

CAP-ASCCP LAST Project: History of Penile/Vulvar Terminology

Penile

The history of terminology of penile and vulvar intraepithelial neoplasia is inextricably bound together because penile, scrotal and vulvar stratified squamous epithelium is similar. The first description of a lesion in the lower genital tract that decades later would be recognized epithelial precancer was by Tarnovsky in 1891, and subsequently, Fournier and Darier in 1893 discussed this finding as mostly found in uncircumcised males. In 1911 the contribution of a French pathologist, Louis de Queyrat, to understanding the pathology of these penile lesions resulted in the name "erythroplasia of Queyrat". However, the understanding that this was a precancerous lesion did not occur until the 1933 report by Sulzberger and Satenstein that erythroplasia of Queyrat was a form of carcinoma in situ (CIS).

In 1912, J. T. Bowen described "chronic atypical epithelial proliferation" under the title "Precancerous Dermatitis" of the skin. Bowen's cases did not involve the vulva, both cases being in males. Erythroplasia of Queyrat and Bowen's disease of the glans penis are terms that essentially describe the same process. In 2000, Cubello et al argued that Bowen's disease, more commonly ascribed to lesions in the shaft of the penis, and erythroplasia of Queyrat, more commonly ascribed to lesions in glands penis, are synonymous with high grade SIL, or squamous cell carcinoma in situ, and should be labeled accordingly. The same author, in 2004, described penile epithelial lesions associated with squamous cell carcinoma (SCC) as: hyperplasia, low grade SIL and high grade SIL. He sub-classified SIL as squamous, warty, basaloid, warty/basaloid and papillary.

The term penile intraepithelial neoplasia (PIN) began to appear in the literature a few years after the 1982 introduction of the term vulvar intraepithelial neoplasia (VIN). The 1987 report by Barrasso et al linked the finding of PIN in the male sexual partners of women with CIN. Della Torre, in 1992, noted that HPV-associated warty/basaloid PIN was more prevalent than non-HPV associated differentiated PIN, findings also being noted in VIN. He also proposed that, like with vulvar cancer, penile

cancer may have more than one etiologic pathway, with one pathway secondary to HPV and one or more pathways non-HPV associated. In 2010, Chaux et al described the association of p16inkra over-expression with penile intraepithelial neoplasia depicting warty and/or basaloid features, linking markers for neoplastic progression to these features.

Vulvar

Vulvar precancer was first described in 1922 by Hudelo et al as "dyskeratose erythroplasiforme de la muqueuse vulvaire", a lesion involving the vulva consistent with "Bowen's disease". In 1929 Pincus and Gould distinguished this from Paget's Disease. In 1953 Gardiner, Stout et al reported "Intraepithelial carcinoma" of the vulva as a replacement for "Bowen's disease", but this terminology was never widely adopted.

In 1960, Abell and Gosling divided intraepithelial squamous neoplasms of the vulva into two histopathologic subtypes: "intraepithelial carcinoma of Bowen's type", also referred to as "intraepithelial squamous cell carcinoma of the Bowen's type", which typically had a prolonged intraepithelial phase and "intraepithelial carcinoma simplex" or "intraepithelial squamous cell carcinoma simplex". The later type was associated with the development of squamous cell carcinoma of the usual type and was recognized as often associated with "leukoplakia vulvitis".

In 1958 Woodruff and Hildebrandt used the term "carcinoma in-situ" of the vulva, which in the gynecologic literature became the predominate reference term for approximately the next 20 years. By the early 1950's leukoplakia had also become a common name, rather than just a description, for these lesions, but in 1961 Jeffcoat and Woodcock recommended that the term "leukoplakia" be abandoned and replaced by the term "dystrophy" which they deemed more specific, and did not include carcinoma in situ.

In 1972 Friedrich reported multifocal papular lesions of the vulva in a pregnant woman referred to "vulvar atypia". In this case, spontaneous regression of papular lesions of the vulvar was described in a pregnant woman that were interpreted as "reversible vulva atypia" rather than "carcinoma in-situ", which these lesions histologically resembled. The lesions in Friedrich's case had epithelial cells that were relatively uniform in size and shape, although they did show lack of maturation. These lesions

did not have evidence of abnormal mitotic activity or nuclear hyperchromasia. This lesion did not have features of what had been referred to as Bowen's disease.

