Brief Report

Clinical and histopathological spectrum of genital lichen sclerosus in 133 cases: Focus on the diagnosis of pre-sclerotic disease

Venkat Ratnam Attili, S. K. Attili

Visakha Institute of Skin and Allergy, Visakhapatnam, Andhra Pradesh, India.

Abstract

Background: Early inflammatory lesions of lichen sclerosus are histopathologically difficult to diagnose until the hallmark of the disease i.e., papillary sclerosis becomes visible in histological sections. Pre-sclerotic and late or resolved phases of the disease have not been extensively studied.

Methods: We retrospectively reviewed all cases diagnosed as genital lichen sclerosus over a ten-year period from 2006 to 2016, correlating the clinical findings with the histological features.

Results: A total of 133 cases of genital lichen sclerosus (90 males and 43 females) were identified. Both genders demonstrated a similar histological spectrum. Fifty eight (44%) cases were identified as having pre-sclerotic lichen sclerosus, 64 (48%) as having progressive disease and 11 (8%) cases were classified as fully resolved with atrophy. Asymptomatic vitiligoid lesions were identified in 19 (14%) cases of which 12 were male. Low-grade squamous cell carcinoma was seen within the areas affected by long-standing lichen sclerosus, in four patients (3%, 2 male).

Limitations: We studied only haematoxylin and eosin stained sections. The presence of basement membrane thickening could have been better illustrated with the periodic acid–Schiff stain.

Conclusion: The pathogenesis of lichen sclerosus probably involves an immune reaction to the basement membrane at the epidermal interface and around the adnexa. The initial band of inflammation shifts gradually downwards from the epidermal interface into the dermis destroying the vascular channels and appendages, resulting in excessive deposition of altered extracellular matrix. Basilar infiltration of lymphocytes along with a grossly vacuolated or thickened basement membrane is proposed as the characteristic diagnostic feature of the pre-sclerotic stage. Greater awareness of the clinicopathological spectrum of lichen sclerosus should enable early diagnosis and treatment, thereby preventing structural damage and possible malignant transformation in chronic cases.

Key words: Basement membrane, interface dermatitis, lichen sclerosus, pre-sclerotic, vitiligo

Plain Language Summary

The finding of papillary dermal sclerosis is essential for the diagnosis of established lesions of lichen sclerosus. However, early inflammatory lesions without such changes can be difficult to diagnose and have not been extensively studied. This is a retrospective review of all cases diagnosed as 'genital lichen sclerosus' over a ten-year period from 2006–2016, based upon clinical and histological correlation. A total 133 cases of genital lichen sclerosus were studied, of which, 58 (44%) cases were identified as having pre-sclerotic disease, and 19 (14%) cases were asymptomatic vitiligo-like lesions. Basilar infiltration of lymphocytes combined with grossly thickened basement membrane was identified as the characteristic diagnostic feature of pre-sclerotic stages. Greater awareness of the clinicopathological spectrum of lichen sclerosus should enable early diagnosis and treatment, thereby preventing structural damage and possible malignant transformation in chronic cases.

How to cite this article: Attili VR, Attili SK. Clinical and histopathological spectrum of genital lichen sclerosus in 133 cases: Focus on the diagnosis of pre-sclerotic disease. Indian J Dermatol Venereol Leprol 2022;88:774-80.

Corresponding author: Dr. Venkat Ratnam Attili, Visakha Institute of Skin and Allergy, Visakhapatnam, Andhra Pradesh, India. vrattili@gmail.com

Received: December, 2020 **Accepted:** October, 2021 **EPub Ahead of Print:** March, 2022 **Published:** November, 2022

DOI: 10.25259/IJDVL_640_20 **PMID:** 35389022

Introduction

Lichen sclerosus is a chronic inflammatory disease of unknown aetiology.[1-3] Early lesions are difficult to characterise until papillary dermal sclerosis [Figure 1], the hallmark of the disease, appears in histological sections.[4,5] The inflammatory cellular infiltrate which destroys the appendages and alters the skin architecture, abates after a variable period resulting in atrophy [Figure 2]. Although the exact pathogenesis is unknown, vacuolar interface dermatitis is usually seen in the early stages.[6,7] Autoimmune mechanisms are suspected[8-10] and association with known autoimmune diseases has been reported.[11-13]

Genital lichen sclerosus has been extensively studied for its destructive changes and predisposition to squamous cell carcinoma.[14-17] However, comprehensive reviews[18,19] have been scarce, with none from Asia. Borda *et al*. from Argentina[20,21] reported a superficial variant – 'vitiligoid lichen sclerosus' presenting with depigmentation alone without textural changes, indicating that the clinical spectrum of lichen sclerosus may be different in people with dark skin. We have also reported oral and genital vitiligoid lichen sclerosus as a frequent presentation among our patients.[22,23] The domain of genital lichen sclerosus is shared by gynaecologists, paediatricians, urologists, general surgeons and dermatologists; each propagating their own perspective and nomenclature as kraurosis vulvae, balanitis xerotica obliterans and lichen sclerosus et atrophicans. In children, often general surgeons simply label it as phimosis, without making a definitive diagnosis.[24-28]

This study reviews the clinical and histopathological spectrum of genital lichen sclerosus with a focus on the diagnosis of early pre-sclerotic disease.

