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The Clinicopathologic Challenge of Nonneoplastic Vulvar Acanthosis

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Objective: The aim of the study was to evaluate clinicopathologic features of cases demonstrating an acanthotic tissue reaction not clearly consistent with psoriasis, lichen simplex chronicus, mycosis, or condyloma.

Materials and Methods: This is a retrospective pathologic case series of biopsies reported as "benign acanthotic lesion" and "acanthotic tissue reaction" that lacked a clear diagnosis on expert review. Cases with nuclear atypia were excluded. Clinical and histopathologic data were collected, immunohistochemistry for p16 and p53 were obtained, and molecular testing for 28 common anogenital human papillomavirus (HPV) genotypes was undertaken.

Results: There were 17 cases with a median age of 47 years. Unilaterality and medial location were clinical reasons for diagnostic difficulty. Histopathologic uncertainty often related to lack of papillary dermal fibrosis to support lichen simplex chronicus or psoriasiform lesions without parakeratosis, subcorneal pustules, and/or mycotic elements. Firm pathologic diagnoses were not possible, but 3 groups emerged: favoring chronic dermatitis, favoring psoriasis, and unusual morphologies. p16 results were negative or nonblock positive while p53 was normal or basal overexpressed. Human papillomavirus testing was negative in 12, low positive for HPV 16 in 1, unassessable in 3, and not requested in 1.

Conclusions: There is a group of acanthotic tissue reactions that cannot be classified with standard histopathologic assessment. Further clinicopathologic research into unilateral acanthotic lesions may provide insight into separation of psoriasis and mycosis when organisms are absent. Once nuclear atypia is excluded, immunohistochemistry for p16 and p53 and HPV molecular testing do not assist in diagnostic identification.

Key Words: vulva, acanthosis, psoriasis, lichen simplex chronicus, chronic dermatitis, condyloma, plaque

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The acanthotic tissue reaction is 1 of 6 patterns described in vulvar dermatopathology.[1] Common acanthotic conditions include psoriasis, lichen simplex chronicus (LSC), condyloma, and mycosis.[2–4] While several histopathologic characteristics favor one diagnosis over others, features may overlap because of comorbidity or biologic variation.

Experienced vulvar clinicians do not obtain biopsies when history and examination point clearly toward psoriasis, chronic dermatitis, or mycosis. Instead, clinicians undertake biopsy if diagnosis is uncertain or features are unusual. Examples include unilaterality of conditions that are usually bilateral or diffuse, medial location of pink-gray plaques, and well-demarcated papules or plaques not typical for condyloma or seborrheic keratosis (SK). This presents a conundrum because difficult clinical cases may also have mixed histopathologic features. Another indication for biopsy is nonresponse to treatment with topical corticosteroids. This represents another challenge for pathologists as steroids alter microscopic appearance. A nonspecific biopsy report of "benign acanthotic lesion" means that clinicians must return to their clinical impression to guide diagnosis and management. If this too is uncertain, options include obtaining more tissue or providing a series of presumptive therapies until one is successful or the lesion spontaneously resolves. There is scant vulva-specific literature on the biologic spectrum of acanthotic lesions and minimal guidance on how to approach these perplexing cases.[5]

The aim of this study is to evaluate the clinicopathologic features of cases with acanthotic tissue reactions not clearly consistent with psoriasis, LSC, mycosis, or condyloma.

METHODS

The local histopathology database was searched for "benign acanthotic lesion" and "acanthotic tissue reaction" between 2014 and 2021. Exclusions were missing slides, organisms seen on the periodic acid–Schiff (PAS) stain, and cases with a clear diagnosis of psoriasis, LSC, condyloma, lichenified lichen sclerosus (LS), or other dermatologic condition on the report or at subsequent slide review. Nonsclerotic LS was identified as horizontal fibrosis thicker than expected in LSC, with or without a lichenoid tissue reaction, and was excluded.

