Laugier-Hunziker syndrome: a case and dermoscopic features

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Abstract

Laugier-Hunziker syndrome (LHS) is a sporadic, acquired, and infrequent condition characterized by the onset of brown macules on the lips, the oral mucosa, and the acral glabrous skin (mainly fingers and toes) in middle-aged patients. In several cases melanonychia of fingernails and toenails coexists. No other systemic involvement is observed. A case of LHS in a 50-year-old woman is described, with particular attention to dermoscopic features. No dermoscopic specific findings of mucosal/cutaneous maculae have been to date described in the literature. Accumulation of dermoscopic observations of pigmented lesions in LHS is needed and if found to be distinct, it may contribute to a more accurate diagnosis in the future.

Keywords: dermoscopy, diagnosis, differential, histopathology, Laugier-Hunziker syndrome

Introduction

In 1970, Laugier and Hunziker described an acquired macular hyperpigmentation of the lip and oral mucosa in five patients, with longitudinal nail pigmentation in two of them [1]. Additional reports emphasized the absence of associated systemic disease and the need to differentiate this disorder from diseases that have similar pigmentary changes but also significant somatic abnormalities [2]. Subsequently, more of 200 cases of Laugier-Hunziker syndrome (LHS) have been described in the literature [2-5]. Therefore, LHS can be considered an infrequent condition.

Case Synopsis A 50-year-old woman referred to the dermatology clinic reported that dark macules had appeared on her lower lip several months before. Over the months after first noticing them, she had observed an increase in number and size of macules, as well as new similar macules on the upper lip, the oral mucosa, the tongue, and some fingers. The patient was a non-smoker and suffered from mild hypertension treated with beta-blockers but was otherwise healthy. There was no familial history of pigmentary disorders, gastrointestinal polyposis, or gastrointestinal tumors.

On physical examination, many dark brown macules with well-defined margins were found on the lower lip (**Figure 1A**), the upper lip, and the tongue (**Figure 1B**), the oral mucosa, the hard palate, and the tips of some fingers. There were no pigmented lesions on the palms, soles, nails, and perineum. She did not have other lentigines on the skin surface. The genital area was not involved. An ophthalmologic examination showed a brown macule on the corneal conjunctiva of her left eye.

On dermoscopic examination, the macules of the lip revealed a diffuse brownish pigmentation with dark brown lines, black dots, and peripheral streaks following the labial markings (**Figure 1C**). The

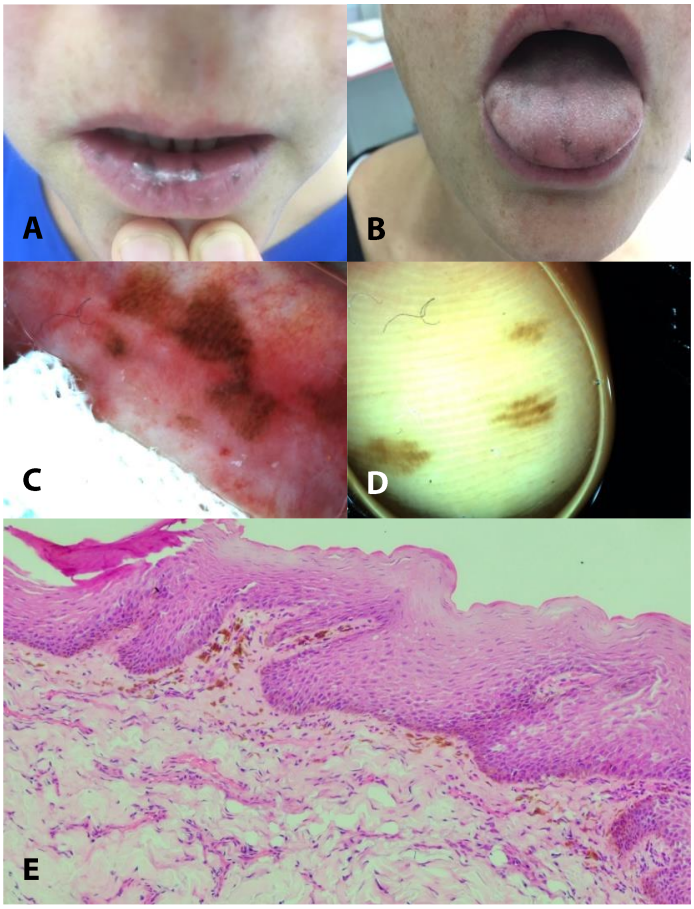

Figure 1. ***A)*** *Brown macules on the lower lip.* ***B)*** *Brown macules on the tongue.* ***C)*** *Linear brown pigmentation with interruptions in the streak on the lip's mucosa.* ***D)*** *Parallel ridge pattern on the pulp finger.* ***E)*** *Increased melanin pigment within the basal layer with some dermal melanophages. H&E, 100×.*

pigmented macules on the fingers showed a prevailingly parallel ridge pattern (**Figure 1D**). These features were evaluated in agreement among all the authors.

