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Research Article

The Precancerous Potential of Male Genital Lichen Sclerosus Seems to be Higher than Female

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Abstract

Objective: Lichen sclerosus (LS) is a common chronic dermatosis predominantly involving external genital organs and having a malignant potential. The disease is usually clinically and morphologically underdiagnosed worldwide and in the Republic of Belarus in particular. To date LS gender morphological differences are still being examined.

Aim: To establish gender morphological differences and the precancerous potential of male and female genital LS.

Materials and Methods: Biopsy and surgical material of the foreskin and glans penis (n=61) and vulva (n=83) with a morphological diagnosis of LS was examined histologically and statistically. Two groups of patients were identified: 1 – Male genital LS, 2 – Female genital LS.

Results: The malignant potential of dermatosis was revealed to be higher in men (6.8%, n=4) than in women (2.4%, n=2). Penile intraepithelial neoplasia (PeIN) on the background LS occurred of both differentiated and undifferentiated types equally. Vulvar precancerous lesions in combination with LS were identified only in the form of high-grade squamous intraepithelial lesion (HSIL). A reliable association of PeIN with the early stage of the dermatosis was determined (p=0.00). In addition, a significantly more frequent association of the penile dermatosis with features increasing the risk of its malignant transformation, particularly squamous hyperplasia (SH) and basal atypia, as well as dyskeratosis and parakeratosis, was described.

Conclusions: The higher proportion of intraepithelial neoplasia and SH on the background of penile LS suggests that the malignant potential of this dermatosis is higher in men than in women.

Keywords: Vulva; Penis; Lichen Sclerosus; Vulvar Squamous Intraepithelial Lesion; Penile Intraepithelial Neoplasia; Squamous Hyperplasia; Basal Atypia.

Abbreviations

LS: Lichen Sclerosus; PeIN: Penile Intraepithelial Neoplasia; dPeIN: Differentiated (Simple) Penile Intraepithelial Neoplasia; uPeIN: Undifferentiated (Usual) Penile Intraepithelial Neoplasia; SIL: Squamous Intraepithelial Lesion; HSIL: High-Grade Squamous Intraepithelial Lesion; VIN: Vulvar Intraepithelial Neoplasia; dVIN: Differentiated (Simple) Vulvar Intraepithelial Neoplasia; uVIN: Undifferentiated (Usual) Vulvar Intraepithelial Neoplasia; SH: Squamous Hyperplasia; SCC: Squamous Cell Carcinoma; LTR: Lichenoid Tissue Reaction; ISSVD: International Society for the Study of Vulvovaginal Disease.

Introduction

Lichen sclerosus (LS) is a chronic progressive idiopathic disease of the skin and mucous membranes, mainly involving the external genitalia area in the form of white atrophic patches and plaques. Long-term follow-up and adequate treatment can delay the LS development and reduce the risk of obligate precancer and squamous cell carcinoma (SCC) rising on its background. Squamous intraepithelial lesion (SIL) in the forms of differentiated vulvar intraepithelial neoplasia (dVIN) and high-grade SIL (HSIL, undifferentiated vulvar intraepithelial neoplasia, uVIN) is considered as obligate

female precancer [1]. Vulvar LS is believed to develop specifically dVIN on its background [1]. Although to the recent data, both dVIN and HSIL without co-existing SCC considered to be associated with vulvar LS in equal parts (0.6%) [2, 3] (Table 1). It should be also noted, some investigators found HSIL to occur in LS much more often than differentiated counterpart [4]. As shown in the table 1, penile intraepithelial neoplasia (PeIN) according to WHO (2016) together with LS without co-existing carcinoma is seen extremely rare, frequently of a differentiated type (dPeIN) (3.5%) rather than undifferentiated PeIN (uPeIN) [5-9].

