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Research Article

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Retinoids in Lichen Planus Pigmentogenes

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1. Introduction

Lichen planus pigmentosum (LPP) is an uncommon variant of Lichen plan clinically characterized by lichenoid lesions of photoexposed. Pruritus may be present in the early active phase, and the disease often has a prolonged clinical course [1].

There is no effective treatment for LPP. Various therapeutic modalities such as topical tacrolimus, topical and systemic corticosteroids, high-dose vitamin A and lasers have been tried with no prometting results [2-6]. Isotretinoin is a first generation retinoid discovered in 1952 and was approved by the FDA for the treatment of nodulokystic acne in 1982. Isotretinoin anti-inflammatory properties have allowed it to be used in disorders other than acne. Its adverse effects range from simple xerosis to teratogenicity. There have been a few isolated reports of isotretinoin (topical/systemic) efficiency in the treatment of LPP but its role in LPP has not yet been totally elucidated [7,8]. The objective of this study was to evaluate the efficiency and safety of low-dose isotretinoin in the treatment of LPP.

2. Materiels and Methods

Prospective open-label study conducted in the Department of Dermatology and Venereology over a period of two years. Twenty-four patients with a clinical diagnosis of LPP were examined during the study period, histologically confirmed, over 18 years of age, who met the inclusion criteria were finally enrolled in the study after informed consent. The following clinical and histological criteria were used for the diagnosis of LPP :

3. Clinical Criteria

Patients with discrete or coalescing slate-grey or brownish macules affecting predominantly sun-exposed areas, mainly on the face, neck and upper limbs.

4. Histological Criteria

Histological criteria included minimal acanthosis, apoptosis of keratinocytes and vacuolar degeneration of the basal layer of the epidermis.The epidermis as well as banded or perivascular lymphocytic infiltration, melanin incontinence and scattered melanophages in the dermis. Data were recorded on duration of disease, symptoms, known precipitating factors such as hair dye, henna, multiple cosmetic use, systemic medications for other diseases, site of onset, extent (body surface area), response to previous treatment, if any, and associated co-morbidities.Disease progression was defined as the appearance of new macules or increase in size of old lesions in the previous 3 months. Body surface involvement was divided into limited disease (two anatomical areas involved) and extensive disease if more than two anatomical areas were involved. Skin biopsies were performed in all patients (punch biopsy, 3-4 mm).

Lipid profile and liver function tests were monitored at baseline and monthly during treatment. After advising patients on the use of strict contraception to avoid pregnancy during the study and a negative pregnancy test, subjects were started on fixed low-dose oral isotretinoin (20 mg/day) per day for 6 months.For low-dose isotretinoin, a dose of 0.3 mg/kg body weight was prescribed and rounded to the nearest multiple of 5, i.e. 20 mg. Patients were also advised to use a broad spectrum sunscreen and to avoid all triggers. During treatment, patients were reviewed monthly. Clinical response and percentage improvement were judged by area of involvement, colour intensity, number of lesions and stability using digital photographs taken before and after treatment. Stability was defined as the complete cessation of disease progression during treatment and post-treatment follow-up. Improvement was classified as mild (≤25%), moderate (26-50%), and good (>50%), based on the stability of the disease and the decrease in hyperpigmentation. During follow-up, details of change, lesion colour, stability and occurrence of side effects were recorded. After the end of treatment, patients were followed up for a further three months.

Patients undergoing systemic treatment for LPP within the last 3 months, pregnant and lactating women, liver, kidney or systemic diseases, and known hypersensitivity or contraindications to

isotretinoin were excluded from the study. Those taking topical treatments, with the exception of sunscreens, were asked to stop all treatment for 4 weeks as a washout period before enrolling.

5. Results

Twenty-four patients completed the study, all of them were femal, aged 20-62 years, and the majority (80%) were aged 20-40 years. The clinical and epidemiological characteristics of the study are summarised in Figure 1. At presentation, twenty-three (85.2%) of the patients had progressive disease manifested by the appearance of multiple new hyperpigmented macules, involvement of new body areas or an increase in the size of older lesions over the last 3-4 months. Pruritus was noted in all patients with progressive disease (85.2%). None of the patients had a history of inflamed lesions before the onset of the disease.The most common trigger in our patients was the application of hair coloring in 20 out of 24 cases (83.3%), followed by the application of henna in three patients . Clinical examination showed symmetrical, well or poorly defined, dark brown or bluish-grey macules, with irregular borders, merging in some places to form large spots. The face, neck and upper limbs were the most frequently affected sites. The site of onset was the face, neck and upper limbs in 12, 10 and two patients respectively .In the majority of cases (77.8%), the colour of the lesions was dark brown, and in the remaining 22.2% of patients, the colour was slat grey. Among the morphological variants of LPP, the diffuse and mottled types were the most common observed in 14 and 6 patients respectively and the remaining four had the reticulated variant.

