Review Article

Genital lichen planus: An underrecognized entity

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Abstract

Genital lichen planus (LP) is an underrecogonized dermatosis. The appearance is often unlike classical LP elsewhere, and hence, the condition goes undiagnosed in many. Vulvo-vaginal LP in particular, can be a distressing condition often leading to scarring and a poor quality of life. Treatment for most of the genital LP variants is similar to managing LP elsewhere; however, the erosive variant requires special attention as treatment outcomes are often disappointing and the disease runs a protracted course. Potential for development of malignancy also exists, as in oral LP, and hence close follow up is essential.

Key words: Complications, erosive, genital, hepatitis C virus, lichen planus, methotrexate, treatment, mucosal, oral

INTRODUCTION

Disorders of the genital tract are not always sexually transmitted. Such nonvenereal genital dermatoses may be confined to the genitalia only or may also involve other body parts.[1] One such often missed dermatosis of the genitalia is lichen planus (LP).

LP affects 0.5%–1% of the general population with adults in the third–sixth decade of life forming the most commonly affected age group.[2] Mucosal LP, in general, runs a much more chronic course than cutaneous LP, does not respond as well to treatment, and carries a possible risk of malignant transformation.

EPIDEMIOLOGY

Genital LP (GLP) forms a small but significant proportion of nonvenereal genital dermatoses. The exact incidence of GLP is not known. The lesions may especially be overlooked by women as self-examination of the vulvo-vaginal area is difficult and occasionally the lesions may be asymptomatic. GLP constituted 7.3% of cases of nonvenereal genital dermatoses, from among 600 male patients, in the series by Shah[3] and 4.6% of 108 patients in the series by Marcos-Pinto *et al*.[4] A similar series from India (on male genital dermatoses) reported the figure at 2%-9%.[1,5] There are unfortunately not many similar estimates available for female GLP. A multidisciplinary vulval clinic study reported a prevalence of 3.7% for biopsy-proven vulval LP. In the same series, the prevalence of invasive squamous cell carcinoma (SCC), vulvar intraepithelial neoplasia Grade 2–3, and lichen sclerosus et atrophicus (LSeA) were 4.1%, 2.0%, and 13.9%, respectively.[6] An audit of 114 vulvar biopsies from another specialist clinic dealing with nonneoplastic diseases of the vagina and vulva, however, reported GLP as a diagnosis in 9% of the biopsies received.[7]

Access this article online

Quick Response Code:

Website: www.ijstd.org

DOI: 10.4103/ijstd.IJSTD_45_19

How to cite this article: Khurana A, Tandon S, Marfatia YS, Madnani N. Genital lichen planus: An underrecognized entity. Indian J Sex Transm Dis 2019;40:105-12.

ASSOCIATION WITH ORAL AND CUTANEOUS LICHEN PLANUS

Oral and genital mucosae form the most commonly involved mucosal sites for LP, and further, there is a strong association between genital and oral LP. Ocular and esophageal mucosae may also be rarely involved. Kirtschig *et al*. hypothesized that LP comprises a clinical spectrum with mucosal predominant and cutaneous predominant disease at opposite ends.[8] The term "plurimucosal LP" has been used and may be appropriate to describe the simultaneous involvement.[8] There are variable estimates of the prevalence of oral LP in vulvovaginal LP -and vice versa. The largest reported series involved 723 patients (75% women and 25% men) with oral LP, of which genital involvement was seen in 25%.[9] Another paper by the same group found GLP in 19% of 399 female patients with OLP and 4.6% of 174 male oral LP patients.[10] A more recent publication, however, found histologically confirmed vulval LP in 57% of 42 female patients with OLP.[11] About 62% of those found to have lesions of vulval LP were symptomatic, while in 38%, the disease was asymptomatic.[11] On the same lines, oral involvement has been reported in up to 47% patients with vulval LP.[12]

Thus, GLP should be actively looked for in patients with oral LP, especially in females where the lesions may go unnoticed by the patient.