Study	Material	n(%)	Intraepithelial neoplasia and LS	
			Undifferentiated type	Differentiated type
Scurry., *et al*. [2]	Vulvar LS	86	2(2.0)	2(2.0)
Micheletti., *et al*. [3]	Vulvar LS	976	4(0.4)	4(0.4)
Total		1062	6(0.6)	6(0.6)
van Seters., *et al*. [4]	Vulvar LS and VIN without SCC	27	27 (100.0)	—
Nasca., *et al*. [6]	Penile LS	86	4(5.0)*	
Barbagli., *et al*. [7]	Penile LS	130	1(0.8)	—
Oertell., *et al*. [8]	Penile LS	53	—	15**
Kravvas., *et al*. [9]	Penile LS	301	6(2.0)	30(10.0)
Total		570	8(1.4)	45(7.9)

Table 1: Intraepithelial neoplasia on the background LS without co-existing squamous cell carcinoma in men and women, n (%).

*uPeIN (n=1); PeIN, not defined histological type (n=3); verrucous carcinoma (n=1).

**In association with squamous hyperplasia (n=15).

In the course of becoming aware of the vulvar and penile precancerous lesions and the preceding processes, researchers in this area paid attention to a number of histological features associated with subsequent malignant transformation. Those included squamous hyperplasia (SH) and basal atypia of the epidermis. Often these changes were identified on the background of male and female genital LS [10]. It is also well known that SH is often observed nearby dVIN, dPeIN or SCC [11].

Since 1976 in vulva "atypical" and «non-atypical» types of SH (so-called "vulvar dystrophy") have been distinguished (International Society for the Study of Vulvovaginal Disease, ISSVD) [10]. The first publications on penile SH entitled "pseudoepitheliomatous, keratotic, and micaceeous balanitis" were made by Bart and Kopf (1977). The authors described the lesion as a solitary, clearly elevated, with keratinization, often in the glans penis of older not circumcised men. Histologically, the process was characterized by pseudocarcinomatous hyperplasia with pronounced horny layer and dermal inflammatory infiltrate [12]. Important in understanding the precancerous potential of the penile LS was the study of Innocenzi., *et al*. (2006). They examined 104 biopsies from 86 patients with LS of the glans penis (90.5%) and from 9 patients with malignant penile tumors (7 SCC, 1 carcinoma *in situ*, 1 verrucous carcinoma) that occurred on the background of LS (9.5%). Squamous hyperplasia was found in 7 of 9 patients with penile SCC in association with LS (78%). The authors concluded that focal hyperplasia of the epidermis with impaired keratinocyte maturation, mitotic and apoptotic figures, may correlate with the malignant transformation of the genital LS in men. It was also suggested that this histological feature can be interpreted as a zone of disease reactivation in the chronic stage [13].

Basal atypia in LS began to be precisely studied at the end of the last century. Jones., *et al*. (1997) noted that in some cases of vulvar LS there was basal epithelial atypia in association with SH, which did not fulfill the criteria for dVIN [14]. Carlson., *et al*. (1998) described and illustrated vulvar LS with "keratinocytic atypia" affecting the basal and parabasal cells [15]. Recently term "atypical LS" was proposed, applied to those LS cases demonstrating basal and suprabasal atypia. Velazquez and Cubilla (2003) found the "atypical LS" of the foreskin in 52 out of 68 men with SCC on the background of LS. In all of them, the associated low-grade SIL (n = 41) and high - grade SIL (n = 11) were noted. Atypia involved non - acantonic ("atrophic") epithelium (n = 2) as well as SH zones (n = 50) [16]. Chiesa-Vottero., *et al*. (2006) published similar study

referring to "atypical LS" in vulva (57%, n = 8). Such a diagnosis was made in the absence of other dVIN histological criteria, in addition to atypia. The authors described epidermal atypia characterized by «nuclear enlargement, enlarged nucleoli, clumped chromatin with parachromatin clearing, and irregularity of the nuclear membrane, usually accompanied by slight nuclear crowding. Some contained scattered normal and occasionally abnormal mitotic figures. The atypical cells were most evident in the lower portions of the epidermis but also occupied higher levels in areas with a thin epidermis. Focally, the atypical keratinocytes had pale or vacuolated cytoplasm. Such areas could be mistaken for extramammary Paget's disease» [17]. Recently van de Nieuwenhof., *et al*. (2011) presented a paper, where suggested that such features as SH, basal cell atypia, dyskeratosis and parakeratosis in the vulvar LS increase the risk of its malignant transformation (p = 0,009). The authors called such cases «LS with progression» [18].

