Beyond the Digits: Vulval Analogue of Aggressive Digital Papillary Adenocarcinoma

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Disclosures

I do not have any relevant financial relationships to disclose.

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Adnexal Neoplasms: *Acral Focus*

- Arise from **eccrine sweat gland** adnexal structures.
- **Common Sites:**
  - **Digits, palms, and soles** – areas with **high eccrine gland density**.
  - Increased gland density → higher likelihood of tumor formation.
- **Benign vs non-benign**
  - **Benign**: well-circumscribed intradermal proliferations with **ducts & tubules**, frequent **cystic change**, sometimes **papillary** architecture.
  - **Non-benign**: **infiltrative borders**, **cytologic atypia (nuclear size; pleomorphism)**, increased **mitoses**, necrosis
  - May show **ductal differentiation** on IHC with basal or myoepithelial evidence in places.

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Pathways

Pathway	Precursor lesion	Metastatic risk	Clinical implications
Pathway 1 (step-wise)	Yes — benign → papillary/cystic → carcinoma	Lower (when caught early)	Good prognosis if excised early; focus on histologic progression signs
Pathway 2 (de novo malignancy)	No benign precursor	Higher metastatic potential	Requires high-index of suspicion, aggressive treatment & follow-up

- **Pathway 1 — Stepwise progression**
  - **Benign → intermediate → carcinoma**
  - Morphologic evolution: rising **nuclear atypia**, **mitoses**, and **transition from circumscribed to infiltrative borders** as lesions progress.
  - Activation of **RAS–MAPK signaling: KRAS/BRAF/MAP2K1**
  - Lower risk
  - Metastasis rate: ~3%
- **Pathway 2 – De Novo Malignancy**
  - *No Benign Precursor*
  - **Virally driven track**
  - High risk of recurrence and metastasis

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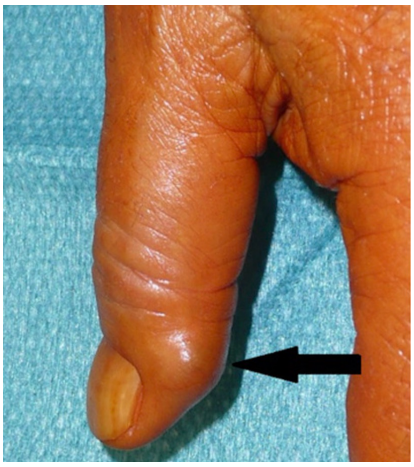

Classic ADPA: clinical pattern

- **Aggressive digital papillary adenocarcinoma (ADPA)** malignant eccrine tumor with **tubulopapillary and nodulocystic** growth
- Predilection: acral surfaces (digits)
- Typical presentation: **painless, slowly enlarging mass**
- Mistaken for cyst, ganglion, infection.
- **Wide excision or amputation** lowers recurrence (~5%) vs limited procedures (~50%).
  - simple excisional biopsies, narrow-margin excisions or curettage
- **HPV-42** strongly associated with ADPA

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Histology and immunophenotype you should recognize

Architecture: well-circumscribed **solid-cystic dermal nodule** with **papillary fronds** and **back-to-back glands**. Myoepithelial **outer layer** present.

Cytology: cuboidal→columnar cells, variable atypia and mitoses.

IHC pattern: CK7+, **SOX10+**, p63 highlights myoepithelial rim; **p16 often block-positive**; **BRAF negative**.

HPV42 nucleic acids detectable by RNA/DNA in situ or qPCR.

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Acral vs Non-Acral ADPA

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Acral predominance: 238/245 reported cases on digits, palms, soles

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7 Non-acral reported cases
- **Vulva (n=3)**
- **Perianalgenital (n=1)**
- **Forearm (n=1)**
- **Scrotal (n=2)**

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HPV-42+ ADPA Cases: 60
- **Acral (n=53)**
- **Non-acral (n=7)**

