Combination therapy with prednisone and isotretinoin in early erythema dyschromicum perstans: A retrospective series

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Key words: erythema dyschromicum perstans; hyperpigmentation; isotretinoin; lichen planus pigmentosus; prednisone.

INTRODUCTION

Erythema dyschromicum perstans (EDP) is an acquired hyperpigmentation disorder characterized by asymptomatic, polycyclic, irregularly shaped light lilac-grey patches surrounded by erythematous borders in the early inflammatory stage and subsequently greyish-blue patches in the later ashy stage. Affected areas include the trunk, neck, face, and upper extremities. Mucous membranes are spared.[1] EDP occurs in both children and adults, has a higher frequency noted in women, and is common among Latin American, Asian, and Indian populations.[2-4] The cause remains largely unknown; however, proton pump inhibitors,[5] radioactive contrast,[6] hypothyroidism, vitiligo,[7] and parasitic and hepatitis C infections,[1] are among the associations with EDP.

Histopathologic findings of EDP include vacuolar interface dermatitis and pigment incontinence.[4] EDP is histopathologically indistinguishable from lichen planus pigmentosus[8]; however, distinct clinical characteristics separate the 2 disorders with lichen planus pigmentosus characterized by pruritic, brown-black macules and patches on the face, upper extremities, and flexures with occasional involvement of mucous membranes.[1]

EDP is cosmetically disfiguring and poses as a therapeutic challenge. Multiple treatments have been proposed that show inconsistent efficacy. Among these are topical steroids, tretinoin, hydroquinone, clofazimine, dapsone, lasers, and narrow-band ultraviolet light B phototherapy.[4]

Abbreviation used:

EDP: erythema dyschromicum perstans

A single case is reported each for the use of isotretinoin[9] and prednisone.[10] In this case series of 4 adult patients with EDP, we report that a combined treatment regimen of prednisone and isotretinoin initiated in the early inflammatory stage leads to rapid resolution of the erythematous border, arrest of progression, and clearance of the hyperpigmentation.

CASES

Case 1

A 54-year-old Hispanic woman with a history of hypothyroidism presented with polycyclic light grey patches with a surrounding erythematous border on the shoulders, arms, forearms, and chest (Fig 1, *A*). A skin biopsy was consistent with EDP (Fig 1, *D*). The patient started topical triamcinolone 0.1% cream daily in conjunction with a 3-week prednisone taper as follows: 60 mg/d for 1 week followed by 40 mg/d for 1 week, followed by 20 mg/d for 1 week. Following the prednisone taper, marked improvement of the surrounding erythematous borders were noted (Fig 1, *B*). In addition to the prednisone, the patient was also started on isotretinoin, which was gradually tapered over 5 months as follows: 40 mg/d for 1 month, followed by 20 mg/d for 3 months, followed by 10 mg/d for 1 month. When

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Funding sources: None.
Conflicts of interest: None disclosed.

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JAAD Case Reports 2020;6:207-13.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.12.015

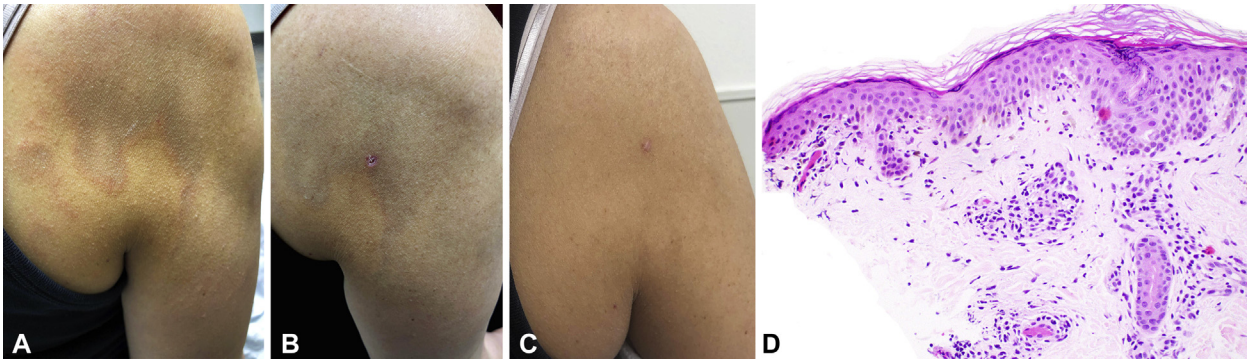

Fig 1. EDP, case 1. **A,** At baseline, a large gray-to-blue irregularly shaped discrete patch with a surrounding erythematous border on the posterior shoulder. **B,** Marked improvement of the surrounding erythematous borders following prednisone taper. **C,** Complete resolution at 10-month follow-up. **D,** Cell-poor interface dermatitis with vacuolar degeneration of basilar keratinocytes and prominent pigment incontinence. (Hematoxylin-eosin stain; original magnification: ×200.)

