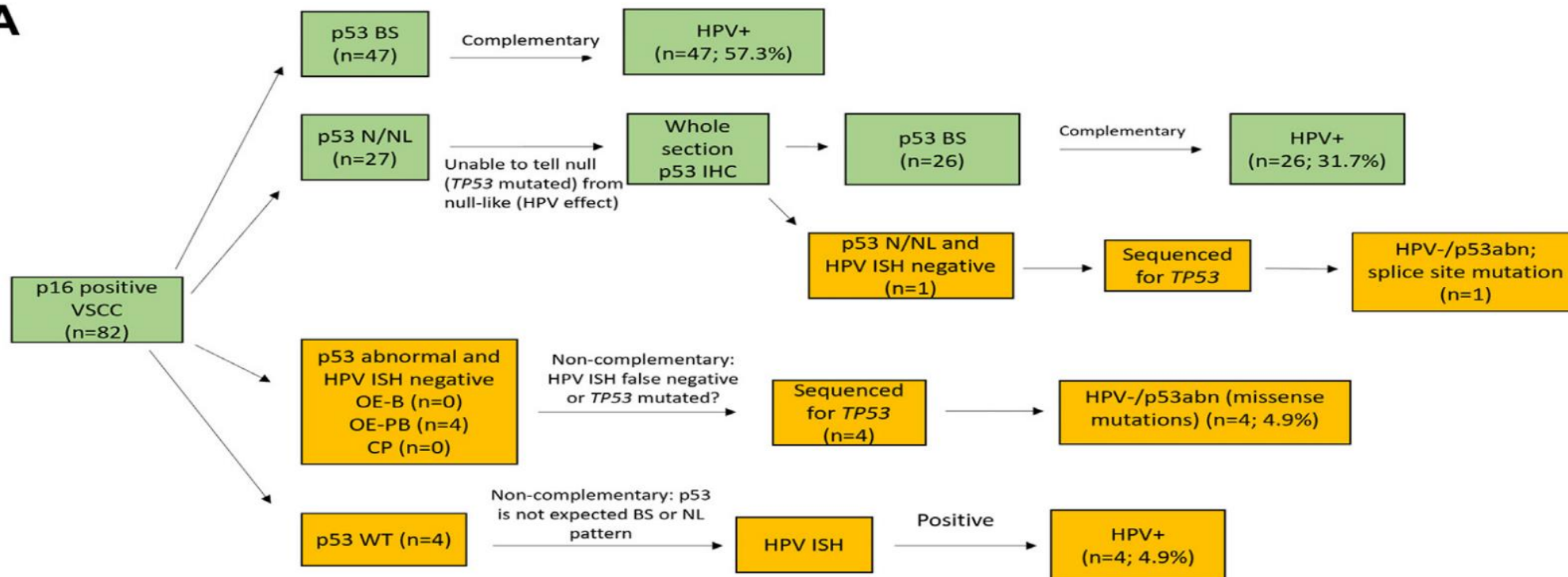
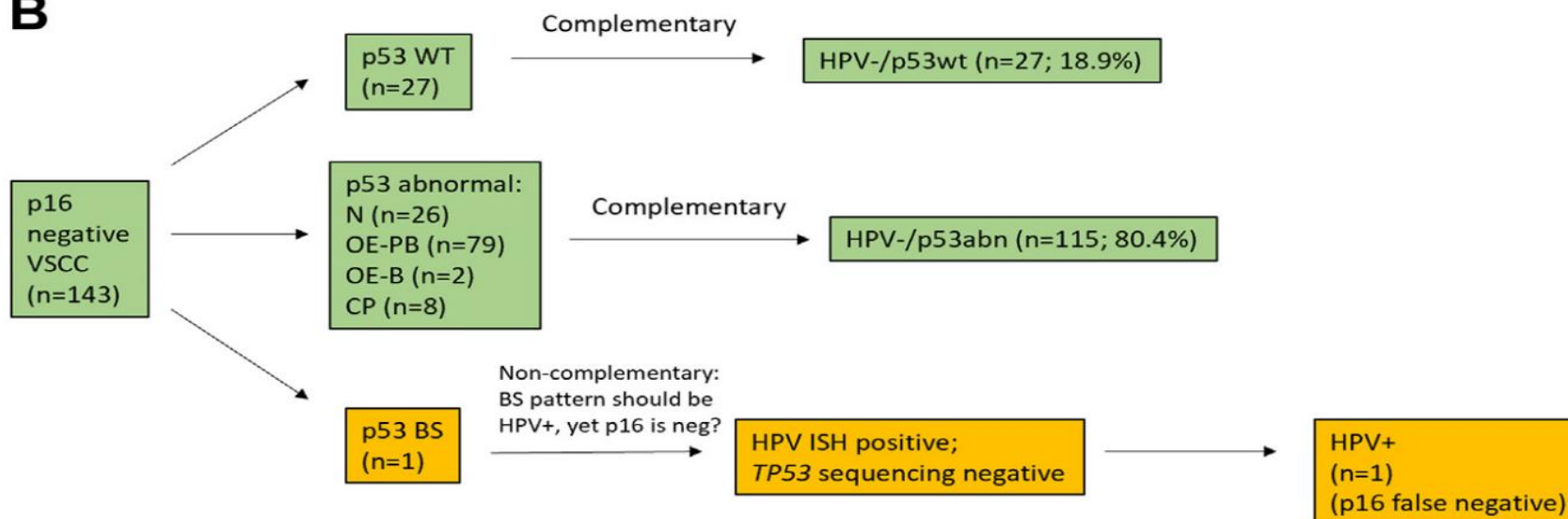
VULVAR SQUAMOUS INTRAEPITHELIAL NEOPLASIA		
<p>HPV-ASSOCIATED VULVAR INTRAEPITHELIAL NEOPLASIA High Grade Squamous Intraepithelial Lesion (HSIL)</p>	<p>HPV-INDEPENDENT p53 MUT VULVAR INTRAEPITHELIAL NEOPLASIA Differentiated VIN (dVIN)</p>	<p>HPV-INDEPENDENT p53 WT VULVAR INTRAEPITHELIAL NEOPLASIA Verruciform/Acanthotic VIN (vaVIN)</p>
<ul style="list-style-type: none"> ● Atypia extending to upper layers ● Large hyperchromatic nuclei ● Loss of polarity and organization ● Loss of maturation with basaloid appearance & brisk mitotic activity with extension beyond basal layers 	<ul style="list-style-type: none"> ● Atypia often confined to the basal layer ● Large nuclei with open chromatin ● Prominent nucleoli ● Retained but abnormal maturation with elongated and/or fused rete ridges, acantholysis & dyskeratotic cells 	<ul style="list-style-type: none"> ● No cytologic atypia ● Verruciform acanthosis with flat (VAAD) or exophytic growth pattern (DEVIL) ● Retained but altered maturation with hypogranulosis & cytoplasmic pallor (VAAD/DEVIL) or hypergranulosis (vLSC)
<p>p16 = Overexpressed * p53 = Wild type (mid-epithelial) **</p>	<p>p16 = Negative or patchy p53 = Mutant pattern **</p>	<p>p16 = Negative or patchy p53 = Wild type (scattered) **</p>

Hang Yang et al. / Mod Pathol 36 (2023) 100145

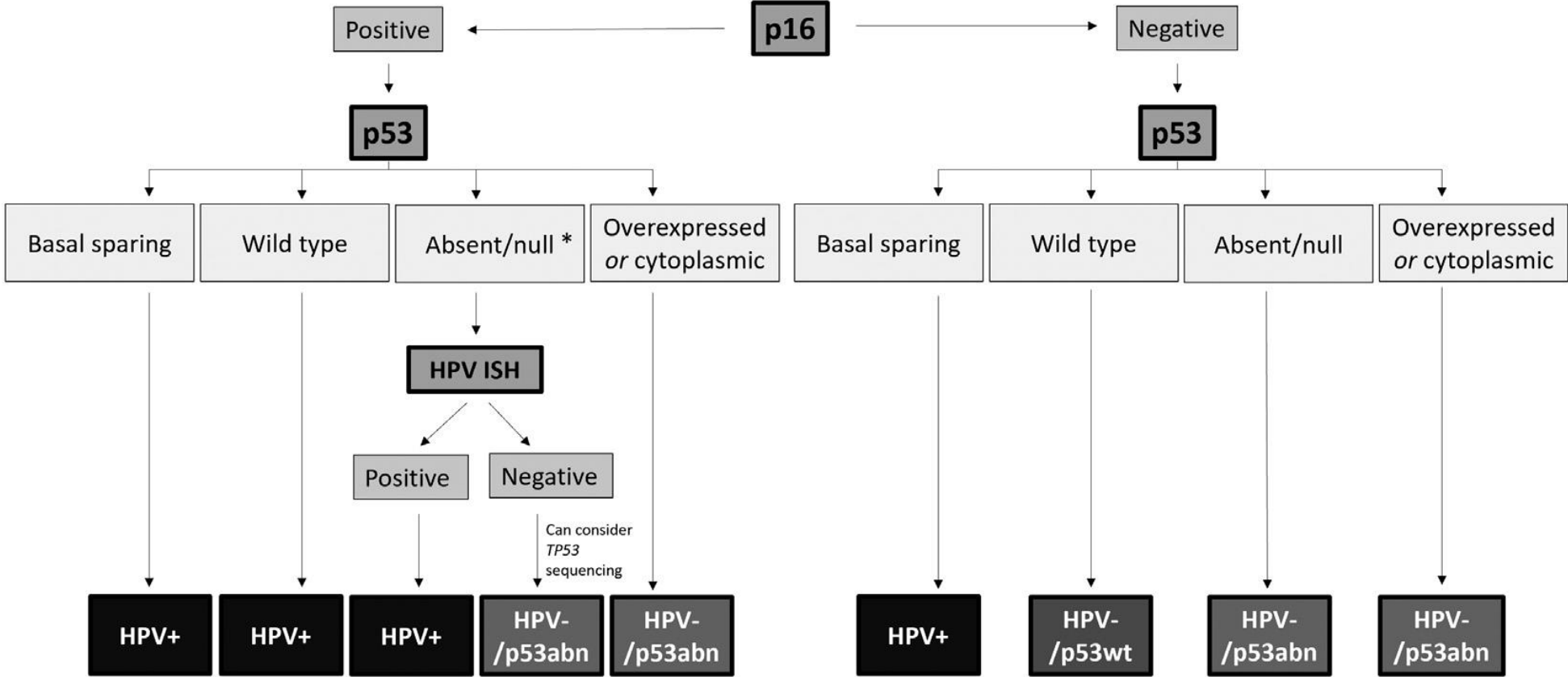
95% cases can be classified based on p16 and p53 immunostaining

5% caveats

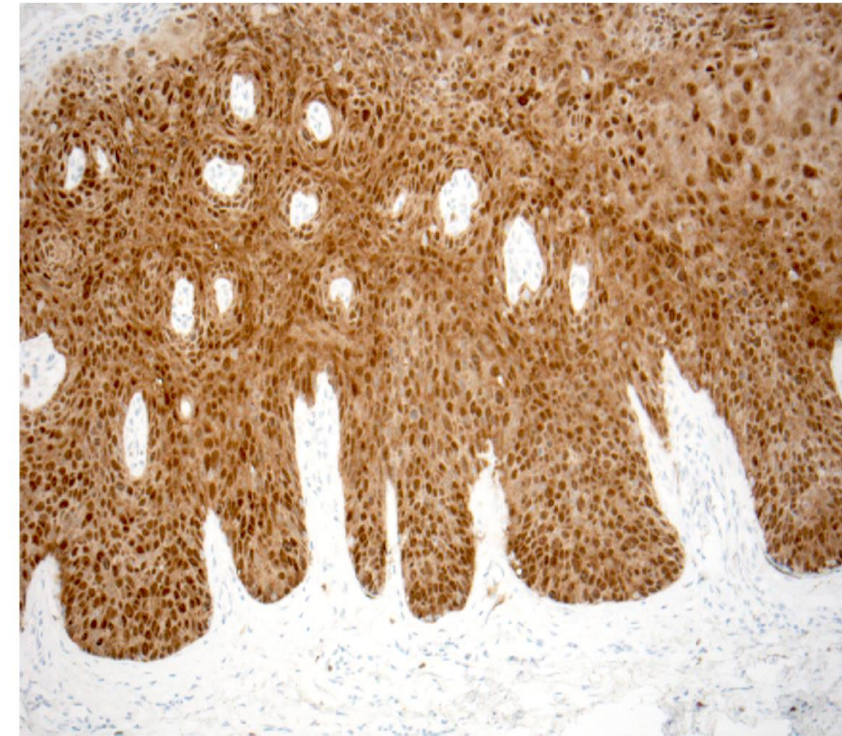
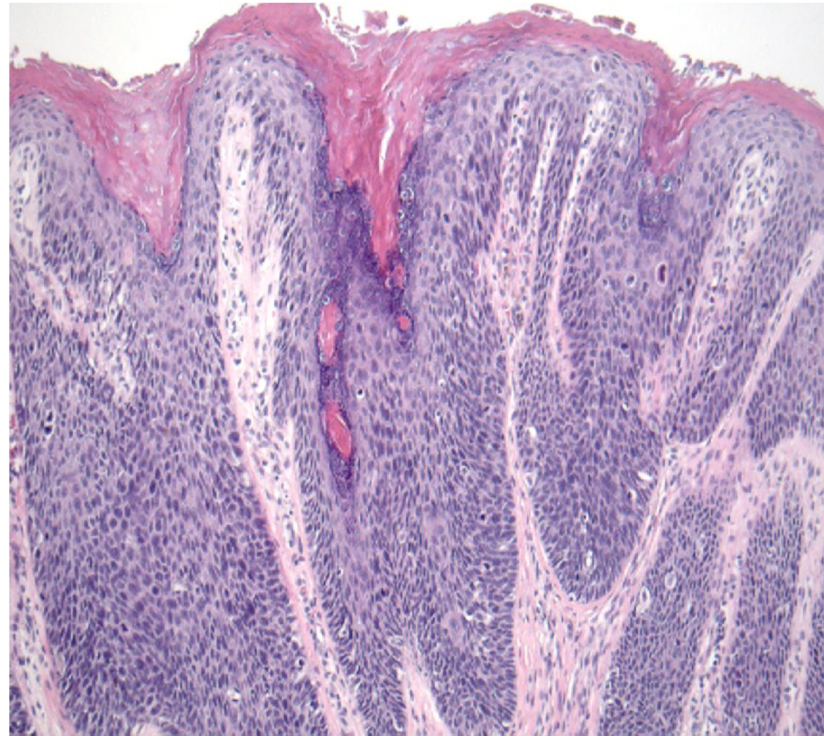
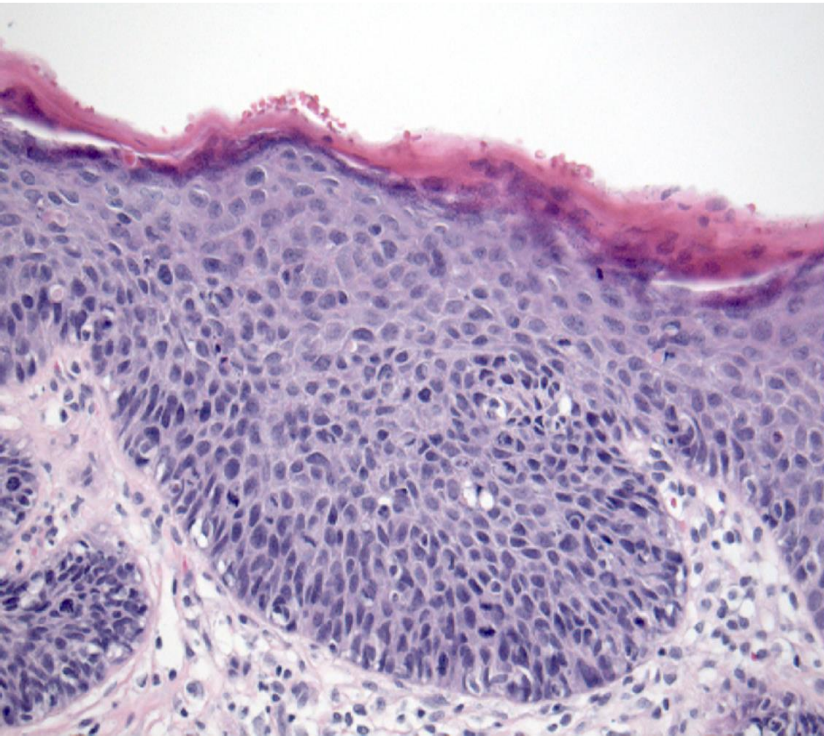
- Double positives p16 and p53
- P16 +/-null-like p53

