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## Original Article

# Vestibulovaginal Sclerosis Versus Lichen Sclerosus

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**Summary:** To determine if vestibulovaginal sclerosis and lichen sclerosus (LS) are 2 distinct entities. Biopsies obtained from the vagina or vulvar vestibule that contained abnormal subepithelial collagen were reviewed. Cases were categorized either as LS or vestibulovaginal sclerosis based on presence or absence of basal layer degeneration and lymphocytic infiltrate. Clinical data collected included examination findings, biopsy site and indication, previous vulvovaginal surgery, medications at time of biopsy, vulvar LS, treatment, and response. There were 15 cases with a mean age of 62 yr (range: 32–86 yr); 12 (80%) specimens were from vestibule and 3 from vagina. Nine cases were categorized as LS because of lymphocytic infiltrate in combination with basal layer degeneration, of these 8 had LS elsewhere on vulvar skin. Six cases were classified as vestibulovaginal sclerosis and had an absent or sparse lymphocytic infiltrate and essentially normal epithelium; none of these had vulvar LS. While vestibulovaginal sclerosis and lichen sclerosus are distinguishable clinically and histopathologically, further studies are needed to determine if vestibulovaginal sclerosis is a subset of LS or a different condition. **Key Words:** Vagina—Vulvar vestibule—Sclerosis—Lichen sclerosus.

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Lichen sclerosus (LS) is a chronic dermatosis with a predilection for keratinized vulvar skin. It has 2 diagnostic histopathologic features: a lichenoid tissue reaction and dermal collagen homogenization. While LS is commonly found on skin, sometimes squamous

mucosa may be affected. Vaginal LS has been described in 3 women with pelvic organ prolapse, all with vulvar LS and white plaques on exposed vagina (1,2). There is a single report of vaginal LS without prolapse in a 54-yr-old woman with prior hysterectomy, vulvar LS managed with topical corticosteroids, and a separate white plaque at the vaginal apex that did not require specific treatment (3). Although these reports describe histopathologic findings of LS, none of the 3 published images demonstrates all standard diagnostic features.

Fadare's (4) description of "vaginal stromal sclerosis" may provide an explanation for cases in which biopsy of a white lesion demonstrates abnormal subepidermal collagen without basal layer alterations. He reported 3 cases of postmenopausal women with dyspareunia, atrophic-appearing mucosa, and white plaques of < 1 cm diameter located in the distal vagina. None had lymphocytic infiltrate, while all had a thick paucicellular band of hyalinized collagen. Fadare hypothesized that focal injury of nonestrogenized vaginal mucosa results in scar

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T.D. is supported by the Australian Government Research Training Program Scholarship. The remaining authors declare no conflict of interest.

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formation seen histopathologically as sclerosis, and that this is unrelated to LS.

This study aims to assess the clinical and histopathologic features of vaginal and vestibular biopsies with abnormal subepidermal collagen, to determine if lichen sclerosus and vestibulovaginal sclerosis are 2 separate entities.

## MATERIALS AND METHODS

The Pathology North, Hunter New England database was searched between January 2010 and April 2017 for biopsies from the vagina or vulvar vestibule and the terms “sclerosis” and “sclerosus.” Clinical notes from the biopsy request form and histologic slides were reviewed. All specimens were stained both with hematoxylin and eosin and periodic acid-Schiff. Biopsy locations described as “hymen,” “introitus,” or “fossa navicularis,” were considered to be vestibule. Site was recorded as squamous mucosa or mucocutaneous junction (MCJ). Histopathologic features of MCJ included continuity with hairless skin or squamous mucosa, parakeratosis, absent granular cell layer, and reduced glycogen compared with squamous mucosa in estrogenized epithelium (5). Cases with keratinized epithelium and an inadequate clinical description of biopsy location were excluded, as it could not be determined if these represented hairless skin, or mucosa that had become keratinized. Vagina referred only to locations cephalad to the hymen, and by definition was squamous mucosa. Immunostaining with antibodies to D2-40, a lymphatic-specific marker, was performed if lymphangiectasia was suspected on histopathology. Hunter New England Research Ethics and Governance Unit approved this retrospective histopathologic case series (HREC 15/11/18/5.02).