therapy was completed, the patient showed substantial improvement with nearly complete resolution. At 10-month follow up, there was no evidence of disease recurrence (Fig 1, *C*). However, at the 16-month follow-up the patient had mild relapse on the bilateral legs; the prednisone taper and isotretinoin were restarted with improvement already evident after 4 weeks of retreatment.

Case 2

A 47-year-old Hispanic woman with no medical history presented with multiple irregularly shaped light gray-to-lilac patches with surrounding erythematous borders on the arms, forearms, and neck (Fig 2, *A*). The patient was started on topical halobetasol 0.05% ointment daily in conjunction with a 3-week prednisone taper as follows: 60 mg/d for 1 week, followed by 40 mg/d for 1 week, followed by 20 mg/d for 1 week. After 3 weeks, the patient showed marked improvement with complete resolution of erythematous borders and improvement of the hyperpigmentation (Fig 2, *B*). Nine months later, the patient presented to clinic with relapsed disease. The 3-week prednisone taper was restarted, which again led to significant improvement, so she was transitioned to isotretinoin, 40 mg/d, which was tapered over the next 4 months as follows: 40 mg/d for 1 month, followed by 20 mg/d for 2 months, followed by 10 mg/d for the final month. Upon completion of treatment, the patient had sustained improvement without disease recurrence at 24 months.

Case 3

A 54-year-old Hispanic woman with a history of Sjogren syndrome and fibromyalgia presented with multiple ill-defined gray-to-blue patches on the volar aspects of her bilateral upper extremities. Skin biopsy was consistent with EDP. The patient was started on topical halobetasol 0.05% ointment daily in conjunction with a 3-week prednisone taper as follows: 60 mg/d for 1 week, followed by 40 mg/d for 1 week, followed by 20 mg/d for 1 week. Significant improvement was noted after the prednisone taper. The patient was then transitioned to a 3-month course of isotretinoin as follows: 20 mg/d for 2 months followed by 10 mg/d for the final month. At the completion of treatment, there was no evidence of erythema or pigmentation. Two months after discontinuation of isotretinoin, the patient reported relapse but declined further treatment.

Case 4

A 54-year-old Hispanic woman with a history of diabetes and hypertension presented with multiple polycyclic hyperpigmented patches and surrounding erythematous borders coalescing on the medial aspect of the bilateral arms and forearms. Skin biopsy was consistent with EDP, and the patient was started on topical halobetasol 0.05% ointment daily in conjunction with a 3-week prednisone taper as follows: 60 mg/d for 1 week, followed by 40 mg/d for 1 week, followed by 20 mg/d for 1 week. At the completion of the prednisone taper, the affected areas were substantially improved with resolution of the surrounding erythematous borders. Thereafter, isotretinoin, 20 mg/d, was initiated. After only 1 month of isotretinoin, the patient discontinued treatment because of satisfaction with the clinical improvement, and reported no signs of relapse 2 months later.

