

Report

Atopic labial pigmentation: a new diagnostic feature in Asian patients with atopic dermatitis

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Abstract

Background Pigmented lesions on the lips can be caused by physiological or pathological factors, along with exogenous or endogenous factors. Many patients with atopic dermatitis (AD) and labial pigmentation are seen in clinical practice. The aim of our study was to further explore the association of labial pigmentation and AD.

Methods We performed a retrospective chart review of patients who visited the Department of Dermatology at Kyung Hee Medical Center, Seoul, Korea, from January 1 to December 31, 2016. The study consisted of 178 patients with AD and a control group of 178 age- and sex-matched patients without AD.

Results The patients with AD had both a significantly higher prevalence of labial pigmented lesions and a significantly higher number of labial pigmented lesions than was observed in the control group. Moreover, the pigmented lesions were found mainly in the middle section of the upper lip and showed multifocal distribution. The patients with AD and labial pigmentation were significantly younger at the onset of AD, showed a greater association with allergic disorder, and had a higher immunoglobulin E (IgE) level than patients without labial pigmentation.

Conclusion Our findings strongly suggest that labial pigmentation occurs in patients with AD. Although labial pigmentation was not present in all patients with AD, this might be a particularly helpful diagnostic feature of AD in Asian patients.

Introduction

Atopic dermatitis (AD) is a chronically relapsing, inflammatory skin disease and is characterized by intense pruritus, dry skin, and typically distributed eczematous skin lesions. The diagnosis of AD is based on the presence of various basic and minor features established through physical examinations by Hanifin and Rajka.¹ Recently, the diagnostic significance of minor features has been shown to vary according to race and age, but minor features and other signs provide important clues for the diagnosis of AD.^{2–4} For example, although not seen in all AD patients, exfoliative cheilitis and recurrent crackled keratotic digital pulpitis can be important features for diagnosis.⁵ Therefore, it is important to uncover new minor features or signs that are often associated with AD.

Pigmented lesions on the lips can be caused by physiological or pathological factors, along with exogenous or endogenous factors. To our knowledge, there was only one report on the association of labial pigmentation and atopic dermatitis, although many patients with AD and labial pigmented macules or patches are seen in clinical practice.⁶ There are also only a few case reports that describe patients with AD who develop

labial melanotic macules after topical application of tacrolimus ointment 0.1%.^{7,8} Therefore, we investigated the incidence of labial pigmentation in Asian patients with and without AD. Furthermore, we compared clinical features between AD patients with labial pigmentation and AD patients without labial pigmentation.

Materials and methods**Study design**

For patient identification, we performed a retrospective chart review of patients who visited the Department of Dermatology at Kyung Hee Medical Center (KHMC), Seoul, Korea, from January 1 to December 31, 2016. The Ethics Committee of KHMC (institutional review board approval #KHMC IRB 2017-07-076) approved the study.

Subjects

The study included 178 patients with AD and a control group of 178 age- and sex-matched patients without AD. All 178 patients were diagnosed with AD in accordance with the AD diagnostic criteria established by Hanifin and Rajka. We excluded subjects

with a history of any of the following diseases that can cause pigmented lesions on the lips: Peutz-Jeghers syndrome, Addison's disease, McCune-Albright syndrome, hyperthyroidism, myxoma syndromes, LEOPARD syndrome, and Nelson syndrome. Subjects who had undergone implantation of a foreign substance including metallic materials, such as lead, mercury, and amalgam, were also excluded. Subjects who had taken specific drugs, such as arsenic, phenothiazines, minocycline, cotrimazole, and tetracycline, were also excluded. Control subjects were selected from patients who did not have AD and visited our hospital dermatology clinic for other conditions from January 1 to December 31, 2016 (Table S1). Subjects who were diagnosed with pigmentary disorders were excluded. All subjects included in the study were Fitzpatrick skin type III or IV.

Clinical assessments

Complete medical histories, physical examinations, and laboratory test results on all subjects were obtained. For patients with AD, age, sex, onset of AD, family history of AD, comorbid allergic disorder (such as allergic rhinitis, asthma, and allergic conjunctivitis), and total IgE level were obtained through chart review. IgE levels above 300 IU/ml were considered elevated.^{9,10} The severity of AD was evaluated using the scoring atopic dermatitis (SCORAD) index and defined as: mild, less than 25 points; moderate, 25–50 points; and severe, over 50 points. After selecting the subjects, the number, location, age of onset, and distribution of pigmented macules or patches in the subjects with labial pigmentation were examined and recorded with a digital camera (EOS 80D DSLR, Canon Inc., Japan). The location of the pigmentation was divided into six sections: right-side, middle, and left-side of upper and lower lips, respectively. The sections were based on the peaks of the Cupid's bow where Cupid's bow and the philtral columns meet. We described the distribution of pigmented lesions in three ways. 'Focal' was defined as macules on one section of the lip (Fig. 1a), even if there were multiple macules within that one section. 'Multifocal' was defined as macules on two or more sections of the lip (Fig. 1b). 'Diffuse' was defined as macules or

patches with irregular edges that were widely distributed in some sections (Fig. 1c).

