

Penile Lichen Sclerosus: Correlation between Histopathologic Features and Risk of Cancer

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SUMMARY The relationship between penile lichen sclerosus (LS) and cancer development has not been clearly assessed so far. In order to define these histological features of LS that may indicate or precede a malignant degeneration, 104 biopsy specimens from 86 patients with LS of the glans (90.5%) and from 9 patients with a penile malignancy (7 squamous cell carcinomas, 1 in situ carcinoma, and 1 verrucous carcinoma) arising on LS (9.5%) were reviewed. Three different histopathologic LS patterns were identified: pattern 1 with a prominent lichenoid inflammatory infiltrate in the dermis (9%), pattern 2 characterized by a band-like infiltrate separated from the epidermis by a band of dermal sclerosis (44%), and pattern 3 showing prominent sclerosis with minimal or absent inflammatory infiltrate (9%). These patterns have previously been described in vulvar LS, and have been considered typical of early, mature, and late LS, respectively. In our study, we also found a fourth pattern in 38% of cases, with overlapping features between the first and third pattern, occasionally showing areas of epidermal thickening, with loss of the normal keratinocyte cytoarchitectural differentiation, mitoses and apoptotic cells. In our opinion, the histological features observed in this last pattern may be interpreted as areas of disease reactivation within a chronic stage. Furthermore, 7 out of 9 cases of penile cancer from our series (78%) were associated with this pattern, suggesting that it may correlate with a malignant degeneration.

KEY WORDS: lichen sclerosus; penile cancer; inflammatory dermatosis

INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory dermatosis that can affect any site but has a predilection for the genital area. Its etiology and pathogenesis are unknown. Vulvar LS has been reported to be a precancerous condition, as 4%-

5% of affected women have been found to develop vulvar squamous cell carcinoma (SCC) (1). LS adjacent to vulvar SCC has often been identified on biopsy specimens (2,3), and it has been hypothesized that LS may act as an inflammatory event promoting vulvar carcinogenesis (4).

As regards men, there are anecdotal reports of SCC arising on penile LS (5,6), however, the relationship between penile LS and cancer development has not been clearly assessed. In a retrospective study, a statistically significant risk of malignant degeneration ($p < 0.05$) was found, with 9.3% of patients with penile LS developing an epithelial cancer (7). In contrast, LS at extragenital sites has no reported malignant potential (8).

Penile LS is a disease less commonly observed compared to vulvar LS (1,8). It usually occurs on the glans and/or the prepuce in prepubertal boys and middle-aged men (Fig. 1) (9). Its histopathologic features include variable hyperkeratosis and atrophy of the epidermis with a hyalinized band of tissue and underlying inflammatory cells in the papillary dermis.

The aim of our study was to define those histological features that may indicate or precede a malignant degeneration from a series of biopsy specimens of penile LS and LS adjacent to penile malignancy.

MATERIALS AND METHODS

All specimens from patients with LS of the glans and penile carcinoma arising on LS, retrieved from our pathology files over a 13-year period (1987-2000), were reviewed.

RESULTS

One hundred and four penile specimens from 95 patients were examined. Eighty-six (90.5%) patients had LS (mean age 53, age range 22-79 years), and nine (9.5%) had a penile malignancy (seven SCC, one in situ carcinoma, and one verrucous carcinoma) arising on LS (mean age 63, age



Figure 1. Penile lichen sclerosus.

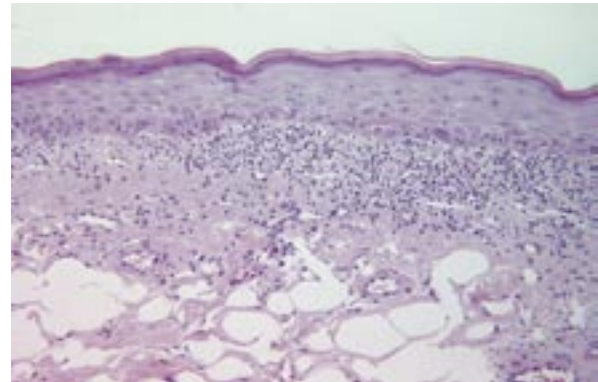
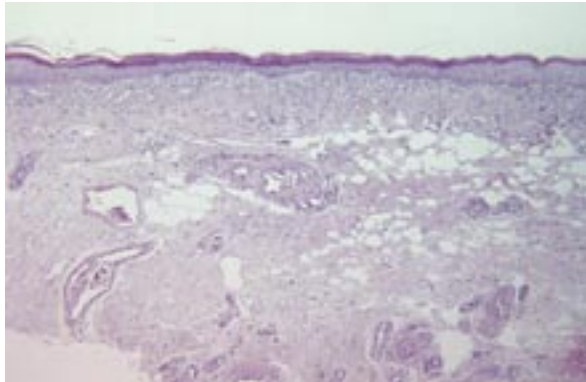
range 47-84 years). In four patients with LS and one patient with SCC arising on LS, two and three biopsy specimens were available, respectively. In one patient with LS, four biopsy specimens from different sites were processed.

