

Patch testing and Histopathology in Thai patients with hyperpigmentation due to Erythema dyschromicum perstans, Lichen planus pigmentosus, and Pigmented contact dermatitis

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Summary

Background: Erythema dyschromicum perstans (EDP)/Ashy dermatosis (AD), Lichen planus pigmentosus (LPP) and Pigmented contact dermatitis (PCD) are common skin diseases featuring abnormal pigmentation which have overlapping clinical features.

Objective: To search for differences in the natural history, clinical features, histopathology and relevant contact allergens in patients those were clinically diagnosed as AD, LPP and PCD in our outpatient clinic.

Method: Materials and Methods: 43 patients were enrolled into the study. Patients' demographic details, histological findings, DIF staining, provisional and histology diagnosis were recorded. Closed patch tests with standard fragrance and cosmetic series allergens were performed in all patients.

Result: 36 of the patients were female and all of them had dark skin complexions (Fitzpatrick's skin type IV-V), as normally found in AD and LPP. The most common histological finding was pigmentary alteration followed by lichenoid infiltration. DIF staining was positive in 6 out of 21 cases, the most common pattern being IgM colloid bodies. Patients with a provisional diagnosis of AD and LPP had positive patch tests in 40 and 36.36% of cases, respectively.

Conclusion: We have found some similarities and differences between these 3 clinically and histologically overlapping pigmentary disorder. Clinical history, histopathology and DIF are necessary together for making the diagnosis. Patch testing should be conducted in all cases that present with AD or LPP. (*Asian Pac J Allergy Immunol 2014;32:185-92*)

Key words: ashy dermatosis, lichen planus pigmentosus, pigmented contact dermatitis, patch test, histopathology

Introduction

Widespread or localized hyperpigmentation is associated with varieties of conditions and may be due to genetic or systemic factors such as metabolic, endocrine, chemical, physical, nutritional, post inflammatory or neoplastic. Skin inflammatory reactions disturb the dermoepidermal junction causing melanin to pass into the dermis giving rise to persistent hyperpigmentation. Many skin diseases also have similar clinical manifestations, for instances, lichen planus pigmentosus (LPP), ashy dermatosis, fixed drug eruption, etc. Hyperpigmentation may also occur in the course of allergic and irritant contact dermatitis. History taking, thorough physical examination, histological findings and proper investigations are required to differentiate between these conditions.

Ashy Dermatitis, lichen planus pigmentosus and pigmented contact dermatitis are hyperpigmented skin problems which are major problem in our institute because of their overlapping clinical features, varying histologic pictures and, especially, the lack of definite criteria to distinguish one from the others. Thus, the objective of this study was to search for differences in clinical appearances, histopathology, including direct immunofluorescence studies, and patch testing in the patients who were diagnosed as either of these diseases.

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Methods

The Institute of Dermatology, Thailand, is a tertiary referral center for patients with dermatologic problems under the department of medical services, ministry of public health, Thailand. Ethics committee and institutional board review approved this descriptive cross-sectional study before patient enrollment. We performed the study on patients who had attended our clinic between January 2002 and September 2012 with a provisional diagnosis either of ashy dermatosis or erythema dyschromicum perstans, lichen planus pigmentosus, or pigmented contact dermatitis. Possible causes of associated conditions with abnormal skin hyperpigmentation, such as thyroid disease, hepatitis, Addison's disease, etc. were excluded in all patients.

The topography, morphology, course, symptoms, location of lesions, and related external factors (drug intake, underlying diseases, contact substances, personal disease-related products or other factors) were analyzed. Histopathologic findings and diagnosis were assessed by a dermatopathologist in all 43 cases. The degree of pigmentary incontinence, presence of interface changes, severity of inflammation with lymphocytes, presence of other inflammatory cells, manifestation of spongiosis, changes of epidermal thickness and presence of civatte bodies were evaluated histologically. DIF was carried out in 21 patients.