Clinical data included demographics, symptoms, location, size, and description of the lesion, biopsy site, HPV-related disease of the lower genital tract, dermatologic or immunologic comorbidities, prereferral treatment, specialist treatment, and outcome. Records were re-reviewed 6 months after case selection to document repeat encounters or biopsies. Histologic data comprised site, thickness of the stratum corneum and epidermis, rete ridge features, exocytosis, and pigment incontinence. Stratum corneum was categorized as compact with normal thickness, hyperkeratosis (HK), or parakeratosis (PK).[6] Spongiosis was separated into suprapapillary and sporadic. Basal layer proliferation was defined as expansion of basilar cells above the basal layer with scattered suprabasilar mitoses and described as a percent of epidermal thickness. The dermal infiltrate was semiquantitatively assessed as absent, scant, or moderate, and the location as perivascular or diffuse. Collagen features included edema or papillary dermal fibrosis. Immunohistochemistry (IHC) for p16 and p53 were obtained on all samples except one with insufficient tissue. Formalin-fixed paraffin-embedded (FFPE) specimens underwent molecular testing for HPV in all but 1 case in which the prolonged interval since collection and small biopsy size made DNA extraction unlikely.

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Total nucleic acids were extracted from FFPE tissue samples using the MagNA Pure 96 DNA and Viral and NA Small Volume Kit, eluted in 100 μL of Roche elution buffer.[7,8] Detection of host β-globin gene was used as quality control for the nucleic acid extraction process.[7] Two reactions with 5 μL each of DNA extracts were tested on Seegene Anyplex II 28HPV (Seegene, Seoul, South Korea), which detects 28 HPV genotypes including 14 high risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and 14 lower risk types (6, 11, 26, 40, 42, 43, 44, 53, 54, 61, 69, 70, 73, 82).[7,8] Nucleic acids were extracted and tested in duplicate or triplicate to increase the chance of HPV DNA detection. Samples were deemed unassessable if they had a negative β-globin test and an invalid Anyplex II internal control. Descriptive statistics were performed.

RESULTS

There were 17 cases with a median age of 47 (see Table 1). Fifteen were unilateral and 2 bilateral. The unilateral cases comprised 11 lesions (65%) described as well-demarcated pink or gray plaques less than 5 cm in diameter and 4 (24%) were papules described as pale, fleshy, or pigmented in color. Of the generalized abnormalities, one showed poorly demarcated erythema and fissures over perianus and posterior labia, and the other had a cobblestone appearance over labia majora with coalescent fleshy nodules. Initial clinical diagnoses were LSC in 6 (35%), psoriasis in 4 (24%), not provided in 2, and 1 each with classic lichen planus, melanosis, nevus, condyloma, and cyst. Two cases were current tobacco users and 5 had body mass index greater than 30 kg/m^2. Cervical screening test results were recorded in 10 of 11 eligible patients; one was positive for HPV type 16 and non-16/18 and all others were negative. Two patients had previous condyloma and one had a cervical excisional procedure with subsequent negative HPV testing. Vulvar comorbidities included estrogen deficiency in 2, and 1 each with hidradenitis suppurativa, candidiasis, and LS. Primary care providers prescribed topical corticosteroids in 5, topical or oral antifungals in 2, topical estrogen, lignocaine, and cryotherapy in 1 each.

Histopathology showed variable thickness of epidermis and rete ridge morphology, frequent PK, and absent to scant infiltrate in 76% (see Table 1). Spongiosis occurred in 5 (29%) and was suprapapillary in 3 cases and sporadic in 2 (see Figures 1, 2). Exocytosis occurred in 2 (12%). Mean basal layer proliferation extent was 23% with a range of 10%–50%. p16 was negative in 12 (71%) and nonblock positive in 5 (29%). p53 was wild type in 8 (47%), showed variable mild overexpression in 4 (24%), and was overexpressed in 5 (29%).

