MICROVASCULAR REMODELING AND THE ENDOTHELIAL-APOPTOTIC SWITCH IN LICHEN SCLEROSUS: AN IMMUNOHISTOCHEMICAL STAGE-BASED STUDY

Omasharifa J. Po - Ph.D., associate professor
Kursk State Medical University (Kursk, Russia)
Akmal A. Sidikov - D.M.Sc., professor, rector
Fergana Medical Institute of Public Health (Fergana, Uzbekistan)
zebooriginal@gmail.com

Abstract. *Purpose: To evaluate stage-specific microvascular and apoptotic changes in lichen sclerosus (LS) using CD31, VEGF and CD95 immunohistochemistry. Methods: The article is based on a dissertation cohort of 60 patients with LS. For stage-oriented immunohistochemical analysis, representative dermal samples from progressive-stage lesions (n=15) and chronic-stage lesions (n=15) were examined. Results: In progressive-stage LS, dermal CD31 expression was detected in 33% of samples, VEGF in 80%, and CD95 in 20%, while all three markers were absent in the epidermis. In chronic-stage LS, dermal CD31 expression was present in 53%, VEGF in 20%, and CD95 in 95% of samples, again with no epidermal expression. Morphologically, progressive-stage lesions showed vacuolar interface dermatitis, lymphocytic exocytosis and lichenoid inflammation, whereas chronic-stage lesions were dominated by papillary dermal fibrosis and sclerosis. Malignant progression to squamous cell carcinoma (SCC) was documented in 5 of 60 patients and was associated with ulceration, bleeding, proliferating irregular vessels, epithelial atypia, pathological mitoses and high CD95 expression. Conclusion: LS demonstrates a stage-dependent shift from endothelial activation and neoangiogenesis to endothelial injury, apoptotic remodeling and sclerosis. Combined clinicopathological and immunohistochemical assessment may improve early recognition of unfavorable disease evolution.*

Keywords: *lichen sclerosus; microcirculation; CD31; VEGF; CD95; squamous cell carcinoma*

Introduction. Lichen sclerosus is increasingly understood as a chronic inflammatory disorder in which immune dysregulation, stromal remodeling and vascular alterations interact over time [1-4]. Standard clinical descriptions emphasize whitening, atrophy, scarring and pruritus, but the mechanisms that drive progression from active inflammatory lesions to chronic sclerosis and, in a subset of cases, malignant transformation remain incompletely characterized [1,2,5].

The dissertation that forms the basis of this article focused specifically on the microcirculatory bed as a potential early pathogenic target. The working hypothesis was that progressive-stage LS is characterized by endothelial activation and neoangiogenesis, whereas chronic disease is marked by endothelial damage, apoptosis and sclerosis. The present manuscript summarizes the immunohistochemical evidence supporting that stage-dependent model.

Materials and Methods. The source cohort included 60 patients with LS, of whom 30 were women and 30 were men. All underwent clinical assessment and skin biopsy. For stage-focused immunohistochemical analysis, representative specimens from progressive-stage LS (n=15) and chronic-stage LS (n=15) were studied. Five patients from the total cohort showed progression to squamous cell carcinoma (SCC) of the skin on clinicopathological assessment.

Formalin-fixed paraffin-embedded sections were evaluated histologically and immunohistochemically using antibodies to CD31, VEGF and CD95. The original dissertation recorded marker positivity separately for epidermis and dermis. Histological interpretation emphasized vacuolar interface dermatitis, lichenoid infiltrate, exocytosis of lymphocytes, papillary dermal fibrosis, sclerosis, and epithelial atypia. Statistical comparisons were performed in the dissertation; the present article reports the validated stage-specific expression profile and its morphological interpretation.

Results. The progressive stage of LS showed a histological pattern of vacuolar interface dermatitis with dense lichenoid inflammatory infiltrates, vacuolar degeneration of epidermal cells, intercellular lymphocytes and lymphocytic exocytosis. This phase represented the biologically active part of the disease. In contrast, the chronic stage was dominated by dense fibrosis of the papillary dermis and sclerosis, with a lower inflammatory burden. The observed stage transition therefore involved not only stromal remodeling but also a major shift in the vascular microenvironment.

Immunohistochemically, no expression of CD31, VEGF or CD95 was detected in the epidermis in either stage. In the dermis of progressive-stage lesions, CD31 expression was found in 5/15 samples (33%), VEGF in 12/15 (80%), and CD95 in 3/15 (20%). The predominance of VEGF together with detectable CD31 supports the interpretation of endothelial activation and active neoangiogenesis in early disease. In this stage, endothelial structures were morphologically more preserved than in chronic lesions.