Closed patch test was conducted in all patients on the upper back with an occlusion time of 2 days and the test was interpreted at 48 and 96 hours, according to ICDRG guideline. We used the routine standard cosmetic and fragrance series. Patient's personal products were also patched in suspected cases with proper preparation. A special metal set was requested in two patients with a suggestive history of metal allergy.

Follow up visits were scheduled at 1, 3 and 6 month after patch testing.

Fisher's exact test was used to analyze associations between provisional diagnosis, histological diagnosis, histological findings, and DIF and relevant patch test results.

Results

43 patients were enrolled in our study. 7 were male and 36 were female (age range 10-76 years, mean age 39.02 +/- 14.77 years). Most of the patients had dark skin complexions, reported as Fitzpatrick's skin type 4 (81.40%) and skin type 5 (18.60%). The duration of disease at presentation

ranged from 1 month to 10 years. The majority of patients, 29/43 (67.44%), had disease durations of 1 month to 2 years, while 14 patients (32.56%) had been symptomatic for more than 2 years. Fragrances (37.21%) and cosmetics (39.53%) were reported as personal products used by more than half of the patients. 2 patients gave a history of metal allergy, one being occupationally related and the other with a significant history of sensitivity to metal framed eyeglasses. Interestingly, one patient developed brown hyperpigmentation after prolonged use of anti-melasma cream. One patient also had abnormal pigmentation after taking Spirulina supplement products.

The face was the major initial site of presentation (46.51%), followed by the upper extremities (21.43%). Most of the patients had hyperpigmentation on sun exposed areas (63.83%); less commonly in normally covered areas (25.53%) or a generalized pattern (10.64%). The most common locations were the face (22.70%) and neck (21.28%). Slate-grey was the most common color of lesions at presentation (60.47%), while erythematous patches were found in 34.88%. One patient had a brownish patch on the face.

20 cases (46.51%) were clinically diagnosed as Ashy dermatosis, 11 as lichen planus pigmentosus (25.58%), 10 as pigmented contact dermatitis (23.26%) and other 2 as post inflammatory hyperpigmentation/PIH (4.65%).

Histological diagnoses were reported as Ashy dermatosis in 14 cases (35.26%), LPP in 11 cases (25.58%), and PIH in 14 cases (35.36%). The other cases were reported as chronic psoriasiform dermatitis, lichenoid drug eruption, dermal melanocyte and ochronosis. The patient diagnosed histologically as ochronosis had brownish hyperpigmentation on the face with a history of prolonged anti-melasma topical treatment. (Figure 1)

With regard to the histopathological findings, pigmentary alteration was found in all biopsy section except the one with diagnosis of ochronosis. Lichenoid infiltration is also another common findings, being present in 22 cases (51.16%, N=42). According to the official histological diagnosis, a lichenoid picture was also recorded 8 cases of ashy dermatosis (57.14 %, N=14) and 10 cases of LPP (90.9%, N=11), and 4 cases of PIH (28.5%, N=14). This inflammation was not statistically correlated with positive patch test reactions ($P = 0.053$). Necrotic keratinocytes were found in 10 cases (23.8%, N=42), 5 of which were histologically

