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Original Article

Lichen sclerosus has two different faces: Western versus eastern face

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Abstract

Background In Western countries, lichen sclerosus is a common disease that affects commonly middle-aged females that presents most commonly as a disease of genital and anal regions in both sexes while extra-genital involvement is less frequent.

Objective To record all cases of lichen sclerosus in Iraqi population as one of Middle East country and to do a full clinical evaluation and to be compared with published literature as seen in Western countries.

Methods This is a cross-sectional descriptive study where all patients with lichen sclerosus were recorded during the period from 2013-2022. Full history and examination were carried out. A histopathological assessment was performed as a confirmatory test.

Results All data related to 28 patients with lichen sclerosus was registered and evaluated. The age of patients has a bimodal peak in incidence from prepubertal to a postmenopausal age group and ranged from 8-63 years with a median of 40 years with 24 (85.7%) females and 4 (14.2%) males with a ratio of 6:1. The clinical features of the disease were found to be genital involvement in three (10.7%) patients, one male with follicular lesions of penis and two females with vulval involvement: one with extensive atrophy of vulva while the other with very early lesions). While 25 (89.2%) cases with extragenital sites where the trunk and limbs were the main locations but lips were affected in one female patient and in another, the ears were involved. The primary lesions in almost half of the cases were follicular whitish sclerosed macules, some with follicular plugs. These lesions over time coalesced together into larger whitish ivory leukoderma in the form of patches and plaques. The rash was localized in 22 (78.6%) cases while extensive in 5 (17.9%) patients. The lesion was asymptomatic apart from slight discomfort and itching but there was severe intractable itching in the female genitalia. The HE-stained sections showed complete atrophy of the epidermis with complete sclerosis of the dermis leaving sub-epidermal cleft.

Conclusion Lichen sclerosus is a disease prevalent in females that commonly presents with extragenital whitish sclerosed leukoderma in the form of follicular macules, patches and plaques while female genital involvement is a rare presentation. The likelihood of extragenital lichen sclerosus following the Blaschko lines was pronounced.

Key words
Lichen sclerosus; Genital disease; Iraqi population; Western countries; Middle East; Leukoderma.

Introduction

Lichen sclerosus (LS) is a rare chronic inflammatory mucocutaneous dermatosis of unknown etiology, it classically involves the genitals. The disease was first described in 1887 and it obtained numerous terms such as leukoplakia and lichen sclerosus et atrophicus, white spot disease, kraurosis vulvae, and balanitis xerotica obliterans. In 1975, the International Society for the study of vulvovaginal diseases gave the final name

"lichen sclerosus".[1,2]

Both genital and extragenital LS had not recognized ethnic predilection but the genetic tendency was detected. The disease arises at any age and affects both sexes however, it is predominant in women.[3,4]

Clinical characteristics of genital LS are pruritic opalescent white papules and plaque. It mainly seems as a figure-of-eight arrangement around the vulval, perianal and perineal skin and it occurs in 83% to 98% of patients.[5,6]

While the extragenital site of LS presents as asymptomatic interfollicular, shining, papules, which join together to form sclerotic plaques, uncommonly telangiectasias and follicular hyperkeratosis are seen.[6,7] It arises on the neck, shoulder and upper trunk following Blaschko lines, and is less commonly found on the palms, soles, scalp, face, and mouth. Extragenital LS takes place in 15% to 20% of cases.[5,8,9] This disease is commonly associated with plaque morphea and it is proposed to share the same pathogenesis.[8]

The immunological aspects of LS

The etiology of LS is unclear, there is increasing evidence suggesting the involvement of immune mechanisms in the pathogenesis of LS. The mechanisms proposed by available literature suggest the activation and maintenance of the T helper 1 (Th1) response and T-cell dermal infiltration, ECM1 dysfunction and aberrant miR155 activity.[2,10-12]

Micro RNA-155 (miR155) plays regulatory roles in cytokine, chemokine and transcription factor production and is expressed in activated immune cells which results in Th1 differentiation. Overexpression of miR155, which is thought to stimulate the Th1 response and dermal sclerosis, has been reported in LS patients. Overexpression of miR155 in CD4+ T cells is also thought to interfere with T regulatory (Treg) cell-mediated suppression and reduce the impact of Treg cells on CD4+ T cells. In addition, a reduction in the expression of Treg cell transcription factor FOXP3 has also been reported. Research suggests this contributes to impaired immune tolerance. Thus, collectively, this results in a loss of self-tolerance, in autoreactive CD4+ effector cells triggering autoimmune responses against self-antigens and the promotion of inflammation.[2,12]

