Update on Vulvar Pathology

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- **Squamous cell carcinoma of the vulva**
- **Squamous cell carcinoma precursors**

Lower Anogenital Squamous Terminology Standardization Project (*LAST*) for HPV-associated Lesions

- **Single set of diagnostic terms for all lower anogenital sites**
- **Two-tiered nomenclature for intraepithelial lesions**
  - **Low grade generally self-limited lesions**
  - **High grade potentially progressive lesions**
- **Recommended terminology:**
  - **Low grade SIL**
  - **High grade SIL**
- **Use p16 only to improve accuracy**
- **Vulvar SISCCA =FIGO IA cancer**

Int J Gynecol Pathol 2013; 32:76-115

WHO Classification of Tumours of the Female Reproductive Organs 2014
Squamous Cell Tumors and Precursors

- **Benign squamous lesions**
  - **Condyloma acuminatum**
  - **Vestibular papilloma**
  - **Seborrheic keratosis**
  - **Keratoacanthoma**

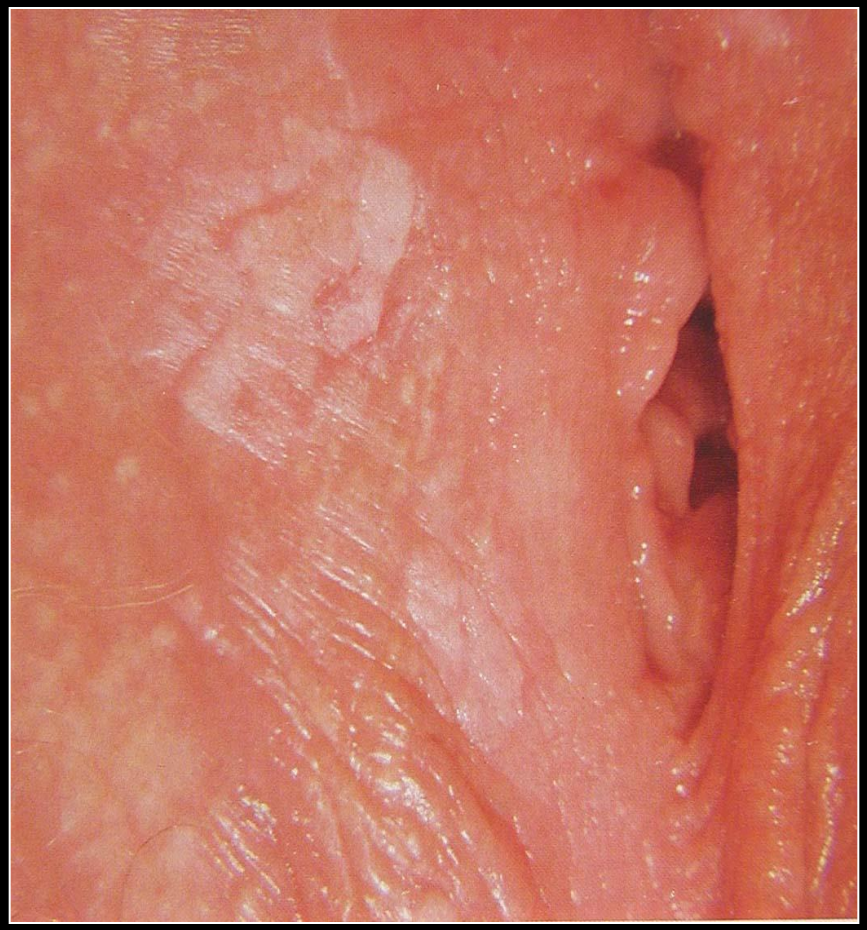
- **Squamous intraepithelial lesions**
  - **Low grade SIL, including flat condyloma and seborrheic keratosis like HPV positive lesions**
  - **High grade SIL**
  - **Differentiated VIN**

High Grade VIN/SIL
Two Types

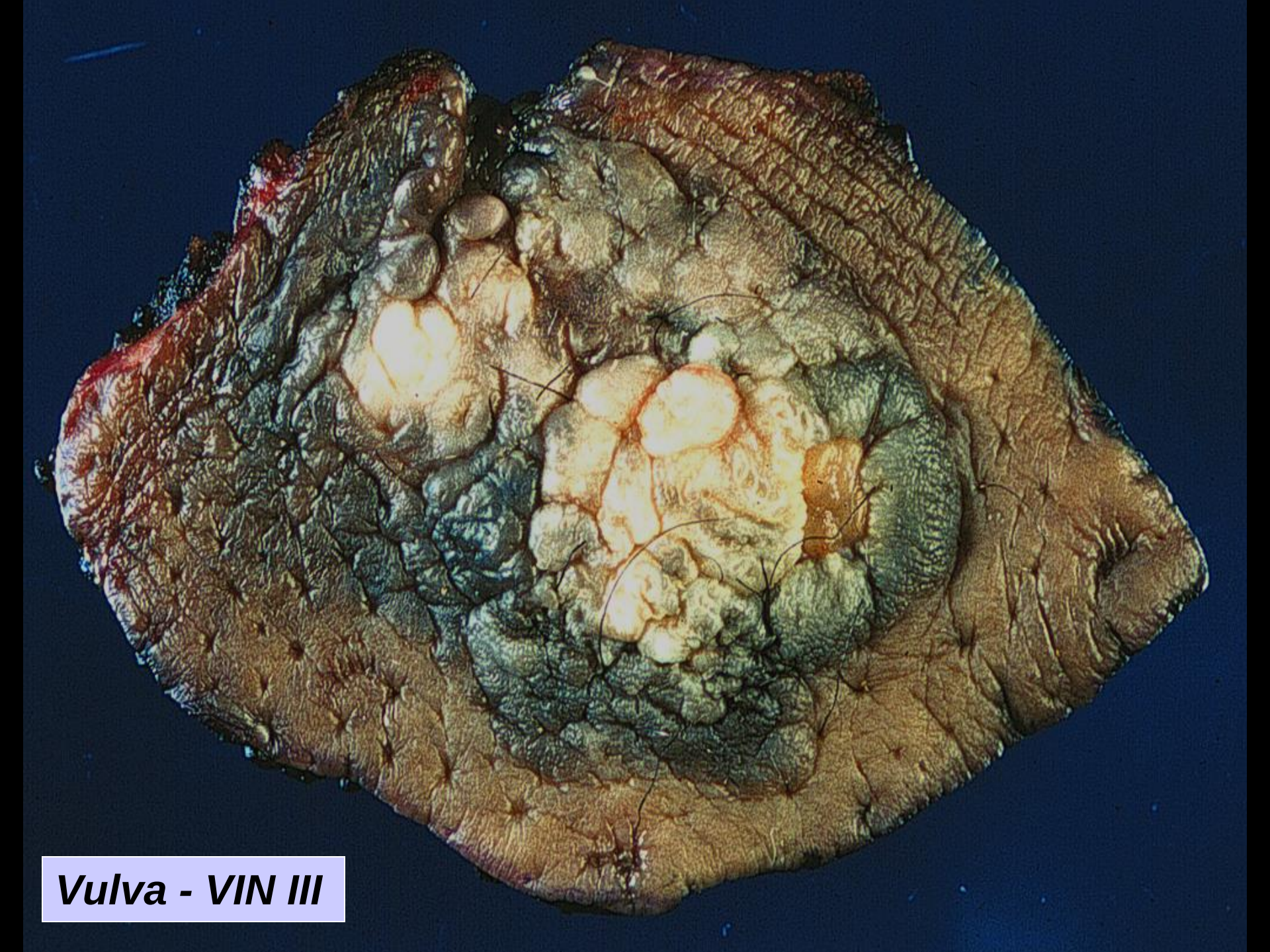
- **Classical (Bowenoid) type**
  - **Basaloid**
  - **Warty**
- **Differentiated (simplex) type**

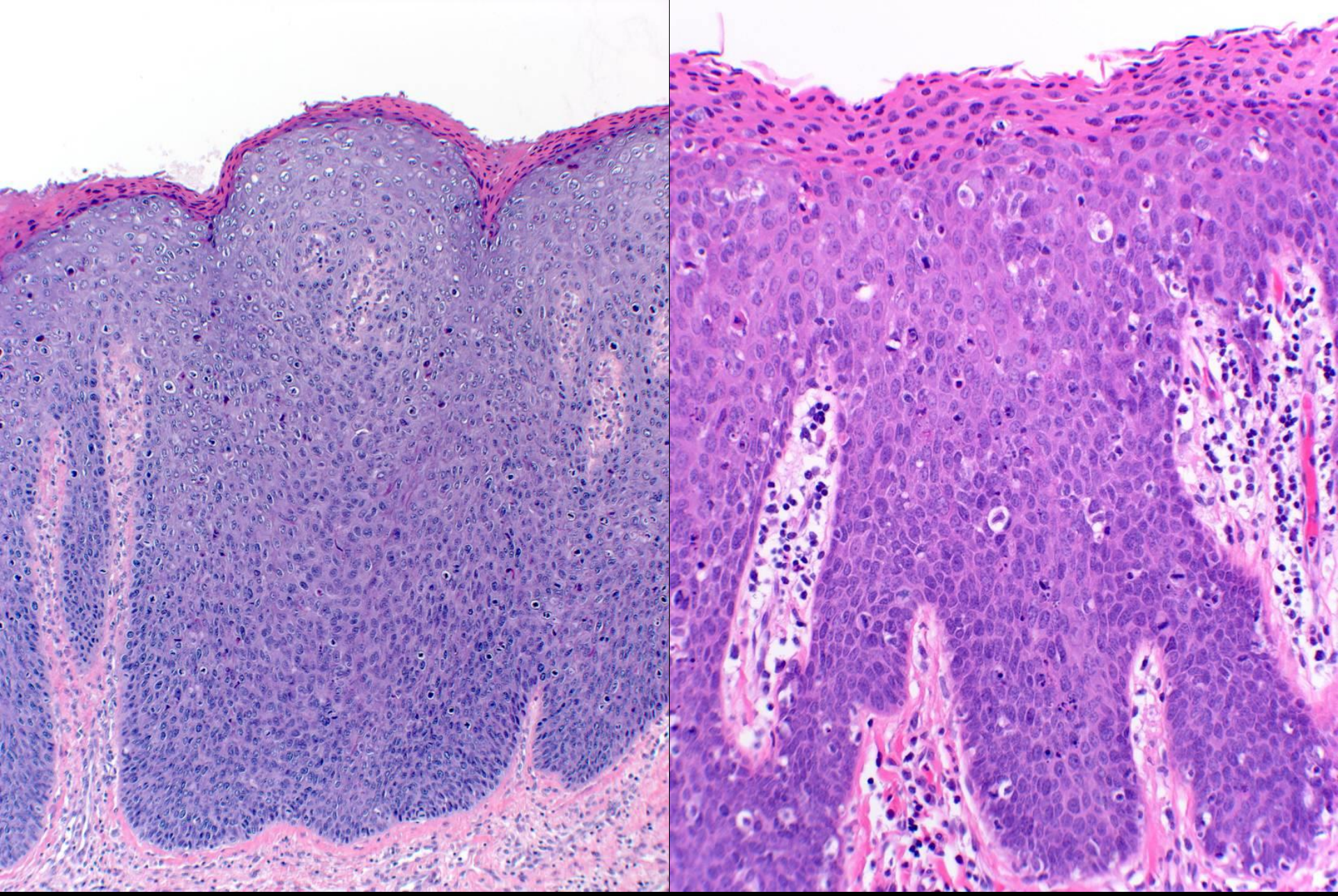
High Grade VIN/SIL
Classic, or Bowenoid Type

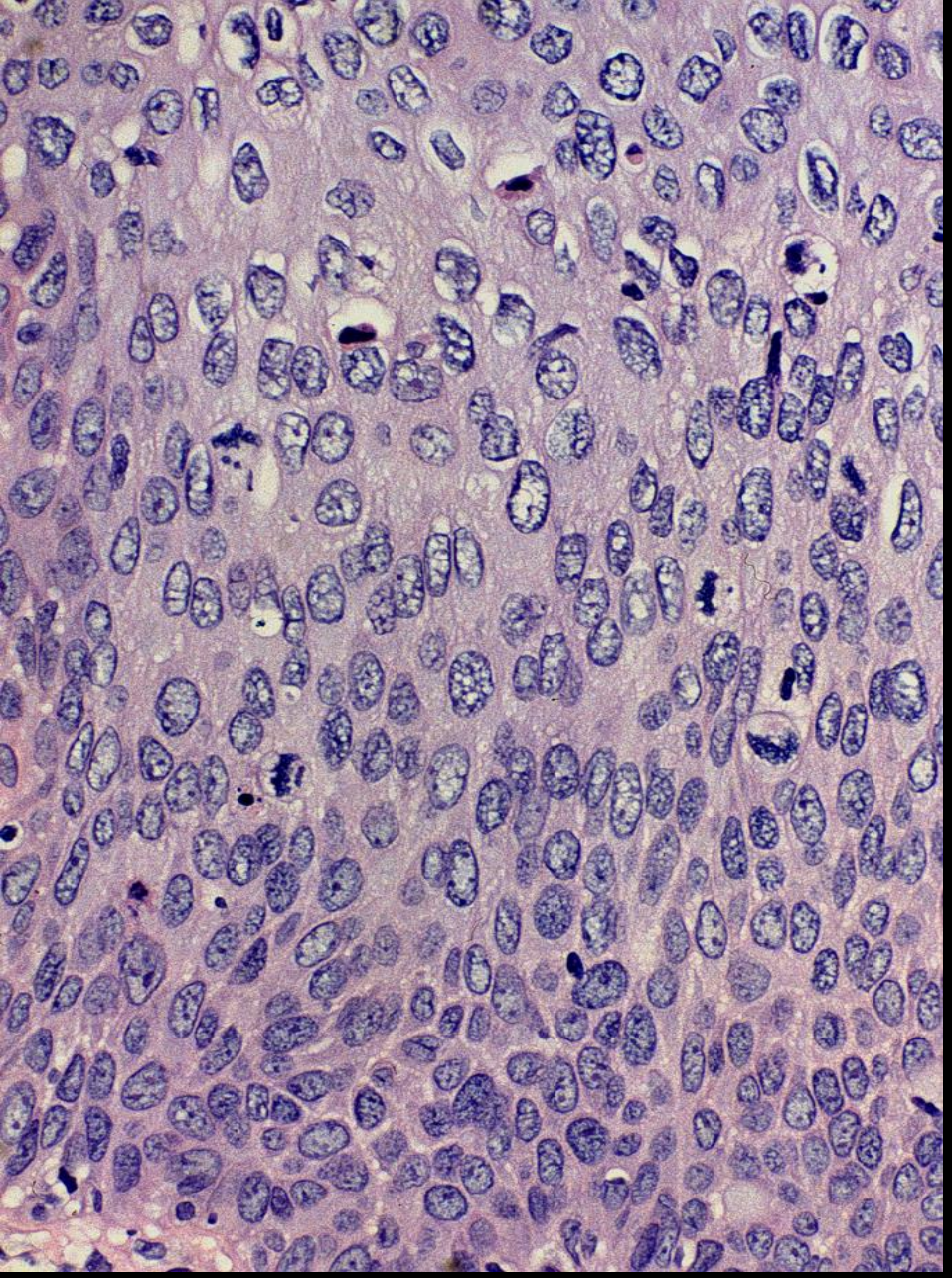
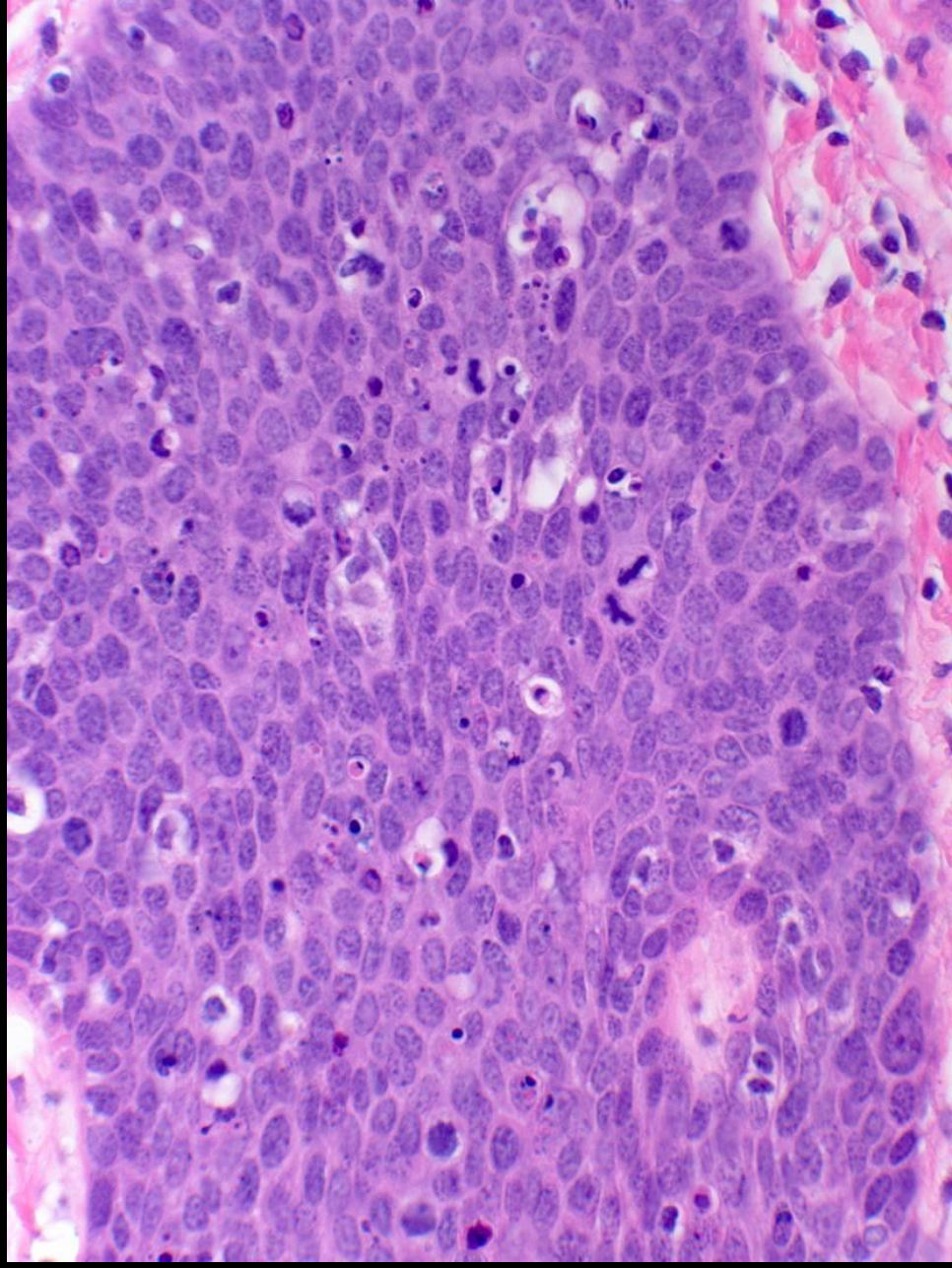
- **Young women - 30'S and 40's - increasing in incidence**
- **History of condylomas, herpes infection, HIV disease, smoking**
- **Linked to HPV, usually HPV 16**
- **Varied appearance:**
  - **Papules, plaques, polyps**
  - **White, red, or pigmented**
- **Multicentric disease in vagina or cervix**

