Erythema dyschromicum perstans: A case report and systematic review of histologic presentation and treatment☆,☆☆

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A B S T R A C T

Objective: Erythema dyschromicum perstans (EDP) can be difficult to diagnose and treat; therefore, we reviewed the literature to assess whether histology can be used to differentiate lichen planus pigmentosus (LPP) from EDP and determine which treatments are the most effective for EDP. We also present a case of a patient who was treated successfully with narrow-band ultraviolet B (NB-UVB).
Methods: A systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was conducted up to July 2017 using four databases.
Results: Histologic analyses from the literature reveal a significant percentage of melanophages, lymphocytic infiltrates, and basal vacuolar degeneration in EDP, and a significant histologic overlap with LPP. The review of the literature on treatment outcomes showed that NB-UVB and tacrolimus were effective with minimal side effects. Clofazimine was effective, but demonstrated significant-to-intolerable side effects. Griseofulvin, isotretinoin, and dapsone provided unsatisfactory results as lesions recurred after discontinuation. Lasers were largely ineffective and may cause postinflammatory hyperpigmentation and fibrosis.
Conclusion: A diagnosis of EDP should not be based on histologic findings alone. Clinical history, morphology, and distribution should be used to differentiate EDP and LPP. NB-UVB and tacrolimus are promising treatments for EDP with minimal side effects. This is the first report to our knowledge of sustained resolution of EDP after treatment with NB-UVB at long-term follow-up of 4 years. Larger studies are needed to confirm these findings.

Introduction

Erythema dyschromicum perstans (EDP) is a disorder of pigmentation that is characterized by gray or blue-brown macules or patches in individuals with Fitzpatrick skin types III-V (Chang et al., 2015). The lesions are usually distributed symmetrically on both sun- and non-sun-exposed areas including the trunk (69.1%), limbs, neck, and face. EDP is a chronic progressive disorder that can present similarly to several other pigmentation disorders, such as lichen planus pigmentosus (LPP), and thereby result in difficulties to establish a diagnosis and treatment (Cutri et al., 2011).

EDP was first noted in 1957 by Ramirez (1957), who described a total of 139 patients in El Salvador with progressive, ash-colored macules and patches on the trunk, arms, and legs, and whom the researchers labeled "los cencientos," or the ashen ones. On histology, a vacuolar liquefactive degeneration of the basal cell layer with dermal melanosis and a perivascular infiltrate was observed. This condition was later named ashy dermatosis. In 1961, Convit et al. reported 5 patients in Venezuela with similar clinical symptoms, except for raised erythematous borders, which disappeared after several months. These authors named this condition EDP, with an emphasis on the erythematous margin of the active lesions. Since then, several authors have attempted to determine whether EDP is a unique entity or within a spectrum of other dyschromias, such as LPP (Bhutani, 1986; Ghosh and Coondoo, 2016). Overall, there is now consensus that EDP and ashy dermatosis refer to different stages of the same condition (Zaynoun et al., 2008).

The exact etiology of EDP is unknown. Damage to melanocytes and basal cell keratinocytes that is observed with EDP is postulated

to be due to an abnormal immune response to antigens with a predominance of CD8 + T lymphocytes in the dermis and HLA-DR +, intercellular adhesion molecule 1 + keratinocytes in the epidermis (Baranda et al., 1997; Pinkus, 1973). A genetic susceptibility conferred by genes located in the major histocompatibility complex (mostly HLA-DR4) has also been described (Correa et al., 2007). In one study, patch testing was used to identify possible triggers of EDP and other dyschromias, such as LPP and pigmented contact dermatitis. The study results showed that 40% of patients with a clinical provisional diagnosis of EDP and 36% of patients with a provisional diagnosis of LPP had a positive patch test (Tienthavorn et al., 2014).

Despite the growing body of literature on EDP since 1957, there are no treatments that are consistently effective (Combemale et al., 1998). In our case report, we describe a patient with EDP who was successfully treated using narrow-band ultraviolet B (NB-UVB) with sustained resolution at a long-term follow up of 4 years. In our systematic review, we investigate whether histology can be used to differentiate LPP from EDP, and summarize reported treatment outcomes and side effects.

