Lichen planus pigmentosus inversus: case report and systematic review

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Abstract

Lichen planus pigmentosus inversus (LPPI) is a rare variant of lichen planus characterized by well-demarcated, often slight pruritic, dark-gray plaques in intertriginous zones, hence the attribute of "inversus". It was originally described by Pock *et al*. in 2001, and less than 100 cases have been reported to date. Here, we present a case of a 52-year-old male with a two-month duration of gray-brownish plaques in bilateral axillary, submammary,

antecubital, and inguinal folds. No triggering agent was present, and the biopsy showed an interface/lichenoid dermatitis with plenty of pigment incontinence. Topical tacrolimus 0.1% ointment was administered with moderate improvement at five weeks. A review of the literature showed no significant differences in involved sites and age distribution among genders, with a slightly longer duration of manifestations in females. The most administered therapeutic agents were topical corticosteroids, alone or in combination with other agents, and tacrolimus.

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Introduction

Lichen planus pigmentosus inversus (LPPI) is a rare variant of lichen planus characterized by well-demarcated, often slight pruritic, dark-gray plaques in intertriginous zones such as the axilla and inguinal areas, hence the attribute of "inversus". Initially described by Pock *et al*. in 2001,[1] fewer than 100 cases have been reported to date. Etiology is not yet elucidated, with some reporting association with hepatitis C[2] and triggering by chemicals, metals, or friction by tight-fitting clothes.[3-5] Standard therapy is not established, with reported variable clinical improvement with steroids and tacrolimus, but with a general impression of a more resistant disease than common lichen planus. Here, we present a case of LPPI in a light-skinned Caucasian male with no other dermatologic conditions or comorbidities, together with a systematic review of the reported cases with a focus on gender differences and response to therapy.

Case Report

A 52-year-old fair-skinned Caucasian man presented with well-demarcated, oval, gray-brownish, slightly pruritic plaques in the axillary, submammary, antecubital, and inguinal folds bilaterally of two months duration (Figure 1). The patient had no significant comorbidities and denied a recent history of trauma, infection, drug use intake, or use of new oils, perfumes, or antiperspirants. Previous treatment with topical corticosteroids and antifungal agents was ineffective. Microbiological testing for fungi and skin bacteria was negative. A punch biopsy was performed, and histological examination showed a superficial, band-like inflammatory infiltrate composed of small lymphocytes with exocytosis in the epidermis, together with features of lichenoid inflammation and interface damage such as hypergranulosis, mild hyperkeratosis, sparse individual necrotic basal keratinocytes, and diffuse evident deposition of pigment with numerous melanophages (Figure 2). A melanocytic component was excluded with a MelanA immunohistochemical stain and fungal infection with periodic acid-Schiff staining. Taking together the histological features and the clinical appearance, a diagnosis of LPPI was established. The patient was treated with tacrolimus ointment 0.1% twice a day for 5 weeks with moderate improvement of the lesions. Subsequently, therapy was switched to isotretinoin to improve renewal of skin layers and has been ongoing for two months at the time of publication with moderate improvement. We inspected published liter-

ature in PubMed and gray literature to gather evidence on potential peculiar epidemiological and clinical features and experience on the effectiveness of therapy. Articles reporting on single cases or case series were reviewed, and information on demographics, sites of involvement, symptoms and their duration, comorbidities, therapy, and follow-up was extracted and tabulated in an Excel spreadsheet. When available, differences in distribution among males and females were tested with a parametric test for continuous variables and a chi-squared test for categorical variables, with significance at p=0.05, with the use of free online calculators.