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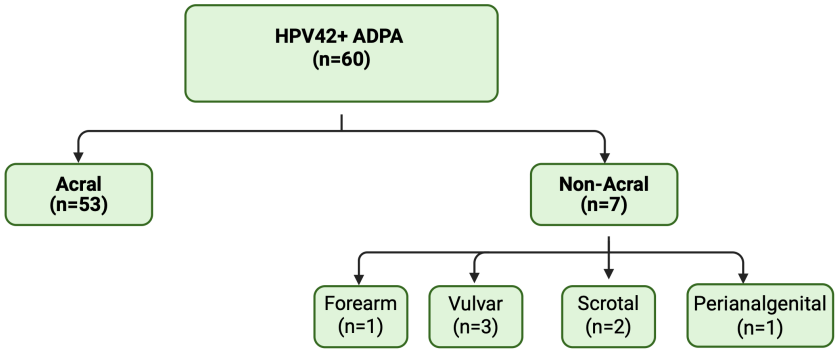
Distribution by Site and HPV42 Status



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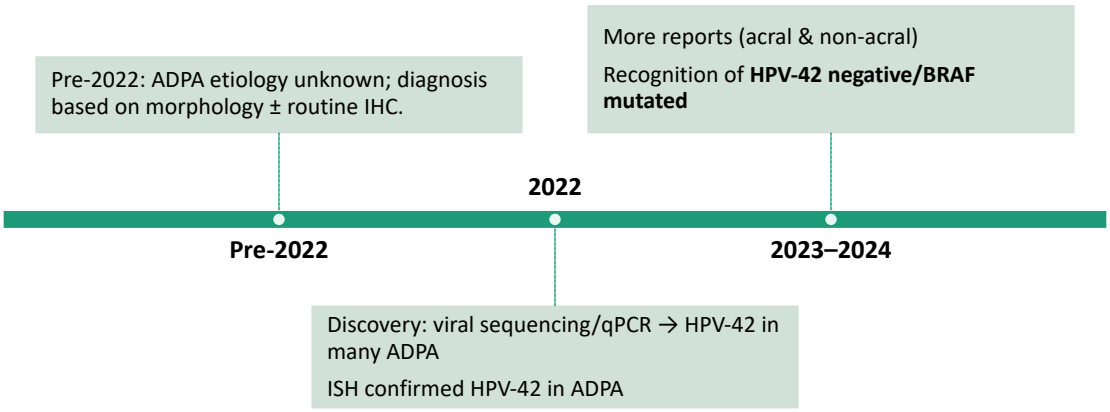
HPV42 drives De Novo ADPA



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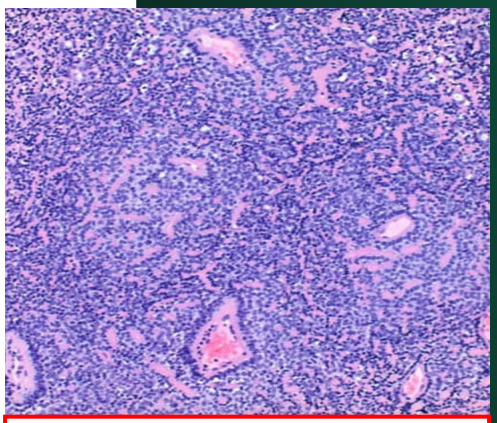
Our Case

- 48-year-old woman with enlarging left vulvar mass (4 months)
- Initial biopsy conclusion: **spiradenoma**
- Second assessment:
  - atypical basaloid adnexal neoplasm with ductal differentiation, cytologic atypia, atypical mitoses
- Decision: partial vulvectomy for definitive diagnosis and staging
  - Primary Diagnosis: HPV42 associated sweat gland adenocarcinoma
  - Final diagnosis: **vulval analog of aggressive digital papillary adenocarcinoma**



Ductal-Glandular Differentiation
Basaloid Cells
Hyaline-Basement Membrane Material