Cutaneous LP is less commonly associated with GLP. Skin lesions have been reported to be present in around 20% patients with vulval LP in the series by Kirtschig *et al*. and Fahy *et al*.[8,12]

PATHOGENESIS

Although the exact etiology of LP has not been ascertained, it is hypothesized that LP is a complex immunologic disease mediated by cytotoxic T-cells directed against basilar keratinocytes. This reaction is triggered by a yet unidentified antigen in a genetically predisposed individual. Gene polymorphisms involving HLA-A3, HLA-DR1, HLA-DRB1*0101, HLA-DQ1, and HLA-DQB1*0201 have been found to be associated with LP.[13]

T-helper and T-cytotoxic lymphocytes, natural killer cells, and dendritic cells are the main inflammatory cells involved. Activated cytotoxic T-cell infiltrate into the epithelium, leading to the apoptosis of basal keratinocytes.[14]

Antibasement membrane zone antibodies chiefly targeting BP180 have been reported to be present in sera of about 61% of patients with erosive vulval LP, suggesting that autoimmune mechanisms may be important in its pathogenesis.[15] It is, however, hypothesized though that these antibodies may have a transient or amplifying role in the pathogenesis but are unlikely to be primarily pathogenic.[16] Similar findings have been reported in LSeA as well.[17] Cooper *et al*. demonstrated circulating autoantibodies in 40% women with erosive vulval LP compared with 20% of controls ($P < 0.001$). Antinuclear (25%) and antithyroid (19%) antibodies were the most frequent antibodies detected.[16] Further, about 31% patients reported a first-degree relatives with one or more autoimmune disorders.

An association of OLP with hepatitis C virus (HCV) infection has been reported from some geographical locations. The reported prevalence of HCV antibodies in various studies varies from 0% to 62% with a high prevalence in Italian (29%) and Japanese (62%) patients and a very low prevalence reported from the USA and Northern European nations.[9,18-20] However, the two studies done so far to explore the association of vulval LP with HCV (both from the UK) have been negative.[21,22] More data from other regions may present a different picture though.

A whole-genome expression study performed on microdissected epithelium from oral LP and GLP and corresponding healthy controls showed many differentially expressed genes in both OLP and GLP epithelium.[23] Several of these are part of the so-called epidermal differentiation complex. In addition, several keratins are differentially expressed as well indicating disturbed epithelial differentiation in mucosal LP.[23] The similar pattern of expression in OLP and GLP indicates that these are both a result of a common disease process affecting different sites, providing further strength to the observed clinical association of the two sites.

CLINICAL FEATURES

Vulval/vulvovaginal lichen planus

Vulval/vulvovaginal LP most commonly affects women in their late 50s or early 60s.[24] The affected group is mostly postmenopausal, and the disease has not been reported before puberty.[25]

The disease produces symptoms of soreness, burning, pain, pruritus, contact/post-coital bleeding, dyspareunia, discharge, or maybe asymptomatic in milder forms.

The clinical forms of LP on the female genitalia are mainly erosive, papulosquamous, and rarely hypertrophic.[26] The presentation varies from subtle

fine white interlacing linear papules/plaque in its mildest form to severe erosive disease leading to scarring. The classical cutaneous LP lesions are uncommon in the genital region. The hair-bearing areas (mons pubis and inner thighs) are uncommon sites for LP. On the labia majora, lesions may appear dusky red or reddish-brown instead of the typical violaceous colour of cutaneous LP. Occasionally, the hyperkeratotic variant exists as firm white papules/plaques with irregular borders and thickened irregular surface [Figure 1].

Erosive disease is the most significant and distressing form of Vulval LP. This most commonly involves the posterior vestibule and often extends anteriorly to the labia minora [Figure 2].[25] Dusky erythema or erosions, surrounded by a typical white lacy border, are visualized in some cases interspersed with whitish areas. Severe long-standing erosive disease can cause loss of normal architecture with fusion of the labia minora, loss of interlabial sulcii, and burying of the clitoris. The erosive form is often associated with inflammatory vaginitis[25] which produces symptoms of vaginal discharge, pain, and burning during micturition. A per-vaginal examination may be extremely painful, and bleeding on manipulation/instrumentation can occur. Vaginal lesions have been variably reported to be present in 20%–58% cases of Vulval LP.[27,28] Adhesions often develop in long-standing disease andnarrowing/shortening or even total obliteration of the vagina is often the final outcome [Figure 3].

