

ELECTRONIC LETTER

Laugier-Hunziker syndrome: an important differential diagnosis for Peutz-Jeghers syndrome

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Laugier-Hunziker syndrome (LHS) is a rare sporadic disorder, which shares some dermatological features with Peutz-Jeghers syndrome (PJS). However, whereas PJS is associated with hamartomatous gastrointestinal polyposis and carries a high risk of malignancy justifying intensive screening protocols,¹ LHS is known to be an entirely benign disease with no systemic manifestations, which requires patient reassurance as the only intervention.²

CASE REPORT

To highlight the importance of this differential diagnosis, we present the case of a 52 year old white man who was referred to our genetics department for advice in view of his diagnosis of PJS. His dentist had first noted the appearance of perioral and intraoral pigmentation in him at the age of 45 and he was normotensive and systemically well with no history of intermittent vomiting, abdominal pain, anaemia, or rectal bleeding. On the basis of the clinical features supported by a biopsy of one of the lesions seven years earlier a dermatological diagnosis of PJS had been made and he had been referred for gastrointestinal screening and surveillance. Over the past six years he had undergone regular oesophagogastroduodenoscopies and two yearly colonoscopies which had disclosed a hiatus hernia and mild diverticulosis but no polyps. Unfortunately, one of his colonoscopies had resulted in a colonic perforation. Nothing abnormal was detected on a barium follow through and blood tests including kidney, liver, and thyroid function tests, full blood count, and measurement of α -fetoprotein and carcinoembryonic antigen were also normal.

The patient was referred to the genetics department with the aim of molecular confirmation of diagnosis. When his family history was ascertained the patient reported that his 79 year old mother had an isolated freckle on her lower lip which had remained unchanged since birth. She was otherwise well with no history of gastrointestinal problems. His father had died from bronchial cancer at the age of 76. The patient had no sibs and both his children were said to be fit and well without any



Figure 1 Photograph of the proband demonstrating multiple lenticular hyperpigmented macules on his lips as well as small melanotic macules on his fingerpulp.

unusual skin pigmentation or gastrointestinal symptoms. The lack of a family history of PJS coupled with the absence of any polyps despite repeated imaging of his entire intestine as well as the fact that his unusual pigmentation only developed at the age of 45 prompted us to question his diagnosis.

Direct sequencing of the patient's *STK11/LKB1* gene in both orientations using Big Dye terminator and 4% sequencing ABI377 gels disclosed two polymorphic changes (IVS1+36G>T and IVS7+7G>C) but no disease causing mutation. Neither the patient's occupational history nor his drug history provided a cause for his pigmentation. A further dermatological review was requested. On examination he was found to have multiple lenticular light to slate and even dark brown macules of 2–5 mm diameter on his lips as well as on the mucosa of his hard and soft palate but no perioral or peri-orbital lesions. He also had multiple pigmented macules on his fingertips and inspection of his thumbnails showed discrete longitudinal hyperpigmented bands but no dystrophic changes (fig 1). Given the patient's history and findings from clinical examination, a diagnosis of LHS was made. He was reassured about the benign and sporadic nature of his LHS and the screening protocol followed previously on the basis of his original diagnosis was abandoned. The patient's previous lip biopsy was subsequently reviewed in the light of his new diagnosis. It showed a focal increase in pigmentation at the basal layer with solar elastosis and a few melanophages in the dermis. There were no naevus cells present. This was considered to be consistent with both PJS and LHS.

Key points

- Laugier-Hunziker syndrome (LHS) is a rare sporadic disorder, which shares some dermatological features with Peutz-Jeghers syndrome (PJS).
- However, whereas PJS is associated with hamartomatous gastrointestinal polyposis and carries a high risk of malignancy, justifying intensive screening protocols, LHS is known to be an entirely benign condition with no systemic manifestations, which requires patient reassurance as the only intervention.
- We present the case of a 52 year old white man to highlight the importance of this differential diagnosis.

Abbreviations: LHS, Laugier-Hunziker syndrome; PJS, Peutz-Jeghers syndrome

DISCUSSION

Peutz-Jeghers syndrome is an autosomal dominant disorder characterised by hamartomatous gastrointestinal polyposis and melanin pigmentation of the skin and mucous membranes. The polyps occur throughout the whole digestive tract with a predilection for the small bowel but have also been found in urinary tract, uterus, biliary tract, and nasal mucosa.³ They typically cause recurrent intussusceptions or intestinal obstruction and most patients present in adolescence or young adulthood with episodes of colicky abdominal pain. Chronic or recurrent gastrointestinal blood loss resulting in iron deficiency anaemia is another common complication. Pigmentation of skin and mucous membranes is the external hallmark of PJS. Irregularly distributed light to dark brownish macules of 1–5 mm diameter occur most commonly on the lips and oral mucosa (mainly the buccal mucosa, gums, and hard palate), but smaller and darker macules can also be found around the mouth, nose, and eyes.⁴ Slightly larger pigmented macules can occur on the palms and soles, volar aspects of the fingers and toes, and occasionally on the external genitalia. Biopsy of the pigmented skin macules shows an increase in basal layer keratinocyte pigmentation but no increase in melanocyte number. Pigmentary nail changes, albeit very rarely, have also been reported in association with this syndrome.⁵ Mucocutaneous pigmentation in PJS is rarely present at birth but starts to appear in infancy or early childhood, reaching a maximum at puberty. The oral lesions usually persist whereas the pigmentation on the skin and lips typically tends to fade from the third decade onwards.⁶ Over recent years several studies have shown a significantly increased risk of malignancy, both gastrointestinal as well as extraintestinal, in patients with PJS, and the chance of an affected person to die of cancer by the age of 57 has been estimated to be as high as 48%.³ The most often reported gastrointestinal sites are the large bowel, duodenum, and stomach whereas extraintestinal cancer sites include the breasts, uterus, cervix, ovaries, testicles, and pancreas. Therefore, comprehensive screening protocols have been drawn up for patients with PJS consisting of two yearly upper and lower gastrointestinal endoscopy and small bowel follow through, early breast screening, and yearly gynaecological evaluation.

