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CASE REPORT

Laugier–Hunziker Syndrome Presenting with Metachronous Melanoacanthomas

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Abstract

Laugier–Hunziker syndrome (LHS, also termed idiopathic lenticular mucocutaneous hyperpigmentation) is an unusual condition characterized by progressive pigmentation of the mucous membranes. LHS displays a benign course and is not associated with malignancy. Here we present a case of LHS with a 7-year follow-up. We document metachronous oral melanoacanthomas in this individual. In addition, we found that the oral melanotic macules in this patient waxed and waned in a cyclical manner. To our knowledge, this is the first report of these findings in the context of LHS. Finally, we provide an overview of other conditions that can present with mucosal hyperpigmentation. It is critical to distinguish LHS from other conditions characterized by mucosal pigmentation in order to facilitate optimal patient care.

Keywords Laugier–Hunziker syndrome · Oral melanotic macule · Melanoacanthoma · Melanin · Hyperpigmentation

Introduction

In 1970, Laugier and Hunziker described a previously unknown hyperpigmentation disorder affecting oral tissues and fingernails [1]. They believed that this phenomenon represented an idiopathic acquired pigmentation disorder. The eponym Laugier–Hunziker syndrome (LHS) was later coined in 1979 [2].

The etiology of LHS is unknown [1, 3–6]. Since there are no established diagnostic tests for LHS, it is a diagnosis of exclusion. LHS is typically acquired in adulthood and cases tend to be sporadic in nature, although family history of the condition is reported [4, 7]. LHS is not associated with underlying systemic conditions [1, 3, 6]. To date, more than 100 cases are described in the literature [3–11]. Some authors report that oral mucosal hyperpigmentation in LHS is twice as common in females as in males, although others dispute this gender predilection [4].

LHS characteristically presents with mucocutaneous pigmentation of the face, conjunctiva, oropharynx, esophagus, vulva, anus, genitalia, perianal region, perineum, palms and soles of feet [1, 3–5, 11, 12]. Longitudinal melanonychia is seen in approximately half of LHS patients and is classified into three different types (Table 1) [3–5, 13, 14]. The oral lesions of LHS may be solitary, multifocal, brown, gray or black pigmentations affecting the lips, buccal mucosae, tongue, and hard palate [6]. The gingiva may also be involved, although this is reported less frequently [4].

The pigmentations in LHS are either linear, round or lenticular (circular) in shape ranging from smooth to ill-defined margins. Histologically, the lesions are identical to oral melanotic macule with or without melanin incontinence and exhibit normal shape and size of rete ridges [4, 5, 14].

Herein, we present a case of LHS with a 7-year follow-up. To the best of our knowledge, we are reporting for the first time the presence of oral melanoacanthomas in a patient with LHS. Moreover, we observed that the oral pigmentation waxed and waned over time in this individual. Although rare, it is important to distinguish LHS from other conditions that

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Table 1 Classification of melanonychia associated with LHS

Type 1	Longitudinal streaks of variable degrees of pigmentation 1–2 mm wide
Type 2	Double longitudinal streaks involving the lateral portion of fingernails 2–3 mm wide
Type 3	Homogenous pigmentation involving the radial and ulnar portion of one or more toes and fingers

are characterized by mucosal pigmentation, as these may be associated with serious systemic sequelae.

Case Report

A 56-year-old white female of Mediterranean origin presented with a chief complaint of "pigmented lesions on my palate". The patient's past medical history was significant for hypertension and anxiety disorder, which were controlled with quinapril hydrochloride (10 mg daily) and paroxetine hydrochloride (10 mg daily), respectively. She denied smoking. The patient reported that 10 years earlier she had been diagnosed with breast cancer and had undergone surgery and chemotherapy. She is currently in remission. In addition, she reported a history of cutaneous lesions diagnosed as seborrheic keratoses that were excised over a span of several years.