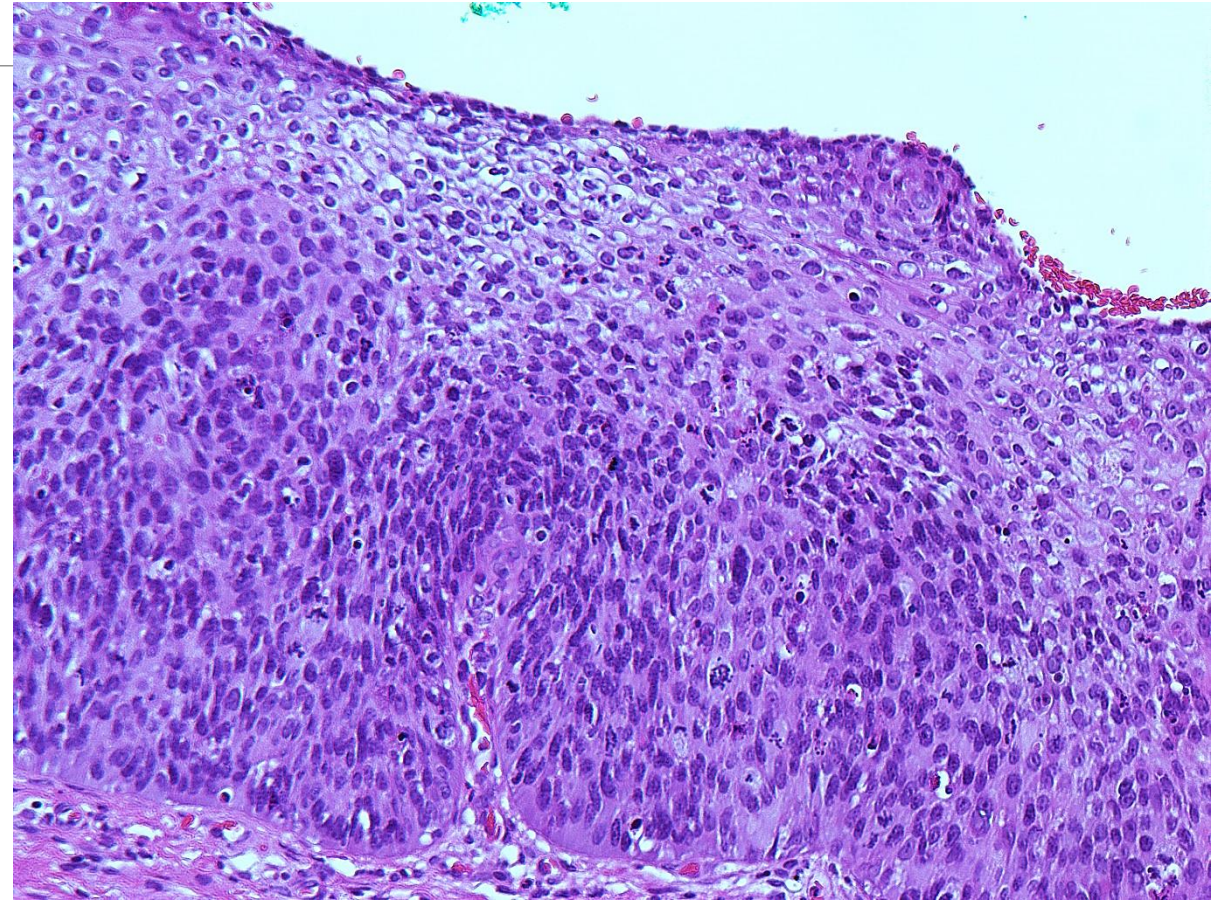
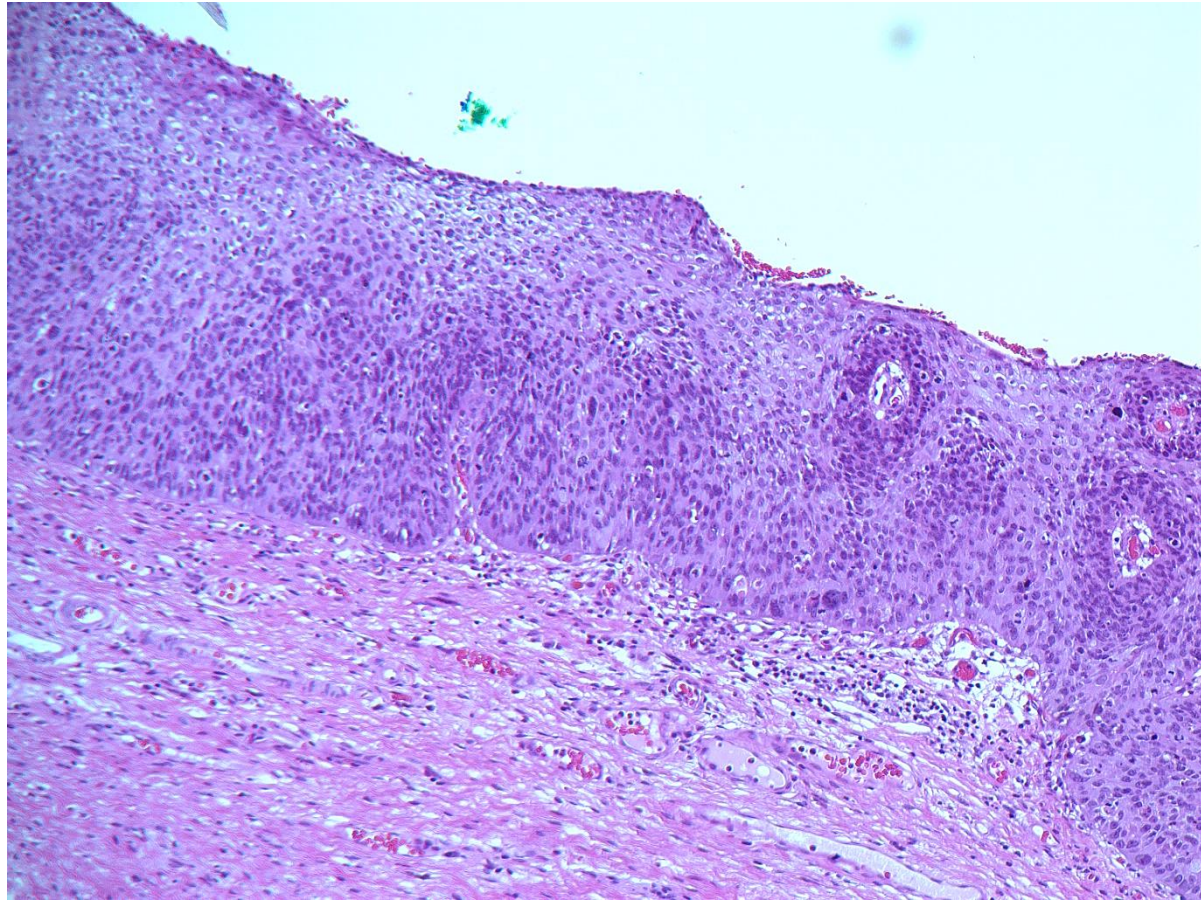
A**B**

Hang Yang et al. / Mod Pathol 36 (2023) 100145

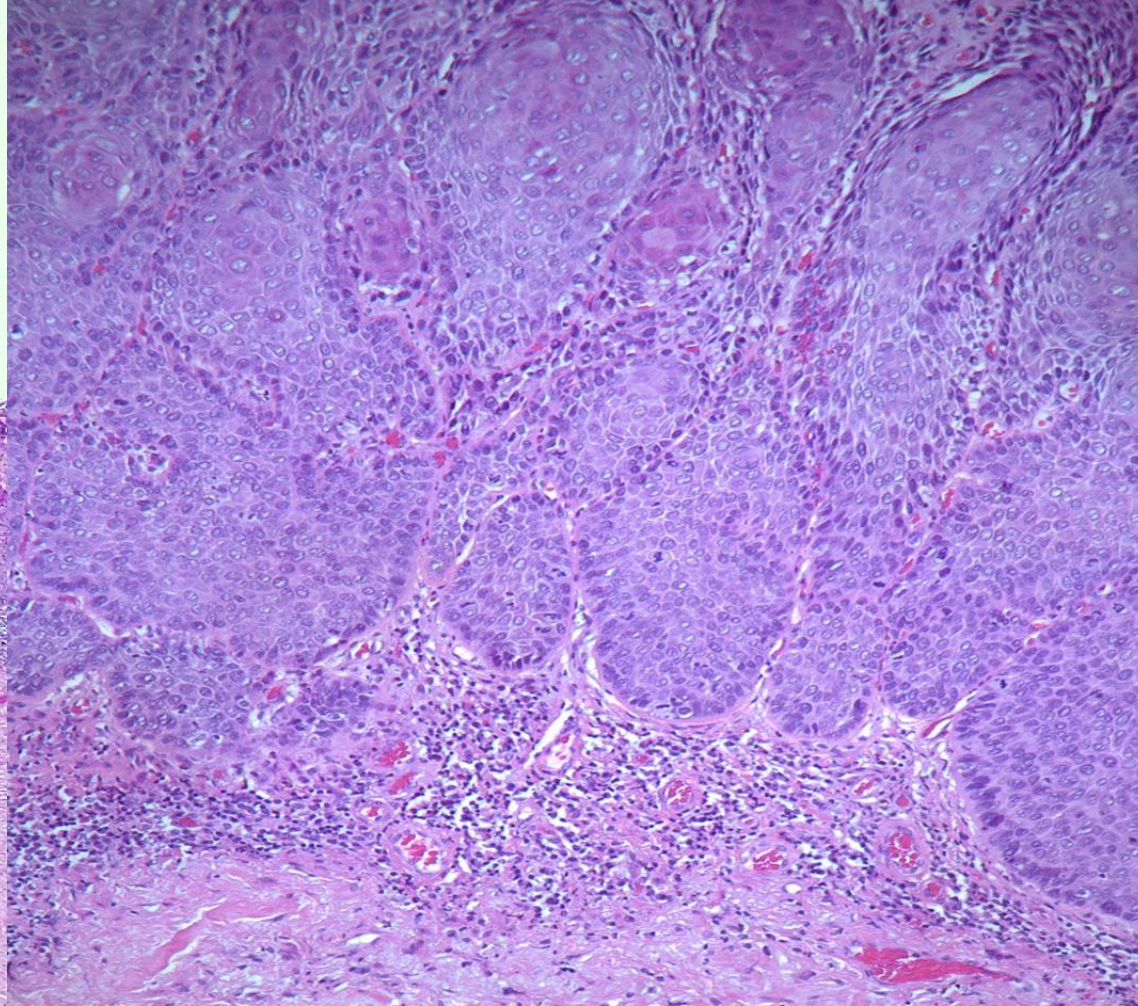
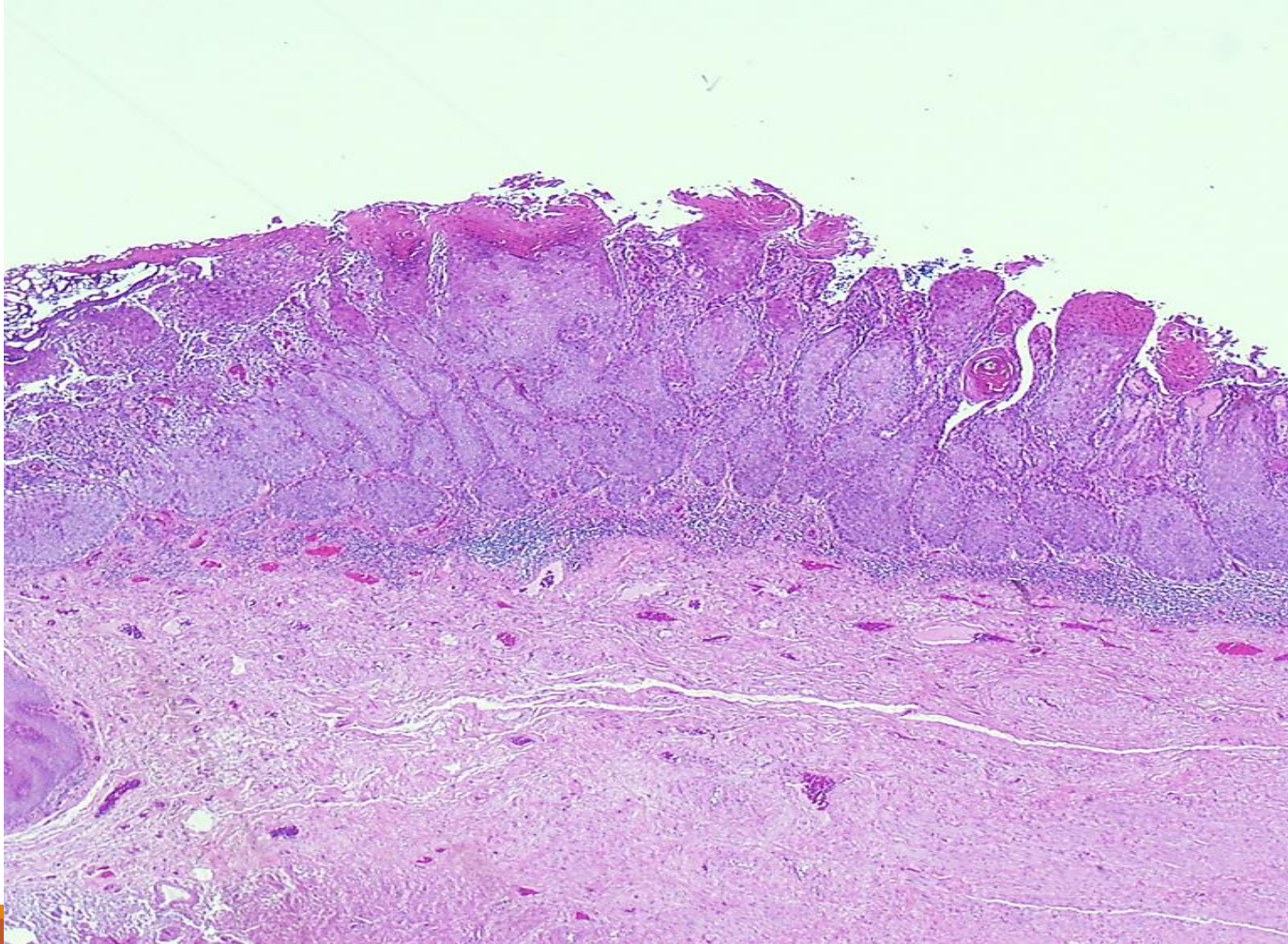


J Clin Pathol 2014;67:290–294.