Disease penetrance in families with known PJS seems to be over 90% by the age of 30⁶ but 10%–20% of cases have no family history and these are therefore presumed to be new mutations. It has been suggested that a definite diagnosis of PJS can be made if a patient fulfils one of the following criteria: (1) two or more histologically confirmed PJS polyps in the gastrointestinal tract; or (2) one PJS polyp in the gastrointestinal tract together with either classical PJS pigmentation or a family history of PJS.⁶ The same authors also suggest that a presumptive diagnosis can be made in people with a positive family history and florid, typical PJS freckling.

Recently, germline mutations in the serine threonine kinase *STK11* (previously denoted as *LKB1*) located on chromosome 19p13.3 have been identified as a cause for PJS^{7,8} and current evidence suggests that they account for between 40% and 60% of all cases.⁹ Our patient did not fulfil either of these clinical criteria and sequencing of his *LKB1/STK11* gene did not disclose a disease causing mutation.

Laugier-Hunziker syndrome is a sporadic condition characterised by essential acquired and benign melanotic pigmentation of the oral cavity and lips which is often associated with spotted macular pigmentation of the fingertips and longitudinal melanonychia.² Since its first description by Laugier and Hunziker in 1970,¹⁰ more than 100 cases have been described worldwide. The basic skin lesions manifest as irregular lenticular hyperpigmented macules of 2–5 mm diameter which can be slate to dark brown in colour with well defined or indistinct margins. These occur singly or as multiple groups and are sometimes confluent.¹¹ They are typically found

intraorally on the lower lip, the hard and soft palate, and the buccal mucosa but can also be seen in the palmoplantar area, on fingertips,¹² and in the genital region. Often multiple lesions can develop progressively.³ One or more fingernails or toenails can be affected with discrete longitudinal hyperpigmented bands of varying width and intensity but without any associated nail dystrophy.¹³ However, not all patients with LHS exhibit both oral and nail involvement and the second is only found in about 60% of cases.¹⁴ Initially a female preponderance with a 2:1 female to male ratio was suggested,¹⁵ but it is now thought that males and females are equally affected¹⁶ with no known familial factors. Laugier-Hunziker syndrome is acquired in early to mid adult life and to date no association with systemic disease has been reported. Histological examination of LHS lesions shows increased melanin deposition in basal layer keratinocytes and dermal pigmentary incontinence as well as an increase in the number of melanophages in the papillary dermis, but no increase in the number of melanocytes.¹⁵ Naevus cells are not seen. Ultrastructurally, an increased number of apparently normal melanosomes can be found in the cytoplasm of the keratinocytes of the basal layer but the melanocytes seem normal in distribution, number, and shape.¹² There have been no reports of malignant change in skin lesions in LHS. Pigmentary changes in LHS involve the skin, mucous membranes, and nails. Pigmentation in these areas can occur in many other conditions which need to be considered in the differential diagnosis.

Pigmented macules are a common finding on skin examination. It is important that normal benign naevi, lentigos, and freckles are recognised as such. Abnormal pigmented macules on the face and hands may occur in McCune-Albright syndrome and the LEOPARD syndrome. Other features of these conditions usually prevent diagnostic confusion. Pigmentation of the lips may also occur in neurofibromatosis.¹⁷ Localised mucosal pigmentation may be caused by amalgam tattooing, naevus formation, malignant melanoma, and Kaposi's sarcoma. More generalised pigmentary changes in mucosa can occur in Addison's disease, McCune-Albright syndrome, and with drugs such as minocycline, anti-malarials, and phenothiazines.¹⁸ Mucosal pigmentation occurs as a normal variant in 38% of people of African ancestry.¹⁹

The characteristic changes in nails in patients with LHS are longitudinal streaks of pigment known as longitudinal melanonychia. When a single digit is affected by longitudinal melanonychia, subungual malignant melanoma must be considered.²⁰ However, the most common cause of longitudinal melanonychia is benign racial pigmentation.²¹

Mucosal and facial pigmentation without evidence of intestinal polyposis has been found in relatives of patients with PJS.²² Several authors have also described patients with characteristic perioral and intraoral pigmented macules but no intestinal polyposis and no family history, postulating a "forme fruste" of PJS.^{23,24} Interestingly, more recently, at least for some of these patients LHS was raised as a possible diagnosis.²⁵ However, LHS remains a diagnosis of exclusion and given the intrafamilial and interfamilial variability of PJS, pigmentary changes suggestive of PJS in any patient need to be interpreted with caution.

In the absence of a family history and of intestinal polyposis our patient does not fulfil any of these listed clinical criteria for either definite or even presumptive PJS. Also, no pathogenic mutation was identified despite direct sequencing of his entire *STK11* gene. The late onset of macular perioral and intraoral pigmentation together with the occurrence of pigmented lesions on his fingertips and longitudinal melanonychia of his thumbnails is, however, entirely in keeping with LHS. Given the major part that clinical genetics departments play in the institution of invasive screening protocols, we think that it is important to recognise this acquired benign disorder to avoid unnecessary and potentially hazardous investigation and treatment for our patients.

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