Histopathologic assessment included epithelial thickness, papillary morphology, and lamina propria lymphocytic infiltrate, which was semiquantitatively assessed as absent, sparse, moderate, or dense. Basal layer alterations were recorded, to include vacuolar change, apoptotic bodies, squamatization, and lymphocytosis. Squamatization was defined as a change in morphology of normal basal keratinocytes to more horizontally disposed cells with a mature squamous appearance. Subepithelial collagen homogenization was characterized as edematous or hyaline.

Cases were categorized either as LS or vestibulovaginal sclerosis. Minimum additional criteria for LS were basal layer vacuolar change, apoptotic bodies, or squamatization, with a lamina propria lympho-

cytic infiltrate; lymphocytosis was supportive. A diagnosis of vestibulovaginal sclerosis was applied when epithelium lacked vacuolar degeneration or apoptotic bodies, and both the lymphocytic infiltrate and lymphocytosis were absent or sparse. Clinical information was obtained on examination findings, biopsy site and indication, previous vulvovaginal surgery, medications at time of biopsy, vulvar LS, treatment, and response. Descriptive statistics were performed and categorical variables were compared with the Fisher exact test.

## RESULTS

There were 15 cases with a mean age of 62 yr (range: 32–86 yr). All biopsies were submitted by gynecologists. Twelve (80%) specimens were obtained from the vestibule, of which 9 (75%) were classified as squamous mucosa and 3 (25%) as MCJ. Confluent keratinization was noted on 1 vestibular specimen and the location of the biopsy was verified with the clinician. Parakeratosis occurred in 3 specimens classified as squamous mucosa—1 from vagina and 2 from vestibule. Nine cases were categorized as consistent with LS and 6 as vestibulovaginal sclerosis; Table 1 summarizes the histopathologic characteristics stratified by assigned diagnosis.

The clinical features of all cases are detailed in Table 2. Compared with vestibulovaginal sclerosis, LS cases were more likely to have LS elsewhere on vulvar skin [8/9 (89%) vs. 0/6;  $P < 0.002$ ]. The 1 case of LS restricted to the vestibule occurred in a 60-yr-old woman with 3 yr of pruritus who underwent 2 sessions of fractional carbon dioxide laser for presumed genitourinary syndrome of menopause. She had persistent symptoms and obtained a second opinion (case 4, Fig. 1). Histopathology of case 1 demonstrates LS across the transition from MCJ to estrogenized nonkeratinized epithelium with abundant glycogen well visualized on periodic acid-Schiff (Fig. 2). Case 2 had biopsies from labium minus and hymen, the former demonstrated LS of hairless skin and the latter showed LS across MCJ and squamous mucosa, as well as histiocytes and lymphangiectases confirmed by positive D2-40 in the endothelium of dilated vessels (Fig. 3). Case 6 was previously published as a case report (6). Steroid ointment was prescribed and yielded improvement in all cases categorized as LS and all women continued maintenance regimens.

Vestibulovaginal sclerosis cases were typified by an incidental finding of a white plaque. One case showed