Methods

A total number of 133 cases diagnosed as lichen sclerosus of the genital region, including 19 cases of vitiligoid lichen sclerosus, were included in this study (ten years; 2006 to 2016). Biopsies were taken from all genital lesions (genito-crural, perianal and pubic areas) including not only those clinically suspected to be lichen sclerosus, but also other lesions that were clinically difficult to diagnose as lichen planus, psoriasis, fungal diseases and eczemas. Thirty nine cases of phimosis that required circumcision were also included in the study and in such cases, multiple sections were examined from lesions on the outer as well as inner surfaces of the prepuce.

The diagnosis of lichen sclerosus was based on conventional histological features seen in haematoxylin and eosin stained sections.[6] Macular depigmented genital lesions which showed clear histological features of lichen sclerosus were categorised as vitiligoid lichen sclerosus while those with ambiguous histological features were excluded as vitiligo.

The diagnosis of pre-sclerotic disease is difficult, as the characteristic features of early lichen sclerosus[6,7] i.e., lichenoid and vacuolar interface dermatitis, may also occur in lichen planus or inflammatory vitiligo. Hence, we considered only basilar infiltration of lymphocytes along with basement membrane abnormalities (gross thickening or diffuse vacuolation) for the diagnosis of pre-sclerotic lichen sclerosus. Clinical features and histological patterns of inflammation, interface changes, vascular changes, dermal sclerosis and epidermal alterations in all 133 cases were analysed [Table 1].

Results

The male-to-female ratio was 2:1 (90 males, 43 females) and all age groups from early infancy to old age were represented, with preponderance in middle age. There were nine children under the age of 12 years, including three infants [Figures 3a-c]. There were 5 (2.2%) familial cases (two instances of a father and son, a single instance of a father and two affected sons and an instance each of two male and two female affected siblings).

Symptoms (burning or itching) were more severe in females. In males, phimosis, painful fissures, or depigmentation were the common complaints. Itching was rare in males but intense pruritus was often a prominent feature of scrotal lesions. Asymptomatic vitiligoid lesions were identified in 19 (14%) patients: 12 males and 7 females.

Clinical spectrum

Associated lip involvement was seen in 14 patients and extragenital lesions in ten patients. There was no association with morphea. Among males, exclusive scrotal skin lesions in 15 cases [Figures 4a-d], perianal areas in four and crural areas in five cases were seen. Among females, the introitus, clitoris and periurethral areas were primarily involved with atrophic depigmentation, sometimes accompanied by erythema. The lesions extended to the perianal, groin and pubic areas in three patients [Figure 3c].

There were four cases (two male, two female) presenting with early squamous cell carcinoma arising within the lesional skin in genital lichen sclerosus that had persisted for over three decades.

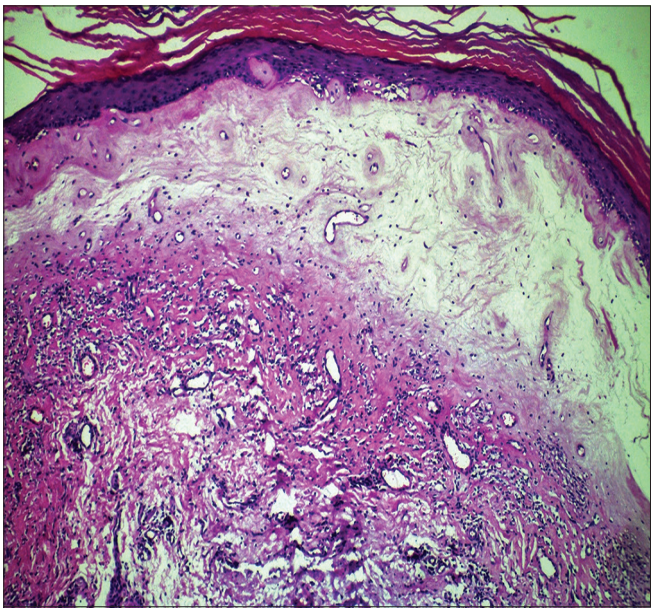

Figure 1: Conventional histological picture of lichen sclerosus with a flat epidermis, papillary oedema, sclerosis and a mid-dermal inflammatory band (haematoxylin and eosin ×100)

Histological spectrum

Lichen sclerosus is known to demonstrate three histological stages[6] as (1) early or pre-sclerotic stage with interface dermatitis, lichenoid or vacuolar type, (2) progressive upper dermal sclerosis underpinned by a band of inflammatory cellular infiltrate and (3) late resolved stage with scant cellular infiltrates with loss of adnexal, vascular structures and homogenisation of the dermis. Of these three, only the progressive stage is considered as the diagnostic stereotype and the other evolutionary stages have not been characterised. With the advantage of examining large number of cases in different clinical stages and histological sections of biopsies taken with multiple sections from the circumcised prepucial skin, we were able to identify sequential and transitional patterns of evolution and resolution [Table 1]. The most initial event appears to be lymphocytic infiltration at the papillary interface [Figure 5a] destroying the basement membrane and capillaries resulting in homogenised and widened papillae [Figure 5b]. Subsequently, the thickened basement membrane formed thick bands around the rete ridges [Figure 5c] and newly formed capillaries merged with the surrounding hyalinised dermal matrix. The inflammatory band appears to shift away from the flatter epidermis leaving an oedematous layer in its wake, with destruction of vascular and adnexal structures, which later gets replaced by homogeneous matrix substance. At the same time, abnormally dilated vessels with thick walls in horizontal orientation were prominently seen within and below the inflammatory band [Figure 6]. Resolved lesions had a consistent histological picture of atrophy with thin epidermal layer and a loose dermal matrix with striking absence of adnexal and vascular structures. [Figure 2], Biopsy from