In 1973 Skinner, Sternberg et al reported spontaneous regression of a vulvar lesion they referred to as "bowenoid atypia" and in 1976 the Committee on Terminology of the International Society of Vulvovaginal Disease (ISSVD), accepted and reported "New Nomenclature for Vulvar Disease" that included the term "squamous cell carcinoma in situ" and added the term "vulvar atypia" for changes that were intraepithelial, but less severe than carcinoma in situ. A sub-classification of atypical changes within vulvar epithelium was included and "atypia" was sub-classified as mild, moderate or severe depending on the extent of the intraepithelial changes. Terms that were not recommended, "because of the confusion associated with the use" included "Bowen's disease, erythroplasia of Queyrat, carcinoma simplex and leukoplakic vulvitis".

In 1979 Wade and Ackerman introduced the term "bowenoid papulosis" in reference to multifocal vulvar and penile lesions that had "histologic features of squamous cell carcinoma in-situ", were typically found in young adults, but did not clinically behave like Bowen's disease.

The term vulvar intraepithelial neoplasia (VIN) was first introduced by R. Richard and subsequently published by C. Crum in 1982. The VIN terminology subsequently gained great acceptance and was accepted by the ISSVD in their 1986 report as a general category of intraepithelial squamous neoplasia. In this report the term vulvar intraepithelial neoplasia (VIN) is defined as "loss of epithelial cell maturation with associated nuclear hyperchromasia, pleomorphism, cellular crowding and abnormal mitosis. Dyskeratotic cells "corps ronds", hyperkeratosis and parakeratosis may be present." VIN I was considered equivalent to mild dysplasia, VIN II to moderate dysplasia and VIN III to severe dysplasia. The term carcinoma in situ was retained for those lesions that have nearly full or full thickness epithelial changes." The ISSVD added the term differentiated type, (VIN III, severe dysplasia, differentiated type), to describe "those cases that have cells with prominent eosinophilic cytoplasm, often with keratin or "pearl-like" changes in the involved epithelium. These changes are usually seen near the tip of the rete ridges

in the lower third of the epithelium. The epithelial cell nuclei in these areas usually have prominent nucleoli with vesicular, rather than coarsely clumped chromatin. The more superficial epithelium may show some maturation." This report also stated that terms iBowen's disease, Erythroplasia of Queyrat and carcinoma simplex were not preferred terms. This report also pointed out bowenoid papulosis was not accepted as a pathologic term, but that it was used by some to refer to cases with multiple papular formations. Features associated with human papillomavirus (HPV), i.e. condyloma acuminatum, were to be noted as an addendum to the VIN description and that terms such as "condylomaous dysplasia" not be used.

The 1989 ISSVD nomenclature replaced the roman numerals in VIN I, II, and III with Arabic numbers 1,2 and 3 and noted that the VIN terminology was intended to replace Bowen's disease, carcinoma in-situ, dysplasia, atypia, hyperplasic dystrophy with atypia, Erythroplasia, Bowenoid Papulosis and Bowenoid Dysplasia.

In 1994, Micheletti L, Barbero M, Preti M, et al Reviewed of 21 cases of "mild vulvar atypia" by the same pathologist who gave the initial diagnosis and a dermatopathologist, blinded to the dx. By 1994 interobserver studies had demonstrated the difficulty of recognizing low-grade atypia.

Also, in 1994 the World Health Organization published a 2nd edition of "Histological Typing of Female Genital Tract Tumors", introducing the term "squamous intraepithelial lesion" (SIL) as a term encompassing lesions classified as dysplasia and CIS. VIN was also included as an alternative to the dysplasia/CIS terminology. The finding of HPV induced cellular changes adjacent to an epithelial lesion was to be noted by adding statements such as "with adjacent, or with remote, HPV changes; or with condyloma acuminatum." The term "Bowenoid Papulosis" was deemed unacceptable as a vulvar histopathologic diagnosis. VIN1/mild dysplasia was defined as "dysplasia confined to the lowest third of the epithelium", VIN2/moderate dysplasia as "Dysplasia involving the lower two thirds of the epithelium", and VIN3/ severe dysplasia as "Dysplasia extending into the upper third of the epithelium, but not involving the full thickness." CIS was also defined as VIN3, but was divided into 2 subsets described as

“differentiated, simplex type” and “undifferentiated, basaloid/warty type”. The terms Bowen disease and erythroplasia of Queyrat, were encompassed as severe dysplasia-carcinoma in situ.