Results

We inspected published literature in PubMed and gray literature to gather evidence on potential peculiar epidemiological and clinical features and experience on the effectiveness of therapy. By searching PubMed for "lichen planus pigmentosus inversus", a total of 41 records were retrieved, ranging from the first description in 2001 to very recent cases in 2023 (*Supplementary Table 1*). With additional reference searching, a total of 49 publications of single cases or case series were retrieved, with a total of 98 patients with an age range of 5-84 years (mean 54.8±18.3, median 58, interquartile range [IQR] 45-68), and 62 (63.3%) females and 36 (36.7%) males. Age distribution did not differ between males and females (male mean age 56.4±17.5, median 58.5 *vs*. female mean age 53.9±18.7, median 54.5, p=0.52). Slight pruritus was present in 44 (44.9%) patients, 43 (43.9%) were asymptomatic, and in 11 (11.2%) instances, this was not reported, with no significant difference between males and females (56.7% *vs*. 47.4%, p=0.50). In the study, 29 patients (29.6%) were identified as Caucasian, followed by 25 (25.5%) Asian or Middle Eastern patients, 13 patients (13.3%) of African descent, and 5 patients (5.1%) categorized as Hispanic. However, the ethnic background was not clearly stated for 26 cases (26.5%). Axillar involvement was present in 70 (71.4%) of cases, alone or with other sites involvement, followed by groins/inguinal folds in 55 (56.1%) cases, submammary folds with 29 (29.6%) cases, neck folds in 13 (13.3%) cases, and popliteal folds with 11 (11.2%) cases; in 7 (7.1%) instances the site was not reported. As reported in a recent case, unilateral involvement is uncommon.[6] Regarding the duration of lesions, the median duration of symptoms was 6 months (IQR 9.75-12) in a range of 0.3-180 months, with a longer median duration in females than in males (median 6 *vs*. 3 months, p=0.03).

Indeed, in the published cases, follow-up after the start of therapy ranged from 0.75-12 months with a median of 3 months (IQR

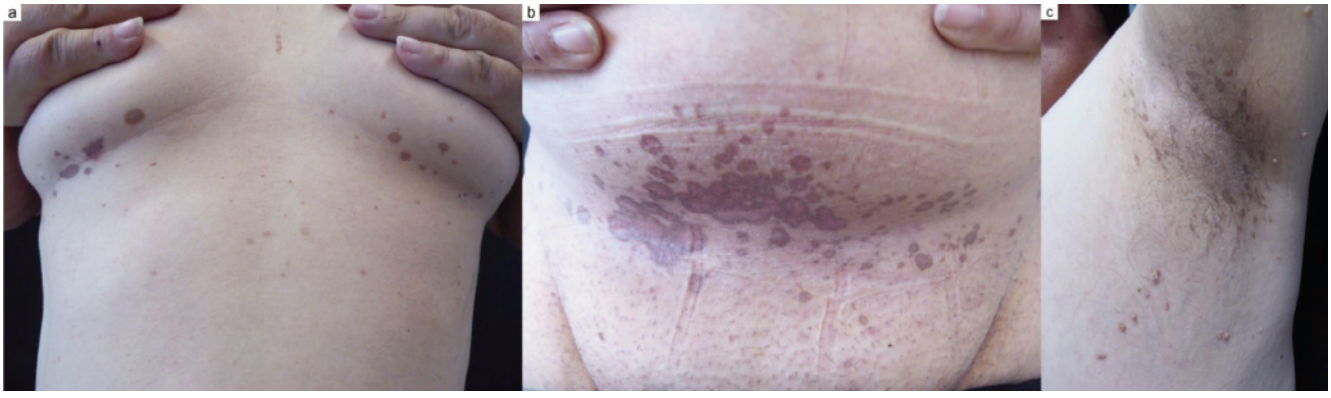

Figure 1. Distribution of lesions on submammary folds (**a**), abdomen (**b**), and axilla (**c**).