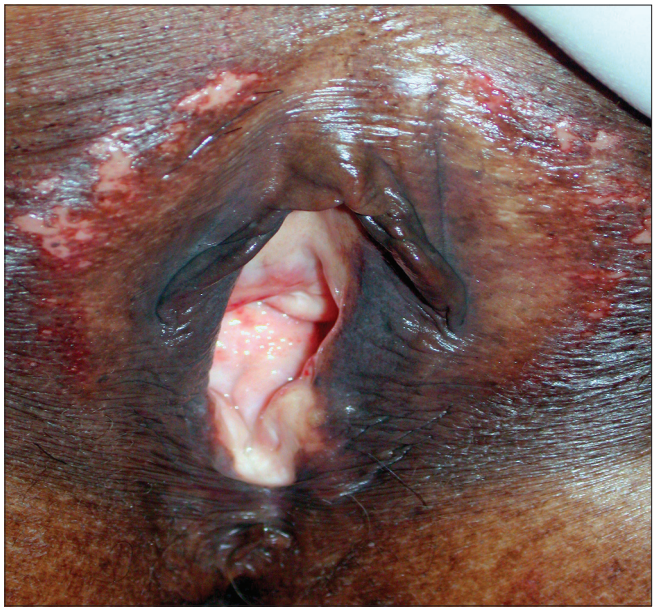

Figure 2a: Resolved lichen sclerosus with vulval atrophy

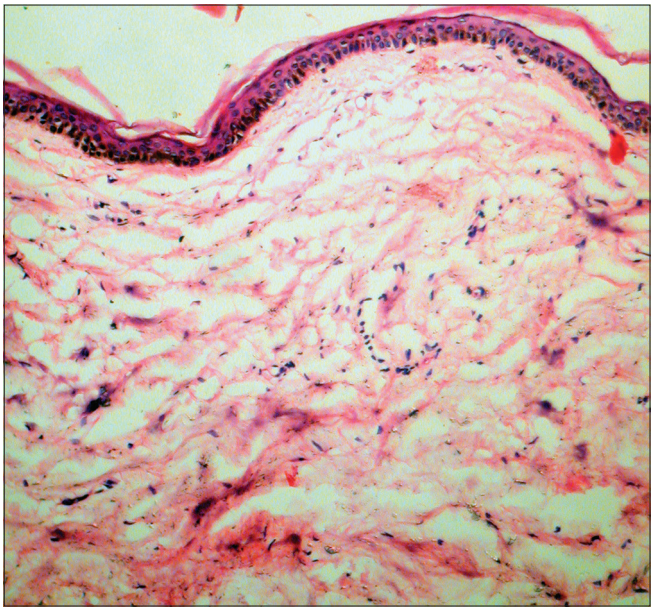

Figure 2b: Histology demonstrating atrophic epidermis and loss of adnexal structures which are replaced by a loose fibrous matrix in the dermis (haematoxylin and eosin ×100)

Table 1: Histological stages of genital lichen sclerosus (133 cases)

	Early pre-sclerotic phase [Figures 5a-c] (58 cases)		Sclerotic phase [Figure 6] Conventional lichen sclerosus (64 cases)		Atrophic phase [Figure 2b] (11 cases)
	Stage 1a(17%) 23 cases	*Stage 1b(27%)36 cases*	*Stage2a(44%) 59 cases*	*Stage 2b(4%) 5 cases*	*Stage 3(8%) 10 cases*
Epidermis	Psoriasiform	Widening of papillae and loss of rete ridge pattern	Thin and flat epidermis	Pseudo-epithelial hyperplasia	Thin and atrophic
Basement zone	Vacuolar/lichenoid interface dermatitis with an indistinct basement membrane	Diffuse dermal lymphocytic infiltrate with thickened or multi stranded basement membrane	Thickened basement membrane merging with hyalinised papillary dermis. Focal Basilar lymphocytic infiltration	Diffuse vacuolar change with basilar infiltration of lymphocytes	Thin basement membrane. No inflammatory cells
Papillary dermis	Normal	Patchy peri vascular lymphocytic infiltrates. New capillaries with thicker walls	Loss of normal structure with hyalinisation and sclerosis	Loss of normal structure with hyalinisation and sclerosis.	Normal structure replaced by loose matrix of fibrosis. Negligible inflammatory cells
Reticular dermis	Normal	Normal	Mid-dermal band of lymphocytic infiltrate along with thick walled and dilated blood vessels	Structural loss with hyalinisation and sclerosis.	Loose matrix of fibrosis. Negligible inflammatory cells

