CASE REPORT

Mucosal pigmentation of the hard palate in a patient taking imatinib

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SUMMARY

Imatinib mesylate is used in the treatment of chronic myeloid leukaemia, among other conditions. Oral mucosal pigmentation as a side effect is rare. We present a summary of the current literature and a case report of a 58-year-old Caucasian woman who presented with a diffuse blue-grey pigmentation of the palatal mucosa, thought to be related to long-term use of imatinib mesylate.

BACKGROUND

Imatinib (imatinib mesylate, brand names Gleevec or Glivec) is a tyrosine kinase inhibitor used in the treatment of certain cancers, including chronic myeloid leukaemia (CML). National Institute for Health and Care Excellence (NICE) guidance published in October 2003 recommended imatinib as a first-line treatment for CML.¹

Prescribing information for imatinib lists the possible side effects, with skin hyperpigmentation risk as 0.1–1%.² There is no mention of oral or mucosal pigmentation. The authors found only eight published articles, detailing 12 cases of imatinib-associated oral mucosal pigmentation.^{3–10}

Pigmentation of the oral mucosa is a common clinical finding. Oral mucosal pigmentation, such as skin pigmentation, may be physiological (racial or ethnic pigmentation). Non-physiological causes may be categorised as exogenous or endogenous, as summarised in table 1.

Kauzman *et al*¹¹ identified several drugs that are commonly associated with oral pigmented lesions, as described in table 1. Imatinib was not mentioned. Thus we report a case of palatal mucosal pigmentation thought to be associated with long-term imatinib therapy, as an addition to the current literature.

CASE PRESENTATION

A 58-year-old Caucasian woman presented to the Maxillofacial Department at Ashford and St Peter's Hospitals with pigmentation of the palatal mucosa (figure 1). The patient was referred by the general dental practitioner, who had first noticed the lesion 2 years previously. There had been no change in size over this period, and there was no history of trauma to the hard palate.

Her medical history included CML, and she had been taking imatinib at various doses (400–600 mg daily) for 13 years. She also took aspirin, as well as over-the-counter vitamin supplements. There was no history of her taking any other medications, including those listed in table 1. She was a non-smoker and consumed alcohol occasionally.

On examination there was a bluish macular discolouration of the hard palatal mucosa, which was not tender, and did not blanch on pressure. There were no areas of cutaneous pigmentation on the head and neck, hands and fingernails.

Table 1 Exogenous and endogenous causes of oral mucosal pigmentation.¹¹

	Example	Suggested cause
Exogenous	Amalgam tattoo	Foreign-body implantation
	Heavy metal pigmentation (eg, lead, mercury, silver)	Deposition of heavy metal particles in mucosa
Endogenous	Smokers melanosis	Stimulation of melanin due to chemicals in smoke
	Addison disease	Stimulation of melanin due to an increased production of adrenocorticotrophic hormone
	Peutz-Jegher syndrome	Stimulation of melanin due to genetic mutation
	Pregnancy	Stimulation of melanin due to hormone levels
	Postinflammatory pigmentation (eg, oral lichen planus)	Stimulation of melanin, cause unclear
	Oral melanoma	Neoplasm arising from melanocytes in the basal layer of squamous mucosa
	Drug-induced pigmentation; eg, chloroquine, hydroxychloroquine, chlorpromazine, clofazimine, tetracycline, minocycline, ketoconazole	Dependant on the drug, but may include: <ul style="list-style-type: none"> ▶ Stimulation of melanin ▶ Deposits of the drug or drug metabolite in mucosa or subcutaneous fat ▶ Deposition of drug in jaw bone ▶ Deposition of iron in mucosa after damage to the dermal vessels

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Figure 1 Palatal mucosa showing bluish macular discolouration.

INVESTIGATIONS

A full blood picture was taken, as well as a screen for Addison disease. No abnormalities were found.

A 4 mm incisional punch biopsy of the lesion was taken under local anaesthesia. The histological report showed unremarkable squamous mucosa, with no melanosis of the basal layer. There were focal depositions seen in the lamina propria, which tested positive with Perl's Prussian blue stain, suggesting the presence of haemosiderin. There was no evidence of malignancy. Fontana-Masson staining, for presence of melanin, was unfortunately not preformed, which would have further confirmed the diagnosis. The available histology and clinical presentation was found to be consistent with drug-induced mucosal pigmentation.