The patient's family history revealed that her father had died of cutaneous melanoma and her mother of myocardial infarction. Extraoral examination revealed numerous pigmented macules on both arms. No evidence of melanonychia was seen. The patient admitted to being an outdoor activity enthusiast with a tendency to tan relatively easily. Intraoral examination revealed the presence of multiple brown-pigmented macules on the hard palate and palatal gingiva that varied in size and color intensity (Fig. 1a). The patient stated that she was concerned because of the progressive pigmentation of her palate and family history of melanoma.

These concerns had prompted her to request biopsies of her oral lesions. A palatal biopsy in 2003 was diagnosed by a dermatopathologist as mixed spongiotic and lichenoid reaction with melanin pigment suggesting post inflammatory pigmentation. In 2004, another palatal biopsy was diagnosed by an oral pathologist as consistent with oral melanotic macule (Fig. 2a). Her lip was biopsied in 2007 and was diagnosed by a dermatopathologist as a benign oral melanotic macule. When we saw her in 2011, she requested another biopsy, which was obtained from the palatal gingiva. The microscopic examination revealed the presence of melanin pigmentation in the epithelial basal cell layer and melanin incontinence in the superficial lamina propria. These findings were consistent with a diagnosis of oral melanotic macule (Fig. 2b). No evidence of melanoma was observed. While we were preparing the biopsy report, we identified a previous biopsy for this patient in our electronic database. This previous biopsy had been taken from a palatal lesion excised in 2008 that we diagnosed in our laboratory as melanoacanthoma (Fig. 3a).

After an evaluation of the patient's clinical presentation and microscopic findings, our differential diagnosis included physiologic pigmentation, post-inflammatory melanosis, smoker's melanosis, drug-induced hyperpigmentation, Addison's disease, Peutz–Jegher's syndrome (PJS), and other rare hematologic, infectious, and syndromic conditions. Physiological pigmentation was briefly considered as a viable explanation since the patient was of Mediterranean descent and some of her relatives were of dark complexion.

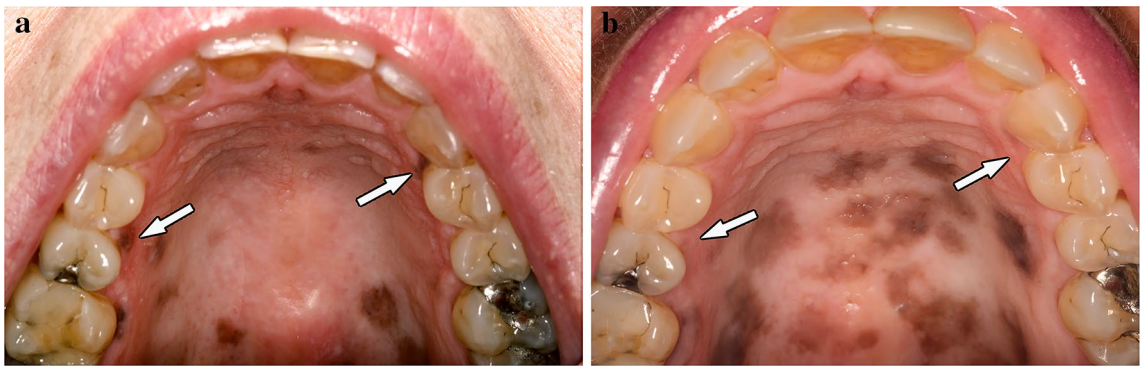

Fig. 1 **a** Multifocal brown macules on the hard palate showing variation in size, shape, location and intensity of discoloration. This clinical picture was obtained in 2013. Notice the presence of melanotic macules on the interdental palatal gingival papillae between right maxillary bicuspids and left maxillary canine and first bicuspid (white arrows) **b** This clinical picture was taken 4 years later and illustrates the progressive pigmentation of the palate. Interestingly, the pigmentation associated with the palatal interdental gingival papillae between the right maxillary bicuspids and the left maxillary canine and first bicuspid involuted (white arrows)