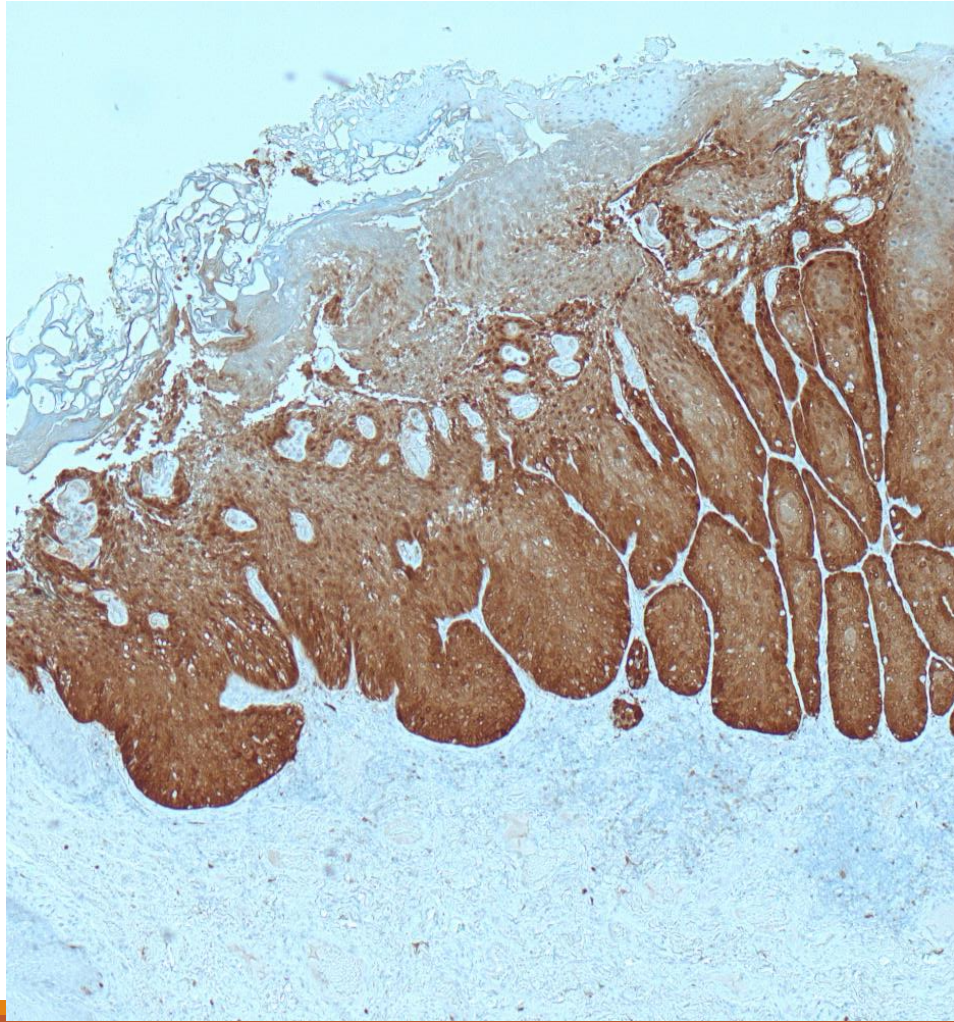




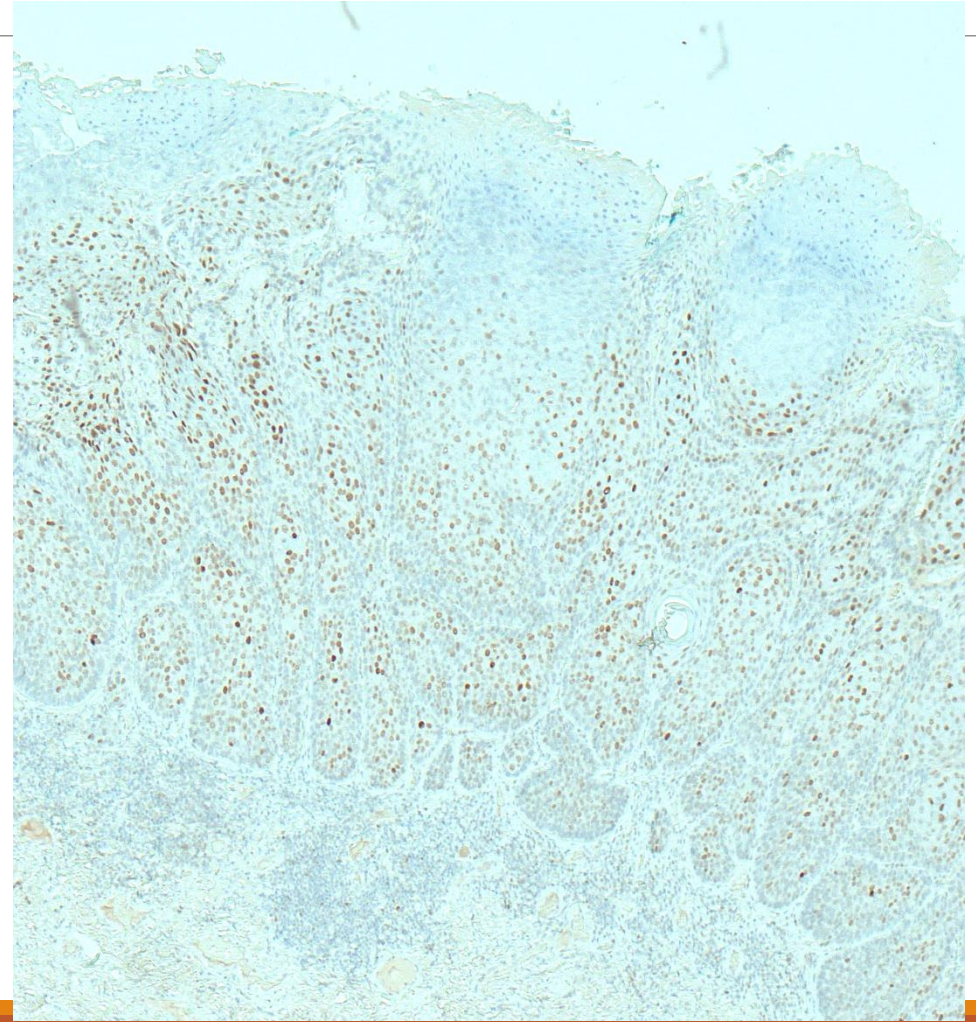
uVIN



p16



p53

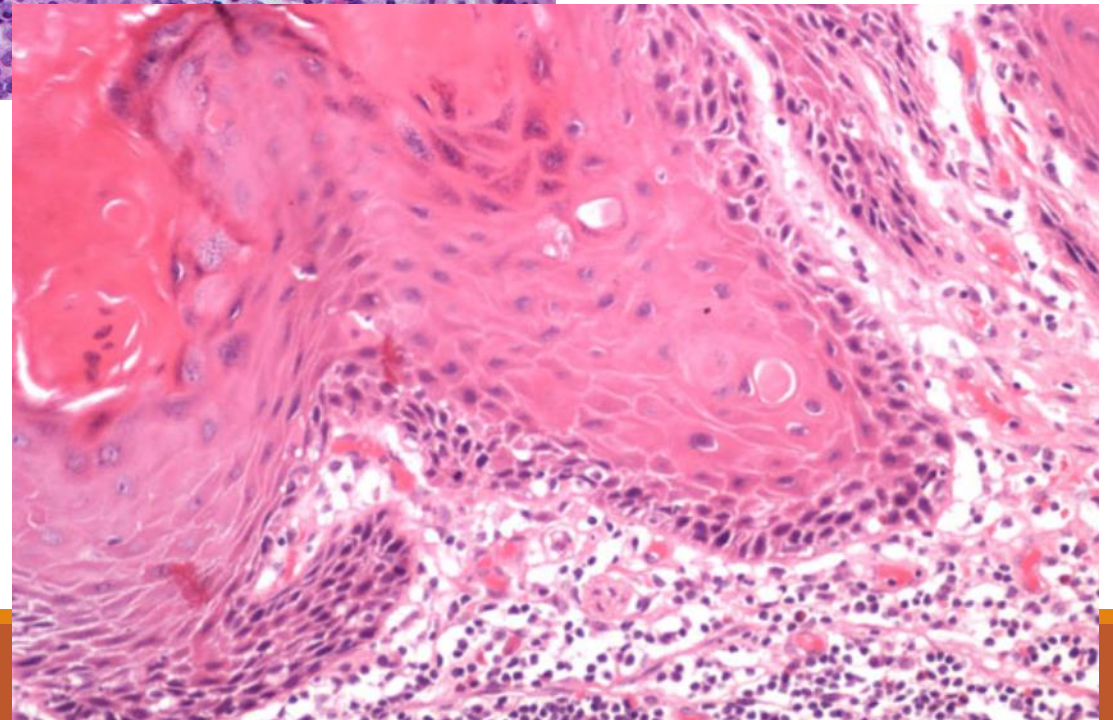
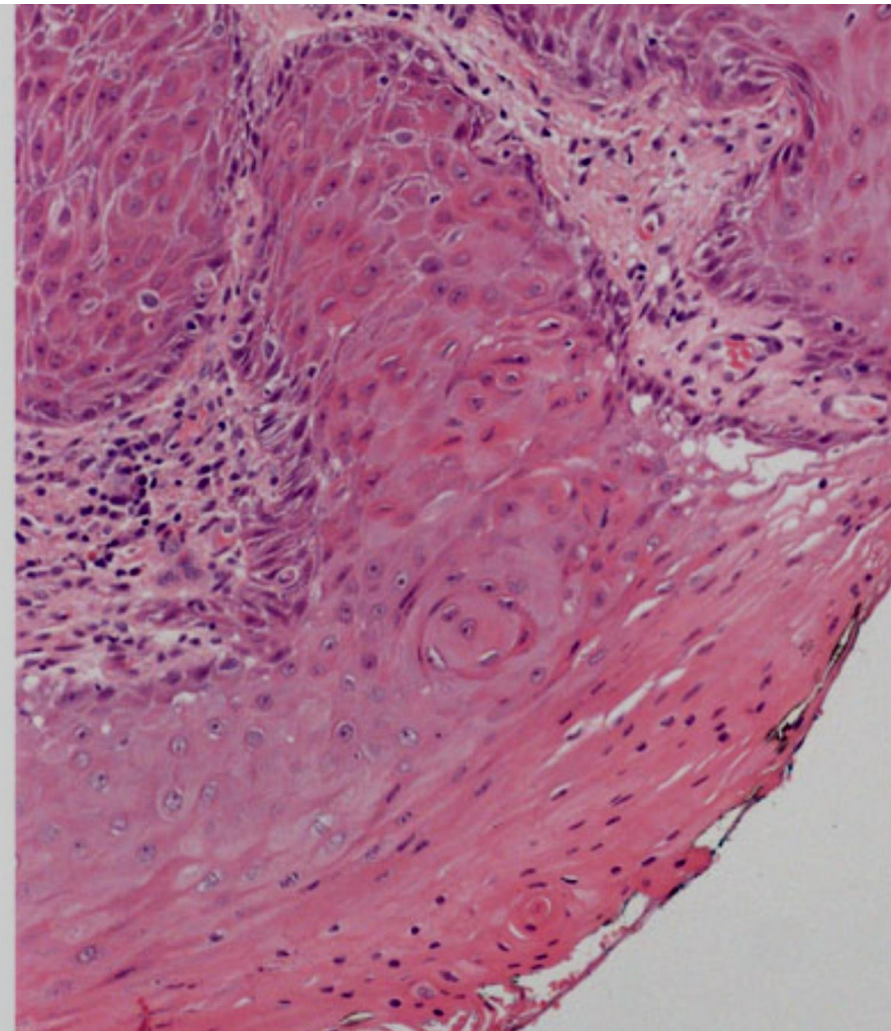
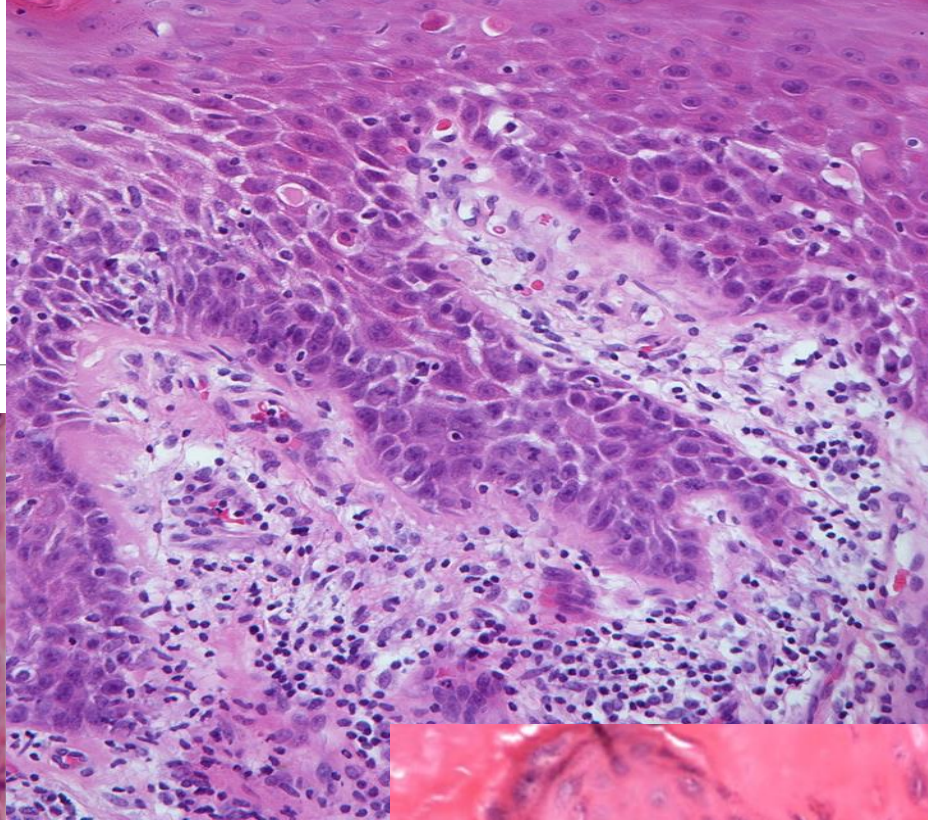


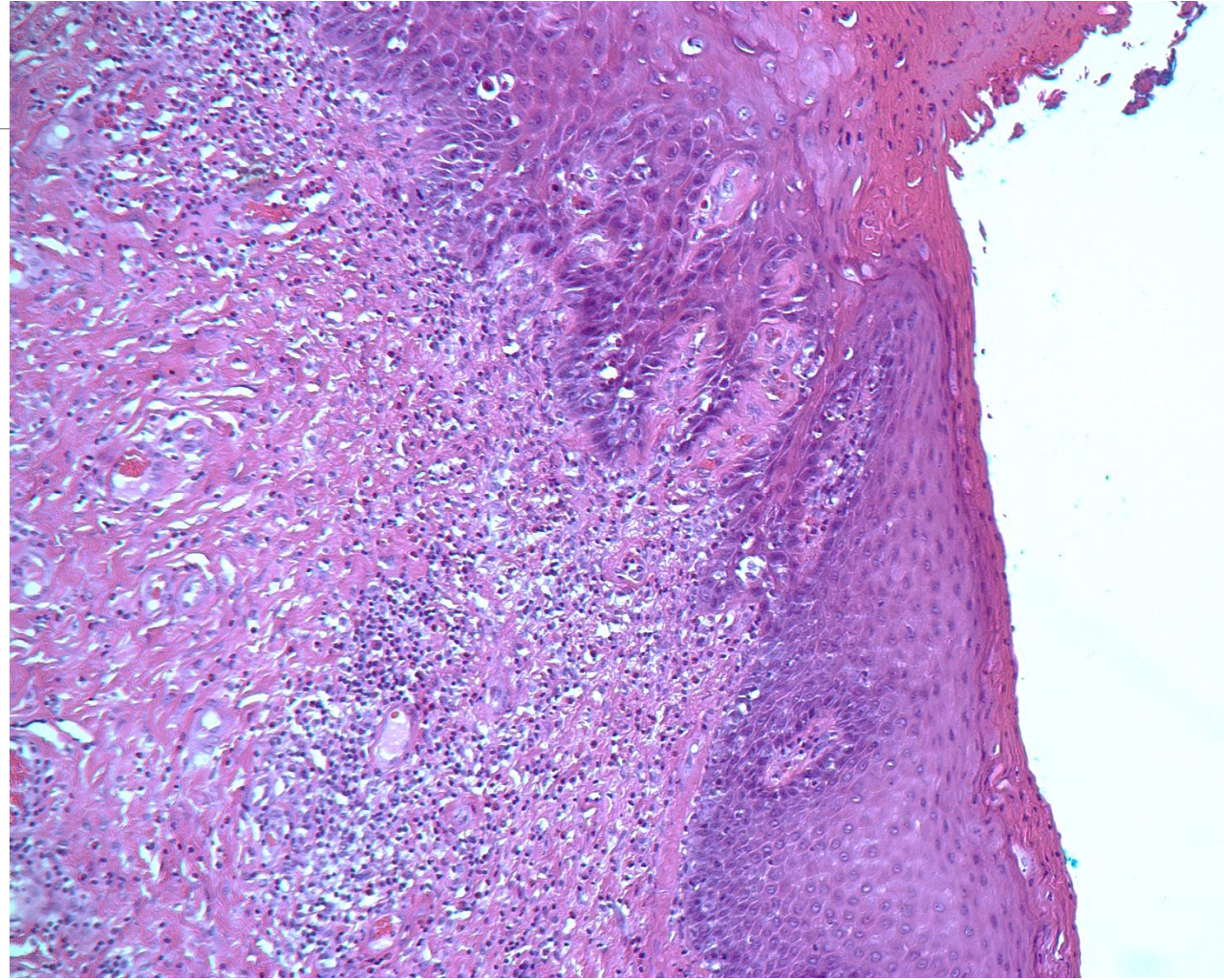
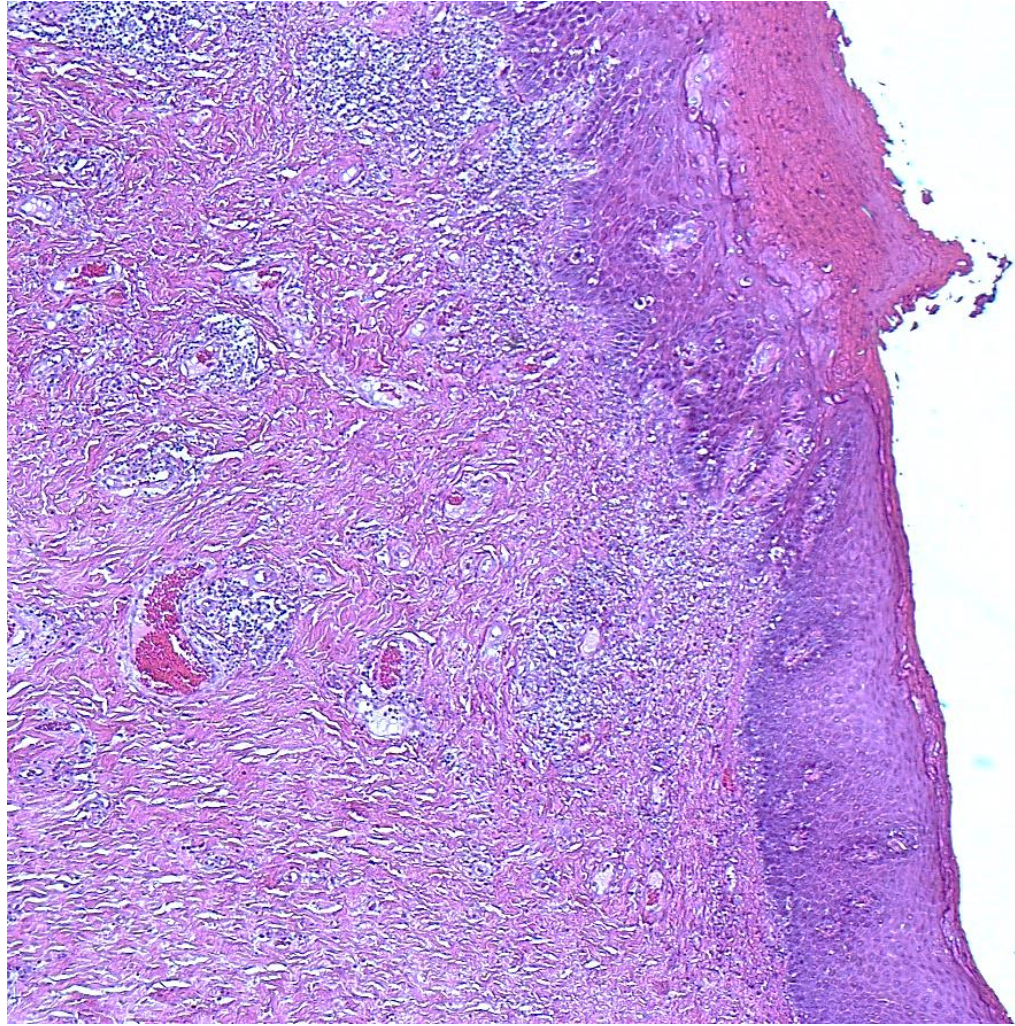
Issues with dVIN diagnosis

Atypia can be subtle

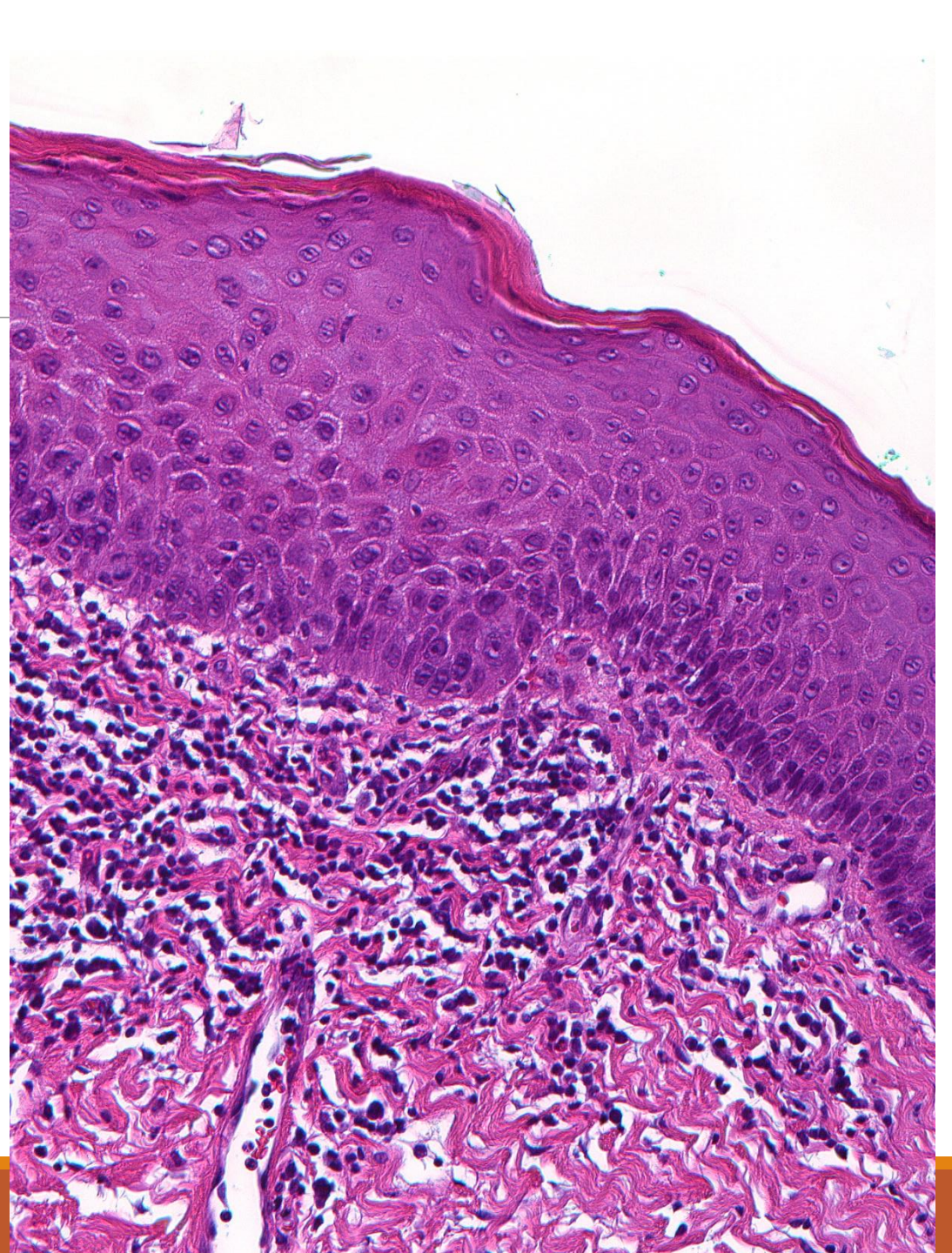
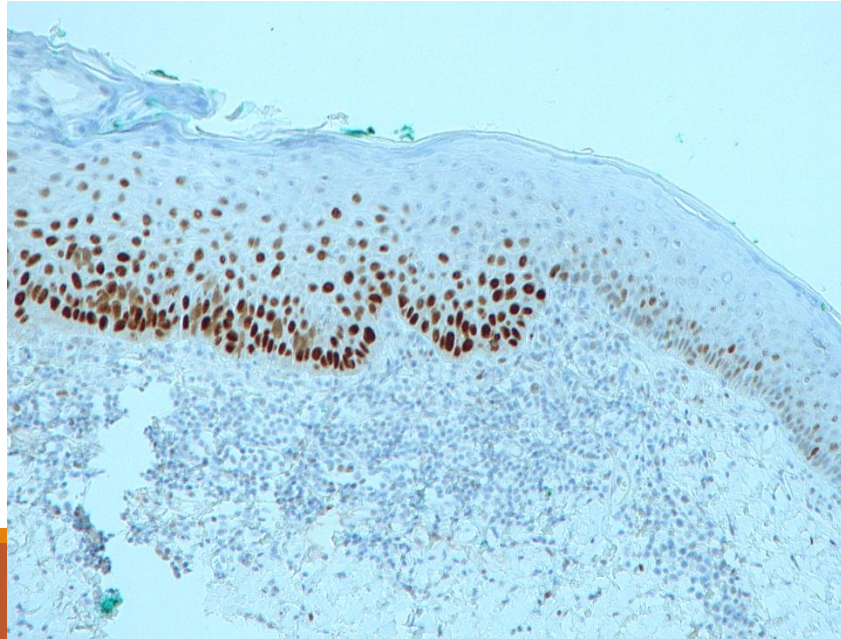
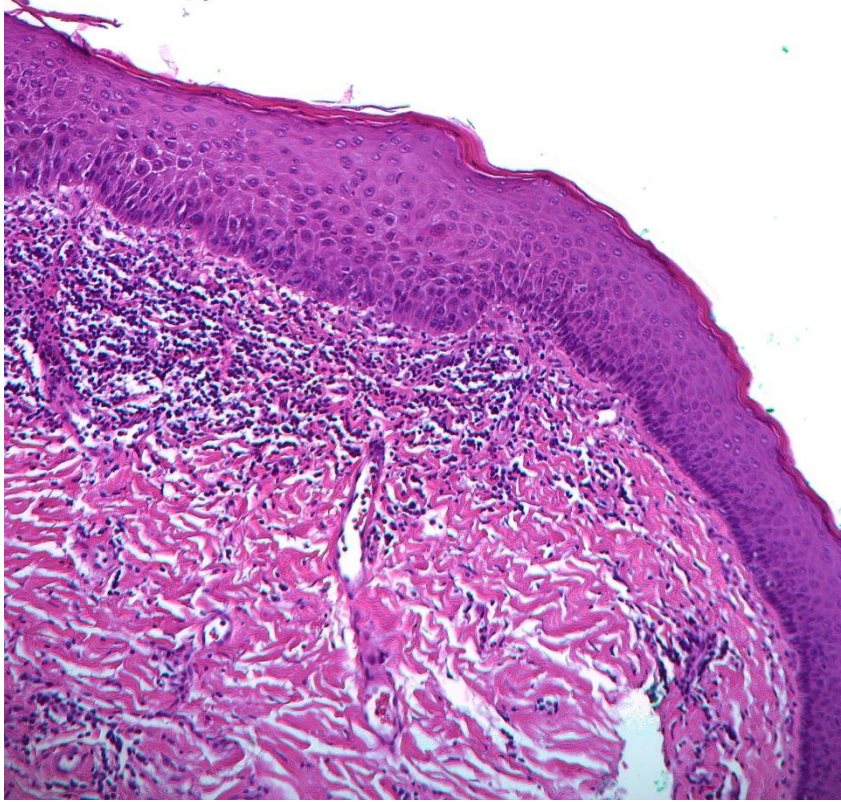
- Only basal/parabasal
- Abnormal mitoses are rare
- Nuclei may be vesicular rather than hyperchromatic