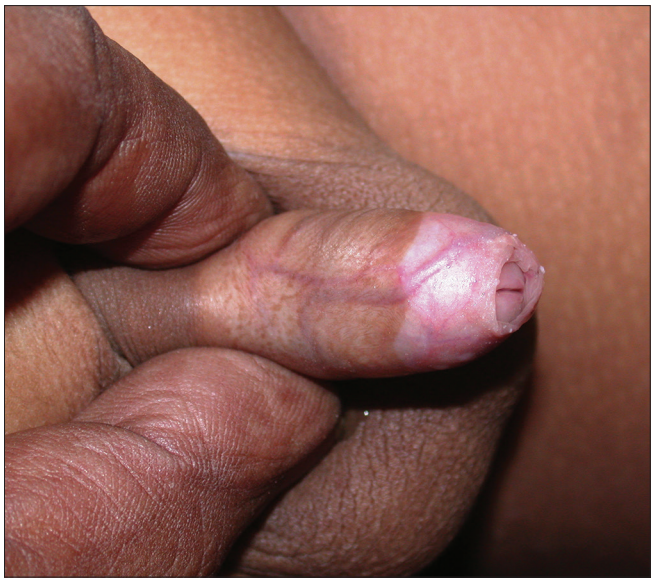

Figure 3a: Scaly erythema and depigmentation of preputial skin in a two-year-old child

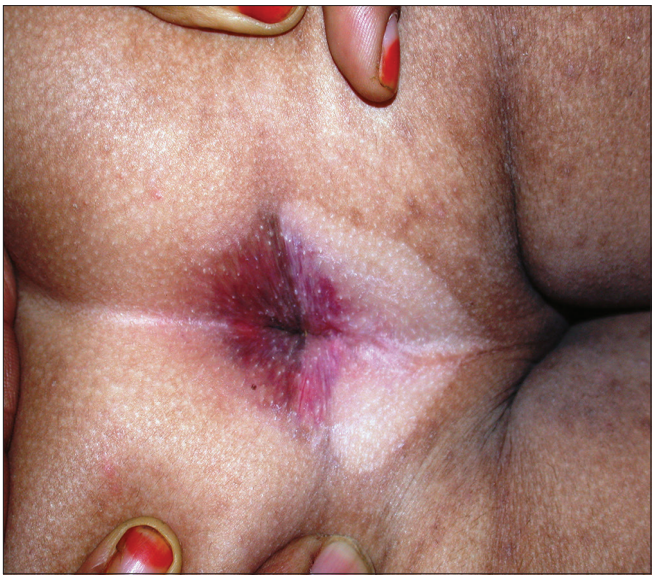

Figure 3b: Same patient as in Figure 3a, showing perianal involvement

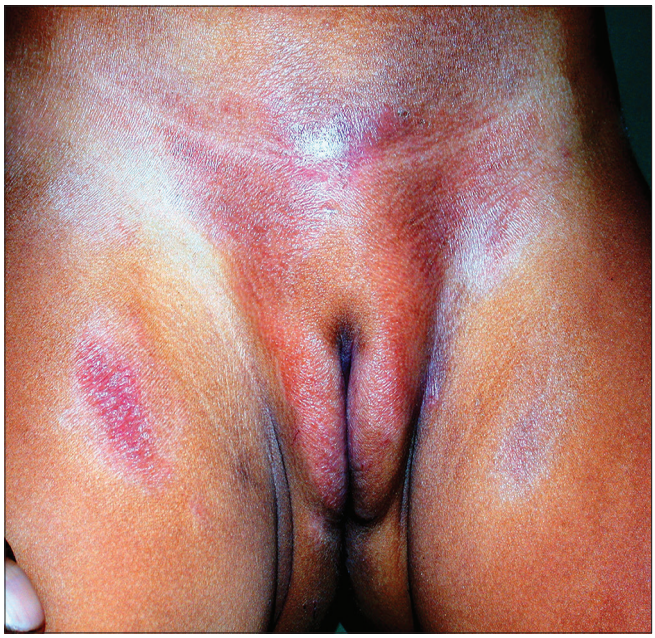

Figure 3c: Inflammatory genital lichen sclerosus extending on to groin and pubic area in an infant

different areas of the same lesion may show varying features, depending on the stage of evolution of the disease.[29] In a few cases, there was epidermal hyperplasia (instead of flattening) with basilar infiltration of lymphocytes accompanied by massive dermal sclerosis. However, a prognostic value cannot be inferred for such features as the numbers are small and as a cross sectional study, it was not possible to determine the time periods of each stage and assess the natural course of disease. The overall impression is that the disease resolves after an indefinite period spontaneously over years. Treatment definitely helps to hasten the resolution and alleviate the symptoms. Multiple sections from the circumcised prepuce consistently demonstrated more advanced stages on the mucosal side indicating that this was involved before the outer surface.

Discussion

Familial aggregation was an interesting observation but as the numbers were small in our study, no clear hereditary pattern was identified. Association of lichen sclerosus with systemic autoimmune diseases appears to be ambiguous.[11-13] We did not find any such association in this study.

The true incidence and prevalence of lichen sclerosus among genital lesions is probably understated as pre-sclerotic and vitiligoid lesions cannot be identified without a biopsy. Vitiligoid lichen sclerosus is a superficial subtype of lichen sclerosus. All the three histological staging patterns were seen on histological examination of these lesions. This subtype was seen in 14% of our patients. We observed vitiligoid depigmentation at the peripheral spreading margins of some typical lichen sclerosus lesions, indicating that vitiligoid changes occurred early in the development of lichen sclerosus. Vitiligo and lichen sclerosus are both interface dermatoses; the inflammation not progressing beyond destruction of melanocytes, in the former. In few instances, the inflammation in vitiligoid lichen sclerosus may also subside early before the emergence of dermal sclerosis, thereby resulting only in post-inflammatory depigmentation. In such cases, distinction from vitiligo becomes difficult both on clinical and histological grounds.