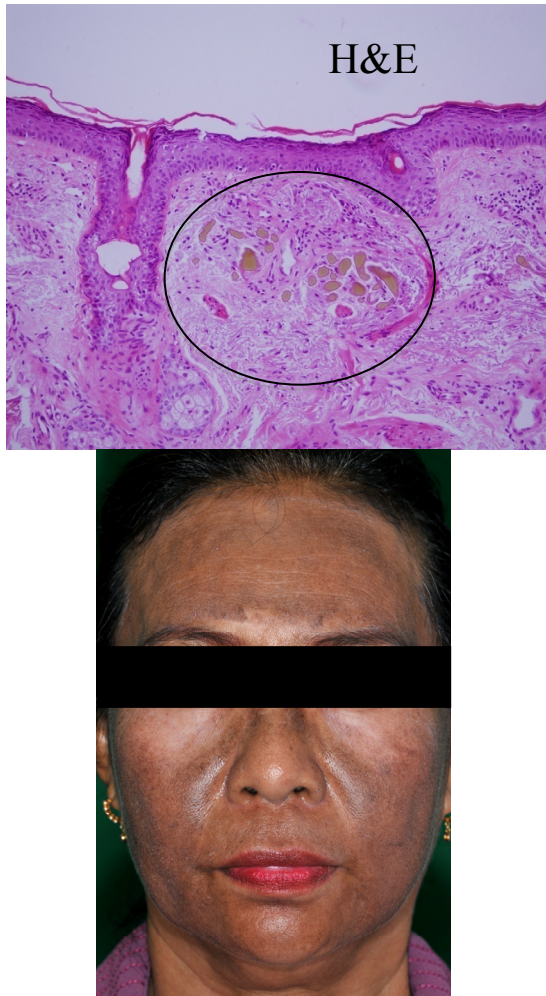


Figure 1. 61 year-old female patient with a brownish patch on her face for 5 years and with history of long term use of whitening cream for her melasma. Histological findings: pigmented lesion containing banana-shaped ochre-colored deposits in the dermis. She was diagnosed with exogenous ochronosis.

diagnosed as LPP, 2 as ashy dermatosis, 2 as PIH, and 1 as lichenoid drug eruption. Epidermal spongiosis was found in only 6 cases (14.2%, N=42), 2 with LPP, Ashy, and 4 with PIH. Dermal infiltration with lymphocytes was a common finding in all sections, with eosinophils in only 1 case with a diagnosis of LPP. Epidermal changes were recorded in 5 cases, acanthosis in 4, and atrophy in one with a diagnosis of lichenoid drug eruption. None of these histological finding was statistically associated with positive results in closed patch testing as assessed by Fisher's exact test.

DIF showed positive results 6 out of 21 cases (28.57%). All of the positive cases showed colloid

IgM. One case with a histological diagnosis of a lichenoid drug reaction was positive for IgM and fibrinogen in a DEJ pattern. In each case the DIF pattern was not significantly associated with positive patch test result. (p IgM=0.412 IgG=0.488 fibrinogen = 0.488)

Closed patch testing was relevantly positive in 21 of 43 cases (48.83%). The most common allergen was Nickel sulfate hex hydrate (8 cases), following by mixed fragrances II in the standard series set (3 cases). Other reported allergens are shown in Tables 1, 2 and 3. Cases with a provisional diagnosis of ashy dermatosis had positive test results in 8 patients (40%, N=20). 4 cases of LPP (36.36% N=11), 8 of PCD (80%, N=10), and 1 of PIH (50%, N=2) also had positive patch tests. The special metal set was also used in 2 patients with a significant history of metal contact allergy. Both of these showed relevantly positive reactions to manganese chloride. 50% spirulina algae supplement in petrolatum produced a positive test in one patient who developed symptoms after drinking the supplement, and bronopol also produced a positive reaction in this patient. (Figure 2)

Table 1. Allergens in the standard series with positive patch test results

Standard series	case
Potassium dichromate	1
Neomycin sulfate	
Thiuram mix	
4-Phenylenediamine base (PPD)	1
Cl+Me-isothiazolinone (Kathon CG)	
Benzocaine	
Formaldehyde	
Colophony	1
Balsam of Peru	1
Mercaptobenzothiazole (MBT)	
Black rubber mix	
Wool alcohols	
Mercapto mix	
Epoxy resin	
Paraben mix	1
4-tert-Butylphenol formaldehyde resin	
Fragrance mix (emulsifier:Sorbitan sesquioleate 5%)	1
Ethylenediamine dihydrochloride	
Quaternium 15 (Dowicil 200)	1
Nickel sulfate hexahydrate	8
Cobalt(II) chloride hexahydrate	2
Fragrance mix II	3