Histopathologically, hyperkeratosis, atrophy of the stratum malpighii with hydropic degeneration of basal cells, pronounced edema and homogenization of collagen in the upper dermis, and inflammatory infiltrate in the dermis were found in all patients labeled as LS. In this group, four different histopathologic patterns were identified (Table 1). Pattern 1 was characterized by normal or thinned

Table 1. Histopathologic patterns observed in 95 patients with penile LS

Pattern	Patients (%)	Hyperkeratosis	Epidermis	Hydropic degeneration	Band-like dermal infiltrate		Dermal edema/homogenization	Dermal sclerosis/hyalinization
					superficial	mid		
1	9	+	normal or thinning	+	+	-	-	-
2	44	+	normal or thinning	+	-	+	+	-
3	9	-	normal or thickening	-	-	+/-	-	+
4	38*	+	thickening	+	+	+/-	-	+

* 7 out of 9 patients with penile cancer arising on LS showed this pattern adjacent to the tumor



Figures 2a,b. Pattern 1- Epidermis with weak hyperkeratosis, hydropic degeneration of basal cells, band-like inflammatory infiltrate in the superficial dermis near the basal layer.

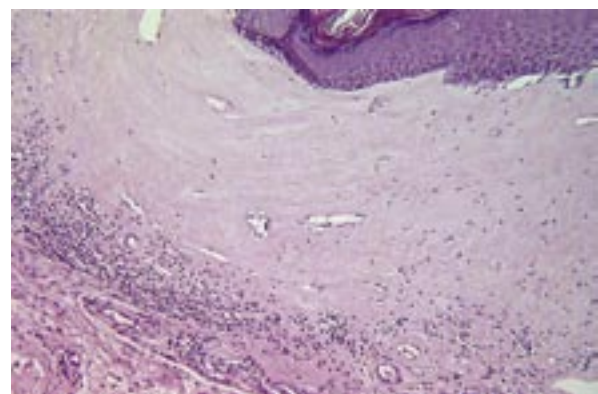
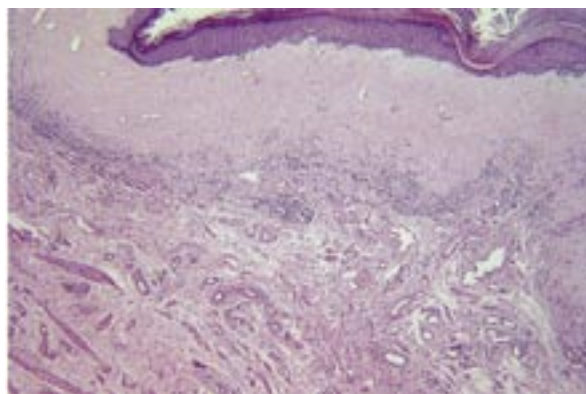
epidermis with weak hyperkeratosis, hydropic degeneration of basal cells, and band-like inflammatory infiltrate in the superficial dermis near the basal layer (Fig. 2a,b). Pattern 2 presented with a normal or atrophic epidermis with hyperkeratosis, hydropic degeneration of basal cells, edema, and homogenization of the superficial dermis with focal extravasated red blood cells and band-like inflammatory infiltrate in the mid-dermis (Fig. 3a,b). Pattern 3 was characterized by normal or thickened epidermis, sclerosis and hyalinization of the dermis, and absence or few inflammatory cells in the dermis (Fig. 4). Pattern 4 consisted of irregular thickening of the epidermis with hyperkeratosis, hydropic degeneration of basal cells, an inflammatory band-like infiltrate in the superficial dermis near the basal layer, and sclerosis with hyalinization of the dermis (Fig. 5). Scattered inflammatory cells were focally observed in the medium and deep dermis. Areas of epidermal thickening, with loss of the normal keratinocyte cytoarchitectural differentiation features, and presence of mitotic

figures and apoptotic cells were occasionally seen (Fig. 6).