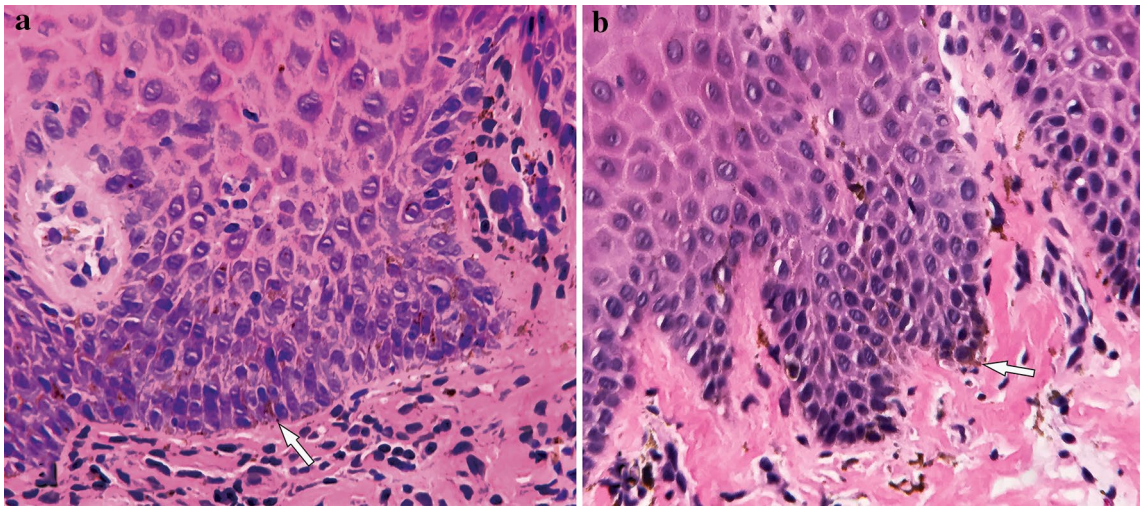

Fig. 2 **a** High power view of a melanotic macule (biopsy from 2004) with typical basal (white arrow) and parabasal cell melanin pigmentation and melanin incontinence in the superficial lamina propria (hematoxylin and eosin, original magnification ×400). **b** High power view (biopsy from 2011) showing melanin pigmentation in the basal cell layer (white arrow) and melanin incontinence. (Hematoxylin and eosin, original magnification ×400)

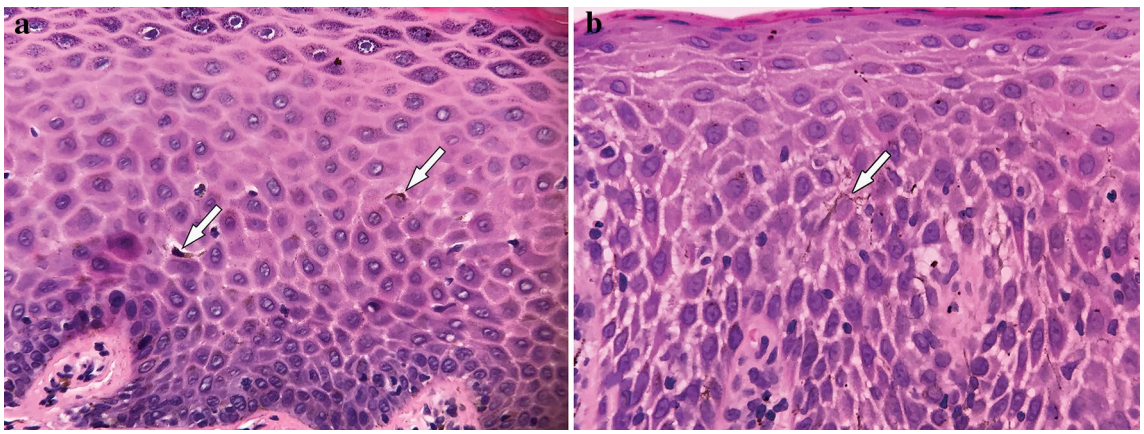

Fig. 3 **a** High power view showing a melanoacanthoma (biopsy from 2008) with characteristic dendritic melanocytes (white arrows) in a spongiotic and acanthotic stratified squamous epithelium. (Hematoxylin and eosin, original magnification ×400). **b** High power view showing a melanoacanthoma (biopsy from 2014) with spongiosis, acanthosis and dendritic melanocytic extensions (white arrow). (Hematoxylin and eosin, original magnification ×400)

However, the late onset and unrelenting progressive multifocal pigmentation of her oral tissues suggested the pigmentation was not physiologic.