Table 2. Allergens in the fragrance series with positive patch test results

Fragrance series	case
Geraniol	
Benzyl salicylate	1
Vanillin	
Cinnamic alcohol(CIN NAMYLCOHOL)	2
Cinnamic aldehyde (CIN NAMAL)	2
Eugenol	
Amylcinnamaldehyde (AM YL CINNAMAL)	
Isoeugenol	
Benzyl alcohol	
Hydroxycitronellal	
Jasmine synthetic	
Ylang-Ylang oil	1
Lavender absolute (LAV ANDULA)	
Lyral	
Musk mix	
Balsam Tolu (MYROXYLON TOLUFERUM)	

Discussion

Various skin and systemic diseases may be causative factors for abnormal localized or generalized skin hyperpigmentation. Ashy dermatosis and Lichen planus pigmentosus are commonly diagnosed skin disorders by dermatologists in Asian country, including Thailand. Pigmented contact dermatitis, a non-eczematous allergic contact dermatitis, is another clinically overlapping picture that could be missed in diagnosis.

Ashy dermatosis (AP) was first described in 1957 by Ramírez as an asymptomatic, slowly progressive, ashy-colored, macular hyperpigmentation and was referred to as “dermatitis cenicienta”.¹ The disorder was subsequently renamed erythema dyschromicum perstans (EDP) or ashy dermatosis. Some authors consider AP to be a separate entity from lichen planus pigmentosus.² Because of the overlapping clinical and histologic features, this view is still controversial. AP as a variant of lichen planus (LP) has been occasionally reported in the literature.^{3,4} AP is described among patients with darkly pigmented skin in Latin American and Asian races with a female predominance. Most cases present with slow progressive gray, gray–brown or gray–blue macules and patches which are commonly found on the face, arms, neck, and trunk in a pityriasis rosea-like pattern. The erythematous peripheral ring is actually uncommon. Generalized hyperpigmentation could develop in the late stage of

Table 3. Allergens in the cosmetic series with positive patch test results

cosmetic series	case
4-Chloro-3-cresol (p-CHLORO-m-CRESOL)	
4-Chloro-3,5-xyleneol (PCMX)	
Propyleneglycol	
Sorbitan sesquioleate	
Euxyl K 400 (ny konc.-99)	
Amerchol L 101 (LANOLN ALCOHL)	1
DMDM Hydantoin	
Polyoxyethylenesorbitan monooleate	
Isopropyl myristate	
Stearyl alcohol	
Cetyl alcohol	
Propyl gallate	
Propyl-4-hydroxybenzoate	
Triethanolamine	
Phenyl salicylate (Salol)	1
Propolis (PROPOLIS CERA)	1
n-Butyl methacrylate	
Abitol (HYDROABIETYLA LCOHOL)	
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	1
2-Phenoxyethanol	
Methyldibromoglutaronitrile (MDBGN)	1
Tea Tree Oil ox (ny-00)	

the disease. The etiology of ashy dermatosis is unknown. Some authors have reported associations with ammonium nitrate, whipworm infestation, HIV seroconversions, and administration of contrast medium (barium -sulfate).⁵ Vacuolization of the basal layer, occasional colloid bodies and a lichenoid lymphocytic infiltrate of a varying degree are typically seen. These histologic findings may be seen even in peri-lesional normal-appearing skin, suggesting that the pathologic processes have already begun in these areas.

Bhutani et al first described lichen planus pigmentosus in 1974.⁶ LPP, an uncommon variant of LP, is commonly found in young to middle-aged female adults with skin phototypes III–V, especially patients of Indian, Latin America or Middle Eastern origin. Clinically it presents as irregularly shaped or oval brown to gray–brown macules and patches in either sun-exposed areas (especially the forehead, temples and neck) or intertriginous zones with asymptomatic to mild pruritis or a burning sensation. Early lesions with an erythematous border in AP are not a feature of LPP, which helps to distinguish between these two conditions, even though it is uncommon. The etiology of LPP is