Of 6 cases thought to be LSC on examination, biopsy location was labium minus or interlabial fold in 3, perineum in 2, and labium majus in 1. The site was hair-bearing skin in all except for 1 from interlabial fold. Three (50%) had compact anucleate keratin, 2 had a combination of PK and HK, and 1 had isolated compact stratum corneum without PK (see Figure 2). Rete ridges were clubbed or anastamosing in all but 1 case (see Figure 1). Spongiosis occurred in 1, infiltrate ranged from nil to moderate and if present was lymphocytic and perivascular. Four (67%) had mild papillary dermal fibrosis.

Among 4 cases with a clinical impression of psoriasis, biopsies were taken from inferior labium minus, periclitoris, labium majus, and perineum, all with hair-bearing skin. Rete ridge morphology was anastomosed, clubbed, or variable. Three (75%) displayed a combination of PK with HK or compact stratum corneum and one had isolated HK. Half had spongiosis, one each had papillary dermal fibrosis or edema, and infiltrate was absent in 1, scant in 2, and moderate in 1 (see Figure 2).

Two cases displayed an unusual epidermal appearance inconsistent with a known diagnosis. Both presented with pruritic plaques less than 3 cm in diameter but otherwise were dissimilar in demographics, demarcation, treatment, and response. These and 2 additional cases displayed features suggestive of HPV-related disease: perinuclear haloes (see Figure 3), squamatized whorls (see Figure 4), suprabasilar apoptotic keratinocytes, and multinucleated squamous cells. These cases all were negative for HPV. The one low-positive result for HPV 16 was a 47-year-old nonsmoker who presented with anogenital discomfort, poorly

TABLE 1. Clinicopathologic Features of Difficult-to-Classify Vulvar Acanthotic Tissue Reactions

	***N* = 17**
Age, median (range)	47 (1–84)
Primary symptom, *n* (%)	
Itch	10 (59)
Pain	2 (12)
Nil or other	5 (29)
Location, *n* (%)	
Perineum/perianus	6 (35)
Labium minus/interlabial sulcus	5 (29)
Labium majus	4 (24)
Vestibule	2 (12)
Color, *n* (%)	
Pink-gray	7 (41)
Pale	4 (24)
Flesh	3 (18)
Pigmented	3 (18)
Nodule or plaque, *n* (%)	15 (88)
Well-demarcated, *n* (%)	12 (71)
Size >1 cm, *n* (%)	11 (65)
Clinical impression, *n* (%)	
Lichen simplex chronicus	6 (35)
Psoriasis	4 (24)
Pigmented lesion	3 (18)
Other, nil, or unknown	4 (24)
Primary treatment, *n* (%)[a]	
Excision	8 (47)
Topical corticosteroids	7 (41)
Other, nil, or unknown	2 (12)
Site, *n* (%)	
Hair-bearing skin	12 (71)
Hairless skin	3 (18)
Squamous mucosa or unknown	2 (12)
Epithelial thickness, median (range)	0.5 (0.21–0.98)
Stratum corneum thickness, median (range)	0.08 (0.02–0.3)
Parakeratosis present, *n* (%)	13 (76)
Rete ridge morphology, *n* (%)	
Branching/anastamosing	8 (47)
Clubbed/bulbous	6 (35)
Variable	3 (18)
Basal layer proliferation present, *n* (%)	12 (71)
Pigment incontinence, *n* (%)	11 (65)
Infiltrate, *n* (%)	
Nil	3 (18)
Sparse	10 (59)
Moderate	4 (24)
Papillary dermal fibrosis, *n* (%)	6 (35)

[a]Some cases had more than 1 treatment.

