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EDITORIAL

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Vulvar lichen sclerosus oncologic risk: italian interdisciplinary Society of Vulvology (SIIV) Position Paper

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1. Background

Lichen sclerosus is a chronic inflammatory progressive skin disorder which mostly affects the anogenital areas [1]. The disease occurs at all ages and in both sexes but is more common in females than males (male-to-female ratio 1:10).

The commonest symptoms of vulvar lichen sclerosus (VLS) are itching, burning and dyspareunia. Typical clinical lesions are represented by white patches or plaques, atrophy, fissuring and ecchymotic lesions caused by intrinsic atrophic alterations and scratching. In addition, post-inflammatory progressive scarring may cause irreversible modifications of anogenital architecture, including burying of the clitoris, fusion or loss of the labia minora and stenosis of the vaginal introitus. Thus, VLS may severely impact on quality of life. The diagnosis of VLS is clinical, but a biopsy may be necessary when the clinical picture is not diagnostic. Typical histological features include ortho-hyperkeratosis, epidermal atrophy, basal cell degeneration, dermal hyalinization with a homogenized band of sclerosis at papillary dermis, and a band-like lymphocytic infiltrate immediately beneath the hyalinization [2]. Dermoscopic examination may support a non-invasive diagnosis and discriminate towards other inflammatory and neoplastic vulvar disorders.

Early intervention with topical corticosteroids may improve quality of life, revert skin changes and prevent both scarring and tumor evolution [3].

There is strong evidence that ultra-potent and potent corticosteroids have an excellent effect on both symptom control and reversal of histopathological and clinical features. Topical clobetasol propionate 0.05% ointment or cream is the gold standard treatment for VLS, as inferred by randomized controlled trials (RCT) [4–6]. Strong evidence also supports the use of Mometasone furoate 0.1% [6].

Due to their immunosuppressive activity, the topical calcineurin inhibitors (TCI) tacrolimus and pimecrolimus have been shown to be effective and safe in treating VLS in both

adult and prepuberal patients [4, 5, 7]. Applied twice a day for 2 to 6 months, they resulted highly effective in improving VLS signs and symptoms, with considerable complete response rates.

VLS is a chronic disorder, so, after an initial attack phase, it is of paramount importance to continue an adequate therapeutic maintenance treatment to prevent or, at least, delay disease recurrences. Topical corticosteroids should be administered on an "as needed" basis ("reactive" scheme) [1] or on a continuative prolonged regimen [8] or even on a low-dose, intermittent regimen ("proactive" scheme) [9].

2. Lichen Sclerosus and Cancer

VLS, unlike the cutaneous extragenital lichen sclerosus (LS), may progress into cancer. Among the different clinical presentations of VLS the hyperkeratotic forms seem at higher risk of transformation.

Chronic inflammation, oxidative DNA damage, altered genetic and epigenetic background, and altered expression of p53 oncogenes, may lead to neoplastic evolution of VLS [10].

Squamous cell carcinoma of the vulva represents about 80% of all vulvar neoplasms which account for 3–6% of malignant tumors of the female genital tract [11]. Cancer in VLS seems to develop via differentiated vulvar intraepithelial neoplasia (VIN) to Squamous cell carcinoma (SCC): the not-HPV related pathways of onset of SCC of the vulva.

Women affected with VLS have a lifetime risk of developing a squamous cell carcinoma estimated to be 2–7%, while up to 65% of vulvar carcinomas arise in a background of VLS [12].

In an Italian study the neoplasia incidence risk was 3.5% while the neoplasia incidence rate was 8.1 per 1000 person-years. The cumulative probability of progression to neoplasia increased from 1.2% at 24 months to 36.8% at 300 months. The median progression-free survival was significantly shorter in older women ($\geq$70 years) when compared with younger women ($p = 0.003$) [13].

In a population-based Finnish Cancer Registry study LS was associated with an increased risk of vulvar cancer with a standardized incidence ratio (SIR) of 33.6 (95% CI 28.9–38.6), more pronounced in the first year of follow-up, while most cancers occurred after 5 years of follow up [14].

A recent Italian retrospective study assessed the risk of vulvar cancer in a cohort of women with LS. The overall SIR was about 40 and the standardized incidence ratio grew when considering the first three years after VLS diagnosis [15].

Other Authors have emphasized that women with LS and concurrent VIN had a 10-year vulvar squamous cell carcinoma (VSCC) risk of 18% compared with 3% in women with LS without VIN [12]. These observations underline the need to adequately follow up women affected with VLS in order to promptly detect any neoplastic evolution of LS.

The role of appropriate treatment is pivotal. A protective effect of therapy from malignant evolution was demonstrated as carcinoma developed only in non-treated or irregularly treated VLS (4.7% of only partially compliant patients after an observational period of 4.7 years range 2 to 6.8 years) [3].

Therefore these data emphasize the crucial role of prompt and adequate treatment of women with LS progressing towards neoplastic evolution.

3. Recommendations in Clinical Practice

A correct and early diagnosis is desirable in order to start correct treatment as early as possible. An appropriate treatment not only improves symptoms, signs (including scarring) and quality of life, but also seems to reduce the risk of progression towards cancer.

Even though the diagnosis of LS is essentially clinical, a biopsy is strongly recommended in the case of persistent signs and symptoms after adequate treatment, in the presence of doubtful clinical aspects or suspected malignancy, localized skin thickening or areas of hyperkeratosis.

Follow up should be modulated considering the course and severity of the disease. Women with stable diseases should be seen annually. They should however be educated to carry out self-examination in order to promptly detect modifications such as ulcers or nodules and white/darkly pigmented areas.

A more stringent follow-up (3–6 months) is required in women with active disease or disease not completely controlled by an adequate therapy.

A strict life-long follow up is advised in women who developed undifferentiated VIN or SCC.

In any case, long-term (maybe life-long) follow up is required in order to detect clinical and histological LS progression towards cancer early.

Abbreviations

LS, lichen sclerosus; RCT, randomized controlled trial; SCC, squamous cell carcinoma; SIR, standardized incidence ratio; TCI, topical calcineurin inhibitor; VIN, vulvar intraepithelial neoplasia; VLS, vulvar lichen sclerosus; VSCC, vulvar squamous cell carcinoma.

Author Contributions

MP designed the project. MC, CS, ADM drafted the first version of the manuscript. MC, CS, ADM, PB, CC, SC, LM, LMi, EP, GR, GT, GTo, AV, MP contributed to literature search, manuscript revision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

MP is serving as one of the Editorial Board members of this journal. We declare that MP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Enrique Hernandez. The other authors declare no conflict of interest.

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