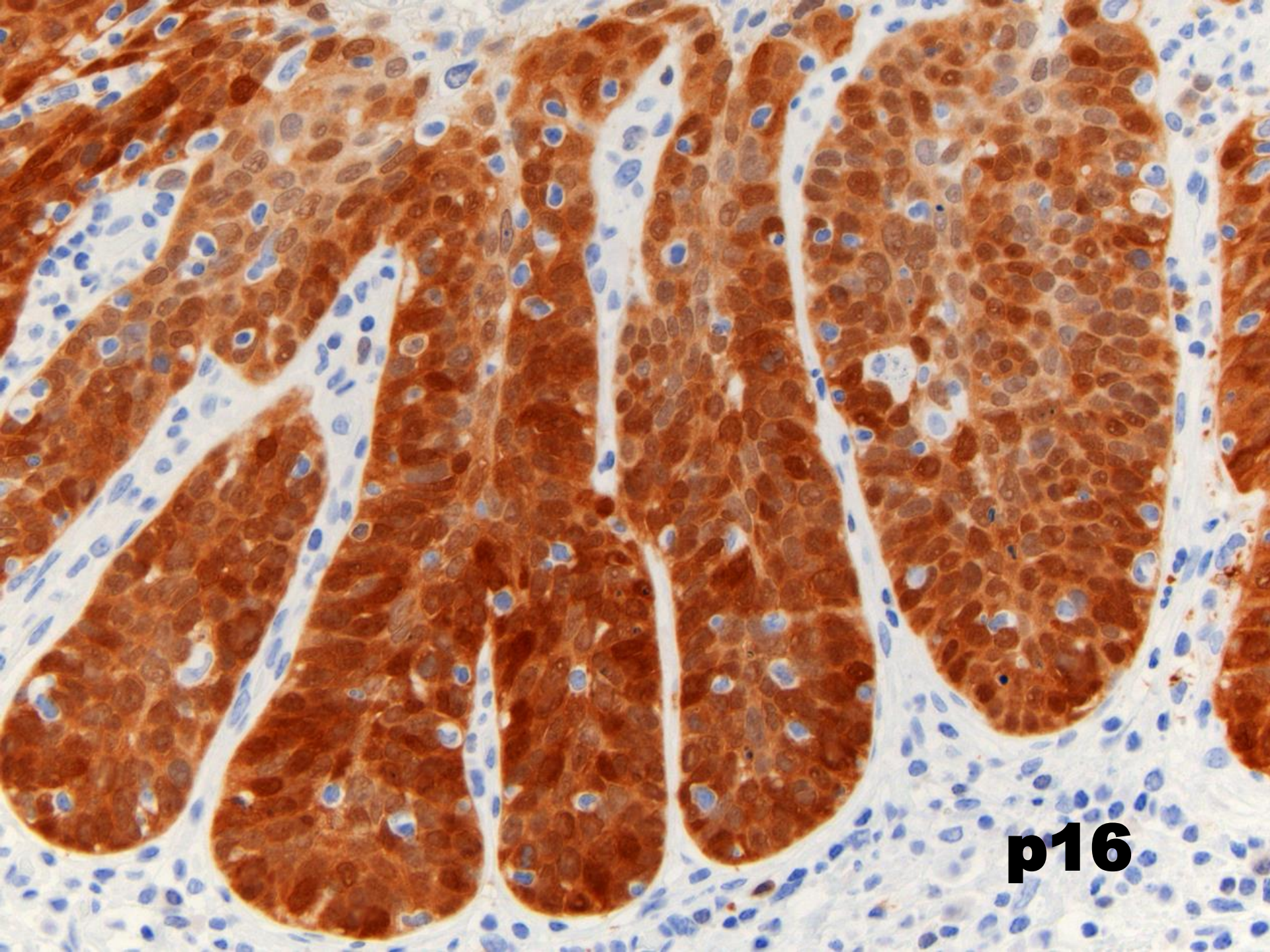


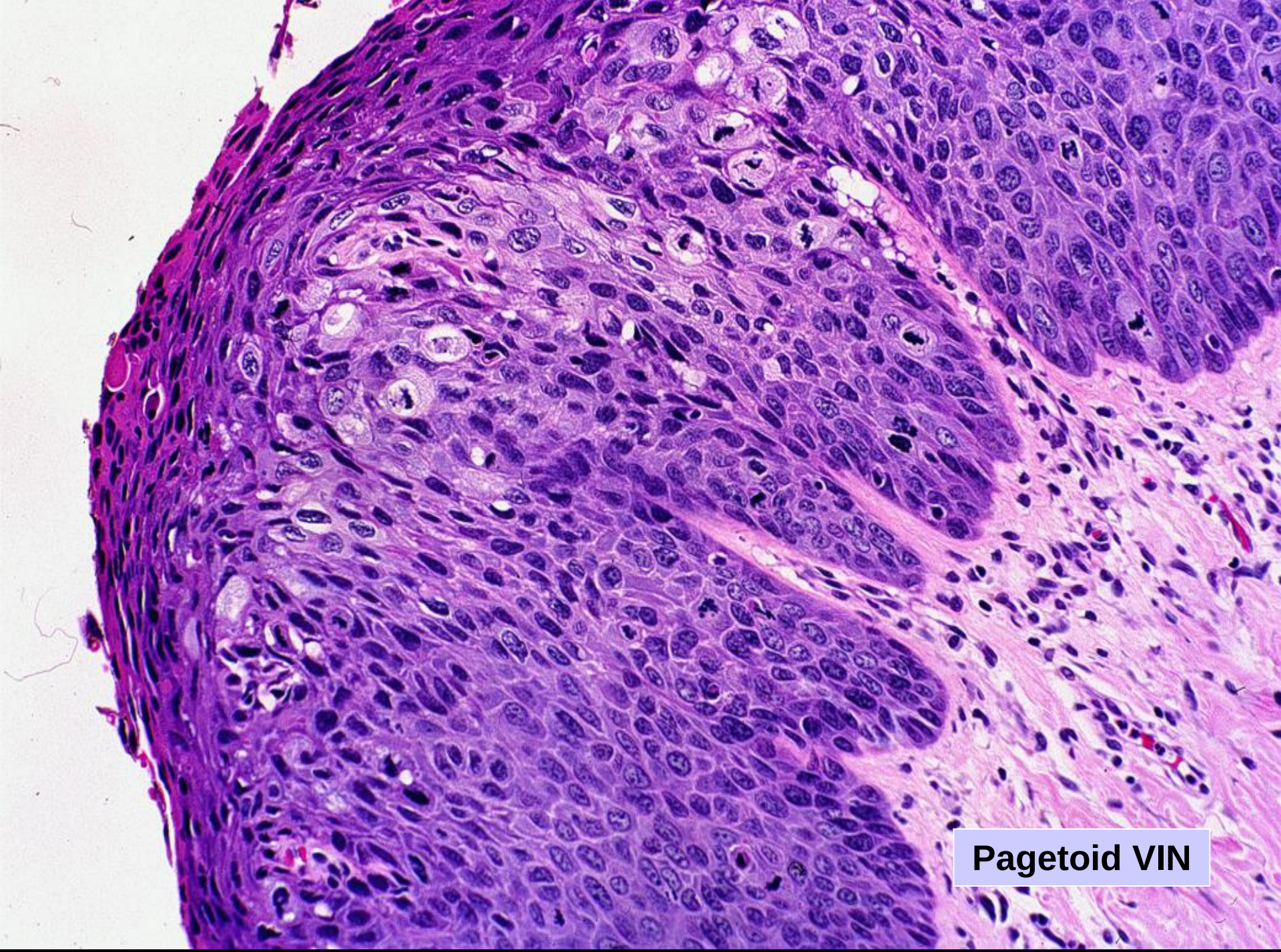
Vulvar intraepithelial neoplasia


Vulva - VIN III




p16


Pagetoid VIN

Pagetoid Lesions of the Vulva

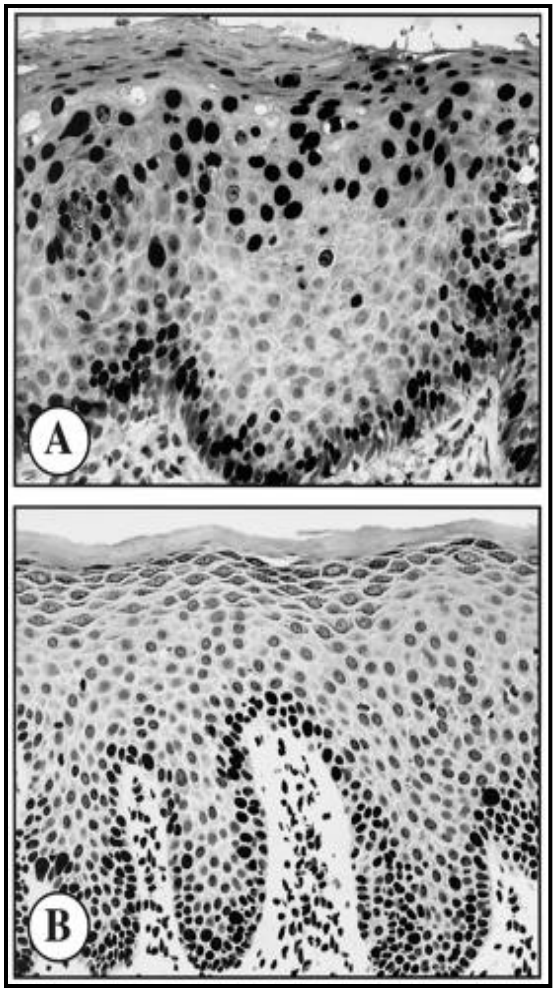
	HMWK	LMWK	CK 7	CEA	S100
VIN	+	-	+	-	-
Melanoma	-	-	-	-	+
Paget's	-	+	+	+	-

VIN
Results of Therapy

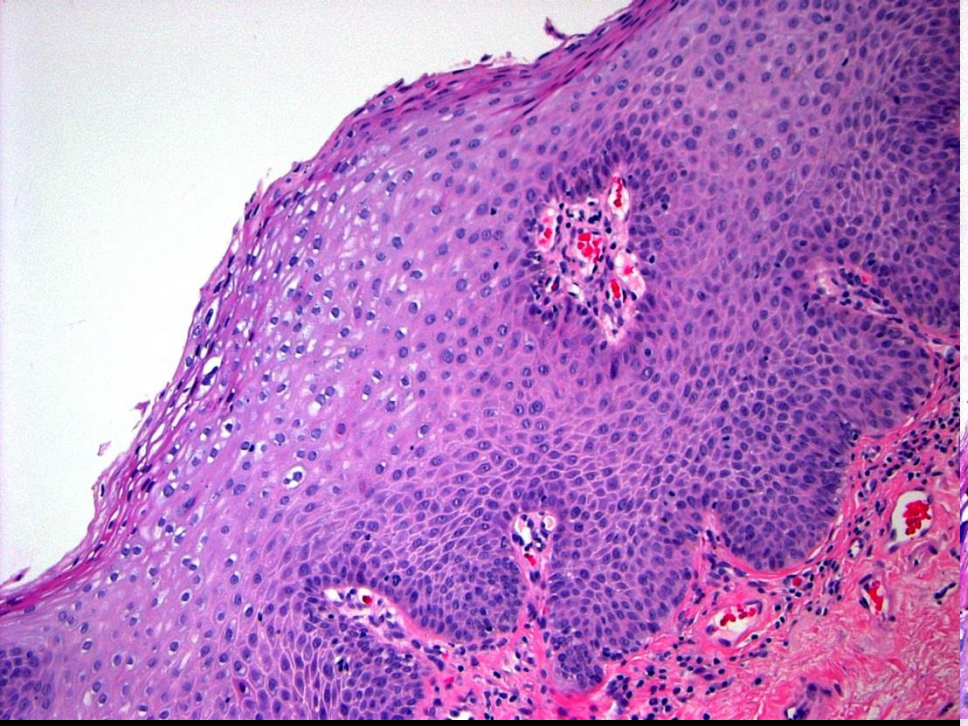
- **Treatment: Excision, laser ablation, topical imiquimod**
- **Local recurrence - up to 35%**
- **Occult invasion - up to 20%**
- **Invasive carcinoma develops in**
  - **3-10% of treated patients**
  - **9% to up to 90% of untreated patients**
  - **Invasive carcinoma is basaloid or condylomatous type**

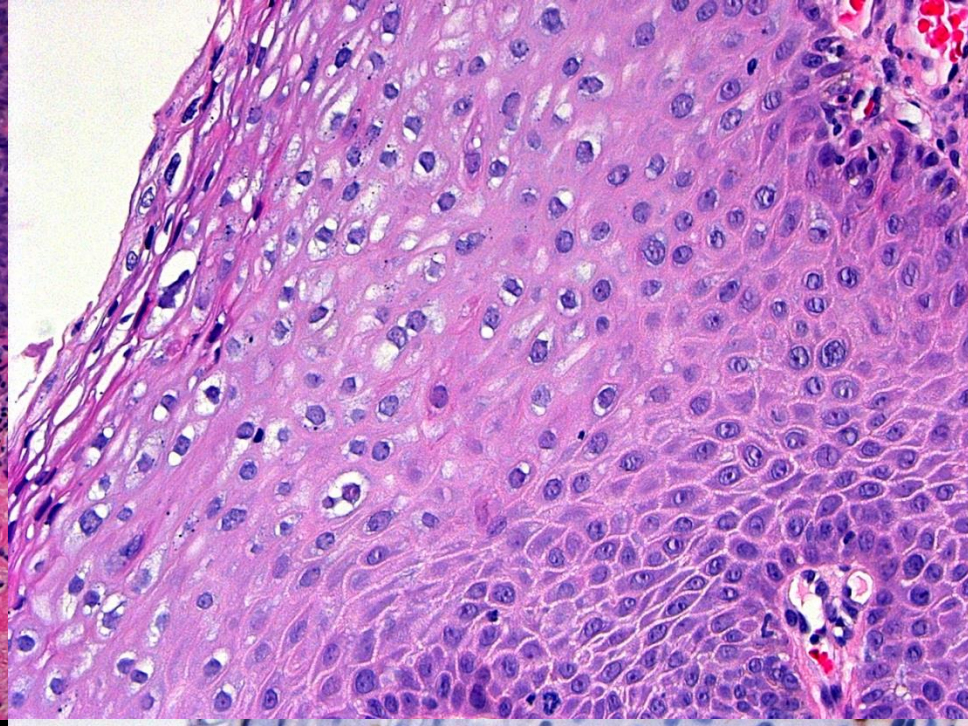
Low Grade SIL
A Problematic Diagnosis

- **Less than 50% of cases of VIN I confirmed on review**
- **70% of cases associated with low risk HPV**
- **MIB-1 positive nuclei in upper epithelium correlate with VIN I**

