Original Article

Labial Melanotic Macules in Atopic Dermatitis: An Observational Study

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Abstract

Background: Labial melanotic macules (LMMs) are benign hyperpigmented macules of unknown etiology. They can affect one or both lips. Their description in patients with atopic dermatitis (AD) is limited in the published literature. **Objectives:** The aim of the study was to describe the clinical characteristics of LMMs developing in Canadian patients with AD. **Methods:** This observational retrospective study was conducted in the period from November 2012 to March 2014. All patients with AD and lip pigmentation were included. Data collected included demographics and other information including AD clinical features, presence or absence of cheilitis, and lip pigmentation characteristics. **Results:** A total of 27 patients with LMMs and AD were enrolled. The condition was more common in females with a female: male ratio of 2.4:1. The median age at presentation was 16 years, and a majority of patients were Asian and had a prior history of cheilitis. There was a strong correlation between the duration of cheilitis and duration of LMMs ($\rho = 0.735$, $P = 0.001$). Lesions presented as oval or round light-to-dark brown macules with a smooth border. The majority of patients (93%) had multiple LMMs and had involvement of both lips. **Conclusion:** Multiple LMMs are seen in Asian patients with AD and are associated with preceding cheilitis. LMMs secondary to AD should be considered among the differential diagnosis of lip pigmentation.

Keywords: Atopic dermatitis, cheilitis, labial, macules, melanosis, melanotic, pigmentation

Introduction

Labial melanotic macules (LMMs) are benign well-defined brown-to-black macules on the lips that affect up to 3% of the population.[1] Description of LMMs in patients with atopic dermatitis (AD) is limited to a few case reports and one case series in the English literature.[2,3] The aim of this study was to describe the clinical characteristics of LMMs in patients with AD.

Methods

This observational study was conducted at two dermatology clinics in Vancouver, British Columbia, Canada, during the period from November 2012 to March 2014. All enrolled patients had AD and LMMs. Patients with LMM who were not known to have AD were excluded. Documented information for each patient included the severity and duration of AD and demographic characteristics such as age, gender, Fitzpatrick skin phototype, and ethnicity. Additional recorded details included the presence of cheilitis, duration of cheilitis, duration of LMMs, number and size of LMMs, lip (s) affected, involved a portion of the lip, presence of pigmented macules on the oral mucosa or hands, and personal and/or family history suggestive of Peutz–Jeghers syndrome. LMMs were classified into four types: solitary macular, multiple macular, diffuse, and mixed (individual macules and diffuse pigmentation). The middle portion of the lip was defined as the area within the boundaries of the philtrum. The application for review was obtained by the Institutional Review Board in Vancouver, Canada.

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Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) Version 20 software (SPSS Inc., Chicago, IL, USA). Frequency and percentages were used to describe qualitative data. The test of normality of quantitative data was done using the Shapiro–Wilk test which revealed a non-normal distribution. Therefore, median values and interquartile ranges (IQRs) were used to describe quantitative data. To compare qualitative data, Chi-square or Fisher's exact test was used depending on the number of groups in each variable. The Mann–Whitney or Kruskal–Wallis test was performed to compare values of quantitative variables within categorical variables where appropriate. The test of correlation between quantitative variables was done using the Spearman correlation coefficient. Missing and nonspecific values for quantitative variables (e.g., many years) were not included in statistical analysis. The level of significance used was ≤0.05.

Results

A total of 29 patients with LMMs were enrolled. Two patients with LMMs were excluded as they had cheilitis and no clinical evidence of AD. The clinical characteristics of the 27 patients with AD and LMMs are shown in Table 1. The median age at presentation was 16 years (IQR 13–27) and more than half of patients were in their second decade of life. Females were more commonly affected (70%) with a female: male ratio of 2.4:1. A majority of patients were Asian (93%) with Fitzpatrick skin phototype III (89%). Three patients had a first-degree relative with clinically documented findings of AD and LMMs [Table 1].