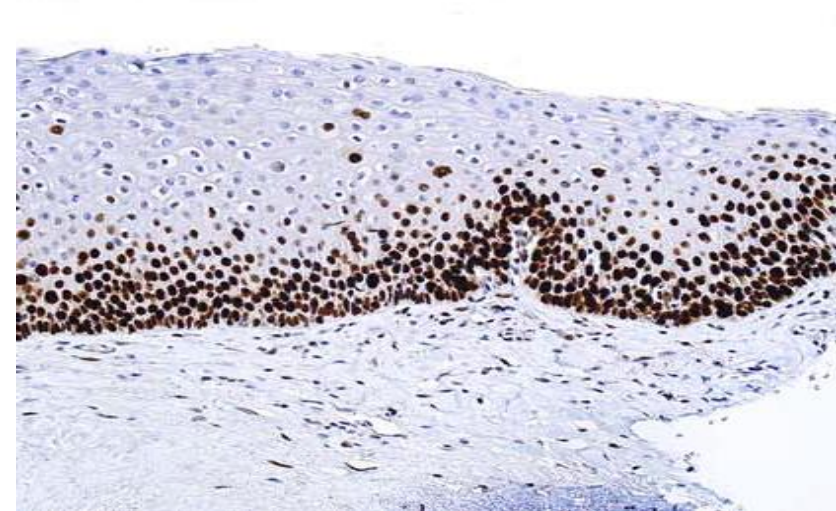
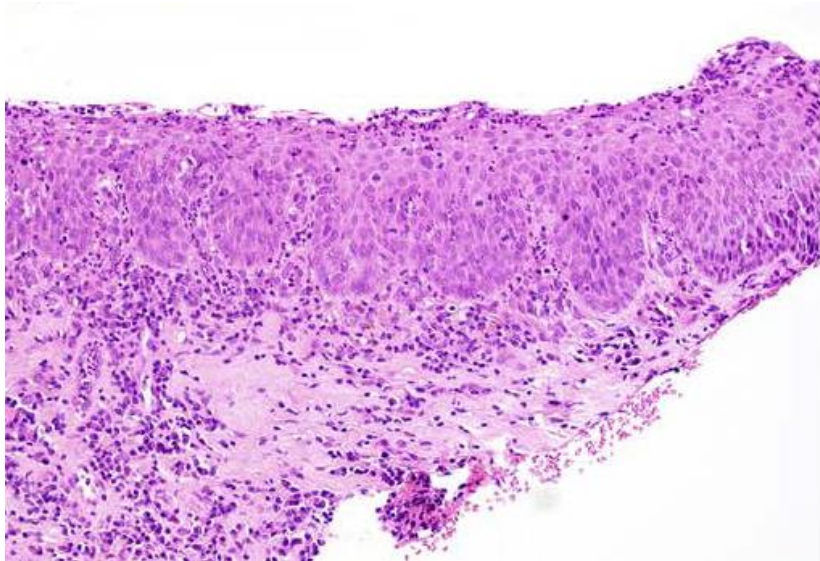
dVIN

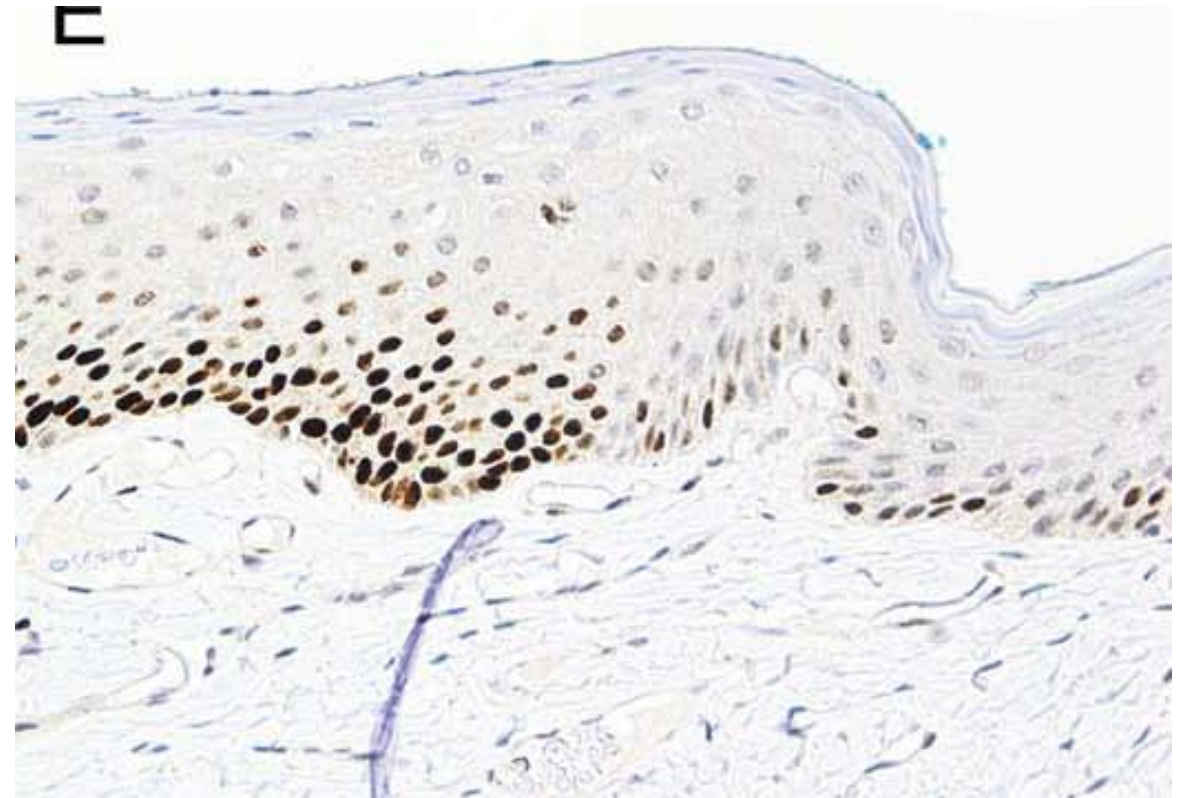
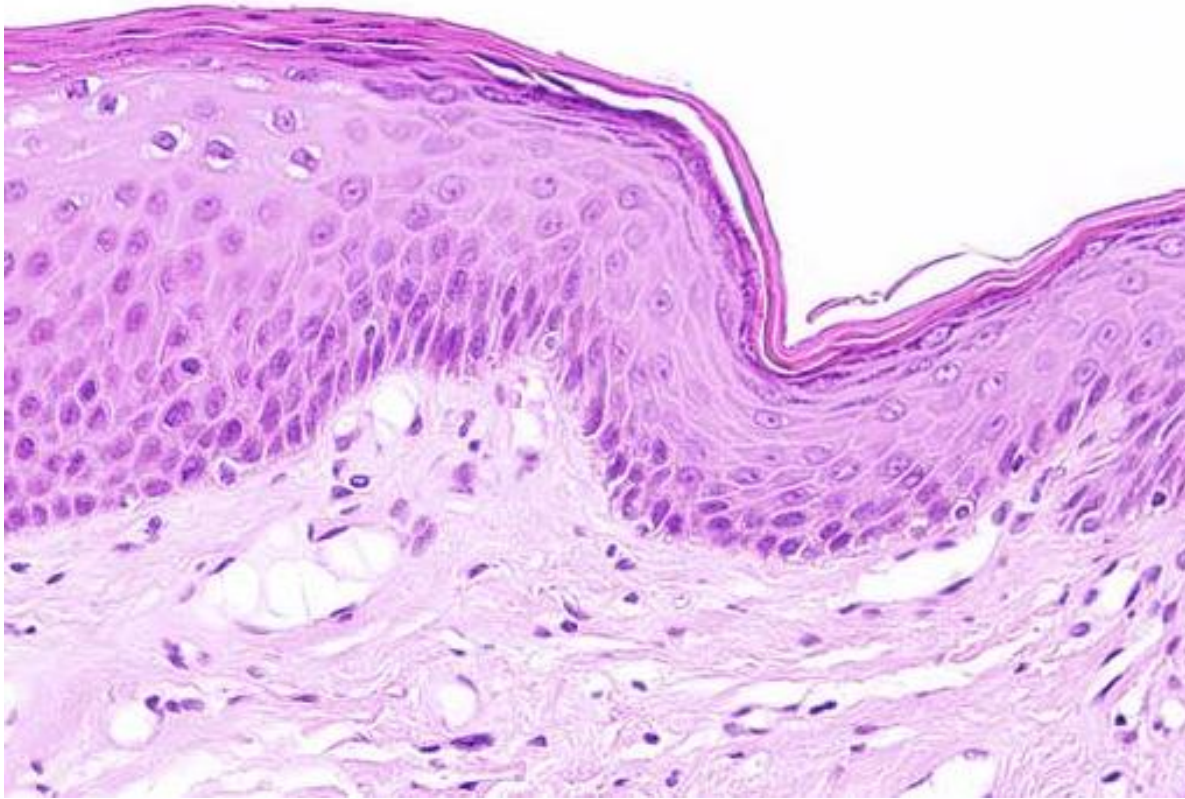




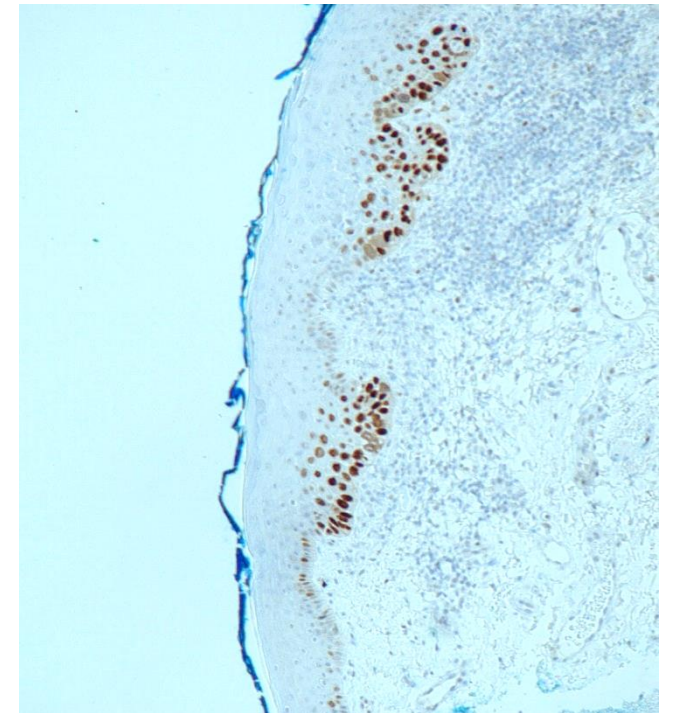
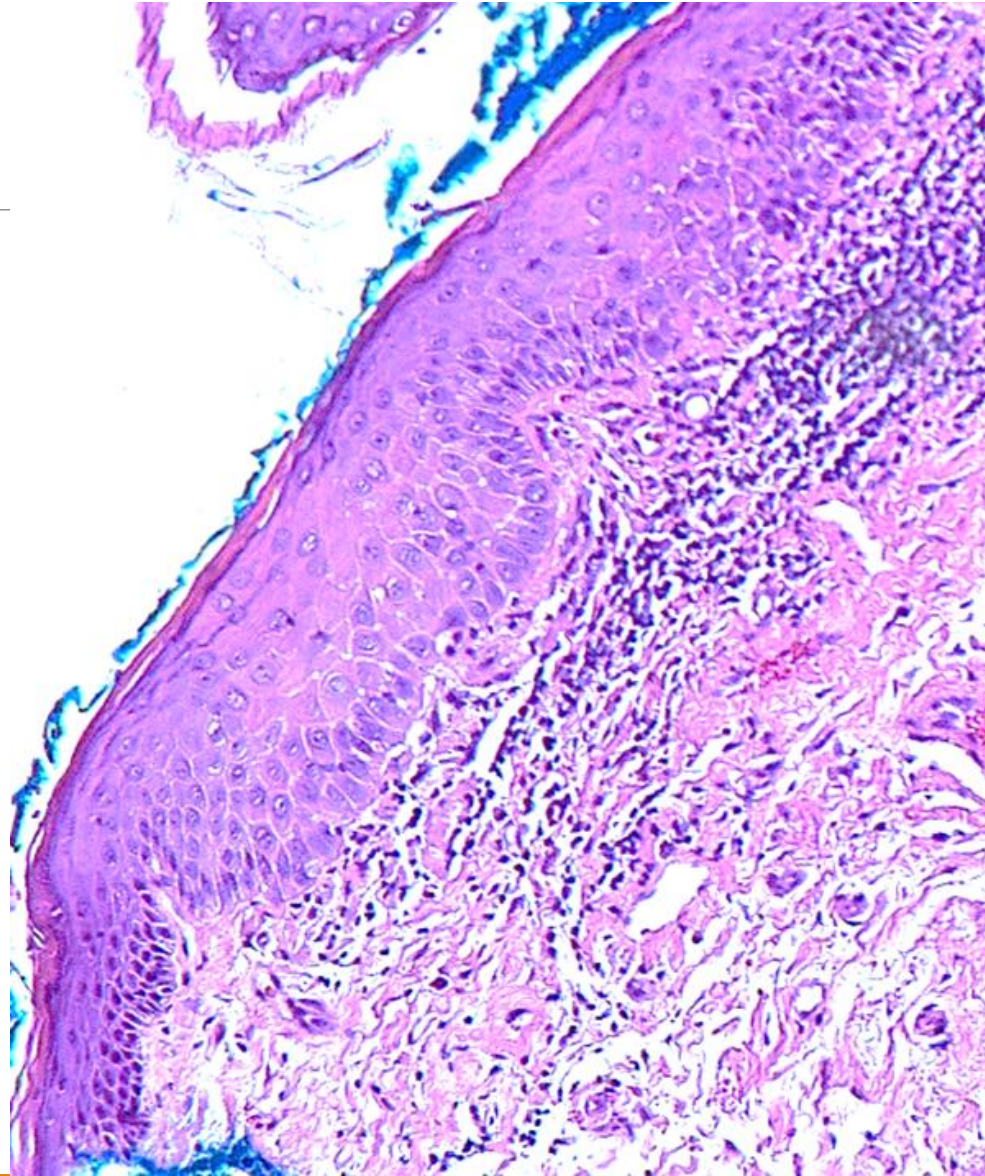
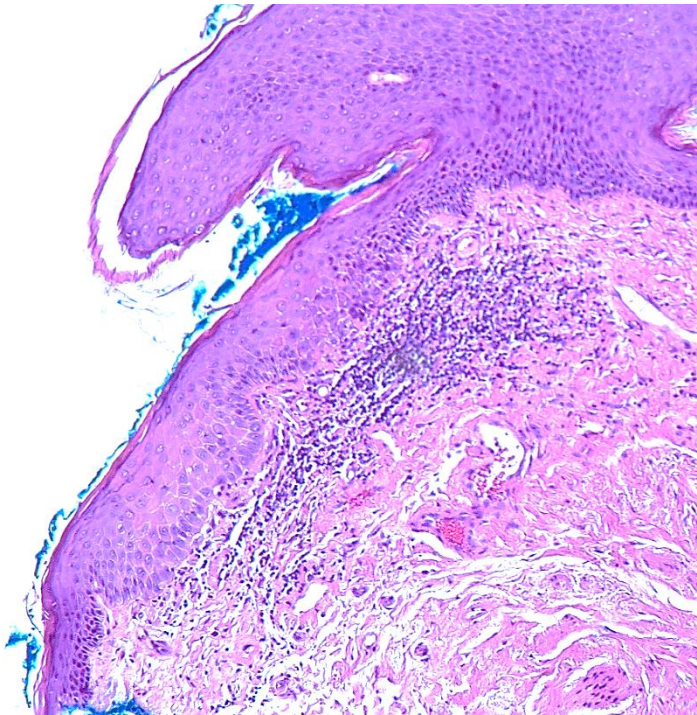
DVIN