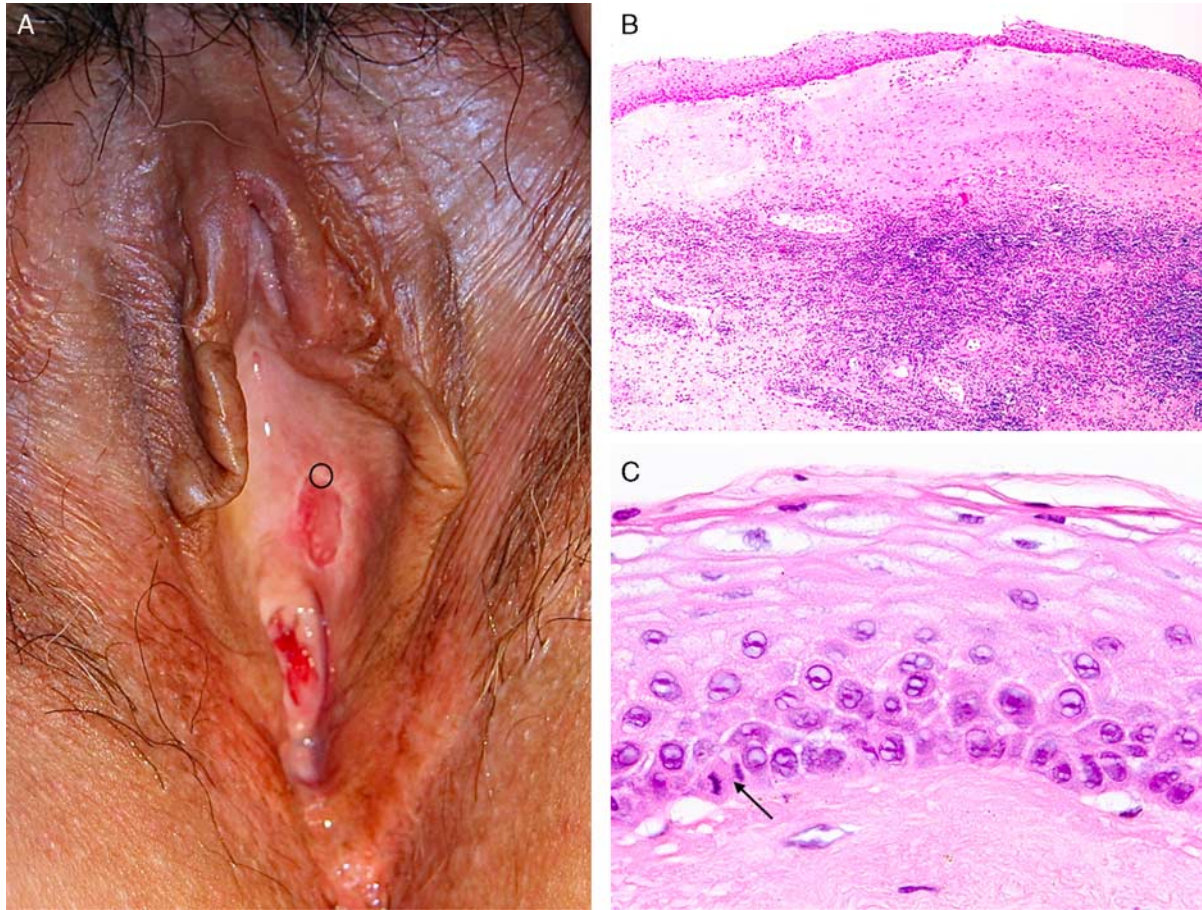
**TABLE 1.** *Histopathologic Characteristics of Vestibular and Vaginal Biopsies With Abnormal Subepithelial Collagen*

	n (%)		
	Total	Lichen Sclerosis (N = 9)	Vestibulovaginal Sclerosis (N = 6)
Age [mean (SD)] (y)	62 (13)	63 (16)	61 (8)
Epithelial thickness [mean (SD)] (mm)	0.1 (0.05)	0.11 (0.07)	0.1 (0.03)
Keratinization status			
Nonkeratinized	8 (53)	4 (44)	4 (67)
Parakeratosis	6 (40)	4 (44)	2 (33)
Keratinized	1 (7)	1 (11)	0
Lymphocytic infiltrate			
Absent	6 (40)	0	6 (100)
Sparse	6 (40)	6 (67)	0
Moderate-dense	3 (20)	3 (33)	0
Abnormal collagen			
Edematous	5 (33)	4 (44)	1 (17)
Hyalinized	8 (53)	3 (33)	5 (83)
Both	2 (13)	2 (22)	0
Lymphocytosis	6 (40)	5 (56)	1 (17)
Basal layer			
Vacuolar change	5 (33)	5 (56)	0
Squamization only	5 (27)	4 (44)	1 (17)
Normal	5 (40)	0	5 (83)