Plasma cortisol levels, adrenocorticotropic hormone, thyroid function tests, blood sugar, blood sodium, and blood potassium were within normal limits. Fecal occult blood was absent. Gastroscopy showed a hiatal hernia and colonoscopy and capsule endoscopy of the small intestine revealed a normal mucosa.

The biopsy of a pigmented lesion of the lower lip showed the presence of epidermal acanthosis with hyperkeratosis and parakeratosis. Additionally, some focal spongiosis was observed. In the basal layer hyperpigmentation of keratinocytes was present. There were increased numbers of melanin-laden macrophages and pigment incontinence in the papillary dermis (**Figure 1E**). The anti-Melan-A immunohistochemical reaction showed a normal number of melanocytes in the basal layer. On the basis of clinical, dermoscopic, laboratory, and histopathological features most potential diseases with similar features of pigmented macules were ruled out. The diagnosis of LHS was made. The diagnosis was supported considering the age of onset of the condition, the negative familial history for similar skin findings, the absence of gastrointestinal polyps, lack of intake of drugs responsible of muco-cutaneous pigmentation, and the normal blood tests. Periodic follow-up of the patient is continuing.

Case Discussion

Laugier-Hunzinger syndrome is more frequent in women and the average age of the reported cases is 47.5 years old. The syndrome is typically acquired in adulthood and cases are sporadic [2].Only one report of familial cases is recorded [2]. Evidence supporting a risk of cutaneous malignancy associated with LHS is lacking; our review of the literature has disclosed only one case of invasive mucosal melanoma of the lip associated with LHS [6]. Association with systemic abnormalities has not yet been described. Pigmentary changes in LHS do not disappear spontaneously but slowly increase over years [2]. A case in which the oral pigmentation had a waxing and waning course was also described [7].

The cutaneous or mucosal lesions manifest as 2-5mm lenticular or oval grey, brown, blue-black macules, with a flat, smooth surface and relatively well-defined margin [2]. The most common lesion sites are the lips (especially the lower lip), (75%), the oral cavity (68%), and the fingers (13%). Genitalia (penis and vulva) are involved in about 34% and other sites (palm, sole, toes, periungual area, conjunctiva and sclera, anal mucosa, and esophagus) are affected in a small percentage [2].

Longitudinal melanonychia is observed in approximately 44%-60% of LHS patients [2]. Baran [8]

Table 1. *Criteria of differential diagnosis between Laugier-Hunziker syndrome and other similar conditions.*

Diagnosis [reference]	Dermoscopic patterns	Other findings
Mucosal melanosis [14]	- Structureless pattern - Parallel pattern - Reticular-like pattern	-Single or multiple macules - Also genital
Incontinentia pigmenti/ Bloch-Sulzberger syndrome [15]	- Lack of gland orifices (glowing white dots) - Hyperpigmented circles/ring, curved/parallel streaks	- Onset in infancy - Linear and whorled streaks with Blaschkoid distribution
Melanoma/melanoma in situ on acral volar skin [16]	Parallel ridge pattern	Single clinically atypical lesion
Peutz-Jegher's syndrome [17]	Parallel ridge pattern	- Early onset - Perioral macules - Macules of hands/feet - Gastrointestinal polyps
Solar lentigo [18]	- Light/dark pseudonetwork - Brown thin pigment network - Symmetric follicular pigmentation - Diffuse opaque yellow-brown pigmentation - Brown cerebriform structures - Fingerprints and moth-eaten bords	Brown macules (face, back, hands)
LEOPARD syndrome [19]	- Lentigines: pigment network, multifocal blotches, black dots/brown globules, branched streaks - Café noir spots: pigment network, brown globules, hyphae-like structures, multifocal blotches	- Early onset - Pigmented macules on lips, face, neck upper trunk, arms. - Buccal mucosal uninvolved
Ethnic pigmentation [20]	N/A	Uniform, symmetrical diffuse or patchy mucosal pigmentation
Smoker's melanosis [20]	N/A	Black-brown diffuse pigmentation of the oral mucosa
Drug-induced hyperpigmentation [20]	N/A	- Pigmented, multiple and diffuse areas - History of putative drug
Carney complex syndrome [20]	N/A	Diffuse brown/black diffuse lentigines
Addison's disease [20]	N/A	Diffuse cutaneous and mucosal hyperpigmentation
McCune-Albright syndrome [20]	N/A	Unilateral/segmental café-au-lait spots with an irregular profile
Amalgam tattoo [20]	N/A	Blue-grayish macules
Melanocytic nevi [20]	N/A	Brown macules and papules
Melanoacanthoma [20]	N/A	- Single, wide macule or plaque - Multiple lesions possible