Case report

We report the case of a 17-year-old male patient with Fitzpatrick skin type IV who had a 1.5 year history of widespread, symmetric, brown-gray, ovoid macules and patches on the lower back that extended to his superior buttocks; some areas had erythematous rims and were associated with mild pruritus (Fig. 1A). Oral and nasal mucosa as well as the palms, soles, scalp, and nails were normal. A diagnosis of EDP was made by using the following clinical and histopathologic criteria: (i) eruption of multiple blue-gray macules or patches in typical distribution; (ii) histopathologically compatible with EDP; and (iii) absence of pigmentation-related, underlying diseases and drug history. There was no history of similar skin lesions and no personal or family history of autoimmune diseases or thyroid disease. The patient was otherwise a healthy man with no history of sexually transmitted diseases, medications, long-term use of cosmetics, or other topical products to the skin. He also did not have any history of photosensitivity or worsening skin lesions with natural sun exposure. A skin biopsy was performed and the test results indicated mild interface dermatitis with dermal melanophages (Fig. 2).

The patient was initially treated with triamcinolone, topical dapsone, clobetasol, and tacrolimus. He used different combinations of these topical medications for 6 weeks without improvement. He had also previously tried topical antifungal treatments and fluocinonide without response. NB-UVB was initiated at 300 mJ three times a week and increased by 10% to 15% per session as tolerated. The patient continued to use topical clobetasol and tacrolimus. After 2 months of NB-UVB therapy, the patient experienced a resolution of the erythema and pruritus and a significant decrease in hyperpigmentation of his lesions (Fig. 1B). The patient was satisfied with the results and did not require any further treatment. The patient has been in remission for 4 years.

Materials and methods

Protocol and registration

The systematic literature review was registered and conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis criteria.

Research strategy

Using our search strategy, we queried ("erythema" and "pigmentation disorders" or "Hyperpigmentation") or ("Erythema dyschromicum perstans") or ("Erithema dyschromicum perstans") or ("Ashy dermatosis") or ("dermatosis cenicienta") or ("blue and gray and hyperpigmentation") in four databases (PubMed, EmBase, Cochrane, and Web of Science) up to July 2017 (Search Addendum). We identified a total of 871 records. Non-human studies and languages other than English were excluded. All references identified were imported into Endnote and duplicates removed, which resulted in 659 remaining records.

Eligibility criteria and study selection

Two authors (MO and NL) examined 659 titles and abstracts independently (Suppl. Fig.). Articles that had a well-established etiology causing hyperpigmentation other than EDP (i.e., systemic causes such as mastocytosis; endocrine diseases such as Addison; auto-immune disorders such as lichen amyloidosis; infection such as syphilis; malignancy such as cutaneous T-cell lymphoma; and drug-related causes such as amiodarone-inducing hyperpigmentation) were excluded. The remaining 127 full-text articles were screened. Full texts that included cases of patients with another cutaneous disorder in addition to EDP were excluded to eliminate confusion of histopathologic presentations and treatment outcomes. Full texts that did not discuss

Fig. 1. Erythema dyschromicum perstans treated with narrow-band-ultraviolet B. (A) A 17-year-old male patient with a 1.5 year history of hyperpigmented macules and patches with areas of peripheral erythema on the lower back and buttocks that was refractory to several topical treatments. (B) Significant improvement of hyperpigmentation and erythema after 2 months of narrow-band ultraviolet B. Patient was satisfied with the results as hyperpigmentation and erythema improved and stopped progressing. Further treatment was not continued when the patient relocated to another state.
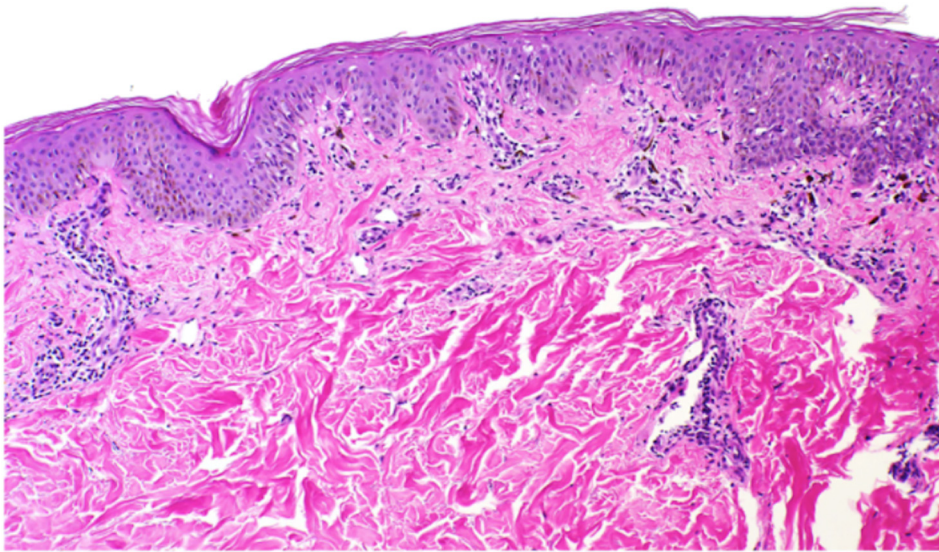
Fig. 2. Erythema dyschromicum perstans biopsy specimen of the right lower back (0.4 cm punch of skin with depth of 0.5 cm; hematoxylin and eosin × 40 magnification), showing pigment incontinence with mild interface dermatitis and perivascular lymphocytic infiltrate in dermis. The periodic acid-Schiff stain was negative for fungi and basement-membrane thickening. The colloidal iron stain demonstrated a normal amount of dermal mucin.