According to research, the Th1 response is an important factor in the initiation, maintenance and exacerbation of chronic inflammation in LS. Studies have reported significant increases in CD8+ T cells and Treg cells in LS patients, as well as CD8+ T cell, Treg cell, and CD4+ T cell dermal infiltration. The chemokine receptors expressed by these cells are indicative of a Th1 profile, as an increase in CxCR3 and CCR5, and a reduction in CCR3 and CCR4 have been reported. Studies also describe the upregulation of proinflammatory cytokines IL-1α, IL-7, IL-15 and TNF-α, and the downregulation of anti-inflammatory cytokines IL-10 and TNF-β in the infiltrate of T-cells. In addition, they may also release cytokines IL-4, a typical marker of the Th2 profile, and TGB-β, which activate fibroblasts and produce altered collagen. This Th1 response is further intensified by the production of the interferon IFN-γ, the upregulation of IFN-γ mRNA and the attraction of more Th1 cells. This collectively provides a basis for Th1-mediated pathogenesis.[2,10,12]

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The extracellular matrix 1 (ECM1) protein is a glycoprotein that plays key roles in structural organization, keratinocyte differentiation and skin integrity. Autoantibodies against ECM1 have been reported in the sera of some LS patients. These autoantibodies are thought to activate MMP9, which subsequently activates TGF-β, resulting in the synthesis of collagen in fibroblasts. Whilst their significance remains unclear, their presence implicates the involvement of autoimmune mechanisms and suggests their importance in disease progression rather than induction.[2,12,13]

However, to the best of our knowledge, no previous study in Middle Eastern countries such as Iraq has ever been used to verify a full clinical evaluation of cases of LS and to be compared with published literature for LS as seen in Western countries.

Patients and methods

This is a cross-sectional descriptive study where all patients with LS were recorded during the period from 2013-2022. Full history and examination were carried out. The name, age, gender, family history, consanguinity of parents, duration and site of disease was recorded for all patients who met the clinical diagnostic criteria for LS. Additionally, searched for any associated autoimmune diseases depending on clinical findings and laboratory tests, which include autoimmune thyroiditis, alopecia areata, vitiligo, and pernicious anemia. Wood's lamp check and histopathological assessment were used as a confirmatory test. Written informed agreement regarding publication and pictures were taken from each individual before enrollment in the study.

Results

Over 9 years; all data related to 28 patients with LS was registered and evaluated. The age of patients ranged from 8-63 years with a median of 40 years and has a bimodal peak in incidence from prepubertal to a postmenopausal group in females. Out of 28 participants, 24 (85.7%) were women while 4 (14.2%) were men with females to male's ratio of 6:1. Consanguinity was positive in 9 (32.1%) of these, 4 (14.3%) had a family history of LS in first-degree relatives. The mean durations of complaints were 1 (0.5-4) years.

The clinical features of the disease were found to be genital involvement in three (10.7%) patients, one male with follicular lesions of the penis **(Figure 1)** and two females with vulval involvement, one with extensive atrophy of vulva (figure of eight shapes) while the other with very early lesions **(Figure 2)**. There were 25(89.2%) patients with extragenital disease of many sites, where the trunk and limbs were the main locations in 21 (75%), and 11 (39.2%) cases respectively. Other reported places **(Figure 3),** either the lips, ears, scalp, or neck, were each site only one case affected as more than one site was involved **(Table 1)**.

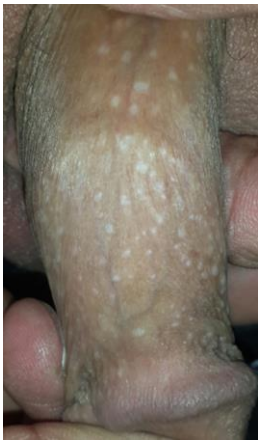

Figure 1 Twenty-five-year-old male with LS showing follicular lesions of penile shaft.

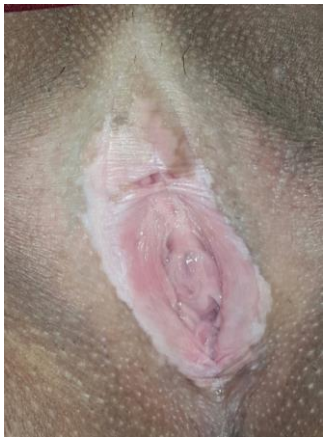

Figure 2 Twenty-three-year-old female with LS showing complete sclerosis and atrophy of vulva.