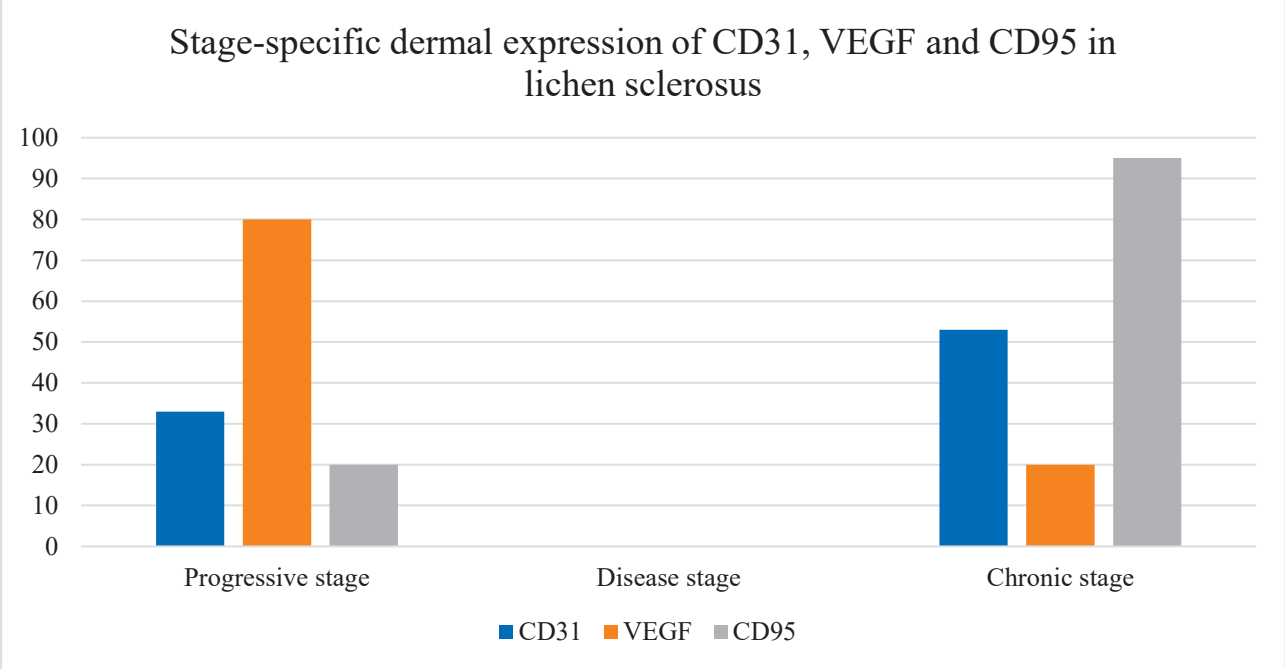


Figure 1. Stage-specific dermal expression of CD31, VEGF and CD95 in lichen sclerosus

A markedly different profile was documented in chronic-stage lesions. Dermal CD95 expression was present in 14/15 samples (95%), CD31 in 8/15 (53%), and VEGF in 3/15 (20%). Histologically, vascular walls displayed severe structural changes, including nuclear shrinkage, swelling and irregular staining continuity. CD31 expression became discontinuous and uneven in morphologically altered vascular cells, whereas CD95 staining intensified in the endothelium and surrounding vascular structures. This pattern indicates a switch from proangiogenic signaling toward apoptotic vascular remodeling.

The dissertation conclusions additionally state that structural disruption of the endothelium contributed to increased vascular permeability and even the formation of mixed thrombi, which was linked to secondary changes in both epidermis and dermis. In this interpretation, endothelial injury is not an epiphenomenon but a pathogenic event that amplifies sclerosis and tissue damage. This concept aligns with the clinical observation that visible dermoscopic vessels may indicate disease activity during the early phase, while chronic lesions lose vascular vitality and become predominantly sclerotic.