The term "vulvovaginal gingival syndrome" has been used to describe a distinctive pattern of erosive plurimucosal LP presenting with a clinical triad of vulval, vaginal, and gingival involvement [Figure 2].[29] This is in contrast to most reported series on erosive vulval LP wherein buccal mucosal involvement has been shown to predominate.[12,22,29,30,31] The erosive form poses many diagnostic difficulties with closest differentials being LSeA, autoimmune blistering disorders, and vulvar intraepithelial neoplasias. LSeA may show histopathological overlap with vulval LP in addition to similarities in clinical presentation. However, LSeA typically involves the outer aspects of labia minora and may extend posteriorly in a figure-of-eight pattern. It occurs in a younger population than vulval LP and may also affect prepubertal girls. The "crinkled" appearance is characteristic and vagina and oral mucosae are not affected unlike vulval LP.[25] Autoimmune blistering disorders can be differentiated on the basis of lesions at other sites and by direct immunofluorescence (DIF) patterns.

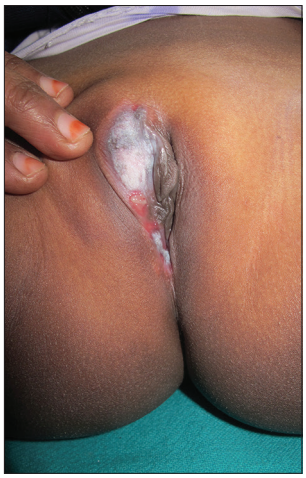

Figure 1: Violaceous-whitish plaque with interspersed erosions

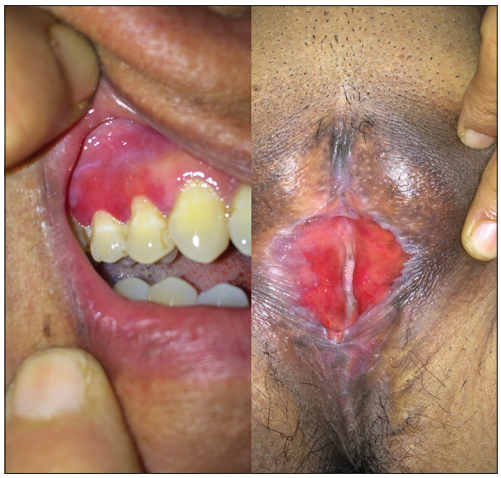

Figure 2: Coexisting erosive gingival and vulvovaginal lichen planus

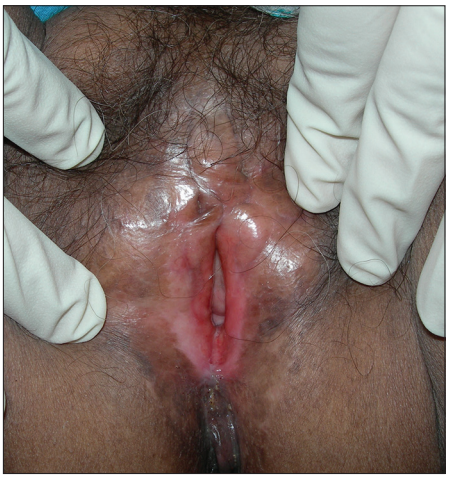

Figure 3: Genital lichen planus with prominent scarring sequelae. Note the burying of the clitoral hood and resorption of labia minora

A diagnostic criteria has been proposed to overcome the difficulties of diagnosis of erosive Vulval LP [Table 1],[32] although it awaits validation in clinical settings. The histopathological changes

in the epidermis (wedge-shaped hypergranulosis and saw-toothed acanthosis), lack of hyalinization, and Direct Immunofluorescence (DIF) findings were excluded from the final criteria.