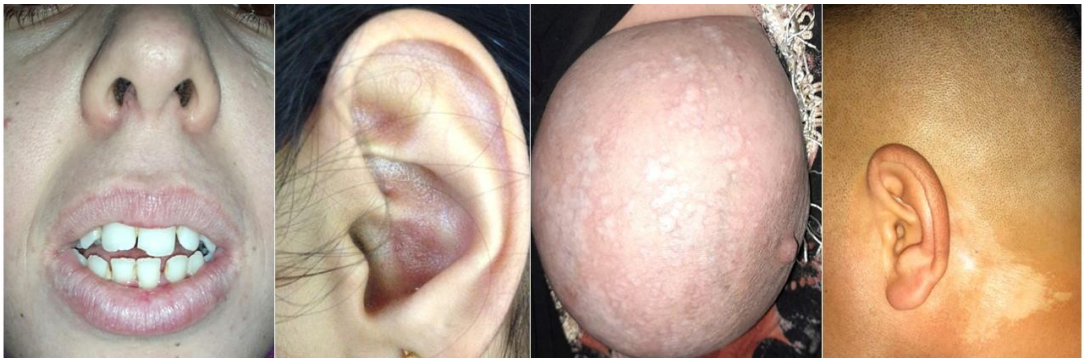

Figure 3 Showing four different patients complaining of extragenital LS of lips, ear, scalp, and neck.

Table 1 Frequency of the sites involved in 28 patients with LS (multiple sites were involved in each patient).

Sites of involvement	*n (%)*
Back	8(28.6%)
Abdomen	6(21.4%)
Chest	5(28.6%)
Arm	5(17.9%)
Forearm	3(10.7%)
axilla	2(7.1%)
Vulva	2(7.1%)
The shaft of the penis, lips, ears, neck, scalp, buttock, thigh, and foot (one patient involved at each site).	1(3.6%)

The primary lesions in nearly half of the patients were follicular, whitish, sclerosed macules affecting 10 (35.7%) cases **(Figure 4)**, and about 5 (17.9%) of them showed follicular plugs. Moreover, atrophic scaly white patches probably following the Blaschko lines were reported in 5 (17.9%) individuals **(Figure 5)**.

Another presentation was multiple papules that overtime coalesce together into larger whitish ivory leukoderma in the form of patches and plaques and with time established atrophy and a wrinkled surface appeared. Five (17.9%) cases **(Figure 6)** had fragility and flattened epidermal-dermal parts and were associated with subepidermal hemorrhage **(Table 2)**.

The rash was localized in 22 (78.6%) cases while extensive in 5 (17.9%) patients and the lesion was asymptomatic apart from slight discomfort and itching. However there was severe intractable itching in 2 (7.1%) female patients with genital involvement. Wood's lamp check showed no fluorescence or accentuation,

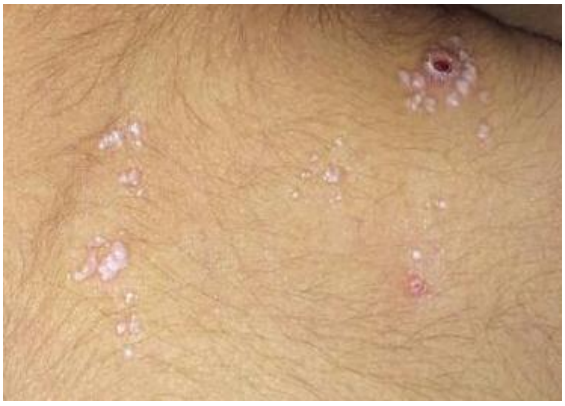

Figure 4 Twenty-nine years old female patient showing extragenital LS characterized by follicular whitish sclerosed macules with follicular plugs affecting the back.

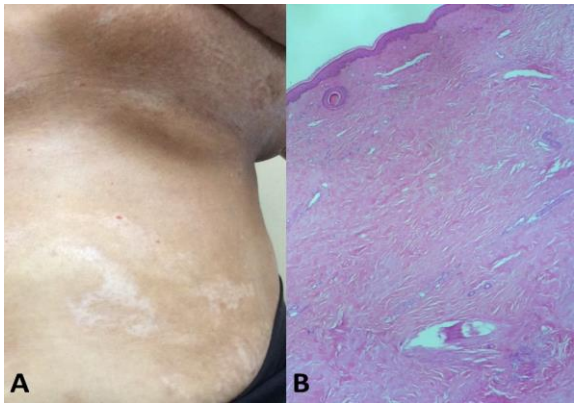

Figure 5 Forty-one-year-old female patient with extragenital LS, showing linear atrophic scaly white patches probably following the Blaschko lines affecting the abdomen (A), The HE-stained sections showing atrophy of the epidermis with complete sclerosis of the dermis leaving sub-epidermal cleft (B).