N/A: not available

categorized the nail pigmentation in LHS into three types: a single 1-2mm wide longitudinal streak, a double 2-3mm wide longitudinal streak on the lateral portion of the nail plate, and a homogeneous pigmentation of the radial or ulnar half of the nail plate. Veraldi et al. [9] reported a fourth type. complete pigmentation of the nail plate. Fingernails are more frequently involved than toenails.

The histopathological hallmark of pigmented lesions in LHS is accumulation of melanin of the basal layer of the mucosal epithelium or epidermis. Melanocytes are normal in number, shape, and distribution. An increased number of melanophages, pigment incontinence, is frequently observed in the upper lamina propria or papillary dermis [2]. Only a few

cases are reported as having an increased number of non-nested melanocytes in the basal layer [10,11].

Ultrastructural studies show within basilar keratinocytes many intracytoplasmic melanosomes (usually increased in size), either solitary or, less frequently, grouped. Also, the melanophages located in the connective tissue are rich in intracytoplasmic melanosomes [9,12].

These observations suggest that LHS is caused by a functional alteration of the melanocytes with an increased synthesis of melanosomes and a subsequent increased release of melanosomes to basal cells [9]. The reason why melanocytes synthesize a greater amount of melanin is not known, but it has been speculated that the trigger is a "chronic stimulus", because LHS follows a chronic course without remission [12]. This hypothesis might be supported by a reported case in which LHS appeared in a patient treated with levodopa. Levodopa (or L-3-hidroxytyrosine) is one of the intermediary metabolites in melanin production that also act as an inducer by activating the tyrosinase enzyme [13]. Because the synthesis of melanin takes place in melanosomes arising from the tyrosine amino acid and with the catalysis of the tyrosinase enzyme, this observation suggests that the defect in LHS could be characterized by an enzymatic hyper-reactivity in the biosynthesis of the melanin involving tyrosinase. A recent report describing the possible transmission of LHS in the recipient by peripheral blood stem cell allogenic transplantation also suggests that a genetic abnormality underlies the pathogenesis of LHS [4]. A broad differential diagnosis should be considered when evaluating labial, oral, and cutaneous hyperpigmentation; as a rule, LHS is a diagnosis of exclusion.

Among focal labial and oral pigmentations, LHS should be differentiated from melanotic macule, melanocytic nevus, melanoacanthoma, and melanoma [2]. Further, among the diffuse pigmentations, other entities in the differential diagnosis include amalgam tattoo, smoker's melanosis, drug-induced mucocutaneous pigmentation, heavy metal poisoning, racial pigmentation, Addison disease, and some genetic syndromes (McCune-Albright syndrome, neurofibromatosis type 1, Carney complex, LEOPARD syndrome, Cronkhite-Canada syndrome, and Bloch-Sulzberger syndrome), [2]. The main conditions for exclusion are reported in **Table 1**, [14-20].

The most important item in the differential diagnosis of LHS is Peutz-Jeghers Syndrome (PJS), [2]. Peutz-Jeghers Syndrome is an autosomal dominant condition characterized by mucocutaneous pigmentation, gastrointestinal hamartomatous polyps, and cancer predisposition. Peutz-Jeghers Syndrome is caused by mutations in the *serine/threonine kinase 11* gene. Hyperpigmented macules on the lips, oral, perianal, genital mucosa, and acral skin are common. The recognition of PJS is of paramount importance since patients with PJS exhibit an increased lifetime risk of gastrointestinal, genital, and breast cancer [2]. In PJS, pigmentation of the lips can occur in childhood and disappear with age, whereas pigmentation of buccal mucosa often persists in adulthood. *Serine/threonine kinase 11* gene testing facilitates the diagnosis [3].