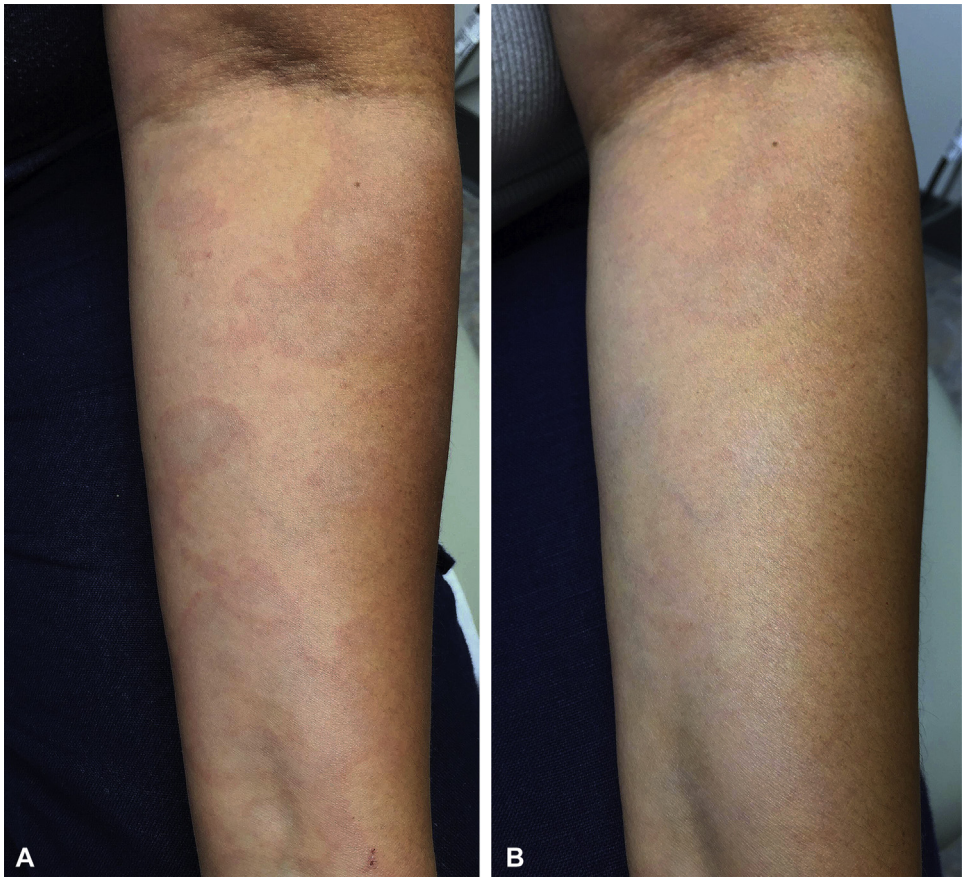

Fig 2. EDP, case 2. **A,** Multiple irregularly shaped gray-to-blue patches with a surrounding erythematous border on the left volar forearm at baseline. **B,** Faint residual pigmentation with disappearance of the erythematous borders following the 3-week prednisone taper.

DISCUSSION

Also known as *ashy dermatosis*, EDP is a chronic progressive hyperpigmentation disorder of unknown etiology, first described in 1957.[4] EDP classically presents as asymptomatic, gray-to-blue patches with an erythematous border in a symmetrical distribution over the neck, trunk, and upper extremities.[1] Histopathologic findings, although not specific, show variation depending on the stage of evolution. Acute or early inflammatory patches display basal vacuolar degeneration, papillary dermal edema, and perivascular lymphocytic inflammation. In contrast, chronic lesions show abundant melanophages and pigment incontinence, with diminished-to-absent inflammation, features that may be indistinguishable from postinflammatory hyperpigmentation of other causes.[2]

To date, no randomized, placebo-controlled clinical trials have been conducted to determine standard therapeutic modalities and appropriate dosing regimens for the management of EDP. Some retrospective studies proposed numerous therapeutic agents, but results are inconsistent. Therapies reported from the years 2000 until now are summarized in Supplemental Table I. There is clearly an unmet need for consistently effective treatment. In this case series, we are the first, to our knowledge, to report a combination therapy of prednisone and isotretinoin in the early inflammatory stage of EDP.

As demonstrated in all cases presented, prednisone appears to both rapidly clear the erythematous border and improve the dyspigmentation, with significant improvement noted after only 3 weeks of treatment. The addition of isotretinoin appears to clear residual hyperpigmentation and maintain remission. Immune dysregulation in EDP is driven by interleukin-2, interferon-γ, natural killer cells, and cytotoxic $CD8^+$ T cells,[11] which may be modulated by prednisone and isotretinoin.[9,10,12]

In this series no patient experienced significant adverse effects. Two of the 4 patients relapsed after stopping isotretinoin, which indicates that long-term treatment may be required to maintain remission. This finding mirrors the only previously reported case of EDP treated with isotretinoin in which the

patient experienced relapse within 2 months of stopping isotretinoin and required long-term isotretinoin to maintain remission.[9] The specific treatment regimens used and patient characteristics from this series are summarized in Supplemental Table II. In our experience, for the combined effect of prednisone and isotretinoin to be maximally successful, EDP should be treated at its earliest inflammatory stage, which is represented by light grey-to-lilac patches with a surrounding erythematous border. We feel it is imperative to recognize EDP early and initiate treatment immediately to achieve optimal response.