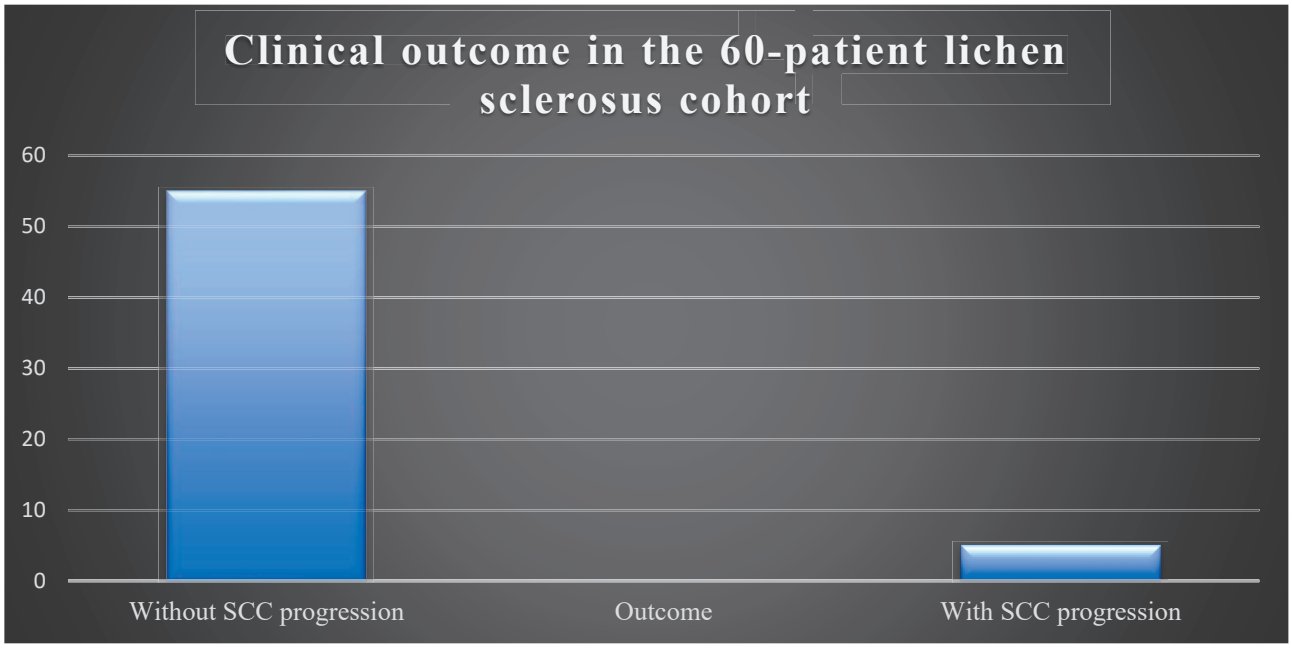


Figure 2. Clinical outcome in the 60-patient lichen sclerosus cohort

Malignant progression to SCC was documented in 5 of the 60 patients. Morphological warning signs included ulceration, induration, bleeding, disturbed stratification of the epidermis, epithelial atypia, pathological mitoses, dermal sclerosis, and proliferation of dotted and irregular vessels. In the practical conclusions of the dissertation, high CD95 expression in the presence of pathological epidermal cells and mitoses was identified as one of the main combined indicators of adverse progression.

Discussion. The stage-specific combination of high VEGF in progressive lesions and high CD95 in chronic lesions suggests that LS evolves through at least two biologically distinct vascular phases. The first is dominated by endothelial activation and angiogenic response, likely reflecting active inflammation and tissue repair. The second is characterized by endothelial exhaustion, apoptosis and fibrosing remodeling. This interpretation is consistent with the general understanding that LS involves immune-mediated inflammation, extracellular matrix remodeling and potential oncogenic evolution in long-standing disease [1,2,6-9].

Prior studies have linked angiogenesis-related signaling to vulvar LS with neoplastic potential and have shown that long-standing untreated or undertreated disease carries a measurable risk of malignant transformation [8-10]. The present dissertation-based findings add a useful stage-oriented model: CD31 and VEGF characterize early endothelial reactivity, whereas CD95 marks late microvascular injury and apoptotic restructuring. For practice, this means that clinical, dermoscopic and immunohistochemical data should be interpreted together rather than in isolation.

The study is strengthened by its balanced sex distribution, consistent pathology review and stage-specific immunohistochemical design. Its main limitation is that the stage-focused IHC analysis was performed on representative subsets rather than all 60 biopsies, and external validation in multicenter cohorts is still required. Nevertheless, the internal coherence between morphology, dermoscopy and biomarker expression makes the proposed model clinically plausible.

Conclusion. Lichen sclerosus shows a reproducible shift from endothelial activation and neoangiogenesis in progressive disease to endothelial apoptosis and sclerosis in chronic disease. The combination of CD31, VEGF and CD95 provides a biologically meaningful framework for lesion staging. High CD95 expression together with epithelial atypia and pathological mitoses should prompt heightened suspicion for malignant progression.

Table 1.

Stage-specific expression of immunohistochemical markers in lichen sclerosus

Disease stage	Sample size	CD31 positive, n (%)	VEGF positive, n (%)	CD95 positive, n (%)
Progressive stage	15	5 (33)	12 (80)	3 (20)
Chronic stage	15	8 (53)	3 (20)	14 (95)

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