Diagnosis of early lichen sclerosus

Genital lesions associated with obvious clinical atrophy/thickening or erosions pose no clinical diagnostic problems and a biopsy in such cases invariably shows fairly advanced disease with progressive sclerosis and irreversible structural damage. In our series, the pathognomonic histological picture of lichen sclerosus [Figure 1] was seen in about 50% of cases [Table 1]. Thus, if strict criteria for the diagnosis of lichen sclerosus had been applied, approximately half the cases would have escaped early diagnosis.

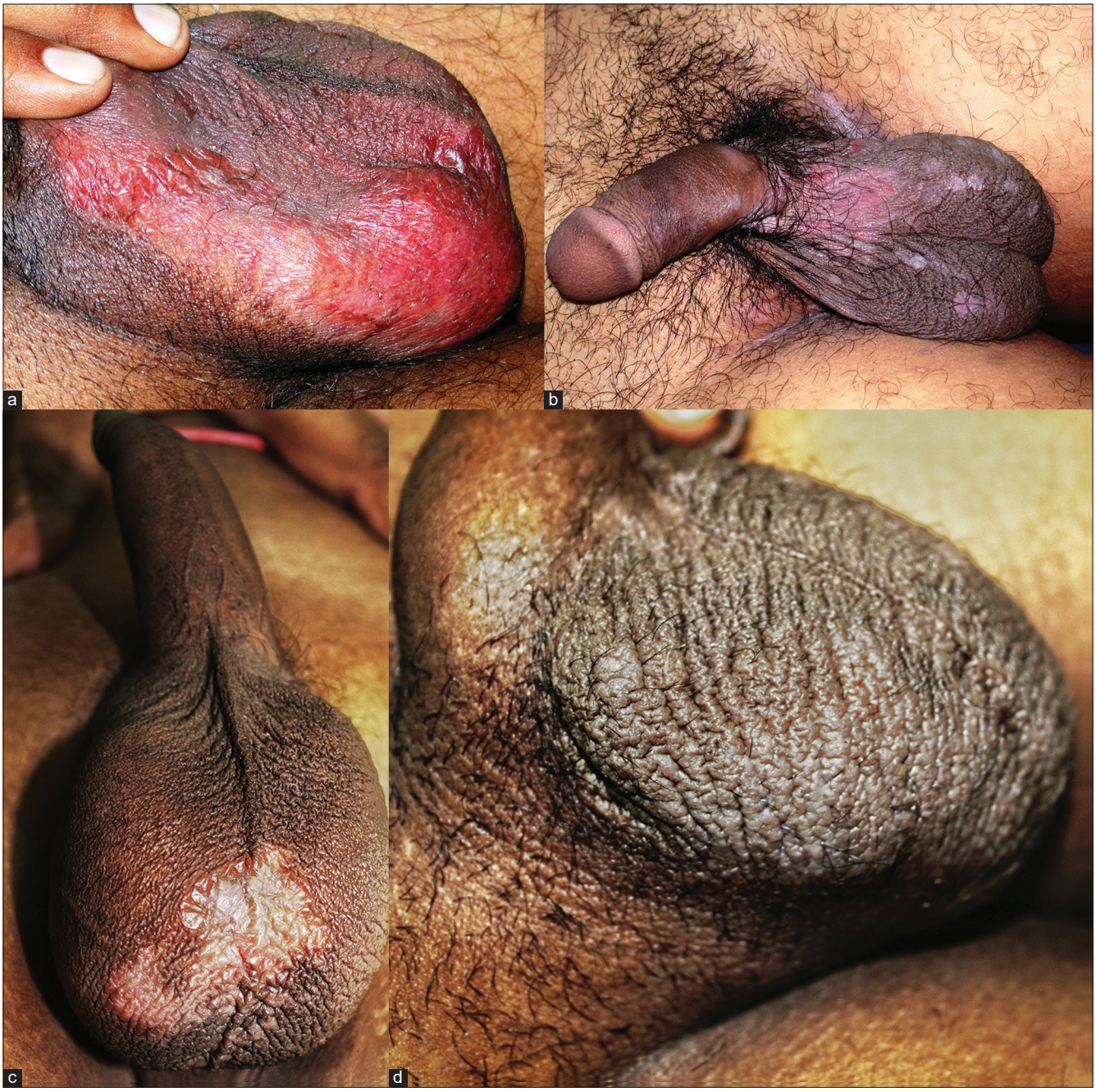

Figure 4(a-d): Different presentations of scrotal lesions

The clinical and histological diagnosis of the early disease is especially problematic when the genital, groin and perineal areas are exclusively affected as non-specific inflammatory lesions and clinically they can easily be confused with atypical psoriasis, seborrhoeic dermatitis, nutritional deficiency syndromes, non-specific intertrigo or scrotal dermatitis. However, histopathological differentiation between lichen planus with saw toothed rete pegs and an evenly elongated pattern in psoriasis is not difficult.

Occasionally, an overlap of lichen sclerosus and lichen planus has been considered[30-32] in cases of early lichen sclerosus where a dense lichenoid infiltrate and an invisible basement membrane makes it difficult to exclude genital lichen planus. At a later stage however, when the cellular infiltrate abates at the interface, the emergence of basement membrane thickening [Figure 5b] becomes a clue to the diagnosis of early lichen sclerosus.[33] We therefore suggest that the combination of basilar infiltration of lymphocytes along with vacuolated and/or thickened basement membrane should be considered diagnostic of pre-sclerotic lichen sclerosus [Figure 5c].