GENITAL LICHEN PLANUS IN THE MALES

The morphological presentation of LP on the male genitalia varies widely.

The disease may present as dusky reddish-brown papules and plaques without scaling [Figures 4-6] or as an atrophic – erosive variant involving the glans penis.[25] The latter may often present with pruritus and burning and can cause impaired sexual function. The typical flat-topped, polygonal, violaceous, pruritic, and shiny papules are seldom seen over the genitalia.[25] Male GLP may also present as annular lesions which are most frequently seen over the penile shaft and the scrotum. The edges are violaceus to white in color, whereas the center appears hyperpigmented. Arciform and streak-like patterns can also be seen [Figure 6]. Annular lesions may develop as a result of the convergence of multiple papules in a ring configuration or because of the central involution of a papule or a plaque with peripheral expansion. The former mechanism is known as "papule-formed rings", and the latter as "ring-formed papules."[2,33,34] Penogingival syndrome has also been described where lesions of LP involve both the penile and gingival mucosae.[35] Long-standing erosions have been implicated in the development of phimosis and SCC.[35,36]

Table 1: Diagnostic criteria of erosive vulvar lichen planus[32]

1. Presence of well-demarcated erosions or glazed erythema at the vaginal introitus
2. Presence of a hyperkeratotic white border to erythematous areas/erosions - Wickham striae in surrounding skin
3. Symptoms of pain/burning
4. Scarring/loss of normal architecture
5. Presence of vaginal inflammation
6. Involvement of other mucosal sites
7. Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermoepidermal junction
8. Presence of an inflammatory band that consists predominantly of lymphocytes
9. Signs of basal cell layer degeneration, e.g., civatte bodies, abnormal keratinocytes, or basal apoptosis

*Atleast 3 out of 9 are required to make the diagnosis

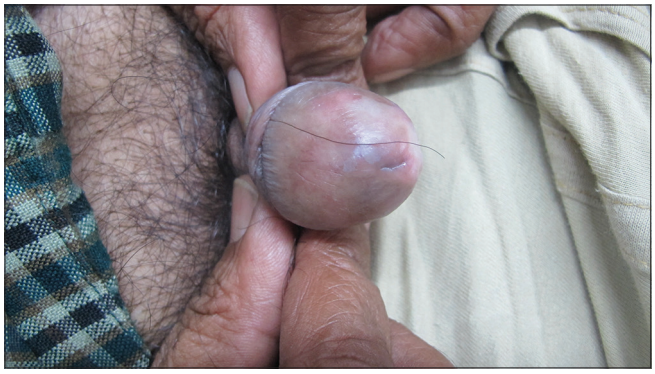

Figure 4: Annular violaceous plaque presents over the glans just proximal to the external urinary meatus

Differential diagnosis of genital lichen planus in males[25]

Genital warts can sometimes be confused with the papules of LP, but a typical genital wart appears pink to brown, can be sessile, or pedunculated and is generally asymptomatic. Penile psoriasis, which is another close differential, presents as erythematous scaly plaques in circumcised males, whereas it looks moist and lacks scaling in the uncircumcised. Extragenital site involvement is often seen. Candidal balanoposthitis when located over the glans in an uncircumscribed male can resemble LP. Bowenoid papulosis presents as pigmented warty lesions in sexually active males. SCC *in situ* may also mimic LP and can also be a long-standing complication of it.

LSeA closely resembles the whitish lesions of LP and presents as atrophic white patches or plaques with telangiectasias and purpura.

Cicatricial pemphigoid and pemphigus vulgaris can resemble the erosive variant of LP, but they are usually associated with blisters and erosions at other sites. Histopathology and immunofluorescence are diagnostic. Fixed drug eruption can be differentiated

Figure 5: (a) Multiple violaceous papules present on the ventral surface of the penile shaft and an ill-defined erythematous plaque with lacy margins present at 6 "o" clock position of the coronal sulcus extending onto the glans penis. (b) The same patient showing an ill-defined violaceous plaque at 12 "o" clock position over the glans penis

Figure 6: Lacy, white, reticular pattern involving the shaft of the penis

by the history of recurrences as opposed to the chronic course of GLP. Zoon's balanitis presents as moist well-defined glistening patches with cayenne pepper spots. Early lesions of erythema multiforme can also be difficult to differentiate, but a preceding history of drug intake/infection and an acute onset provide the clues for differentiating it from LP.