In 2003 the WHO defined VIN was defined as, "an intraepithelial lesion of vulvar squamous epithelium characterized by disordered maturation and nuclear abnormalities, i.e., loss of polarity, pleomorphism, coarse chromatin, irregularities of the nuclear membrane and mitotic figures, including atypical forms. Synonyms include dysplasia/carcinoma in situ." VIN lesions of warty or basaloid types were recognized to be associated with oncogenic (high-risk) HPV (hrHPV), and could be further graded as VIN 2 or VIN 3 as previously described by WHO. In contrast, it was recognized that VIN/CIS, simplex type, was “highly differentiated, and not associated with hrHPV . Bowenoid papulosis was recognized as a clinical term that is used in some settings.

In 2004 The Oncology Committee of the ISSVD, proposed classifying VIN as either the HPV associated “usual type” encompassing high grade “undifferentiated” VIN lesions (VIN 2 and VIN 3), and the non-HPV associated “differentiated or simplex type”. VIN1 was designated a non-neoplastic disorder, i.e. condyloma acuminatum. In 2006 Maclean described two types of vulvar squamous carcinoma (SCC): one associated with HPV and the other with lichen sclerosus (LS).

In 2010 the American Registry of Pathology published its Fourth Series Fascicle, Fascicle 13 “Tumors of the Cervix, Vagina, and Vulva”, by Kurman RJ, Ronnett BM, Sherman ME and Wilkinson EJ. In this work VIN is designated as either high-grade VIN (VIN2 or VIN 3) or low-grade VIN (VIN 1). Several types of VIN are presented including warty, basaloid, mixed warty-basaloid, pagetoid, and differentiated (simplex) VIN.

REFERENCES

1. Abell MR, Gosling JRG. Intraepithelial and infiltrative carcinoma of vulva: Bowen's Type. *Cancer* 14:318, 1961.
2. Barrasso R, De Brux J, Croissant O, Orth G. High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. *N Engl J Med.* 1987;317(15):916-23.

Berger BW, Hori Y: Multicentric Bowen's disease of the genitalia: Spontaneous regression of lesions. *Arch Dermatol* 114:1968, 1978.

Bowen, JT: Precancerous dermatoses; study of 2 cases of chronic atypical epithelial proliferation. *J. Cutan. Dis. Inc. Syph.* 30:241-255, 1912.

Cancer eponyms: Bowen's disease, *Cancer bulletin*, 7(6) p. 104, 1955.

Crum CP, Fu YS, Levine RU, Richart RM, Townsend DE, Fenoglio CM. Intraepithelial squamous lesions of the vulva: biologic and histologic criteria for the distinction of condylomas from vulvar intraepithelial neoplasia. *Am J Obstet Gynecol.* 1982 Sep 1;144(1):77-83.

Crum CP. Carcinoma of the vulva: epidemiology and pathogenesis. *Obstet Gynecol* 1992;79: 448-454.

Crum CP; Granter SR. Squamous neoplasia of the vulva, In: *Diagnostic Gynecologic and Obstetric Pathology.* Elsevier Saunders, Philadelphia, Pennsylvania, 2006, pp. 109-148.

3. Della Torre G, Donghi R, Longoni A, Pilotti S, Pasquini G, De Palo G, Pierotti MA, Rilke F, Della Porta G. HPV DNA in intraepithelial neoplasia and carcinoma of the vulva and penis. *Diagn Mol Pathol.* 1992;1(1):25-30.

Friedrich EG Jr: Reversible vulvar atypia: A case report. *Obstet Gynecol* 39:173-181, 1972.

Friedrich EG. Report of the Committee on Terminology. New Nomenclature for Vulvar Disease. *Obstetrics and Gynecology* 47:122,-124 1976.