Statistical analysis

The data were analyzed using the chi-square and Mann–Whitney tests. A *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical features of atopic labial pigmentation

A comparison of 178 patients with AD and 178 control subjects without AD showed significant differences in prevalence, number, and distribution of labial pigmented lesions (Table 1). Sixty-one of 178 patients with AD (34.3%) had labial pigmentation. The prevalence of labial pigmentation in patients with AD was significantly higher than the prevalence of labial pigmentation in the control group (27 of 178 patients, 15.2%). The number of labial pigmented macules or patches was also significantly higher in the patients with AD (3.60 ± 0.33) than in the control group (1.07 ± 0.71). The most common locations of labial pigmented macules or patches were different between the two groups. In the AD group, they were commonly found in the middle section of the upper lip, while in the control group they were commonly found in the middle section of the lower lip. Nearly all patients from both groups did not know the exact timing of onset. In the AD patient group, the focal, multifocal, and diffuse distributions of labial pigmentation were observed in nine patients (14.8%), 41 patients (67.2%), and 11 patients (18.0%), respectively. However, in the control patient group, the focal, multifocal, and diffuse distributions of labial pigmentation were observed in 24 patients (88.9%), 3 patients (11.1%), and 0 patients, respectively.

Comparison of clinical characteristics of patients with and without atopic labial pigmentation

Within the AD patient group, we compared the clinical characteristics between the subset of 61 patients with labial



Figure 1 Distribution of labial pigmentation: (a) focal: macules in one section of the lip; (b) multifocal: macules on two or more sections of the lip; (c) diffuse: macules or patches with irregular edges and widely distributed in multiple sections of the lip

Table 1 Clinical features of labial pigmentation in patients with and without AD

	Patients with AD	Patients without AD	P-value
Number of patients with pigmentation	61 (34.3%)	27 (15.2%)	<0.001*
Number of macules or patches (mean $\pm$ SE)	3.60 $\pm$ 0.33	1.07 $\pm$ 0.71	<0.001*
Location of pigmentation most common site	Middle side of upper lip	Middle side of lower lip	
Age at onset	Unknown, in most cases	Unknown, in most cases	
Distribution			
Focal	9 (14.8%)	24 (88.9%)	<0.001*
Multifocal	41 (67.2%)	3 (11.1%)	
Diffuse	11 (18.0%)	0 (0%)	

AD, atopic dermatitis; SE, standard error.

*Difference between groups is statistically significant ($P < 0.05$).

Table 2 Characteristics of AD patients with and without labial pigmentation

	AD patients with labial pigmentation (n = 61)	AD patients without labial pigmentation (n = 117)	P-value
Age (y) (mean $\pm$ SE)	22.8 $\pm$ 1.02	21.7 $\pm$ 1.07	0.218
Sex			
Female	30 (49.2%)	62 (53.0%)	0.629
Male	31 (50.8%)	55 (47.0%)	
Age at onset of AD (mean $\pm$ SE)	8.48 $\pm$ 1.05	11.9 $\pm$ 0.94	0.018*
Family history of AD	19 (31.2%)	34 (29.1%)	0.773
Allergic disorder	25 (41.0%)	31 (26.5%)	0.048*
IgE (IU/ml) > 300	36 of 49 (73.47%)	47 of 89 (52.81%)	0.018*
Severity of AD			
Mild	2 (3.3%)	9 (7.7%)	0.203
Moderate	28 (45.9%)	63 (53.8%)	
Severe	31 (50.8%)	45 (38.5%)	

Allergic disorder, one or more of the following: allergic rhinitis, asthma, allergic conjunctivitis.

AD, atopic dermatitis; SE, standard error.

*Difference between groups is statistically significant ($P < 0.05$).

pigmentation and the subset of 117 patients without labial pigmentation (Table 2). There were no significant differences between the age or the sex in the subset of patients with labial pigmentation (age 22.8 $\pm$ 1.02 years; female 49.2%; male 50.8%) and the subset of patients without labial pigmentation (age 21.7 $\pm$ 1.07 years; female 53.0%; male 47.0%). There was a significant difference in the age of onset of AD between the two patient subgroups: AD was diagnosed at an earlier age in the subset of patients with labial pigmentation (age 8.48 $\pm$ 1.05 years) than the subset of patients without labial pigmentation (age 11.9 $\pm$ 0.94 years). There was no significant

difference in family history of AD between the two patient subgroups. Comorbid allergic disease was significantly more frequent in the subset of AD patients with labial pigmentation (41.0%) than in the subset of AD patients without labial pigmentation (26.5%). The severity of AD according to SCORAD was not significantly different between the two subgroups.