One or more of these histopathologic patterns were present in the same patient and, occasionally, in the same specimen. Nine (9%) specimens were histologically identified as pattern 1, 46 (44%) as pattern 2, 9 (9%) as pattern 3, and 40 (38%) as pattern 4. A remarkable finding was the presence of pattern 4 adjacent to penile malignancy in 7 out of 9 (78%) specimens, the remaining showing pattern 3.

DISCUSSION

On review of our LS specimens, the most striking feature was the extreme variation of epithelial changes and dermal alteration present in the majority of samples. This variability, most likely, correlates with the duration of the disease. Such a correlation has been suggested by some authors, based on the evidence that the inflammatory infiltrate, initially located near the dermoepidermal



Figures 3a,b. Pattern 2 - epidermis with hyperkeratosis, hydropic degeneration of basal cells, edema and homogenization of the superficial dermis with focal extravasated red blood cells and band-like inflammatory infiltrate in the mid-dermis.

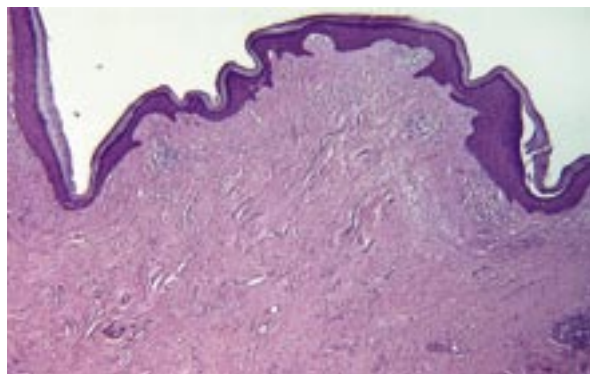


Figure 4. Pattern 3 - sclerosis and hyalinization with absence or few inflammatory cells in the dermis.

junction, with time moves downwards, and in turn the thickness of the zone of dermal sclerosis increases. This latter phenomenon grossly correlates with the duration of symptoms and may be observed in vulvar (1,10) as well as penile LS (11). Three different LS patterns have been identified: a lichenoid pattern, characterized by a band-like lymphocytic infiltrate focally separated from the dermoepidermal junction by edema and/or sclerosis, mostly seen in evolving or early LS; a second pattern, characterized by a band-like infiltrate separated from the epidermis by a band of dermal sclerosis with varying degrees of edema, considered typical of a mature stage; and a third pattern, showing a broad zone of dermal sclerosis with minimal or absent inflammatory infiltrate, commonly observed in older LS (4). However, clinical studies in female patients aimed to verify the association between different histological findings and duration of symptoms found no correlation (12).

In our study, besides the above mentioned histopathologic patterns, we found another pattern in 38% of cases, named pattern 4, showing overlapping features, i.e. focal irregular thickening of the epidermis with hyperkeratosis, hydropic degeneration of basal cells, inflammatory band-like infiltrate in the superficial dermis near the basal layer, and sclerosis with hyalinization of the dermis and scattered inflammatory cells in the medium and deep dermis. These features, showing areas of pattern 1 on a background typical of pattern 3, in our opinion may be interpreted as areas of disease reactivation within a chronic stage.

The pathogenesis of penile SCC is still unclear, but high-risk conditions such as chronic dermatoses, including genital LS, HPV infections, and sequels associated with the lack of circumcision,

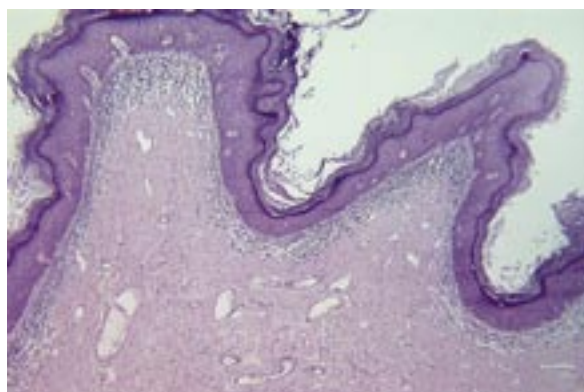


Figure 5. Pattern 4 - irregular thickening of the epidermis with hyperkeratosis, hydropic degeneration of basal cells, an inflammatory band-like infiltrate in the superficial dermis near the basal layer and sclerosis with hyalinization of the dermis.

e.g., phimosis and smegma retention, have been considered to play a role (13). In a recent study on 20 patients with penile SCC, LS was histologically found in 40% of biopsy specimens (14). Our group had previously demonstrated a high incidence of penile cancer on LS, as 8 of 86 (9.3%) patients with LS developed a malignancy (7). Whether penile LS, similarly to vulvar LS, should be regarded as a premalignant condition has not been demonstrated so far. In the present study, we found that 7 of 9 (78%) cases of penile cancer were associated with pattern 4 of LS, suggesting that this pattern correlates with a malignant degeneration. Also, the frequent finding at this stage of areas of epidermal thickening, with loss of the normal cytoarchitectural differentiation organization of keratinocytes, mitotic figures and apoptotic cells, suggests that the disease is moving from a resting to a more active phase.