Pathogenesis

Unlike other interface dermatitides, the band of inflammation in lichen sclerosus slowly recedes from the epidermal interface along with the deposition of hyaluronic acid in the papillary dermis.[34,35] Altered distribution of tenascin, fibrinogen and fibronectin has been reported indicating a significant disorganisation of the extracellular matrix.[36]

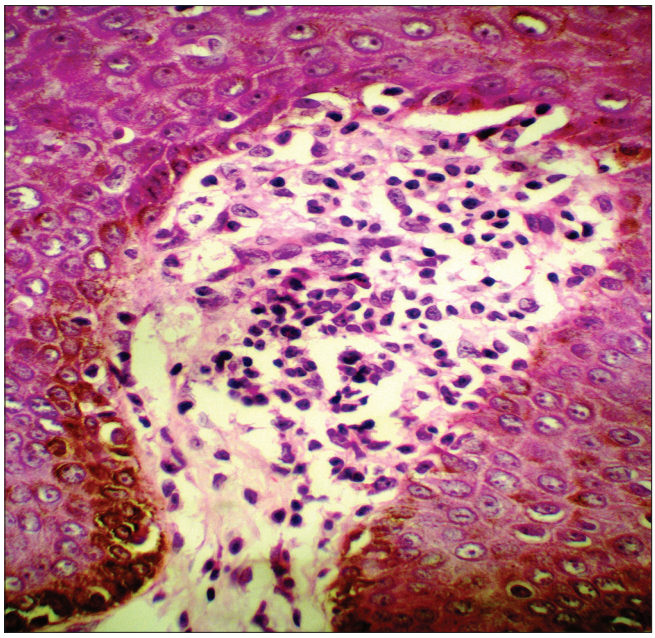

Figure 5a: Papillary lymphocytic infiltrate destroying the basement membrane (haematoxylin and eosin ×400)

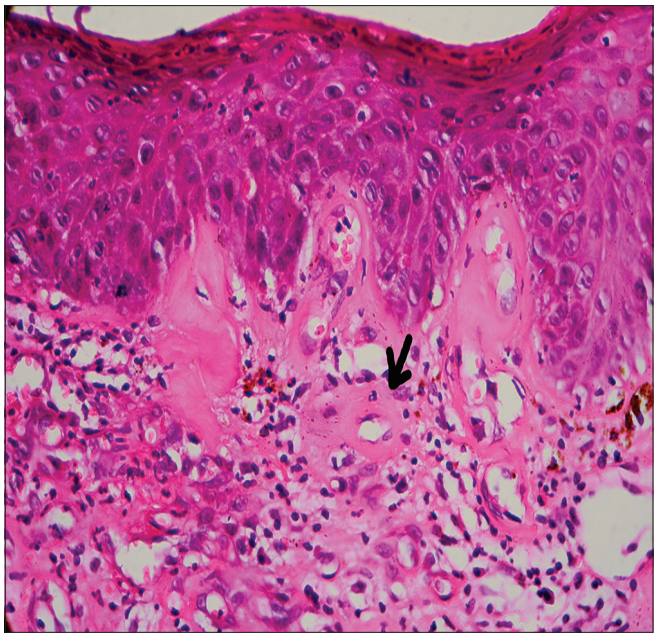

Figure 5b: Widening of papillae, thickened epidermal and capillary basement membrane merging with papillary sclerosis. New capillary formation is also appreciated. Black arrow shows basement membrane thickening is even evident around the capillaries (haematoxylin and eosin ×200)

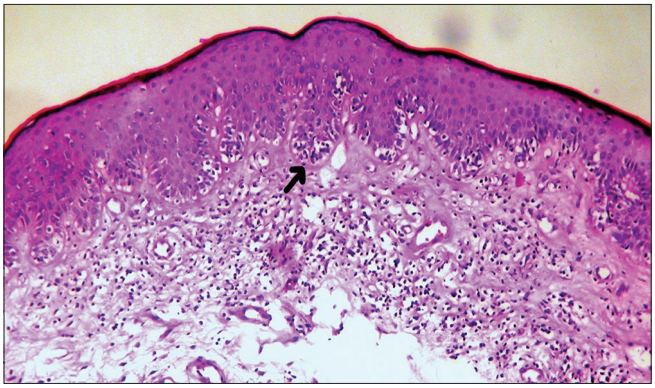

Figure 5c: Thickened basement membrane forming thick bands around the rete ridges (haematoxylin and eosin ×200)

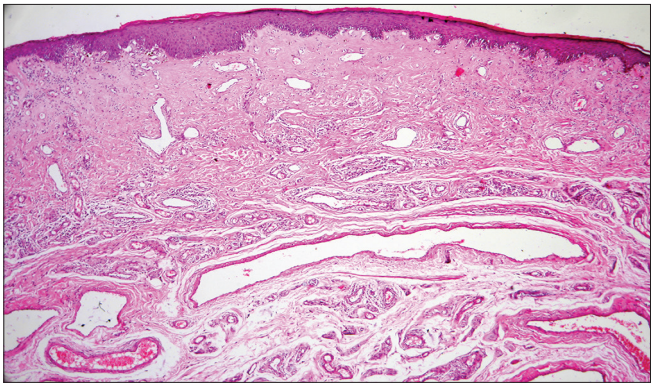

Figure 6: Abnormally large blood vessels with thick walls within the dermal inflammatory band (haematoxylin and eosin ×100)

Vascular changes in lichen sclerosus are an under-recognised feature.[37-39] The presence of a band-like inflammation, despite the hyaline band of sclerosis separating the inflammatory cells from the epidermal basement membrane, suggests that inflammation possibly follows the capillary basement membranes (angiogenesis) in the dermis. We noted destruction of papillary capillaries in early lesions [Figure 5a-c], gross thickening of basement membrane around capillaries with enormously dilated dermal vessels in the progressive stages [Figure 6] and complete absence of normal vascular channels in resolved lesions [Figure 2]. This indicates that inflammation with destruction of papillary capillaries involves the dermal vasculature progressing downward along the vertical channels to the superficial horizontal plexus. The thin basement membrane of capillaries is usually not visible in histopathological sections but becomes visibly thickened when it becomes the specific target of inflammation.