Table 2 Clinical presentations of LS and the sites of involvement (n=28).

Clinical features	*Sites of involvement (one patient for each site)*	*N (%)*
1- Multiple follicular whitish sclerosed macules	Back[*], arm (right), forearm (left), chest, buttock, scalp, vulva, the shaft of the penis, ears.	10(35.7%)
2- Leukoderma: ivory-white patches and plaques	(Back, abdomen &chest),[*] vulva (figure of 8), lips, abdomen (Single patch), thigh (right), forearm (Bilateral).	7(25%)
3- Atrophic, thin, glistening patches and plaques, sometimes with fine scales.	Back,[*] (back, abdomen &chest), abdomen (Single patch), arm (right), left foot.	6(21.4%)
4- Atrophic scaly white patches along the Blaschko lines	(Symmetrical, bilateral of arms, axilla, chest, abdomen and back), both arms, (right arm & forearm), (chest & left axilla), neck.	5(17.9%)
Accompanying follicular plugs	Back,[*] scalp, arm (right), forearm (left)	5(17.9%)
Associated subepidermal hemorrhage	Back,[*] both arms, forearm, buttock.	5(17.9%)

[*] *2 patients involved the same sites*

excluding the possibility of pre-vitiligo and pityriasis versicolor. Patients with LS did not report any autoimmune diseases at the time of examination.

In all patients, the HE-stained sections showed basket weave hyperkeratosis, complete atrophy of the epidermis with complete sclerosis of the superficial dermis leaving sub-epidermal cleft **(Figure 7)**.

Discussion

The etiology of LS is not well elucidated but there are increasing evidences supporting immune mechanisms in the pathogenesis of LS. The mechanisms suggested by available literature propose the activation and maintenance of the T helper 1 (Th1) response and T-cell dermal infiltration, ECM1 dysfunction and aberrant miR155 activity.[2,10,12]

Genital LS and extragenital LS are two variants that are characterized clinically by white shiny sclerotic patches and/ or plaques. Their cause is largely unknown and has no defined racial predilection, although there are genetic predispositions, based on detected family clusters.[3]

The age of participating individuals showed a bimodal peak of onset and the median age was at the fourth decade of life, with 85.7% women and 14.2% men, and females to male ratio of 6:1. Ongoing studies agreed with the present work and found that genital and extragenital LS was predominant in women with male-to-female ratio of 1:6, and could occur at any age, and they supported having two peaks of incidence but the maximum incidence occurred in women between 50- 60 years, and there was another peak in girls between 8 and 13 years.[4,14]

On the other hand, patients with untreated vulvar LS had significantly decreased serum levels of dihydrotestosterone, and this was suggested as an etiologic factor for LS.[15] Moreover, genital and extragenital LS provided evidence for the loss of androgen receptors during disease evolution in skin lesions.[16]

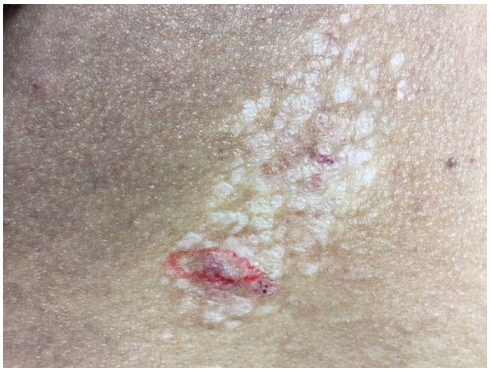

Figure 6 Thirty-two years old female patient with extragenital LS showing white papules and plaques of the back associated with subepidermal hemorrhage.