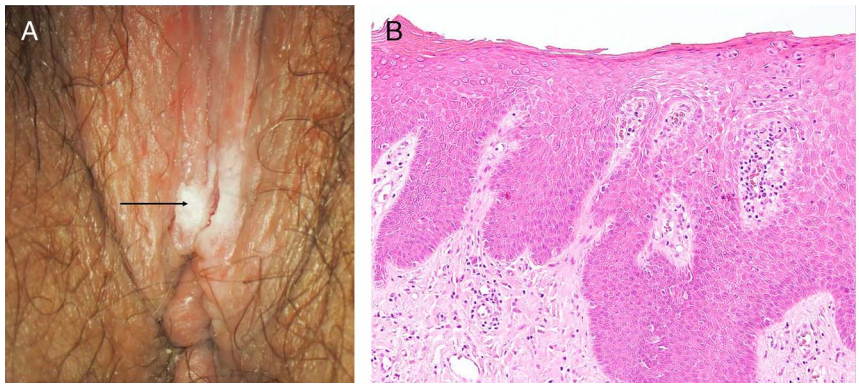

FIGURE 1. Clinicopathologic assessment favors nodular prurigo. A, a 47-year-old patient with a pruritic well-demarcated perineal white nodule (arrow) that resolved with excision and 6 weeks of potent topical corticosteroids. B, Hair-bearing skin with HK and PK, marked acanthosis with irregular clubbed rete ridges, suprapapillary spongiosis, exocytosis, a moderate perivascular lymphocytic infiltrate, and papillary dermal fibrosis, hematoxylin-eosin (H&E) ×100.

demarcated mild erythema, a perianal fissure, recent negative CST, and vaginal microbiology positive for *Candida albicans* (see Figure 5). The HPV 16 result occurred in 1 of 3 extracts with DNA at the lower limit of assay detection. Clinical impression was dermatitis with candidiasis and symptoms improved on a combination of topical corticosteroids, oral fluconazole, and modified vulvar care practices. The 3 cases unassessable for HPV DNA were obtained from a poorly demarcated pink-gray plaque in 2 and a periurethral white plaque in 1. The case not sent for molecular assessment was a 42-year-old patient with a clinical impression of LSC.

Lesional excision was the most common management approach, followed by topical corticosteroids in 7 (41%), emollient in 3 (18%), systemic estrogen in 2 (12%), and 2% liquor picis carbonis in zinc in 1 (6%). Resolution of the symptoms and lesion was universal in those managed with excision. Among cases managed medically, 6 (67%) improved and 3 (33%) were lost to follow-up.

At 6 months after case selection, no patient had a subsequent vulvar biopsy. Of the 4 cases with presumed psoriasis, 3 did not return for subsequent visits and 1 required maintenance antifungal therapy for recurrent candidiasis and intermittent topical corticosteroids for psoriasis. Among 6 with presumed LSC, 3 had no further appointments and 3 had resolution of symptoms and signs. Two cases that lacked a dermatologic impression had subsequent encounters for colpocleisis and colposcopy, respectively; in both cases, vulvar examination was normal. Of the remaining 5 cases, 4 had excisions with no recurrence to date and records were unavailable in 1.

DISCUSSION

Clinicians experienced in vulvar disorders identify LSC and psoriasis based on history and examination, with biopsy obtained in the setting of nontypical appearance or location, a concern for comorbid disorders, or nonresponse to therapy. A small proportion of vulvar acanthotic tissue reactions show mixed or unusual features not readily identified as psoriasis, LSC, condyloma, or mycosis. In this series, the clinicopathologic conundrum was resolved through lesion excision in half of patients, several of whom never received a specific diagnosis. The other half received and usually responded to topical corticosteroids combined with enhanced vulvar care, signaling likely diagnoses of psoriasis or LSC. These results highlight that vulvar histopathology may be nondiagnostic, so clinicians must integrate examination, microbiology, treatment response, and clinical trajectory to arrive at a best-fit diagnosis.

