Penile Carcinoma in Patients With Genital Lichen Sclerosus: A Multicenter Survey

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Purpose: In this observational descriptive study we reviewed the histology and the clinical records of 130 patients with LS involving the male genitalia to determine the presence of premalignant or malignant lesions.

Materials and Methods: A total of 130 male patients (from 1991 to 2001) with genital LS were treated at our centers. Mean patient age at diagnosis was 42.5 years. In all patients with a clinical diagnosis of LS, the histology was reexamined to look for evidence of LS, applying strict histological criteria. All cases of histologically proven epithelial malignancy, namely SCC, VC and EQ, were reviewed to confirm the presence of neoplastic changes and ascertain the degree of SCC differentiation.

Results: Of 130 men 11 (8.4%) with genital LS showed premalignant or malignant histopathological features including 7 (64%) with SCC, 2 (18%) with VC, 1 (9%) with EQ and 1 (9%) with SCC associated with VC. In 6 of 11 patients (55%) the histological study showed the presence of epithelial dysplasia.

Conclusions: Survival of patients with penile carcinoma depends on early diagnosis and treatment, and all patients with genital LS should be observed closely to detect the development of neoplastic or preneoplastic lesions as early as possible.

Key Words: lichen sclerosus et atrophicus, penis, carcinoma, squamous cell, carcinoma, verrucous, erythroplasia

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S of the male genitalia is a chronic, sclerosing, atrophic process involving the glans penis, the coronal sulcus, the foreskin, the external urinary meatus and the anterior urethra. It causes destructive scarring which can lead to devastating urinary and sexual problems, and a dramatic reduction in quality of life.

Studies of large groups of women with LS have shown that the risk of SCC of the vulva is in the range of 4% to 5%, and in longitudinal case-control studies the rate of SCC in an LS afflicted cohort appeared to be 317 times higher than in unaffected women of the same age.

The association of premalignant or malignant lesions arising on a background of LS has not been examined as fully in males, and the risk of penile carcinoma in patients with LS remains uncertain. The incidence of neoplastic changes among patients with LS has been reported to range from 2.3% to 5.8%. On the contrary, some authors suggest that 20% of men with penile SCC, 50% had histological evidence of LS. Porter et al have shown an increased prevalence of LS (50%) in patients with erythroplasia of Queyrat compared to those patients with other forms of penile intraepithelial neoplasia or the normal population.

We retrospectively reviewed by an observational descriptive method the histology and the clinical records of 130 patients with LS involving the male genitalia to determine the presence of premalignant or malignant lesions in association with LS.

PATIENTS AND METHODS

From 1991 to 2001, 130 male patients with LS involving the genitalia were treated at our centers. Mean patient age at diagnosis was 42.5 years (range 11 to 82) but symptoms had been present for up to 10 years before the diagnosis was made. Only 3 patients were younger than 12 years old. In all patients with a clinical diagnosis of LS the histology was reexamined for evidence of LS according to strict, accepted pathological criteria. LS was defined as an epithelial-stromal lesion characterized by squamous atrophy or hyperplasia, band-like infiltrate, hyalinization of the papillary dermis, hyperkeratosis, pigment incontinence and dermal edema. All patients were prospectively followed up with special attention to LS complications (penile scars and urethral disease) and cancer development.

All cases of histologically proven epithelial malignancy associated with genital LS, namely SCC, VC and EQ, were reviewed to confirm the presence of neoplastic changes and ascertain the degree of SCC differentiation. Lastly we recorded whether there were associated lymph nodes or metastases.

RESULTS

Of 130 men 11 (8.4%) with genital LS showed premalignant or malignant histopathological features (see table ). Seven men (64%) had SCC (fig. 1), 2 (18%) had VC, 1 (9%) had EQ (fig. 2) and 1 (9%) had SCC associated with VC (figs. 3 and 4). Of the 7 cases of SCC 2 (29%) were well differentiated, 2 (29%) moderately differentiated and 3 (42%) poorly differentiated. The SCC associated with VC was well differentiated. Mean age at diagnosis was 52 years (range 43 to 64). The
mean time between the diagnosis of LS and the presentation of cancer was 12 years. In 4 patients (37%) the lesion involved the glans penis, in 3 (27%) it involved the glans, the coronal sulcus and the foreskin, in 2 (18%) the glans and the coronal sulcus, in 1 (9%) the glans and the urethra, and in 1 (9%) the penile stump after previous amputation for SCC (fig. 5). In 6 of 11 cases (55%) the histological study showed the presence of epithelial dysplasia (figs. 4 and 6). One patient (9%) had lymph node involvement and documented metastases.

**DISCUSSION**

The exact number of patients with penile LS that has evolved into premalignant or malignant lesions is difficult to quantify.\(^7,9\) In adult male patients with genital LS, SCC and VC have been sporadically described but some reports do not include documentation of histological findings, they never had prior documentation of LS, or allude to personal communications of other cases.\(^10\)

Recently the incidence of association of penile neoplasia arising on a background of LS has been fully examined applying strict histological criteria.\(^6,9\) In 1999 Nasca et al reported malignant changes (SCC, VC, EQ) in 5.8% of a cohort of uncircumcised patients and suggested that patients with genital LS are at risk for penile neoplasia.\(^6\) In 2000 in a large series of male genitalia with LS, Depasquale et al reported 12 cases (2.3%) of SCC in uncircumcised and circumcised patients.\(^3\) In 2001 Powell et al suggested that patients with penile SCC commonly have a background of genital LS in 50% of cases.\(^7\) Finally, in our series of 130 male patients with genital LS, penile carcinoma developed in 8.4%.