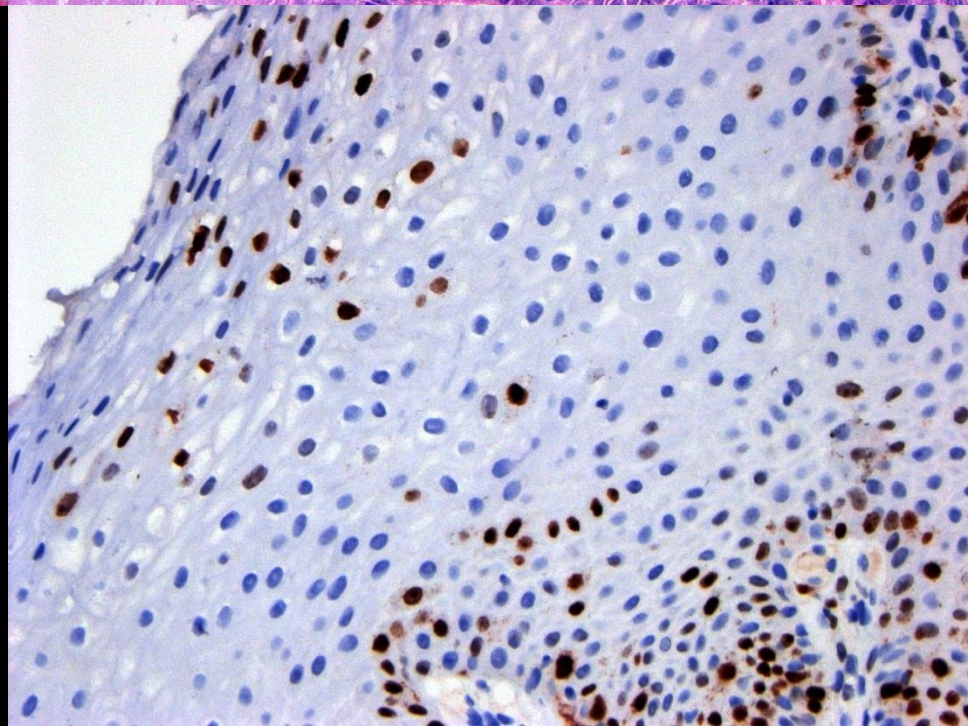


Logani S, et al. Mod Pathol 2003;16(8):735-741



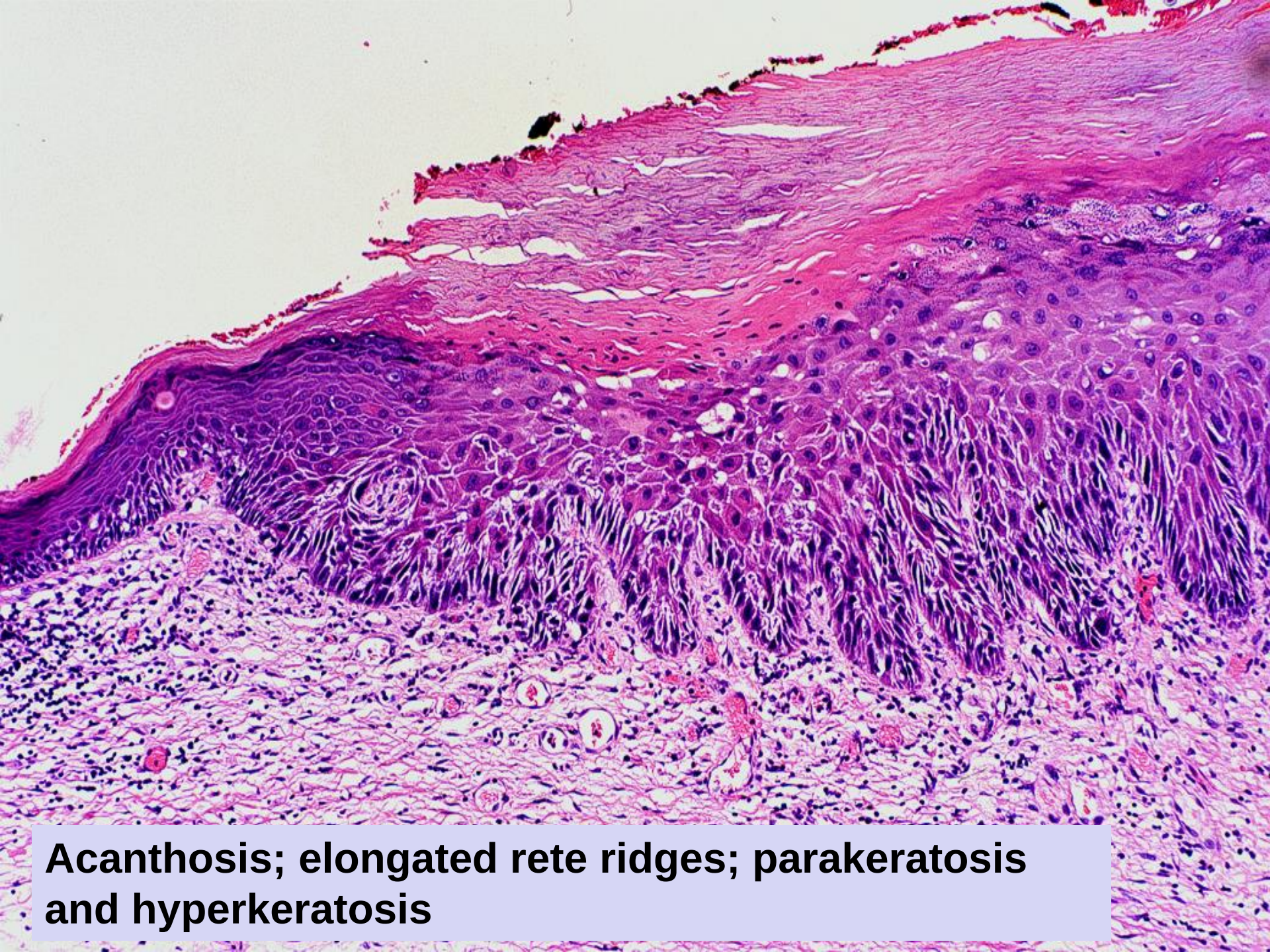


Low grade SIL of the vulva, “flat condyloma” type

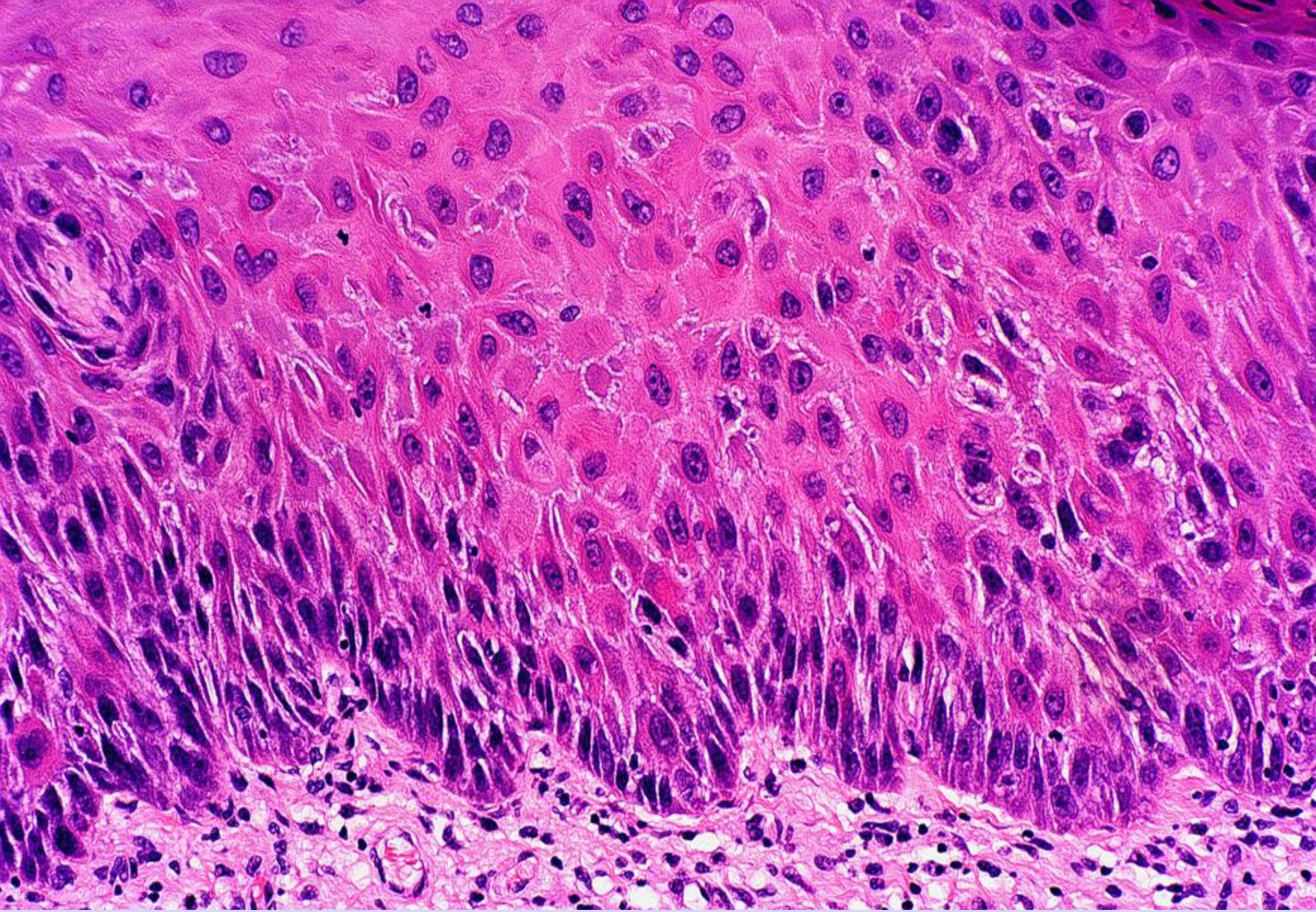


Simplex or Differentiated Type VIN
Abell, 1965; Yang & Hart, 2000

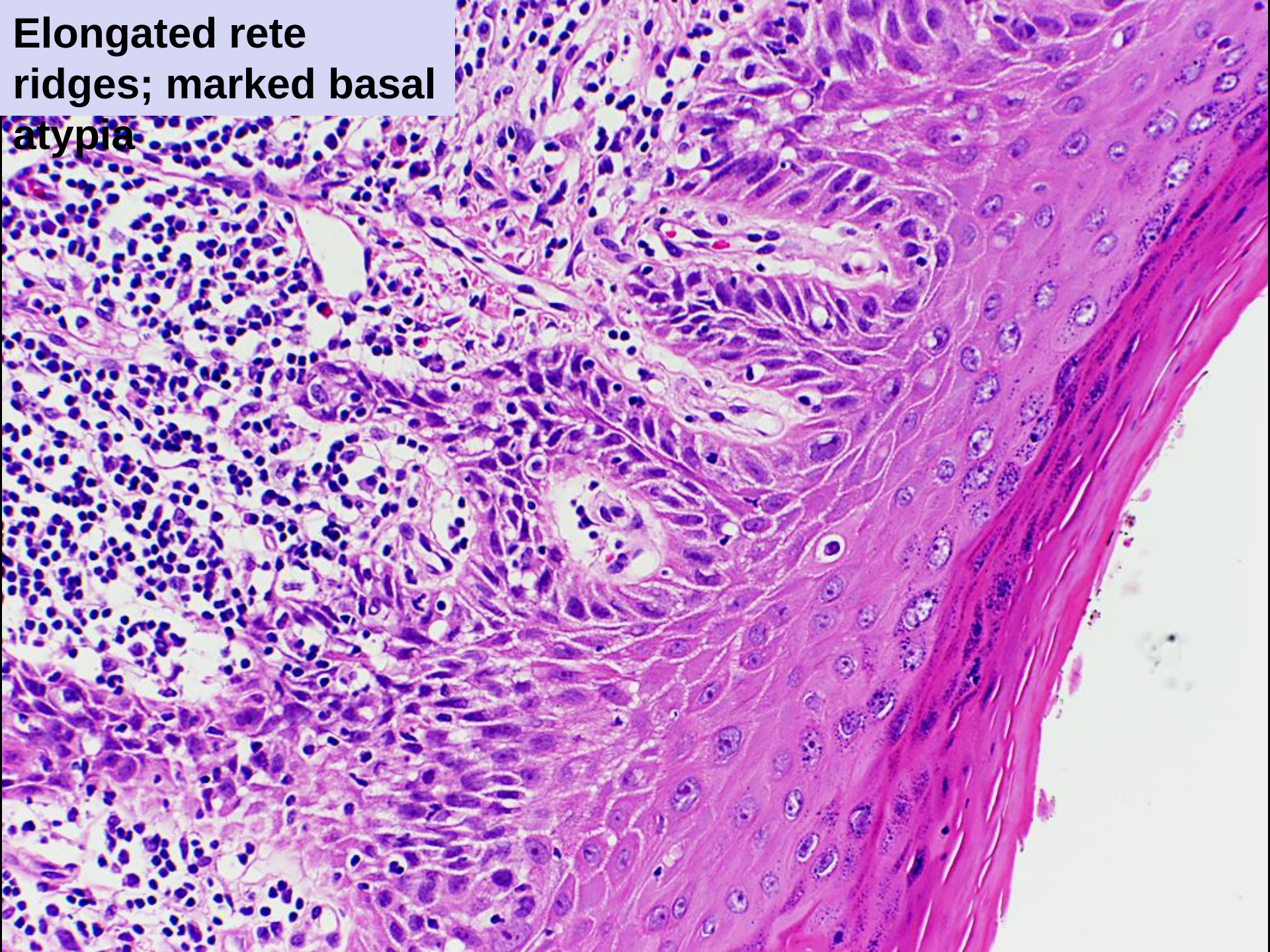
- **2-10% of VIN**
- **Postmenopausal women, average age late 60's**
- **Small lesions, roughened gray white, or white plaques, may be multifocal**
- **Lichen sclerosis may also be present**
- **Not associated with HPV**
- **? Greater potential for progression to invasive carcinoma; invasive carcinoma is keratinizing squamous cell type**

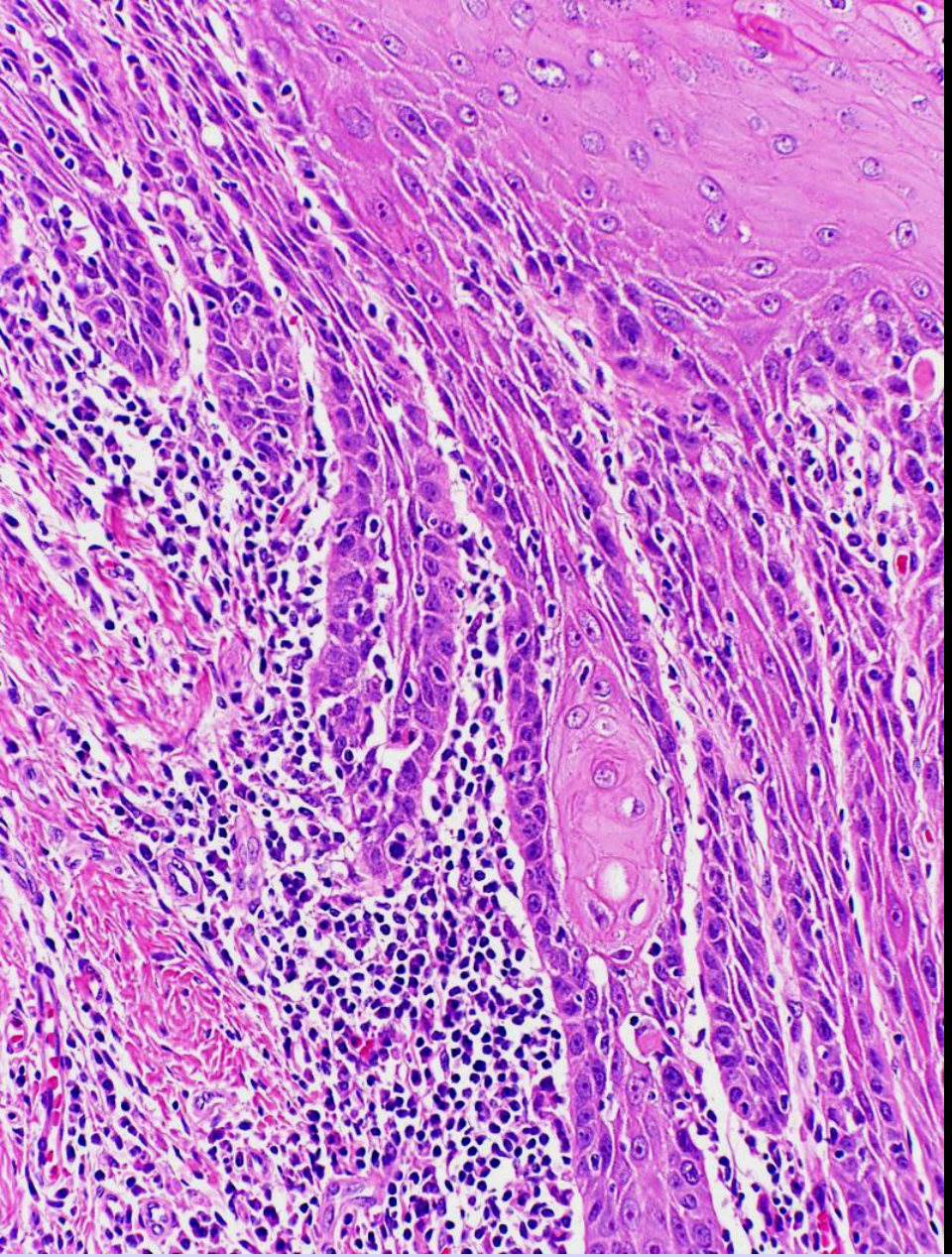


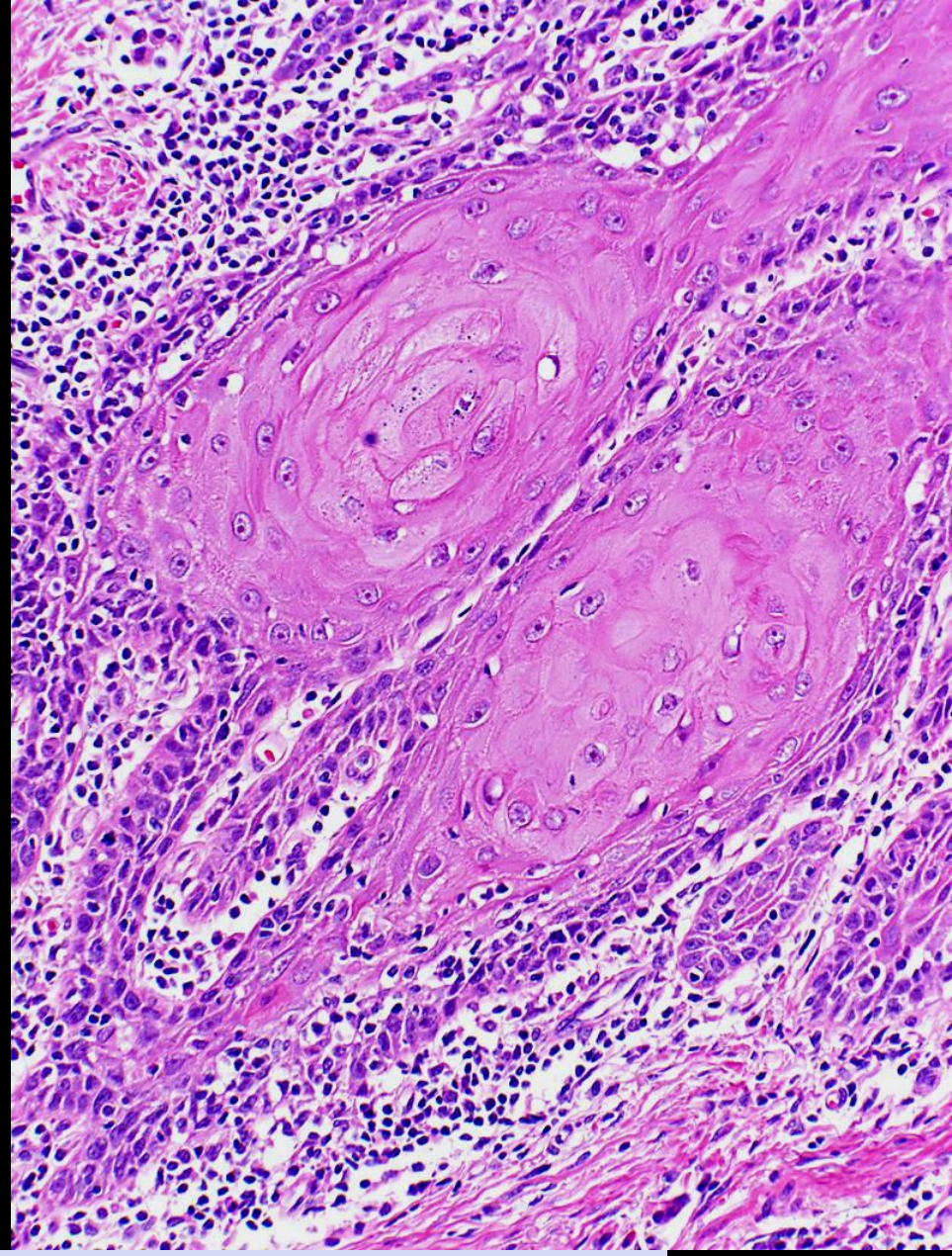
Acanthosis; elongated rete ridges; parakeratosis and hyperkeratosis



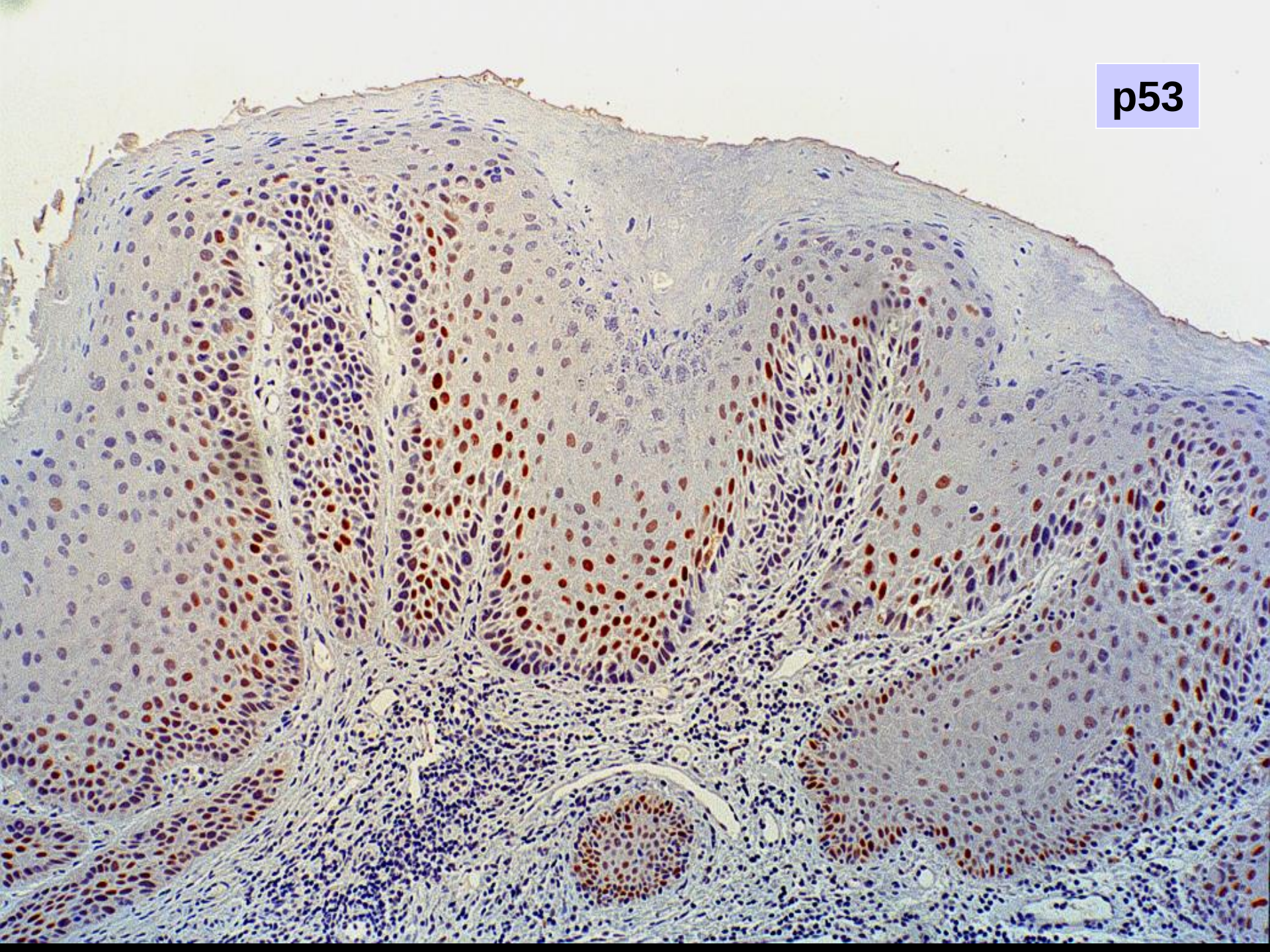
Marked basal atypia; intermediate zone hypereosinophilia


Elongated rete ridges; marked basal atypia





Inappropriate differentiation; whirls of keratinized cells in rete ridges


p53

Differentiated vulvar intraepithelial neoplasia contains Tp53 mutations and is genetically linked to vulvar squamous cell carcinoma.

Pinto AP, et al. Mod Pathol (2010) 23: 404-412.

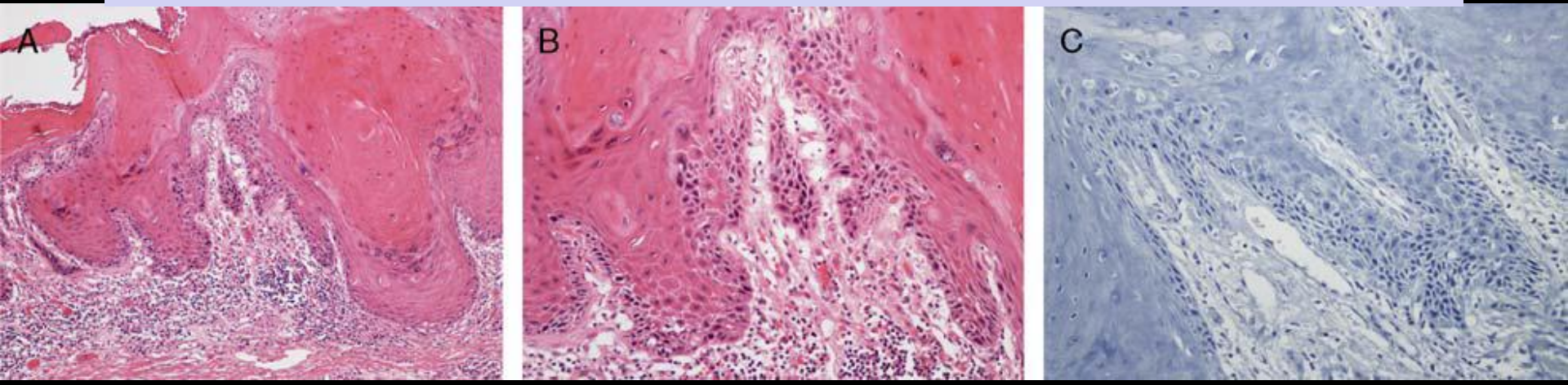
- **6 of 10 dVIN cases had at least 1 VIN focus with 1 or more Tp53 mutations**
- **4 were p53 immunopositive (missense or splice) and 2 were p53 negative (deletions)**
- **5 had SCC associated with dVIN, 4/5 had Tp53 mutations**
  - **2 missense, p53 positive**
  - **2 nonsense, p53 negative**
- **2/4 cases had same p53 mutation in dVIN and SCC**
- **Multiple foci dVIN with different mutations in some cases**

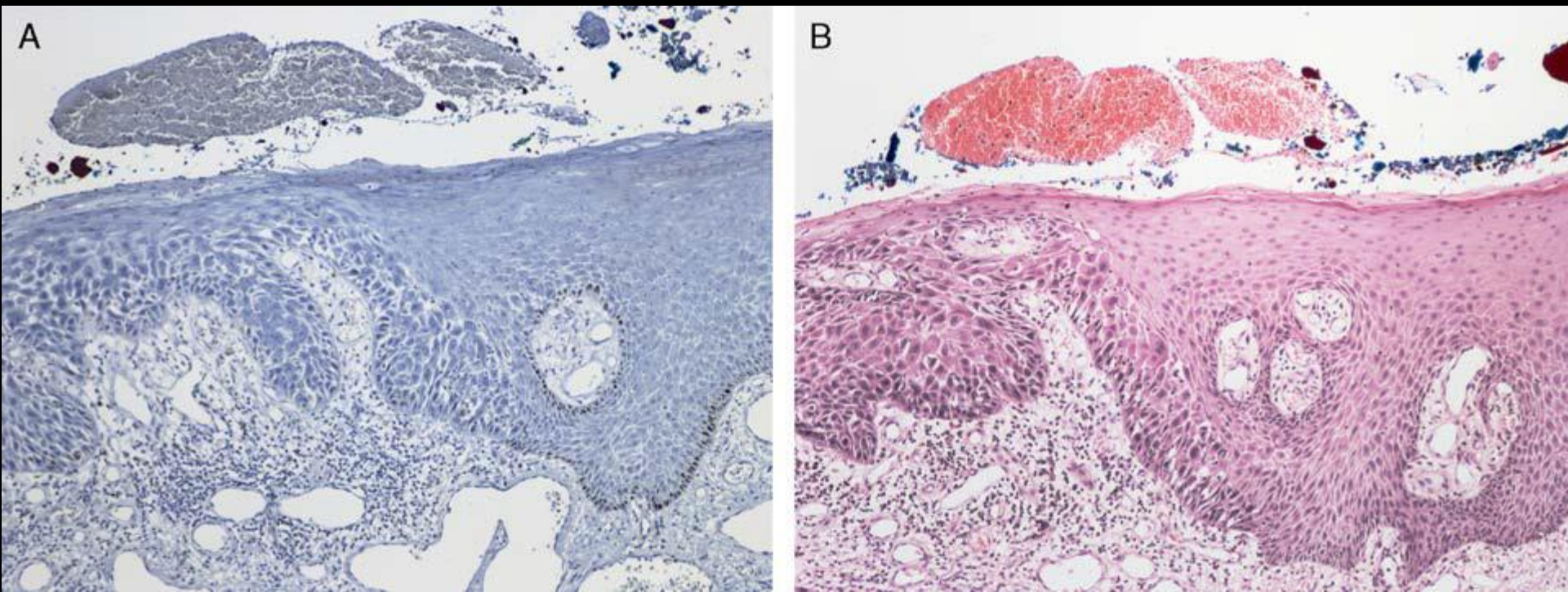
Expanding the morphologic spectrum of differentiated VIN (dVIN) through detailed mapping of cases with p53 loss.