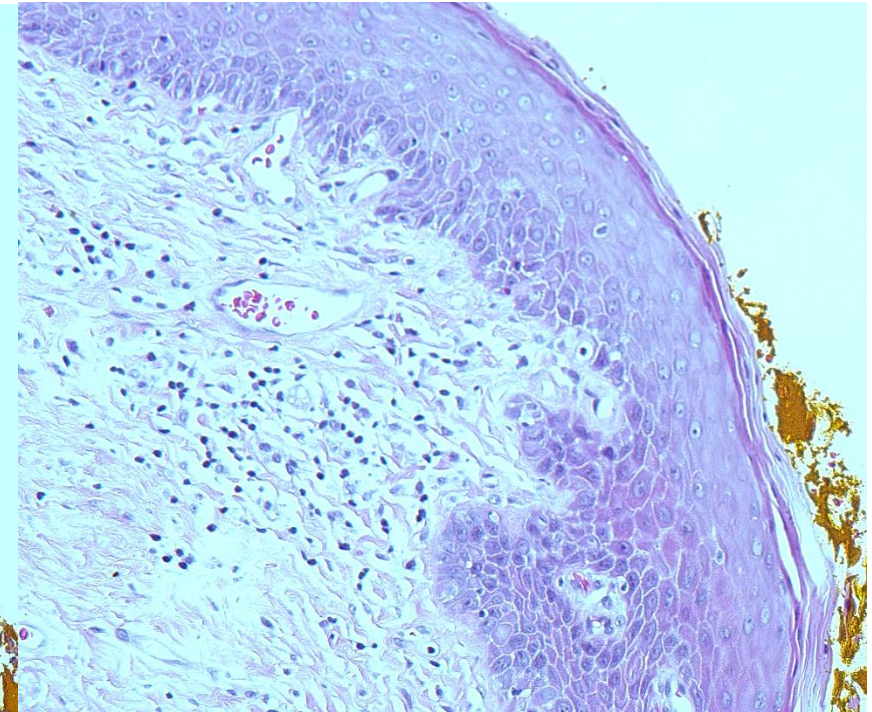
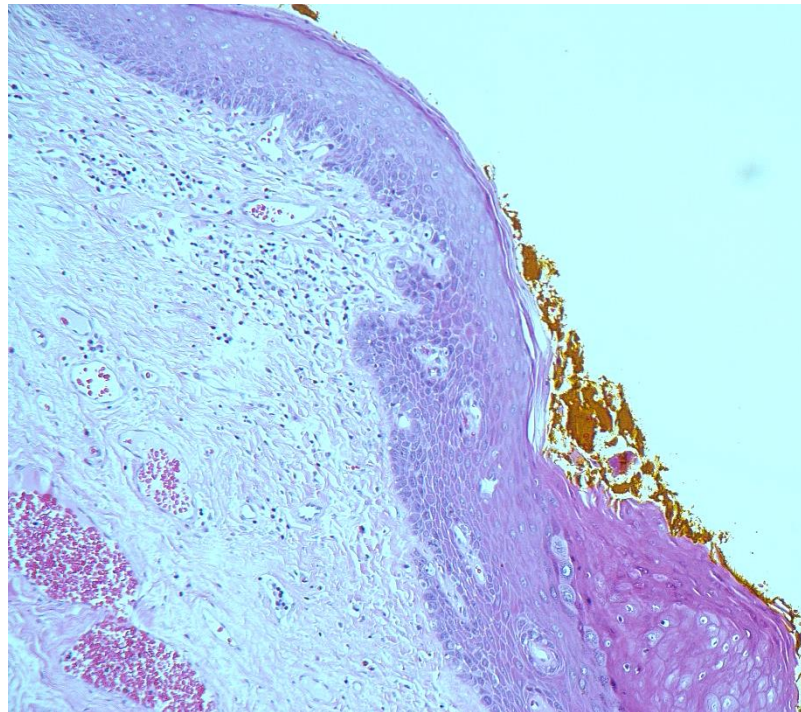
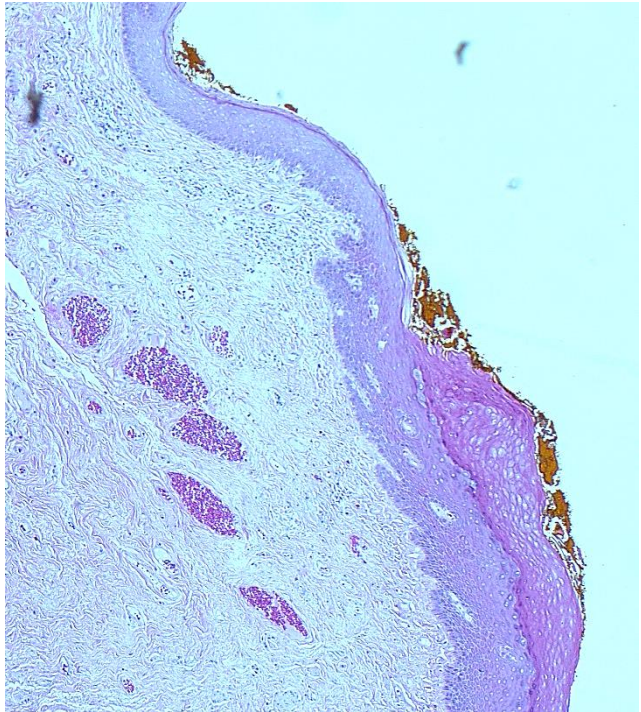




dVIN

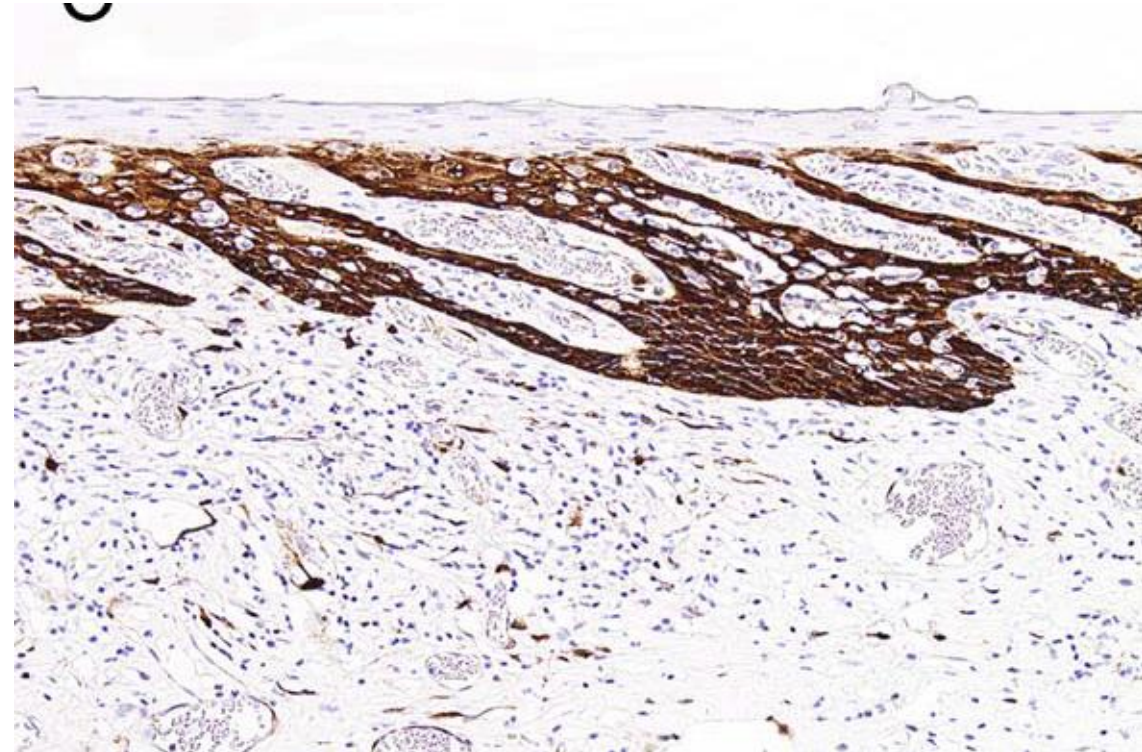
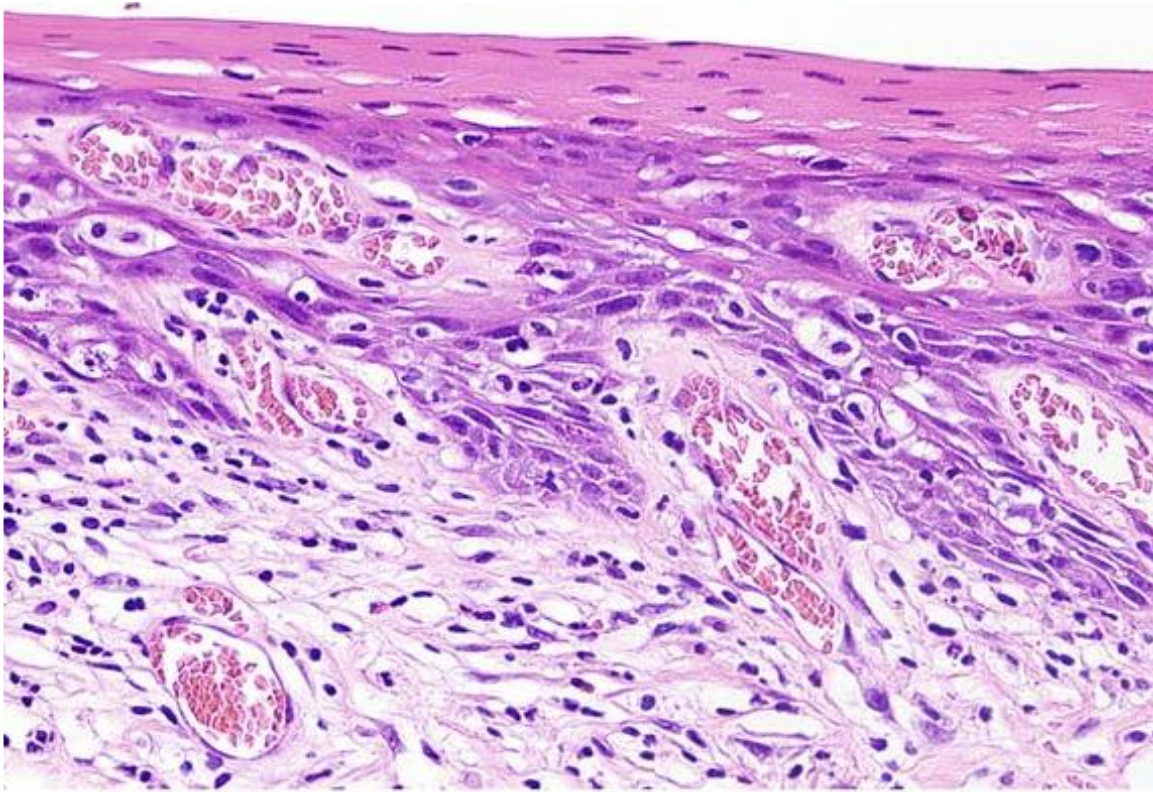


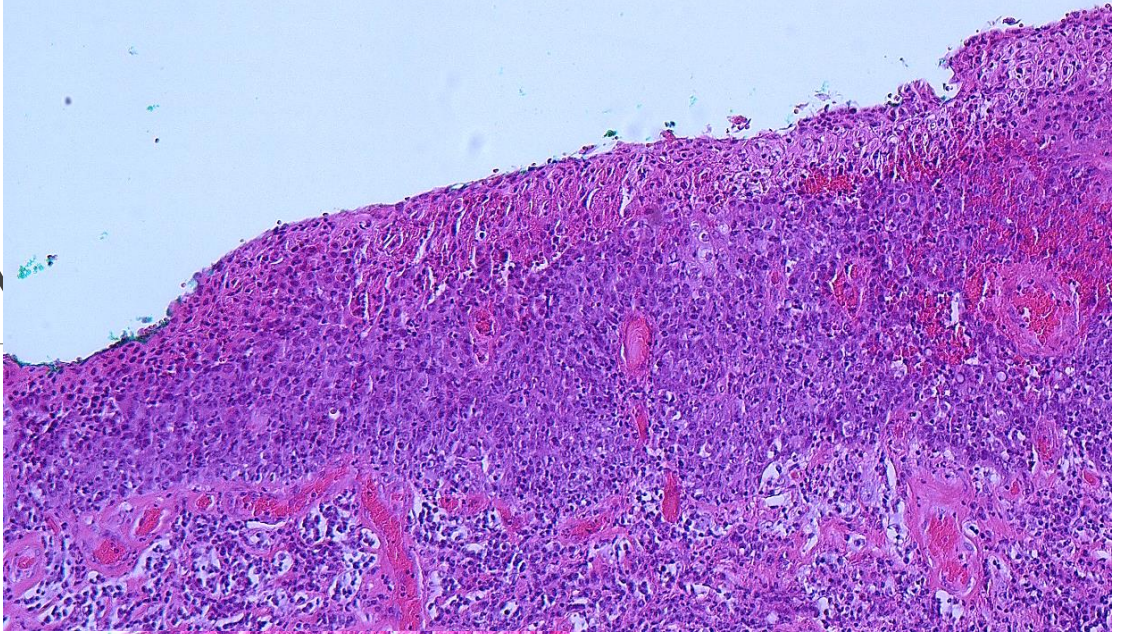
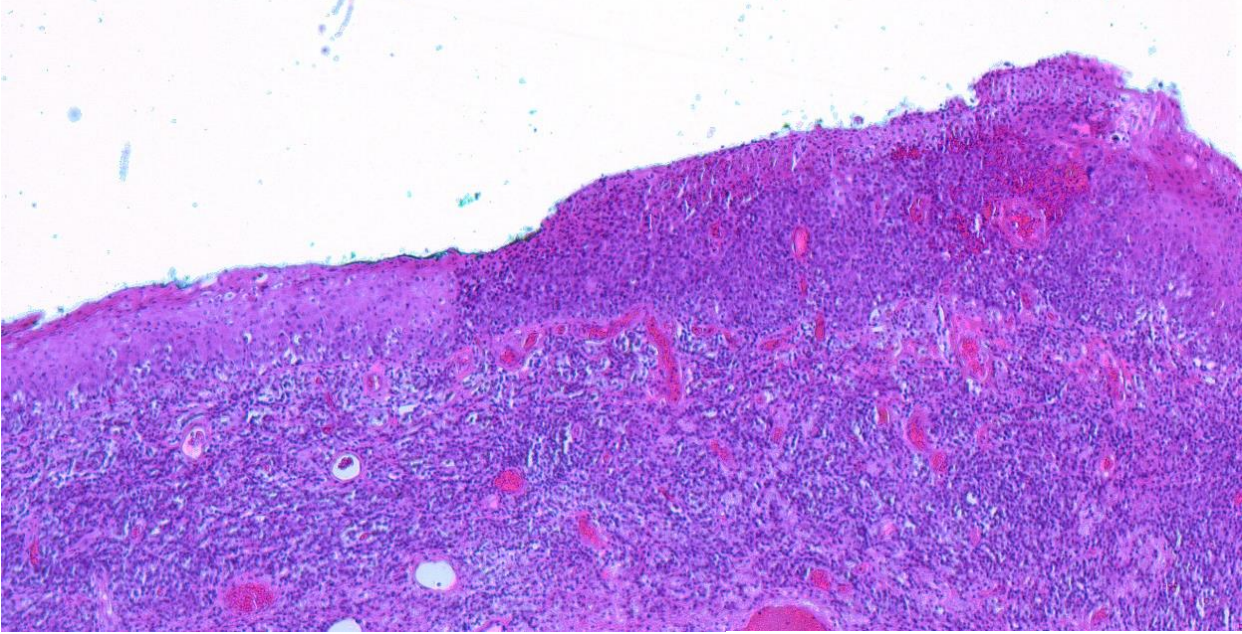
dVIN