Nowadays SH is used as a descriptive histological term, characterizing an incensement of the squamous epithelium thickness in vulva or penis and is not a diagnostic entity. The histological criteria of basal atypia in genital LS, to our knowledge are still not defined. According to WHO (2014), SH on the background LS increases the risk of its malignant transformation [1]. The identification of basal - suprabasal atypia should alert the pathologist, dermatologist, gynecologist and urologist towards the future development of precancer and invasive tumors on the background of LS. To date LS gender morphological differences are still being examined.

The aim of the study was to establish gender morphological differences and the precancerous potential of male and female genital LS.

Materials and Methods

All vulvar and penile biopsy and surgical cases were retrieved from the pathology files (2012 - 2016) of the City Pathology Bureau in Minsk, Belarus. Slides from the original biopsy specimens of 392 female and 196 male patients were collected and revised for the presence of LS and VIN/Pe IN without co-existing invasive SCC. The pieces were fixed in a 10% neutral buffered formalin, embedded in paraffin blocks, cut serially, placed on slides and stained with hematoxylin and eosin. The diagnosis of advanced LS was based on the presence of basal cell vacuolization, band-like dermal homogenization and a variable dense lymphohistiocyte infiltrate beneath it, whether or not accompanied by epidermal atrophy or acanthosis. An early LS lesions were characterized by focal but evident homogenization along with the features above. Vulvar LS was observed in 53,3% (n = 209), penile one – in 41,8% (n = 82). SIL terminology was used for vulvar lesions according to the latest WHO (2014) and ISSVD (2015) classifications [1,19]. For penile lesions the current WHO classification (2016) with dPeIN and uPeIN was applied [5].

Eighty two female and 59 male representative LS specimens from 82 and 59 patients, respectively, were found. Among them there were two cases associated with VIN without SCC, and four cases in combination with PeIN without carcinoma. One vulvar SIL and two PeIN cases on the background of LS, detected in 2018 were added to the present study. The representation criteria included: non - oblique sectioning of the piece, the absence of extensive vesicular - bullous and artificial changes in the epidermis, the size of the piece more than 10 mm for men and 4 mm for women. Cases of the LS in association with vulvar SIL (n = 2) and PeIN (n = 5) were studied immunohistochemically using p16, p53, Ki - 67 markers. Two groups of patients were identified: 1 – Male genital LS, 2 – Female genital LS. The groups were subdivided into 4 subgroups: 1.1 – Penile LS without intraepithelial neoplasia, 1.2 – LS with PeIN, 2.1 – Vulvar LS without SIL, 2.2 – Vulvar LS with SIL.

Positive p16 expression («block - type» pattern) was assessed with continuous linear horizontal nuclear-cytoplasmic staining of the basal and suprabasal regions of the surface squamous epithelium. The individual basal - suprabasal keratinocyte's nuclei p53 staining was designated as "wild type" (negative), continuous basal - suprabasal nuclear staining was considered positive. The proliferative activity index (Ki - 67) was treated elevated in cases where expression was observed in a larger number of basal and suprabasal keratinocyte nuclei in comparison with a relatively intact vulvar or penile squamous epithelium.