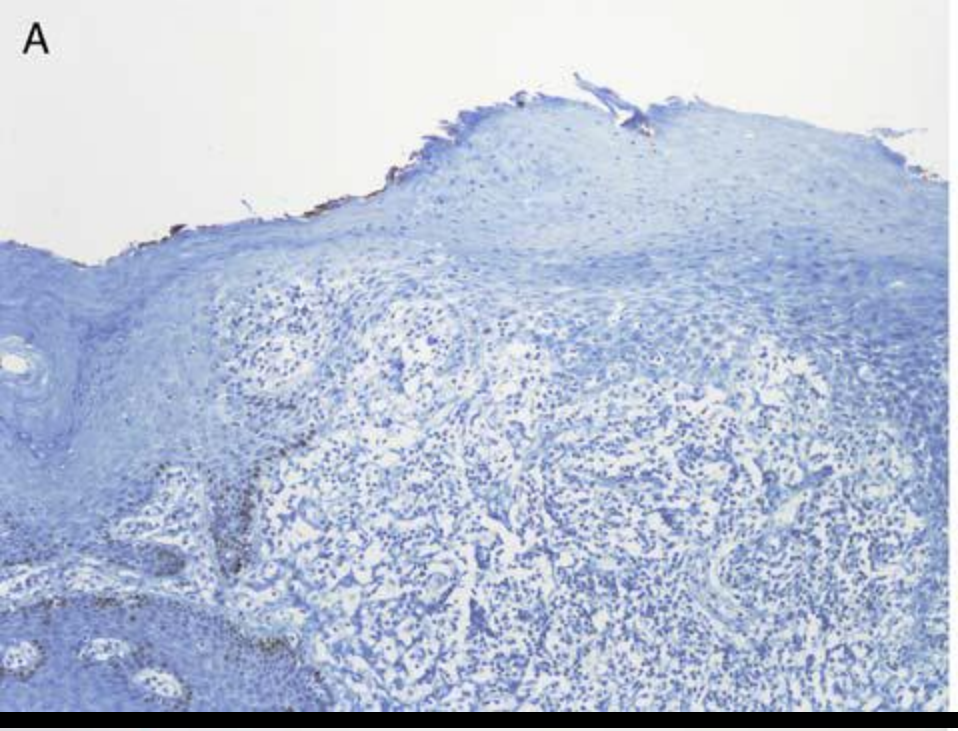
Singh N, et al. Am J Surg Pathol, 2014 PAP

- **p53 negative dVIN and SCC, when present, in 14 specimens from 10 patients**
- **27% of dVIN cases at Vancouver General Hospital**
- **1 case reclassified as not dVIN**
- **In 5/13 the p53 negative areas corresponded to the morphologic dVIN**
- **In 8/13 the p53 negative areas were more extensive than the morphologic dVIN and in some were at margins**

Expanding the morphologic spectrum of differentiated VIN (dVIN) through detailed mapping of cases with p53 loss. Singh N et al. Am J Surg Pathol 2014 in press



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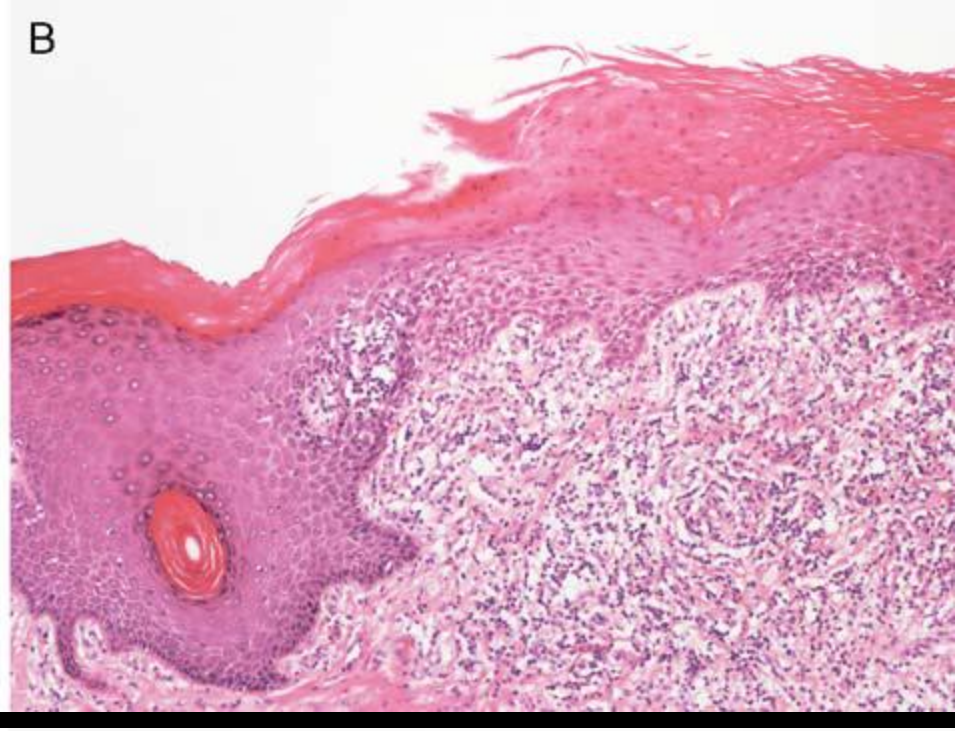
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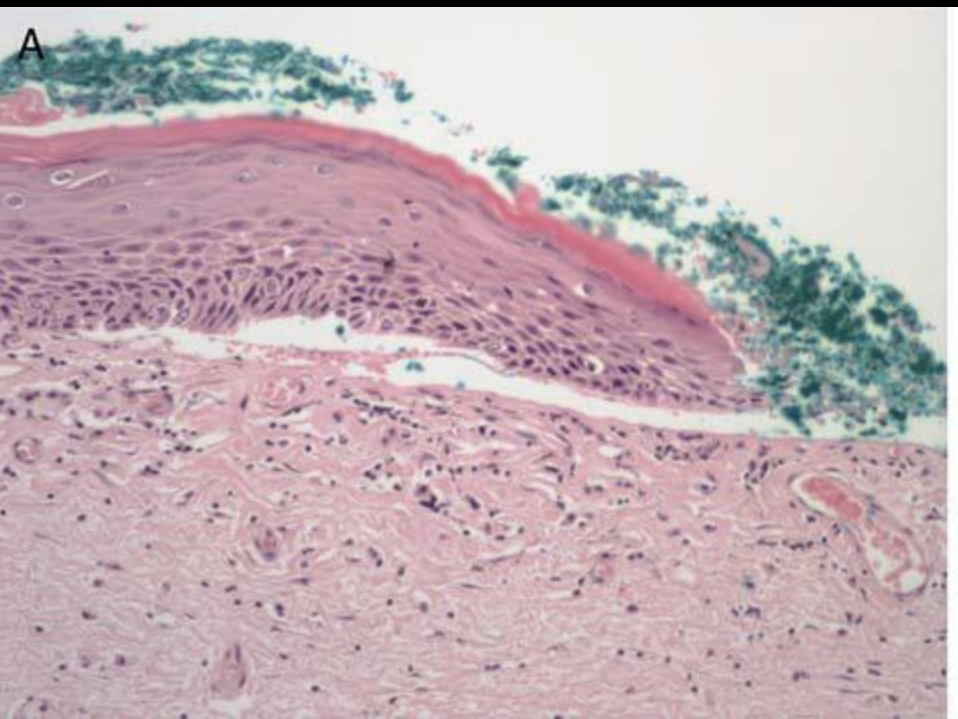
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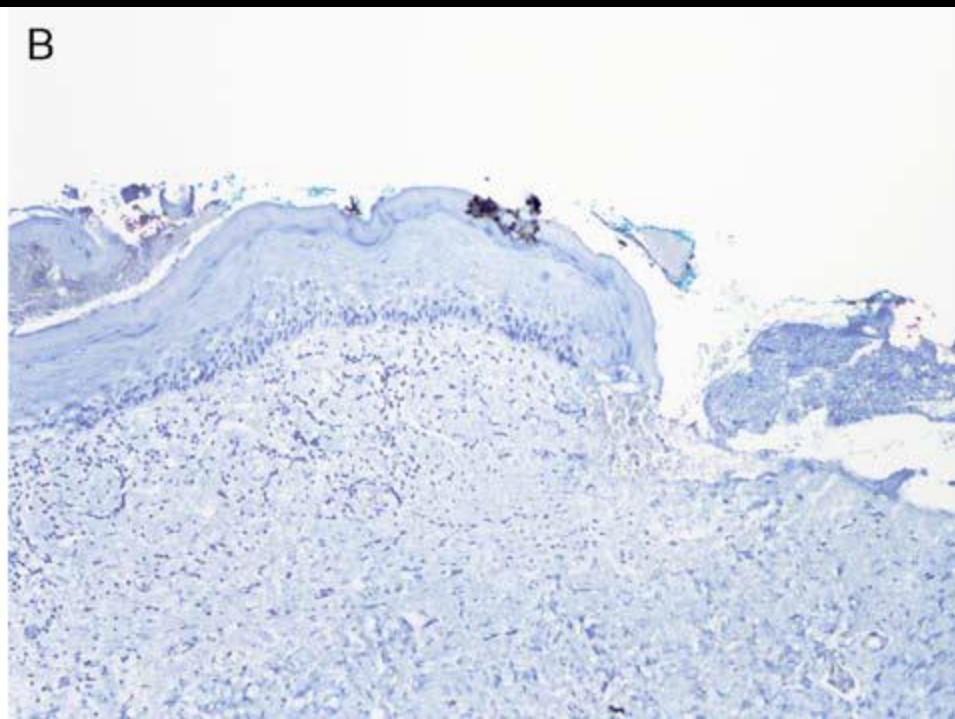
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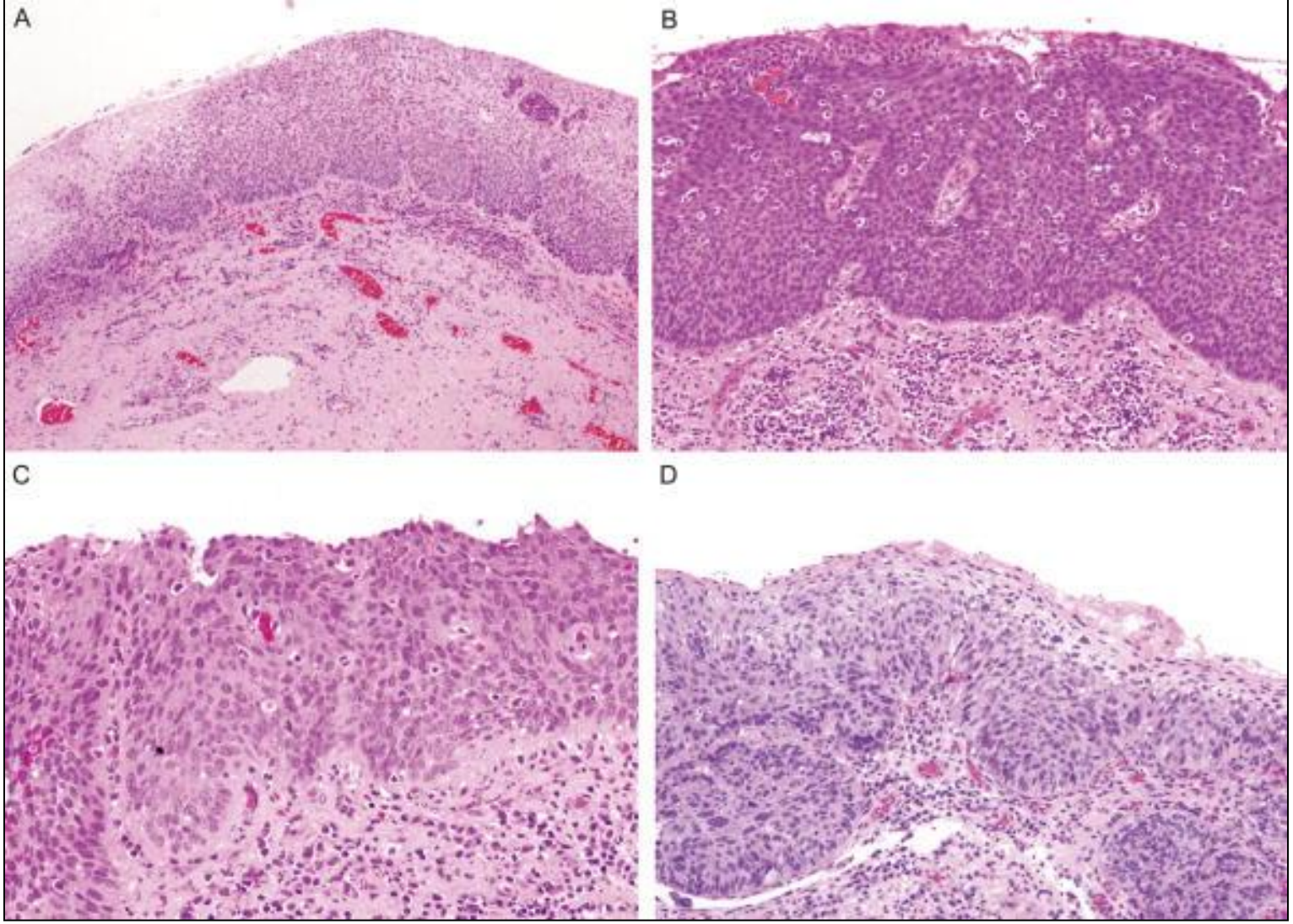
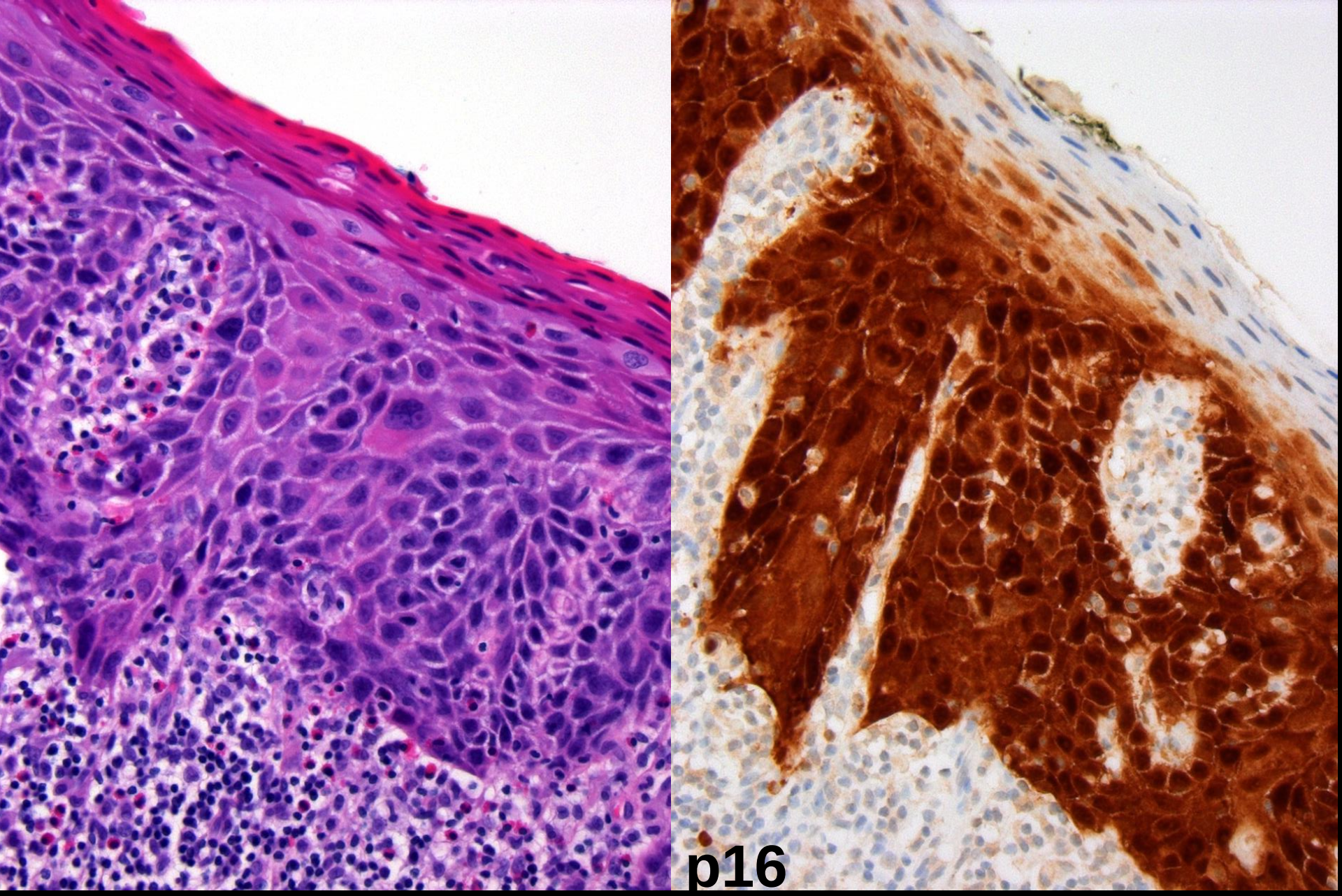


FIGURE 1. A, Simplex vulvar intraepithelial neoplasia, grade 3 of basaloid type. Diffuse replacement of the whole epidermis by a homogeneous population of small, "undifferentiated" keratinocytes with scanty cytoplasm extending throughout the entire thickness of the epidermis, showing no or only minimal maturation in superficial layers. Normal vulvar squamous epithelium is present on the left. B, The epidermis is thickened and shows a parakeratotic surface reaction. The rete ridges are elongated and markedly enlarged and coalescent. C, Small cells, with scant cytoplasm, showing large vesicular nuclei, with visible nucleoli. D, Moderate to severe atypia, with nuclear pleomorphism, multinucleation, and dyskeratosis.