Limitations of this series include a small sample size limited to only adult female Hispanic patients. Nonetheless, this observation provides insight for a readily available therapy that may improve pigmentation and arrest disease activity in a historically recalcitrant disorder. Larger, long-term observational or prospective studies are warranted to determine the optimal length of treatment to produce clinical resolution and prevent relapse.

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Supplemental Table I. Summary of previous therapies used in erythema dyschromicum perstans

Year, Study	Study type	no, Sex	Age range (yr)	Ethnicity	Therapies used	Reported treatment outcomes
2018,[S1]	Retrospective study	26, NA	16-65	Asian	Topicals: steroid, hydroquinone, tacrolimus, tretinoin; oral steroid	Five showed improvement following combined topical hydroquinone and steroid; remaining showed stable disease at 0.5- to 3-mo follow-up
2018,[S2]	Case report	1 Male	17	NA	Narrow-band UVB, topical clobetasol and tacrolimus	Sustained resolution at 4-yr follow-up
2017,[S3]	Case report	1 Female	57	White	Clofazimine	No improvement
2017,[S4]	Case report	1 Female	35	NA	Fractionated nonablative laser and tacrolimus ointment	Improvement >75% and maintained at 5-mo follow-up
2016,[S5]	Case report	1 Male	48	Asian	Isotretinoin	Recurrence upon discontinuation of treatment.
2015,[S6]	Retrospective study	39 Female; 29 Male	3-76	Asian	Topicals: steroid, tretinoin, hydroquinone; dapsone, clofazimine, minocycline	Most exhibited no improvement or worsened progression at >1-yr follow-up
2015,[S7]	Case report	1 Female; 1 Male	19, 29	NA	Topical tacrolimus	Resolution following therapy with no recurrence at 2- to 3-mo follow-up
2015,[S8]	Case report	2 Female	53, 59	NA	Narrow-band UVB	Improvement noted
2015,[S9]	Case report	1 Female	25	Hispanic	Topical clobetasol, pimecrolimus, tacrolimus; dapsone	No response to therapies; self-resolution noted at 5-yr follow-up
2012,[S10]	Preliminary study	4 Female; 4 Male	20-54	NA	Nonablative fractional laser	No improvement
2012,[S11]	Randomized, observer-blinded study	6, NA	NA	NA	Nonablative fractional laser therapy	No improvement
2011,[S12]	Case report	1 Female 1 Male	11, 21	Asian	Q-switched ruby laser	No improvement
2010,[S13]	Case report	1 Male	39	Hispanic	Narrow-band UVB	Improvement following therapy
2009,[S14]	Case report	1 Female	34	NA	Clofazimine	Resolution following therapy
2004,[S15]	Case report	1 Male	16	NA	Dapsone	Resolution following therapy
2001,[S16]	Case report	1 Male	21	Hispanic	Prednisone	Improvement following therapy
2001,[S17]	Case report	1 Female	48	NA	Interferon-α and ribavirin	Improvement following therapy

NA, Not available; *UVB*, ultraviolet B.

Supplemental Table II. Clinical demographics and treatment outcomes

No.	Age (yr)	Sex	Ethnicity	Medical history	Treatment regimen	Treatment outcome
1	54	Female	Hispanic	Hypothyroidism	Triamcinolone 0.1% cream 3-wk prednisone taper (60 mg: 40:20) 5-mo isotretinoin taper (40 mg: 20:20:20:10)	Complete resolution but with mild relapse after 16 mo
2	47	Female	Hispanic	None	Halobetasol 0.05% ointment 3-wk prednisone taper (60 mg: 40:20) 4-mo isotretinoin taper (40 mg: 20:20:10)	Marked clinical improvement without recurrence at 24 mo
3	54	Female	Hispanic	Sjogren syndrome, fibromyalgia	Halobetasol 0.05% ointment 3-wk prednisone taper (60 mg: 40:20) 3-mo isotretinoin taper (20 mg: 20:10)	Marked clinical improvement but with subjective recurrence at 2 mo
4	54	Female	Hispanic	DM II, HTN	Halobetasol 0.05% ointment 3-wk prednisone taper (60 mg: 40:20) 1-mo isotretinoin, 20 mg/d	Complete resolution without recurrence at 2 mo

DM, Diabetes mellitus; *HTN*, hypertension.