The subepidermal connective tissue homogenization referred to the replacement of the latter with an amorphous, homogeneous, slightly eosinophilic mass, almost devoid of cells, with scattered ectasized thin - walled vessels and fibroblastic nuclei. Basal mem-

brane was treated as thickened when it was broad (larger than the size of a lymphocyte) homogeneous and eosinophilic. Depending on the severity, basal cell vacuolization was considered mild if the intracytoplasmic vacuoles were small (smaller than the keratinocyte nucleus), or pronounced if the size of the vacuole exceeded the size of the epidermocyte nucleus. The basal cell vacuolization was focal when involved one to four epidermal ridges, diffuse – more than four rete ridges.

Keratinization was regarded as pronounced when the increased thickness of the stratum corneum changed from the normal basket-weave pattern to a compact arrangement of the stratum corneum cells. Hyper granulosis referred to an increase in thickness of the granular layer of the epidermis of three or more layers. Epithelium was called atrophic in cases of the Dec easement of the total Malpighian layer thickness, thinned – with the only loss of epidermal ridges, acanthotic (SH) – with the increase in the thickness of the Malpighian layer. Saw - tooting of the epidermis referred to an alteration in the pattern of the dermal-epidermal junction where dermal papillae were expanded and the tips of the rete pegs were pointed. Lichenoid tissue reaction (LTR) was characterized by a band - like infiltrate in the upper dermis consisting predominantly of mononuclear cells with the effacement of the dermo-epidermal junction.

Guided by the data provided by Chiesa – Vottero., *et al*. (2006), as well as the current WHO criteria for VIN (2014) and PeIN (2016), term atypia was implied to the cases demonstrating anisonucleosis, karyomegalia, and nuclear hyperchromasia in the basal and suprabasal epidermal layers, in the absence of other histological VIN/PeIN criteria such as atypical mitoses and koilocytosis [1,5,17]. In the course of the study, it was revealed that «atypical» basal keratinocytes often formed clusters (small groups) of cells. Such clusters were characterized by poor cytoplasm, nuclear hetero- or euchromatin with a prominent nucleolus.

A P-value of <0.05 was considered to be statistically significant. Mann-Whitney U-test, two-tailed Fisher's exact test and χ^2 analysis were used.

Results and Discussion

Significant differences were established between group 1 (male – 45 years) and 2 (female – 59.5 years) by the median age (p=0.00, U=1181). Penile intraepithelial neoplasia in association with LS was revealed in 6.8% (n=4), of differentiated (50%, n=2) and undifferentiated types (50%, n=2) on the early stage of the dermatosis (n=4) (Figure 1). In two additional cases (2018) PeIN was found in the form of dPeIN (n=1) on the early LS, and uPeIN (n=1) – on the advanced LS. A reliable association of PeIN with the early stage of the dermatosis was determined (p=0.00). In women, SIL associated with LS was detected in 2.4% of observations (n=2) in the form of high-grade lesions, on the background of both the early (n=1) and advanced stage of dermatosis (n=1). In the third case (2018), the SIL was also found on the early LS stage (n=1). The relationship of vulvar SIL with the early stage of the dermatosis was not statistically reliable (p=0.55). Penile intraepithelial neoplasia in association with LS was observed at a younger age (median 38.5 years) compared with vulvar precancerous lesions (median 77 years) (p=0.09, U=2).

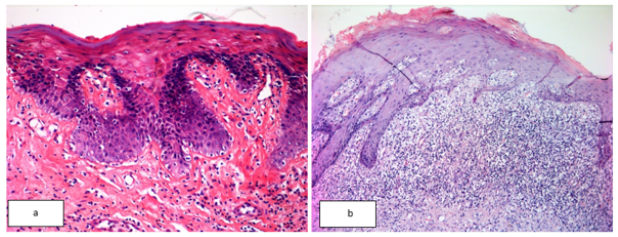

Figure 1: Penile intraepithelial neoplasia on the background of early LS. Hematoxylin and eosin (h&e) staining. A: uPeIN associated with early LS, ×200; b: dPeIN associated with early LS, ×100.