**TABLE 2.** *Clinical Characteristics of Vestibular and Vaginal Biopsies With Abnormal Subepithelial Collagen*

	Age (y)	Vulval LS	Prior Vulvovaginal Surgery	Medications at Biopsy	Indication for Biopsy	Biopsy Location	Treatment
Lichen sclerosis							
1	32	Yes	No	None	Dyspareunia, suspect LS	Vestibule	Topical corticosteroids
2	47	Yes	No	None	Dyspareunia, suspect LS	Vestibule	Topical corticosteroids
3	58	Yes	No	Topical corticosteroids	Suspect LS	Vestibule, keratinized	Topical corticosteroids
4	60	No	Vaginal fractional laser	None	Suspect LS	Vestibule	Topical corticosteroids
5	62	Yes	Vaginal hysterectomy, prolapse repair	Topical estrogen	Suspect LS	Vagina	Topical corticosteroids
6	70	Yes	Excisions of basal cell carcinomas	None	Suspect LS	Vestibule	Topical corticosteroids
7	73	Yes	Vaginal hysterectomy	Topical corticosteroids	LS exacerbation	Vestibule	Topical corticosteroids
8	79	Yes	No	Topical corticosteroids	LS exacerbation	Vestibule	Topical corticosteroids
9	86	Yes	Excision of differentiated vulvar intraepithelial neoplasia	None	Exclude neoplasia	Vagina	Topical corticosteroids
Vestibulovaginal sclerosis							
10	47	No	No	Topical estrogen	Dyspareunia, introital stenosis	Vestibule	Excision with flap repair
11	56	No	No	None	Incidental finding of white plaque on hymen	Vestibule	None
12	59	No	No	None	Dyspareunia, pallor at posterior fourchette	Vestibule	Oral tricyclic antidepressant
13	66	No	No	None	Incontinence-associated dermatitis, incidental finding of white plaque	Vagina	Topical corticosteroids
14	69	No	Vaginal hysterectomy, prolapse repair	None	Nodular scar seen at hysterectomy	Vestibule	Scar excised
15	70	No	Transobturator tape, pessary placement	Systemic hormone replacement	Incidental finding of suburethral white plaque	Vestibule	None

LS indicates lichen sclerosis.