DIAGNOSTIC EVALUATION

A diagnostic biopsy may not be required in all cases but is worthwhile for erosive GLP. The edge of an erosion should be biopsied (and not the erosion itself wherein the epidermal changes would be missed) and if present the white lacy striae provide the best yield.[24,25] In addition, any atypical/hyperkeratotic lesion/nonhealing ulcer must be biopsied to rule out malignancy.

The classical epidermal findings of GLP include saw-toothed acanthosis, hyperkeratosis, and wedge-shaped hypergranulosis with a band-like lymphohistiocytic infiltrate obscuring the dermoepidermal junction. The basal layer shows hydropic degeneration with the presence of apoptotic bodies.[2] Plasma cells are often present.[31]

Direct immunofluorescence demonstrates globular deposits of immunoglobulin M (IgM) around necrotic keratinocytes with the occasional presence of IgG and thus helps to differentiate it from other autoimmune blistering disorders.[37,38]

Microscopic examination of the vaginal discharge from patients with erosive vulval LP demonstrates a picture similar to atrophic vaginitis, with high pH and reduced lactobacilli. In addition, there may be immature epithelial cells.

TREATMENT

The success rate of the treatment for GLP varies with the morphological presentation of the disease. The treatment of GLP is similar to treatment of LP on other cutaneous surfaces, but it is the erosive form which requires aggressive management, right at the outset, to improve the patient's quality of life and prevent disabling sequelae. We would mostly be discussing treatment with respect to the erosive vulval LP as that is the most distressing and recalcitrant manifestation of GLP.

Patients with erosive LP should be counseled that the goal is control rather than complete cure.[25] Erosive LP also hinders sexual activity of the patient and hence psychosexual counseling also plays an important part in the management.[25]

There are no randomized controlled trials (RCTs) pertaining to treatment of erosive LP, except one on the use of photodynamic therapy.[39] Thus, treatment is largely empirical and based on documented results in the reported case series. The results of treatment are often poor, but treatment is mandatory to avoid permanent scarring sequelae.

Nonspecific measures[25]

- Saline compresses can provide symptomatic relief. This can be followed by covering the erosions with petrolatum
- Application of lidocaine jelly over the erosion can soothe the burning associated with micturition. Alternatively, the patient may be asked to urinate in a tub of water to lessen the burning
- Regular retraction of foreskin to avoid the development of phimosis in uncircumscribed males
- In erosive vulval LP, once the activity is controlled, gentle insertion of vaginal dilators covered with hydrocortisone cream routinely can prevent synechiae formation[31] and forms an essential part of therapy
- Since immunosuppressives form the mainstay of therapy, patient should be regularly screened for superadded bacterial, viral, and fungal infections, as these can lead to worsening of symptoms and resistance to regular treatment. In recalcitrant cases, a course of broad-spectrum antibiotic covering *Staphylococcus* and *Streptococcus* or antifungals can be given.[40]

Topical therapy

Topical steroids form the mainstay of treatment of GLP. For nonerosive disease, a mid-potency steroid given once a day is effective. For erosive disease, potent topical steroids are needed.[39] Clobetasol propionate (preferably ointment preparation for its lower irritancy over eroded mucosa) is the most

commonly prescribed preparation. A reducing regimen, as suggested for LSeA, is apt for erosive GLP as well.[40] This involves using 0.05% clobetasol propionate nightly for 1 month, then alternate nights for 1 month, followed by twice-weekly use for 1 month at which point a review is done. Although the atrophogenic adverse effects of topical steroids are uncommon on modified mucosae, spread to surroundings can produce these effects on the groins and thighs with striae formation. Patient should be explained on the judicious use of appropriate amounts (about one fingertip unit for vulva and one for vagina) at the appropriate sites. Vaginal application carries a risk of iatrogenic Cushing's over long term due to increased absorption owing to thin epithelium and the effect of occlusion. This must be kept in mind and testing done in suggestive clinical settings. Furthermore, vaginal pessaries containing 1% hydrocortisone are recommended for vaginal insertion.