Inflammation-induced pigmentation was ruled out due to the lack of supporting clinical evidence. Smoker's melanosis and pharmacologically-induced pigmentation were also ruled out because the patient did not smoke and the medications she reported (quinapril and paroxetine) are not known to promote mucosal pigmentation.

The patient's family history was negative for PJS. A colonoscopy was performed that was negative for intestinal polyposis. This result in conjunction with other diagnostic tests, ruled out the condition [15]. In addition, serum cortisol levels of 17.8 μg/dL were obtained at 8 AM (normal range; 5–23 μg/dL). This finding excluded Addison's disease [16]. Other disorders capable of inducing cutaneous and mucosal hyperpigmentation such as hemochromatosis, acromegaly, HIV infection, beta-thalassemia, McCune–Albright syndrome and neurofibromatosis type I were ruled out based on the clinical manifestations and normal laboratory serum values of our patient [17–20].

Since we excluded all other conditions associated with oral pigmentation, we rendered a diagnosis of LHS and subsequently placed the patient on a biannual follow-up program. During a follow-up visit to our clinic in 2014, it was noted that a pigmented macule on her palate displayed

worrisome changes characterized by a relatively rapid expansion with increased pigmentation. These changes prompted another biopsy. The microscopic examination yielded a diagnosis of melanoacanthoma (Fig. 3b). Figure 1b shows the clinical findings in 2017. A comparative mapping of the pigmented lesions illustrated in these pictures shows clear evidence of progressive multifocal melanosis. It is also evident that some pigmented macules increased in size and became darker, while others had faded over time. Since the mucosal pigmentation in LHS is progressive and not associated with systemic disease and/or malignant transformation [4, 5, 14, 21], no additional treatment was necessary [6, 13, 21] and the patient continues to be followed.

Discussion

The genesis of melanotic hyperpigmentation in the oral cavity is diverse. It is important to consider a broad differential diagnosis when evaluating oral mucosal hyperpigmentation, as this finding may be physiologic, or may be due to, medication use, inflammation, environmental or genetic conditions (Table 2). We will review the most common causes of oral pigmentation and discuss the features that can aid in distinguishing these conditions from LHS.

The most common etiology of mucosal pigmentation is physiological. Physiological pigmentation presents with early onset of multifocal macules and the pattern and intensity of pigmentation remains stable over time. These macules are typically diffuse and bilateral [17, 18, 20, 22]. In contrast to LHS, the most common site of oral physiologic pigmentation is the attached gingiva, although other sites may also be affected [17]. The marginal gingiva is spared in patients with physiological pigmentation [17, 18]. Although typically unnecessary, biopsy reveals heightened pigmentation in the basal layer of the epithelium with melanin incontinence. Melanophages may be observed in superficial lamina propria [23]. LHS may appear similar to physiologic pigmentation on intraoral and histological examination. However, the pigment is typically seen in the attached gingiva in the physiologic condition, while the pigment in LHS is seen most commonly in the lips, buccal mucosae, tongue, and hard palate [6]. In addition, the late onset of the mucosal pigmentation suggests the presence of LHS rather than a physiologic origin.

Smoker's melanosis should be considered in all patients who report a history of smoking, as melanosis is seen in approximately 25% of tobacco smokers [18]. Data suggest that the increased melanin production may be a protective response induced by exposure to polycyclic amines found in tobacco smoke [24]. Biopsies from individuals with smoker's melanosis show elevated pigmentation of the basal layer of the epithelium as well as melanin incontinence in the superficial connective tissue. Similar to physiologic pigmentation, isolated melanophages are also observed [24]. While this pigmentation may be permanent, resolution is reported following elimination of the habit [18]. In patients with smoker's melanosis, the color changes are restricted to the oral mucosa. In contrast, patients with LHS typically exhibit mucocutaneous pigmentation at other sites, and the presence of longitudinal melanonychia may be a helpful feature that is not observed in smoker's melanosis.