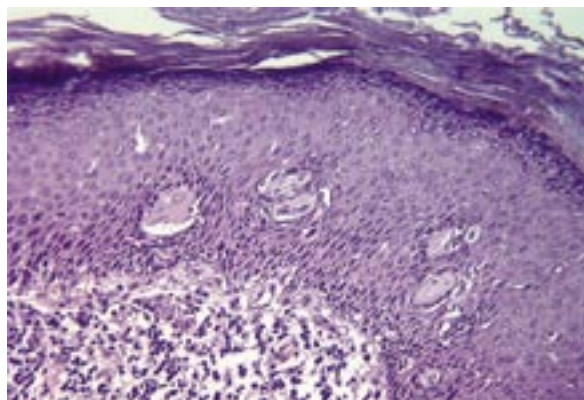


Figure 6. Presence of mitotic figures and apoptotic cells

Based on these considerations, when dealing with penile LS, we suggest to properly evaluate patients showing those histological signs we interpreted as pattern 4. LS, belying its atrophic appearance, may be a metabolically active disease not devoid of malignant potential when reactivation from a chronic stage occurs, supporting the clinical impression that LS is not a static condition but may relapse and fluctuate.

References

1. Powell JJ, Wojnarowska F. Lichen sclerosis. *Lancet* 1999;353:1777-83.
2. Vilmer C, Cavelier Balloy B, Nogues C, Trassard M, Le Doussal V. Analysis of alterations adjacent to invasive vulvar carcinoma and their relationship with the associated carcinoma: a study of 67 cases. *Eur J Gynecol Oncol* 1998;19:25-31.
3. Rouzier R, Morice P, Haie-Meder C, Lhomme C, Avril MF, Duvillard P, Castaigne D. Prognostic significance of epithelial disorders adjacent to invasive vulvar carcinomas. *Gynecol Oncol*. 2001;81:414-9.
4. Carlson JA, Ambros R, Malfetano J, Ross J, Grabowski R, Lamb P, *et al.* Vulval lichen sclerosis and squamous cell carcinoma: a cohort, case control and investigational study with historical perspective. Implications for chronic inflammation and sclerosis in neoplastic progression. *Hum Pathol* 1998;29:932-48.
5. Nasca MR, Innocenzi D, Micali G. Penile cancer among patients with genital lichen sclerosis. *J Am Acad Dermatol* 1999;41:911-4.
6. Paricio Rubio JF, Ravenga AF, Alfaro TJ, Ramirez GT. Squamous cell carcinoma arising on lichen sclerosis et atrophicus. *J Eur Acad Dermatol Venereol* 1999;12:153-6.
7. Micali G, Nasca MR, Innocenzi D. Lichen sclerosis of the glans is significantly associated with penile carcinoma. *Sex Transm Infect* 2001;77:226.
8. Ridley CM. Genital lichen sclerosis (lichen sclerosis et atrophicus) in childhood and adolescence. *J R Soc Med*. 1993;86:69-75.
9. Meffert JJ, Davis BM, Grimwood RE. Lichen sclerosis. *J Am Acad Dermatol* 1995;32:393-416.
10. Fung MA, Le Boit PE. Light microscopic criteria for the diagnosis of early vulvar lichen sclerosis: a comparison with lichen planus. *Am J Surg Pathol* 1998;22:473-8.
11. Fung MA, Le Boit PE. Incidence of penile lichen sclerosis. *J Am Acad Dermatol* 2001;44:878-9.
12. Marren P, Millard PR, Wojnarowska F. Vulval lichen sclerosis: lack of correlation between duration of clinical symptoms and histological appearances. *J Eur Acad Dermatol Venereol* 1997;8:212-6.
13. Micali G, Innocenzi D, Nasca MR, Musumeci ML, Ferràù F, Greco M. Squamous cell carcinoma of the penis. *J Am Acad Dermatol* 1996;35:432-51.
14. Powell J, Robson A, Cranston D, Wojnarowska F, Turner R. High incidence of lichen sclerosis in patients with squamous cell carcinoma of the penis. *Br J Dermatol* 2001;145:85-9.