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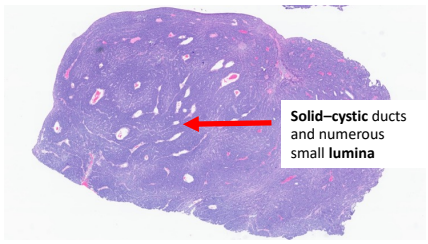
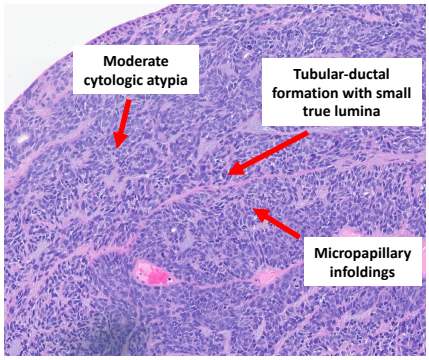
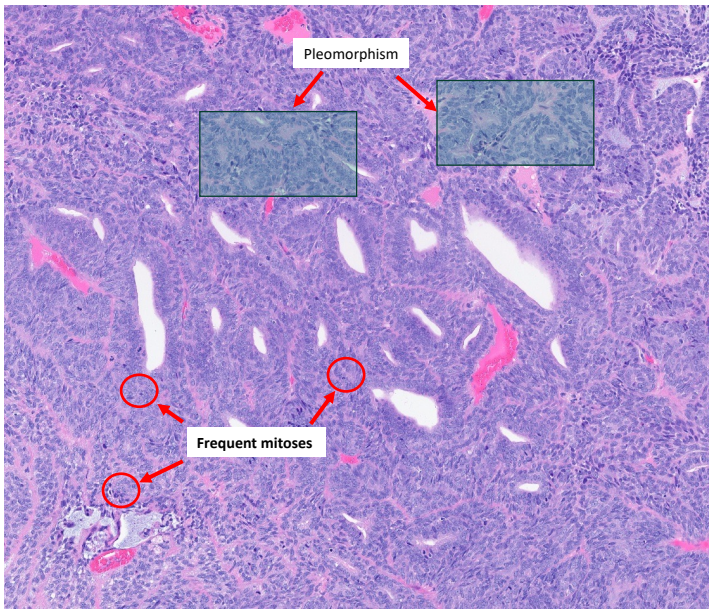

Solid–cystic ducts and numerous small lumina


Moderate cytologic atypia
Tubular-ductal formation with small true lumina
Micropapillary infoldings


Pleomorphism
Frequent mitoses

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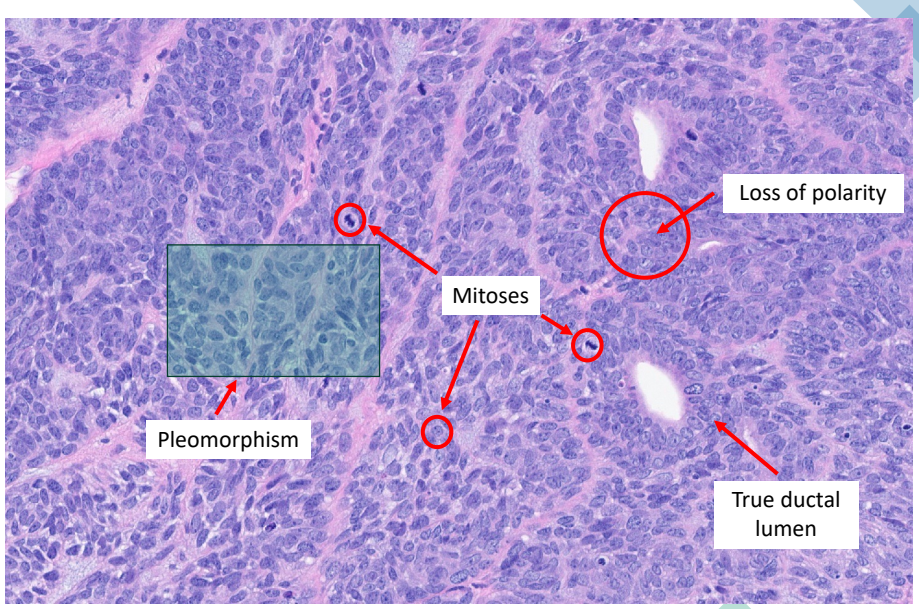
Loss of polarity
Mitoses
Pleomorphism
True ductal lumen

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Histopathology, immunophenotype, and HPV testing

CK7+	• Marks gland & duct epithelium • supports ductal adnexal carcinoma
p63+	• Smooth muscle myosin positive • Patchy staining W/O continuous myoepithelial layer: supports invasion
SOX10+	• Nuclear marker: neural crest & adnexal/myoepithelial cells • supports digital papillary adenocarcinoma
Ki-67	• Proliferation index • High index → malignant behavior
HPV ISH	• Detects HPV nucleic acids • No intranuclear punctate signal: HPV negative?
p16 block positive	• Surrogate for HPV-driven oncogenesis when block-positive • Diffuse labeling but HPV ISH is negative: non-HPV driven?
BRAF negative	• Diffuse cytoplasmic positivity when mutated • Negative: Argues against BRAF mutation origin
HPV42+	• HPV42 detected on targeted testing • De Novo Pathway