Ordi J et al. Am J Surg Pathol 2009 33:1659-1665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WHO 2014

- **Squamous cell carcinoma**
  - **Keratinizing**
  - **Non-keratinizing**
  - **Basaloid**
  - **Warty**
  - **Verrucous**

Squamous Cell Carcinoma of the Vulva

- ***Type I***
  - **Younger women, average age 55**
  - **VIN, HPV associated, usually HPV 16**
  - **Basaloid, condylomatous types**

- ***Type II***
  - **Older women, average age 77**
  - **No or simplex VIN, no HPV, some LS or SH**
  - **Keratinizing squamous cell carcinoma**

HPV Testing in Vulvar Carcinoma

Toki, Kurman, et al 1991

	Ave. Age	*HPV+*	*Adj. VIN*	*Adj. SH, LS*	*Adj Nl*
SCC	77	4/19	2/19	14/19	3/19
BC	54	6/8	7/8	0	1/8
WC	47	3/3	3/3	0	0

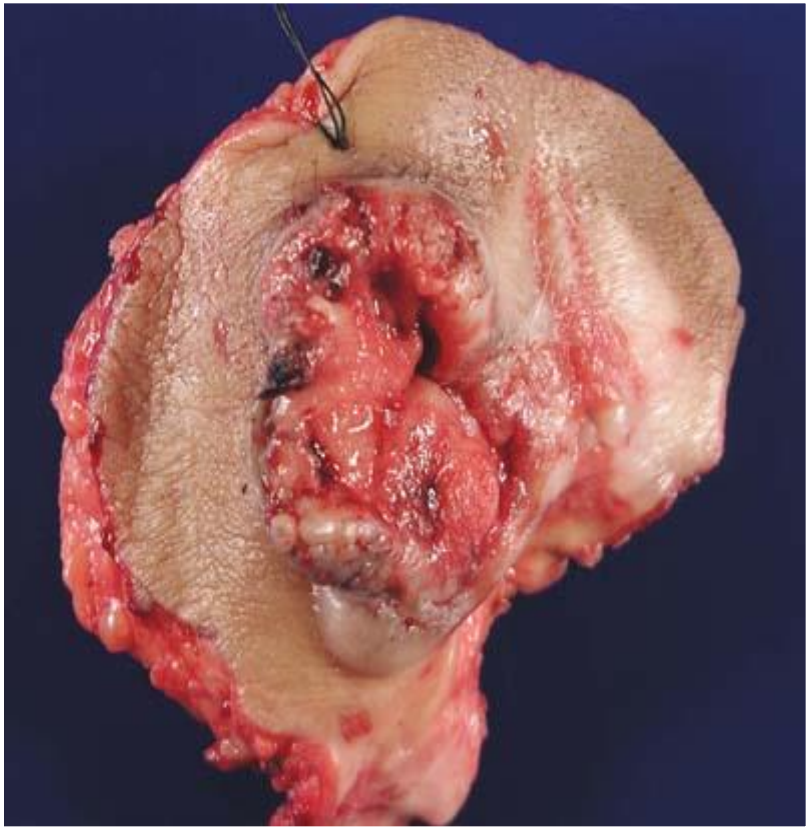
VIN Adjacent to Thin SCC

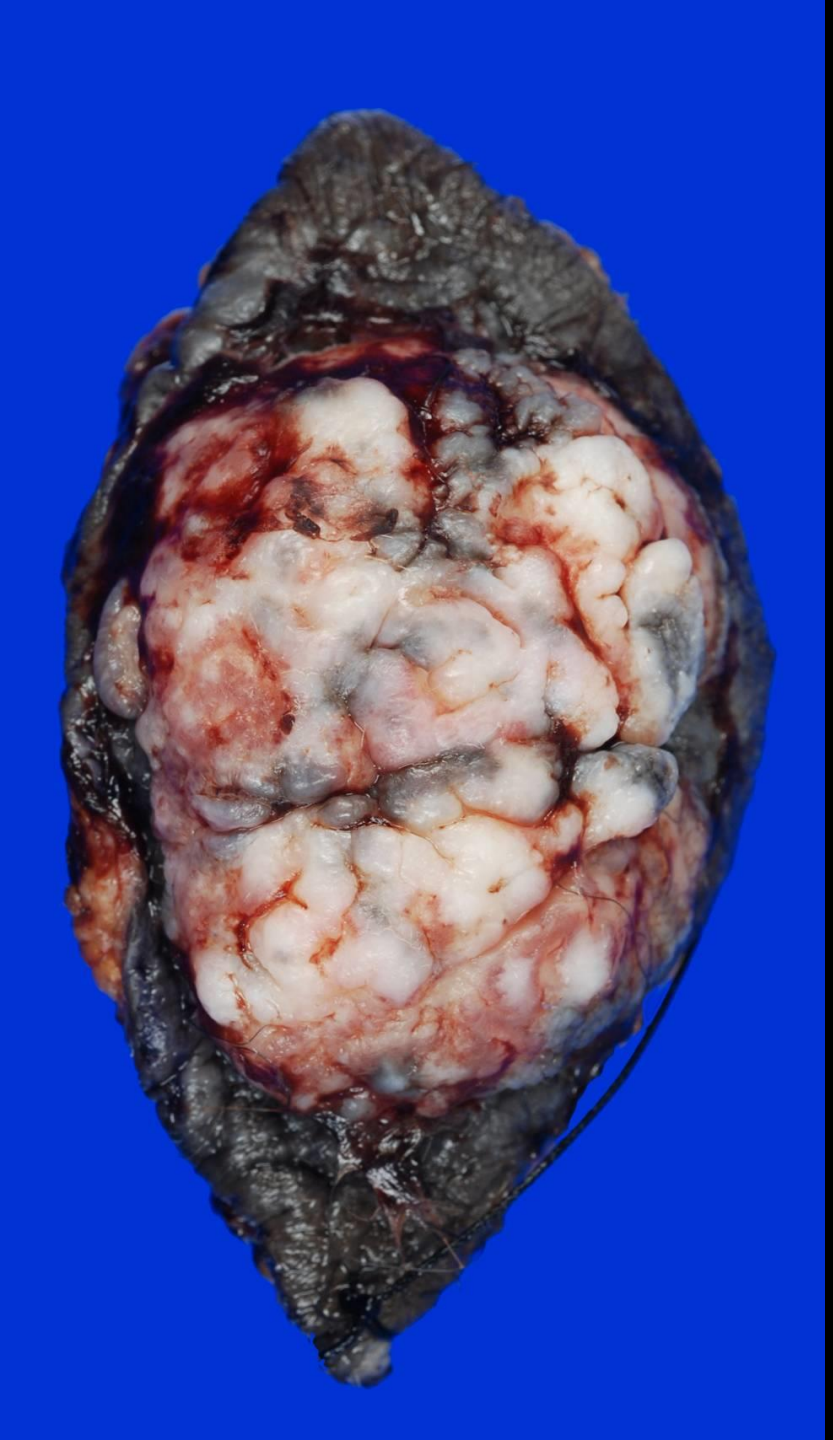
Type CA	c VIN	d VIN	No VIN	LS	At LS
Keratinizing SCC 38	9	18	11	14	8
Warty SCC 6	6	0	0	0	0
Basaloid SCC 4	4	0	0	0	0
Age	62	78	75		

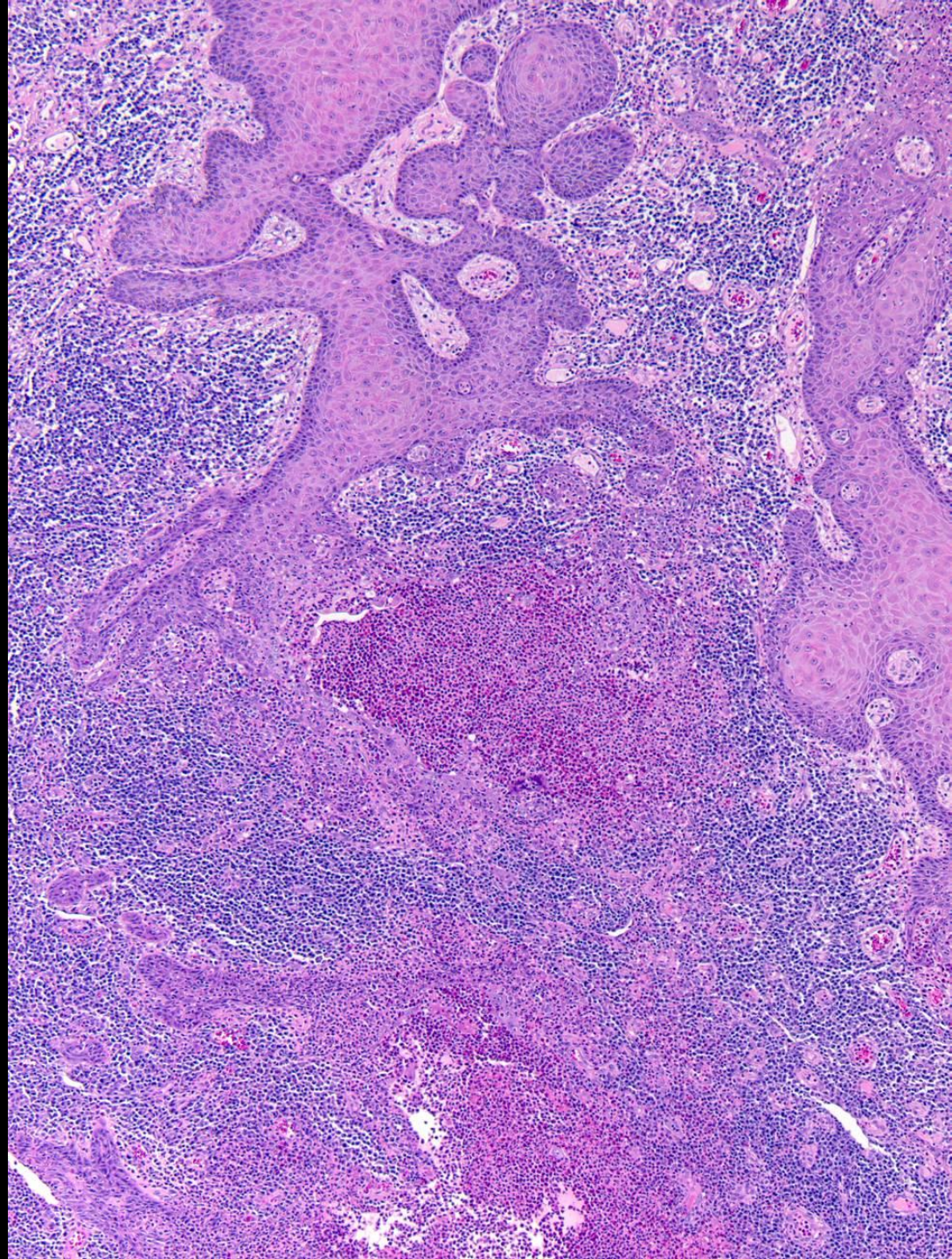
Am J Surg Pathol 2006;30:310-318

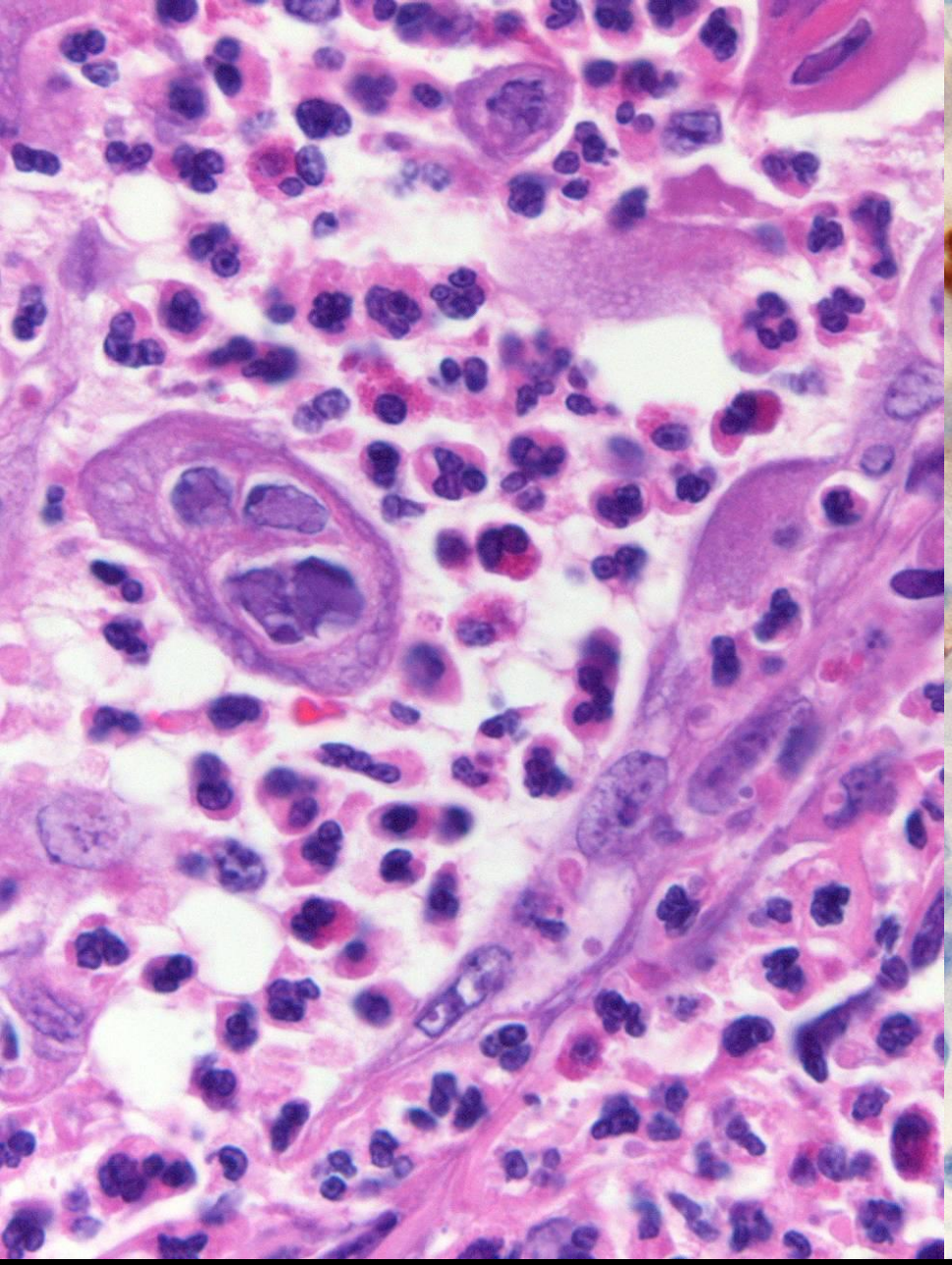
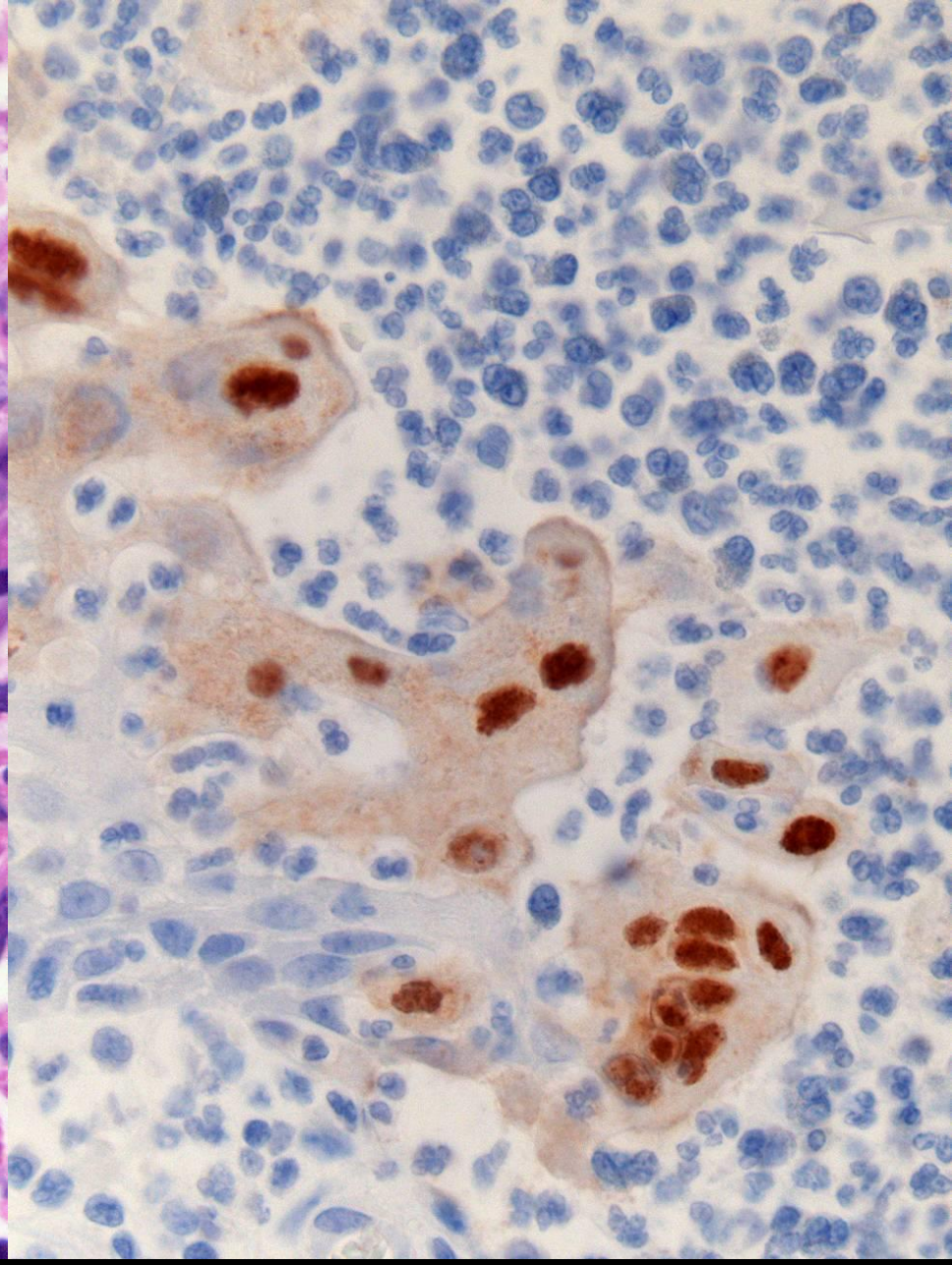
Squamous Cell Carcinoma of the Vulva

- Most occur on labia
- Clitoris involved in <15%
- Multifocal in <10%
- Exophytic papillary mass or endophytic ulcer







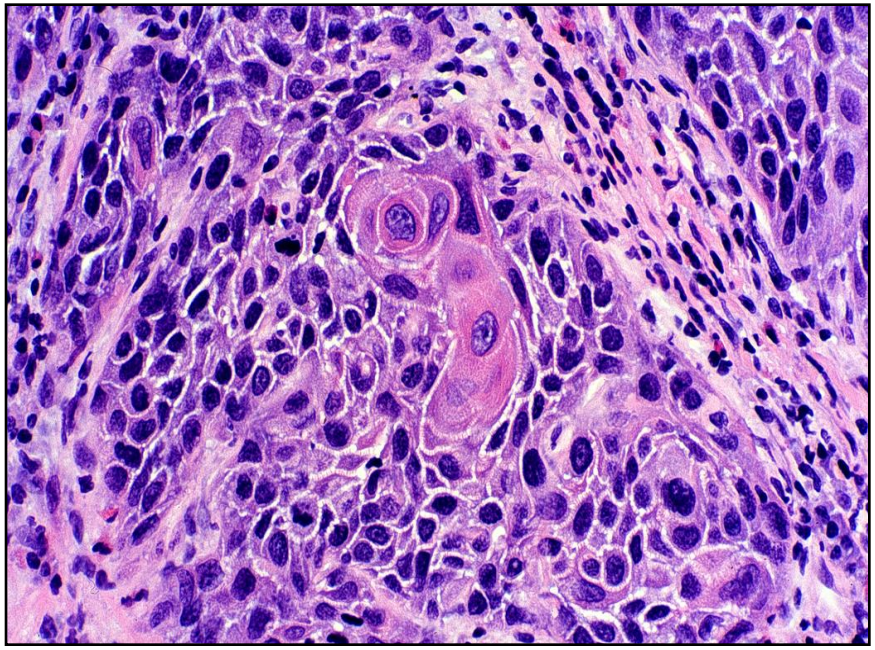
Chronic hypertrophic vulvar herpes simulating neoplasia.

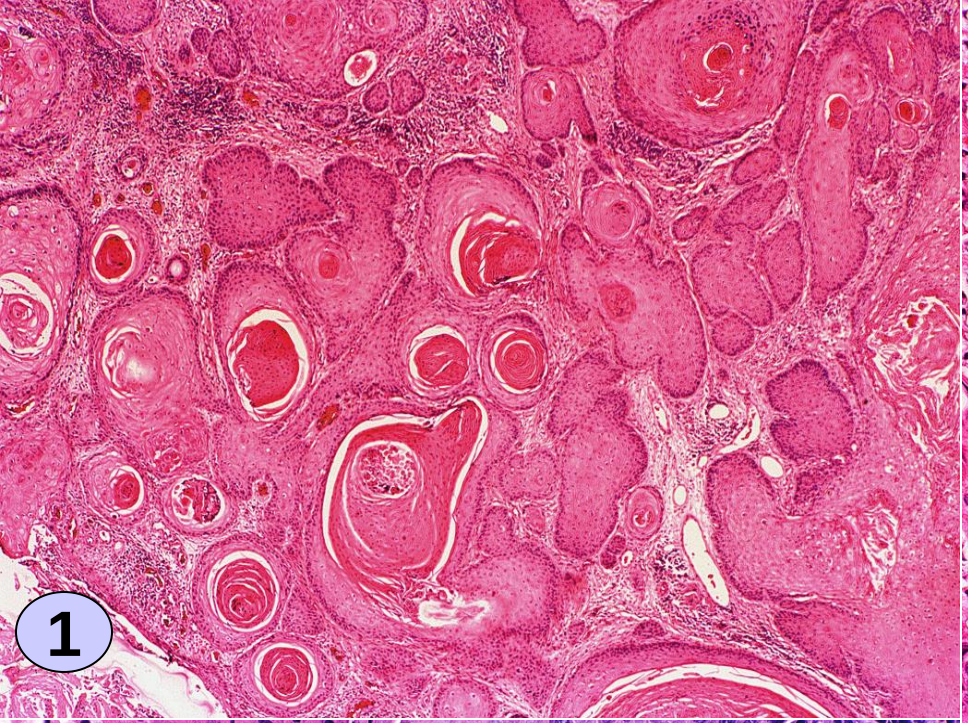
International Journal of Gynecological Pathology 2012;31(1):33-37.