Signs in the AD patient group with atopic labial pigmentation

We examined the signs and minor features of the AD patient group with labial pigmentation. Most patients had facial and neck lesions; xerosis, cheilitis, and lichenification on the philtrum were observed in more than half of the patients, and we observed a difference in severity among the patients. Many patients also had Denie-Morgan folds, anterior neck folds, orbital darkening, facial erythema/pallor, and hand-foot eczema. Some patients showed Hertoghe's sign, nipple eczema, white dermographism, and a tendency toward cutaneous infections. In rare cases, we observed food intolerance, recurrent conjunctivitis, and cataract. Notably, lichenification on the philtrum was observed in many patients with labial pigmentation, which differs from patients with general AD (Fig. 2).

Discussion

In our study, labial pigmentations were more frequent in the AD patient group than in the control patient group, tended to appear as several macules or patches, and were most common in the middle section of the upper lip. As opposed to the focal distribution of labial pigmentation within the control patient group, multifocal distribution of labial pigmentation was most common in the AD patient group. There are some reports that describe the clinical features of cases with labial pigmentations. Span *et al.* reported a series of 41 cases of melanotic lesions of the lip between 1980 and 1984.¹¹ In those 41 cases, the lesions were most often found on the lower lip of young adult women. In a review of 79 cases by Gupta *et al.*,¹² labial pigmentation was commonly present in adult women within the central third of the

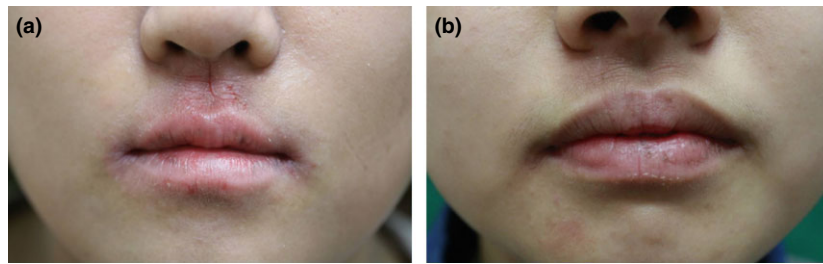


Figure 2 Atopic dermatitis patients with labial pigmentation showed characteristic lichenification on the philtrum

lower lip. Other reports have shown consistent results.^{13–15} In our study, the middle section of the lower lip was the most common area for labial pigmentation in the control patient group without AD, which was consistent with previous studies. However, in the AD group, there was a significant difference in the prevalence, number, location, and distribution of pigmented lesions.

The etiology of labial pigmentation can be physiological or pathological and result from exogenous or endogenous causes. Therefore, the color, location, distribution, and duration of pigmented lesions as well as drug treatments, family history, and changes in the pattern of pigmented lesions are important for differential diagnosis. Dark or black pigmented lesions can be focal, multifocal, or diffuse macules and can include the following list of conditions: racial pigmentation, melanotic macule, melanocytic nevus, blue nevus, smoker's melanosis, oral melanoacanthoma, pigmentation by foreign bodies or induced by drugs, Peutz-Jeghers syndrome, Addison's disease, and oral melanoma.¹⁶ Therefore, we selected subjects by excluding patients with pigmented lesions caused by external factor or systemic disease in this study. We described the macules or patches associated with AD as 'atopic labial pigmentation.'

The exact etiology of atopic labial pigmentation is unknown. However, sun exposure is thought to cause labial melanotic macules. Since most lesions were found within the central third of the lower lip, which is a site receiving maximal sun exposure, it is suggested that ultraviolet radiation might play a role in the development of labial melanotic macules.¹² Our study showed that there is a higher prevalence of labial pigmentation and a difference in the most prevalent location of labial pigmentation in patients with AD than in patients without AD. The reason for this is unknown, but a defect in the function of the skin barrier that blocks ultraviolet radiation could be an explanation. Ishikawa *et al.*⁶ reported that 59 of 106 patients (56%) had a combination of labial melanotic macules and AD. They reported that the lips of AD patients were markedly dry and scaly and proposed that the mucous membrane was damaged as the lips were rubbed together, which presumably caused the pigmentation. In our study, the most prevalent location of labial melanotic macules in patients with AD was the middle section of the upper lip, which is the most prevalent site of atopic cheilitis. In more

than half of the subjects, lichenification was observed in the philtrum and in the areas adjacent to the middle part of the upper lip. Also, allergic disorder, including allergic rhinitis, was significantly more common in patients with atopic labial pigmentation. These findings suggest that longstanding inflammation and friction contribute to the development of atopic labial pigmentation.