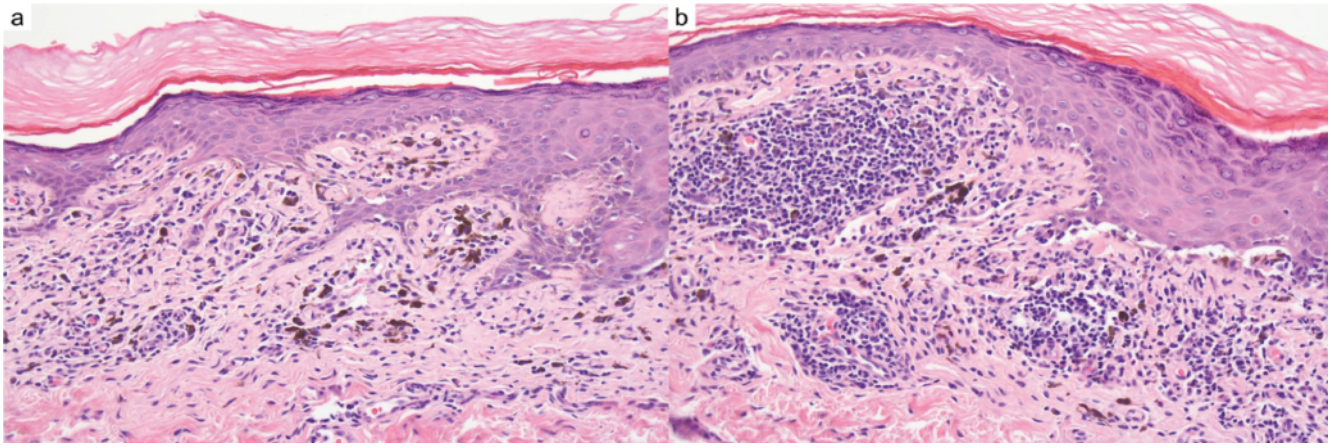

Figure 2. Biopsy showing lichenoid dermatitis with band-like chronic infiltrate, interface changes such as vacuolization and cytoid bodies, and diffuse deposition of brown pigment in the superficial dermis. Hematoxylin and eosin, 20x magnification (**a, b**).

2-6), with no differences among males and females (median 4 *vs*. 3 months, p=0.20). The most used therapeutic agents were topical corticosteroids alone in 35 cases (35.7%) or in combination with other agents in 9 cases (9.2%), followed by topical tacrolimus alone or with other agents in 15 cases (15.3%). Other agents used were oral corticosteroids (3, 3.1%), Chinese herbs (3, 3.1%), narrow-band UVB (2, 2%), and propolis creme (1, 1%). In 21 (21.4%) cases, however, information regarding therapy was not reported, while in 4 (4.1%) cases no therapy was administered, and no information on follow-up was present. In 12 of 44 cases with the use of corticosteroids alone or in combination with other agents, there was a relevant response with corticosteroids, while in 32 of 44, there was little or no response; therapy based on tacrolimus alone or in combination resulted in an improvement of lesions in 6 of 15 cases. However, therapeutic regimens were too different in terms of specific agent, dose, and length of administration to allow a conclusion on the comparison of effectiveness.

Discussion

LPPI is a rare variant of lichen planus pigmentosus (LPP), with less than 100 cases reported to date. Differently from LPP, which is more frequently reported in dark-skinned patients with phototype III-VI coming from India, Asia, and Latin America, LPPI was first described in Europe, and it is diffused worldwide.[5] Etiology is not yet elucidated, with some association reported with hepatitis C[2] and triggering by chemicals, metals, or friction by tight-fitting clothes.[3-5] Our patient had no remarkable medical history nor suspected risk factors. Moreover, no special triggers were found, particularly infectious conditions or the recently described association with COVID-19 vaccination.[7-9] Diagnosis is usually suspected clinically, but there are reports of the utility of dermatoscopy and line-field confocal optical coherence tomography.[6,10] Our patient exhibited characteristics similar to those found in the literature, and the therapy administered was consistent with those findings, as tacrolimus was the second most commonly administered agent, and the disease showed a slight improvement, which was also consistent with the literature.

In conclusion, LPPI is an uncommon disease with yet unelucidated etiology, with literature suggesting a broad spectrum of presentation in terms of age and ethnicity, a longer duration of disease in females, and variable response to common therapies such as corticosteroids and tacrolimus. Given the rarity of the disease, a high level of suspicion is necessary, and only histological examination can lead to confirmation of the diagnosis after clinic-pathological correlation.

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Online Supplementary Material:
Supplementary Table 1. By searching PubMed for "lichen planus pigmentosus inversus" a total of 41 records were retrieved, ranging from the first description in 2001 to very recent cases in 2023.