We present a case of a 40-year-old woman with a history of human immunodeficiency virus infection and a nodular, hyperkeratotic 3.5-cm vulvar mass that increased in size over a 2-month period. Histopathologic examination of the excised mass was diagnostic of chronic hypertrophic vulvar herpes simulating neoplasia. Hypertrophic vulvar herpes presents a diagnostic challenge for both pathologists and clinicians because of its unusual clinicopathologic features that mimic neoplasia and its rarity. There is therefore the need for the correct diagnosis of this entity, so that appropriate therapy can be given. The pertinent literature is reviewed and discussed.

Grading of Vulvar Squamous Cell Carcinoma

- ***Grade 1:*** **No poorly differentiated component**
- ***Grade 2:*** **< 50% poorly differentiated component**
- ***Grade 3:*** **> 50% poorly differentiated component**

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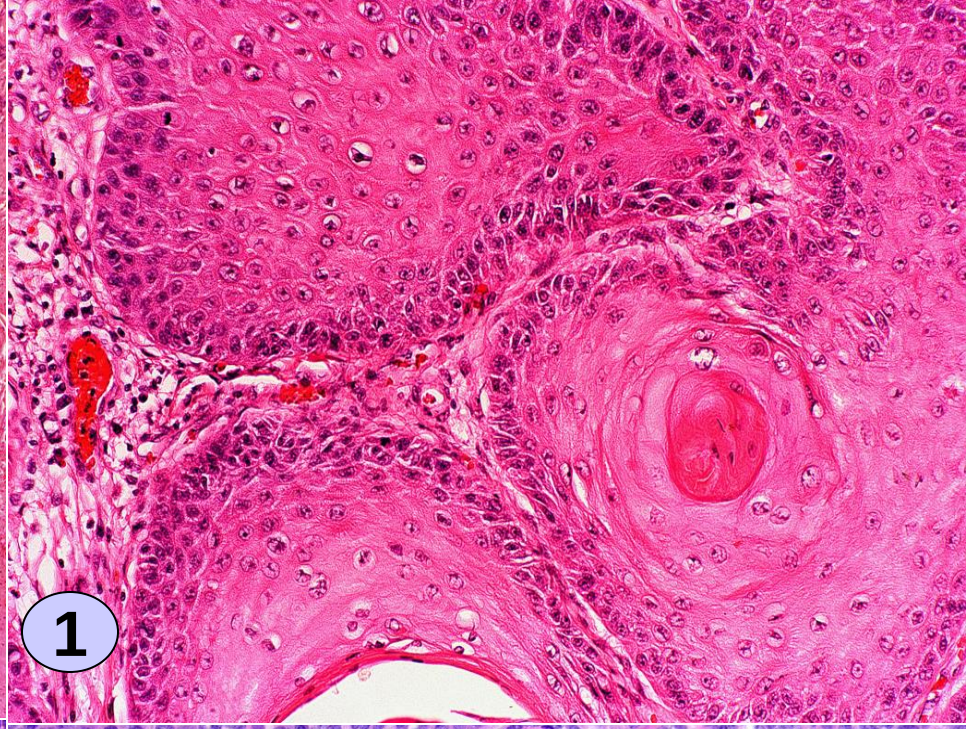
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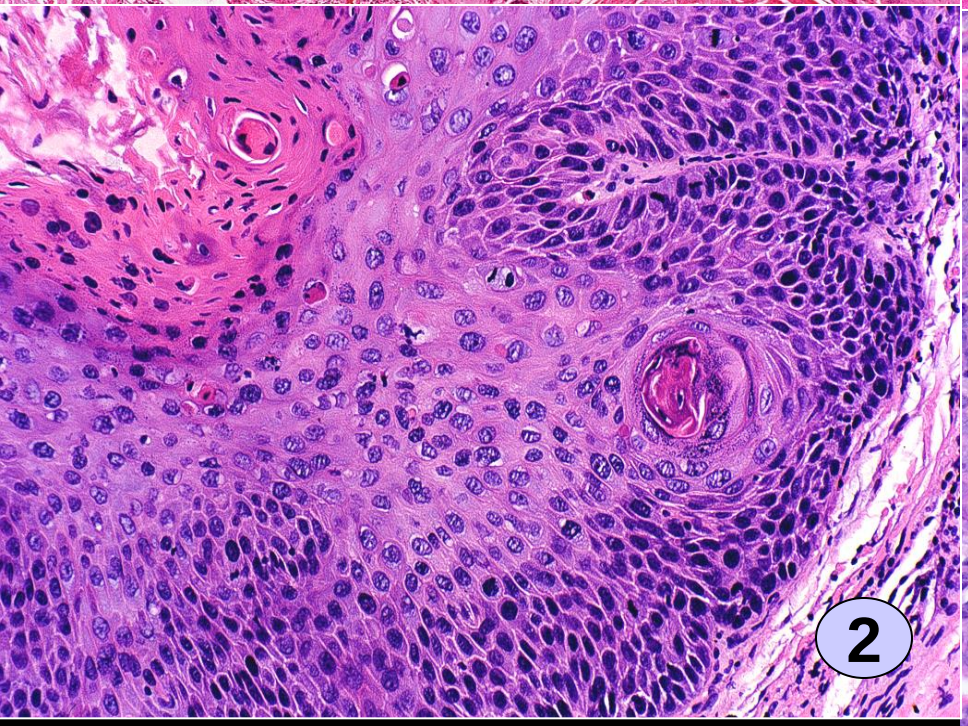
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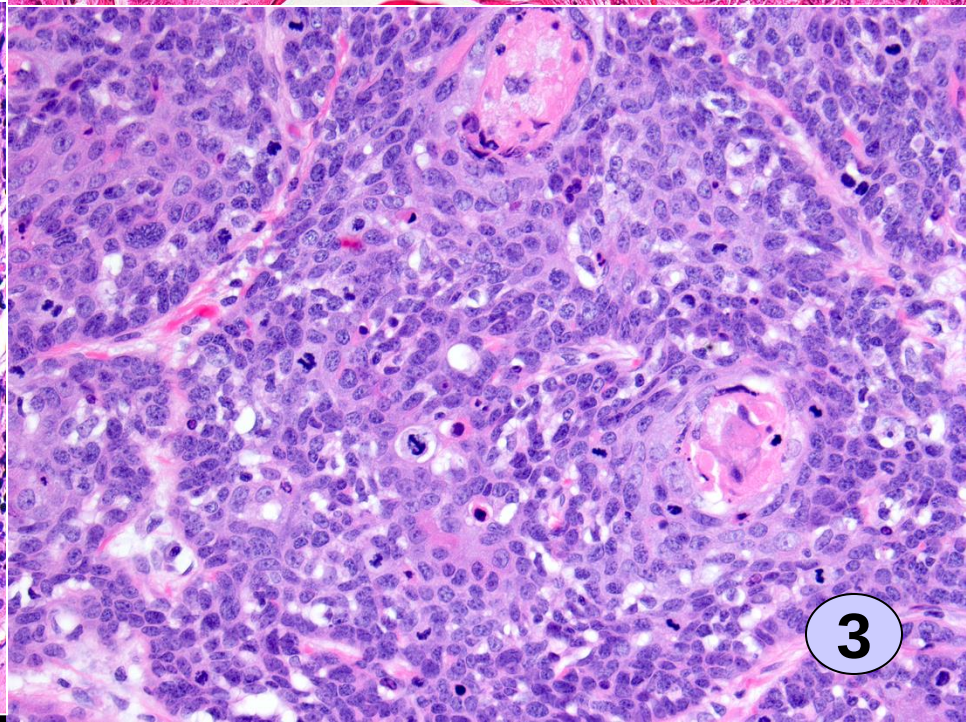
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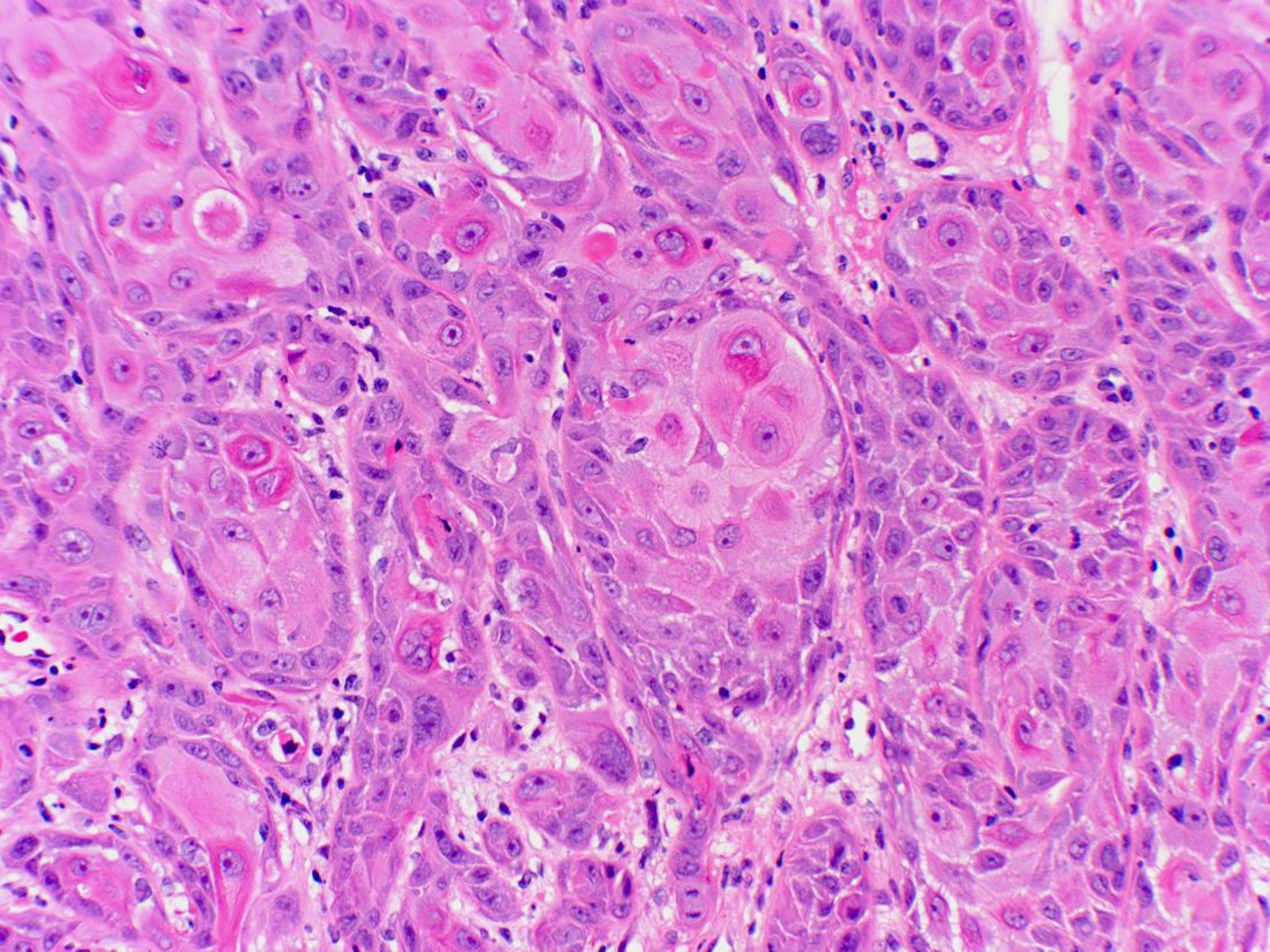
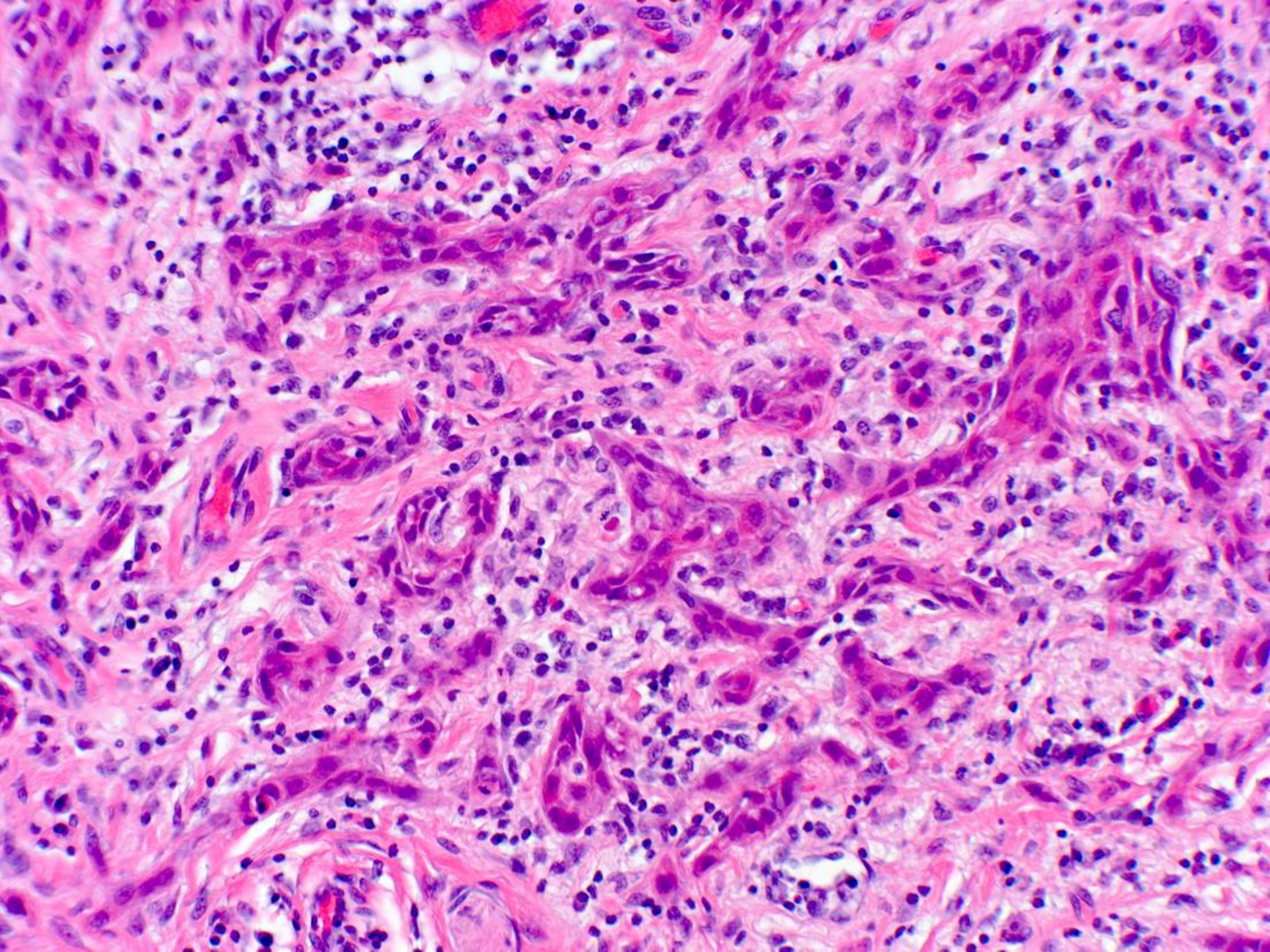
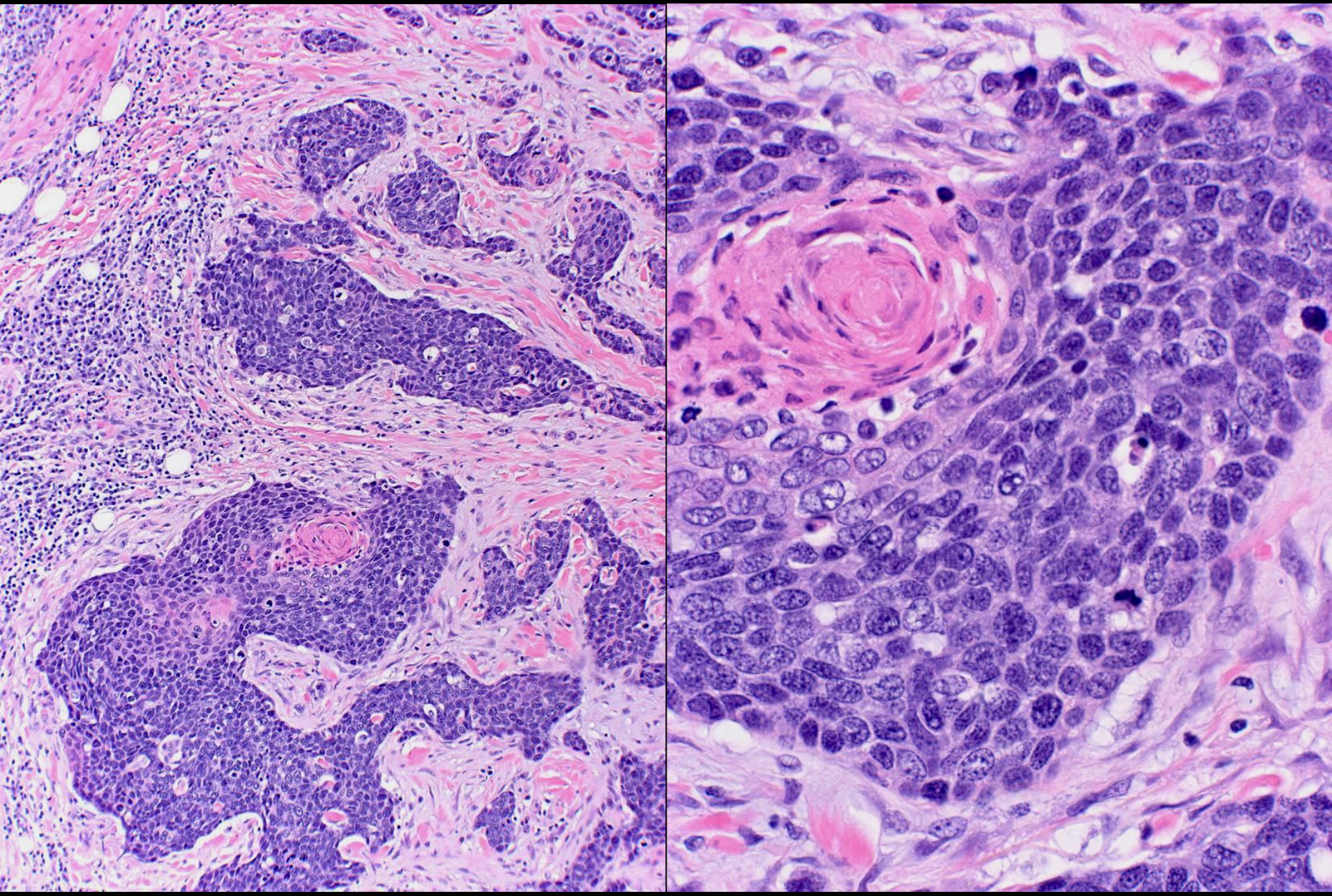
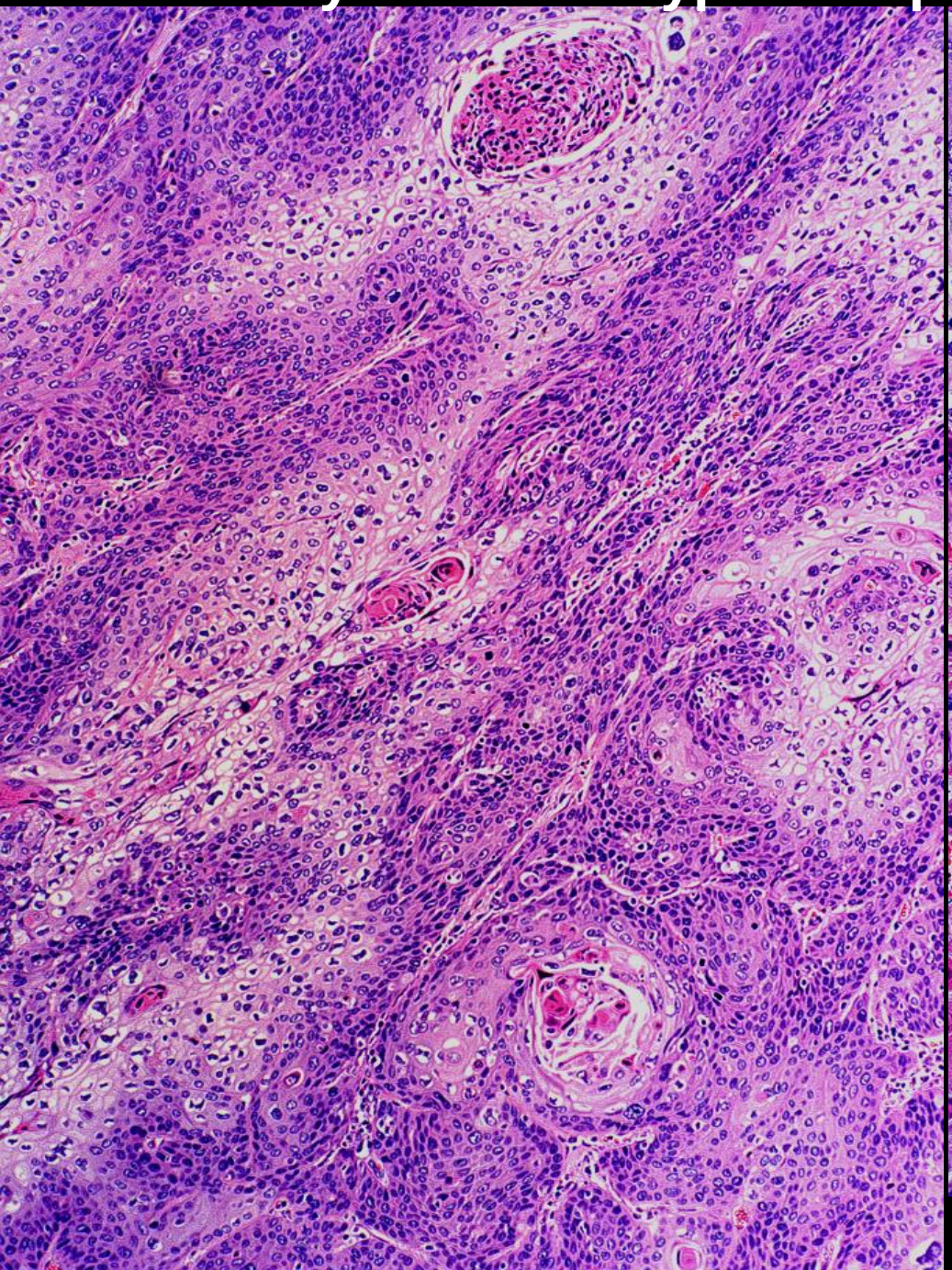