In addition, there were some reports on labial melanotic macule after application of topical tacrolimus.^{7,8} Although the exact mechanism is unknown, tacrolimus could induce melanocyte activation, both directly and by its immunosuppressive activity. In our study, most of the subjects did not know when labial pigmentation had first occurred, but two patients stated that they had macules at 8 and 11 years of age. These two patients could not completely rule out the association of labial pigmentation with tacrolimus because they had a history of tacrolimus treatment on the face and neck, including the perioral area, before the pigmented lesions occurred. However, careful follow-up would be necessary to evaluate the long-term evolution of labial pigmentation.

In patients with AD, pigmentary lesions can appear in areas other than the lips. For instance, pigmentary lesions can appear on the neck, which is called 'atopic dirty neck.' Atopic dirty neck was first proposed by Colver *et al.*¹⁷ in 1987 to describe acquired hyperpigmentation that predominantly affects the anterolateral aspects of the neck in patients with AD. An epidemiological and clinical study of atopic dirty neck from the National Skin Centre in Singapore showed that atopic dirty neck was present in about 14.3% of AD patients and was more common in Asian patients.¹⁸ In comparison, we observed that atopic labial hyperpigmentation was more common in AD than in atopic dirty neck. The pathology is thought to be due to frictional melanosis and post-inflammatory hyperpigmentation, similar to atopic labial hyperpigmentation.^{18,19}

In this study, we compared patients with AD and labial pigmentation to AD patients without labial pigmentation. We observed significant differences in the age at onset of AD, in the comorbidity of allergic disorder, and in IgE level. AD patients with labial pigmentation were younger at the onset of AD, showed more frequent allergic disorders, and had higher IgE levels than AD patients without labial pigmentation. In addition,

characteristic lichenification on the philtrum was observed. Other minor criteria and signs were similar to those observed in Korean AD patients.²⁰ All of our findings strongly suggest that labial pigmentation occurs in many patients with AD. Although labial pigmentation was not present in all patients with AD, this can be a particularly useful feature in patients without other characteristic physical findings at the time of evaluation.

This study is limited by a small sample size and selection bias. Because the Department of Dermatology is part of a general hospital, there could be a bias toward patients with moderate or severe AD. We performed chart reviews of medical history, physical examinations, photographic records, and dermoscopic images as needed but did not perform histopathologic studies. Additional well-controlled, long-term studies should be conducted to determine the association between AD and labial pigmentation and to ensure that labial pigmentation is a worthwhile new minor criterion for the diagnosis of AD.

In conclusion, atopic labial pigmentation is an important clinical feature in Asian patients with AD. Atopic labial pigmentation was more commonly found in patients with early onset of AD, allergic disorder, and high IgE level. Most of the patients with atopic labial pigmentation also had lichenification on the philtrum. The underlying pathology is assumed to be due to an increase in UV radiation exposure because of defects in the function of the skin barrier due to friction or inflammation. These findings suggest that atopic labial pigmentation is a new diagnostic feature in Asian AD patients and that an appropriate treatment of face and neck lesions would be helpful in preventing atopic labial pigmentation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Diagnoses of patients without AD (control group).

Table S1. Diagnoses of patients without AD (control group)

Diagnosis	Number of patients
Abrasion	2
Accessory nipple	1
Acne	39
Androgenic alopecia	5
Alopecia areata	6
Burn	3
Congenital melanocytic nevus	2
Eccrine poroma	1
Epidermal cyst	6
Erythema multiforme	2
Foreign body granuloma	1
Folliculitis	1
Hemangioma	4
Herpes simplex	1
Herpes zoster	2
Hidradenitis suppurativa	1
Hyperhidrosis	1

Ingrown nail	1
Irritated dermatitis	4
Juvenile xanthogranuloma	1
Keloid	6
Lichen striatus	2
Lupus erythematosus	4
Molluscum	3
Mucocele	3
Nevus flammeus	3
Nevus sebaceous	3
Onychomycosis	3
Pseudolymphoma	1
Psoriasis	11
Rosacea	6
Scar	8
Sebaceous hyperplasia	2
Seborrheic dermatitis	5
Seborrheic keratosis	3
Stevens–Johnson syndrome	1
Traumatic tattoo	1

Urticaria	11
Viral wart	18
Total	178