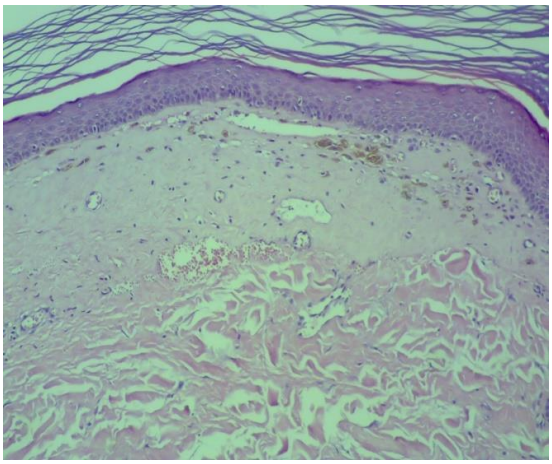

Figure 7 Showing typical histopathological features of LS including atrophy of epidermis, sub-epidermal cleft and sclerosis of superficial dermis. HE stains 10X.

The current research noticed consanguinity involvement, and positive family history of LS in 32.1%, and 14.3% of patients respectively, highlighting the idea of genetic predisposition. Many preceding studies found that both women and men with LS more frequently had human leukocyte antigen (HLA) DQ7, DQ8 and DQ9.[3,17-19] Also case studies pronounced vulvar LS in monozygotic twins.[20,21] A large, cohort study of a total of 1052 patients with vulval LS observed that 12% had a family history of LS. The first-degree relative involvement by LS had more often been associated with autoimmune disease.[3] Further study described a positive familial history with LS that reached up to 17% of cases.[22]

This present study took place in a Middle Eastern state and revealed that the disease involved the genital part in 10.7% of patients, which were characterized by follicular whitish sclerosed macules of the penis and vulva. This low frequency of genital LS could not be explained very well but we can speculate that cases of genital LS are seen by gynecologists and not referred to dermatologists. 89.2% of the cases presented with extragenital LS and this could be explained due to continuous pressure and trauma induced koebnerization. Other reported sites were either the lips, ears, scalp, or neck, one case for each were affected. The lesions were asymptomatic apart from slight discomfort and itching. Regarding western countries, LS comprised a very significant quantity of cases with a predilection for the anogenital area in 83–98% of women and were categorized in referral centers for vulvovaginal diseases. While accompanying extragenital LS was observed in 15-20% of cases. However, further report observed only 6% of the patients had the extragenital form and these were similarly detected on the trunk, arms, neck, and shoulders.[14,23-25]

The extragenital LS skin manifestations vary and triggering factors are not well defined but according to present work, the clinical presentations of extragenital LS included 4 types. Including multiple follicular whitish sclerosed macules in 35.7%, follicular plugs in 17.9%, leukoderma in 25%, while 17.9% of cases showed atrophic thin glistening scaly patches and plaques, and 17.9% of patients were associated with subepidermal hemorrhage probably due to atrophy and pruritus. While literature review concerning extragenital LS from Australia revealed that the skin lesion appeared as asymptomatic parchment-like paper, characterized by white shiny papules and plaques frequently accompanied by purpuric spots, generally involving the trunk, shoulders and neck.[26]

The current study revealed an original fourth dermatological appearance of extragenital LS that manifested by the streaky whitish linear atrophic scaly patches possibly following the Blaschko lines and pronounced in 17.9% of cases. These linear lesions are unusual in LS and very limited, such cases were recorded in Egypt, India, and Korea.[9,27-30] This could be because the skin disorders that affect cutaneous areas

matching the lines of Blaschko are often produced as an outcome of genetic mosaicism, and it is speculated that two different cell clones arise early in embryogenesis.[30]

Many previous studies have described a relationship between LS and morphea, either coexistent or evolution from LS to morphea or vice versa. We can suggest that early lesions of morphea could appear whitish mimicking LS and other features of morphea will appear later on. Other investigators believed that they are separate diseases and that those coexistent lesions are accidental.[31,32] But the histopathological features could easily differentiate the two conditions as the present study revealed typical histological features of LS, like complete atrophy of the epidermis with complete sclerosis of the dermis leaving a sub-epidermal cleft. This picture is completely different from morphea which has a characteristic picture, including acanthosis and pigmentation of the basal layer of epidermis, dermal thickening, dermal sclerosis and collagen homogenization reaching the panniculus together with superficial and deep infiltrate with abundant plasma cells.[33,34]

Conclusion

In the Middle East society, including Iraq, the extragenital involvement of LS is significantly more frequent than genital LS. It is a disease prevalent in females, that commonly presents with extragenital whitish sclerosed leukoderma in the form of follicular macules, patches and plaques while the female genital involvement is an unexpected, rare presentation. Diagnosis is mainly based on clinical manifestations of LS, and the histopathology has typical features of the disease. The possibility of extragenital LS following the Blaschko lines was pronounced in 17.9% of cases.

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