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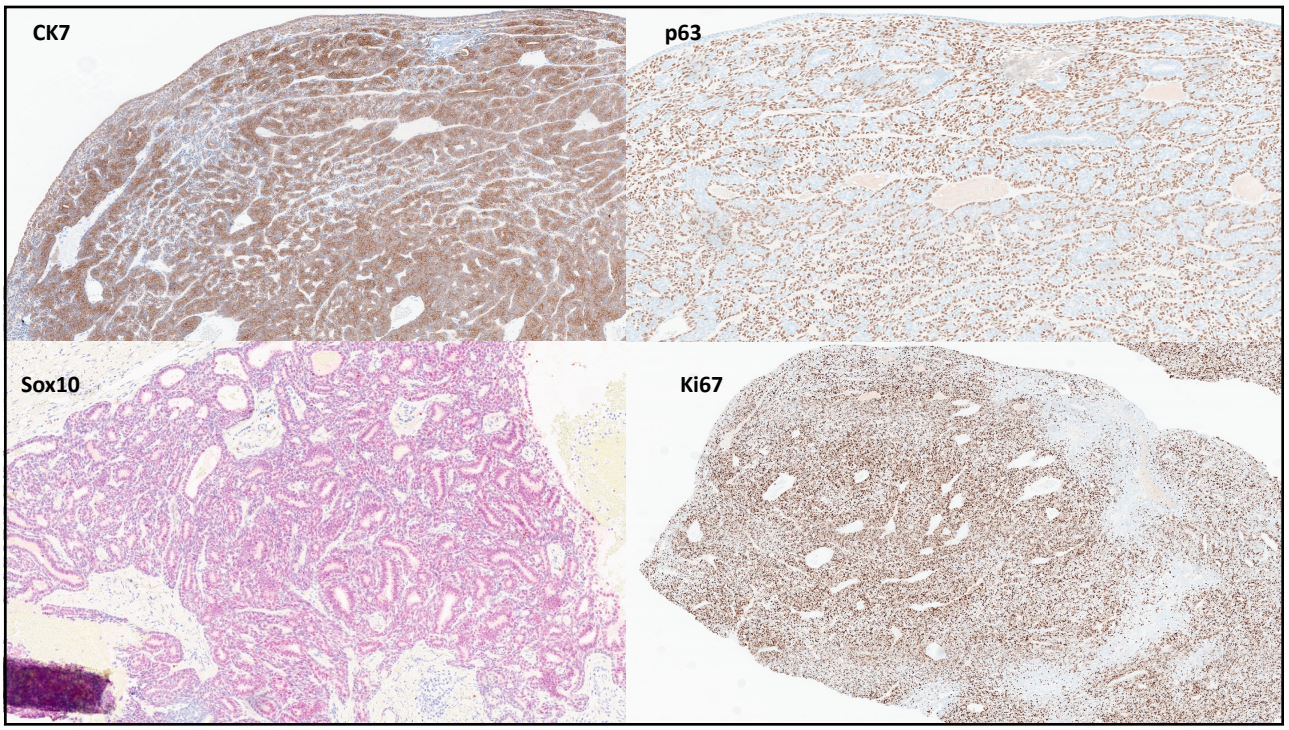