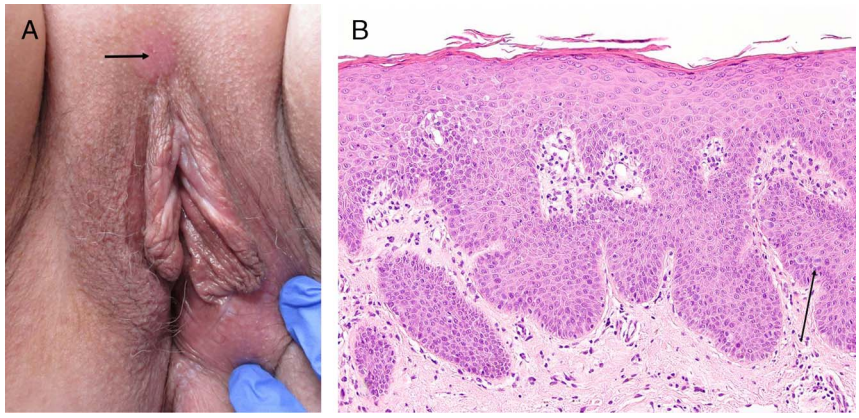

FIGURE 2. Clinicopathologic assessment favors psoriasis. A, a 56-year-old patient attended for surveillance of LS with a new asymptomatic well-demarcated periclitoral pink plaque (thick arrow) that resolved with modified placement of topical corticosteroids and emollient. B, Hair-bearing skin with thin PK and hypogranulosis, irregular acanthosis with bulbous rete ridges, suprapapillary spongiosis, basal proliferative zone with mitosis (thin arrow), dermal papillary vascular dilation, and scant lymphocytic perivascular infiltrate, H&E ×100.

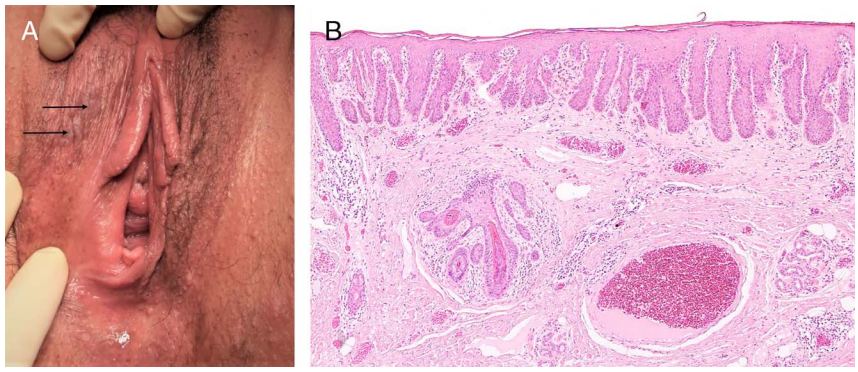

FIGURE 3. Uncertain clinicopathologic diagnosis. A, A 38-year-old patient with localized itch and a purple-brown well-demarcated plaque on labium majus (arrows) nonresponsive to potent topical steroids; excision was curative. B, Hair-bearing skin with compact stratum corneum, normal granular cell layer, and acanthosis with unusual, branched thinned rete ridges, pigment incontinence, scant lymphocytic infiltrate, and arborizing follicular epithelium, H&E ×40.

