*Running section head: A memorable patient*

*Short title: LHS transmitted by blood stem cell transplant*

**Possible transmission of Laugier-Hunziker syndrome by allogeneic peripheral blood stem cell transplantation**

**Authors**

L Steele,1,2 K Hill,3 NCP Cross,4 HL Cooper1

1. Department of Dermatology, Portsmouth Hospitals NHS Trust, Portsmouth, UK.
2. Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, London, UK.
3. Department of Haematology, University Hospital Southampton, Southampton, UK.
4. Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury, UK.

Word count: 614

Figure count: 1

Table count: 0

**Corresponding author**

Lloyd Steele

Email: lloyd.steele@nhs.net

Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, UK. E1 1FR

**Funding:** There was no funding for this article.

**Conflict of interest statement:** There is no conflict of interest for all authors.

**Consent:** Both patients consented to this publication.

**Keywords**

Hyperpigmentation, Hematopoietic stem cell transplantation, High-throughput nucleotide sequencing, Melanosis

A 56-year-old woman was diagnosed with Laugier-Hunziker syndrome (LHS) after presenting with asymptomatic hyperpigmentation periorally, on the oral mucosa, and on the fingers (Fig. 1A-C). Her past medical history was significant for atopic eczema and familial hypercholesterolaemia. Histological examination of a lesional biopsy from the right thumb demonstrated mild acanthosis, basal hypermelanosis, and pigmentary incontinence (Fig. 1D). The patient used no regular medications and had no family history of hyperpigmentation. Investigations, including full blood count, adrenocorticotropic hormone (ACTH), and colonoscopy, were normal.

Several years later, she became a donor for a peripheral blood stem cell transplantation for her brother. He had developed secondary acute myeloid leukaemia (AML), transformed from chronic myelomonocytic leukaemia (CMML). Three years post-transplant, after successful engraftment and achievement of full donor chimerism, pigmentary changes in a similar distribution were noted in the recipient. The hyperpigmentation faded when AML recurred and increased in intensity after a donor lymphocyte infusion (Fig. 1E-F). The patient had used hydroxyurea pre-allograft for CMML, but no other potential causes for hyperpigmentation were identified.

To investigate the possibility of a *KIT* gene mutation, we sequenced the whole *KIT* gene (Illumina TruSight One Expanded panel; 100% of the *KIT* gene covered at ≥20x) using peripheral blood leukocyte DNA from the donor of the blood stem cell transplantation. No variants were found apart from a known benign polymorphism. We also sequenced the STK11 gene (100% of gene covered at ≥20x) and no variants were found.

In 1970, Laugier and Hunziker reported five cases of macular hyperpigmentation affecting the mouth, lips, and in some cases, nails.1 Since referred to as LHS, more than 100 cases have been reported. Systemic associations to date have been rare and inconsistent. Haematologic abnormalities were most commonly reported (two reports of anaemia, two reports of thrombocytopaenia, and one report of hypocellular marrow with anaemia and thrombocytopaenia).2-4 The cause of LHS is unknown.

One case of familial LHS has been reported,1 although the authors suggested this entity may be underrepresented due to misdiagnosis as Peutz-Jeghers syndrome (PJS) without intestinal involvement. PJS is an important consideration in the differential diagnosis, but in addition to hamartomatous polyps, it is associated with various neoplasias. Moreover, a serine threonine kinase (STK11) gene mutation is identified in >94% of cases.2 A STK11 mutation was not detected in our case, consistent with previous LHS reports.2 Whilst the existence of a second yet-to-be-identified causative genetic locus is possible, the likelihood of this lessens as mutation detection rates improve with advances in genetic testing.

Iatrogenic causes also need to be considered. Hydroxyurea was used in this case, which can cause perioral and acral hyperpigmentation. However, the long latency period between drug cessation and the development of hyperpigmentation, together with the temporal association observed between AML status and hyperpigmentation intensity, favoured the allograft as the cause.

We did not identify a mutation in *KIT*, which encodes a multifunctional tyrosine kinase receptor. The rationale for investigation was its association with disorders which can cause oral/perioral and acral hyperpigmentation. These include familial gastrointestinal stromal tumour (GIST), occasionally called ‘GIST cutaneous hyperpigmentation disease’;5 acral and mucosal melanomas; and imatinib-induced hyperpigmentation, although the exact mechanism of the latter is uncertain as imatinib inhibits *KIT,* and thus more commonly causes hypopigmentation. The *KIT* pathway also has a role in haematopoietic stem cell maintenance.5 A limitation of this study was that the gene for *KIT* ligand was not assessed.

Whilst a causative mutation was not identified, this case may provide an insight into the aetiology of LHS. The transmission of genetic abnormalities via allogeneic haematopoietic stem cell is not unprecedented,6 although other possible explanations are possible. These include engraftment of cells with congenital defects, engraftment of autoimmune effector cells, and pathogen transmission.