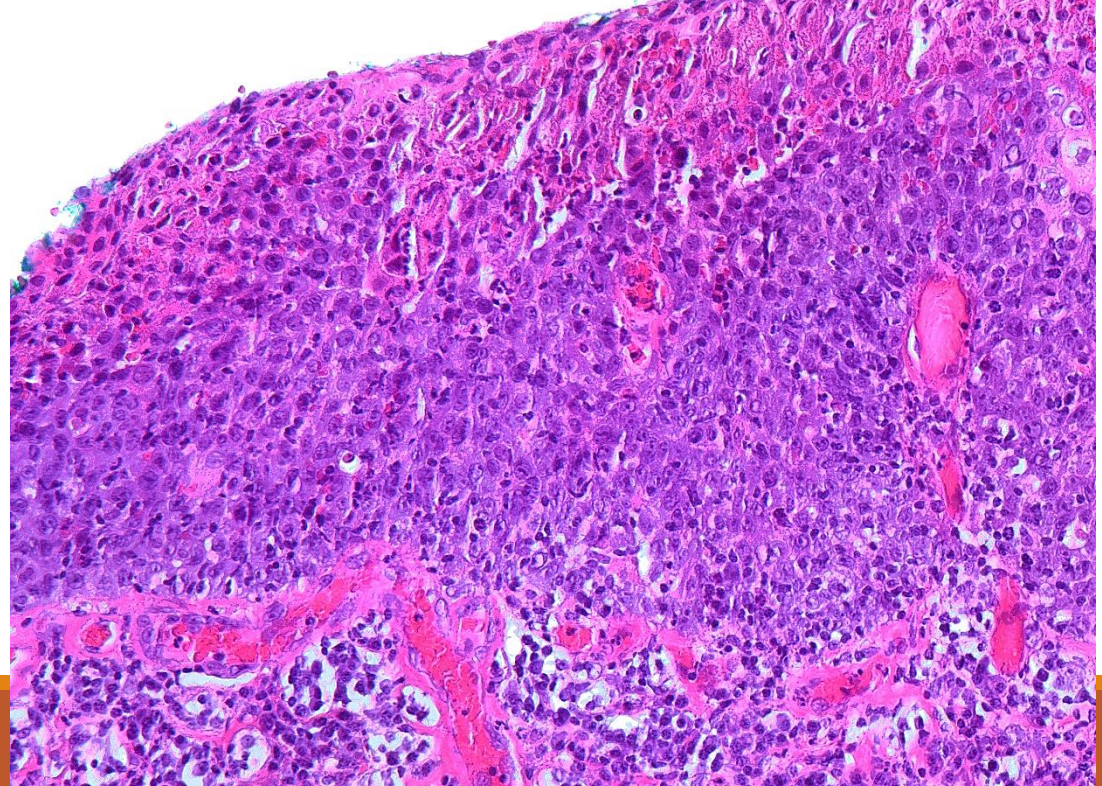
uVIN mimicking dVIN

Journal of Lower Genital Tract Disease • Volume 25, Number 1, January 2021



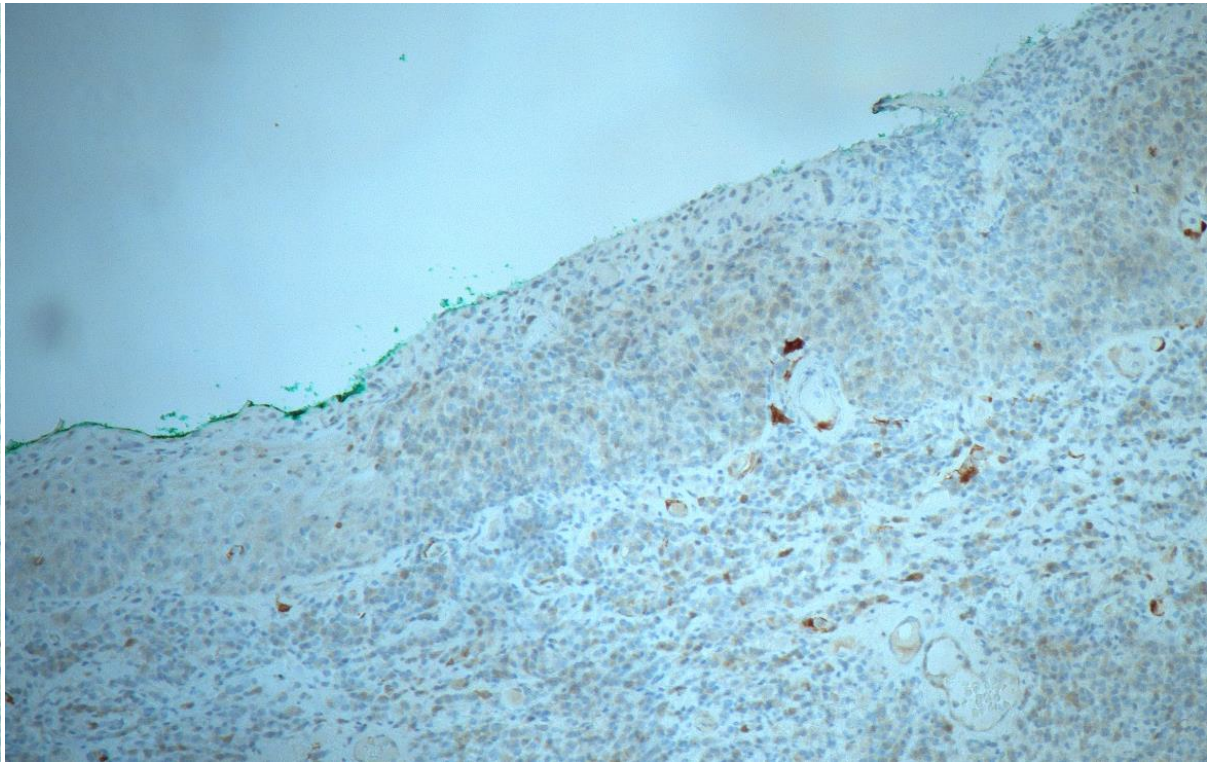
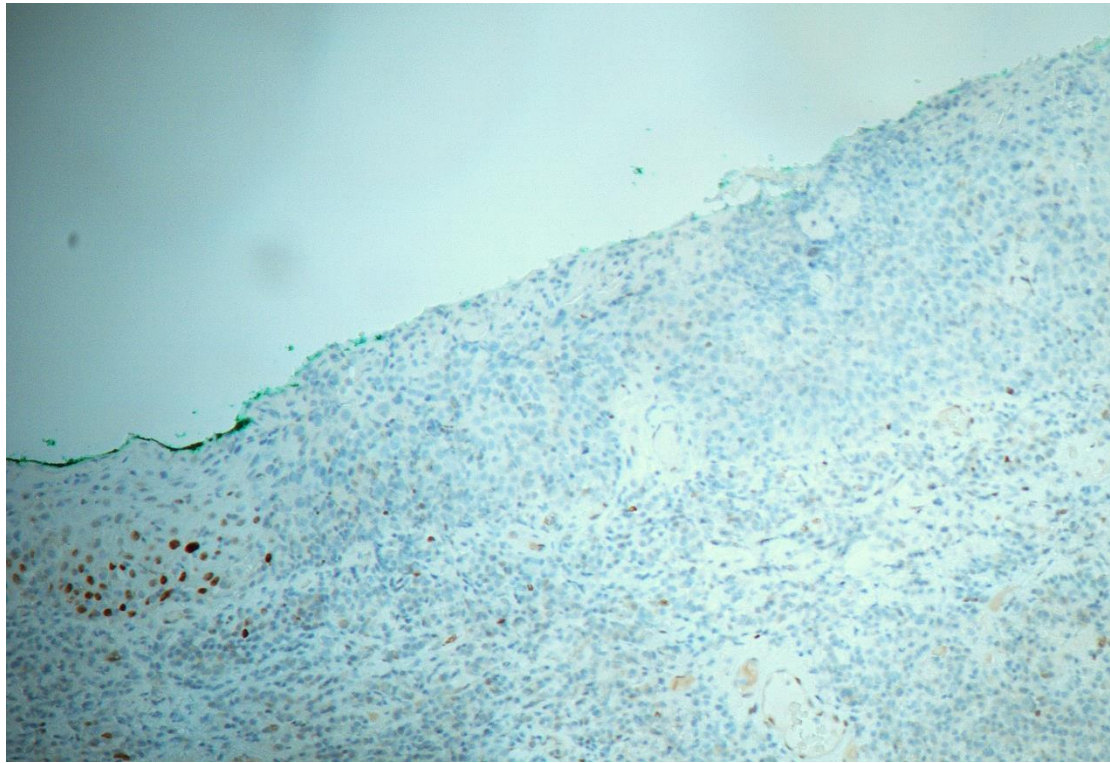


dVIN mimicking uVIN

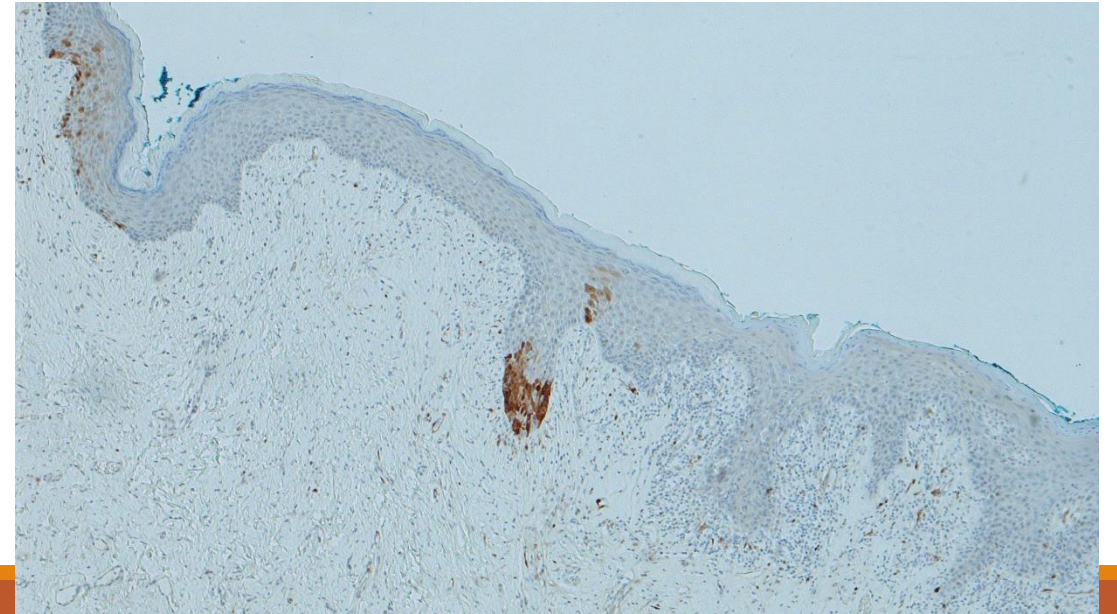
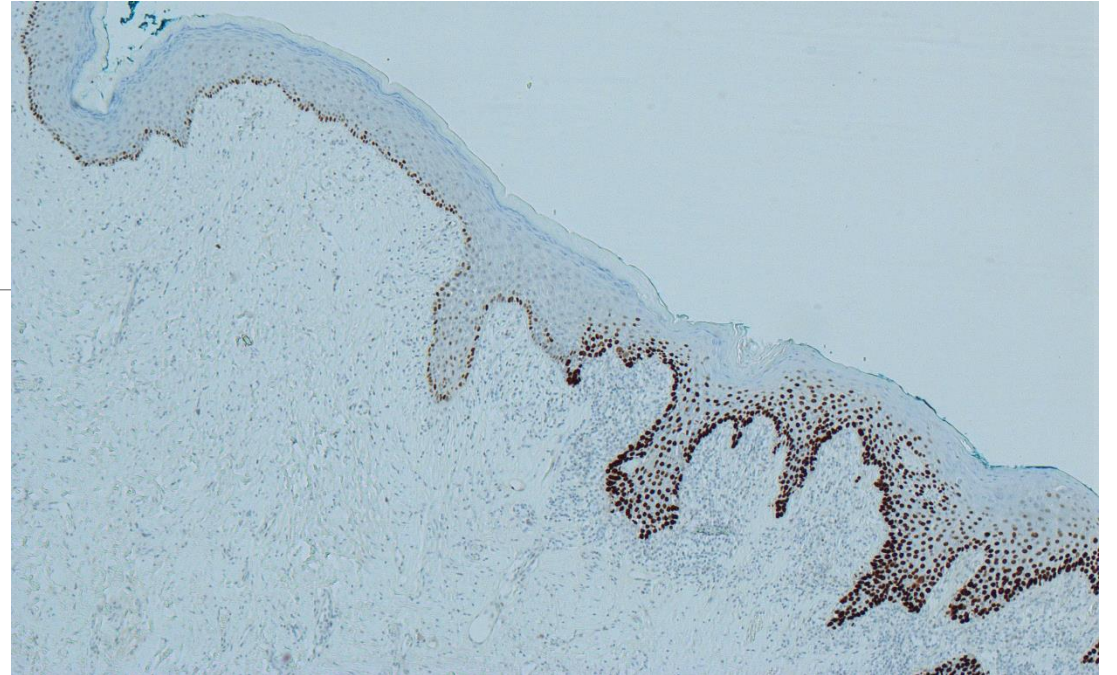
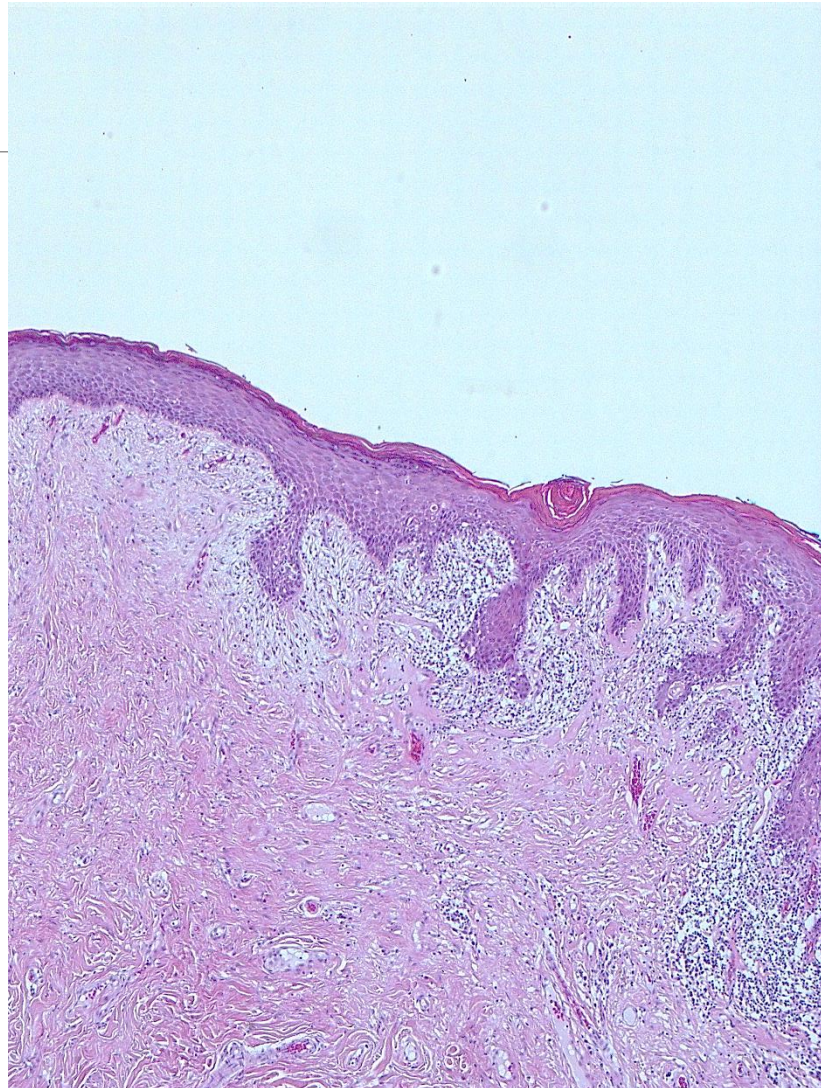


p53

p16



dVIN (subtle)



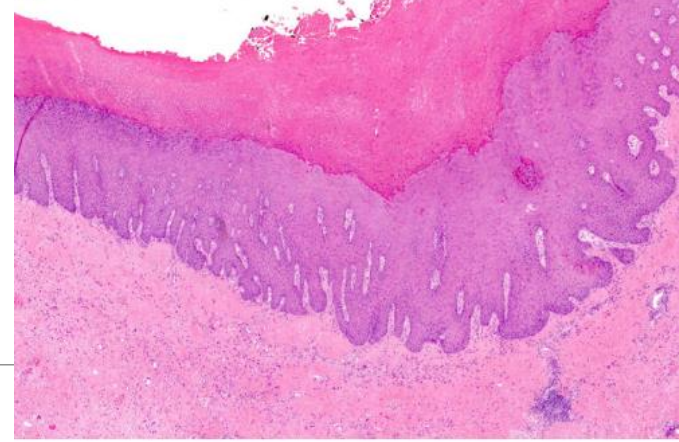
Take home messages

- uVIN shows more nuclear pleomorphism, large nuclei and brisk mitoses. (more blue)
- uVIN atypia extends along appendages
- Always do both p16 and p53
- P16 + and p53 BS or wt = HPV
- High index of suspicion for dVIN (always check adjacent epithelium)
- P53 m with p16-/+ = dVIN
- Be aware of null-like p53 pattern in HPV cases
- P16- and p53 wt = VaVIN

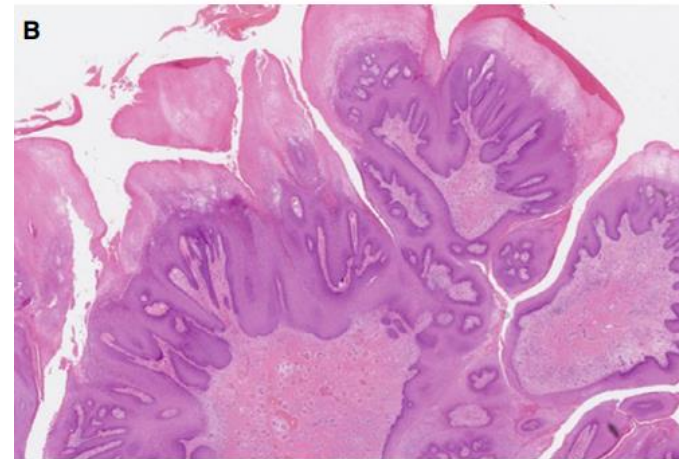
HPV independent p53 wt VIN

- Marked acanthosis
- Verruciform growth
- Altered maturation
- Association with verrucous Ca and conventional SCC
 - VAAD
 - DEVIL
 - vLSC

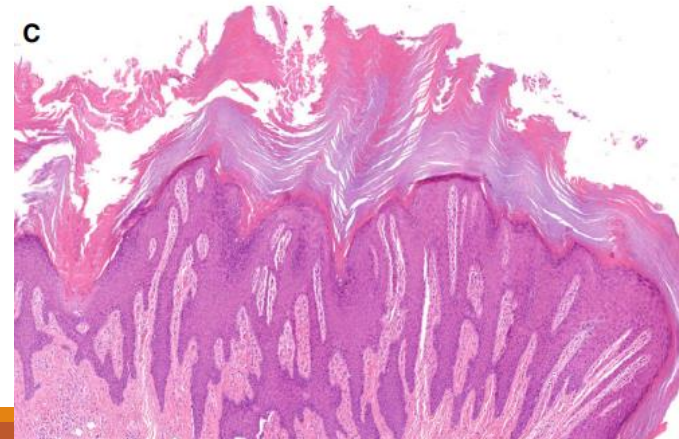
A. VAAD



B. DEVIL



C. vLSC



DEVIL, VAAD and vLSC constitute a spectrum of HPV-independent, p53-independent intra-epithelial neoplasia of the vulva

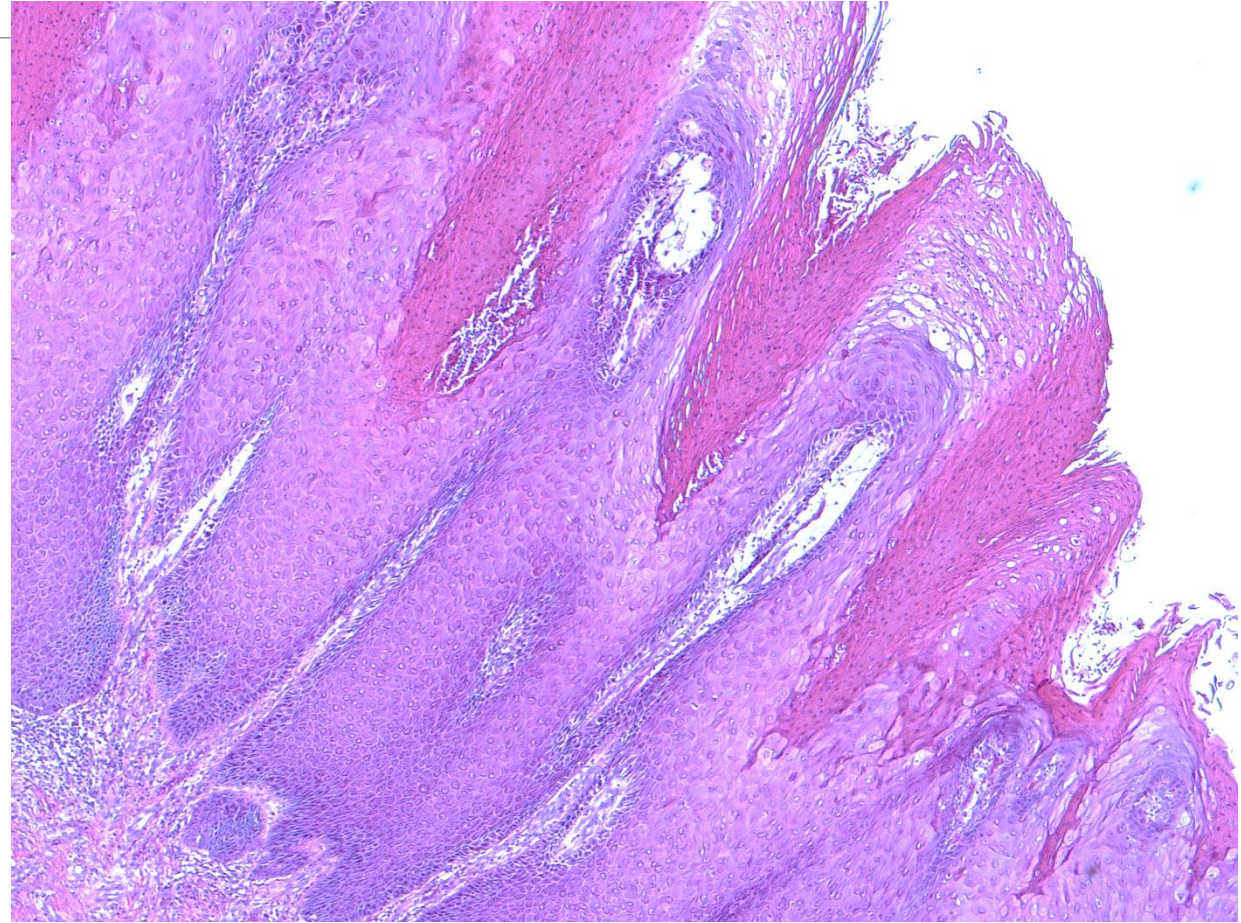
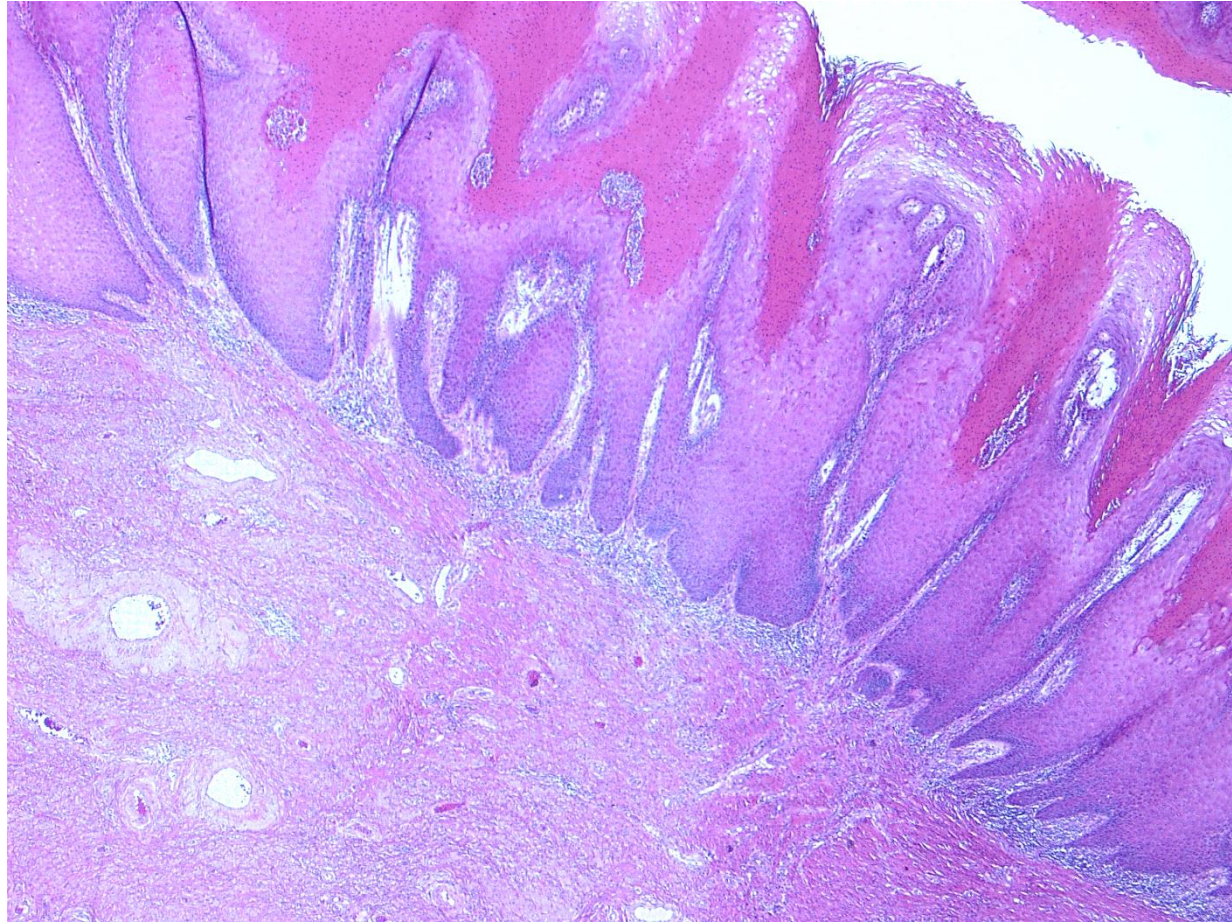
- No significant morphological differences
- vLSC in vicinity of VAAD/DEVIL
- Frequent recurrences
- Similar rates of subsequent SCC