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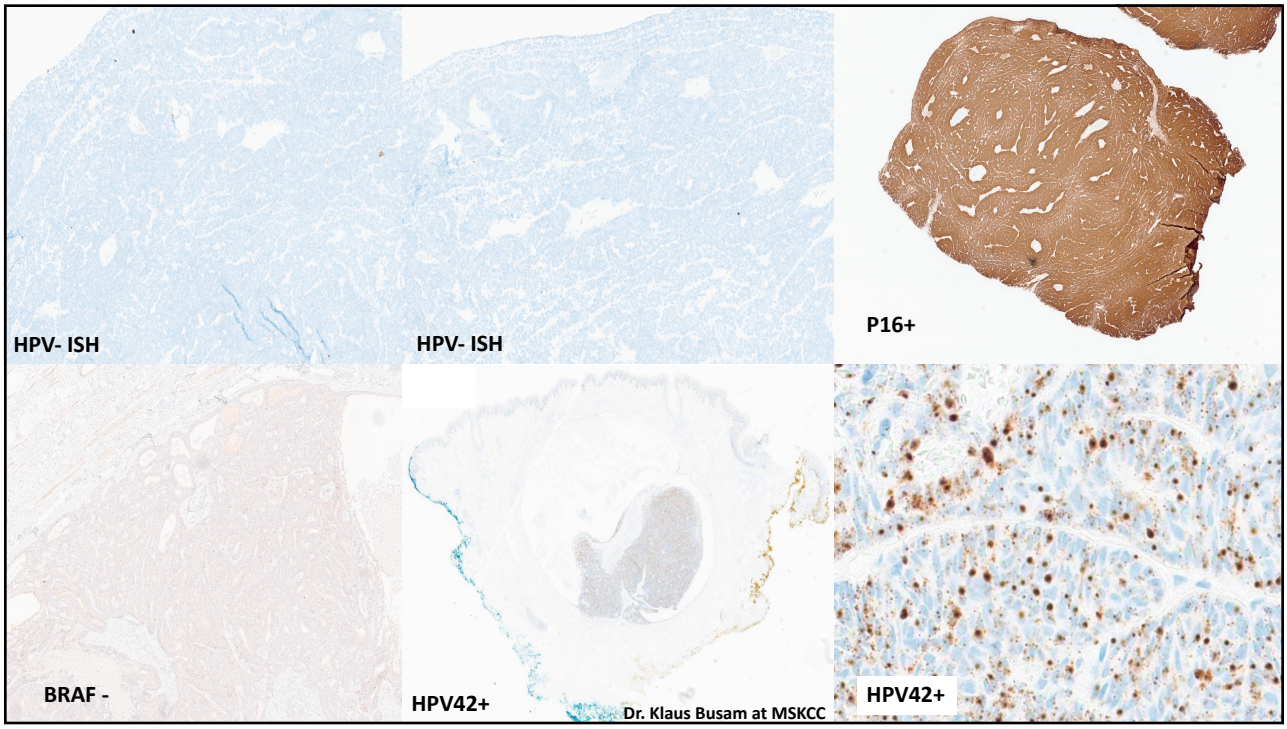

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Final diagnosis, staging, outcome

Final diagnosis: vulval analogue of digital papillary adenocarcinoma

Margins: negative

Sentinel lymph node: negative

PET/CT: negative

Current status: remission under surveillance

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Diagnosing ADPA when HPV-42 testing isn't available

1. **Morphology first (H&E):** deep multinodular **solid–cystic duct-forming** tumor with **infiltrative cords**, **atypia**, and **mitoses**.
2. **Ductal/primary adnexal panel: CK7, EMA, CEA**
3. **Myoepithelial assessment (to show loss): p63**, **SMA, calponin** → expect **no continuous rim** in DPA.
4. **Exclude mimics/metastases**
5. **Proliferation: Ki-67** (often high)
6. **HPV work-around:** If HPV status matters but HPV-42 not available, use **broad high-risk HPV RNA/DNA ISH or PCR genotyping**
7. **Optional molecular profiling:** targeted **DNA/RNA Next Generation Sequencing** to survey **MAPK/PI3K** genes and support exclusion of metastasis.

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HPV "cocktails" and Limitations

- **Don't rely on "high-risk" HPV cocktails:** they usually **don't include HPV-42** → a negative result **does not rule out** HPV-42 ADPA.
- **p16:** often positive in low-risk HPV but **not specific** → **supportive only**.
- **BRAF IHC is key: BRAF V600E positive** → **MAPK-pathway tumor** (BRAF-driven mimicker) and **effectively excludes the viral (HPV-42) pathway** in practice.
- **If BRAF–negative but morphology suggests ADPA:** order **HPV-42–specific testing**
- **If available: RNA-ISH** (targets **6/11/40/42/43/44**) can demonstrate **HPV-42 activity**

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Conclusion

- ADPA is overwhelmingly **acral**
- Rare **non-acral** cases
- Two largely **mutually exclusive** routes: **BRAF/MAPK** vs **HPV-42 driven**
- Standard high-risk HPV panels miss HPV42 → use **type-specific testing**
- **Architecture drives the call:** when HPV-42 not on the panel, **negatives are expected** in HPV-42–driven ADPA
  - Lean on **morphology + targeted tests**.

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Thank you!

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References

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