The median age at onset of LMMs was 12.5 years (IQR 8.5–21), with a median duration of 2 years (IQR 1–4). All patients except one (96%) had a history of cheilitis preceding the development of LMMs. The LMMs developed at a median duration of 3 years from the onset of cheilitis. There was a strong correlation between the duration of cheilitis and duration of LMMs ($\rho = 0.735$, $P = 0.001$). Lesions presented as oval or round brown macules with a smooth border. Multiple macular LMM was the most common type seen (93%) [Figure 1a]. One patient had the solitary macular type [Figure 1b] and another had a mixed type [Figure 1c]. The median number of LMMs was 4.5 (IQR 3–8.5) with a median size of 2.5 mm (IQR 1.9–4). The number and size of LMMs did not differ significantly with regards to gender. There was no significant correlation between the duration of LMMs and their number or size. The majority of patients had LMMs involving both lips (74%) with 19% and 7% of patients having isolated lower and upper lip involvement, respectively. The involvement of both lips was seen in all patients with severe AD and skin phototype IV; however, this finding was not statistically significant. The distribution of LMMs was along the entire lip (middle and lateral) in the majority of cases (93%) and did not involve the perioral area.

The intraoral mucosa was affected in only one patient. The patient was a 12-year-old female with a solitary brown macule measuring 1 mm in diameter and involving the right buccal mucosa. The assessment for the presence or absence of melanonychia was not documented. None of the patients had any gastrointestinal symptoms and only one patient had a family history of colon cancer.

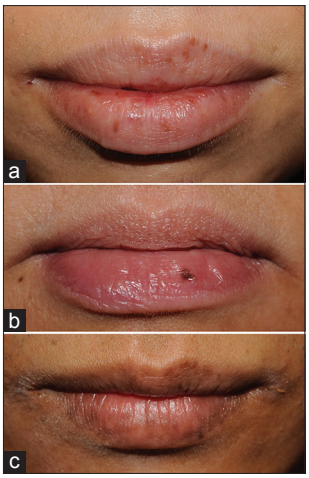

Figure 1: Labial melanotic macules in atopic dermatitis. (a) Multiple macular type. A 26-year-old female with multiple 1–4-mm light brown oval-to-round macules scattered over both lips. Note the associated cheilitis involving middle portion of the lower lip. (b) Solitary macular type. A 2 mm in diameter dark brown macule involving the middle portion of the lower lip in a 47-year-old female. (c) Mixed type (multiple macules in addition to diffuse pigmentation). A 27-year-old male with multiple dark brown macules mixed with areas of diffuse dark brown pigmentation. There is evidence of angular cheilitis

Discussion

The study of LMMs in AD patients demonstrated a predominance in Asian females and an association with preceding cheilitis and long-standing AD.

Studies of LMMs in the literature are limited. Ho *et al*.[1] (29 patients) and Gupta *et al*.[4] (79 patients) reported their case series of patients with LMMs but did not describe any association with AD. These studies showed a female predominance (86% and 83.5%, respectively) as was seen in our case series. Our patients differ from these studies in that our patients had multiple pigmented macules on both lips and almost all patients had evidence of preceding cheilitis.

There are several reports of LMMs developing after the application of a topical calcineurin inhibitor (TCI).[2,5] All patients had evidence of cheilitis and/or AD, and the LMMs persisted in all patients despite discontinuing TCIs. The development of LMMs in these patients may have been due to the associated cheilitis rather than the use of a TCI. Many of our patients had never applied a TCI on their lips.

Kang *et al*.[3] reported a series of 178 Korean patients with AD and demonstrated the presence of LMMs in 34.3% patients compared to 15.2% of age- and sex-matched controls without AD. They found that the LMMs in patients with AD were most often multifocal and located in the middle of the upper lip.

Table 1: Clinical characteristics of the 27 patients with atopic dermatitis and labial melanotic macules