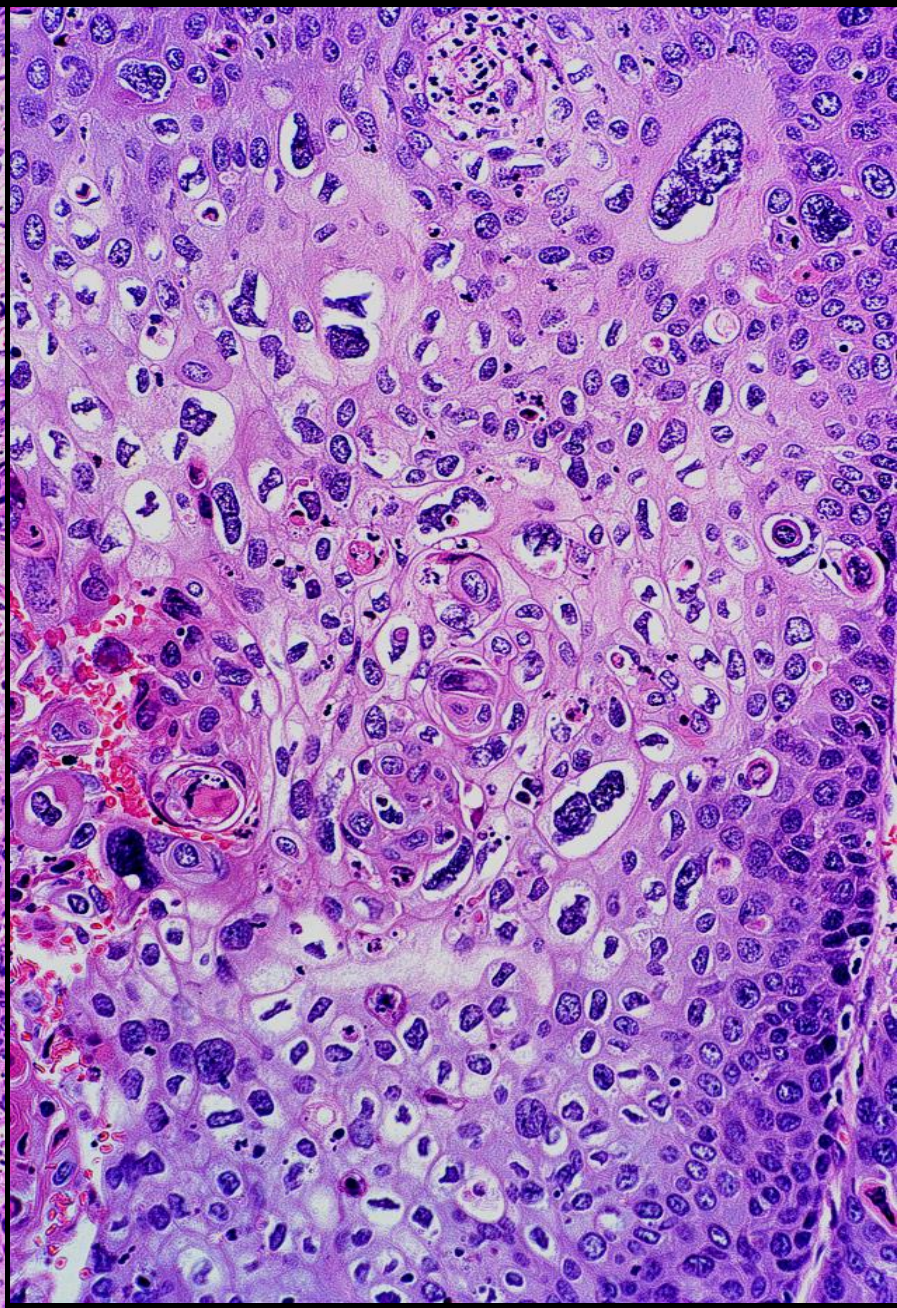


Basaloid Type of Squamous Cell Carcinoma



Condylomatous Type of Squamous Cell Carcinoma





Squamous Cell Carcinoma of the Vulva
Therapy and Results

- **Radical vulvectomy in the past**
- **Treatment now more conservative - wide excision, hemivulvectomy for lateralized tumors**
- **About 30% of patients have LN metastases, lymphadenectomy generally performed; role for SLN Bx**
- **Survival 75% overall, 90-100% stage I**

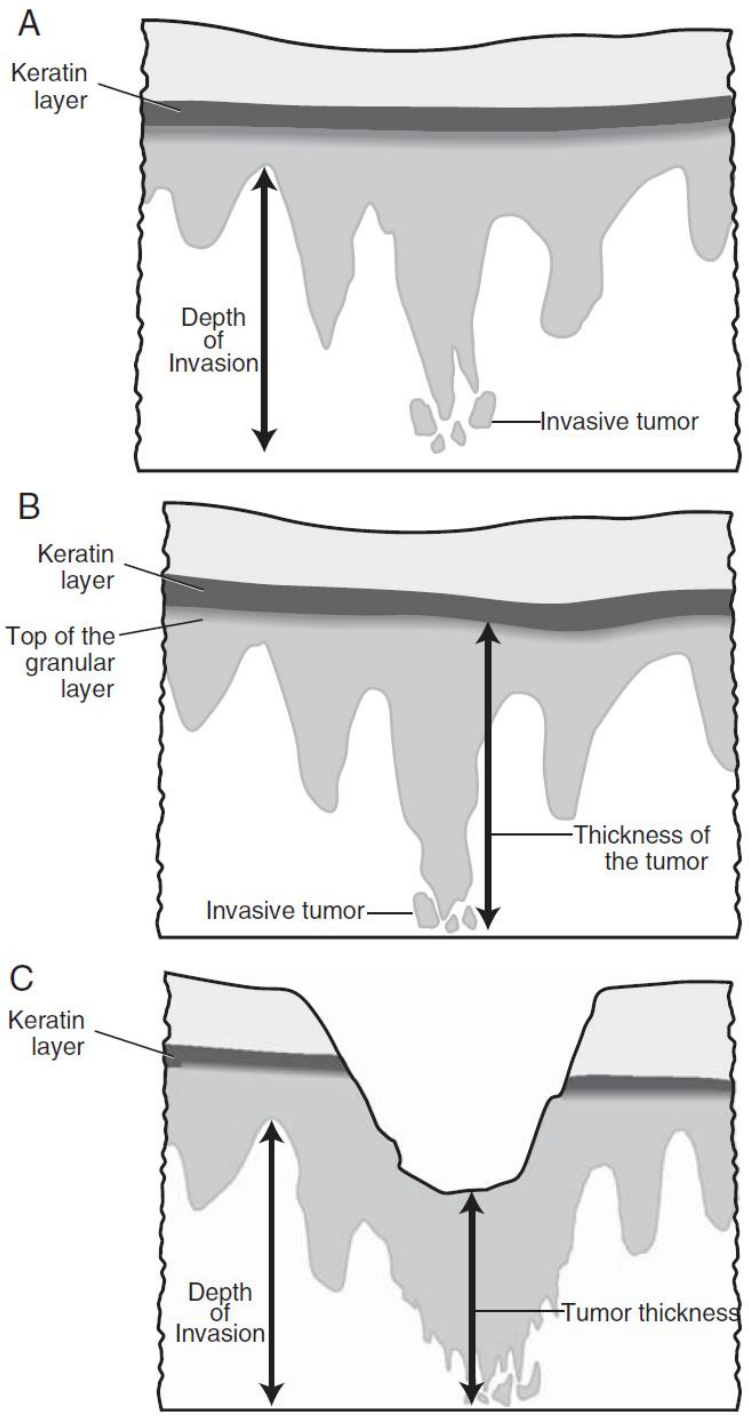
Superficially Invasive Squamous Cell Carcinoma of the Vulva (Stage IA)

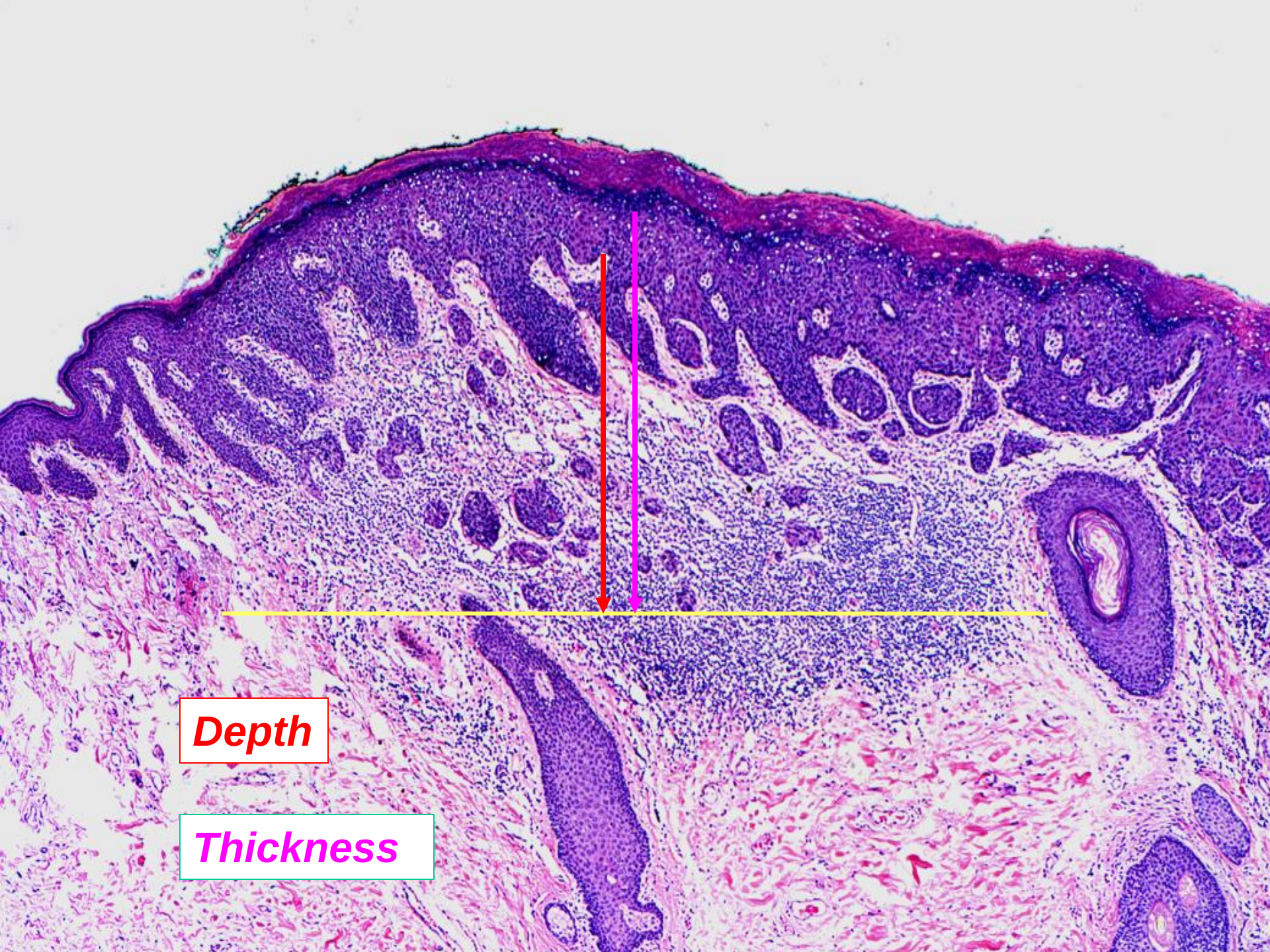
- **The term “microinvasive carcinoma” is not used in the vulva**
- **The category of stage IA is an attempt to define a group with a very low risk of lymph node metastasis**
- **Definition: ≤ 1 mm in depth and ≤ 2 cm diameter**
- **Lymphovascular invasion, growth pattern do not exclude tumors from this category**

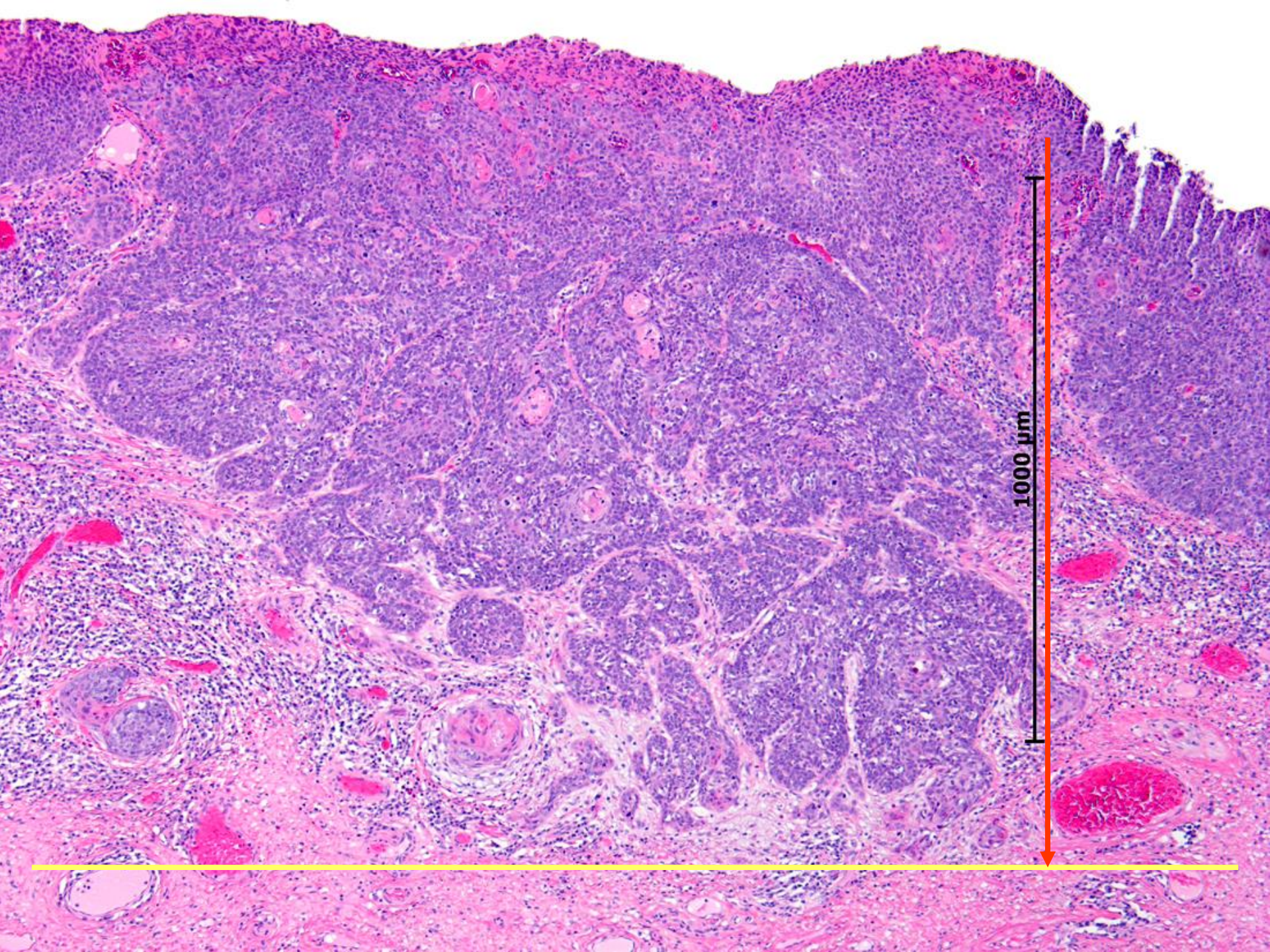
Squamous Cell Carcinoma of the Vulva

Measurements of Invasion

Depth = From the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion




Depth
Thickness


1000 µm

Verrucous Carcinoma of the Vulva

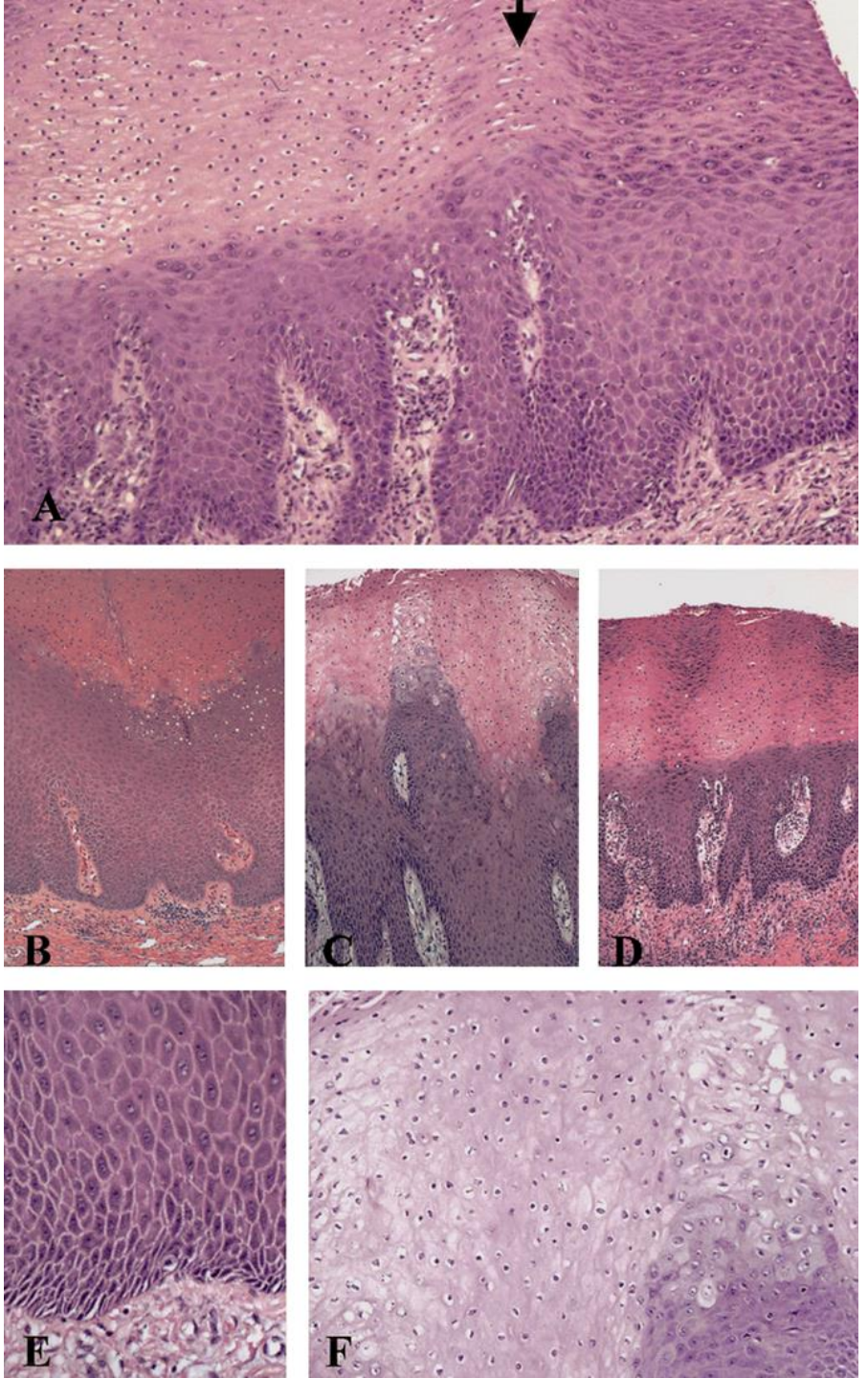
- **Elderly women**
- **Locally aggressive with eventual formation of a large warty tumor**
- **Lymph node metastases are rare**
- **Treatment is by wide local excision; vulvectomy may be necessary**
- **5-year survival ~ 80%**