The presence of CD4 and CD8 lymphocytes in the inflammatory infiltrate and increased expression of HLA DR suggests a T cell-mediated reaction.[10,40] Humoral mechanisms may also be involved and autoantibodies against extracellular matrix protein have been observed in 75% of patients with lichen sclerosus.[8,9,41] While the significance of humoral[8,9] and cellular immune mechanisms in the actual pathogenesis is not clear, the involvement of the basement membrane as the likely target is evident from the histopathological spectrum. The specific antigen targeted among the components of basement membrane remains elusive,[10] but ultra-structural studies have reported several small holes in the basement membrane as well as its complete absence in some places.[39]

The specific role of ECM 1 protein in the reconstruction of basement membrane is unclear. A parallel has been drawn with lipoid proteinosis, a hereditary disease in which pathogenic mutations in ECM 1 gene generate similar abnormalities in dermal blood vessels and a hyaline appearance of dermis as seen in established

lesions of lichen sclerosus.[37] It is, however, considered angiogenic[41] and may indirectly contribute to the pathogenesis by enhancing the target, i.e., the basement membrane around new blood vessels. Thickening of basement membrane appears to be a natural response of the homeostatic repair mechanisms at the interface. A sequence of events causing destruction and regeneration can explain the enormously thickened basement membrane seen in some cases. Enormously large and dilated vessels with thick walls within the inflammatory layer may be a compensating phenomenon for the loss of vascular network in upper layers.

Limitation

We studied only haematoxylin and eosin stained sections. The presence of basement membrane thickening could have been better illustrated with periodic acid–Schiff staining.

Conclusion

Lichen sclerosus may be a more common disease than currently believed as many pre-sclerotic lesions and vitiligoid lichen sclerosus are likely to be misdiagnosed. Diagnostic hallmarks of pre-sclerotic lichen sclerosus are widened papillae, thickened or distorted basement membrane and basilar infiltration of lymphocytes. The histological spectrum presented in this study endorses the hypothesis that lichen sclerosus may be due to an immune reaction targeting basement membrane components.