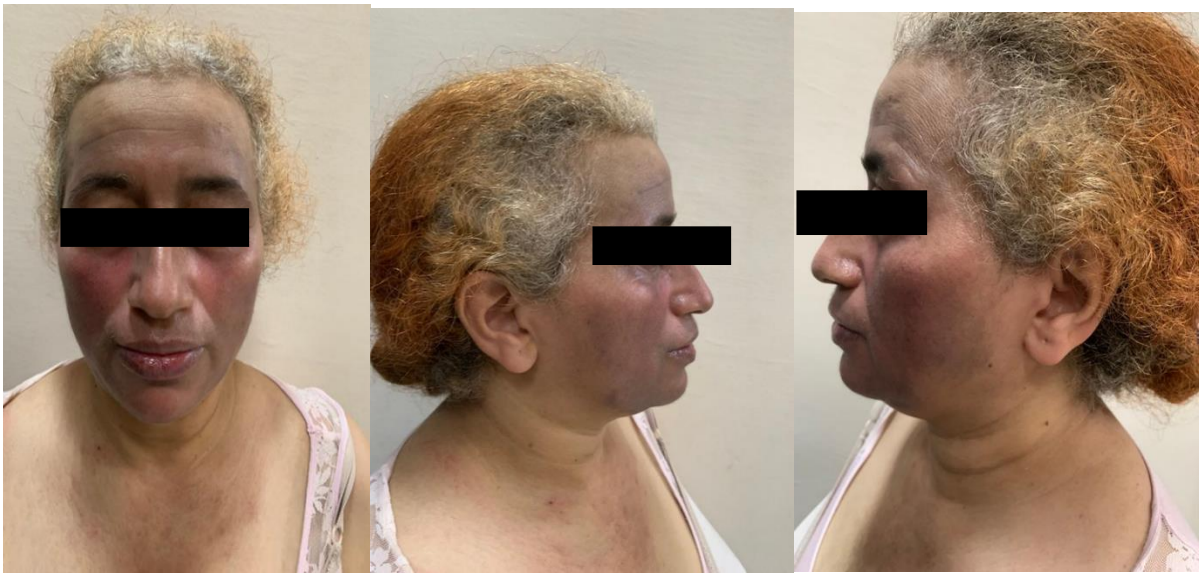
Clinically, pruritus was the earliest symptom to abate 15 days after the start of isotretinoin. Pruritus was an associated symptom in 23 of 24 patients, all of whom had complete resolution of itching ($P < 0.001$). Stabilisation of the disease was observed after 4-6 weeks. An initial decrease in the intensity of hyperpigmentation in LPP lesions was identified only after 3 months of regular treatment.15 (55.7%) patients showed moderate (25-50%) improvement in hyperpigmentation.Patients had a good and mild response, respectively. At the end of the study period, three patients did not respond to treatment. Lesions on the face and neck responded better than other areas of the body; patients with mottled LPP had the best response to treatment ($P < 0.001$).

Isotretinoin was well tolerated by all patients. Minimal adverse events in the form of mild cheilitis, transient xerosis were observed in a few patients, which did not warrant discontinuation of treatment.

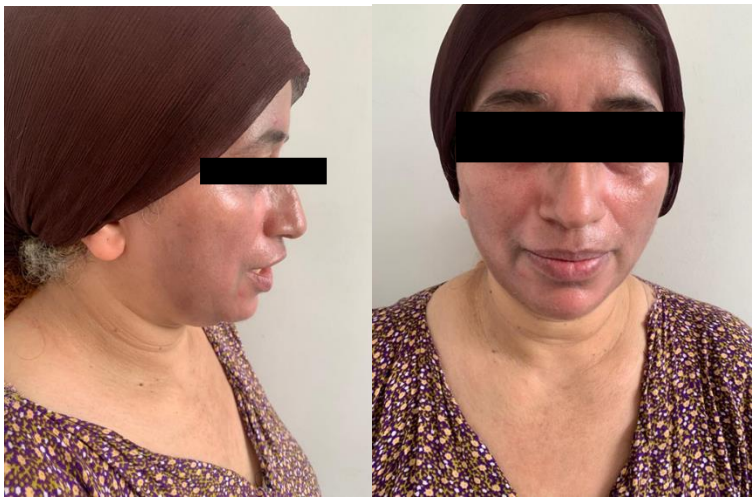
6. Follow-up

During the 3-month post-treatment follow-up, the disease stability achieved during the treatment phase was maintained in all responding patients, with no relapses observed.