Friedrich, E.G., Jr.; Wilkinson, E.J.: *Pathology of the Vulva.* In: *Pathology of the Female Genital Tract.* Springer-Verlag, New York, New York, 1977, first ed., pp. 13-58.

Gardiner SH, Stout FE, Arbogast JL and Huber CP: Intraepithelial carcinoma of vulva. *Am. J. Obst. & Gynec.* 65:539-549, 1953.

Hertig AT, Gore H. Tumors of the vulva, vagina and uterus IN *Tumors of the Female Sex Organs, Atlas of Tumor Pathology, Section IX, Fascicle 33,* 1959.

Hertig AT, Gore H. *Tumors of the Female Sex Organs, Part 2: Tumors of the Vulva, Vagina and Uterus.* Armed Forces Institute of Pathology, Bethesda Maryland, 1960..

Hertig AT, Gore H. Supplement: *Tumors of the Female Sex Organs, Part 2 Supplement: Tumors of the Vulva, Vagina and Uterus.* Armed Forces Institute of Pathology, Bethesda Maryland, 1968.

Hudelo, Oury, Cailliau: Dyskeratose erythroplasiforme de la muqueuse vulvaire. Bull. Soc. Franc. Dermatol. Et syph. 29:139-142, 1922

Indianer L: Controversies in dermatopathology. J Dermatol Surg Oncol 5:321, 1979.

Japaze H, Garcia-Bunuel RG, Woodruff JD. Primary vulvar neoplasia: A review of In Situ and Invasive Carcinoma, 1935-1972. Obstetrics and Gynecology 49(4), 404-411, 1977.

Jeffcoate NA, Woodcock AS. Premalignant Conditions of the Vulva. British Medical Journal 380, 1961.

Jeffcoate TNA, Woodcock AS: Premalignant conditions of the vulva, with particular reference to chronic epithelial dystrophies. British Medical Journal 131, 1961.

Kaufman RH, DiPaola GR, Friedrich EG, Hewitt J, Woodruff JD. New Nomenclature for Vulvar Disease. Journal of Cutaneous Pathology, 3(3) p. 159-61, 1976.

Kaufman RH, Woodruff JD: Vulvar dystrophies, atypias and carcinomata in situ: an invitational symposium. Historical background in developmental stages of the new nomenclature. J Repr Med, 17(3) p. 131-6, 1976.

Kaufman RH. Intraepithelial carcinoma of the vulva. Obstetrics and gynecology annual, 6, p. 317-39, 1977.

Knight R, Van D: Bowen's disease of vulva. Am. J. Obst. & Gynec. 46:514-524, 1943.

4. Kurman, R.J.; Norris, H.J.; Wilkinson, E.J.: Tumors of the Cervix, Vagina, and Vulva. In Atlas of Tumor Pathology Rosai, J., ed., Fascicle 3rd series: Armed Forces Institute of Pathology, American Registry of Pathology, Washington, District of Columbia, 1992.

Kurman, R.J.; Ronnett, J.; Sherman, ME; Wilkinson, E.J.: Tumors of the Cervix, Vagina, and Vulva. In: Atlas of Tumor Pathology Rosai, J. et al, eds., Fascicle 4th series: Armed Forces Institute of Pathology, American Registry of Pathology, Washington, No. 13, District of Columbia,, 2010.

Maclean AB. Vulval cancer: prevention and screening. Best Pract Res Clin Obstet Gynaecol. 2006 Apr;20(2):379-95. Review.

McAdams and Kistner 1958 (reference here)

Medeiros F, Nascimento AF, Crum CP. Early vulvar squamous neoplasia: advances in classification, diagnosis, and differential diagnosis. Adv Anat Pathol. 2005 Jan;12(1):20-6. Review.

Micheletti L, Barbero M, Preti M, Zanotto Valentino MC, Chiringhello B, Pippione M.: Vulvar intraepithelial neoplasia of low grade: a challenging diagnosis. *Eur J Gynaecol Oncol.* 1994;15(1):70-4.

Patterson JW, Kao GF, Graham JH, Helwig EB. Bowenoid papulosis. A clinicopathologic study with ultrastructural observations. *Cancer.* 1986 Feb 15;57(4):823-36.