Vulvar aberrant maturation (VAM) proposed (ISSVD)

New term proposed to go with current WHO- HPV_i (p53wt) VaVIN

VaVIN

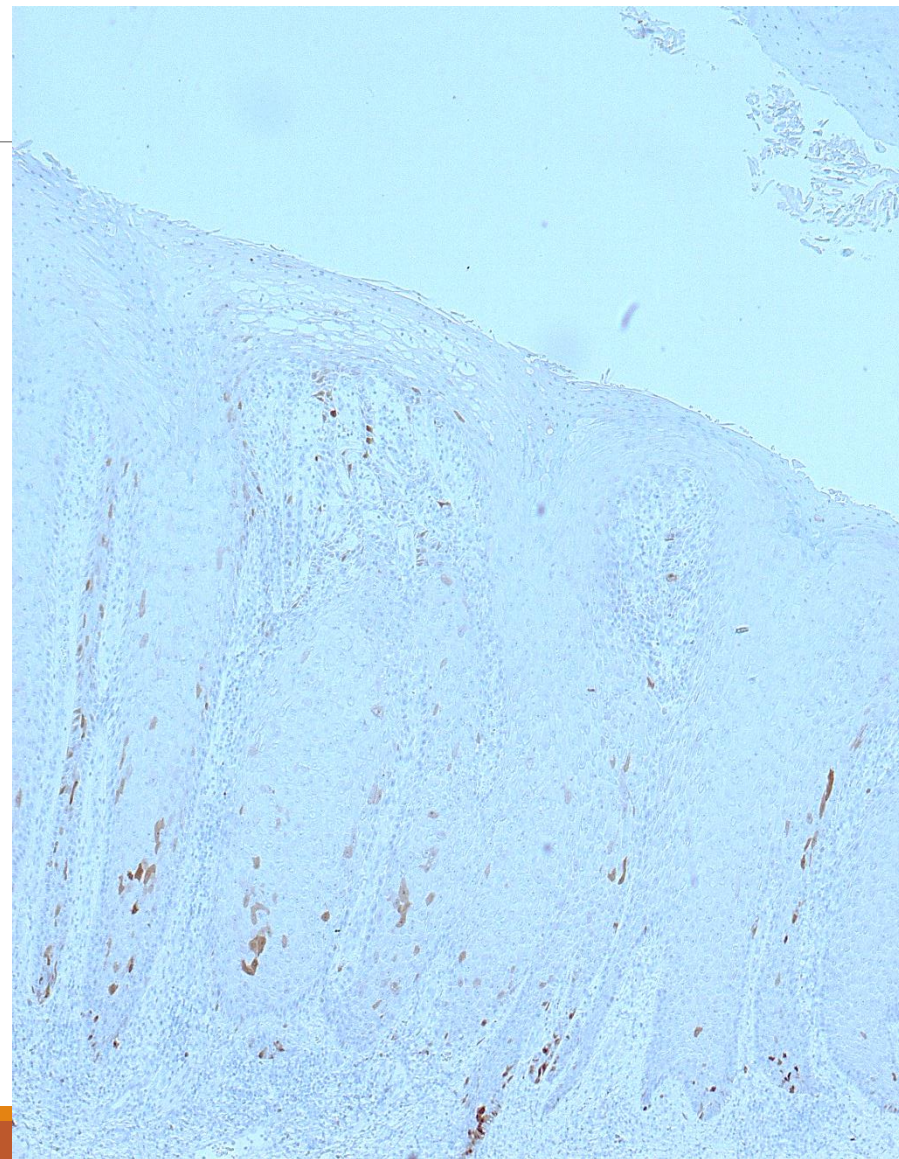
- Acanthotic and verruciform architecture
- Altered maturation
- Absence of cytological atypia
- Low mitotic activity largely basal
- Negative/patchy p16
- Wild type p53



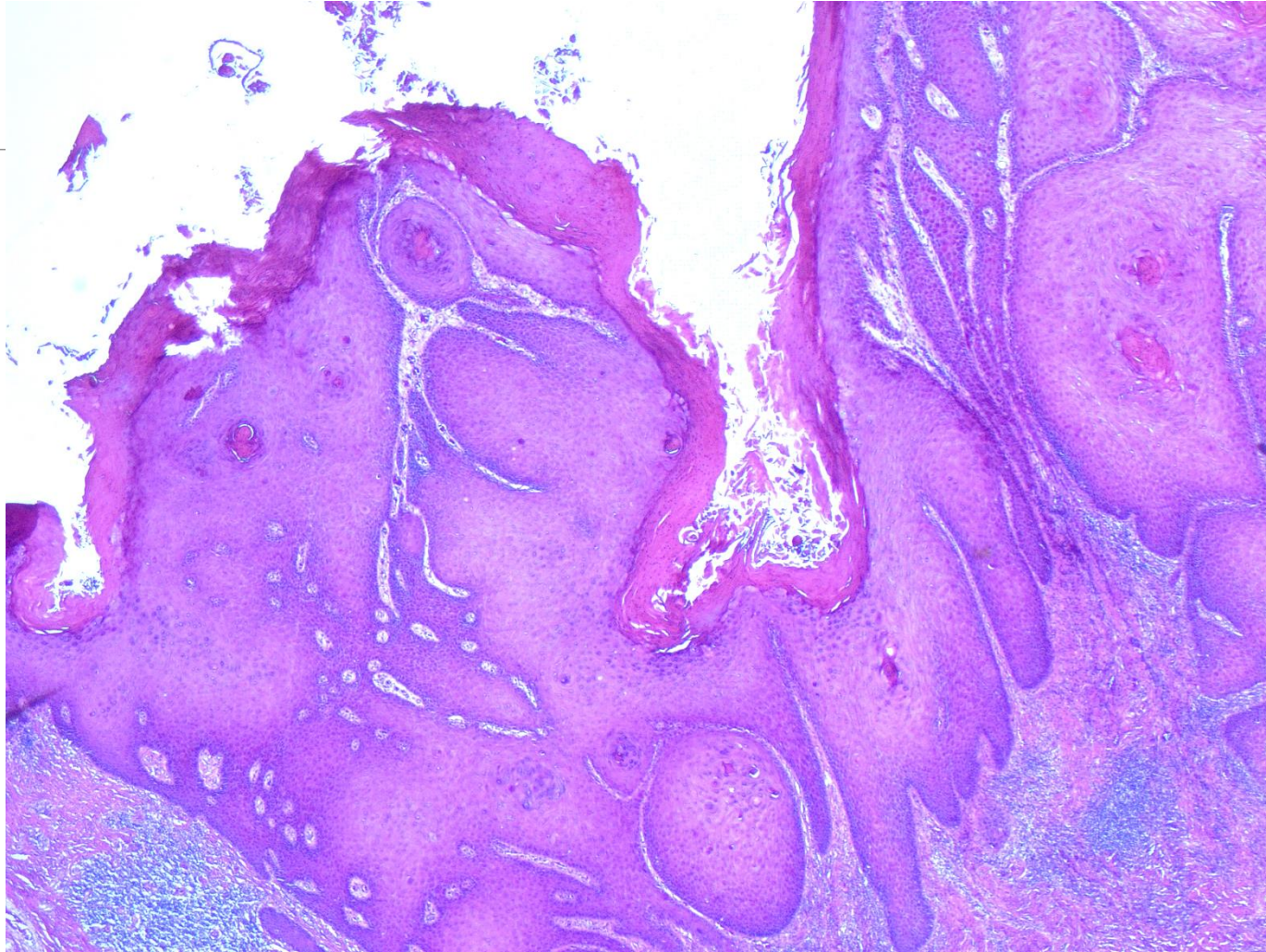
p53



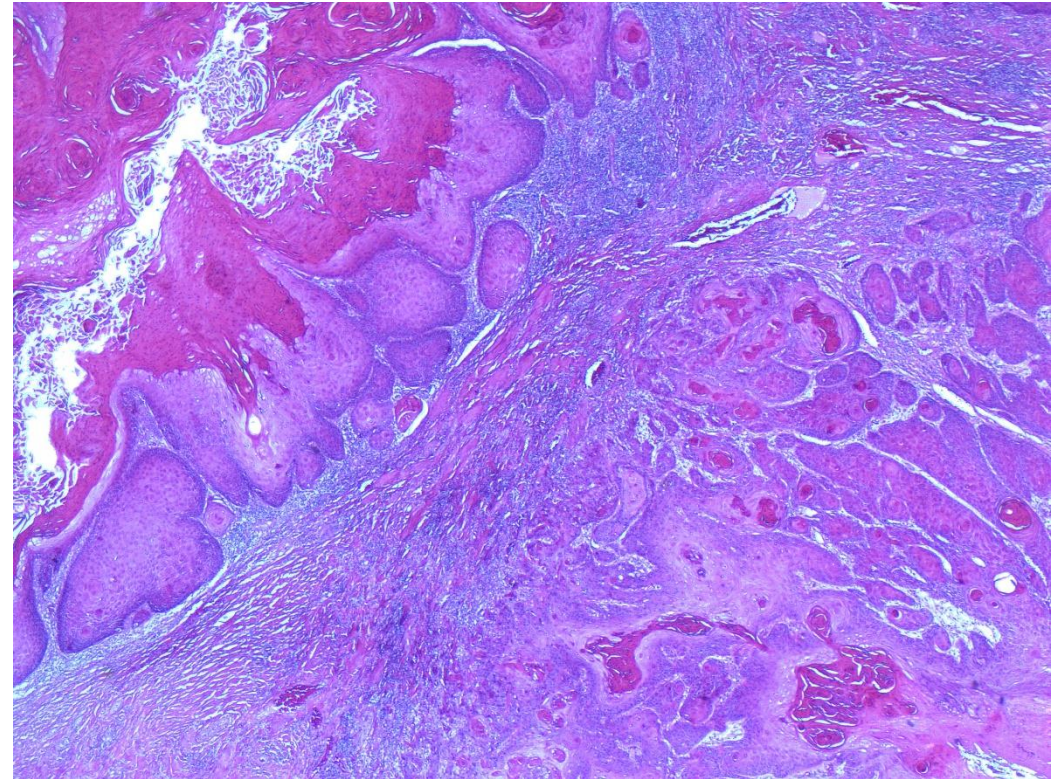
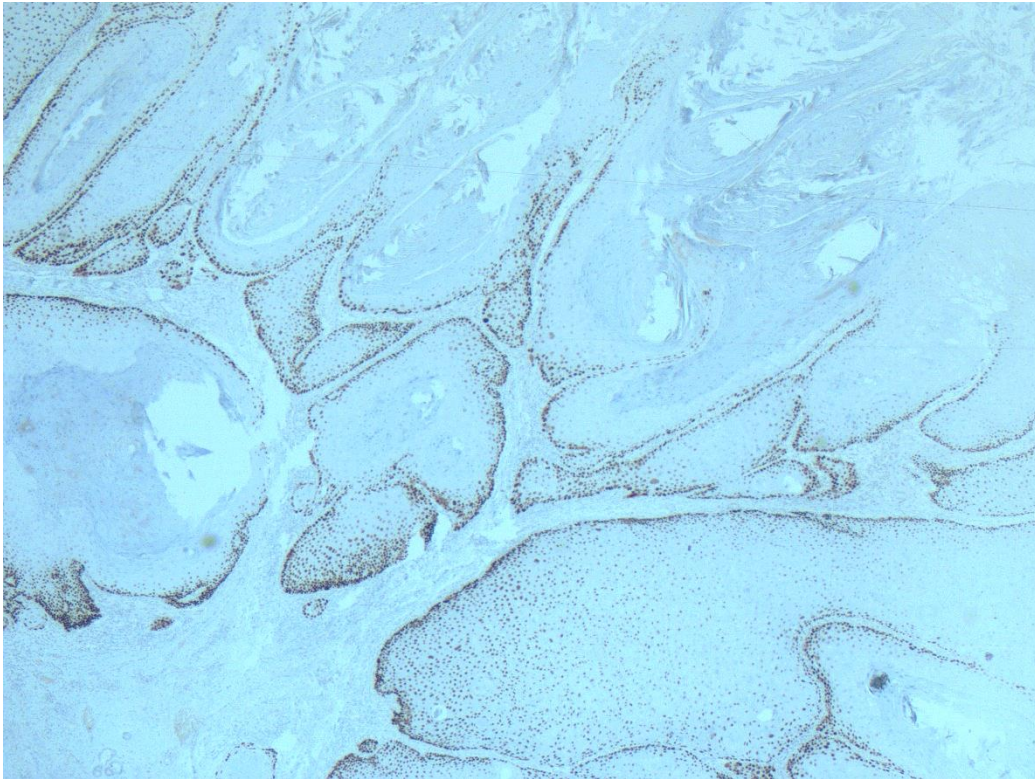
p16



Is this VaVIN?