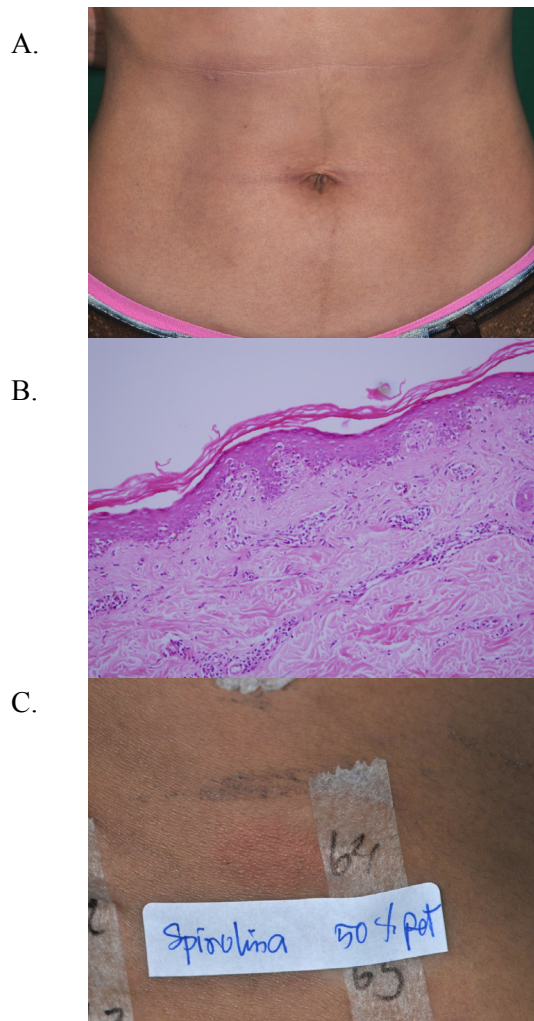


Figure 2. A: 31 year-old female patient with a generalized rash after taking spirulina supplement
 B: histopathology: epidermal necrotic keratinocytes with melanophages in papillary dermis corresponding to ashly dermatosis (histological official report)
 C: Positive patch test with 50% spirulina in petrolatum. This patient was finally diagnosed as 'systemic contact dermatitis'.

unknown. The photodistribution in some patients suggests that UV light can play a pathogenic role, and topical application of mustard oil (which contains allyl isothiocyanate, a potential photosensitizer) and amla oil have been proposed as possible inciting agents. 20% of cases have an association with classic LP.⁵

As previously discussed, the existence of these two diseases as separate entities is controversial. Histopathological findings have also been described,

such as basal vacuolar degeneration of the basal cell layer, a perivascular mononuclear cell infiltrate in the upper dermis, and increased epidermal melanin, dermal melanophages. Lichenoid reaction and colloid bodies are more pronounced in LPP and only occasionally seen in AD.² DIF in active lesion of AD has been reported as positive for IgM, IgG and fibrinogen and C3 staining of colloid body is also seen in LPP.

Pigmented contact dermatitis (PCD) is a non-eczematous variant of contact dermatitis. It was firstly described by Osmunsen, a Danish dermatologist, in 1970.⁷ He identified sensitization to 'spyraxoline', a component of optical whitener as the cause of an epidemic of melanosis in Copenhagen. PCD is characterized by erythema, papules, swelling, and itching with little or no sign of dermatitis leading to hyperpigmentation by frequent and repeated contact with very small amounts of the contact sensitizer, mainly in textiles, fragrances or washing materials.⁸ Pigmented cosmetic contact dermatitis (PCCD) is a variant of PCD proposed by Nakayama et al.,⁹ the only differences being the causative allergen are the many ingredients in cosmetics such as fragrances (e.g. benzyl salicylate, cinnamic derivative, balsam of Peru), pigments, coal tar dyes, and lanolin applied to the sites affected. Diffuse or patchy brown pigmentation is also the main clinical manifestation with predilection for the face and forehead. The main histology of PCD is basal cell liquefaction accompanied by the formation of melanophages in the papillary dermis. Nakayama et al. believe the liquefaction is provoked by accumulation of low concentrations of fragrances producing type 4 allergic cytolytic reaction in the epidermal basal layer. The melanin from destroyed cells is sprayed into papillary dermis and ingested by macrophages. This could be suggestive of a lichenoid allergic reaction rather than a toxic reaction.