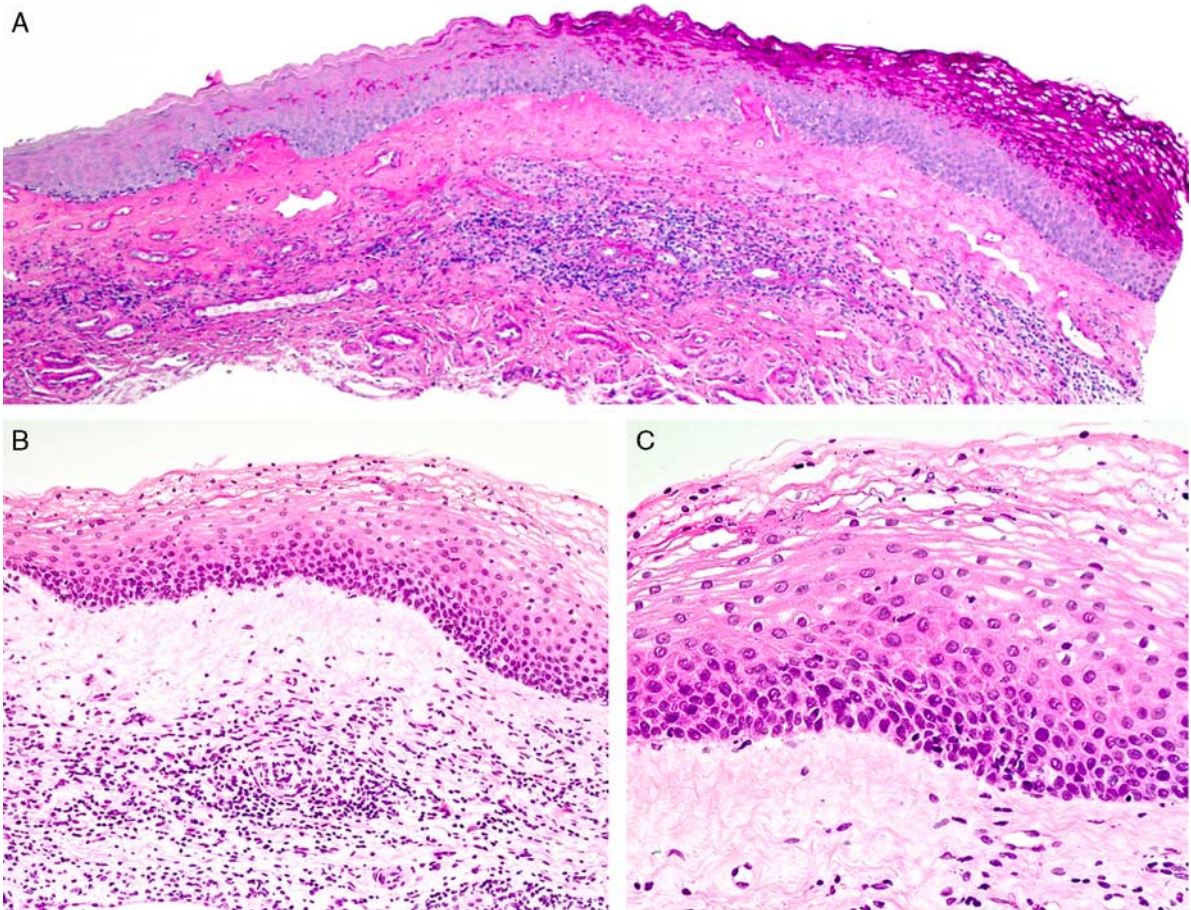
**FIG. 1.** (A) Pallor between clitoris and urethra, biopsy sited at the edge of an ulcer. (B) Histopathology consistent with lichen sclerosis: squamous mucosa with erosion, a band of hyalinized collagen, and dense lymphocytic infiltrate, hematoxylin and eosin 40 × . (C) Basal layer squamatization and mitosis (arrow), hematoxylin and eosin 400 × .

focal squamatization of thinned and parakeratotic epithelium overlying a sclerotic protruberance (case 14, Fig. 4). Focal lymphocytosis and spongiosis were seen in a biopsy of posterior fourchette, with absent lymphocytic infiltrate (case 12). The remaining sclerosis cases were characterized by normal epithelium (case 11, Fig. 5). Two (29%) women improved after excision of the lesion, 2 required no treatment, 1 (14%) had resolution of sexual pain with neuro-modulators, and 1 used intermittent topical steroids for dermatitis.

**DISCUSSION**

Vestibular and vaginal biopsies with abnormal subepithelial collagen may be classified into 2 groups: those diagnostic of LS, and those without evidence of inflammation. The former demonstrates a lichenoid tissue reaction, which is the manifestation of basal

layer damage mediated by the closely applied band of T cell-predominant lymphocytes (7). The latter shows abnormal collagen without evidence of interaction between the lymphocytes and the epithelium. The pathophysiology of the collagen change is not well understood. It appears that dermal homogenization begins as an edematous protein-rich exudate from blood vessels, which becomes hyalinized through dehydration, deposition of type 5 collagen, loss of elastic fibers, and accumulation of decomposed fibrin (8–11). In some cases, this may progress to fibrosis with loss of the inflammatory infiltrate. It is not known if vestibulovaginal sclerosis represents inactive LS that has lost the lymphocytic infiltrate either from treatment or spontaneous remission. Arguing against this, none of the 6 sclerosis cases in this study had LS on vulvar skin, and none were treated at time of biopsy. In contrast, 89% of women with LS on a vestibular or vaginal biopsy had LS