The precancerous lesions of the penis predominantly involved the region of the inner layer of the foreskin, and were accompanied by the presence of plasma cells and eosinophils in the inflammatory infiltrate, as well as papillomatosis, SH, parakeratosis and pronounced keratinization (Table 2). The infiltrate was predominantly of plasma cell in two cases of dPeIN and in one uPeIN (p=0.33).

In women, SILs were localized in the zone bearing skin appendages (hair follicles) and were characterized by papillomatosis, pronounced keratinization, hypergranulosis, SH, dyskeratosis, and also by the presence of plasma cells in the infiltrate. A significant association of predominantly plasmacytic infiltrate and SIL was established (p=0.01).

Histological feature	PeIN		VIN
	N=6	P- value (χ^2, Fisher)	N=3
Involved zone without skin adnexa with skin adnexa	 5 1	 1.00 1.00	 — 3
Pronounced keratinization	4	0.61	3
Hypergranulosis	3	0.66	3
Squamous hyperplasia	5	0.65	3
Parakeratosis	5	0.39	2
Dyskeratosis	5	1.00	3
Papillomatosis	6	0.08	3
Plasma cells in the infiltrate predominantly plasma cells	6 3	0.17 0.33	3 2*
Eosinophils in the infiltrate	4	0.06	1

Table 2: Comparative morphological characteristics of PeIN and VIN in association with lichen sclerosus in the biopsy and surgical specimens, n (%).

*p=0,01.

The morphological LS picture in groups 1 and 2 was mostly similar. Male and female LS lesions were predominantly characterized by the pronounced hyperkeratosis, presence of granular layer, uneven epidermal thickness, variable degree of the homogenization and the inflammation, telangiectasia and pigment incontinence. The basal cell vacuolization in both genders tended to be focal and mild in the early LS stage (p=0.24 in men, p=0.02 in women) being diffuse and pronounced in the advanced one (p=0.00 in men, p=0.07 in women). Statistically significant differences between two groups were identified in a number of histological parameters. Male LS significantly more often affected the inner aspect of the foreskin without skin appendages (p=0.01). The LS lesions in men were more often characterized by the presence of parakeratosis (p=0.00), SH (p=0.00), saw-toothing (p=0.00), pronounced basal cell vacuolization (p=0.02), papillomatosis (p=0.00), dyskeratosis (p=0.00), satellite cell necrosis (p=0.01), severe (sometimes lichenoid) lymphoplasmacytic inflammation (p=0.01), and an occasional lymphocytic vasculitis of the large vessels (p=0.07). In group 2, meanwhile, thinning of the epidermis (p=0.00), moderate inflammation (p=0.02), milia (p=0.02), and elastosis (p=0.40) were revealed to be more frequent. The saw-toothing of the epidermis in group 1 was predominantly observed on the background of SH (p=0.00), while in group 2 the epidermis was mostly thinned (p=0.00).

It should be emphasized, histological features increasing the risk of LS malignant transformation, namely SH and basal atypia (Figure 2), were significantly more frequently observed in men than in women. Male LS demonstrated SH in 39.6% (n=57), and female – 20.5% (n=17) (p=0.00). Male LS lesions had atypia in 42.6% (n=26), while female cases were atypical in 11.3%, (n=9) (p=0.00). In males the significant association between SH, atypia and parakeratosis was detected (Table 3). Female LS with SH was significantly more often associated with parakeratosis, dyskeratosis, hypergranulosis and fibrinoid necrosis of subepidermal collagen fibers. Atypia in vulvar LS was more frequently combined with dyskeratosis (p=0.01). As shown in table 1, compared with the vulvar LS, the SH of the penis was significantly more often accompanied by atypia and saw-toothing.