Declaration of patient consent

Patient consent was not required as the identity of patients was not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tasker GL, Wojnarowska F. Lichen sclerosus. Clin Exp Dermatol. 2003;28:128-33.
2. Yesudian PD, Sugunendran H, Bates CM, O'Mahony C. Lichen sclerosus. Int J STD AIDS. 2005;16:465-73.
3. Powell JJ, Wojnarowska F. Lichen sclerosus. Lancet 1999;353:1777-83.
4. Regauer S, Liegl B, Reich O. Early vulvar lichen sclerosus: A histopathological challenge. Histopathology 2005;47:340-7.
5. Fung MA, LeBoit P. Light microscopic criteria for the diagnosis of/ early vulvar lichen sclerosus: A comparison with lichen planus. Am J Surg Pathol 1998;22:473-8.
6. Ackermann AB, Boer A, Bennin B, Gottlieb GJ. Histologic Diagnosis of Inflammatory Skin Diseases. 3rd ed. New York: Ardor Scribendi Ltd.; 2005. p. 134.
7. Carlson JA, Lamb P, Malfetano J, Ambros RA, Mihm MC Jr. Clinicopathologic comparison of vulvar and extragenital lichen sclerosus: Histologic variants, evolving lesions, and etiology of 141 cases. Mod Pathol. 1998;11:844-54.
8. Howard A, Dean D, Cooper S, Kirtshig G, Wojnarowska F. Circulating basement membrane zone antibodies are found in lichen sclerosus of the vulva. Australas J Dermatol 2004;45:12-5.
9. Oyama N, Chan I, Neill SM, Hamada T, South AP, Wessagowit V, *et al*. Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. Lancet 2003;362:118-23.
10. Farrel AM, Marren P, Dean D, Wojnarowska F. Lichen sclerosus: Evidence that immunological changes occur at all levels of the skin. Br J Dermatol 1999;140:1087-92.
11. Meyrick Thomas RH, Ridley CM, Black MM. The association of lichen sclerosus et atrophicus and autoimmune-related disease in males. Br J Dermatol 1983;109:661-5.
12. Meyrick Thomas RH, Ridley CM, McGibbon DH, Black MM. Lichen sclerosus et atrophicus and autoimmunity—a study of 350 women. Br J Dermatol 1988;118:41-6.
13. Harrington CI, Dunsmore IR. An investigation in to the incidence of autoimmune disorders in patients with lichen sclerosus et atrophicus. Br J Dermatol 1981;104;563-6.
14. Carlson JA, Ambros R, Malfetano J, Ross J, Grabowski R, Lamb P, *et al*. Vulvar lichen sclerosus and squamous cell carcinoma: A cohort, case control, and investigational study with historical perspective; implications for chronic inflammation and sclerosis in the development of neoplasia. Human Pathol 1998;29:932-48.
15. Carli P, Cattaneo A, de Magnis A, Biggeri A, Taddei G, Giannotti B, *et al*. Squamous cell carcinoma arising in vulval lichen sclerosus: A longitudinal cohort study. Eur J Cancer Prev1995;4:491-5.
16. Barbagli G, Palmineteri E, Mirri F, Guazzoni G, Turini D, Lazzeri M. Penile carcinoma in patients with genital lichen sclerosus: A multicenter survey. Australas J Dermatol 1997;38 Suppl1:S20-5.
17. Scurry JP, Vanin K. Vulval squamous cell carcinoma and lichen sclerosus. Australas J Dermatol 1997;38:S20-5.
18. Wallace HJ. Lichen sclerosus et atrophicus. Trans St Johns Hosp Dermatol Soc 1971;57:9-30.
19. Meffert JJ, Davis B, Grimwood RE. Continuing medical education: Lichen sclerosus. J Am Acad Dermatol 1995;32:393-416.
20. Borda JM, Abulafia J, Jaimovich L. Syndrome of circumscribed scleroatrophies. Dermatol Iber Lat Am1968;3:179-202.
21. Borda JM, Balas RE. Lichen sclerosus et atrophicus of a vitiligoid type. Arch Argent Dermatol 1961;11:419-24.
22. Attili VR, Attili SK. Vitiligoid lichen sclerosus: A reappraisal. Indian J Dermatol Venereol Leprol 2008;74:118-22.
23. Attili VR, Attili SK. Lichen sclerosus of lips—a clinico-pathologic study of 27 cases. Int J Dermatol 2010;49:520-5.
24. Gairdner D. The fate of the foreskin, a study of circumcision. Br Med J 1949;2:1433-7.
25. Kayaba H, Tamura H, Kitajima S, Fujiwara Y, Kato T, Kato T. Analysis of shape and retractability of the prepuce in 603 Japanese boys. J Urol1996;156:1813-5.
26. Yang C, Liu X, Wei GH. Foreskin development in 10 421 Chinese boys aged 0-18 years. World J Pediatr2009;5:312-5.
27. McGregor TB, Pike JG, Leonard MP. Pathologic and physiologic phimosis: Approach to the phimotic foreskin. Can Fam Physician 2007;53:445-8.
28. Kiss A, Kiraly L, Kutasy B, Merksz M. High incidence of balanitis xerotica obliterans in boys with phimosis: Prospective 10-year study. Pediatr Dermatol 2005;22:305-8.
29. Attili SK. "Interface" Dermatoses: Revisited. Indian J Dermatopathol Diagn Dermatol 2019;6:14-24.
30. Fung MA, LeBoit PE. Light microscopic criteria for the diagnosis of early vulvar lichen sclerosus: A comparison with lichen planus. Am J Surg Pathol 1998;22:473-8.
31. Yashar S, Han KF, Haley JC. Lichen sclerosus-lichen planus overlap in a patient with hepatitis C virus infection. Correspondence. Br J Dermatol 2004;150:155-77.
32. Marren P, Millard P, Chia Y, Wojnarowska F. Mucosal lichen sclerosus/ lichen planus overlap syndromes. Br J Dermatol 1994;131:118-23.
33. LeBoit PE. A thickened basement membrane is a clue to lichen sclerosus! Am J Dermatopathol 2000;22:457-8.
34. Kaya G, Augsburger E, Stamenkovic I, Saurat JH. Decrease in epidermal CD_{44} expression as a potential mechanism for abnormal hyaluronate accumulation in superficial dermis in lichen sclerosus et atrophicus. J Invest Dermatol 2000;115:1054-8.
35. Kuroda K, Fujimoto N, Tajima S. Abnormal accumulation of inter-a-trypsin inhibitor and hyaluronic acid in lichen sclerosus. J Cutan Pathol 2005;32:137-40.
36. Farrella AM, Deana D, Charnockb FM, Wojnarowska F. Alterations in distribution of tenascin, fibronectin and fibrinogen in vulval lichen sclerosus. Dermatology 2000;201:223-9.
37. Kowalewskia C, Kozłowskaa A, Chan I, Górska M, Woźniak K, Jabłońska S, *et al*. Three-dimensional imaging reveals major changes in skin microvasculature in lipoid proteinosis and lichen sclerosus. J Dermatol Sci 2005;38:215-24.
38. Kowalewski C, Kozłowska A, Gorska M, Woźniak K, Krajewski M, Błaszczyk M, *et al*. Alterations of basement membrane zone and cutaneous microvasculature in morphea and extragenital lichen sclerosus. Am J Dermatopathol 2005;27:489-96.
39. Regauer S, Liegel B, Reich O, Beham-Shmid C. Vasculitis in lichen sclerosus: An under recognized feature? Histopathology 2004;45:237-44.
40. Marren P, Dean D, Wofnarowska F. The basement membrane zone in lichen sclerosus: An immunohistochemical study. Br J Dermatol 1997;136:508-14.
41. Han Z, Ni J, Smits P, Underhill CB, Xie B, Chen Y, *et al*. Extracellular matrix protein 1 (ECM1) has angiogenic properties and is expressed by breast tumour cells. FASEB J 2001;15:988-94.