OUTCOME AND FOLLOW-UP

As the patient was asymptomatic, no treatment was necessary and the patient will be regularly reviewed. There was no indication to change the patient's medication.

DISCUSSION

Imatinib is more commonly associated with skin hypopigmentation, and oral or mucosal hyperpigmentation appears to be

rarely reported. One study of 118 patients taking imatinib for CML reported 40.9% developed skin hypopigmentation to some degree, and only 3.6% skin hyperpigmentation.¹² It did not mention oral or mucosal pigmentation.

The findings from this case are consistent with previous case reports of oral mucosal pigmentation in patients taking imatinib (summarised in table 2).

Of the 12 patient cases found, 4 included histological results, showing deposits of melanin, with or without haemosiderin, in the lamina propria. In the other eight patients, a biopsy had not been taken, and the diagnosis made solely on clinical grounds. In this case, haemosiderin deposits were found in the lamina propria, however, staining for melanin was not preformed. Nevertheless, the available histological findings and clinical presentation were consistent with previous cases, and a diagnosis was made of drug-induced pigmentation thought to be associated with imatinib.

From the cases summarised in table 2, this condition appears to have affected males and females, aged 13–70, and in a majority of cases affected only the mucosa of the hard palate, with buccal gingivae as the only other intraoral site mentioned.

The pathogenesis of oral mucosal pigmentation in patients taking imatinib remains unclear. It has been suggested that imatinib increases melanin production, through the stimulation of C-kit (a growth factor receptor found on skin basal cells, melanocytes and mast cells) leading to transactivation of the tyrosinase pigmentation gene promoter in melanocytes.¹² Another case report suggests an imatinib metabolite chelates with iron and melanin.³ There is no current suggestion as to why mucosa of the hard palate is invariably affected.

It would seem from the literature that imatinib-associated pigmentation of the oral cavity is rare, although it is entirely possible that the oral mucosa is not routinely examined by non-dentists, and therefore, this condition is under-reported. Indeed, in at least four of the case reports mentioned in table 2, the condition was first noticed by the general dental practitioner. It is sensible, therefore, that dental and medical practitioners are aware of mucosal pigmentation as an uncommon finding in patients taking imatinib.

Table 2 Summary of previous published case reports of imatinib-associated oral mucosal pigmentation

Author(s), year	Age and sex of patient	Site(s)	Length of time imatinib was taken	Condition for which imatinib was taken	Histological findings
Singh and Bakhski, 2007 ¹⁰	13 F	Gingivae, teeth	4 years	CML	Clinical diagnosis only
Lewis, 2009 ⁵	70 M	Palate	Unknown	CML	Melanin and haemosiderin deposits in lamina propria
Mcperson <i>et al</i> , 2009 ⁸	59 F	Gingivae, toes, fingernails	6 years	CML	Clinical diagnosis only
Wong <i>et al</i> , 2011 ⁹	43 F	Palate	3 months	CML	Melanin deposits in lamina propria
Mattsson <i>et al</i> , 2011 ⁶	66 F	Palate	5 years	Metastatic gastrointestinal stromal tumour	Melanin deposits in lamina propria
Li <i>et al</i> , 2012 ³	66 F	Palate	5 years	CML	Clinical diagnosis only
	64 F	Palate	5 years	CML	
	64 M	Palate	4 years	CML	
	53 M	Palate	10 years	CML	
	29 F	Palate	4 years	Pelvic fibromatosis	
Resende <i>et al</i> , 2012 ⁴	38 M	Palate, nose, earlobes	5 years	Post haematopoietic stem cell transplant	Clinical diagnosis only
Song and Kang, 2014 ⁷	58 M	Palate, nose	Unknown	CML	Clinical diagnosis only
Lyne <i>et al</i> , 2015	58 F	Palate	13 years	CML	Haemosiderin deposits in lamina propria

Learning points

- General dental and medical practitioners, and specialist practitioners should be aware of oral mucosal pigmentation associated with imatinib mesylate.
- Oral pigmentation has a variety of causes, and any underlying disease or malignancy should be excluded.
- The mechanism of imatinib associated mucosal hyperpigmentation remains unclear.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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