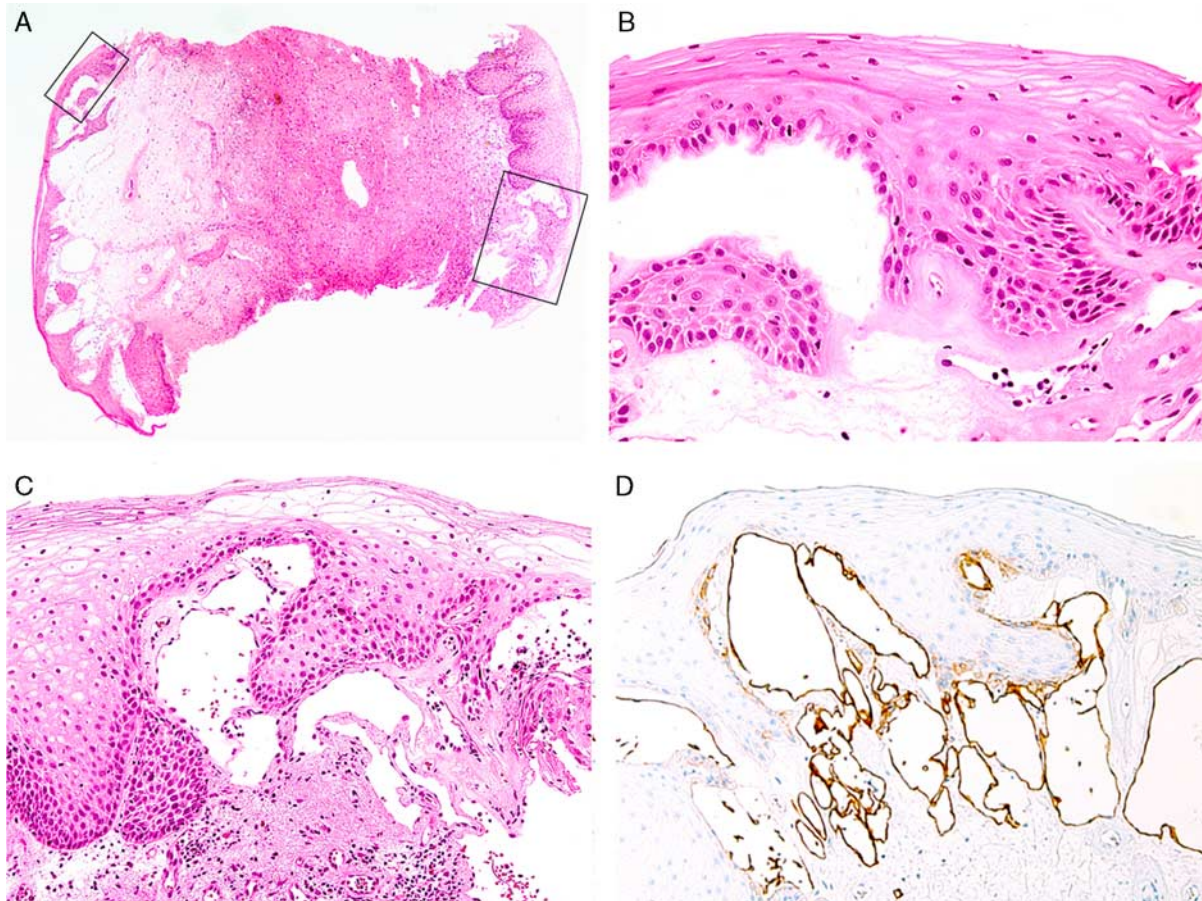
**FIG. 2.** Biopsy of pallor at vestibule consistent with lichen sclerosus: (A) mucocutaneous junction (left) and squamous mucosa with abundant periodic acid-Schiff positive glycogen (right) both show subepithelial sclerotic collagen overlying a band of lymphocytes, periodic acid-Schiff 40 × , (B) squamous mucosa with basal layer degeneration overlying a band of edematous collagen, hematoxylin and eosin 100 × , (C) basal layer with lymphocytosis and squamatization, hematoxylin and eosin 400 × .