histopathology results or treatment outcomes of EDP were excluded from the analysis. Ultimately, four studies on histopathology and 16 articles on treatment that met our criteria were analyzed (Tables 1 and 2).

Outcomes

Treatment outcomes data that were retrieved included (1) improvement, no change, or worsened clinical presentation; (2) adverse events such as postinflammatory hyperpigmentation (PIH), severe skin irritation, pruritus, or erythema; and (3) length of remission or follow up of EDP. Since heterogeneity and subjectivity rendered an analysis of the results difficult, we devised a simple scale of –1 to 1 where (–1) = side effects; (0) = no effects; and (1) = improvement. Our primary histopathologic outcomes included presence, absence, and percentages of melanophages, lymphocytic infiltrate, basal vacuolization, and hyperkeratosis. We retrieved data on study size of all studies and case reports.

Result

Histopathological presentation of erythema dyschromicum perstans

We found four studies on histopathologic and ultrastructural presentation of EDP. The author, publication year, study size, and results are shown in Table 1. The earliest study to characterize the histologic changes of EDP dates back to 1969. Soter et al. (1969) evaluated the ultrastructural changes in four patients with presumed EDP and observed that all patients presented with characteristic ultrastructural changes: widening of the intercellular spaces, desmosome retraction, vacuolar changes, membrane-free clear spaces in both basal and spinous cells, discontinuity of the basal lamina, and dermal melanophages. These ultrastructural changes, when individually analyzed, are nonspecific, but together provide a consistent ultrastructural indication of EDP. No additional ultrastructural studies were subsequently published to support these findings. In 1992, Vega et al. analyzed and compared the histopathologic features between EDP and LPP in 31 patients in Mexico (n = 20 for EDP; n = 11 for

Table 1
Histopathologic presentation of erythema dyschromicum perstans

Lead author, year, country	Study size (n)	Results
Soter, 1969, USA	4	• Melanophages • Liquefaction degeneration in the basal and lower spinous cellular layers • Perivascular infiltration of cells in the papillary dermis • Large translucent areas devoid of cytoplasmic organelles surrounded the nuclei, with indented nuclear envelope
Vega, 1992, Mexico	31 (20 EDP, 11 LPP)	• Melanophages (100% for EDP vs. 100% for LPP) • Basal vacuolization (85% for EDP vs. 91 % for LPP) • Hyperkeratosis (80% for EDP vs. 91% for LPP) • Thinned epidermis (65% for EDP vs. 81% for LPP) • Lymphohistiocytic infiltrate (perivascular; 95% for EDP vs. 91% for LPP)
Vasquez-Ochoa, 2006, Colombia	43	• Melanophages (100%) • Lymphohistiocytic infiltrate (100%) • Perivascular in 86% of patients, diffuse in 9%, and band-like in 5% • Basal vacuolization (58%)
Chang, 2015, Korea	68	• Melanophages (83.8%) • Lymphohistiocytic infiltrate (73.5%) • Band-like lymphocytic infiltration (19.1%) • Basal vacuolization (48.5%)