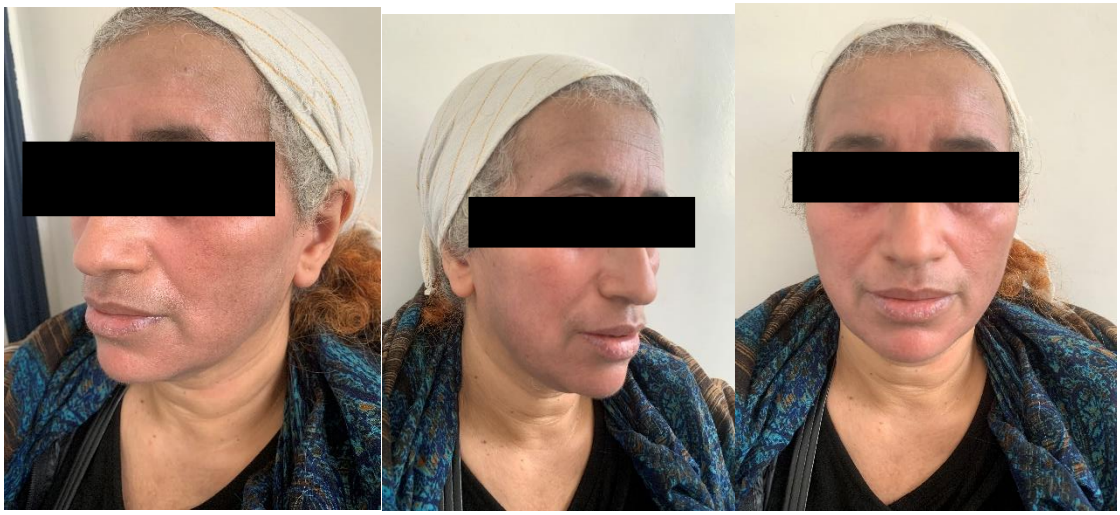
7. Before Treatment



8. After 3 Months Of Treatment



9. After 6 Months



10. Discussion

The exact prevalence of LPP is unknown.However, Indian studies have reported that it accounts for 4.1% of patients visiting pigmentation clinics. Treatment of LPP has generally been unsatisfiying. Isotretinoin, with its anti-inflammatory properties, has been shown to be effective in LP.However, its role in LPP remains to be elucidated. In our study, we found a useful role in LPP.

Since the preliminary description of LPP by Bhutani et al, its exact etiopathogenesis and nosology have been debated. Few consider it a variant of LP because of its histologic similarities Kashima suggested that in LPP, the cytotoxic damage to keratinocytes was less extensive and intense than in classic LP, which has extensive keratinocyte damage [2,9-13]. The various precipitating factors that have been hypothesized are the application of mustard oil and amla, the use of hair dyes and henna, multiple cosmetic products, and environmental pollutants [10,14]. In our study, the most commonly identified precipitating factor was the application of hair coloration. The use of mustard oil and amla oil is quite common in the Indian population; however, its association with LPP has not been proven.

Indian studies have reported a female preponderance (M/F = 1:1.2), but Al-Mutairi(2) and El-Khalawany (1)from Kuwait noted a male preponderance (M/F = 1.75:1). In our study, our patients were exclusively women . This could be attributed to the increased use of cosmetics/oil in women. There was no history of inflammatory lesions before the onset of hyperpigmentation.Clinically, in LPP, the lesions present as small, ill-defined oval to round macules, which may be discrete or become confluent to form large plaques. The color of the pigmentation varies from slate gray to dark brown, although in some patients the pigmentation is usually uniform. AlMutairi and El-Khalawany observed that the majority (81.8%) of their patients had dark brown pigmentation, while 18.2%had blue-gray [1,2].

In our study, dark brown color was a predominant finding . Among the different clinical patterns of LPP(diffuse, spotted, reticular, and

follicular) described in the literature,19 patients showed a diffuse pattern followed by spotted, in 4, two, and reticuled in one patients, respectively. Another study from the Middle East also noted a diffuse pattern in 54.5% of its patients, followed by a reticular pattern in 21.2% of patients [2].

Even 40 years after its initial description, treatment of LPP generally remains unrewarding. Topical tacrolimus deflazacort high-dose vitamin A6 lasers in combination with topical tacrolimus and topical clobetasol [2,3,5,6,14). This last therapeutic option have been tried in a small group of patients or as case reports, with variable results,None of which have completely reversed the hyperpigmentation.