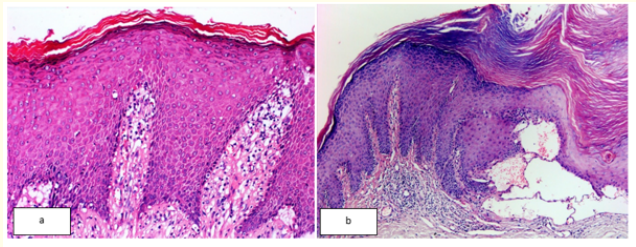

Figure 2: LS with risk of neoplastic progression. H&e staining. a: Early male LS with SH, saw-toothing and basal atypia, ×200; b: Early female LS with SH, basal atypia and angiokeratoma-like changes, ×100.

Histological feature	Men		Women		P- value (χ^2, Fisher)
	35(100.0)	P- value (χ^2, Fisher)	17(100.0)	P- value (χ^2, Fisher)	
Atypia	23(65.7)	0.00	4(23.5)	0.08	0.01
Parakeratosis	28 (80.0)	0.01	10(58.8)	0.00	0.11
Dyskeratosis	31(88.6)	0.26	13(76.5)	0.00	0.41
Saw-toothing	25(71.4)	0.85	4(23.5)	0.30	0.00
Hypergranulosis	17(48.6)	0.18	10(58.8)	0.00	0.49
Fibrinoid necrosis of the collagen	15(42.9)	0.57	11(64.7)	0.00	0.14

Table 3: Comparative morphological characteristics of the dependence of SH on other histological features of genital LS in men and women, n (%).

When calculating the relative risk of the occurrence of atypia, SH, parakeratosis and dyskeratosis (Table 4), it was found that each of the signs significantly increases the risk of developing the other from this list in both genders. The relationship between these histological characteristics was much stronger in men than in women.

Histological feature	Atypia		Squamous hyperplasia		Parakeratosis		Dyskeratosis	
	m	f	m	f	m	f	m	f
Atypia	—	—	10.86	3.75	5.13	6.0	2.0	13.14
Squamous hyperplasia	10.86	3.57	—	—	4.89	5.31	2.58	6.08
Parakeratosis	5.13	2.12	4.89	5.31	—	—	7.03	1.46
Dyskeratosis	2.0	13.14	2.58	6.08	7.03	1.46	—	—

Table 4: Relative risk of development of atypia, SH, parakeratosis and dyskeratosis between themselves in males (m) and females (f).

In the present study, the following gender features of the disease were established. In men, LS occurs at a younger age (median 45 years) than in women (59.5 years). Male genital LS is statistically significantly more often accompanied by SH with saw-toothing, parakeratosis, dyskeratosis, satellite cell necrosis, pronounced basal cell vacuolization, pronounced and lichenoid lymphoplasmacytic inflammation. The tendency of basal cell vacuolization to increase with the development lymphoplasmacytic genital LS in both genders is also described.

Penile intraepithelial neoplasia on the background of LS can occur of both differentiated and undifferentiated types. Vulvar precancerous lesions in association with LS are more often observed in the form of HSIL (uVIN). The latter is consistent with the available literature data. In the present study it was established that the malignant transformation of the genital LS in men occurs at a young age (median 38.5 years), in women – in the senile (median 77 years) (p=0.09). Moreover, a reliable association of PeIN with the early stage of dermatosis (p=0.00) was detected. In addition, a significantly more frequent association of the penile LS with SH and atypia, signs increasing the risk of its malignant transformation, as well as dyskeratosis and parakeratosis were described. The malignant transformation of the LS in the early stage of dermatosis may occur due to the prolonged cytotoxic effect of T-lymphocytes of the inflammatory infiltrate on keratinocytes.

It was also revealed that each of the features with a high risk of malignant transformation (namely SH, atypia, dyskeratosis, parakeratosis) significantly increases the risk of developing the other from this list in both genders.

Conclusion

The higher proportion of PeIN and SH on the background of penile LS suggests that the malignant potential of this dermatosis is higher in men than in women. Early LS should be examined morphologically with caution regarding the associated PeIN and VIN.

Conflict of Interest

The authors have no conflict of interest.

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