Post-inflammatory melanosis is another potential cause of pigmentation in the oral cavity. This tends to arise following chronic inflammation of the mucosa, and is associated with long-standing lichen planus, mucous membrane pemphigoid or pemphigus vulgaris [18, 23]. The mechanism of post-inflammatory melanosis is poorly understood, although it occurs more frequently in patients that have darker skin [23]. Clinically, the pigmented areas are located adjacent to lesional tissue [23]. The histological findings of post-inflammatory melanosis show elevated melanin production by melanocytes and increased melanophages in the superficial connective tissue [17]. Post-inflammatory melanosis

Table 2 Conditions associated with generalized mucocutaneous pigmentation

Syndromes		Systemic conditions	Other
Bloom syndrome	Laugier–Hunziker syndrome	Vitamin B12 deficiency	Drug-induced pigmentation
Carney complex	LEOPARD syndrome	Hemochromatosis	Melanoma
Cronkhite–Canada syndrome	McCune–Albright syndrome	HIV–AIDS related hyperpigmentation	Physiologic pigmentation
Cushing's syndrome	Neurofibromatosis type I	Hyperthyroidism	Post-inflammatory melanosis
Dunnigan syndrome	Oculocerebrocutaneous syndrome	Primary biliary cirrhosis	Smoker's melanosis
Dyskeratosis congenita	Peutz–Jeghers syndrome	Adrenal insufficiency/Addison's disease	Yusho (chronic exposure to polychlorinated biphenyls)
Endocrine candidiasis syndrome	Rothmund–Thomson syndrome		Systemic metallic intoxification
Incontinentia pigmenti	Trisomy 14 mosaicism		
Xeroderma pigmentosum	Unusual facies, vitiligo, spastic paraplegia syndrome		

may decrease with resolution of the underlying inflammatory condition [23]. Histologically, post-inflammatory melanosis may be challenging to distinguish from LHS, although the history of chronic inflammation enables the diagnosis.

Pharmacologically-induced pigmentation of the oral cavity is documented in association with a number of medications (Table 3). Amiodarone, minocycline, cyclophosphamide, quinidine and oral contraceptive drugs are well known for their ability to cause oral pigmentation [5, 25–27]. Drug-induced pigmentation typically appears as a grayish-blue staining that is restricted to the gingiva and hard palate. The mechanism of drug-induced pigmentation varies and even a single therapeutic may cause pigmentation by different means [17]. For example, minocycline is thought to induce hyperpigmentation by increasing melanin production and a minocycline metabolite also produces discoloration [28]. Pigmentation of the oral cavity resulting from medication use will typically resolve when the drug is withdrawn, although permanent staining is reported [18]. A comprehensive medical history will aid in distinguishing drug-induced melanosis from LHS.

PJS should also be considered in patients exhibiting diffuse mucosal pigmentation. Patients with PJS also exhibit gastrointestinal (GI) hamartomatous polyposis and are at significant risk for malignancies of the pancreas, GI tract, and breast [29]. PJS is an autosomal dominant condition caused by mutation in the *STK11/LKB1* gene on chromosome 19 [30, 31]. Patients with PJS are characterized by discrete areas of multifocal hyperpigmentation in the perioral region. Pigmentation is also noted in the oral and nasal cavities, conjunctiva, rectum, and skin [17, 29]. Rarely, pigmentation may be seen in the intestinal mucosa and nail plate [29]. The pigmentation develops in early childhood and precedes GI disease [15]. While the oral mucosal lesions typically persist, the skin lesions of PJS often fade with age [32]. Genetic testing for *STK11/LKB1* mutations is important to identify patients with PJS prior to the development of malignancy [15, 33]. Importantly, individuals with LHS do not harbor this mutation [33], and thus genetic testing can be used to distinguish PJS from LHS.