EDP, erythema dyschromicum perstans; LPP, lichen planus pigmentosus

Table 2
Treatment outcomes in erythema dyschromicum perstans

Treatment	Dose	Lead author (year)	No. treated	Skin color	Results (+, 0, −)[*]	Length of Remission	Side effects
Clofazimine	<40 kg: 100 mg orally, alternative days	Piquero-Martin, 1989	8	I-V	+ (7 of 8 patients with improvement)	n/a	7 of 8 patients with side effects of reddish hue of skin, epigastralgia, xerosis cutis
	>40 kg: 100 mg/d 3m, then decreased to 200 mg/wk or 400 mg/wk, according to weight, 3-8m total						
	100 mg/d, 3 m	Baranda, 1997	6	n/a	+	n/a	2 patients removed from study. Reddish-orange skin, pruritus
Corticosteroid	Prednisone, oral, 3 weeks	Osswald, 2001	1	n/a	+ (Resolved erythema at 1 month; partial fading of blue-gray discoloration at 3 months)	n/a	n/a
Dapsone	100 mg/day for 8-12 weeks	Kontochristopoulos, 1998	2	n/a	+ (8 and 12 weeks, no new lesions, regression of prior lesions)	6 months	Recurred after discontinuation
	100 mg/d, 3 months	Bahadir, 2004	1	n/a	+	n/a	n/a
Griseofulvin	n/a	Berger, 1989	1	n/a	+	n/a	Recurred after discontinuation
Low potency topical steroid and hydroquinone 4%	Twice daily	Munoz, 2011	1	V	n/a	n/a	n/a
Laser							
•Non-ablative 1550 nm FLT alone	0.17 kJ (mean) energy per treatment, 5 treatments, 3 week intervals	Kroon, 2012	8	II-V	− (at 3 months)	None	PIH
•Non-ablative 1550 nm FLT with intermittent triple topical therapy cream (hydroquinone 5%, tretinoin 0.05%, triamcinolone 0.1%)	4.1 (mean) treatments, pulse energy-15 mJ/ microbeam, 0.17 kJ (mean) energy per treatment, 3 months	Wind, 2012	6	III, IV	− (at 3 months)	None	PIH
•Ablative 10,600 nm FLT with intermittent triple topical therapy cream (hydroquinone 5%, tretinoin 0.05%, triamcinolone 0.1%)	2.7 (mean) treatments, pulse energy- 10 mJ/microbeam, 3 m	Wind, 2012	6	III, IV	− (at 3 months)	None	PIH, fibrosis
•1550-nm erbium FLT and tacrolimus 0.1% ointment	4.65-4.91 kJ, 5 sessions, 4-6 week intervals; 5 months; 400-525 μm depth, targets pigment in epidermis and papillary dermis; daily ointment	Wolfshohl, 2017	1	IV	+	8 months	Mild erythema and edema
•Q-switched ruby laser	n/a	Imanishi, 2011 (unilateral EDP)	2	n/a	0	None	n/a
Tacrolimus 0.1% ointment	Twice daily	Mahajan, 2015	2	n/a	+	2m	n/a
Isotretinoin	Low-dose for 7 years; required maintenance at 10 mg/d	Wang, 2016	1	n/a	+	n/a	Recurred after discontinuation; dry skin
UVB	3 times/week for 4 weeks, total dose 4716 mJ/cm^2	Fabbrocini, 2015	2	n/a	+	n/a	n/a
UVB and sunlight	n/a	Tlougan, 2010	1	n/a	+	n/a	n/a
Sunlight	n/a	Antonov, 2015	1	IV	+ (Found improved at 6 years follow up)	n/a	n/a

EDP, erythema dyschromicum perstans; FLT, fractional laser therapy; LPP, lichen planus pigmentosus; PIH, postinflammatory hyperpigmentation; UVB, ultraviolet B
[*] + means improved; 0 means no effects; − means worsened; None indicates noted to have none; and n/a means was not noted.

LPP). Due to the significant overlap in features, the authors concluded that EDP and LPP are two different clinical conditions with non-differentiable histopathologic findings.

In 2006, Vasquez-Ochoa et al. analyzed the clinical and histologic findings of EDP in 43 patients in Colombia, and found that 100% of patients had melanophages and dermal lymphocytic infiltrate and 58% had basal vacuolization, in contrast with the 85% found by Vega et al. (1992). Unlike others, these authors suggest that histopathology could aid in differentiating between EDP and LPP. Most recently, in 2015, Chang et al. (2015) conducted a retrospective study of 68 patients with EDP from six tertiary centers in Korea between 2002 and 2012 and found an 83.8% prevalence of melanophages and 73.5% of lymphocytic infiltrate, which is lower than previously described.

Taken together, these four studies demonstrate that melanophages and lymphocytic infiltrate are present in nearly all patients with EDP, and basal vacuolization is present in more than half of the patients. Furthermore, EDP and LPP were found to have significant overlap in histology.