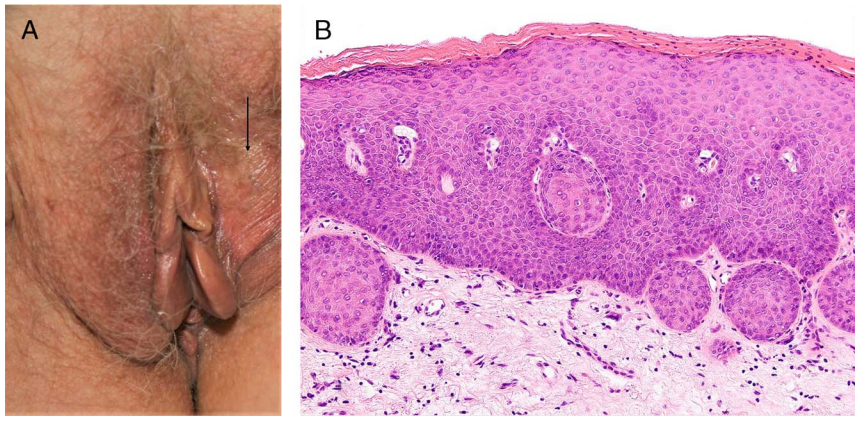

FIGURE 4. Uncertain clinicopathologic diagnosis. A, A 84-year-old patient presented with pain, itch, and a well-demarcated pink plaque at the interlabial fold that faded to a vague pale patch (arrow) after application of 1% hydrocortisone ointment. B, Hairless skin with HK with hypergranulosis, PK, irregular acanthosis with unusual nested proliferation of more mature squamous cells, scant lymphocytic perivascular infiltrate, and absent fibrosis, H&E ×100.

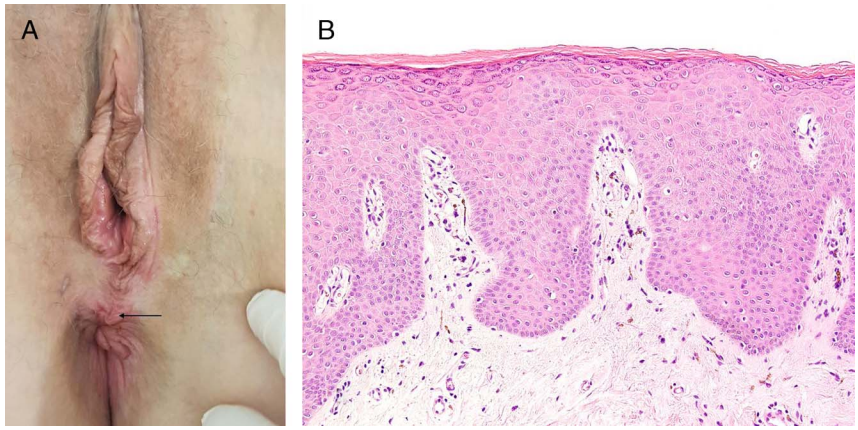

FIGURE 5. Clinical assessment favors mycosis. A, A 47-year-old patient with poorly demarcated perianal (arrow) and interlabial sulcus erythema, edema, and fissures with low-positive HPV 16 DNA. B, Hair-bearing skin with compact stratum corneum, irregular acanthosis with variable rete width, scant lymphocytic infiltrate, and pigment incontinence, H&E ×100.

Lichen simplex chronicus is the clinicopathologic manifestation of an itch-scratch cycle, precipitated by atopy, irritant or allergic contract dermatitis, mycosis, or another underlying chronic dermatosis.[9] The usual appearance is symmetric poorly demarcated gray-pink plaques on hair-bearing skin with increased skin markings, often accompanied by erosions, excoriations, and fissures.[2] However, it may appear dark or pigmented and the subset of nodular prurigo may be localized and well demarcated.[10,11] In this series, unilaterality and location medial to labium majus were unusual clinical features. Medical literature is scant on biopsy rates in presumed LSC and expert commentary describes tissue sampling as "rarely necessary or even desirable unless the presence of an underlying disease… is suspected."[2] The histopathologic appearance of LSC involves HK, hypergranulosis, acanthosis with broad rete ridges, papillary dermal fibrosis, absent basal layer damage, and negative PAS for mycotic elements.[4] In addition to their nonclassic clinical appearance, cases of presumed LSC reviewed in this series had absent papillary fibrosis, PK, and/or unusual rete ridge patterns. Some of these cases may represent secondary lichenification of an underlying unidentified well-demarcated lesion.