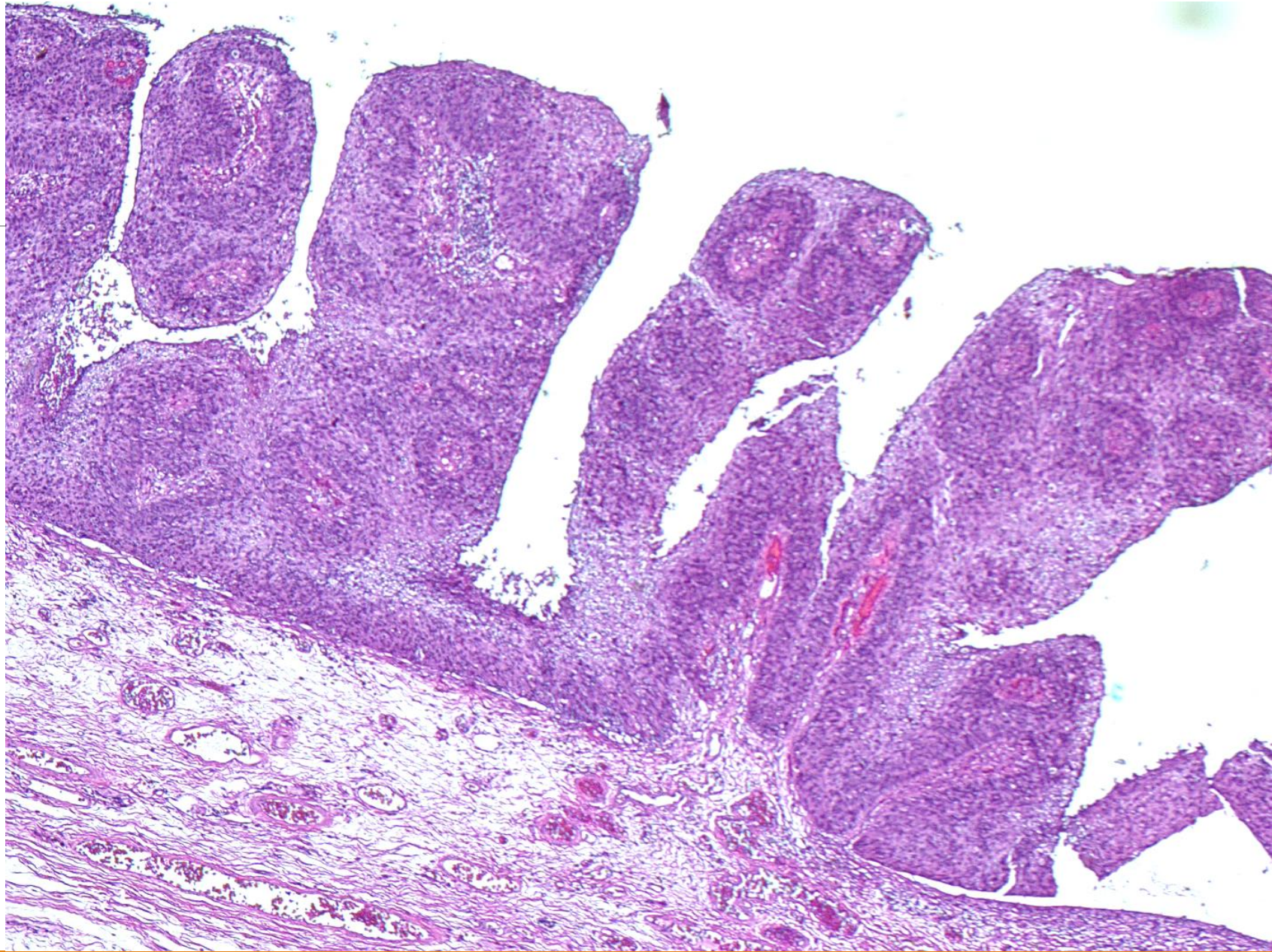


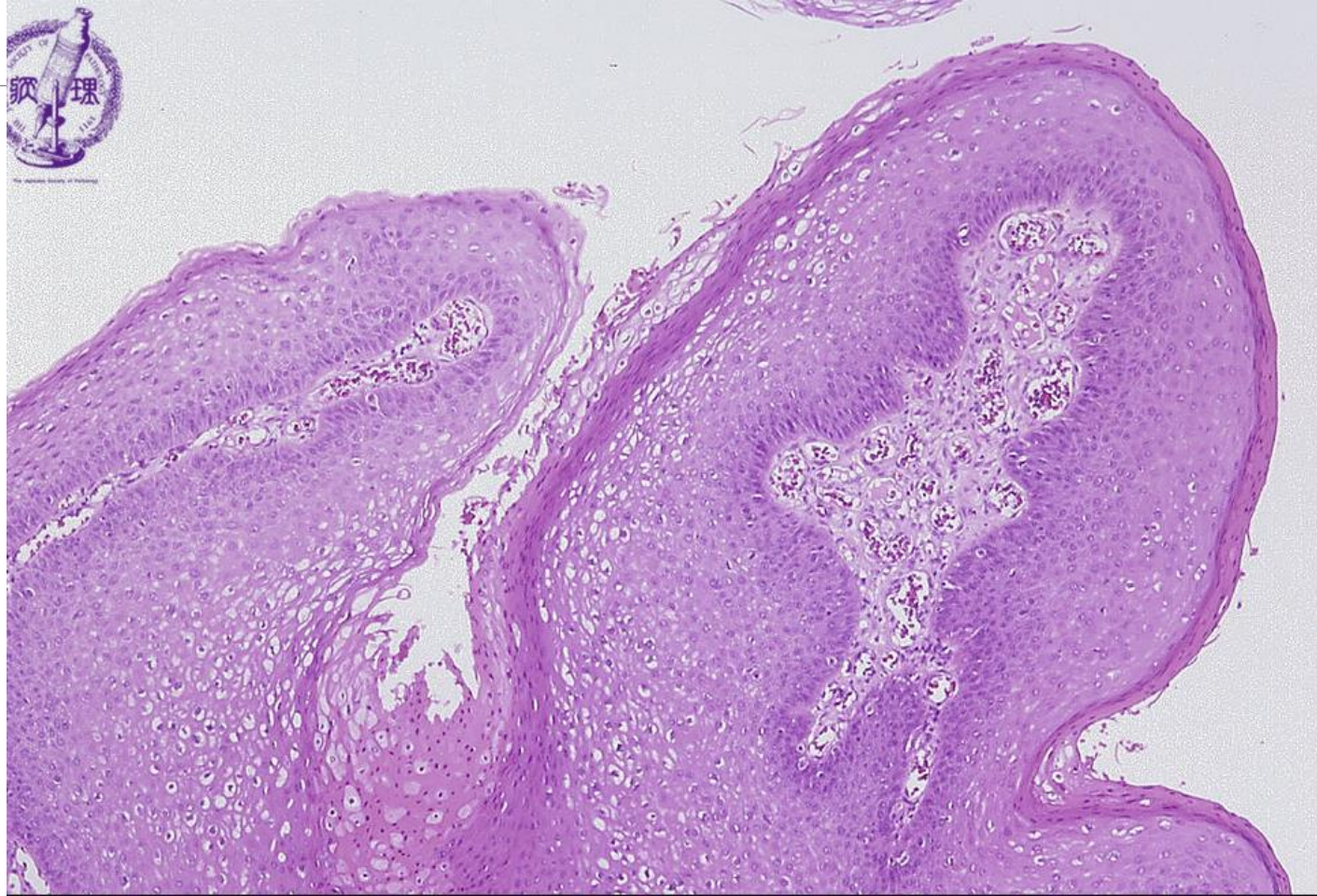
HPV independent p53m vSCC



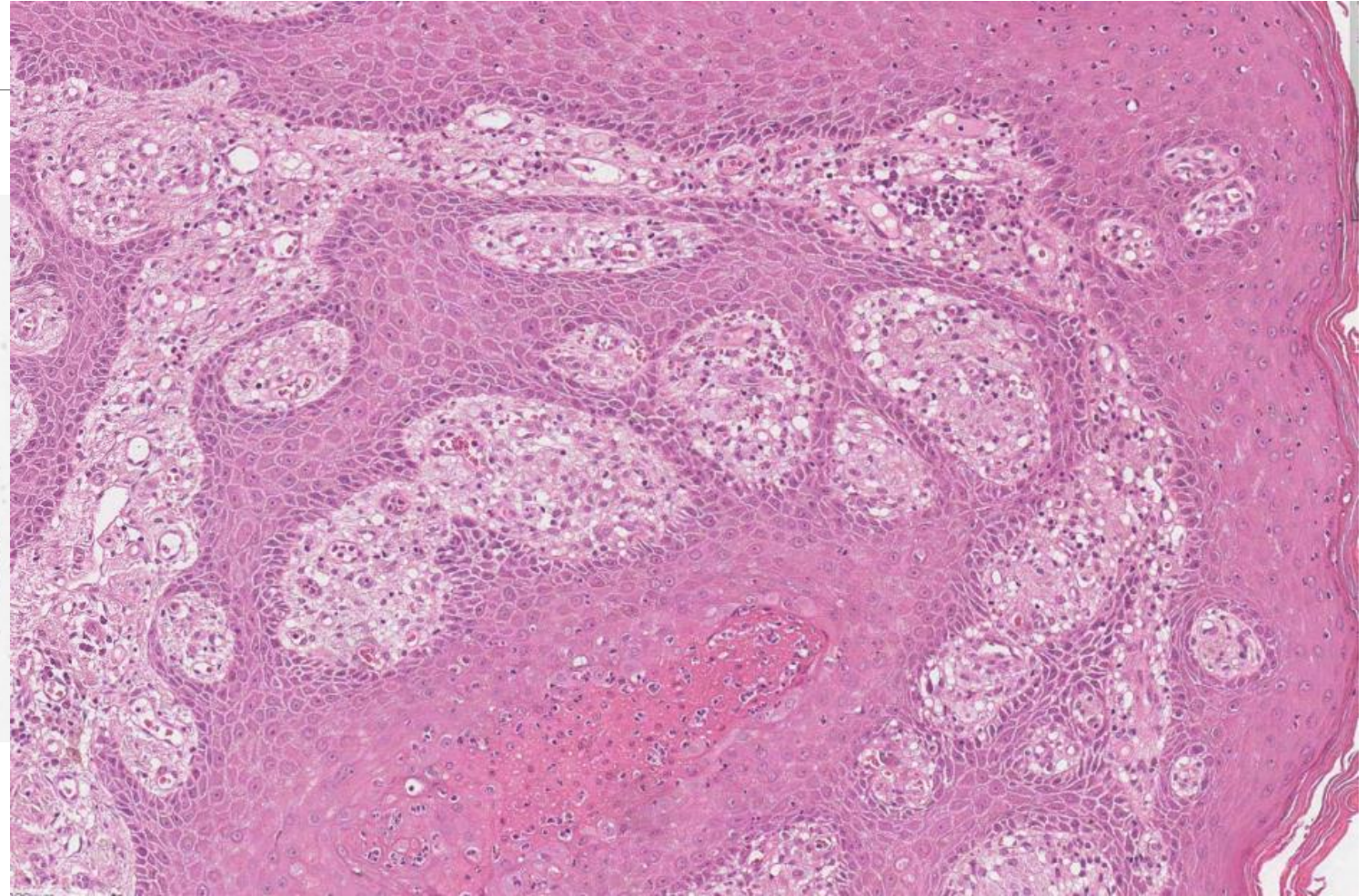
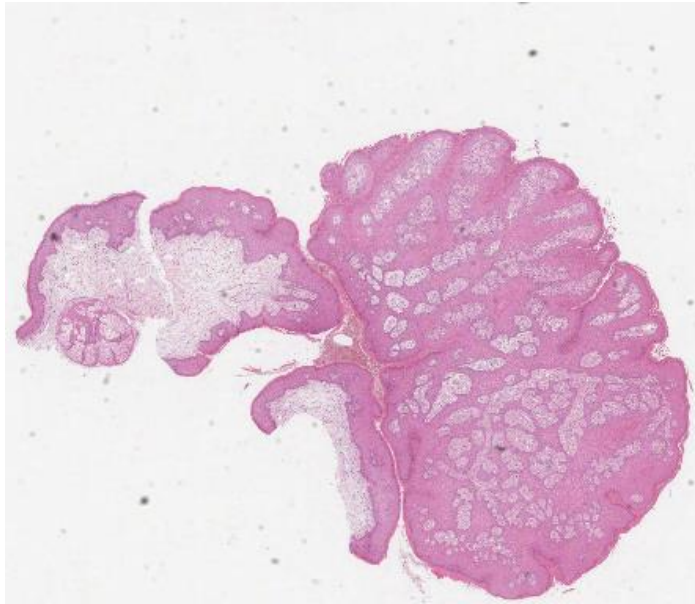
Differential diagnosis of VaVIN

- DVIN
- uVIN
- Conventional SCC
- Verrucous carcinoma
- Vulvar exophytic condyloma
- Lichen simplex chronicus
- Hypertrophic lichen sclerosus
- Psoriasis
- Verruciform xanthoma

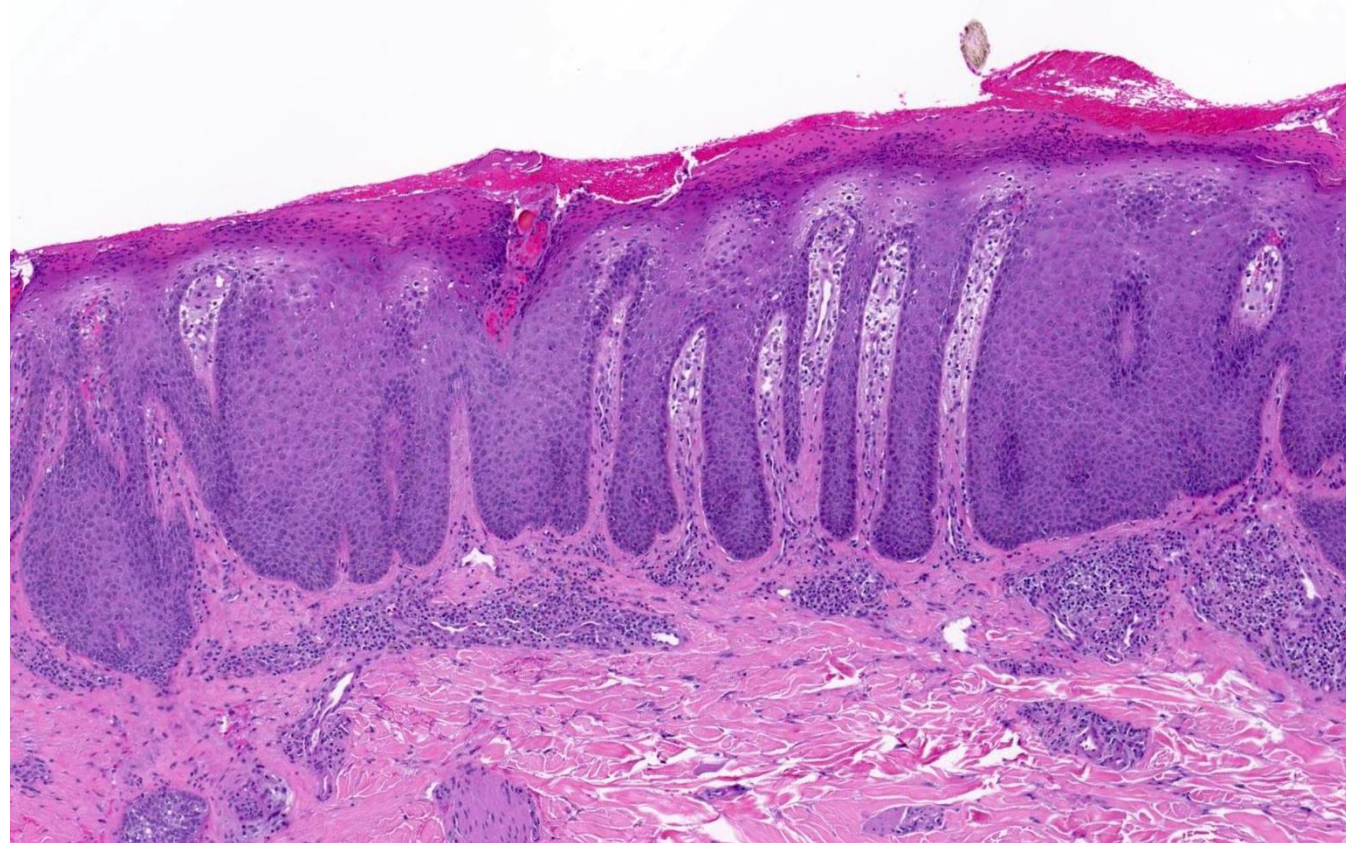


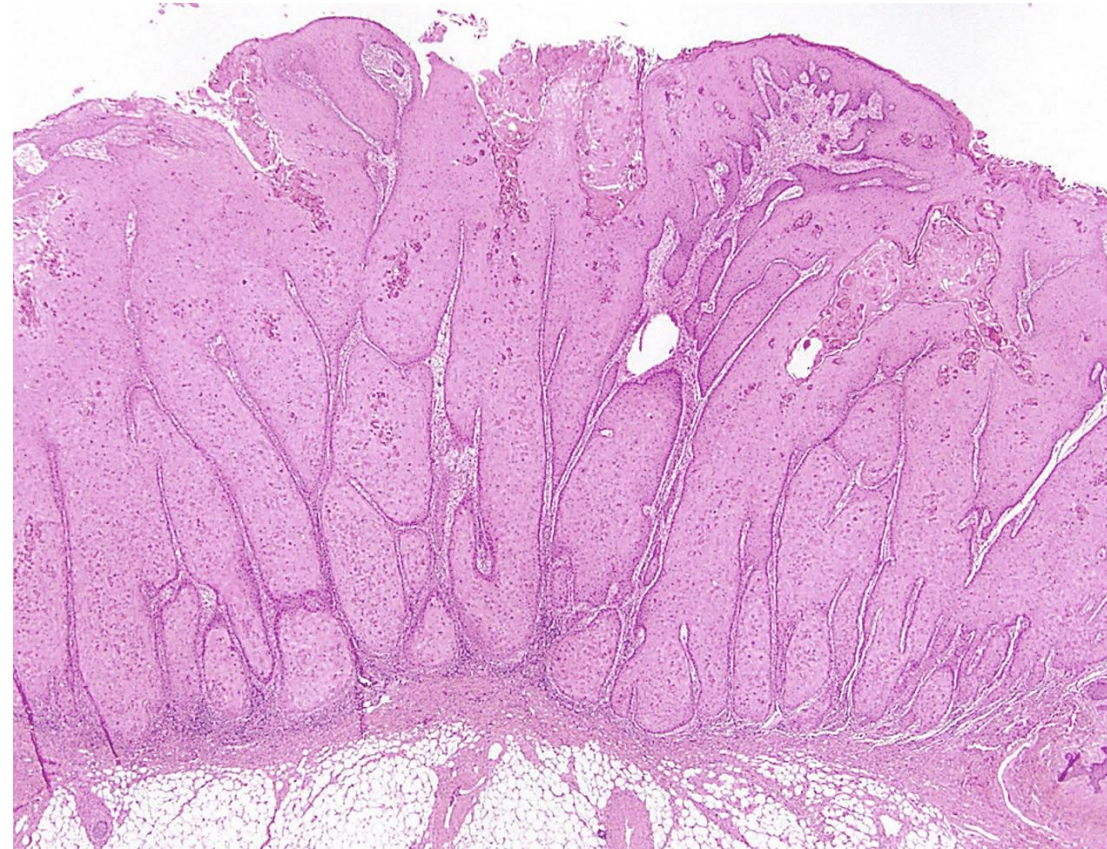


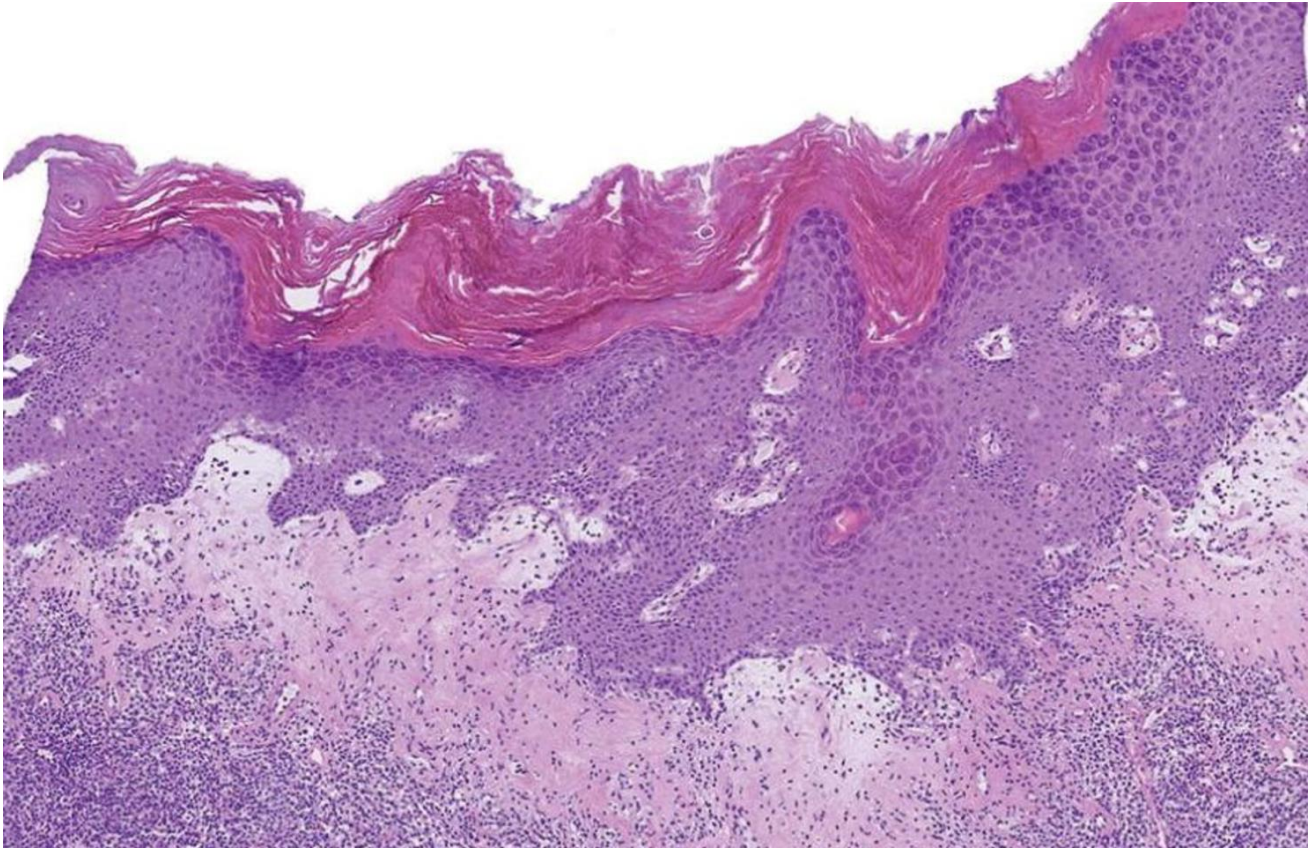
Thanks Dr Shenjere











Take home messages

- VaVIN- 7th to 9th decade
- Discrete lesion
- Complete excision or close surveillance
- Only diagnose on a biopsy after excluding the D/D
- If diagnosis not possible- atypical verruciform lesion and discuss D/D

Diagnosis of verruciform acanthotic vulvar intra-epithelial neoplasia (vaVIN) using CK17, SOX2 and GATA3
Immunohistochemistry

Histopathology 2024, 84, 1212–1223.



Thank you!