Treatment outcomes in erythema dyschromicum perstans

Sixteen articles on the treatment of EDP were found. Author, publication year, treatment used, dose, Fitzpatrick skin type, treatment outcome, length of remission, and adverse outcomes are noted in Table 2. One of the earliest treatments published on was clofazimine. In a study from 1989, 7 of 8 patients treated with clofazimine obtained a good-to-excellent response, but all experienced side effects such as discoloration of the skin, xerosis cutis, and epigastralgia (Piquero-Martin et al., 1989). Later, another study reported significant improvement in 4 of 6 patients treated, where 2 patients dropped out of the study (one due to intolerable side effects; Baranda et al., 1997). Furthermore, discerning whether the discoloration of the skin was camouflaging the lesions was difficult. Dapsone led to improvement; however, lesions recurred after discontinuation of use in one of three cases (Bahadir et al., 2004; Kontochristopoulos et al., 1998). Likewise, griseofulvin helped temporarily, but lesions recurred after discontinuation in one patient (Berger et al., 1989).

The most promising topical treatment at this time is tacrolimus. Tacrolimus is a macrolide antibiotic medication with immunosuppressive properties, exerting its effects principally through the inhibition of calcium-dependent events such as the interleukin (IL) 2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis (Thomson et al., 1995). Tacrolimus was described with success in the treatment of EDP either as a monotherapy or in combination with laser (Mahajan et al., 2015) and, in our case, with NB-UVB. NB-UVB has been successfully used to treat EDP in three case reports including our case, all with minimal to no side effects (Fabbrocini et al., 2015; Tlougan et al., 2010). One case presented a patient with a resolution of EDP after a prolonged period of intense sun exposure (Antonov et al., 2015). Our report notes the longest of any follow-up period of EDP after treatment and demonstrates sustained resolution.

The treatment of EDP with fractional lasers have largely been unsuccessful and in several occasions were associated with postinflammatory pigmentation changes. Q-switched lasers have been used with ineffective results in two patients (Imanishi et al., 2011). In 2012, Wind et al. compared non-ablative with ablative fractional laser therapy in a randomized-controlled observer-blinded study in 6 patients with EDP. Both methods were ineffective and caused PIH. Fibrosis also developed with ablative fractional laser.

In a randomized, controlled, observer-blinded study in 2012, Kroon et al. treated 8 patients with non-ablative 1550 nm fractional laser therapy (FLT). Three months after the last treatment, an improvement of hyperpigmentation was assessed with melanin index, reflectance spectroscopy, physician's assessment, patient assessment, and patient satisfaction. No clinical improvement of hyperpigmentation was observed, but PIH occurred and patients considered FLT unsatisfactory. The only case of EDP that was successfully treated using laser was in 2017, as reported by Wolsfshohl et al. In this study, a patient was successfully treated with a combination of monthly treatments of 1550-nm erbium-doped, fractionated laser and topical tacrolimus over a period of 5 months. The success of the treatment was hypothesized to be secondary to the laser settings and the additive effect of tacrolimus.

Comparison of erythema dyschromicum perstans and lichen planus pigmentosus

Studies by Cheng et al. (2018) and Vega et al. (1992) compared LPP and EDP. EDP is more likely than LPP to have a generalized distribution and erythema at the time of onset (Table 3). Vega et al. (1992) noted that EDP presents with blue-gray or ashy hyperpigmented macules whereas LPP presents with dark brown, more irregularly shaped, and ill-defined macules. Patients with LPP most commonly have localized face and neck lesions, but EDP presents with lesions in more than one location and most commonly on the upper extremities, face, neck, and trunk. Vega et al. (1992) emphasized that lesions in LPP are either on sun-exposed areas such as the face and neck or, when on the trunk, only present in flexural areas. This finding was supported by Cheng et al. (2018) in their conclusions. They further specified that LPP generally originates symmetrically at the temples or pre-auricular locations. EDP generally has predominance in female patients, but no sexual predominance in LPP has been identified. EDP occurred at a younger average age (33.6 years in the study by Vega et al., 1992; 38.8 years in the study by Cheng et al., 2018) compared with LPP (46 years for Vega et al.; 42.7 years for Cheng et al.), although both can occur in children and adults. Both studies concluded that EDP and LPP do not have significant differences in histopathology. Treatments for these patients were not detailed in either study, but topical medications were infrequently and inconsistently effective to treat EDP and LPP.