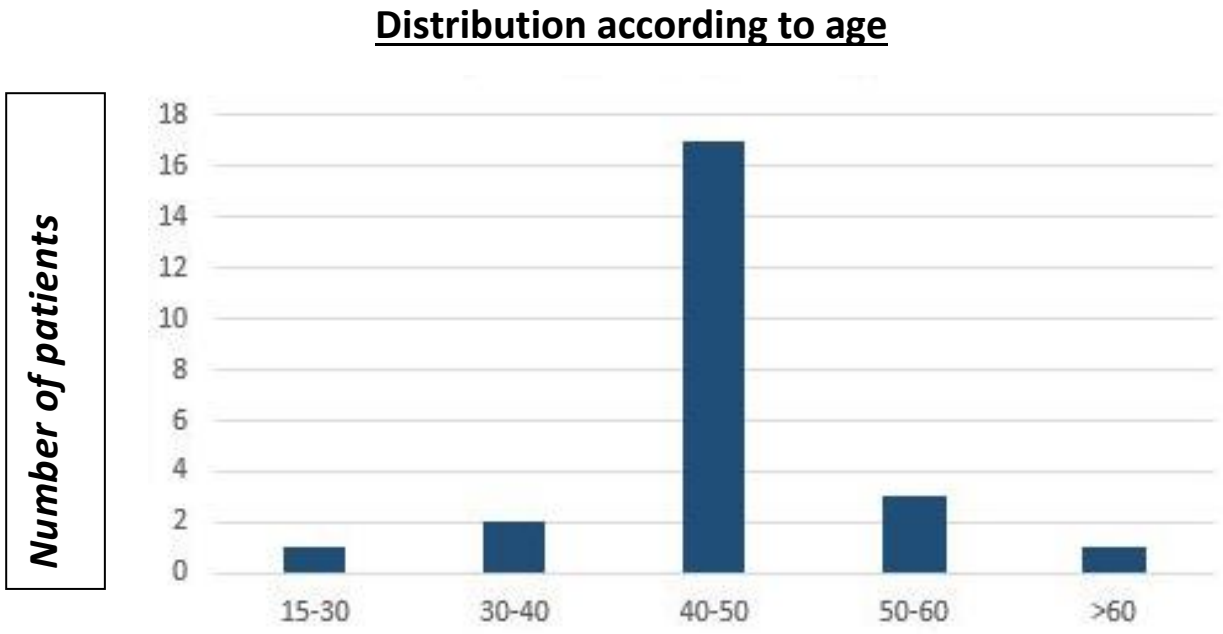
Woo and al revealed the efficacy of oral isotretinoin in cutaneous LP and oral LP. Therefore, in LP, it is plausible that isotretinoin probably acts through its various immunomodulatory and anti-inflammatory effects explained above, stabilizing the disease [7]. Improvement was seen primarily in patients who presented to us earlier in the course of the disease ,and had involvement of only two anatomic areas, in the form of (face and neck only) or (neck and limbs).

Nonresponders had longer disease duration and extensive involvement of the (≥25% of body surface area involved). Among morphological, the spotted type responded well to treatment compared with the others.

Although most patients noted a moderate decrease in color intensity, none of our patients experienced complete disappearance of hyperpigmentation. Maximum improvement (75%) i in pigmentation was noted in three patients with lesions on the face and neck. The drug was well tolerated by all the patients. A few patients experienced transient transaminitis during treatment, which did not warrant discontinuation of the drug and rapidly returned to normal upon discontinuation after 6 months, in accordance with the study protocol.

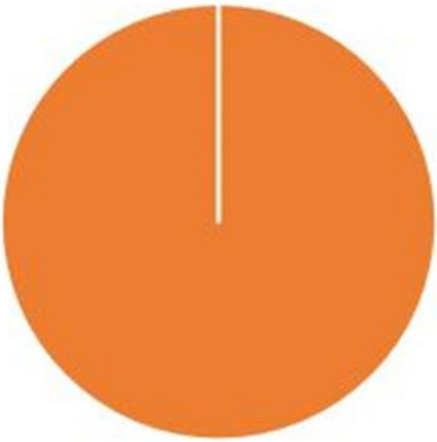
11. Conclusion

Our study has shown that low-dose oral isotretinoin is effective in stabilising and decreasing hyperpigmentation in LPP, particularly in patients with limited and short-lived disease. It can be considered an effective alternative/adjunctive treatment in the early course of the disease to stop its progression. However, controlled studies with a larger sample size and longer follow-up are needed to better establish the role of isotretinoin in the management of this enigmatic pigmentary disorder.



Age range

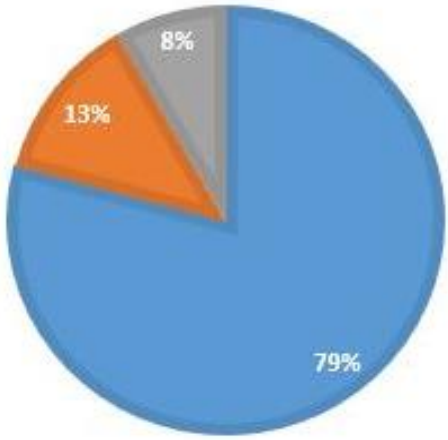
Distribution by gender



Men Women

Type of Lichen

Diffuse type Spotted type Other



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