# 

**CPD QUESTIONS**

Learning objective

To gain an up-to-date knowledge on Laugier-Hunziker syndrome and other disorders with peri-oral and/or acral hyperpigmentation.

Question 1

Which of these medications most commonly causes oral/perioral hyperpigmentation and melanonychia?

1. Amiodarone
2. Bleomycin
3. Imatinib
4. Ibrutinib
5. Minocycline

Answers to question 1

1. Amiodarone. Incorrect. Amiodarone is associated with blue-grey pigmentation of sun-exposed areas.
2. Bleomycin. Incorrect. Bleomycin is classically associated with flagellate hyperpigmentation.
3. Imatinib. Correct. Hyperpigmentation localised to the oral mucosa and/or nail can occur with imatinib, although this is much less common than generalised hypopigmentation.
4. Ibrutinib. Incorrect. This is an oral inhibitor of Bruton's tyrosine kinase (BTK). Perioral/oral and acral hyperpigmentation has not been reported.
5. Minocycline. Incorrect. Hyperpigmentation is a well-recognised side-effect of minocycline, but this does not typically occur in an acral and perioral/oral distribution.

Question 2

Which of these conditions is most commonly associated with perioral and/or acral hyperpigmentation?

1. Chronic myeloid leukaemia (CML).
2. Dowling-Degos disease.
3. Dyschromatosis universalis hereditarian (DUH).
4. Familial gastrointestinal stromal tumour (GIST).
5. Familial progressive hyperpigmentation (FPH).

Answers to question 2

1. Chronic myeloid leukaemia (CML). Incorrect. CML is not associated with such hyperpigmentation. However, imatinib mesylate, whose introduction in the early 2000s led to a paradigm shift in the treatment of CML, can cause this.
2. Dowling-Degos disease. Incorrect. Although Dowling-Degos disease typically presents in adult life (most commonly in the 20s or 30s), hyperpigmentation is typically flexural. It is due to mutations in the *KRT5* gene, which encodes keratin 5.
3. Dyschromatosis universalis hereditarian (DUH). Incorrect. This dyschromatosis is characterised by hyperpigmented and hypopigmented macules over much of the body. Lesions on the face, palms, and soles are generally less prominent or absent.
4. Familial gastrointestinal stromal tumour (GIST). Correct. *KIT* mutations cause 80% of cases of familial GIST. When due to certain *KIT* mutations, it has been associated with perioral and acral hyperpigmentation (as well as perineal and trauma-induced hyperpigmentation).
5. Familial progressive hyperpigmentation (FPH). Incorrect. Unlike Laugier-Hunziker syndrome, it is associated with more diffuse hyperpigmentation and an onset at birth or early infancy. It is caused by gain-of-function mutations in the ligand for *KIT* (also called stem cell factor (SCF)).

**Acknowledgements**

We would like to thank both patients for their participation at a very challenging time. We would also like to thank Dr Joanne Cook for kindly providing the histology photos and Prof Edel O’Toole for reviewing the manuscript.

**References**

1 Makhoul EN, Ayoub NM, Helou JF, Abadjian GA. Familial Laugier-Hunziker syndrome. *J Am Acad Dermatol* 2003; **49**: S143-5.

2 Duong BT, Winship I. The role of STK 11 gene testing in individuals with oral pigmentation. *Australas J Dermatol* 2017; **58**: 135-8.

3 Lee JS, Park KC, Shin JW, Huh CH, Na JI. Two cases of Laugier-Hunziker syndrome with thrombocytopenia. *Eur J Dermatol* 2018.

4 Tan J, Greaves MW, Lee LH. Laugier-Hunziker syndrome and hypocellular marrow: a fortuitous association? *Clin Exp Dermatol* 2007; **32**: 584-5.

5 Ke H, Kazi JU, Zhao H, Sun J. Germline mutations of KIT in gastrointestinal stromal tumor (GIST) and mastocytosis. *Cell Biosci* 2016; **6**: 55.

6 Nishihori T, El-Asmar J, Shah B, Hussaini M, Komrokji R, List A, Anasetti C, Kharfan-Dabaja MA. Donor-derived constitutional chromosomal abnormalities after allogeneic hematopoietic cell transplantation: a single-center experience and a review of the literature. *Bone Marrow Transplant* 2015; **50**: 1388-92.

**Figures**

**Figure 1.** In the donor of the haematopoietic stem cell transplant, hyperpigmentation was present (A) periorally, (B) on the fingers, and (C) on the oral mucosa. (D) Histological examination demonstrated basal hyperpigmentation and pigmentary incontinence on Masson Fontana staining. In the recipient of the haematopoietic stem cell transplant, hyperpigmentation was observed (E) on the oral mucosa and (F) periorally.

A picture containing photo, food, room

Description automatically generated