Discussion

We conducted a systematic review of the literature on EDP up to July 2017 to summarize data on the histologic presentation and treatment outcomes of EDP. Our findings demonstrate that histology has its role in differentiating EDP from other disorders that can present with hyperpigmentation, such as mycosis fungoides, pigmented contact dermatitis, syphilis, mastocytosis, drug-induced hyperpigmentation, or postinflammatory pigmentation changes. However, because the histologic presentation was found to have a significant overlap between EDP and LPP, we recommend that histology alone must not be used to differentiate these entities. Clinical history, morphology, and distribution should instead be used to differentiate EDP and LPP.

LPP is largely localized to photo-exposed areas of the face and neck, and photo-aggravation was identified as a precipitating cause of LPP in 12 of 16 patients (Bhat et al., 2017). This is in contrast to EDP, which is not limited to photo-exposed areas and improves with light therapy. With regard to treatment, our findings suggest that NB-UVB and tacrolimus were effective therapies to treat EDP with minimal side effects (Bilsand et al., 1997; Hearn et al., 2008). Studies in a larger patient population are needed to confirm this data. No evidence of postinflammatory pigmentation changes was observed in our patient who substantially improved with NB-UVB. Of note, the use of UVB, either via natural sunlight exposure or NB-UVB, was reported to improve EDP. This is in contrast with LPP where sunlight appears to have a causative effect, which suggests these may be separate entities with different pathophysiology (Rieder et al., 2013).

Studies on the subpopulation of immune cells in patients with EDP indicate a dermal lymphocytic infiltrate of predominantly CD8 + T lymphocytes, with an upregulation of intercellular adhesion molecules 1 + and macrophages adjacent to extracellular melanin pigment (Gross et al., 1987). Both NB-UVB and tacrolimus may be effective to treat EDP due to their immunomodulatory effect on T cells and suppression of proinflammatory cytokines, including tumor necrosis factor-alpha, IL-17A, IL-6, IL-1, and IL-8 in the epidermis and upper part of the papillary dermis (Schneider et al., 2008).

Conclusion

In our review, we found that EDP and LPP overlap significantly in their histologic presentation. We recommend using clinical history, morphology, and distribution to differentiate EDP from LPP, and histology can be used to rule out other etiologies. EDP lesions are more likely to be generalized and located on the trunk, upper extremities, face, and neck. LPP lesions generally originate near the temples and pre-auricular areas of the face and are localized to photo-exposed areas such as

Table 3
Comparison of erythema dyschromicum perstans and lichen planus pigmentosus

	Patient characteristics	Clinical morphology	Distribution	Pathology	Treatment options
EDP	Female predominance; intermediate to dark skin types	Blue-gray or ashy-brown macules Erythematous rash prior/active red border in some	More likely to be widespread with truncal predominance but can involve face, neck, arms, legs	Hyperkeratosis, thinned epidermis, basal vacuolization, perivascular infiltrate, melanophages present	Topical corticosteroid Topical tacrolimus Narrowband UVB Oral dapsone
LPP	No sexual predominance Darker skin types (more frequently found in patients of Indian descent)	Dark brown irregularly shaped and ill-defined macules	More likely to be localized to the face and neck (sun-exposed areas) Often starts on temples and preauricular area Flexural areas can be involved	Hyperkeratosis, thinned epidermis, basal vacuolization, perivascular infiltrate, melanophages present	Topical corticosteroid Topical tacrolimus Photo-protection/ sun avoidance Topical tretinoin Low dose isotretinoin Oral dapsone

EDP, erythema dyschromicum perstans; FLT, fractional laser therapy; LPP, lichen planus pigmentosus; UVB, ultraviolet B

the face and neck. In LPP, when lesions are present on areas other than the face and neck, lesions are likely in flexural areas. EDP presents with blue-gray, regularly shaped, hyperpigmented macules compared with dark brown, irregularly shaped, and ill-defined hyperpigmented macules in LPP. EDP was more likely to present with erythematous raised active borders than LPP.

We conclude for EDP, NB-UVB and tacrolimus are promising and effective treatments with significantly fewer side effects compared with clofazimine, and opposed to LPP, for which sun-avoidance is recommended. Treatment with isotretinoin, dapsone, and griseofulvin led to the recurrence of EDP after discontinuation of these drugs in several cases. Lasers were consistently ineffective treatments. The histopathologic description of EDP presentation was consistent across four studies, but treatment outcome data were largely limited to case reports and studies with a maximum of 8 patients in each study, which indicates that larger studies to evaluate treatment outcomes are needed.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijwd.2018.08.003.

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