HPV 16 is frequently reported as associated with the development of SCC, and rarely associated with EQ and VC.\(^12\) Moreover, the relationship between LS and HPV infection is controversial.\(^1,6,7,12\) Perceau et al reported that in patients with LS associated penile SCC, of specimens which underwent polymerase chain reaction analysis, none was positive for the
Velazquez and Cubilla studied the anatomic distribution and prevalence of LS in patients with SCC of the penis and concluded that LS might represent a preneoplastic condition for at least some types of penile cancers, in particular those not related to human papillomavirus. Regardless, it has been proposed that LS provides a fertile field on which an oncogenic virus may cause dysplastic changes. Nasca et al found a high incidence of HPV 16 in cases of most frequently found mucosal oncogenic HPV types.

Fig. 3. Association between SCC and VC involving distal part of penis.

Fig. 4. Patient 7. A, VC of glans, coronal sulcus and foreskin. Broad based bulbous projection forming regular pushing border. Reduced from ×100. B, SCC arising in background of VC. Reduced from ×100. C, foreskin showing low grade dysplasia (top) with lack of maturation involving lower half of epithelium. Lichen sclerosis (bottom) with hyperkeratosis, dermal collagen hyalinization and mild inflammatory infiltrate. Reduced from ×50.

Fig. 5. Recurrent squamous cell carcinoma in penile stump (patient 5).

Fig. 6. Patient 1. A, SCC of glans. Irregular nests of cells invading underlying stroma. Reduced from ×50. B, LS of foreskin and glans. Hyperkeratosis, dermal collagen hyalinization with telangiectasias, mild inflammatory infiltrate. Reduced from ×50. C, glans showing high grade dysplasia. Atypical cells involving more than two-thirds of epithelium and showing lack of maturation. Reduced from ×100.
carcinoma in which penile LS developed (all uncircumcised men), and suggested that HPV infection may have an important role in the pathogenesis of epithelial malignancy, although other factors may be involved. In our present series the polymerase chain reaction study for the presence of HPV was not available. One patient had a clinical history of previous HPV genital disease, and the majority of patients presented with a clinical history negative for those factors known to promote penile carcinoma, including phimosis related hygiene problems (5 patients were circumcised).

The origin of penile carcinoma arising on a background of LS remains unclear. The onset of penile carcinoma could be preceded by epithelial dysplasia or focal dyskeratotic hyperplasia. Nasca et al showed that transition from LS to frank neoplastic foci was histologically evident in all cases of SCC, and areas of epithelial dysplasia were evident in the tumor periphery. In our study the presence of low or high grade epithelial dysplasia was documented in 55% of cases (figs. 4 and 6), suggesting the hypothesis that epithelial dysplasia may represent a precancerous stage before the development of neoplasia in atrophic nonproliferative LS lesions. Moreover, the time lag between the onset of LS and the development of penile neoplasia may be 10 to 23 years. In several years the epithelial changes may evolve in different neoplastic lesions, including SCC, VC, EQ or SCC associated with VC.

LS may be clinically undetected or not diagnosed histologically despite circumcision before the advent of penile carcinoma because many surgeons still fail to send the circumcision specimen for histology. Moreover, circumcision in these patients should not be delegated to an unsupervised trainee surgeon as the presence of suspicious lesions may go unrecognized, and all circumcision samples should be sent in for histological examination.

Finally, the high incidence of penile carcinoma observed in our series emphasizes the importance of subgroup analysis of patients with penile carcinoma. Indeed the main potential of subgroup analysis, to investigate the characteristics of patients with an association between penile carcinoma and LS, is not only the identification of heterogeneity of pathophysiology, biology and genetic, but is also in answering practical questions about what treatments for LS should be used, at what stage of disease circumcision is more effective, and what are the risks and benefits of treatment related to the comorbidity of LS. Only wide international multicenter studies could offer an answer to these questions which are the most demanding for the health of our patients.

CONCLUSIONS

At the time of diagnosis of LS, the patient should be given full information about likely causes, the course of the disease, and the possible association with penile cancer. Survival in patients with penile carcinoma depends on early diagnosis and treatment, and all patients with genital LS should be observed closely to detect the development of neoplastic or preneoplastic lesions as early as possible. We recommend a baseline color photograph with followup examination every 6 months, including careful palpation with a biopsy of any area of indurations. Finally, a more accurate examination and followup are required in patients in whom the LS is associated with epithelial dysplasia.

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**Abbreviations and acronyms**

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>EQ</td>
<td>erythroplasia of Queyrat</td>
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<tr>
<td>HPV</td>
<td>human papillomavirus</td>
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<td>LS</td>
<td>lichen sclerosus</td>
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<td>SCC</td>
<td>squamous cell carcinoma</td>
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<td>VC</td>
<td>verrucous carcinoma</td>
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**REFERENCES**