Pincus H, Gould EE: Extramammary Paget's disease and intraepithelial carcinoma. *Arch Dermatol Syph* 39:479, 1929.

Ridley CM: ISSVD: New nomenclature for vulvar disease. *Am J Obstet Gynecol* 160:769, 1989.

Scully, R.E.; Bonfiglio, T.A.; Kurman, R.J.; Silverberg, S.G.; Wilkinson, E.J.: In collaboration with Pathologists in 10 Countries: Histological Typing of Female Genital Tract Tumours. World Health Organization International Histological Classification of Tumours. Springer-Verlag, New York, 1994.

Scurry J, Wilkinson EJ. Review of terminology of precursors of vulvar squamous cell carcinoma. *J Low Genit Tract Dis.* 2006 Jul;10(3):161-9. Review.

Skinner MS, Sternberg WH, Ichinose H, et al: Spontaneous regression of Bowenoid atypia of the vulva. *Obstet Gynecol* 42:40-46, 1973.

Sideri M, Jones RW, Wilkinson EJ, Preti M, Heller DS, Scurry J, Haefner H, Neill S. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med.* 2005 Nov;50(11):807-10.

Taylor DR, South DA: Bowenoid Papulosis: A Review. *Cutis; cutaneous medicine for the practitioner* 27(1) p. 92-8, 1981.

Wade TR: Bowenoid Papulosis. *JAMA*, 246(7) p. 732.

5. Wallace HJ: In *Modern Trends in Obstetrics and Gynaecology*, 2nd ser., ed. K. Bowes, P. 386. Butterworth, London, 1955. (1951 Wallace and Whimster is the earlier reference).

Watson BP, Gusberg SB: Prevention and treatment of carcinoma of the vulva. *Am J Ob Gyn*, 50, p. 179-90, 1946.

Way S: *Malignant Disease of the Female Genital Tract.* Churchill, London, 1951.

Wilkinson EJ, Kneale B, Lynch PJ. Report of the ISSVD Terminology Committee. *The Journal of Reproductive Medicine*, 31, 973-4, 1986.

Wilkinson EJ. The 1989 Presidential Address. International Society for the Study of Vulvar Disease. *The Journal of Reproductive Medicine.* 35(11) p. 981-90, 1990.

Wilkinson, E.J.: Vulvar Intraepithelial Neoplasia and Squamous Cell Carcinoma with Emphasis on New Nomenclature. Progress in Reproductive and Urinary Tract Pathology. Damjanov, I.; Cohen, A.H.; Mills, S.E.; Young, R.H., eds., Field and Wood Medical Publishers, Inc. 2(1):1-20, 1990.

6. Wilkinson EJ and Taxiera MR.: Tumors of the Vulva: in; Tavassoli FA and Deville T: Pathology & Genetics, Tumours of the Breast and Female Genital Organs, *In: World Health Organization Classification of Tumours*, IARC Press, Lyon, France, 2003.
7. Wilkinson, EJ :Premalignant and malignant tumors of the vulva, *In: Blaustein's Pathology of the Female Genital Tract*, 6th ed., Kurman, R.J, Elienson LH, and Ronnett BM, pp: 55-104. Springer, New York, 2011.

Woodruff JD, Hildebrandt EE: Carcinoma in situ of vulva. *Obstet. and Gynec.* 12:414-424, 1958.

Zanio, RJ, Husseinzadeh N, Nahhas W, Mortel R.: Epithelial Alterations in Proximity to Invasive Squamous Carcinoma of the Vulva. *Int J. Gynecol Pathol* 1;173-184,1992.

Copyright 2012, American Society for Colposcopy and Cervical Pathology and College of American Pathologists. All rights reserved.

Disclaimer

The information, data, and draft recommendations and summaries provided by the College of American Pathology Center-American Society for Colposcopy and Cervical Pathology LAST Project Work Groups are presented for informational and public feedback purposes only. The draft recommendations and summaries will be removed from this website on February 13, 2012 and, along with the public comments received, will be reassessed by the Work Groups in order to finalize their presentations for the March 2012 LAST Consensus Conference. These draft materials should not be stored, adapted, or redistributed in any manner.