Topical tacrolimus and cyclosporine can later replace potent topical steroids, but experience is limited with these (especially cyclosporine) and cost and irritant potential (mostly initially) are added disadvantages.[41-44] Pimecrolimus 1% cream has demonstrated efficacy in erosive and hypertrophic LP in a case series and a report respectively.[45,46] Topical azoles are useful in secondary yeast infections but may irritate the eroded surfaces.

Systemic therapy

Systemic therapy should be initiated if topical treatment has been a failure. This can be ascertained by the following guidelines:[25]

- Treatment has been adhered to
- There is no superadded yeast/herpetic infection
- Vulvodynia has been ruled out.

Systemic steroids are possibly the most effective agents and have shown consistent efficacy. Long-term use should, however, be avoided owing to the potential adverse effects. A dose of 40–60 mg may be used for short term to promote healing and prevent adhesions.[11] Methotrexate can be used following discontinuation of steroids or primarily and has reports of efficacy to its credit. A dose of 7.5 mg or higher per week has been used, although there may be benefit with lower doses as well.[47,48] Methotrexate has a good safety record and is commonly used for this indication. Regular monitoring, as indicated for use in other inflammatory dermatoses, should be adhered to.

Cyclosporine at 3 mg/kg/day shows rapid results in erosive GLP.[49,50] Oral retinoids have been reported to be beneficial in erosive oral LP, but as yet there is only a single report of benefit of acitretin 25 mg daily in erosive genital (penile) LP.[51] The dose in the reported case was reduced to 25 mg thrice a week after substantial improvement was achieved in 6 weeks. Thalidomide is effective for erosive cutaneous and oral LP and may be efficacious in erosive GLP as well.[52,53,54]

Hydroxychloroquine has been used in GLP extrapolating its reported efficacy in oral LP, although the results are not consistent.

Azathioprine, cyclophosphamide, and mycophenolate mofetil have limited literature to their credit.[11] Mycophenolate mofetil 500 mg twice daily BD was beneficial in a patient unresponsive to methotrexate and acitretin.[55] Dapsone and colchicine are other possible treatment options.[11]

A study by Simpson *et al*. is the first RCT to assess the second-line treatment options for erosive VLP. Adjunctive systemic therapies being assessed under this trial are hydroxychloroquine, methotrexate, and mycophenolate mofetil. The trial is a four-armed, open-label, pragmatic RCT which uses a blinded independent clinical assessor. The results of this trial are awaited.[56]

Surgery is required for patients who have scarring with narrowing of the introitus, or for patients who develop urinary complaints as a result of their urethra being obliterated with scarring. This is a complex procedure, and postprocedure topicals and systemic treatment must be maintained, as well as regular dilatation to prevent relapse.

PROGNOSIS

Mucosal LP involving the genitalia follows a chronic course and can be recalcitrant. Complete remission unfortunately occurs in only a small percentage of erosive vulval LP. In a series of 100 patients with vulval/vulvo-vaginal LP, only 11 achieved remission over 24 months follow-up.[12] Progressive disease can lead to scarring of vulva, resorption of labia minora, and even shortening of the vagina which, in turn, hinders the sexual activity of the patient. In males, scarring can result in phimosis. Adhesiolysis may be needed for severe cases. Long-standing cases of erosive LP may develop a SCC, although the exact incidence is not known. In the above-mentioned series, three patients developed vulvar dysplasia on follow-up.[12] Out of these, one had carcinoma *in situ* and two had invasive vulvar SCC. In another series, two of the 95 patients female patients with

GLP developed SCC over follow up.[24] Thus, regular follow-up with prompt biopsy of any atypical lesion such as a persistent nonhealing erosion/ulcer or whitish thickened areas should be carried out.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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