elsewhere on the vulva, and the 3 treated at time of biopsy still showed a lichenoid reaction.

Previous reports suggest that keratinization is required to establish susceptibility to LS. Of the 3 published images of vaginal LS, 1 shows parakeratosis and 2 show keratinized epithelium (2,3). A study of 99 men with LS of penile skin reported 14 biopsies showing LS at the navicular or penile urethra, all of which were keratinized (12). The authors hypothesized that urinary obstruction because of LS-related distal stenosis provided the irritant stimulus. In contrast, this study demonstrates that nonkeratinized epithelium may be affected by LS. Likewise, keratinization is variable in vestibulovaginal sclerosis. The histopathologic images in Fadare's (4) report suggest a nonkeratinized epithelium in 1 and keratinization in 2, while the 6 cases in

this study were all nonkeratinized. It is possible that the Koebner phenomenon is one pathway toward abnormal subepithelial collagen, given that vulvovaginal surgery occurred in half of cases (13). The long-term impact of intracavitary fractional laser on vulvovaginal skin and mucosa is unclear, and there are no studies regarding outcomes in women with chronic inflammatory dermatoses.

Basal layer squamatization is infrequently mentioned in dermatopathology publications as a feature of the basal layer degeneration required for diagnosis of LS and lichen planus (14–16). In isolation, basal layer squamatization is not diagnostic of a lichenoid tissue reaction; thus we classified the case of nodular scar with a squamatized basal layer and absent lymphocytic infiltrate as vestibulovaginal sclerosis. One of the histopathologic images from Fadare's



**FIG. 3.** Biopsy of pallor at hymen consistent with lichen sclerosus: (A) mucocutaneous junction (left) and squamous mucosa (right) with edematous and hyalinized subepidermal collagen and a moderate lymphocytic infiltrate, hematoxylin and eosin (H&E) 40 $\times$ , (B) mucocutaneous junction with basal layer squamatization and dilated lymphatics, H&E 200 $\times$  (C) squamous mucosa with basal layer squamatization and dilated lymphatics, H&E 100 $\times$ , (D) positive D2-40 immunohistochemistry of the lymphatic vessel endothelium.

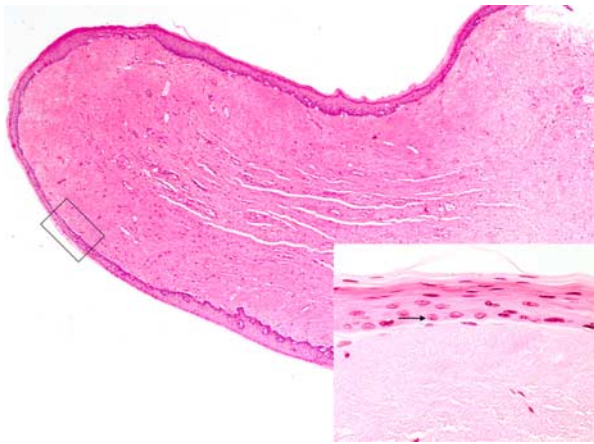
report also shows a squamatized basal layer. The combination of squamatization and abnormal dermal collagen yields a differential diagnosis that also includes dermal scar related to trauma or radiation, morphea, mycosis fungoides, and malignant atrophic papulosis (17–20). However, these conditions have multiple other clinicopathologic features that help distinguish them from LS and vestibulovaginal sclerosis.