In our study, Most of patients were in the middle aged group with a female preponderance, dark complexion skin and had a chronic course of their disease, mostly around 1-2 years but sometimes as long as 10 years. The face was the major site of initial presentation and the most common site of involvement. Hyperpigmentation can be found on sun exposure skin more than normally covered areas, so that could be another aggravating factor. A few patients may have erythematous

Provisional Diagnosis VS Positive Patch Test

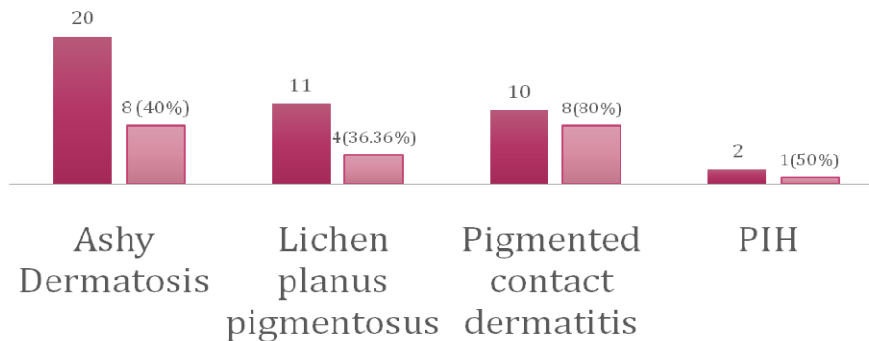


Figure 3. Comparison between provisional diagnosis and actual cases with positive patch test results by diagnosis. (PIH = post inflammatory hyperpigmentation)

lesions before developing slate grey pigmentation. Only a few patients had the annular lesions of AD, but neither the classic lesions of AD, erythematous rimming, nor the lesions of classic LP were found in our patients. One case in our study had brownish pigmentation on both cheeks with history of prolonged use of bleaching agents. This patient was subsequently histologically diagnosed as ochronosis. (Figure 1)

Exogenous ochronosis is a clinical reaction, which occurs in dark skinned patients and is caused by a number of chemicals such as phenol, hydroquinone, and resorcinol mostly when used in too high a concentration.¹⁰ This phenomenon develops after a few years and takes place when the melanocytes have overcome the bleaching effect of the chemicals. Some authors have reported positive patch test reactions, which are probably allergic reactions with a secondary hyperpigmentation effect, but an association with allergic contact hypersensitivity to hydroquinone is infrequent and our case had a negative patch test result.¹¹

Provisional clinical diagnoses were made of Ashy dermatosis, LPP, PIH, and PCD. Ashy dermatosis seemed to be the most frequently used term among dermatologists in our clinic. LPP might be diagnosed less often because patient should have more evidence of classic LP and that were not found in this study. PCD was diagnosed in 10 cases in our study by thorough history taking. Those who were diagnosed as PCD had positive patch tests in 80% of cases, while in the other cases provisional diagnosed as AD, LPP or PIH had positive patch test results in about half of the cases. These should prompt us to keep in mind patch testing in some recalcitrant cases.

All of the cases had melanin incontinence and melanophages corresponding to the clinical hyperpigmentation. More than half of the cases had lichenoid band-like reactions in the upper dermis, especially those histologically diagnosed as LPP (90%) and ashy dermatosis (57%). This might support the concept expressed by Covit et al.¹² that this reaction in AD is a manifestation of prolonged damage to the basal cell layer, as seen in other conditions with a lichenoid pattern. AD and LPP may apparently be the same entity, as reported in other studies. 14 of 23 patients (60%) with lichenoid reaction had positive results on patch testing and only a few patients had spongiosis. These findings support another concept of Tomotsu et al.¹³: that pigmented contact dermatitis is caused by exposure of small amounts of contact allergen everyday which is insufficient to provoke ordinary symptoms of contact dermatitis, such as spongiosis. Basal liquefaction was commented on in this review as a major histological feature resulting in melanin dropping from cytolysis of epidermal basal cells. We believe that PCD is another disease which has prolonged damage of the basement membrane zone, as seen in AD and LPP, but has different causative factors. We also used Fisher's exact to look for correlation between lichenoid infiltration and spongiosis with cases in which there were positive patch tests but the result were not statistically significant.