Findings Adjacent to Verrucous Carcinoma of Vulva

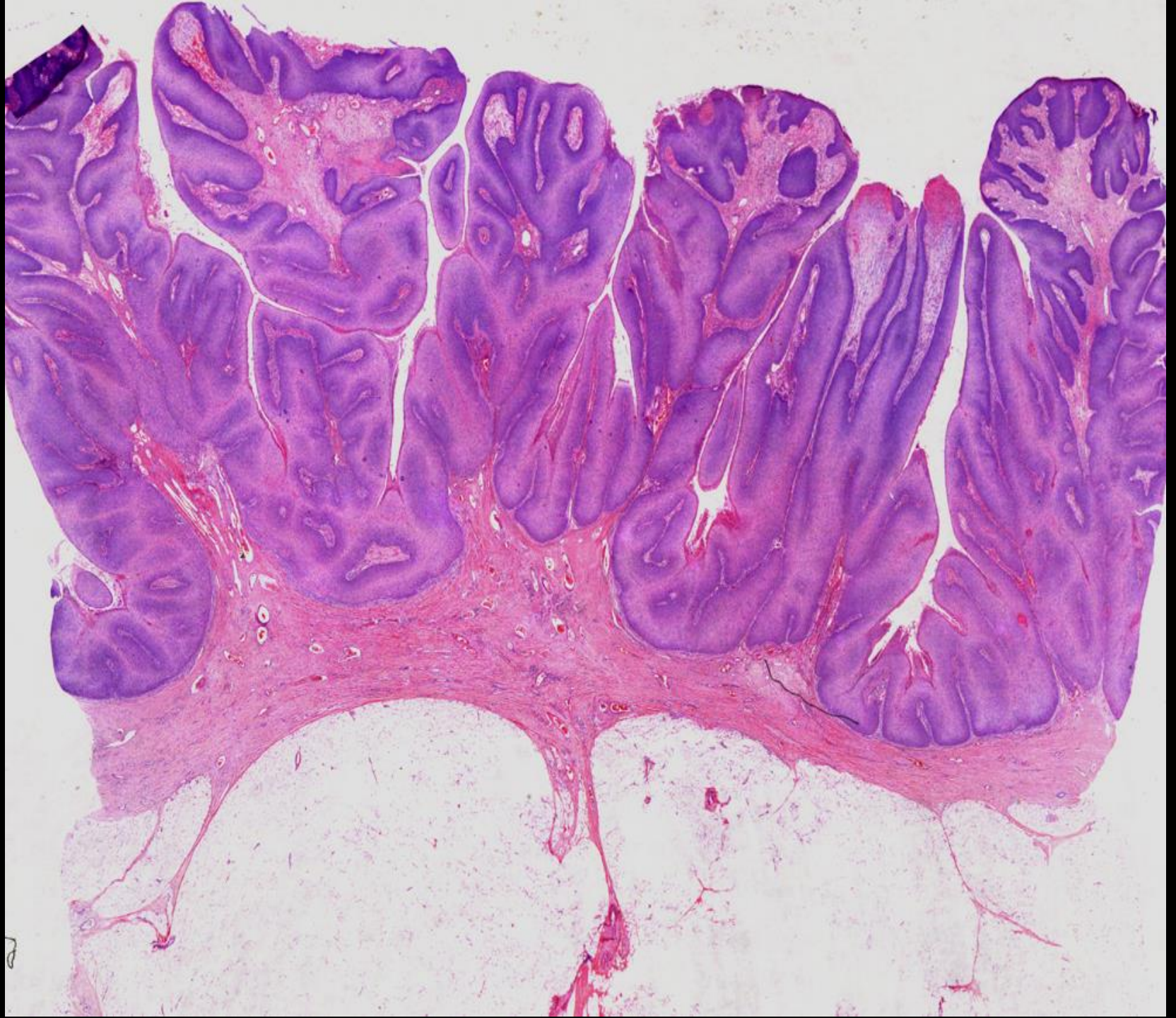
- **Lichen Sclerosis – 1**
- **LSC with verrucous features – 7**
- **VAAD – 7**
  - **Vulvar acanthosis with altered differentiation**
  - **Variable verruciform architecture**
  - **Plaque like parakeratosis**
  - **Cytoplasmic pallor due to loss of granular layer**
- **No Classic or differentiated VIN**

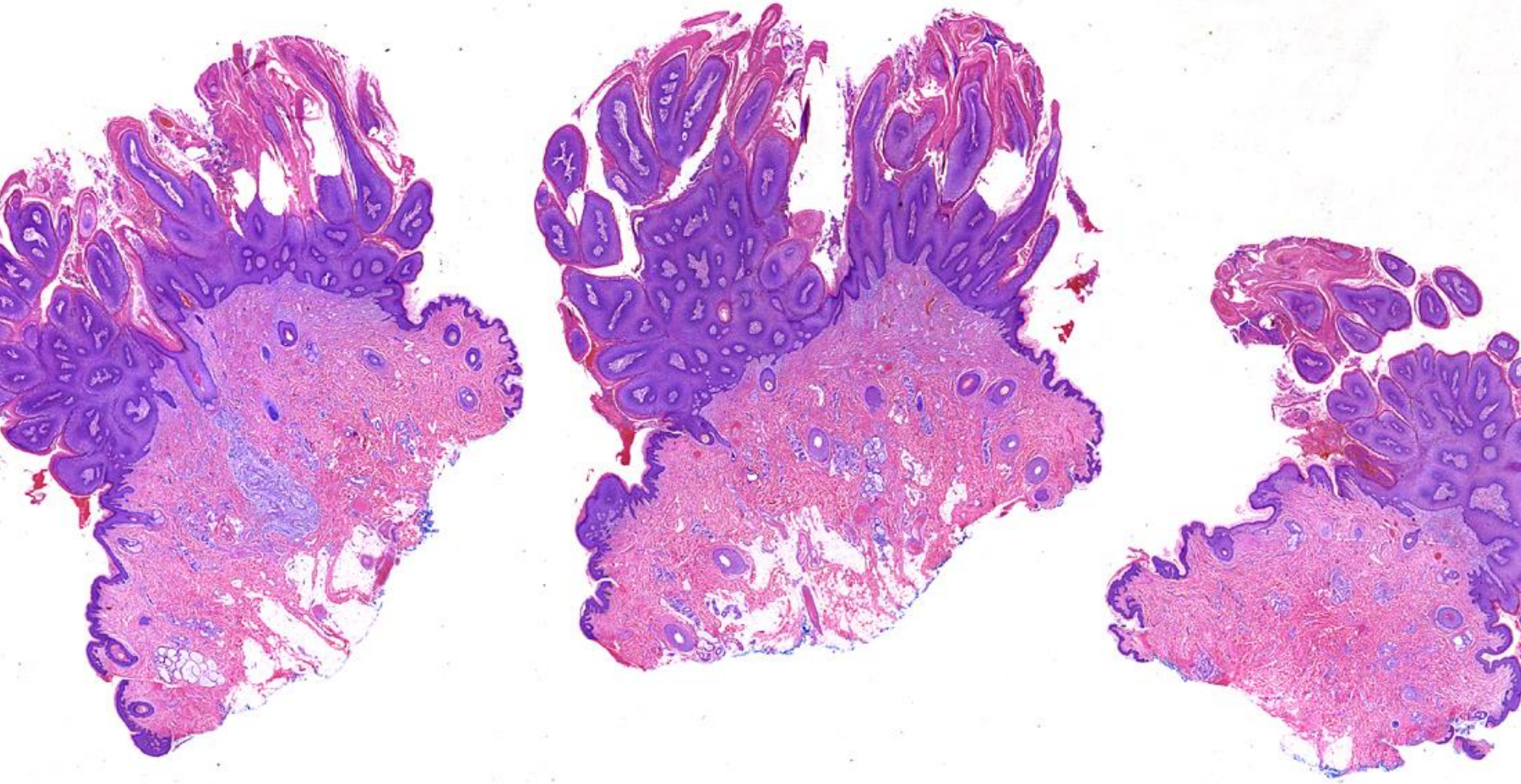
Am J Surg Pathol 2004;28:638-643

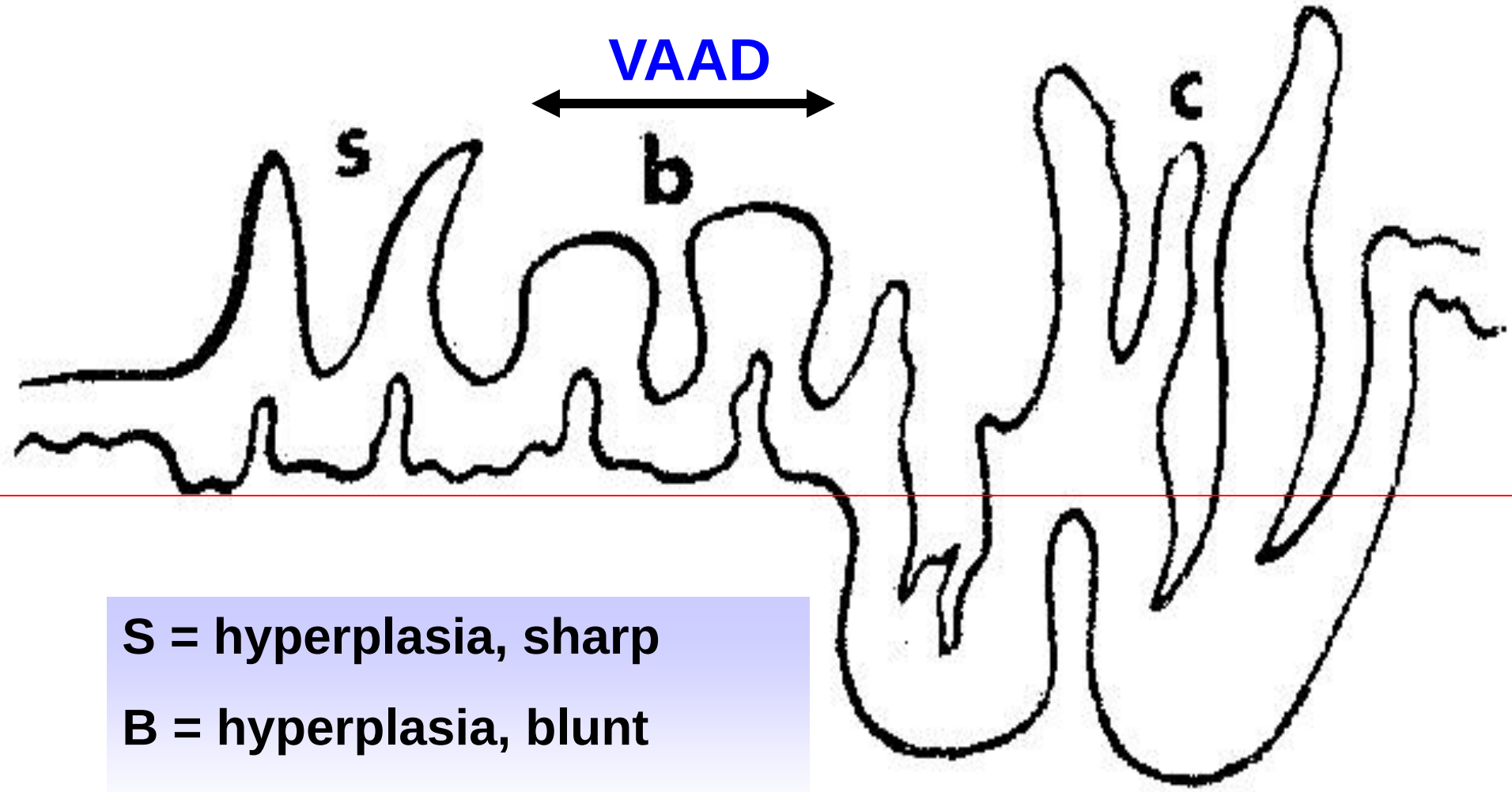
Vulvar acanthosis with altered differentiation



Am J Surg Pathol 2004;28:638-643



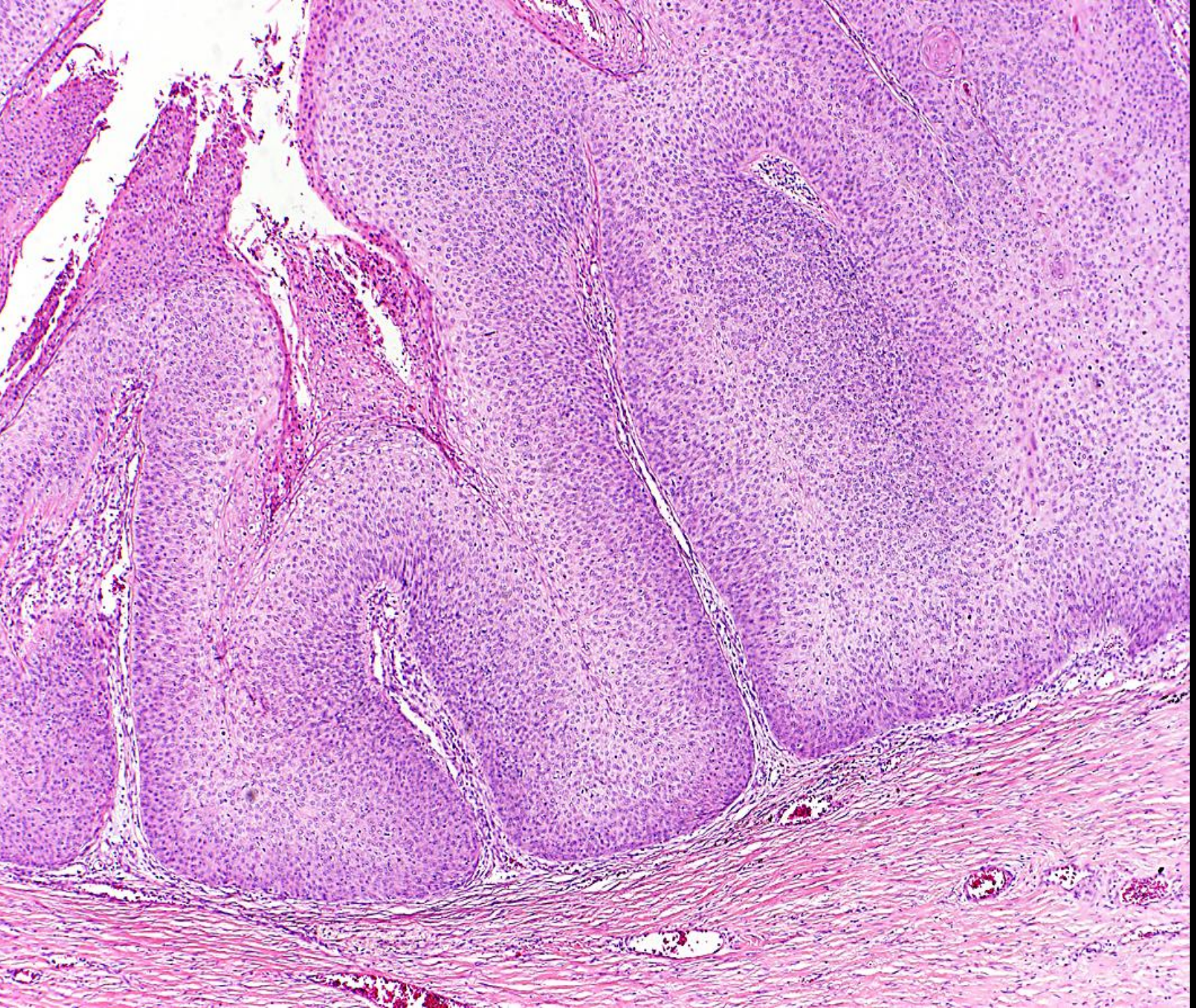


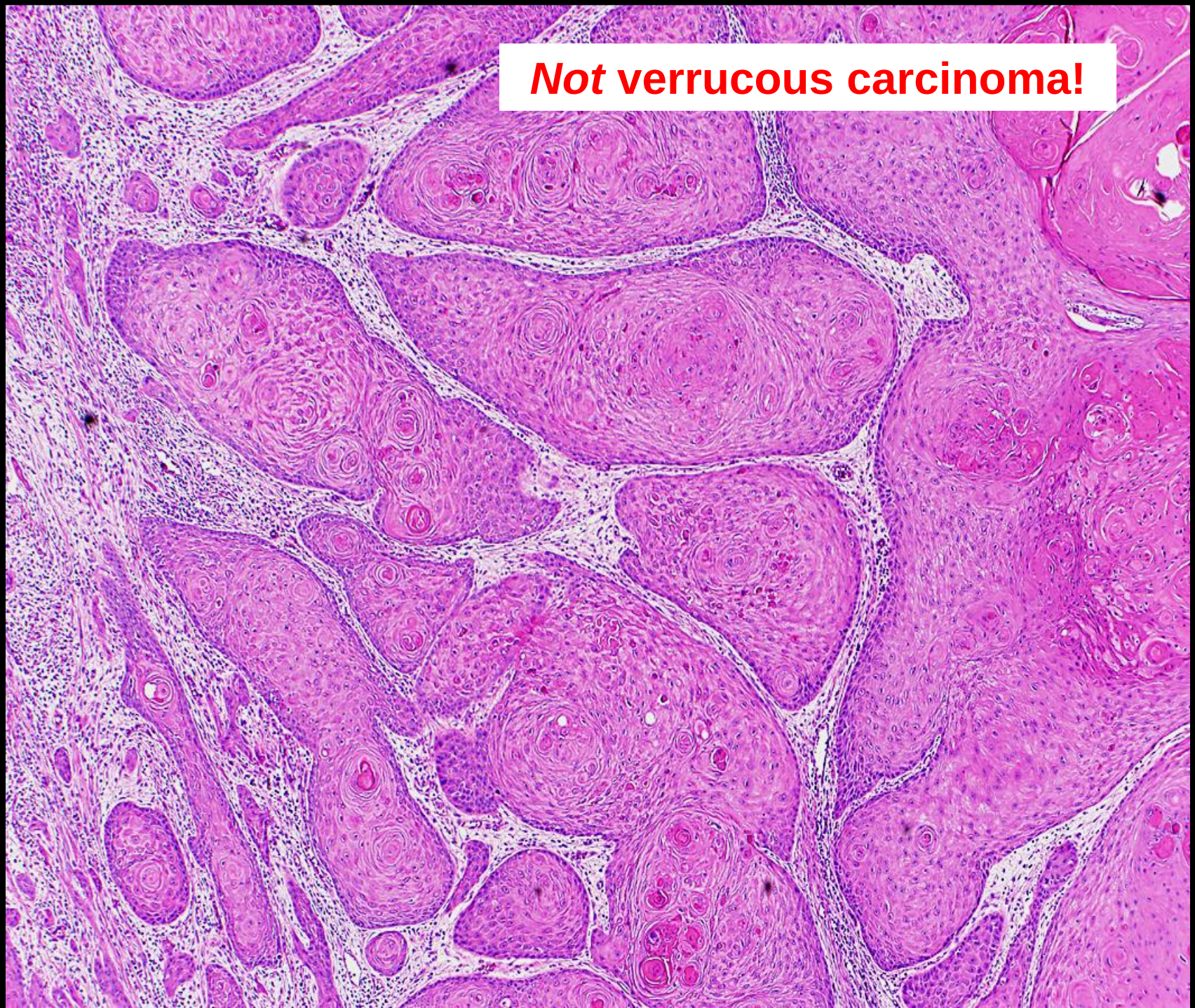


S = hyperplasia, sharp

B = hyperplasia, blunt

C = verrucous carcinoma




Not verrucous carcinoma!

Despite the name "verrucous" carcinoma…

No good evidence of an association with HPV

Verrucous Carcinoma and HPV

- **27 cases initially classified as VC reviewed; after review 13 accepted**
- **11 cases initially classified as VC of vulva/perineum**
  - **5 accepted as VC – none had HPV**
  - **4 reclassified as SCC – none had HPV**
  - **2 reclassified as giant condylomas, 1 had HPV 6, 1 had HPV 11**
- **Conclusions**
  - **HPV unlikely to be causally related to VC**
  - **Positive HPV test favors giant condyloma over VC**

Mod Pathol 2012; 25:1354-1363

Low risk HPV in situ in a giant condyloma