CORRESPONDENCE

Comment on *HPV-independent, p53-wild-type vulvar intraepithelial neoplasia: a review of nomenclature and the journey to characterize acanthotic precursor lesions of the vulva. Parra-Herran C. et al Mod Pathol 2022 Apr 18 doi: 10.1038/s41379-022-01079-7*

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TO THE EDITOR:

The pathway from lichen sclerosus (LS) to vulvar squamous cell carcinoma (SCC) is a biological continuum; pinpointing the transition from inflammatory to neoplastic is difficult. This conundrum manifests in the controversy surrounding nomenclature and classification of unusual acanthotic lesions more concerning than LS but lacking the atypia required for differentiated vulvar intraepithelial neoplasia (dVIN). Multiple terms are applied to these lesions: squamous cell hyperplasia, vulvar acanthosis with altered differentiation (VAAD), differentiated exophytic vulvar intraepithelial lesion (DEVIL), verruciform lichen simplex chronicus (vLSC), and atypical verruciform lesion (AVL). Three recent publications address this problem and reach differing conclusions[1–3]. This letter highlights the disagreements and advocates for integration of clinicians into decision-making on proposed terminologies.

Clinicians biopsy treatment-resistant plaques in a field of LS; most show lichenified LS and have medical management. Less often, biopsy shows basal atypia, negative p16 immunohistochemistry (IHC), and null, overexpressed, cytoplasmic, or wild-type p53 pattern; this is dVIN and management of *neoplasia* is excision. Rarely, there is acanthosis, abnormal maturation, absence of basal atypia, negative p16, and p53 interpreted as wild-type or overexpressed1[4]. Biologic status of these *lesions* is uncertain as features may represent response to inflammation or neoplastic transition. Since some regress, clinicians opt for excision or intensified medical management; regardless of treatment modality, close interval follow-up is required.

When considering how to report these biopsies, several issues arise with previous terms. The definition of VAAD is specific—acanthosis, variable verruciform architecture, plaque-like parakeratosis, foci of conspicuous cytoplasmic pallor - as is the verrucous carcinoma precursor hypothesis[5]. "Exophytic" and "verruciform" are contained in DEVIL, but these describe only a subset of lesions. Verruciform LSC wrongly suggests a subtype of lichen simplex chronicus and not all lesions are papillomatous. The word "atypia" in AVL is often understood by clinicians to imply cancer, provoking anxiety and overtreatment. Among these, only VAAD references aberrant maturation, the most consistent and striking lesional feature. Thus, the ISSVD proffered vulvar aberrant maturation (VAM) to (1) describe a spectrum of histopathologic features under a single simple name, (2) signal pathologists' concern that transition to neoplasia may soon arise or has occurred, (3) avoid making premature determinations about "intraepithelial *lesion*" vs "intraepithelial *neoplasia*" status and (4) facilitate individualized decision-making about treatment and follow-up.

Parra-Herran et al. express disapproval of VAM and instead propose "HPV-negative, p53 wild type, verruciform acanthotic vulvar intraepithelial neoplasia" [HPVi(p53wt)vaVIN]. They argue these cases are always neoplastic, pointing to mutations in NOTCH1, RAS, and PIK3CA, and progression to SCC in 40% in 3 to 4 years. They advocate for abandonment of VAAD, DEVIL, and vLSC to better align terminology with tumor biology rather than morphology. In contrast, the 2020 WHO classification categorizes DEVIL and VAAD as sub-types of dVIN, under a heading of HPV-independent neoplasia.

Beyond non-alignment, there are several concerns with both proposed nomenclatures.

- Mutations are not definitive evidence of clinical neoplasia. Sun-damaged skin contains numerous mutations to include *TP53*, but SCC arises when there is basal atypia as in actinic keratoses and Bowen's disease[6]. Genetic testing is unavailable outside of research settings so extrapolation of neoplastic potential from mutational analysis cannot yet guide clinical practice.
- The relationship of p53 IHC patterns to *TP53* mutations, other oncogene mutations, abnormal protein expression, and neoplasia is complicated and not fully understood. Wild type p53 was traditionally defined as variable staining of scattered basal and/or suprabasal nuclei, similar to expression in normal skin. However, wild type p53, suggesting a "resting state", is a dysfunctional response to neoplasia. The meaning of "overexpressed" recently shifted from a descriptive term signifying more intense and continuous staining than wild type, to a stringent definition of ≥80% of basal nuclei darkly stained, indicative of *TP53* mutation. An intermediate pattern between wild-type and this recent conceptualization of overexpressed exists in 15% of dVIN cases. In vulvar disease, the behavior and mutational status of intermediate cases is unclear and IHC

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interpretation is variable. In endometrial carcinoma, the definition of wild type was broadened to include moderate to strong intensity staining of the majority of nuclei; degree of staining was subdivided into with "low" and "high" wild type, reflective of varied proliferative activity[7]. "High" wild type may be difficult to distinguish from tumors with splice site or nonsynchronous *TP53* mutations interpreted as p53 overexpressed but with "lesser degree of p53 staining than would be expected". Within the HPVi(p53wt)vaVIN, it is unclear how to classify lesions with acanthosis, aberrant maturation, nonatypical nuclei, and p53 patterns at the high end of wild type or low end of overexpression.

- A criticism of VAM is clinicians may not "acknowledge the neoplastic status of these lesions" nor recognize "the need for excision and close follow up by gynecologic oncology specialists"2. Many gynecologic oncology units lack the resources to monitor complex LS, are less familiar with topical or intralesional corticosteroids than vulvar specialist colleagues, and their surgical expertise is not required to perform excision if indicated.
- Interpretation of these biopsies and IHC patterns is difficult even for experts cross-trained in gynecologic and dermatopathology and engaged in collaboration with experienced vulvar clinicians. Inter-observer agreement in dVIN remains suboptimal; assessment of nuclear atypia is a persistent challenge[8]. When pathologic findings sit in the middle of a spectrum, the 2-sided system of non-neoplastic vs neoplastic forces a decision when expression of uncertainty may be preferable.
- Nomenclature and classification systems must be understandable for clinicians and acceptable to patients. The acronym DEVIL is objectionable to clinicians explaining pathology reports to patients. HPVi(p53wt)vaVIN is too cumbersome for practical use and off-putting for learners.

Frequent changes to terminology confuse and frustrate practitioners, so are best undertaken when knowledge acquisition stabilizes and interpretational challenges are addressed. This is not the situation with unusual acanthotic lesions arising in LS. We agree with removal of VAAD and DEVIL and advocate for revision of the WHO classification to separate these from dVIN. We continue to support VAM as a practical, easily communicated term in a difficult area of pathology that gives clinicians flexibility to individualize management of patients based on assessment of neoplastic versus surgical risks.

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ADDITIONAL INFORMATION

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