Direct immunofluorescence staining was performed and was positive in one third of cases (6 of 21 cases). IgM in a colloid pattern is the most common DIF staining picture among these patients. Positivity of DIF could not differentiate AD and

LPP from PCD. Therefore, this procedure might not be worth performing in all cases with diffuse hyperpigmentation.

Interestingly, patch testing showed relevant positive results in about half of the patients in our study. As discussed earlier, cases with either a provisional diagnosis or histological diagnosis of AD or LPP also showed positive results about 40% of cases, so we may conclude that a clinical or histologically assessment cannot differentiate exclude the possibility of a diagnosis of pigmented contact dermatitis. Alternatively, these contact allergens may be the causes of LPP or AD. A comparison between the provisional diagnosis and positive patch results is shown in Figure 3.

As commonly seen worldwide in contact dermatitis clinics, Nickel sulfate hex hydrate is most common contact allergen in our study. However, another study which included screening by patch testing in Israel,¹⁴ showed perfume was the most common relevantly positive allergen, followed by nickel sulfate. The other reported contact allergens are shown in the Table. Our standard series had a higher positive yield (15 cases), as compared to fragrances (3 cases), cosmetics (3 cases) and metals (2 cases), whereas in the study in Israel, fragrances and cosmetics gave a low yield of positive results.

One patient gave a history of abnormal hyperpigmentation on her face, chest, trunk, and upper arms after taking spirulina supplement. Patch testing showed relevant positivity to spirulina in pet. (Figure 2) Many of the products claimed to contain 'spirulina' are from *Arthrospira* sp., which is a Cyanobacteria, commonly but erroneously known as blue-green algae, and are common inhabitants of freshwater lakes and reservoirs throughout the world. Stewart et al.¹⁵ conducted a pilot study in 39 patient with allergens from various cyanobacteria in aqueous suspensions and concluded that hypersensitivity reactions to cyanobacteria appear to be infrequent in both the general and dermatological outpatient populations. Cyanobacteria-associated cutaneous eruptions in susceptible individuals are primarily irritant reactions, and the role of immediate hypersensitivity or delayed contact hypersensitivity responses is not at all clear. This could be a limitation in the accurate diagnosis since cyanobacterial allergens are not available in Thailand.

Six months after patch testing, most of patients claimed improvement in colors, itchiness and the

area of involvement. None of the patient had total clearance of hyperpigmentation.

Unfortunately, our study was performed in a limited number of cases but seems to be the largest to include histopathology and patch testing in patients with these three skin diseases. Furthermore, clinical and histological diagnoses were made by from clinician experiences recorded in the OPD notes and histological official histological reports and this might bias the exact diagnosis in each patient. Closed patch tests were individually interpreted with careful history taking to identify the relevant causative allergens. This might be the case in allergic contact dermatitis with secondary pigmentary alteration but we also believe that lichenoid band-like infiltration in the dermis could provide some information about prolonged damage to the basement membrane zone by small amounts of allergen. The follow-up time was too short (6 months) to determine prognosis in those with relevant result. A larger study with more patients and a longer period of follow-up time should be conducted to clarify the situation.

Conclusion

AD, LPP and PCD are skin disorders with skin hyperpigmentation presenting with overlapping clinical features. Systemic involvement should be excluded before these diagnoses are made. Clinical characteristics, histopathology and DIF results which have been claimed in literatures as specific finding in AD and LPP do not rule out cases with pigmented contact allergy. We would recommend thorough history taking about systemic medication, and contact substances in these patients to facilitate appropriate management. Closed patch testing using the standard series with or without additional allergens, such as fragrances, cosmetics, and metals may provide more valuable information in patients with either histological changes suggesting contact dermatitis and those who are recalcitrant to treatment. Avoidance of the actual contact sensitizer may be beneficial in curing the hyperpigmentation.

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