Among the 9 cases of vestibular and vaginal LS, 1 had lymphangiectasia with histiocyte infiltration. Carlson et al. (21) raised the possibility of an association between lymphedema and LS in a study of the quantity and size of lymphatics in 18 LS cases compared with 9 controls, hypothesizing that dermal sclerosis disrupts lymphatic drainage leading to lymphostasis. However, neither the association nor

the mechanism has been investigated by other authors.

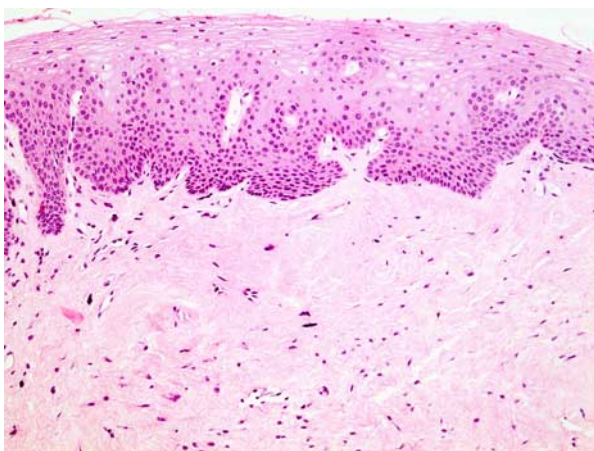
There were no common exposures apparent in the 6 cases of vestibulovaginal sclerosis encountered in this study. This contrasts with the 3 cases described previously, all of whom were postmenopausal, not on hormone replacement, complained of dyspareunia, and had no other skin disease or vulvovaginal surgery (4). There may be exposures common to both studies that are difficult to obtain retrospectively, such as obstetric lacerations or sexual trauma. Estrogen deficiency may not be a prerequisite for vestibulovaginal sclerosis, as one third of cases in this study were on topical or systemic hormone replacement.

It is unclear if vestibular and vaginal LS is as rare as suggested by the sparse examples encountered in



**FIG. 4.** Excision of nodular scar at hymen consistent with vestibulovaginal sclerosis: protuberance with marked hyalinized and fibrotic subepidermal collagen and absent lymphocytic infiltrate, hematoxylin and eosin 40 $\times$ , inset shows overlying parakeratotic epithelium with basal layer squamatization (arrow), hematoxylin and eosin 200 $\times$ .

the literature. White plaques at the vestibule may be interpreted as lichen planus, as its clinical appearance is described as glazed erythema with white striations or plaques at the periphery (22,23). When a skin disease is generalized, clinicians may avoid biopsy of the vestibule and vagina due to challenges with exposure and concerns about patient discomfort and healing. Speculum examination is unlikely to be performed unless the woman has symptoms attributable to the vagina, and nongynecologists may be hesitant to obtain a vaginal biopsy (2,22).



**FIG. 5.** Biopsy of pallor at vestibule consistent with vestibulovaginal sclerosis: squamous mucosa with normal basal layer, band of hyalinized collagen, and absent lymphocytic infiltrate, hematoxylin and eosin 100 $\times$ .

Access to biopsies from specialist vulvovaginal clinics across Australia permits the study of uncommon diagnoses and unusual sites, but the total number of cases meeting inclusion criteria was small nevertheless. The limitations of this study are those inherent to the retrospective design including incomplete clinical data, differences in practice between clinicians, and access only to the cases in which a clinician detected an abnormality and decided to obtain a tissue sample. Most women with clinically diagnosed vulvar LS did not have biopsy verification of this diagnosis. Universal clinical photography would have permitted a more nuanced description of the difference in appearance of the 2 diagnostic categories.

In summary, the differential diagnosis for abnormal subepithelial collagen on vaginal or vestibular biopsies includes vestibulovaginal sclerosis and LS. Although the 2 may be distinguished clinically and histopathologically, further studies are needed to determine whether vestibulovaginal sclerosis is a subset of LS or is a different condition.

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