The classic appearance of genital psoriasis is bilateral symmetric well-demarcated erythematous thin plaques on hair-bearing skin, lacking in scale.[12,13] Presence of fissures and natal cleft extension are helpful features. Diagnosis relies on the combination of this appearance with a prolonged waxing and waning trajectory, supported by psoriasis at other sites and/or a family history. In a series of 194 adults and children with expert diagnosis of vulvar psoriasis, 5 biopsies were performed—2 for suspicion of LS, 2 to exclude extramammary Paget disease, and 1 at patient request.[12] None of these had classic histopathologic features of psoriasis, a situation reported to be more frequent in vulvar compared with extragenital psoriasis.[5,14] Variation by site has been documented in intertriginous versus flexural psoriasis, with the former more often displaying spongiosis, focal mounds of PK with neutrophils, and irregular rete ridges.[3] Cases of likely psoriasis reviewed for this series had histologic overlap with LSC with isolated HK, clubbed or anastamosing rete ridges, absent neutrophils, or papillary dermal fibrosis. It is unclear whether this is because of intertriginous site, lichenification of psoriasis due to scratching, incorrect clinical diagnosis, or inadequate knowledge of histopathologic diversity of vulvar psoriasis.

A particular diagnostic problem of vulvar psoriasis is overlap with mycosis. The 2 conditions have similar histopathologic findings of PK, neutrophils in the stratum corneum, acanthosis, and a dermal lymphocytic infiltrate. Presence of hyphae on PAS signals mycosis, but organisms are often lacking in cases with positive microbiology and rapid response to antifungals.[15] Interleukin 17, a family of cytokines produced mostly by T cells, plays a role in pathogenesis of psoriasis and mycosis through keratinocyte hyperproliferation and neutrophil recruitment.[16,17] Several biologic medications targeting interleukin 17 are effective as psoriasis treatment but increase susceptibility to mucocutaneous candidiasis.[16] Overlapping features may arise from this common pathophysiologic pathway.

Condyloma and SK often present as nodules rather than plaques, but these fall within the differential diagnosis of acanthotic reactions because textural differences are less apparent to pathologists if biopsies are sited within a lesion. Similarities between SK and condyloma include acanthosis, proliferation of basaloid cells, pigmentation, squamous whorls, horn cysts, and papillomatosis.[18,19] Features favoring condyloma include PK and dermal lymphocytic infiltrate. Genotyping for HPV is positive in up to 70% of genital SK and more than 95% of condyloma, with nononcogenic types comprising nearly all SK and over 65% of condyloma.[18–23] Both condyloma and SK display patchy nonblock-positive p16 expression.[18] The negative HPV results of 16 of 17 cases (94%) argue against condyloma or SK as a cause of histologic findings in this series. The single positive case likely represents HPV latency or genital cross-contamination as clinical findings were inconsistent with HPV-related disease. Acanthotic tissue reactions that demonstrate nuclear enlargement, pleomorphism, hyperchromasia, or atypical mitoses require consideration of a neoplastic process and further assessment with p16 and p53. In this setting of benign clinical appearance and bland nuclei, p16, p53, and HPV genotyping did not aid in distinguishing between competing diagnoses.

The limitations of this study are those inherent to retrospective methodology and study of an unusual clinicopathologic conundrum. Missing variables, individual practice variation, and real-life uncertainties limit individual case interpretation. Clinical photography was not universally performed and molecular study of small FFPE specimens may entail a false-negative rate. Prolonged clinical follow-up supported the presumed diagnoses of psoriasis in 1 and LSC in 3. In 8 cases, nonrecurrence after excision was reassuring but did not elucidate the original diagnosis. In the remainder, limited clinical follow-up due to nonattendance or lack of perceived need posed an impediment to establishing final diagnoses. A larger prospective study design would provide additional insights into diagnoses and outcomes for vulvar acanthotic lesions.

CONCLUSIONS

Vulvar biopsies showing a benign acanthotic reaction pattern are often nondiagnostic but usually may be categorized as psoriasis, LSC, condyloma, or mycosis. Rarely, the clinical appearance is not suggestive of any of these and biopsy shows mixed or bizarre features yielding a nonspecific report of benign acanthotic lesion. The majority of these cases are not HPV related and respond either to topical corticosteroids or lesional excision. Research into the clinicopathologic appearance and differential diagnosis of vulvar LSC, psoriasis, and mycosis may permit improved recognition and directed therapy of common vulvar dermatoses.

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