Table 3 Drugs that induce oral pigmentation

AIDS-related medications	Chlorpromazine	Mepacrine
Amiodarone	Clofazimine	Methacycline
Amodiaquine	Estrogen	Methyldopa
Arsenic	Gold	Minocycline
Azidothymidine	Hydroxychloroquine	Phenolphthalein
Bismuth	Hydroxyurea	Premarin
Bleomycin	Imatinib	Quinacrine
Busulfan	Imipramine	Quinidine
Chloroquine	Ketoconazole	Zidovudine

Addison's disease (primary hypoadrenalism) is characterized by the destruction of the adrenal cortex that results in decreased production of adrenal cortical hormones. This in turn stimulates adrenocorticotropic hormone (ACTH), thereby promoting release of melanocyte stimulating hormone which culminates in mucocutaneous pigmentation [17]. Addison's disease manifests with generalized bronzing of the skin, depression, fatigue, weakness, hypotension and diffuse melanin pigmentation of the oral cavity [17]. The diagnosis of Addison's disease is usually confirmed by a rapid ACTH stimulation test and measurement of serum cortisol and plasma ACTH levels [16]. Since patients with LHS do not exhibit any systemic disease manifestations, Addison's disease is easily distinguished from LHS on the basis of serological studies and clinical findings.

We report the presence of metachronous oral melanoacanthomas in a patient with LHS. Oral melanoacanthoma is a rare pigmented lesion in which proliferative dendritic melanocytes populates a spongiotic spinous cell layer [24, 34]. Oral melanoacanthoma is considered a reactive process most frequently affecting black females in their third and fourth decades of life [24, 34]. Oral melanoacanthoma may present as either solitary, bilateral or multifocal lesions. The most frequent intraoral site is the buccal mucosa followed by the labial, gingival, palatal and alveolar mucosae [24]. Because oral melanoacanthoma can exhibit ominous rapid growth and progressive darkening, a biopsy is required to rule out melanoma. Several reports have shown that an incisional biopsy may result in spontaneous resolution of oral melanocanthoma [24]. Multiple metachronous melanoacanthomas have been documented in the literature [35]. Despite recurrence and development of new lesions, there is no potential for malignant transformation [24]. The presence of oral melanacanthomas in association LHS may be a helpful diagnostic feature, as none of the other pigmented conditions in the differential diagnosis are characterized by this finding. However, it is important to point out that it is unknown if the melanoacanthomas in our patient represent an unrelated serendipitous finding or if they are a component of LHS. Further studies are necessary to establish this association conclusively.

Moreover, we report that the oral melanotic macules associated with LHS can wax and wane. This is significant because most other conditions associated with oral pigmentation are stable over time (i.e. physiologic pigmentation, drug-induced pigmentation, PJS) or fade with time once the inciting agent is removed or attenuated (i.e. smoker's melanosis, post-inflammatory melanosis, drug-induced melanosis). Therefore, careful documentation of the episodic nature of the pigmentation may be consistent with the diagnosis of LHS. Sequential intraoral and, if applicable, skin photographs coupled to a long-term follow-up should be integrated in the management of patients with suspected

LHS. As mentioned above, further studies are warranted to determine whether additional LHS patients show pigmentation that varies over time.

In conclusion, LHS is a rare condition characterized by mucocutaneous pigmentation and longitudinal melanonychia. Currently, there are no established diagnostic tests for LHS and so it is a diagnosis of exclusion. Many different conditions display intraoral pigmentation, and it is important to distinguish these from LHS to facilitate appropriate patient care.

Summary

- Laugier–Hunziker syndrome (LHS) is a sporadic, idiopathic disorder characterized by mucocutaneous macular hyperpigmentation, often coupled with melanonychia.
- We report metachronus melanoacanthomas in a patient with LHS. In addition, we found the oral pigmentation waxed and waned in this individual.
- Further studies are needed to determine whether these findings are characteristic oral manifestations in patients with LHS.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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