Patient, gender	Age[a]	Ethnicity	Skin type	AD duration[a]	AD severity	Cheilitis	Cheilitis duration[a]	LMM duration[a]	LMM number	LMM size (mm)	Lip (s) involved	Lip part involved	Oral macules
1, male	27	A	IV	27	Moderate	Yes	27	15	Mixed	N/A	Both	Medial and lateral	No
2, female	12	A	III	9	Severe	Yes	9	4	3	1-3	Both	Medial and lateral	Yes
3, female	17	A	III	17	Moderate	Yes	7	3	4	2-3	Both	Medial and lateral	No
4, female	26	A	III	26	Severe	Yes	26	Many years	13	1-4	Both	Medial and lateral	No
5, female	53	A	III	50	Mild	No	N/A	10	3	1-3	Lower	Medial and lateral	No
6, female	28	A	III	20	Severe	Yes	20	Many years	4	2-4	Both	Medial and lateral	No
7, male	33	A	III	>20	Severe	Yes	>20	Many years	4	1-3	Both	Medial and lateral	No
8, male	27	A	IV	27	Moderate	Yes	Many years	<1	6	1-2	Both	Medial and lateral	No
9, female	47	A	III	47	Mild	Yes	20	2	1	2	Lower	Medial	No
10, male	8	A	III	8	Moderate	Yes	6 months	3 months	4	1-2	Both	Medial and lateral	No
11, male	13	A	III	13	Moderate	Yes	6	4	13	1-2	Both	Medial and lateral	No
12, female	27	A	III	26	Moderate	Yes	4	1	2	1-2	Lower	Medial and lateral	No
13, female[b]	8	A	III	8	Moderate	Yes	3	1	8	2-3	Both	Medial and lateral	No
14, female[b]	35	A	III	2-3	Mild	Yes	19	19	20	4	Both	Medial and lateral	No
15, female[b]	17	A	III	4	Moderate	Yes	4	1	4	4	Upper	Medial and lateral	No
16, female[b]	54	A	III	20	Mild	Yes	Many years	1	5	4	Both	Medial and lateral	No
17, female[c]	15	A	III	15	Moderate	Yes	15	2-3	7	4-6	Both	Medial and lateral	No
18, female[c]	20	A	III	20	Mild	Yes	10	10	4	4-6	Upper	Medial and lateral	N
19, female	14	A	III	13	Mild	Yes	5	2	10	1-2	Both	Medial and lateral	No
20, female	14	AC	IV	14	Moderate	Yes	5	1	12	1-2	Both	Medial and lateral	No
21, male	13	A	III	13	Moderate	Yes	10	1.5	3	7	Both	Medial and lateral	No
22, male	16	A	III	15	Severe	Yes	UK	UK	8	2-3	Both	Medial and lateral	No
23, female	16	A	III	15	Mild	Yes	UK	UK	6	2-8	Both	Medial and lateral	No
24, male	13	A/C	III	12-13	Mild	Yes	UK	UK	8	2-3	Both	Medial and lateral	No
25, female	10	A	III	2	Mild	Yes	2	2	2	4-6	Lower	Lateral	No
26, female	16	A	III	16	Mild	Yes	1	1	>30	2-6	Both	Medial and lateral	No
27, female	10	A	III	10	Moderate	Yes	4-5	3-4	3	2-4	Lower	Medial and lateral	No

[a]Years, [b]Mother and daughter, [c]Siblings. AD: Atopic dermatitis, A/C: Asian/Caucasian, A: Asian, LMM: Labial melanotic macules, AC: Aboriginal Canadian, N/A: Not applicable, UK: Unknown

It is interesting to note the similarities between the patients in our study and that by Kang *et al*. Although our study was performed in Vancouver, BC, which has a significant Asian population, there was a definite Asian predominance in the patients presenting with AD and LMMs. While this may reflect a local, selection or referral bias, we think this is a true

association. Although they did not document the presence of cheilitis explicitly, Kang *et al*. noted that more than half of their patients had lichenification of the philtrum.

LMMs seen in patients with AD should be differentiated from other conditions associated with lip pigmentation.[1,4,6-19] Several hereditary lentiginosis syndromes have lip pigmentation as a common feature and these include Peutz–Jeghers syndrome, Addison disease, Carney complex, and Laugier–Hunziker syndrome. In most of these conditions, lip pigmentation is evident in infancy or early childhood. Unlike patients with LMMs, patients with hereditary lentiginosis syndromes typically present with pigmented macules affecting the oral mucosa.

Our study had several limitations. Data were collected in a retrospective fashion and were only able to report a small sample of patients. We did not obtain biopsies for histologic examination due to the benign nature of LMMs previously reported in the literature.[1,2,4,5] We did not perform gastrointestinal screening in our patients to rule out intestinal polyposis. Additional limitations include the lack of a control group and the prevalence of LMMs within a cohort of patients with AD.

Conclusion

We have shown that some patients with AD might develop multiple LMMs. Patients were Asian with darker skin and a female predominance. The presence of cheilitis was noted in almost all patients, and there was a strong correlation between the duration of lip pigmentation and the duration of cheilitis. It is important to recognize this apparently common cause of lip pigmentation to avoid unnecessary investigations for rare hereditary lentiginosis syndromes such as Peutz–Jeghers and Carney complex. Patients with AD and LMMs can be instructed to frequently moisturize their lips which might help prevent the appearance of more LMMs. Future prospective studies on a larger scale can better characterize this entity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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