Dermoscopy of mucocutaneous macules and of nail melanonychia in LHS shows several features (**Table 2**), [3,21-28]. The mucosal/lip dermoscopy show a large variability of the observed patterns. Interestingly, LHS has some patterns that are different from mucosal melanosis [14]. Instead, the dermoscopic features of acral skin consist mainly of a parallel ridge pattern. Tamiya et al. [23] emphasized that the dermoscopic patterns of the macules on the palms and the soles can be difficult to differentiate from pigment lines of melanoma. Some authors attempted to correlate the dermoscopic pattern of LHS with the respective histopathological features. Gencoglan et al. [22] correlated the mucosal parallel pattern associated to multiple brown dots with melanin pigmentation of basal cells and dermal melanophages, suggesting that the dots would be an expected finding when a patient has a superficial pigmentary incontinence. Instead, the dermoscopic pattern observed on the vulva, a partially linear and partially curvilinear brown streaming along the cutaneous profile was concordant with dermoscopic features of benign genital melanosis [22]. According to Ko et al., in the mucosal lesions, diffuse pigmented

Table 2. *Dermoscopic features of Laugier-Hunziker syndrome.*

Author [reference]	Oral mucosa/lips	Acral skin/fingers	Nail	Genital mucosa
Ronger et al. [14]	N/A	N/A	Gray regular lines regular in a grayish background	N/A
Gencoglan et al. [15]	PFP associated with multiple brown dots	PFP	Homogeneous, brownish, regular bandlike pigmentations with indistinct borders. No Hutchinson's or micro-Hutchinson's sign	Parallel linear/curvilinear pattern, with light- to dark-brown streaks following the cutaneous profile
Simionescu et al. [6]	Regular brown pigmented network with reticular-like pattern; homogeneous blue area	N/A	N/A	N/A
Sendagorta et al. [17]	N/A	PRP	Homogeneous, brownish, regular, bandlike pigmentation. No Hutchinson's or micro-Hutchinson's sign	N/A
	N/A	PRP	N/A	N/A
Tamiya et al. [16]	Multiple brown and blue-gray granular pigmentation with whitish pink areas and linear/dotted vessels	PRP	Thin longitudinal grayish lines in a regular linear grayish background; fibrillary pattern with pseudo-Hutchinson's sign	N/A
Ko et al. [18]	Regular brown reticular pattern with linear/curvilinear vasculature	PRP	Homogeneous brown-gray linear lines and bands with indistinct borders	N/A
Kaçar et al. [19]	Parallel lines, reticular lines, globules	N/A	Brown-to-gray longitudinal regular lines	N/A
Cusick et al. [20]	Fish scale-like pattern	Brown-grayish homo-geneous pattern	N/A	N/A
Wei et al. [21]	Regular brownish reticular pattern with streaks, granules and networks; linear and dotted vessels with a whitish pink area	N/A	N/A	N/A
Sputa-Grzegrzolka et al. [3]	Blue-gray lesions with linear, reticular, and circular pattern	N/A	N/A	N/A
Present case	Linear pigmentation with interrupted streaks	PRP	N/A	N/A

N/A: not available; PFP: parallel furrow pattern; PRP: parallel ridge pattern.

basal cells along the junction of mucosa and submucosa correlate to the reticular pattern, whereas on the glabrous skin the melanocytic pigmentation in ridges or furrows could reflect a parallel ridge or parallel furrow pattern [25]. Instead, according to Sendagorta et al., on the palms, soles, fingers, and toes, the hyperpigmentation is more prominent in basal keratinocytes located at the crista

intermedia profunda, the epidermal rete ridges underlying the surface ridges and a parallel ridge pattern is observed [24]. The same histopathologic findings have been observed in acral maculae of PJS, [17]. In fact, a dermoscopic parallel ridge pattern is described in PJS [17]. Accordingly, dermoscopy cannot allow to distinguish LHS from PJS.

The random hyperpigmentation of the basal layer and the pigment incontinence, both distributed on both sulci and cristae cutis, may be responsible for the varied dermoscopic patterns in LHS [23]. Some authors, however, think that the differences between the parallel furrow pattern and parallel ridge pattern, observed on the glabrous skin in different cases of LHS, should be related to variation in pigment deposition according to different ages of patients and to different stages of the disease [24].

Conclusion

Laugier-Hunziker is an uncommon condition, which has a benign course and requires no specific therapy. The diagnosis of LHS is made clinically and histologically, after exclusion of many other disorders with similar cutaneous findings but with systemic involvement and/or risk of malignancy. Only a few reports have described the dermoscopic findings of the mucosal, cutaneous, and ungual pigmentation in LHS. To date, these findings, although interesting, seem to be not specific and therefore not contributory to the clinical diagnosis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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